11

Narcotic Analgesics (Opiate Analgesics)

Chapter

11

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1. INTRODUCTION

Opium was known to man many centuries ago. This is evident from the **Ebers Papyrus** and **Homer's Odyessey** where the use of opium was mentioned. Opium is obtained by making superficial incisions on the immature and unripe capsules of *Papaver somniferum* (or **poppy plant**). The exudate is air-dried and then powdered to give the official powdered opium. A systematic study of the plant material led to the isolation and identification of the most important alkaloid known as morphine in 1803. Other alkaloids isolated from opium include **codeine, papaverine and thebaine.**

The opium class of narcotic drugs are considered not only as the most potent and clinically useful agents causing depression of central nervous system, but also as very strong analgesics. **Morphine** and **morphine-like drugs** are referred to as **opioids** or **opiates**. They are also known as **narcotic analgesics** (**'narcotic'** is derived from the Greek word **'narcotic'** meaning drowsiness. The term **narcotic** is now used to refer to dependence producing drugs.

Morphine possesses a host of diverse pharmacological properties and uses, a few of which are, to check diarrhoea, ease dyspnea, suppress cough and above all, to induce sleep in the presence of pain. Though **morphine** and **morphine-like drugs** may not alter the sensation of pain but they modify the emotional reaction to pain. The pain may be present but may not be perceived as painful.

The narcotic analgesics tend to produce euphoria which is an important factor in their addictive property which limits their use. Other limitations include : *respiratory depression, decreased gastrointestinal motility leading to constipation, increase biliary tract pressure and pruritus due to histamine release.* Because of these setbacks in the use of morphine there has been a constant effort to develop analgesics with fewer side-effects and minimal addictive actions.

As on date a plethora of **CNS-depressants,** such as : **anti-psychotics, barbiturates** and **ethanol** have been shown to afford effectively a substantial lowering in the **'pain perception'.** It has been already demonstrated beyond any reasonable doubt that two vital phenomenon taking place *in vivo*, namely : (*a*) **norepinephrine** re-uptake (*viz.*, antidepressant drugs) ; and (*b*) preventors of **serotonin*** are extremely beneficial therapeutically when administered either in conjunction (adjuvant) with **'opiates'** or alone in the control and management of certain typical incidences of chronic pain.

*A chemical, **5-hydroxy tryptamine (5-HT)**, present in platelets, gastro intestinal mucosa, mast cells, and carcinoid tumours. It is a potent vasoconstrictor ; and also a neurotransmitter in the CNS, and is important in sleep-walking cycles.

With the advent of **'new mechanisms'** emphatically based on latest trend of research activities geared into the antinociceptive effects of certain centrally acting **cannabinoid, α-adrenergic-,** and above all the **nicotinic-receptor agonists** may ultimately give rise to a host of therapeutically potent and efficacious analgesics. Besides, basic fundamental research conducted with inhibitors to tachykinin (neurokinin) receptors evidently shows adequate promising results leading to the discovery of newer breed of analgesic drug substances into the therapeutic armamentarium. It is, however, pertinent to state at this juncture that while the constant efforts are still on with respect to the evolution of **'new-drugs'** the **chronic** as well as **acute pain** is invariably circumvented with the aid of **'opioid analgesics'** most efficaciously.

2. LIMITATIONS OF OPIATE ANALGESICS

There are several disadvantages as well as limitations of **'opiate analgesics'** that are enumerated as under :

(*a*) these are usually *contraindicated* in patients who have essentially a past record of Addison's disease, myxedema, and hepatic cirrhosis.

(*b*) these **'drugs'** exhibit a tendency of minimising ventilation that ultimately give rise to hypercapnia and lead to cerebrovascular dilatation resulting into enhanced intracranial pressure ; therefore, great caution has got to be observed in such situations (conditions) as : cerebral edema, head injuries, and delerium tremens.

(*c*) these are required to be used with utmost caution and restriction in patients having a history of cardiac arrythmias, inpaired kidney function, and chronic ulcerative colitis.

(*d*) these **'drugs'** have a tendency to cross the **placental barrier** ; therefore, newborn infants, whose mothers have been treated with such drugs during labour, must be observed very meticulously for probable symptoms of **respiratory depression,** and should be treated adequately for narcotic overdosage, if so required.

(*e*) an individual who is sensitive either to a specific narcotic agent or a group of agents, must avoid them as far as possible to get into serious complications that may even prove fatal.

(*f*) these '*drugs*' invariably exhibit amalgamated **'analgesic'** and **'depressant'** effects that form the basis for a large number of **drug-drug interactions** with other therapeutic agents.

Examples : (1) A plethora of **'drug substances',** for instance : muscle relaxants, sedatives-hypnotics, tricyclic antidepressants, antipsychotic, antihistaminics, and alcohols are observed to interact with **opiate analgesics** to augment and accelerate their overlapping pharmacological activities, namely : anticholinergic effects and respiratory depression.

(2) **Monoamine oxidase inhibitors (MAOIs)** must be administered with utmost caution in conjunction with **'narcotic analgesics'** by virtue of their extremely intensified activity, for instance : patients treated with MAOIs when treated with '**meperidine**' give rise to such a severe reaction that may sometimes even prove to be fatal.

In short, one may infer from the aforesaid statement of facts (*a*) through (*f*) that the **'opiate analgesics'** on one hand produce wonderful much needed therapeutic excellence, but on the other extreme care, caution and wisdom need to be applied in their usage in treating specific conditions.

3. CHARACTERISTIC FEATURES OF OPIOIDS

There are several specific characteristic features of **opioids (opiates)** as detailed below which would be treated individually here under :

(*i*) Opioid peptides,

(*ii*) Opioid receptors,

(*iii*) Orphan opioid receptor,

(*iv*) Mu opioid receptors,

(*v*) Kappa opioid receptors,

(*vi*) Delta opioid receptors, and

(*vii*) Opioid receptors : identification and activation.

3.1. Opioid Peptides

Akil *et al*., (1984) observed that the **endogenous opioid peptides** are invariably synthesized as essential component associated with the structures of specific large precursor proteins. Evidently, each of the major types of opioid peptides does have an altogether different and specific precursor protein.

Examples :	**Opioid Peptide**	**Precursor**
(*i*)	**Proenkephalin A**	— Met- and Leu-Enkephalin
(*ii*)	**Propiomelanocortin (PMOC)**	— β-Endorphin
(*iii*)	**Proenkephalin B (Prodynorphin)**	— Dynorphin, and α-Neoendorphin

Salient Features. The various salient features of the **opioid peptides** are stated as under :

(1) Most of the **pro-opioid proteins** are usually synthesized very much within the cell nucleus, and subsequently transported meticulously to the terminals of the nerve cells from where they are being released gradually.

(2) Active peptides are found to be undergoing hydrolysis from the corresponding large proteins by the aid of proteases which particularly, take cognizance of the **'double basic amino acid sequences'** strategically located just prior and immediately after the opioid peptide sequences.

(3) **Endogenous opioid peptides** are found to afford their analgesic activity both at the supraspinal and spinal sites :

(*a*) Cause analgesia alternatively by the help of a peripheral mechanism of action intimately linked with the pervailing inflammatory process, and

(*b*) CNS-happens to be the ideal most preferred site where the opioids are found to exert either a neuromodulator or an inhibitory neurotransmitter action at the following *two* prevalent sites, namely :

(*i*) interconnecting neuronal pathways meant for the exclusive **'pain signals'** within the brain, and

(*ii*) afferent pain signalling neurons located in the dorsal horn of the spinal cord.

3.2. Opioid Receptors

Generally, there exist *three* main categories of the '*opioid receptors*', namely : (*a*) mu ; (*b*) kappa designated by '*k*' ; and (*c*) delta designated by 'δ'.* It is, however, pertinent to state here that all the aforesaid opioid receptors have been adequately characterized and also '*cloned*'.** Based on the most recent universally adopted and recognized **'nomenclature'** classifies the said three opioid receptors in the actual order by which they were eventually cloned.*** According to this classification the various receptors are commonly termed as follows :

OP_1—Receptors : Delta opioid receptors (δ) ;

OP_2—Receptors : Kappa opioid receptors (κ) ;

OP_3—Receptors : mu opioid receptors ;

Interestingly, all the three **'opioid receptor types'** are found to be strategically located either in the human brain or spinal cord tissues ; furthermore, each of them essentially possesses a specific role to play in the control, regulation and management of pain threshold. As on date, however, both **mu** and **kappa** agonists are already in clinical application abundantly across the globe ; whereas, a good number of **delta receptor** selective drug substances are in the regimen of both extensive and intensive **'clinical trial procedures'.**

3.3. Orphan Opioid Receptor

Importantly, an absolutely different 4th receptor, besides mu-delta-kappa opioid receptors, has been duly identified and cloned derived from the homology with the cDNA sequence of the known ones. One of the most predominant feature of the new 4th receptor is that it never got bound to the classical opioid peptide or prevailing antagonists or known non-peptide agonists with high affinity. Therefore, this new receptor has been legitimately termed as the **orphan opioid receptor**. Inspite of the copious volume of research carried out to establish the exact mechanism of this receptor no definite experimental evidence(s) to suggest adequately the importance of this system with respect to the pain transmission and its prevailing association to the classical opioid systems.

3.4. Mu Opioid Receptors

Zadina *et al.***** (1997) made a pivotal observation that the *two* vital **endogenous opioid peptides,** namely : (*a*) **endomorphin-1** ; and (*b*) **endomorphin-2.** showed an extremely high degree of selectivity for the mu (OP_3) receptors exclusively.

Salient Features. The salient features of **mu opioid receptors** are as follows :

1. A plethora of therapeutically potent and useful compounds, such as : **morphine, sufetanil, ndomorphin-1, ndomorphin-2, are potent Mu (μ) opioid agonists.**
2. A number of other pharmacologically active compounds, for instance : **Naloxone, Cyprodime, Naltrexone are Mu (μ) opioid antagonists.**
3. Practically all the **'opioid alkaloids'** and most of their synthetic structural analogues are precisely the mu selective agonists.

*Lord JAH *et al.* **Endogenous opioid peptides : multiple agonists and receptors,** *Nature,* **267** : 495-499, 1977.

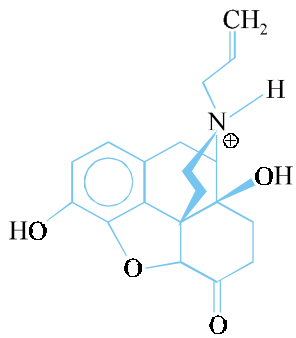
Satoh and Minami, **Molecular pharmacology of the opioid receptors, *Pharmacol. Ther.*, **68,** 343-64, 1995.

***Dhawan BN *et al. Pharmacol. Rev.*, **48**, 567-592, 1996.

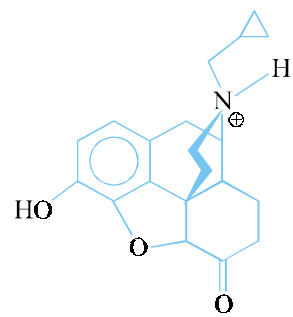
****Zadina JE *et al. Nature*, **386 :** 499-502, 1997.

4. Three **'drug substances',** namely : **morphine, normorphine,** and **dihydromorphinone** are found to have 10–20 times more **mu receptor** selectivity.
5. Kieffer* (1999) amply demonstrated that almost all the major pharmacologic activities, as studied **with mu receptor knockout mice,** after having been treated with morphine injection usually take place by interactions with mu receptors. Such observed activities are : decreased gastric motility, emesis, tolerance, analgesia, respiratory depression and withdrawl symptoms.
6. **Cyprodime** happens to be the most selective non-peptide mu antagonist *i.e.*, showing 100 time more selectivity for mu over delta ; and 30 times more selectivity for mu over kappa.
7. **Naltrexone** and **Naloxone** are recognized as opioid antagonists which exhibit only negligible *i.e.*, 5 to 10 fold more selectivity for the mu receptors.

SAR-Mu Antagonists. It has been observed that there are only *two* drug substances which are recognized as **'pure antagonists'** *i.e.*, they behave as antagonists at all opioid receptor sites, such as : **naloxone** (*i.e.*, N-allyl) ; and **naltrexone** (*i.e.*, N-cyclopropylmethyl) structural analogues of **noroxymorphone.** The 14β-OH functional moiety is regarded to be the most important characteristic feature for attributing the pure antagonistic properties of these two aforesaid compounds.



Naloxone



Naltrexone

However, it has not yet been expatiated completely as to why a minor alteration from an N-methyl to an N-allyl moiety can reverse the activity of **'an opioid'** from being a **potent agonist** into a **potent antagonist**. Perhaps a logical explanation may be put forward with regard to the capability of opioid receptor protein to couple with **G-proteins**** efficaciously in the event when it got bound by an agonist but no such coupling with **G-proteins** when got bound by an antagonist. Furthermore, one may draw an inference that in the instance of an opioid with an N-substituent of 3-4 carbon number, exerts a distinct conformational change either in the receptor or blocks essential receptor areas that might specifically hinder the possible interaction between the receptor and the **G-proteins.**

3.5. Kappa Opioid Receptors

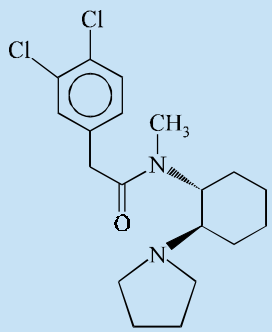
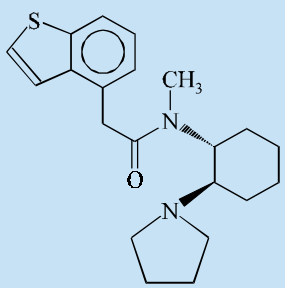
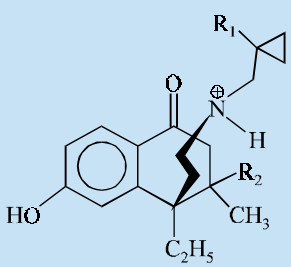
The two prominent 6, 7-benzomorphan structural analogues are the racemate of **ethylketazocine** and **bremazocine** which predominantly exhibit **kappa opioid receptor** selectivity. These two compounds gained prominence as they were used initially to evaluate the **kappa receptors** ; but later on found to be possessing not-so-high a selectivity. However, quite recently, a variety **'arylacetamide'**

*Kieffer BL, *Pharmacol, Sci.*, **20**, 19-25, 1999.

**Signal transduction proteins.

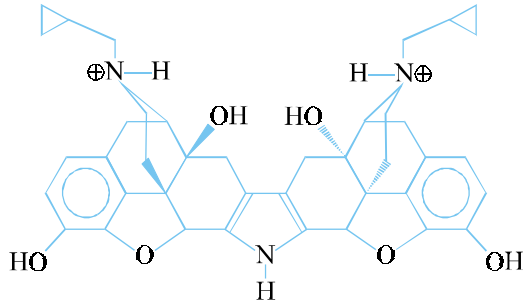
structural analogues, which showed a distinctly higher selectivity for kappa in comparison to mu or delta receptors, have seen the light of the day. The *two* new racemic compounds investigated largely are : U50488 and PD117302, whose characteristic features along with the earlier ones are enumerated in Table 10.1.

Table 11.1 : Characteristic Features of Kappa (κ) Opioid Agonists

S. No.	Racemate Compounds	Characteristic Features
1.	**(±)-U50488** 	1. It shows 50 times more selectivity for kappa over mu receptors. 2. It enjoys the reputation of being the most-important '*pharmacological tool*' in the characterization of the kappa opioid activity solely.
2.	**(±)-PD117302** 	1. It exhibits almost 1000 times selectivity for kappa over mu or delta receptors. 2. Generally, the kappa agonists cause distinct analgesia in humans and animals.
3.	**(±)-Ethylketazocine [R_1 = H ; R_2 = H]** **(±)-Bremazocine [R_1 = OH ; R_2 = CH_3]** 	1. Used earlier to help in the investigational studies with regard to kappa receptors. 2. Not found to be possessing enough sensitivity and selectivity ; and hence, replaced by U-50488 and PD-117302 (*i.e.*, the *arylacetamides*).

In the search for **kappa (κ) opioid antagonists** only one drug substance gained cognizance, which is **(±) nor-binaltorphimine,** and it showed fairly good selectivity for the kappa receptors.*

*Choi H *et. al., J Med. Chem.*, **35** : 4638-39, 1992.



(±) nor-Binaltorphimine

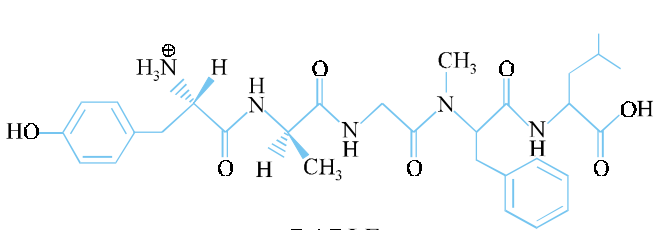
SAR-Kappa Receptor Agonists. Most of the clinically used kappa agonists essentially have their chemical structures very much related to the rather '**rigid opioids**', and those having the additional functional moieties attached to the N-atom, such as : **allyl ; cyclopropylmethyl (CPM)** ; and **cyclobutylmethyl (CBM).** Interestingly, all these compounds are observed to be **kappa receptor agonists ;** besides being **mu receptor antagonists**. Importantly, the **kappa agonist** activity may be increased substantially by the following *two* minor structural modifications as stated under :

(*a*) introduction of the O-atom placed strategically at the 8-position [*e.g.*, **ethylketazocine** (Table 11.1)], and

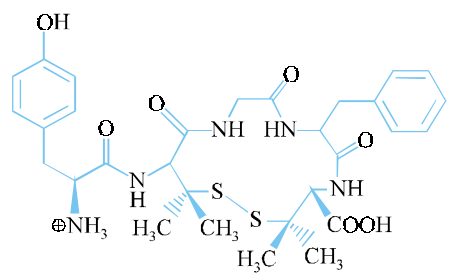
(*b*) introduction of the O-atom right into the N-substituent [*e.g.*, **bremazocine** (Table 11.1)].

3.6. Delta Opioid Receptors

Adequate modifications and alterations in the amino-acid sequence and composition of the **enkephalins** (pentapeptides produced in the brain) give rise to such compounds that significantly demonstrate both high potency and distinct selectivity for the delta opioid receptors. James *et. al.** (1984) introduced **[D-Ala^2, D-Leu^5] enkephalin,** also termed as **DADLE ;** whereas, Mosberg *et al.*** (1983) introduced the cyclic peptide **[D-Pen^2, D-Pen^5] enkephalin,** also known as **DPDPE,** which enjoyed the reputation of being the peptides invariably and frequently employed as **selective delta receptor ligands.**



DADLE



DPDPE

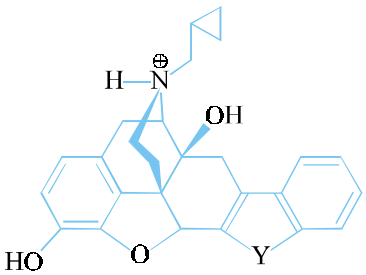
Both **DADLE** and **DPDPE** together with some other **delta-receptor-selective peptides** have been employed extensively and intensively for carrying out numerous *in vitro* studies initially. Based on

*James IF *et al., Mol. Pharmacol.*, **25** : 337-342, 1984.

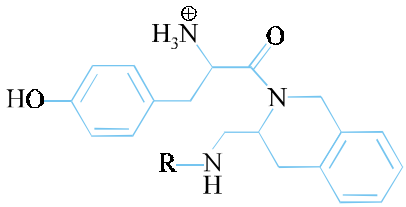
Moseberg HI *et al., Proc Natl Acad Sci* USA, **80 : 5871-4, 1983.

their two cardinal characteristic negative qualifications, namely : (*a*) metabolic instability ; and (*b*) poor distribution properties*, their overall usefulness for *in vivo* studies have been restricted immensely.

Takemori *et al.*** (1992) introduced *two* highly selective nonpeptide delta (OP_1) opioid antagonists for the delta receptors exclusively, as illustrated below : *i.e.*, **naltrindol,** and **naltiben.**



Naltrindol, Y = NH ;
Naltiben, Y = O ;



Tipp : R =

Tipp – ψ : R = OH

Of the two compounds stated above the former is observed to penetrate the CNS and shows antagonist activity which is particularly selective for the delta (OP_1) receptors both *in vitro* and *in vivo* systems.

Schiller *et al.**** (1993) reported **two peptidyl antagonists TIPP and TIPP-Ψ,** as shown above which are found to be selective for **delta receptors.** Unfortunately, their clinical usefulness as well as their ability to give fruitful results for *in vivo* studies have been virtually jeopardized and negated by virtue of their absolutely poor pharmacokinetic characteristics.

Interestingly, the **opioid receptor** antagonists have surprisingly demonstrated appreciable clinical potential both in the treatment of cocaine abuse, and as an immuno suppressive agent.

SAR-Delta Receptor Agonists. The various cardinal factors with respect to the SAR of delta receptor agonists are enumerated as under :

- SARs for the delta receptor agonists have been least explored/investigated amongst the **'opioid drugs'.**
- **Naltrindol** and naltiben *i.e.*, the two **nonpeptide delta selective agonists,** are picking up investigative interest gradually.
- Peptides having high selectivity for delta receptors are already established and documented.
- Number of selective delta agonists are very much still under the required **'clinical trials',** and may be approved as a potential **'drug substance'** of the future.

3.7. Opioid Receptors : Identification and Activation

The identification of **'multiple opioid receptors'** has been adequately accomplished with the subsequent discovery of certain selective potential agonists as well as antagonists ; and the *two* most sophisticated and reliable '**assay methods**' as given below :

*Penetration into the blood-brain.

Takemori *et al. Life Sci.*, **149 : 1–5, 1992.

***Schiller PW *et al. J. Med. Chem.*, **36** : 3182-7, 1993.

(*a*) **Leslie's Method* (1987).** For the identification of sensitive assay techniques, and

(*b*) **Satoh and Minami's Method** (1995).** For the ultimate cloning of the receptor proteins.

Salient Features. The various salient features with respect to the identification and activation of the **'opioid receptors'** are, namely :

(1) Two techniques are used predominantly, such as : (*a*) the radioligand binding assays on the brain-tissues ; and (*b*) the electrically stimulated peripheral muscle preparations.

(2) To differentiate the **'receptor selectivity'** of test compounds the following specific assay procedures may be adopted :

(*a*) computer aided line-filling, and

(*b*) selective blocking by using either reversible or irreversible binding agents with certain types of receptors.

(3) Signal transduction mechanism for mu, delta, and kappa receptors is *via* the **Gi/o proteins.** Thus, the activation of the ensuing opioid receptors is directly associated with the G protein to an inhibition of the critical **adenylate cylase activity.** Consequently, the ultimate lowering in cAMP production essentially affords an efflux of k^+ ions, and finally gives rise to **hyperpolarization of the nerve cell.*****

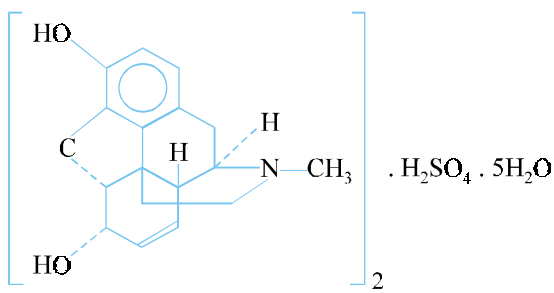
4. CLASSIFICATION

The narcotic analgesics are usually classified on the basis of their basic chemical structures as discussed below along with a few classical examples from each category.

4.1. Morphine Analogues

Morphine and related drugs possessing potent narcotic analgesic properties, are used in clinical practice. A few examples belonging to this class of compounds are morphine sulphate ; **diamorphine hydrochloride ; codeine ; dihydrocodeine phosphate ; hydromorphone hydrochloride ; hydrocodone tartrate ; oxymorphone hydrochloride.**

A. Morphine Sulphate BAN, Morphine Sulfate USAN.



7, 8-Didehydro-4, 5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2 : 1) (salt) pentahydrate ; Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2 : 1) (salt), pentahydrate ; B.P., U.S.P., Int. P., Ind. P ; Duraphine(R) (Elkins-Sinn).

*Leslie FM, *Pharmacol. Rev.*, **39,** 197–249, 1987.

Satoh M and Minami M., *Pharmacol. Ther.*, **68, 343-64, 1995.

***Childers SR, *Life Sci.*, **48**, 1991–2003, 1991 ; Georgoussi *et al. Biochem. J.*, **306,** 71-5, 1995.

Preparation

Morphine can be prepared by total synthesis, but due to the complexity of the molecule renders such an approach not viable commercially. Even today the main bulk of morphine is derived from the natural source and various analogues prepared therefrom.

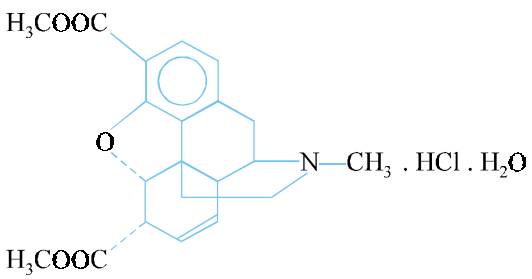
Method-I. The aqueous extract after concentration is neutralized, a solution of calcium chloride is now added, and the resulting mixture is filtered and further concentrated. The crude morphine hydrochloride separates out and is purified by precipitation with ammonia and recrystallised finally as the sulphate.

Method-II. The concentrated aqueous extract is mixed with ethanol and made sufficiently alkaline with ammonia, when morphine being sparingly soluble in dilute ethanol separates out while the remaining alkaloids are left in solution. The crude **morphine** thus obtained is usually purified by repeated crystallization as the corresponding sulphate.

It is employed extensively as an analgesic, antitussive, adjunct to anaesthesia and nonspecific antidiarrheal agent. In small doses it helps to alleviate continued dull pain, wheras in large doses to relieve acute pain of traumatic or visceral origin. **Morphine** is responsible for altering the psychological response to pain and thereby suppresses anxiety and apprehension, and enables the subject to be more tolerant to discomfort and pain. It is specifically used in the **management of postoperative pain and also for alleviating pre-operative apprehension.**

Dose : *Usual, adult, oral, 10 to 30 mg 6 times daily.*

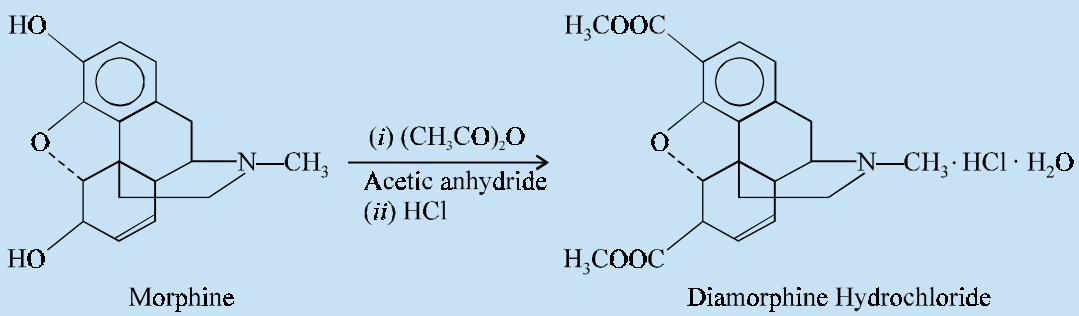
B. Diamorphine Hydrochloride BAN, Diacetylmorphine Hydrochloride USAN.



3, 6-*o*-Diacetylmorphine hydrochloride monohydrate ; Heroin Hydrochloride ; Diamorphine Hydrochloride B.P., Diacetylmorphine Hydrochloride U.S.P. IX ;

Diamorphine(R) (Roche, U.K.)

Synthesis



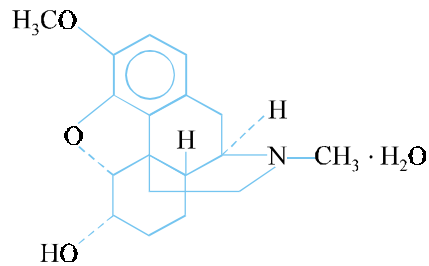
Morphine Diamorphine Hydrochloride

It may be prepared by the acetylation of **morphine** and subsequent treatment with hydrochloric acid.

Diamorphine hydrochloride possesses similar actions to that of **morphine**. It is found to be a more potent analgesic than **morphine** but it has a shorter duration of action stretching up to 3 hours only. It is generally *employed for the relief of severe pain particularly in terminal illnesses.* Used pre- and post-operatively and being a strong addictive, diamorphine is rigidly controlled and not available in international market.

Dose : *Oral, subcutaneous, intramuscular, 5 to 10 mg.*

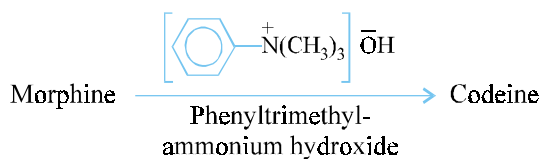
C. Codeine BAN, USAN,



7, 8-Didehydro-5, 5α-epoxy-3-methoxy-17-methyl-morphinan-6α-ol mono-hydrate ; Morphinan-6-ol, 7, 8-didehydro-4, 5-epoxy-3-methoxy-17-methyl-, monohydrate ; B.P., U.S.P., Eur., P., Int. P.

Synthesis

The consumption of codeine is much more than morphine and hence it may be prepared by the partial synthesis of **morphine** as stated below :

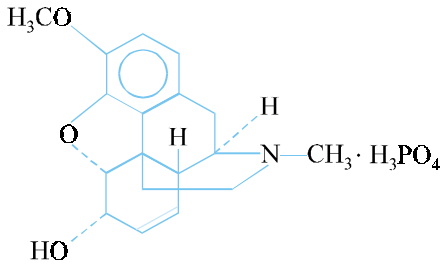


One of the phenolic OH groups in **morphine** is methylated by phenyltrimethyl ammonium hydroxide. The process involves dissolution of **morphine** in a solution of KOH in absolute alcohol along with the appropriate quantity of the methylating agent and the resulting solution warmed to 130°C. Afer cooling, water is added and the remaining solution is acidified with sulphuric acid. The generated dimethylaniline is separated and the excess of alcohol is removed by distillation under reduced pressure. The codeine is precipitated by the addition of sodium hydroxide and may be purified by crystallization as the sulphate salt.

It is a narcotic analgesic with utilities similar to those of **morphine,** but its analgesic activity is relatively much less. It exhibits only mild sedative effects.

Dose : *Usual, adult, oral, analgesic, 30 mg 6 times a day ; as antitussive, 5 to 10 mg every 4 hours.*

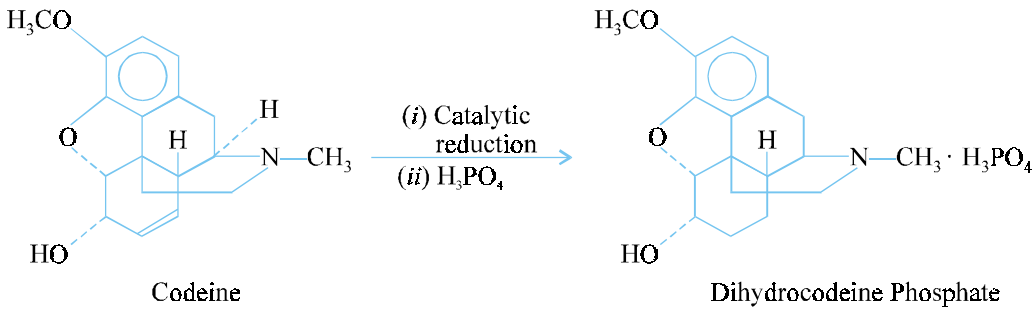
D. Dihydrocodeine Phosphate BAN, Dihydrocodeine INN, Drocode USAN,



7, 8-Dihydrocodeine phosphate ; Hydrocodeine Phosphate ; Jap. P.,
Rapocodin(R) (Knoll)

Synthesis

It may be prepared by the catalytic reduction of codeine and treating the resulting product with phosphoric acid.

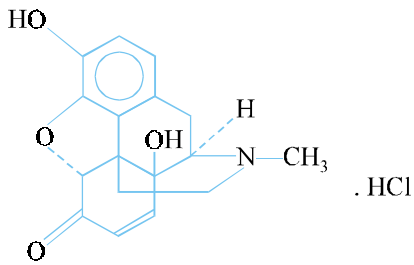


Codeine Dihydrocodeine Phosphate

It is used for the relief of mild to moderate pain.

Dose : *Usual, oral, 30 mg 4 to 6 times a day.*

E. Hydromorphone Hydrochloride BAN, USAN, Hydromorphone INN.



4, 5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride ; Morphinan-6-one, 4, 5-epoxy-3-hydroxy-17-methyl-, hydrochloride, (5α)- ; Dihydromorphinone Hydrochloride ; U.S.P., Int. P.,
Dilaudid(R) (Knoll) ;

Synthesis

Method-I ; From Morphine

$$\text{Morphine} \xrightarrow[(ii)\ \text{Reaction with HCl}]{(i)\ \text{Reduction}} \text{Hydromorphone Hydrochloride}$$

It may be prepared by the reduction of morphine and then treating the resulting product with an equimolar quantity of hyrochloric acid.

Method-II : From Dihydromorphine

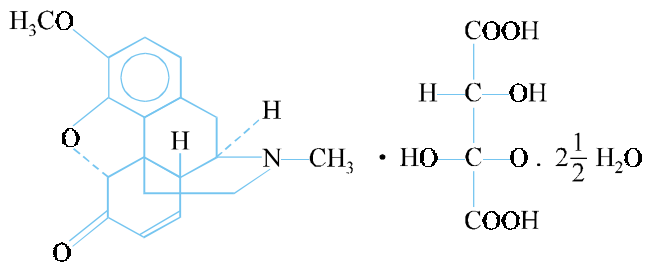
$$\text{Dihydromorphine} \xrightarrow[(ii)\ \text{Reaction with HCl}]{(i)\ \text{Oxidation}} \text{Hydromorphone Hydrochloride}$$

It is prepared by the oxidation of **dihydromorphine** and then reacting with an appropriate amount of hydrochloric acid.

It is a semisynthetic opiate analgesic, similar in action to that of morphine, normally used in the *treatment and subsequent relief of mild to severe pain due to cancer, trauma, myocardial infarction, biliary and renal colic, post-operative pain and severe burns.* It is more potent than morphine and the analgesic effect commences within 15 minutes and lasts for about 5 hours.

Dose : *Subcutaneous and oral, 1 to 1.5 mg ; Usual, 2 mg every 4 hours.*

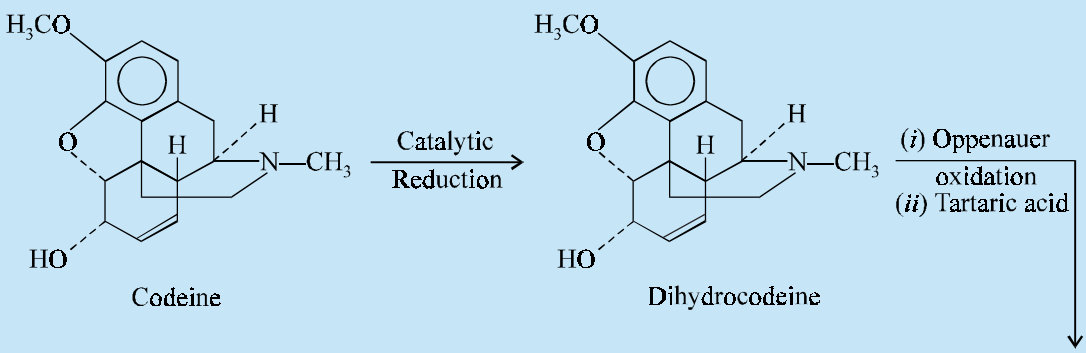
F. Hydrocodone Tartrate BAN, Hydrocodone Bitartrate USAN, Hydrocodone INN,



4, 5α-Epoxy-3-methoxy-17-methylmorphinan-6-one, tartrate (1 : 1) hydrate (2 : 5) ; Morphinan-6-one 4, 5-epoxy-3-methoxy-17-methyl-, (5α)-, [*R*-(*R**, *R**)]-2, 3-dihydroxybutanedioate (1 : 1), hydrate (2 : 5), U.S.P., Int. P.,

Dicodid(R) (Knoll) ; Mercodinone(R) (Merrell Dow)

Synthesis



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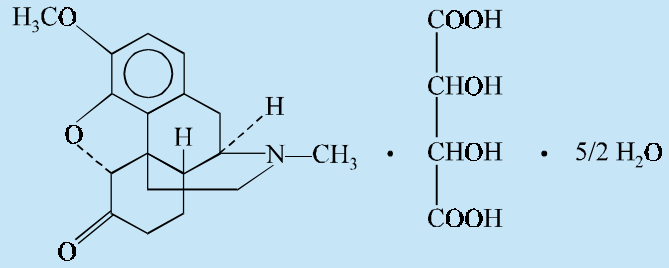


Hydrocodone Tartrate

It may be prepared by the catalytic reduction of codeine to yield **dihydrocodeine** which on being subjected to **Oppenauer oxidation** and treatment with equimolar quantity of tartaric acid gives rise to **hydrocodone tartrate.**

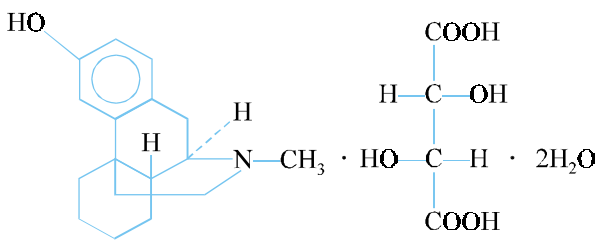
It is mostly used for the *relief of moderate to severe pain and also for the symptomatic treatment of cough.* It is a narcotic analgesic and considered to be more addictive than codeine.

Dose : *Usual, adult, oral, 5 to 50 mg per day.*

4.2. Morphinan Analogues

Grewe (1946) introduced a vital alkylation reaction *via* a very specific **stereo-selective** *(trans)* **synthesis** followed by acid-catalyzed intramolecular, aromatic substitution, which caused the B/C-*cis* C/D-*trans* ring fusions found to be common in either morphine or its natural congeners. This study has paved the way for an altogether new morphinan analogues known as **'benzomorphans'**. A few classical examples of this group of compounds are listed below, *viz.,* **levorphanol tartrate ; dextromethorphan hydrobromide ; butorphanol tartrate ;**

A. Levorphanol Tartrate BAN, USAN, s INN.



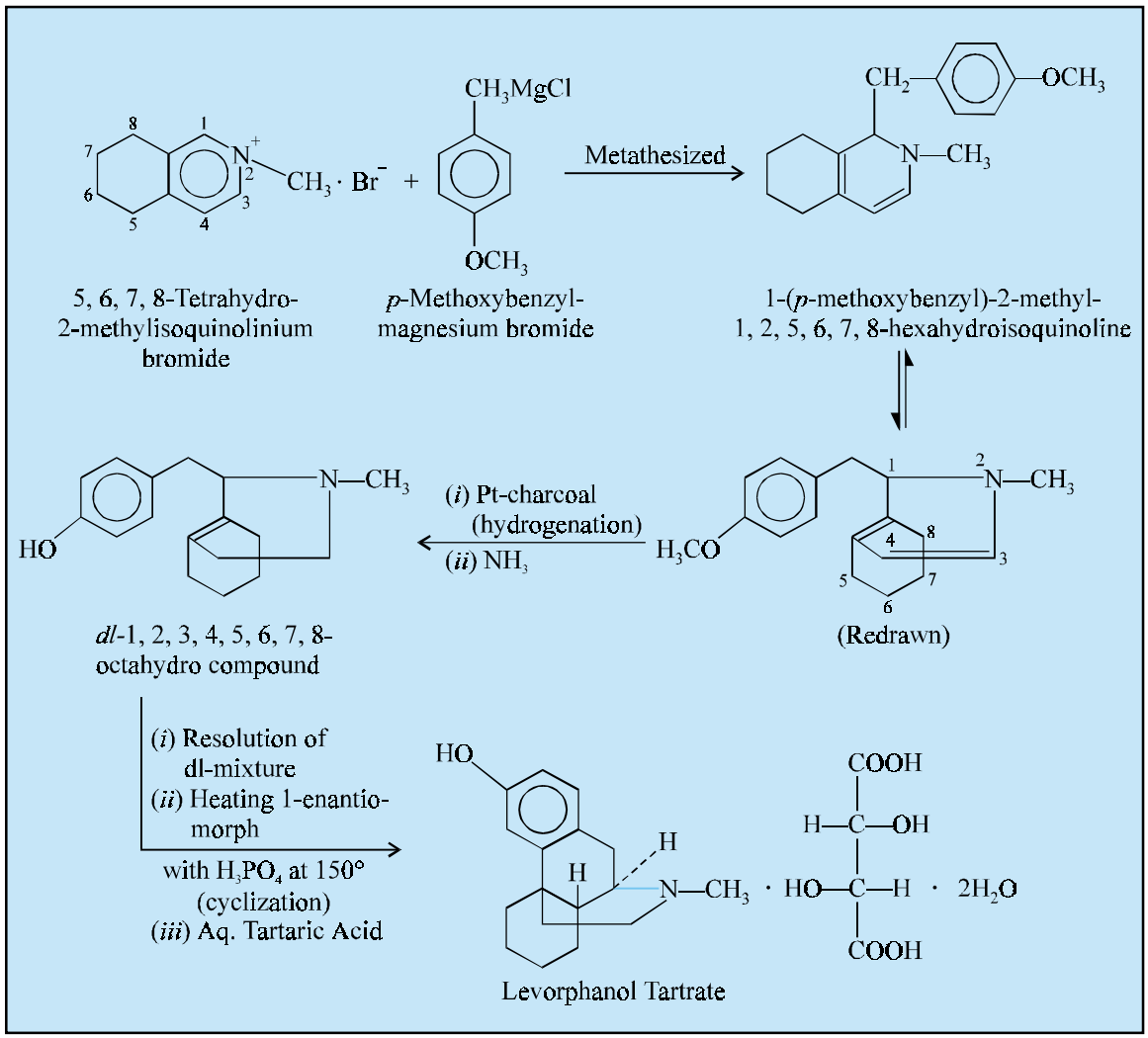
17-Methylmorphinan-3-ol, tartrate (1 : 1) (salt) dihydrate ; Morphinan-3-ol, 17-methyl-, (R-*R**, *R**]-2, 3-dihydroxybutane-diotate (1 : 1) (salt) dihydrate ; B.P., U.S.P.,

Levo-Dromoran(R) (Roche)

Synthesis

1-(*p*-Methoxybenzyl)-2-methyl-1, 2, 5, 6, 7, 8-hexahydroisoquinoline may be prepared by the interaction of 5, 6, 7, 8-tetrahydro-2-methylisoquinolinium bromide and *p*-methoxy-benzyl magnesium bromide, when the former gets metathesized and the resulting product rearranges at the expense of the 1, 2-double bond. The said compound may be redrawn so as to show the subsequent reactions more vividly. The resulting product is dissolved in hydrochloric acid, hydrogenated at C_3 and C_4 with platinized charcoal and treated with ammonia to yield the corresponding *dl*-1, 2, 3, 4, 5, 6, 7, 8-octahydro derivative from which the *1*-enantiomorph is resolved by standard methods. The *1*-enantiomorph on

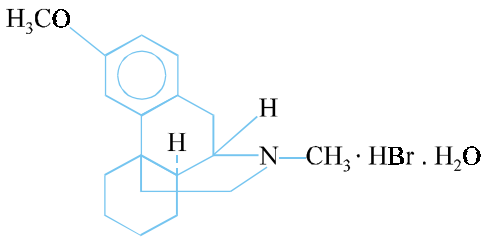
heating with phosphoric acid at 150° affords cyclization between the isoquinoline residue and the benzene ring at the expense of the lonely double bond existing in the isoquinoline nucleus. Conversion of the methoxy group to hydroxy usually takes place during heating with phosphoric acid earlier and the subsequent treatment with aqueous tartaric acid yields the official compound.



It is a potent narcotic analgesic having actions and structure similar to that of morphine. It is used effectively for the management of both moderate and severe pain. It produces significant analgesia at a dose level much lower than that of either **morphine** or **meperidine** and proves to be longer-acting than these drugs. *It is 2 to 3 times more potent than morphine*.

Dose : *Oral, severe pain 1.5 to 4.5 mg 1 or 2 times daily ; Subcutaneous, intramuscular, usual single dose 2 to 4 mg.*

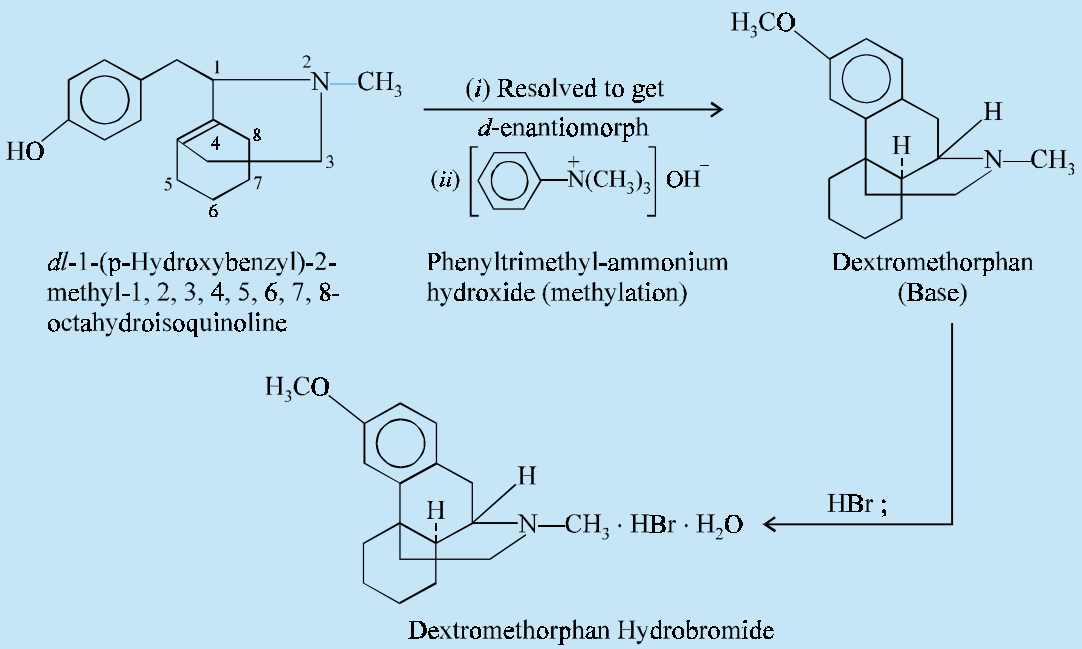
B. Dextromethorphan Hydrobromide BAN, USAN, Dextromethorphan INN,



3-Methoxy-17-methyl-9α, 13α, 14α-morphinan hydrobromide monohydrate ; Morphinan, 3-methoxy-17-methyl-, (9α, 13α, 14α)-, hydrobromide, mono-hydrate ; B.P., U.S.P.

Romilar(R) (Roche) ; Dormethan(R) (Dorsey) ; Benilyn DM(R) (Parke-Davis) ; Methorate(R) (Upjohn)

Synthesis

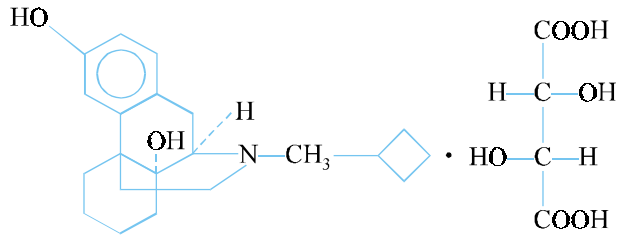


The racemic mixture (*dl*) of 1-(*p*-hydroxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydro-isoquinoline may be obtained exactly in the same manner as described for **levorphanol tartrate** (in 1 above). This is now resolved to get the *d*-enantiomorph and then treated with phenyltrimethyl ammonium hydroxide to cause methylation and yield the **dextromethorphan** base. Treatment of the base with appropriate amount of hydrobromide gives the corresponding hydrobromide.

It is a synthetic **morphine** derivative used as an antitussive agent exclusively. It has been reported to possess a cough suppression potency nearly one-half that of **codeine**. It exhibits no depression of the central nervous system, lacks analgesic actions and is free from addiction characteristics, which collectively render it possible for its use in cough syrups meant for infants and children.

Dose : *Usual, adult, oral, 10 to 30 mg 3 to 6 times a day ; not to exceed 60 to 120 mg in a day ; Children (6 to 12) : 2.5 to 5 mg 6 times a day, not to exceed 40 to 60 mg in a day ; Children (2 to 6) : 1.25 to 2.5 mg 3 to 4 times daily ; not to exceed 30 mg per day.*

C. Butorphanol Tartrate BAN, USAN, Butorphanol INN.



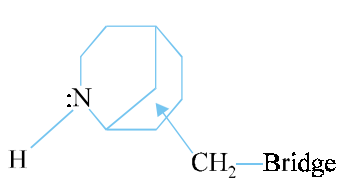
(-)-17-(Cyclobutylmethyl) morphinan-3, 14-diol D-(-)-tartrate (1 : 1) (salt) ; Morphinan-3, 14-diol, 17-(cyclobutylmethyl)-, (-)-, [S-(R^*, R^*)]-2, 3-dihydro-butanedioate (1 : 1) (salt) ; U.S.P., Stadol$^{(R)}$ (Bristol)

It is a synthetic opioid parenteral analgesic with actions and uses similar to those of **morphine**. It is usually employed *for the relief of moderate to severe post-surgical pain.*

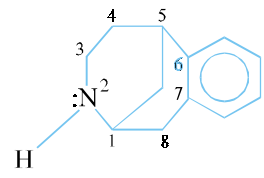
Dose : *Usual, adult, intramuscular, 2 mg 6 to 8 times a day ; usual, intravenous, 1 mg every 3 to 4 hours.*

4.3. Morphan Analogues

The morphan nucleus is nothing but a bridged perhydroazocine. The numbering pattern of benzomorphan, and the 6, 7-benzomorphan nomenclature has been adopted in the text.



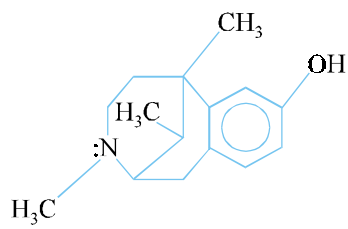
Bridged perhydroazocine



6, 7-Benzomorphan

A few members belonging to the morphan analogues are described here, *e.g.*, **metazocine ; cyclazocine ; pentazocine ;**

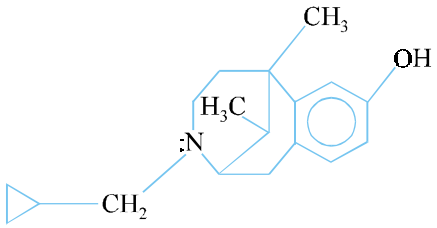
A. Metazocine INN, BAN, USAN,



2′-Hydroxy-2, 5, 9-trimethyl-6, 7-benzomorphan

It possesses analgesic activities but owing to its overwhelming psychotomimetic side-effects it is more or less unsuitable for use as an analgesic.

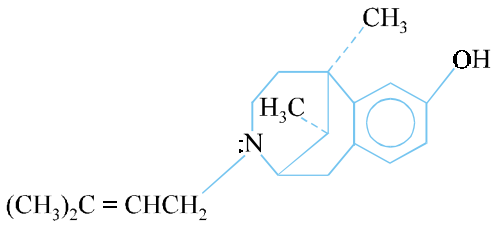
B. Cyclazocine INN, BAN, USAN,



3-(Cyclopropyl-methyl)-1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl-2, 6-methano-3-benzazocin-8-ol ; 2, 6-Methano-3-benzazocin-8-ol, 3-(cyclopropylmethyl)-1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl

It is a **benzomorphan analogue** about 40 times more potent than morphine as an analgesic and about 100 times more potent than nalorphine as an antagonist. The addiction potential of this drug seems to be much less than that of morphine. It has been used clinically to **treat diamorphine or morphine addicts.**

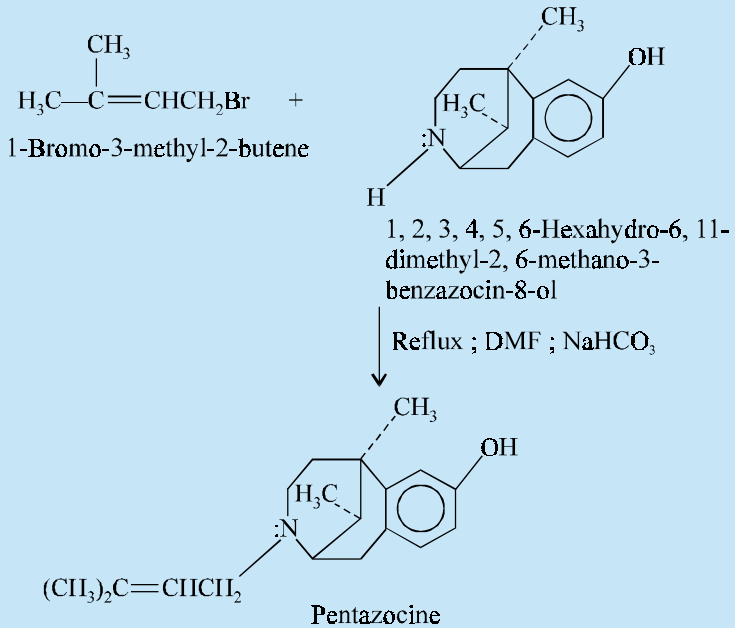
C. Pentazocine INN, BAN, USAN,



(2*R**, 6*R**, 11*R**)-1, 2, 3, 4, 5, 6-Hexahydro-6, 11-dimethyl-3-(3-methyl-2-butenyl)-2, 6-methano-3-benzazocin-8-ol ; 2, 6-Methano-3-benzazocin-8-ol, 1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl-3-(3-methyl-2-butenyl)-, (2α, 6α, 11R*)- ; B.P., U.S.P.,

Fortral(R) (Winthrop) ; Talwin(R) (Winthrop)

Synthesis



It may be prepared by the condensation of 1, 2, 3, 4, 5, 6-hexahydro-6, 11-dimethyl-2, 6-methano-3-benzazocin-8-ol with 1-bromo-3-methyl-2-butene by refluxing them together in dimethylformamide as a medium and in the presence of sodium bicarbonate. The crude pentazocine is extracted with an appropriate solvent and purified by recrystallization from aqueous methanol.

It is a synthetic analgesic agent commonly used *for the control of moderate to acute pain.* It exerts some sedative actions. It causes incomplete reversal of the respiratory, cardiovascular and behavioural depression produced by either **meperidine** or **morphine**.

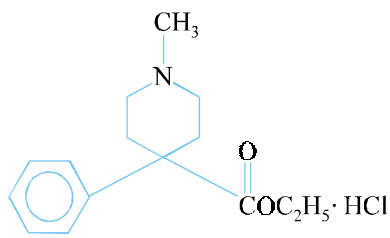
It behaves both as an agonist and as an antagonist. It is reported to be 3 to 4 times less potent than morphine and about 50 times less potent than nalorphine.

Dose : *Parenteral, 20 to 60 mg (as lactate) ; usual, 30 mg 6 to 8 times a day ; daily dose must not exceed 360 mg.*

4.4. 4-Phenylpiperidine Analogues

A spectacular accidental discovery of meperidine, in the course of search for structural analogues of atropine with a view to evolve anticholinergic drugs, proved to be a successful attempt towards the synthesis of 4-phenylpiperidine derivatives as narcotic analgesics. This finding has further strengthened the belief that the synthesis of relatively simpler components of the complex molecule of morphine may give rise to a more rational approach towards more efficacious analgesics having lesser nonaddictive liabilities. This ultimately led to the synthesis of a number of the following interesting compounds, namely : **pethidine hydrochloride ; diphenoxylate hydrochloride ; fentanyl citrate ; anileridine hydrochloride ; phenoperidine hydrochloride ;**

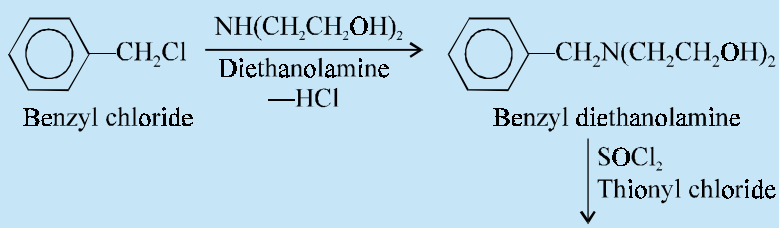
A. Pethidine Hydrochloride BAN, Meperidine Hydrochloride USAN, Pethidine INN,



4-Piperidinecarboxylic acid, 1-methyl-4-phenyl-, ethyl ester, hydrochloride ; Ethyl-1-methyl-4-phenyl-isonipecotate hydrochloride ; Pethidine Hydrochloride B.P., Eur. P., Int. P., Ind. P., Meperidine Hydrochloride U.S.P.,

Denerol(R) (Breon) ; Mepadin(R) (Merrell Dow)

Synthesis



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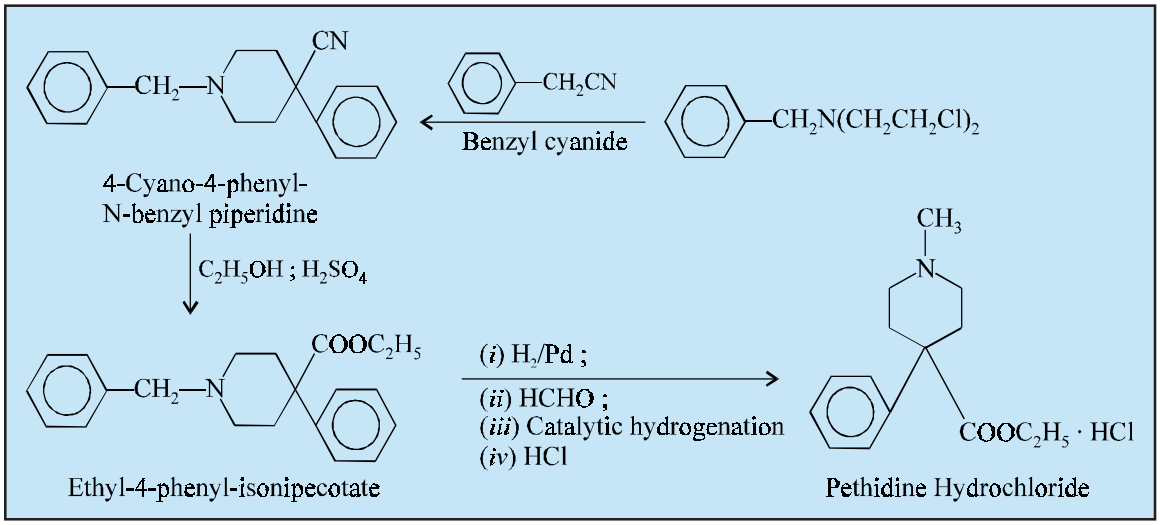
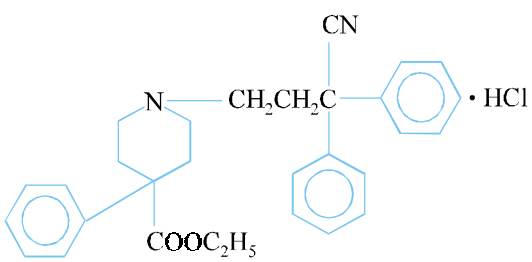


Benzyl diethanolamine is prepared by the interaction of benzyl chloride and diethanolamine with the elimination of a mole of HCl. Chlorination with thionyl chloride gives the corresponding chloride analogue which on treatment with benzyl cyanide yields 4-cyano-4-phenyl-N-benzyl piperidine. Esterification with ethanol in the persence of a small amount of concentrated sulphuric acid yields the ethyl ester. The N-benzyl group is removed by means of catalytic hydrogenation in acetic acid solution employing a palladium catalyst. Addition of formaldehyde to the reduction mixture followed by further catalytic hydrogenation yields **pethidine** which is finally converted to the hydrochloride by neutralization with hydrochloric acid.

It is a **synthetic narcotic analgesic** which possesses the action and uses of morphine and may be used **for the relief of a variety of moderate to severe pain including the pain of labour and post-operative pain. Pethidine has atropine-like action on smooth muscle.** It is normally used to induce both sedation and analgesia simultaneously.

Dose : *Parenteral, usual, adult, oral, 50 to 150 mg 6 to 8 times a day as necessary.*

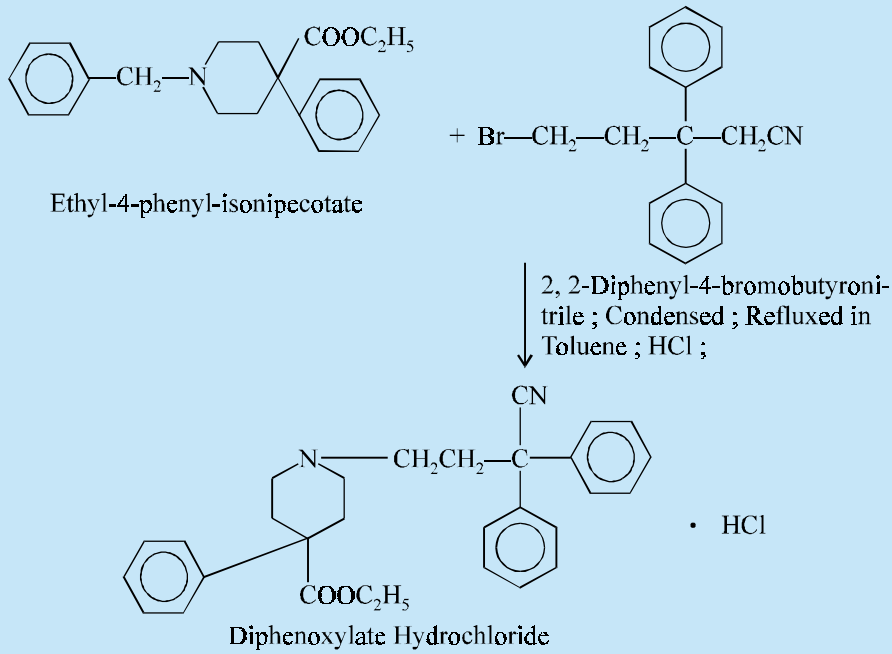
B. Diphenoxylate Hydrochloride BAN, USAN, Diphenoxylate INN,



Ethyl, 1-(3-cyano-3, 3-diphenylpropyl)-4-phenylisonipecotate monohydro-chloride ; 4-Piperidinecarboxylic acid, 1-(3-cyano-3, 3-diphenylpropyl)-4-phenyl-, ethyl ester, monohydro-chloride ; B.P., U.S.P.,

Component of Lomotil$^{(R)}$ (Searle)

Synthesis

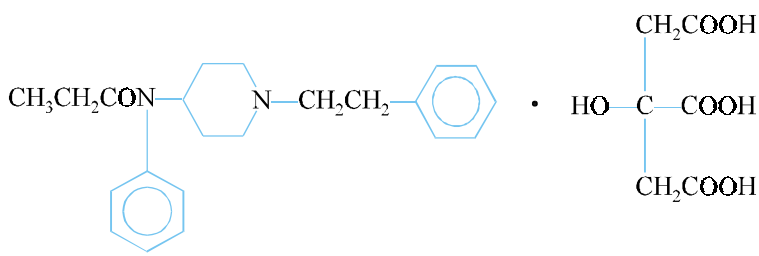


Ethyl-4-phenylisonipecotate is perpared as described above in pethidine hydrochloride, which is then condensed with 2, 2-diphenyl-4-bromobutyronitrile by refluxing together in toluene using an excess of the ester.

It is a synthetic analogue of **pethidine** with some analgesic activity but is mostly used in the *treatment of diarrhoea associated with gastroenteritis, irritable bowel, acute infections, hypermotility, ulcerative colitis and sometimes even food poisoning. It prevents hypergastrointestinal propulsion by reducing intestinal motility.*

Dose : *Usual, adult, oral 5, mg 4 times daily.*

C. Fentanyl Citrate BAN, USAN, Fentanyl INN,

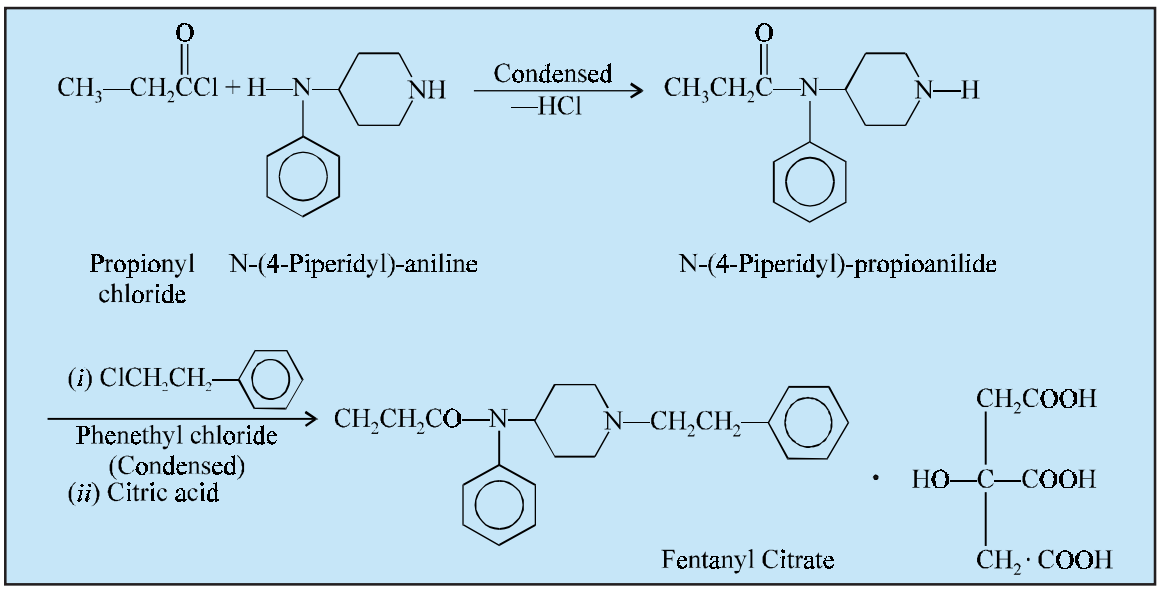


Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1, 2, 3-propanetricarboxylate (1 : 1) ; N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1 : 1) ; Phentanyl citrate ; B.P., U.S.P.,

Sublimaze(R) (Janssen).

Synthesis

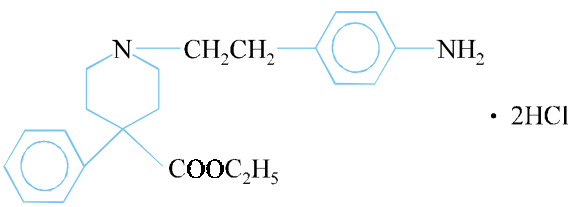
N-(4-Piperidyl) propioanilide is prepared by the condensation of propionyl chloride with N-(4-piperidyl)-aniline. The resulting product is further condensed with phenethyl chloride to obtain the corresponding fentanyl base which on reaction with an equimolar portion of citric acid gives rise to the (1 : 1) citrate.



It is a potent narcotic analgesic *primarily employed as an analgesic for the arrest of pain after all types of surgical procedures. It possesses an inherent rapid onset and short duration of action. It may be employed also as an adjuvant to all such drugs mostly used for regional and general anaesthesia.*

Dose : *Intramuscular, usual, in pre-operative medication 0.05 to to 0.1 mg 30 to 60 minutes before surgical treatment ; for rapid analgesic action, 0.05 to 0.1 mg intravenously.*

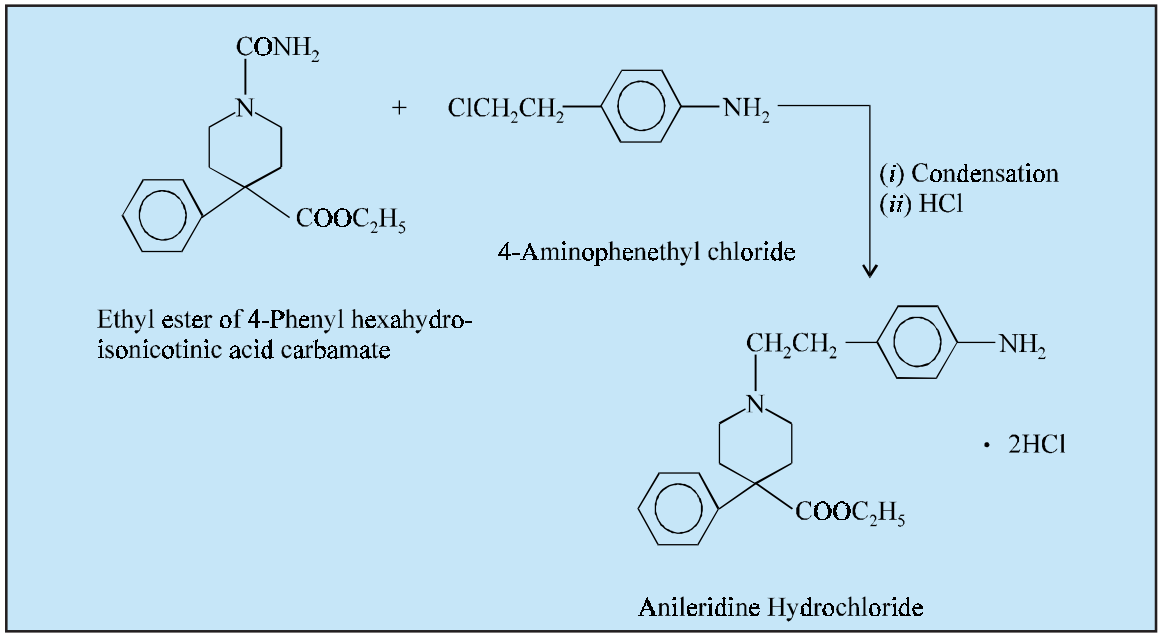
D. Anileridine Hydrochloride BAN, USAN, Anileridine INN,



4-Piperidinecarboxylic acid, 1-[2-(4-aminophenyl) ethyl]-4-phenyl-, ethyl ester, dihydrochloride ; Ethyl-1-(*p*-aminophenethyl)-4-phenylisonipecotate dihydrochloride ; U.S.P.

Synthesis

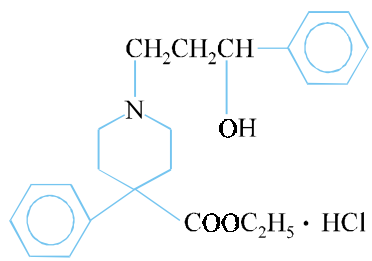
Anileridine hydrochloride is prepared by the condensation of the ethyl ester of 4-phenylhexahydroisonicotinic acid carbamate with 4-aminophenethyl chloride and subsequently treating the base with hydrochloric acid.



It is a narcotic analgesic having related chemical structure to that of pethidine and possesses an action similar to it, but with longer duration.

Dose : *Usual, oral, 25 mg every 6 hours.*

E. Phenoperidine Hydrochloride BAN, Phenoperidine INN, USAN,



1-(3-Hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester hydrochloride ; Ethyl 1-(3-hydroxy-3-phenyl-propyl)-4-phenylpiperidine-4-carboxylate hydrochloride ;

Operidine$^{(R)}$ (Janssen, U.K.)

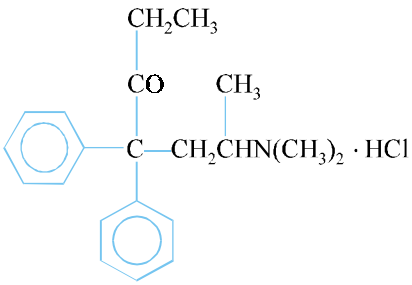
It is a potent analgesic with actions similar to morphine. It produces neurolepanalgesia, when administered with a major tranquillizer or neuroleptic agent like droperidol, that enables a patient to become calm and indifferent to his environment thereby offering the required co-operation with the surgeon.

Dose : *Average, initial, IV, for anaesthesia, 1 mg ; supplemented by 500 mcg every 40 to 60 minutes.*

4.5. Phenylpropylamine Analogues

Methadone, a repersentative of this class of compounds may have emerged purely from the molecular design and development of diphenylaminoethyl-propionates ior from the cleavage of piperidine ring present in pethidine molecule. These are considered to be the extremely flexible amongst most analgesic analogues *conformationally*. The following are a few classical examples of this group of analgesics, *viz.*, **methadone hydrochloride ; dextro-moramid tartrate ; dextropropoxyphene hydrochloride ; methotrimeprazine**

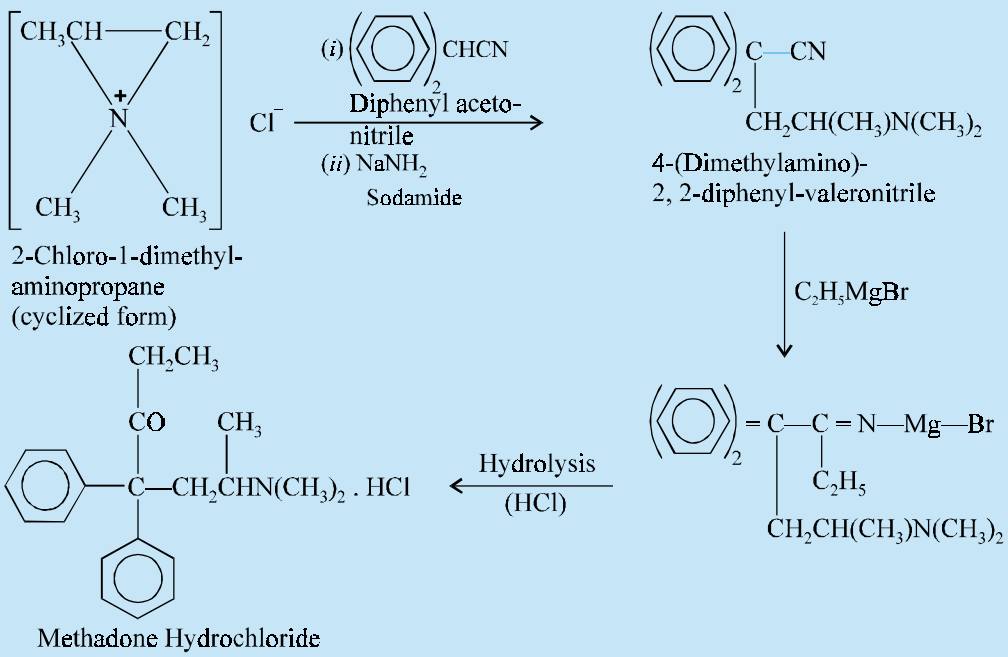
A. Methadone Hydrochloride BAN, USAN, Methadone INN,



6-(Dimethylamino)-4, 4-diphenyl-3-heptanone hydrochloride ; 3-Heptanone, 6-(dimethylamino)-4, 4-diphenyl-, hydrochloride ; Amidone Hydrochloride ; Phenadone ; B.P., U.S.P., Eur. P., Int. P., Ind. P.,

Dolophine Hydrochloride(R) (Lilly) ; Adanon Hydrochloride(R) (Winthrop)

Synthesis

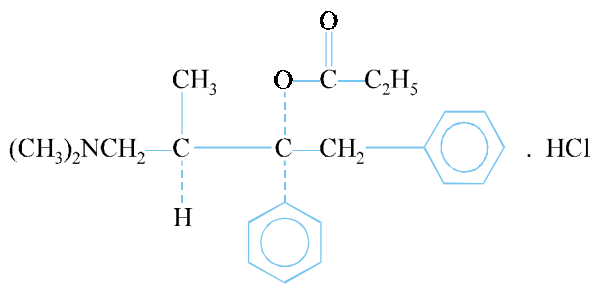


4-(Dimethylamino)-2, 2-diphenylvaleronitrile may be prepared by the condensation of the cyclized form of 2-chloro-1-dimethylaminopropane with diphenyl acetonitrile in the presence of sodamide; together with an undesired equimolar proportion of an isomeric nitrile. The undesired isomer is separated and rejected, while the right isomer is subjected to **Grignard Reaction** with ethyl magnesium bromide to yield an addition compound which on acidic hydrolysis forms the official compound.

It is a potent narcotic analgesics having actions quantitatively comparable to morphine though slightly less potent than morphine as an analgesic. Besides, it exerts sedation and antitussive properties. It also helps in the temporary maintenance and treatment of dependence on narcotic drugs, because its withdrawal syndrome has slow onset and much less intense than mrophine.

Dose : *Analgesic, oral, adult, im., 2.5 to 10 mg 6 to 8 times daily.*

B. Dextropropoxyphene Hydrochloride BAN, Propoxyphene Hydrochloride USAN, Dextropropoxyphene INN,



(2S, 3R)-(+)-4-(Dimethylamino)-3-methyl-1, 2-diphenyl-2-butanol propionate (ester) hydrochloride ; Benzeneethanol, α-[2-(dimethylamino)-1-methyl-ethyl]- α-phenyl-, propanoate (ester), hydrochloride, [S- (R^*, S^*)]- ; B.P., U.S.P.,

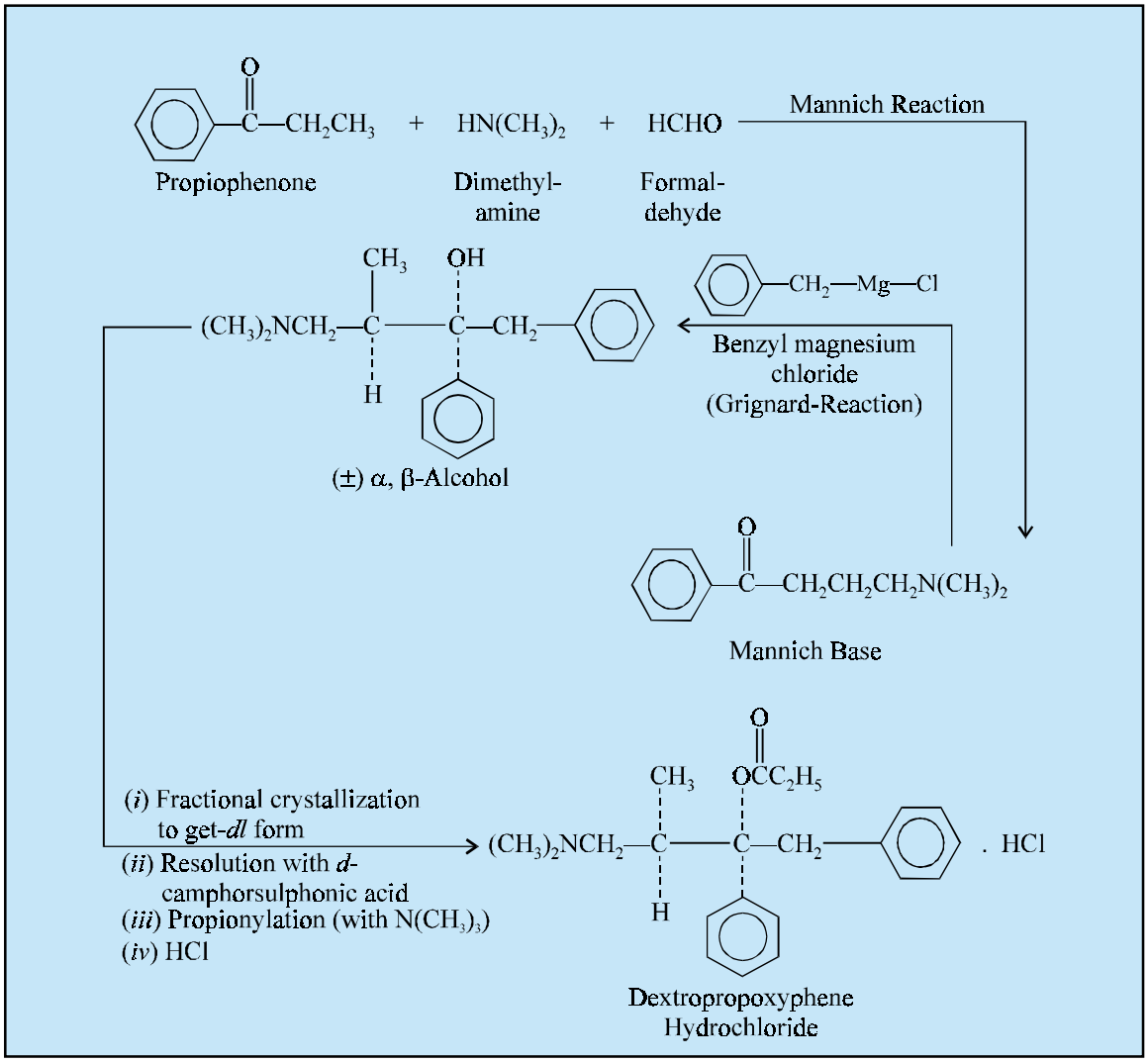
Darvon$^{(R)}$ (Lilly) ; SK 65$^{(R)}$ (SK & F) ; Dolene$^{(R)}$ (Lederle)

Synthesis :

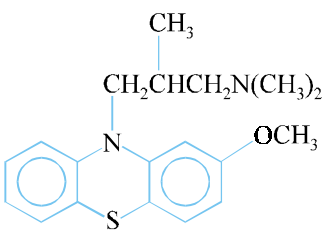
Interaction between propiophenone and dimethylamine in the presence of formaldehyde yields the Mannich base which is subjected to Grignardization with benzyl magnesium chloride to yield a racemic mixture of the two diastereoisomers designated as α- and β-alcohol. Fractional crystallization helps in the separation of α-*dl* form which is subsequently resolved by *d*-camphor-sulphonic acid to obtain (+)-α-form. This is now propionylated with propionic acid in the prsence of trimethylamine tio give dextropropoxyphene which takes up a mole of hydrochloric acid to form the desired official compound.

Dextropropoxyphene is a narcotic analgesic possessing relatively milder actions and bearing structural resemblance to methadone. **It is usually used to control mild to moderate pain and chiefly used along with other analgesics having anti-inflammatory and antipyertic properties like paracetamol and aspirin.**

Dose : *Usual, 65 mg, 3 or 4 times per day.*



C. Methotrimeprazine BAN, USAN, Levomepromazine INN,



(-)-10-[3-(Dimethylamino)-2-methylpropyl]-2-methoxy-phenothiazine ; 10H-Phenothiazine-10-propanamine, 2-methoxy-N, N, β-trimethyl-, (-)- ; B.P., U.S.P.,

Levoprome(R) (Lederle)

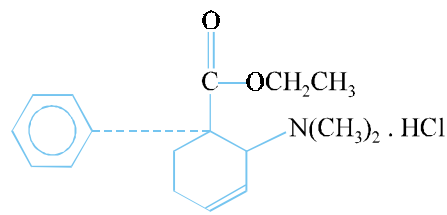
Methotrimeprazine possesses the histamine-antagonist characteristics of the antihistamines besides CNS effects comparable to those of chloropromazine. It exhibits significant analgesic properties and is *used in the management of severe chronic pain either alone or in conjunction with other analgesics.*

Dose : *Usual, adult, oral 25 to 50 mg per day for the treatment of mild psychoses and the severe psychoses 100 to 200 mg with a maximum up to 1 g daily.*

4.6. Miscellaneous Analogues

No discourse is usually given a touch of completeness unless and until the miscellaneous structures, which bear essentially the same pharmacological actions are grouped together. There are a few compounds that are analgesic but structurally do not belong to any of the earlier classified groups of compounds (A-E) :

A. Tilidate Hydrochloride BAN, Tilidine Hydrochloride USAN, Tilidine INN,



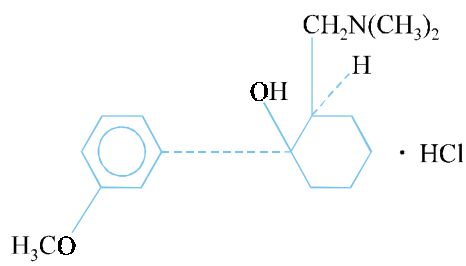
(±)-Ethyl *trans*-2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate hydrochloride ; 3-Cyclohexene-1-carboxylic acid, 2-(dimethylamino)-1-phenyl-, ethyl ester, hydrochloride (*trans*)-(±)- ;

Valoron(R) (Warner) ; Tilidine(R) (Parke-Davis)

It is a narcotic analgesic *mostly employed in the teratment of moderate to severe pain.*

Dose : *50 to 100 mg 4 times a day.*

B. Tramadol Hydrochloride BAN, USAN, Tramadol INN,



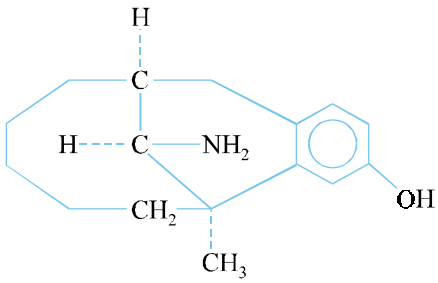
(±)-*trans*-2-[(Dimethylamino) methyl]-1-(*m*-methoxyphenyl) cyclohexanol hydrochloride ; Cyclohexanol, 2-[(dimethylamino) methyl]-1-(3-methoxy-phenyl)-, hydrochloride, *trans*-(±)- ;

Melanate(R) (Upjohn) ; Tramal(R) (Grunenthal, W. Ger.)

Tramadol is a potent narcotic analgesic.

Dose : *1 m or iv injection 50 to 100 mg ; as suppository 100 mg.*

C. Dezocine INN, BAN, USAN,



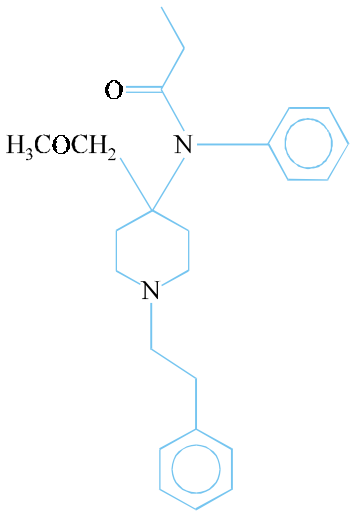
(-)-13 β-Amino-5, 6, 7, 8, 9, 10, 11α, 12-octahydro-5α-methyl-5, 11-methano-benzocyclodecen-3-ol ; 5-11-Methanobenzocyclodecen-3-ol, 13-amino-5, 6, 7, 8, 9, 10, 11, 12-octahydro-5-methyl-, (5α, 11α, 13S*)-, (-)- ;

Dalgan(R) (Wyeth).

Dezocine possesses analgesic as well as narcotic antagonist properties and is *usually administered by injection for the relief of severe pain.*

Dose : *10-15 mg.*

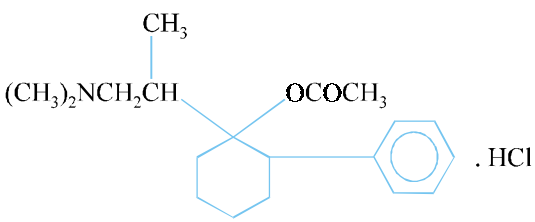
D. Sufentanil INN, BAN, USAN



N-[4-(Methoxymethyl)-1-[2-(2-thienyl) ethyl]-4-piperidyl] propionanilide ;

It is a narcotic analgesic.

E. Nexeridine Hydrochloride USAN, Nexeridine INN,



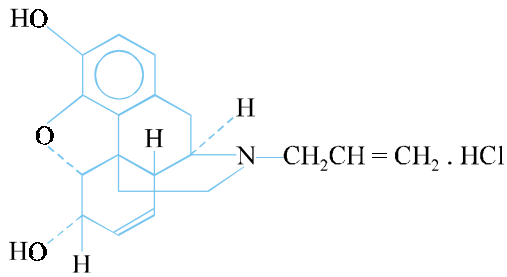
1-[2-(Dimethylamino)-1-methylethyl]-2-phenylcyclohexanol acetate (ester) hydrochloride ; Cyclohexanol, 1-[2-(dimethyl-amino)-1-methylethyl]-2 phenyl-, acetate (ester), hydrochloride.

Nexeridine is a narcotic analgesic.

5. NARCOTIC ANTAGONISTS

In 1915, it was shown that N-allylnorcodeine abolished both heroine- and morphine-induced respiratory depression. Almost 25 years later (1940), it was observed that N-allylnormorphine (commonly known as **nalorphine**) possessed more marked and significant morphine antagonizing actions. Thirteen years later (1953), it was demonstrated that nalorphine had the ability to *arrest severe abstinence syndromes in postaddicts* who were earlier treated briefly with either **morphine**, **methadone** or **heroine**. Examples of **narcotic antagonists** include : **nalorphine hydrochloride ; naloxone hydrochloride ; propiram fumarate and pentazocine**.

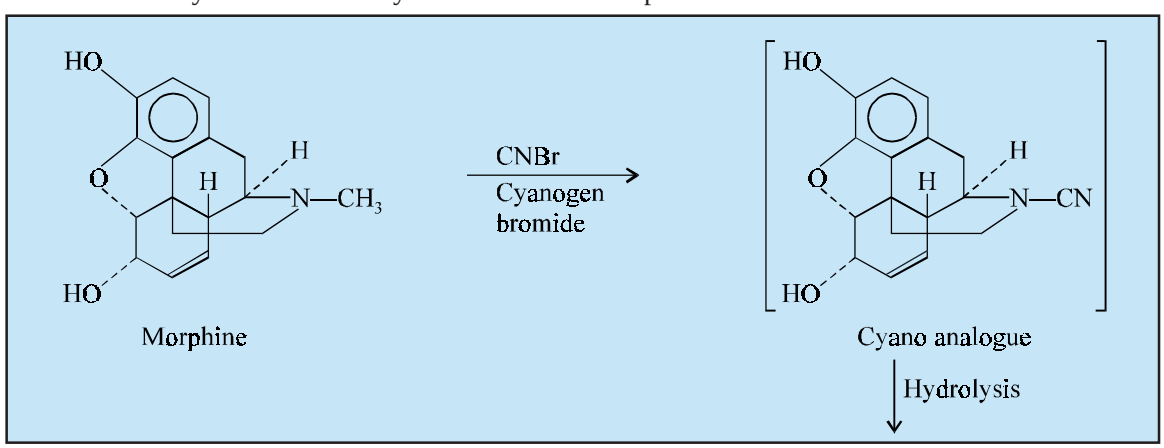
A. *Nalorphine Hydrochloride* BAN, USAN, *Nalorphine* INN,



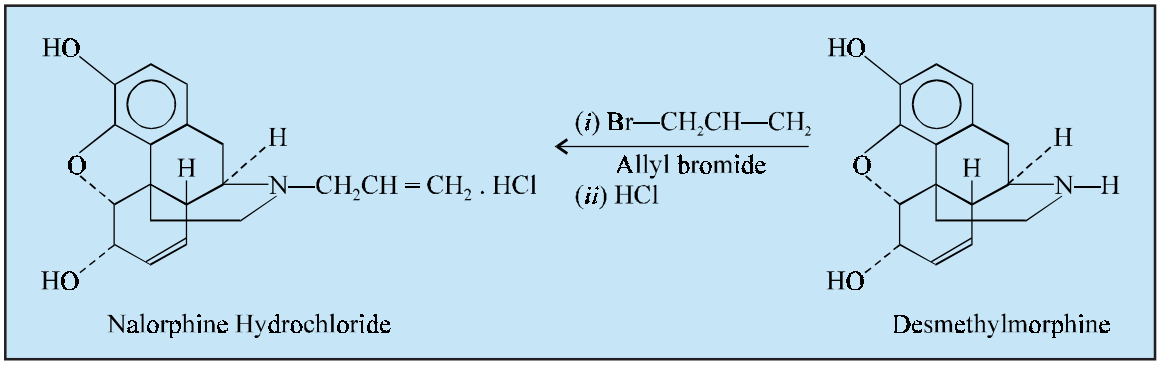
17-Allyl-7, 8-didehydro-4, 5α-epoxymorphinan-3, 6α-diol hydrochloride ; Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-(2-propenyl)-(5α, 6α)-, hydrochloride ; U.S.P., Int. P., Ind. P., Nalline$^{(R)}$ (MS & D)

Synthesis

Morphine on treatment with cyanogen bromide gives the corresponding cyano analogue which upon hydrolysis forms the desmethylmorphine. This on reaction with allyl bromide and subsequent treatment with hydrochloric acids yields the official compound.



(*Contd...*)

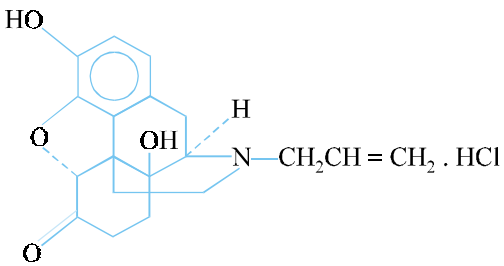


Nalorphine Hydrochloride — Desmethylmorphine

It is a narcotic antagonist having certain agonist actions that reduce the depressant actions particularly of **morphine** together with other narcotic drugs . It is pertinent to observe here that nalorphine does not exert its antagonistic effect caused by either barbiturates or other non-narcotic depressants. It possesses analgesic properties but is not used owing to its undesirable side-effects. **It is effectively employed to reverse narcotic-induced respiratory depression.**

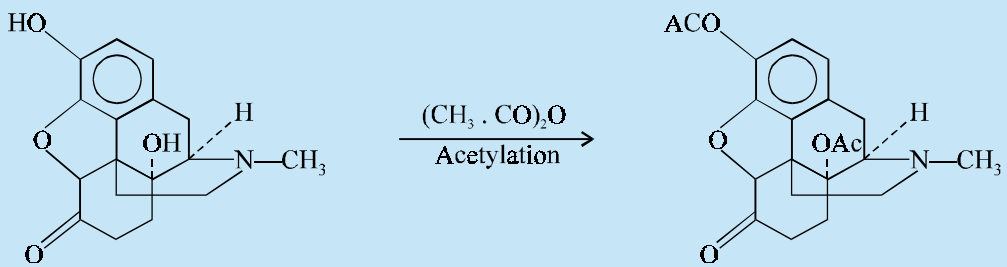
Dose : *Intravenous, 2 to 10 mg per dose ; usual, 5 mg repeated twice at 3 minute intervals if required.*

B. Naloxone Hydrochloride BAN, USAN, Naloxone INN,



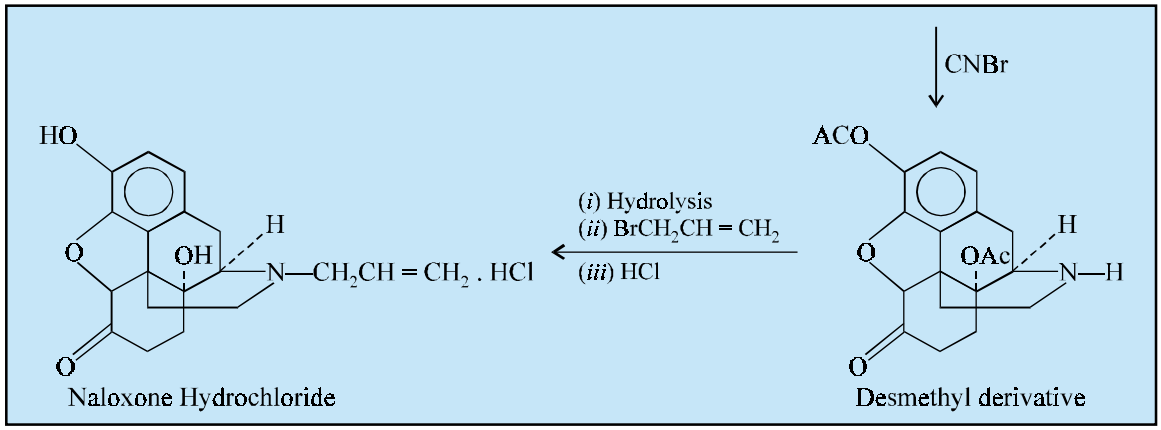
17-Allyl-4, 5α-3, 14-dihydroxymorphinan-6-one hydrochloride ; Morphinan-6-one, 4, 5-epoxy-3-[4-dihydroxy-17-(2-propenyl)-, hydrochloride, (5α)- ; (-)-N-Allyl-14-hydroxy-nordihydromorphinone hydrochloride ; Allylnoroxy-morphone Hydrochloride ; U.S.P., Narcan(R) (Endo)

Synthesis



Oxymorphone — 3, 6-Diacetate derivative

(*Contd...*)



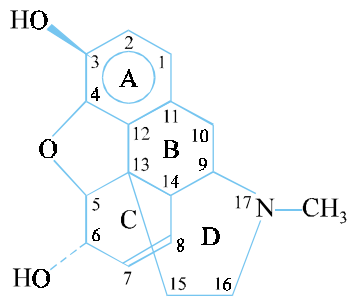
It may be prepared by the acetylation of **oxymorphone** to give 3, 6-diacetate derivative which on treatment with cyanogen bromide yields the desmethyl derivative.This on hydrolysis, followd by alkylation with allyl bromide and finally treating with hydrochloric acid forms the official compound.

Naloxone is a specific narcotic antagonist which, unlike nalorphine, possesses no morphine-like properties. It is considered to be an effective antagonist for mixed agonist-antagonist like pentazocine. It may also reverse some of the adverse effects of narcotic antagonists having agonist actions. **Owing to its lack of respiratory depressant property, it can be safely administered to patients suspected of narcotic overdosage without having the risk of further increasing respiratory depression. It has been found to reverse narcotic analgesic and possesses little analgesic properties of its own.**

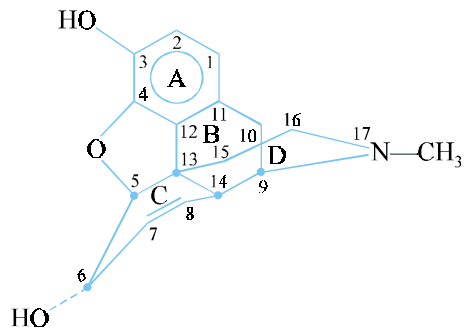
Dose : *Usual, parenteral, 0.4 mg (1 ml)*

6. MORPHINE : STRUCTURAL REPRESENTATIONS

In fact, the most probable structure of morphine was put forward in the year 1925 ; however, its confirmation by total synthesis was accomplished in 1955. Interestingly, the paucity of the knowledge with regard to the correct structure of **morphine,** nevertheless subsided the zeal and enthusiasm amongst the medicinal chemists to synthesize several morphine structural analogues by taking advantage of the various known chemical reactions with the peripheral functional moieties present in morphine, such as :



'*Flat*'-Representation
(A)



'*Steric*'-Representation
(B)

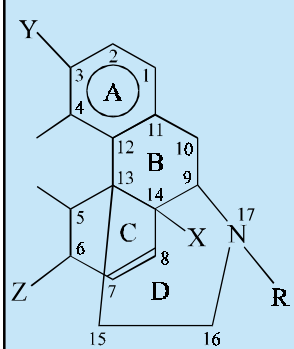
C-3 phenolic hydroxyl ; C-6 allylic alcohol ; and C = C between C-7 and C-8 as depicted in the following structure(s). It is, however, pertinent to mention here that several synthesized structural analogues even before 1930 are still constituted as vital and potential **'drugs'** in the therapeutic armamentarium, for instance : **codeine ; ethyl morphine** (*Dionin*$^{(R)}$) ; **diacetyl morphine** (heroin) ; **hydromorphone** (*Dilaudid*$^{(R)}$) ; **hydrocordone** (*Dicodid*$^{(R)}$) ; and **methyldihydromorphinone** (*Metopon*$^{(R)}$).

Morphine may be diagramatically represented as **'flat'** (A) configuration, and also as **'steric'** (B) configuration as illustrated above. Emphatically, in (B) the *ring* '*C*' essentially has the **'BOAT'**-conformation ; whereas the *ring*-'*D*' has the **'CHAIR'** conformation. Besides, the carbon atoms numbered 5, 6, 9, 13, and 14 (marked with a dark spot) are **chiral in nature** (*i.e.*, these are asymmetric C-atoms).

Morphine-related Antagonists and Agonists/Antagonists

The **National Research Council's Committee on Drug Addiction** established in the year 1929 under the leadership of Small LF (a chemist) and Eddie NB (a pharmacologist), synthesized a large number structural modifications of the **'morphine molecule'** with regard to its peripheral structural variants, intact morphine skeleton, and derivatives of compounds which could be considered as structural 'components' of the morphine molecule ; that ultimately gave rise to nearly **125 morphine analogues.** A comprehensive analgestic evaluation certainly helped in the emergence of emperical structure-activity relationships (SARs) as given in Table 11.2.

Table. 11.2 : Morphine-Related Antagonists and Agonists/Antagonists

General Structure	Name	R	X	Y	Z	Other	Therapeutic Category
	**Nalorphine**	—CH_2—CH = CH_2	H	OH	OH	—	Narcotic antagonist
	Levallorphan	—CH_2—CH = CH_2	H	OH	H	*a**	Narcotic antagonist
	Naloxone	—CH_2—CH = CH_2	OH	OH	=O	*b***	Narcotic antagonist
	Naltrexone	—CH_2— 	OH	OH	=O	*b*	Narcotic antagonist
	Nalbuphine	—CH_2— 	OH	OH	OH	*b*	Narcotic analgesic
	Butophanol	—CH_2— 	OH	OH	H	*a*, *b*	Narcotic analgesic

**a* = No *o-atom* between C_4 and C_5.

***b* = No *'double bond'* between C_7 and C_8.

7. MECHANISM OF ACTION OF CERTAIN NARCOTIC ANALGESICS

The mechanism of action of certain **'narcotic analgesics'** included in this chapter are discussed below :

7.1. Morphine Sulphate

Its most important action is on the brain more specifically its higher functions. It has been observed that an initial transitory stimulation is usually followed by a distinct depression of the brain, its higher functions, and above all its medullary centres. Besides, the spinal functions and reflexes are normally stimulated. Interestingly, it causes a visible change in perception in such a manner that the patient shows more to tolerance to pain and discomfort perhaps due to possible interference with '*pain conduction*'.

Because of its high addition potential and abuse, the 'drug' is classified as **Schedule II** drug under the **Controlled Substances Act.**

7.2. Codeine

Codeine is chiefly metabolized in the liver where it undergoes *o*-demethylation, N-demethylation and partial conjugation with glycuronic acid. It is mostly excreted in the urine as *narcodeine* and *morphine* (both as its free and conjugated form). It is found to be less apt than 'morphine' to produce nausea, vomitting, constipation and miosis. It also causes addiction liabilities resulting into enhanced tolerance limits.

Note. Naloxone is a '*specific antagonist*' in the situations arising from '*acute intoxication*'.

7.3. Hydromorphone Hydrochloride

It has less tendency to effect sleep than morphine when administered in equivalent analgetic doses. Therefore, the consequent relief from pain may be accomplished either without any sleep or stupefaction. It is a semi-synthetic analgetic, chemically and pharmacologically very much akin to morphine.

7.4. Hydrocodone Bitartrate (Dihydrocodeinone Bitartrate)

The pharmacological action is found to be lying almost midway between those of **codeine** and morphine. It has been observed that while on one hand it possesses more addition liability than **'codeine',** and on the other it displays absolutely very little evidence of its dependence or addiction with long-term administration.

Note. 'Tussionex$^{(R)}$—is an ion-exchange resin complex with it, that essentially releases the drug gradually in a sustained rate and is said to produce effective cough-suppression over a span of 10-12 hours.

7.5. Levorphanol Tartrate

It is a potent synthetic analgetic very much related chemically and pharmacologically to '*morphine*' ; and is invariably employed for the relief of acute pair. It is in many aspects closely related to morphine but its action is 6 to 8 times more potent. However, it has been observed that the gastro intestinal effects of this compound are appreciably on the lower range than those experienced with morphine. It is a narcotic with addiction liability quite akin to morphine ; therefore, almost same stringent precautions must be observed when prescribing this **'drug substance'** as for **morphine.**

7.6. Dextromethorphan Hydrobromide

Dextromethorphan is well absorbed from the GI-tract. It has been observed that the **'drug'** is largely metabolized in the liver ; and consequently, excreted through the urine either as *unchanged* **dextromethorphan** or as its **demethylated metabolites** including *dextorphan*, that interestingly possesses cough-depressant activity to a certain extent.

7.7. Butorphanol Tartrate

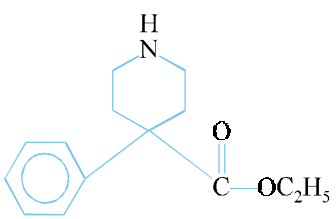
It is a potent synthetic opiate analgesic that gets completely absorbed from the GI tract after oral administration ; and, importantly, it undergoes almost 80% **first-pass metabolism.** It has been duly established that this '**drug**' enhances arterial resistance and the work of the heart (an action very much akin to **'petazocine'**) ; consequently, it is usually contra indicated in such patients who have a history of **acute myocardial infarction.**

7.8. Pentazocine

It happens to be a weak **'antagonist'** (1/30th than **'naloxone'**) at **mu receptors** ; and also acts as an **'agonist'** at **kappa receptors.** Its half-life after IM administration is 2.1 hour. It is found to exert weakly (nearly 1/50th than **'nalorphine'**) antagonizing effect on the analgesic effect produced by **morphine** and **meperidine**. Besides, it causes incomplete reversal of the cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. It also possesses certain degree of sedative action. The bioavailability of pentazocine after oral administration is only 20-50% due to the first pass metabolism. The **'drug'** gets metabolized extensively in the liver ; and subsequently, excreted by the urinary tract. It is, however, pertinent to mention here that the *two* major metabolites of **petazocine** are, namely : (*a*) *hydroxylation* of the *two* terminal methyl functional moieties attached to the N-substituent ; and (*b*) 3-*o*-conjugates, which are virtually **inactive**.

7.9. Meperidine Hydrochloride (Pethidine Hydrochloride)

The **'drug'** is largely metabolized in the liver with only a small quantum of it ~ 5% gets excreted unchanged. However, the short duration of action of meperidine is caused on account of its rapid metabolism *in vivo*. Importantly, the **'esterases'** predominantly cause cessation of the **ester linkage** (as ethyl ester at *para*-position) to leave as residue the **inactive-carboxylate analogue.** It also undergoes N-demethylation to yield the corresponding product known as **'normeperidine'**—a metabolite which gets accumulated after a prolonged medication with meperidine.



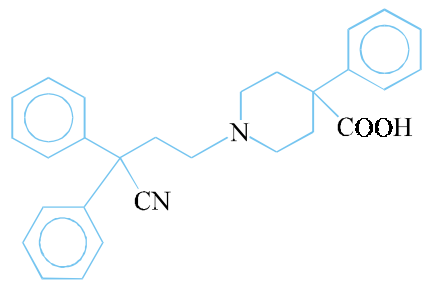
Normeperidine

Note. Normeperidine has only weak analgesic property, but it gives rise to sufficient CNS stimulation ; and it may end up grand mal seizures. Hence, it must be discontinued immediately in a subject showing the slightest symptoms of CNS stimulation apparently.

The elimination half-life of the **'drug'** is between 3-4 hours, but it may be simply doubled in patients with the liver malfunction. It has been observed that **'acidification'** of the urine may on one hand *increase the clearance of meperidine*, whereas on the other it may *retard the clearance of the toxic metabolite normeperidine.*

7.10. Diphenoxylate Hydrochloride

The '**drug**' itself possesses relatively low mu opioid agonist activity. It is, however, metabolized rather swiftly by means of ensuing *ester hydrolysis* to the corresponding **'free carboxylate'**, **difenoxin,** that exhibits 5 times more potent activity when administered orally. Interestingly, the inherent excessive higher polarity of difenoxin perhaps restricts its easier penetration into the CNS ; and, therefore, it provides an adequate explanation with regard to the comparatively **low abuse potential** of this narcotic analgesic.



Difenoxin

7.11. Fentanyl Citrate

It exhibits a profile of pharmacological action very much identical to morphine, and differs exceptionally on *two* accounts, namely : *first*-it does not cause emesis ; *secondly,* it does not release histamine. Its safety measure in frequency cases has not yet been fully understood. It is observed to cross the *placental barrier* ; therefore, its usage during labour may ultimately give rise to respiratory depression in the newly born infant. However, Fentanyl's transient action after the parenteral administration is caused solely on account of redistribution, rather than to '*metabolism*' or '*excretion*'. Hence, longer usage of this **'drug'** may cause in accumulation and toxicities.

Note. Recent advancement in its 'dosage forms' are :

(*a*) Fentanyl Transdermal Patch : It is used for the treatment of severe chronic pain, and it affords analgesia effictively for a duration ranging between 24—72 hours ; and

(*b*) Lollipop Dosage Form. It was introduced in the year 1999 for absorption from the buccal cavity (mouth).

7.12. Anileridine Hydrochloride

It is found to be more potent as compared to meperidine ; and, hence, possesses the same usefulness and limitations. Furthermore, its **'dependence capacity'**is significantly much lower ; and, therefore, it is well accepted as an appropriate and legitimate substitute for meperidine.

7.13. Phenoperidine Hydrochloride

It undergoes absorption from the GI-tract to a certain extent. It has been found that the **'drug'** gets extensively metabolized in the liver to **peltidine** and **norpeltidine**, that are subsequently excreted in the urine.

7.14. Methadone Hydrochloride

The cardinal activities of therapeutic value essentially comprise of : analgesia, sedation and detoxification or temporary maintenance in narcotic addiction. It has been observed that the '*drug*' is most rapidly absorbed (perhaps rather incompletely) after the oral administration, by virtue of the fact that only 52% of a given dosage gets discharged in urine. The mean plasma levels ranging between 182 to 420 mg. mL^{-1} are found in patients administered on a daily oral dose of 40 and 80 mg respectively ; of which 71 to 87% is in the '*bound form*'. Its biological half-life is nearly 25 hour, with a range of 13 to 47 hours.

Note. (1) It is one of the drugs of choice in the withdrawal management of patients addicted to morphine, heroin, and allied narcotic drugs.

(2) NALOXONE—is an effective '*antagonist*' in instances of acute intoxication.

(3) It is a '*Schedule II Drug*' under the *Controlled Substances Act* in US.

7.15. Propoxyphene Hydrochloride (Dextropropoxyphene Hydrochloride)

It is found, to be absorbed completely after oral administration ; however, **first-pass elimination** ranging between 30-70% reduces its **'bioavailability'** appreciably. The volume of distribution is 700 to 800 L ; oral clearance varies between 1.3 to 3.6 L. min^{-1} ; and the biological half-life is 6 to 12 hours. **Norpropoxyphene** happens to be the **'major metabolite'** having a half-life of 30-36 hours.

7.16. Methotrimeprazine (Levomepromazine)

A phenothiazine structural analogue, very intimately related to chlorpromazine, and exhibits extremely potent analgesic activity. Importantly, it is devoid of any dependence liability, besides it does not produce respiratory depression. It is specifically of **some extent of advantage** in such patients for whom **addiction** as well as **respiratory depression** are serious problems.

7.17. Tramadol Hydrochloride

The **'drug'** exhibits its a analgesic effect by categorically inhibiting the uptake of **norepenephrine** and **serotonin** which is believed to contribute to its analgesic effects. Its major metabolite is about 6 times more potent as an **analgesic ;** besides, it has 200 times greater affinity for the mu receptor.

7.18. Dezocine

It is a synthetic **opioid 'agonist'** *or* **'antagonist'** structurally akin to pentazocine, and having analgesic actions almost identical to morphine. Interestingly, it is a **'primary amine'** whereas the rest of the **'nonpeptide opioids'** are **'tertiary amines'.** Although, its exact receptor selectivity profile has not been reported so far, yet its pharmacological activities are quite similar to that of buprenorphine. It is observed to be a partial agonist at mu receptor sites, practically devoid of any effect at the kappa receptors ; and exhibits agonist effect at delta receptors to a certain extent.

Dezocine gets metabolized largely by glucuranidation of the phenolic hydroxy moiety and also by N-oxidation. Its metabolites are quite inactive, and gets excreted invariably through the renal passage.

7.19. Sufentanil

The introduction of the *para*-methoxymethyl moiety and the subsequent replacement of the bioisosteric phenyl group with a 2-thiophenyl into the **'fentanyl molecule'** give rise to a **10 times enhancement in the prevailing mu opioid activity**.

Hence, the resultant compound *i.e.*, **sufetanil** is found to exhibit higher potency to the extent of 600-800 times in comparison to morphine. When administered IV it gets metabolized rapidly having a biological half-life 2.4 hour. Its volume of distribution is 2.5 L kg^{-1}, 92.5% is bound to plasma protein ; and the plasma clearance is 0.8 L min^{-1}.

7.20. Nalorphine Hydrochloride

It has a **'direct antagonistic effect'** against **morphine, meperidine, methadone** and **levorphanol.** Interestingly, it does not show any antagonistic effect toward barbiturate or general anaesthetic depression. **Nalorphine** exerts its effect on the circulatory disturbances thereby reversing the effects of morphine. It is found to cause depression in the respiratory activity itself, that may potentiate the prevailing depression produced by **morphine.**

7.21. Naloxone Hydrochloride

It has been adequately proved based on the available evidence that naloxone specifically antagonizes the opioid effects, such as : respiratory depression, psychotomimetic effects, and pupillary constriction, by means of genuine competition for the receptor sites. The drug disappears from serum in man in a much rapid fashion. After an IV administration it is distributed quite rapidly in the body. It is found that the biological half-life in adults ranges between 30 to 81 minutes ; whereas, the mean half-life in neonates is 3.1 and 0.5 hour.

Naloxone is largely metabolized in the liver, primarily by glucuronide conjugation ; and ultimately excreted in the urine.

Note. Because of its short duration of action it is absolutely necessary to administer a multiple-dosing system that obviously limits its value.

Probable Questions for B. Pharm. Examinations

1. (*a*) What are narcotic analgesics ? Enumerate the **four**-serious limitations of these drugs.
(*b*) Give the structure, chemical name and uses of MORPHINE.
(*c*) What are the **three** important alkaloids isolated from *Papaver somniferum* ?

2. Classify narcotic analgesics by giving at least **one** typical example with its structure, chemical name and uses.

3. Discuss the **'morphine analogues'** and give the synthesis of :
(*a*) Diamorphine Hydrochloride and
(*b*) Hydrochloride Tartarate

4. Give the structure, chemical name and uses of any **two** important members of Morphinan Analogues. Discuss the synthesis of **one** of them.

5. Based on the **'morphan nucleus'** *i.e.*, a bridged perhyrozocine **three** drugs have been synthesized, namely : Metazocine, Cyclazocine and Pentazocine. Give their structure, chemical names and uses.

6. How would you synthesize **Pentazocine** from 1-bromo-3-methyl-2-butene ? Explain the route of synthesis.

7. The **4-phenylpiperidine analogue** led to the synthesis of much simpler compounds having potent analgesic properties. Discuss the synthesis of any **one** compound stated below :

(*a*) Meperidine hydrochloride and

(*b*) Fentanyl citrate

8. Give the names of any **two** important drugs based on **phenylpropylamine analogues** and describe the synthesis of **one** of them.

9. Discuss briefly Tilidate hydrochloride, Dazocine, catanlanil and Nexonine as **narcotic analgesics.**

10. Give a brief account of '**Narcotic Antagonists'.** Discuss Nalorphine hydrochlroide in details.

RECOMMENDED READINGS

1. CO Wilson, O Gisvold and R F Doerge **Textbook of Organic Medicinal and Pharmaceutical Chemistry** (10th edn.) Philadelphia J B Lippincott Company (1998).
2. D Lednicer and L A Mitscher, **The Organic Chemistry of Drug Synthesis** John Wiley and Sons, New York (1995).
3. G de Stevens (ed.) **Analgesics,** Academic Press New York (1965).
4. HW Kosterlitz, H O Collier and J E Vilareal (eds.) **Agonist and Antagonist Actions of Narcotic Analgesic Drugs,** *University* Park Press, Baltimore (1973).
5. JEP Reynolds (ed.) **Martindale the Extra Pharmacopoeia,** (31st edn) The Pharmaceutical Press London (1997).
6. J Hellerbach *et al.* **Synthetic Analgetics, Part IIa, Morphinans,** Pergamon Press, New York (1966).
7. ME Wolff (ed.) : **Burger's Medicinal Chemistry and Drug Discovery,** (5th ed) John Wiley & Sons, Inc., New York (1995).
8. NB Eddy and EL May *Synthetic Analgetics (Part II(b)) 6, 7-Benzomorphans* Pergamon Press, New York, (1966).
9. PAJ Janssen **Synthetic Analgetics,** *Part I, Diphenyl-propylamines,* Pergamon Press, New York (1960).
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12

Cardiovascular Drugs

Chapter

12 Cardiovascular Drugs

1. INTRODUCTION

Cardiovascular drugs generally exert their action on the heart or blood vessels in a direct or indirect manner thereby affecting the distribution of blood to certain specified portions of the circulatory system. Therefore, they essentially embrace a rather wide spectrum of such drugs which possess cardiovascular actions.

In a broader perspective the term **'cardiovascular drugs'** mostly connotes particularly such drugs that are invariably employed for their cardiovascular actions. In reality, therefore, almost every **'autonomic drug'** normally exerts marked and pronounced cardiovascular activities which are clinically useful in combating the serious human ailments.

Based on several scientific evidences one may observe that there are a plethora of categories of 'drug substances' which may be used effectively as cardiovascular drugs, such as :

(*a*) **Sympathomimetics** are mostly employed to enhance blood pressure, lower the reflexity of heart, stimulate the heart, which are solely dependent on the specific drugs *vis-a-vis* the therapeutic requirements.

(*b*) **α-Adrenergic Blocking Drugs** are commonly used in the *vasospastic** conditions, specifically in the diagnosis, control and management in the malignant and toxemic hypertensive crises ; besides, in *pheochromocytoma***.

(*c*) **β-Adrenergic Blocking Drugs** are invariably made use of in the treatment of essential hypertension, portal hypertension, angina pectoris and certain instances pertaining to dysrhythmias.

(*d*) **Anticholinesterase** (*e.g.* **edrophonium**) is judiciously used in the ensuing diagnosis and treatment of *paroxysmal atrial tachycardia.****

(*e*) **Atropine and other Antimuscarinic Drugs** are beneficially employed to block either the cardiac vagus nerve in the **Adams-Stokes Syndrome** or some other **bradycardias.**

Interestingly, a plethora of **'drug substances'** other than the autonomic agents have been observed to exert powerful as well as useful actions on the cardiovascular system, for instance :

*Characterized by *vasospasm i.e.,* spasm of a blood vessel.

**A chromaffin cell tumour of the sympathoadrenal system that produces catecholamines.

***A sudden periodic attack of atrial tachycardia.

(*i*) **Digitalis and its related derivatives**, the peripheral and coronary dilators, and above all the antidysrhythmic agents,

(*ii*) **Parenteral fluids** that find their application in the treatment of severe shock, and

(*iii*) **Diuretics** that are invariably used as an adjunct in the treatment and management of heart failure as well as hypertension.

2. CLASSIFICATION

Cardiovascular drugs may be conveniently classified into the following *four* heads, namely :

(*a*) Cardiac Glycosides

(*b*) Antihypertensive and Hypotensive Drugs

(*c*) Antiarrhythmic Agents, and

(*d*) Vasopressor Drugs

This chapter mainly deals with the above categories of drugs with specific examples.

3. CARDIAC GLYCOSIDES

Cardiac glycosides or **digitalis** essentially refer to a group of chemically and pharmacologically related drugs, that act on the heart by causing atrioventricular conduction and vagal tone. They are invariably employed to slow the heart rate in atrial fibrillation and also administered in congestive heart failure.

A large number of **'drug substances'** are able to enhance the force of contraction of the heart. It is, however, pertinent to state here that this ionotropic activity may be specifically of great utility and importance in the ultimate treatment of congestive heart failure*. Evidently, a defective and failing heart is not capable of pumping the requisite quantum of blood supply so as to maintain the bear minimum body needs. Keeping in view the enormous incidence of congestive heart failure across the globe the **'inotropic drugs'** have gained its legitimate importance and cognizance throughout the world.

There is absolutely no reason to believe that the host of **'inotropic drugs'** do help positively in prolonging the life-span of an individual, but nevertheless even with the long-term treatment, the longivity of such patients cannot be improved to an appreciable extent.

3.1. Designing the Cardiac Glycoside Receptor

In fact, there are *three* most prevalent questions that invariably arise with regard to the ultimate **structure-activity relationships (SARs)** of any known class of drugs, namely :

(*a*) How does a '*drug molecule*' fit into the receptor site ?

(*b*) What are the most probable structures and conformations that may allow the best fit ?

(*c*) Which parts of the drug molecule are actually responsible for effective binding**, and also for exhibiting the specific pharmacological activity*** ?

An enormous amount of concerted research particularly related to fundamental aspects of drug design, synthesis, conformational energy studies, and **computer-aided molecular modelling (CAMM)**

*Hsu L., *J Am Pharm Assoc.* NS **36**(2) : 93, 1996.

***Binding* : Affinity.

***Intrinsic activity.

have been exploited both extensively and intensively to reveal the intricacies pertaining to the basic structural requirements of the desired cardiac glycoside binding site.

Na^+, K^+—ATPase is a **'dimer'** which is composed of two catalytic **α-subunits** together with two inert **β-subunits.** It has been well established that the two catalytic α-subunits essentially consist of the required binding sites for the cardiac glycosides, besides ATP, Na^+, K^+ and phosphorylation. Though the two β-subunits are absolutely necessary for the cardiac activity, yet these are not found to exert any direct catalytic action. Perhaps the **β-subunits** aid in holding the α-subunits in a strategically active configuration ; however, their exact intention is yet not quite established. It has been observed that the Na^+ K^+-ATPase enzyme extends across the plasma membrane, having a large quantum of the enzyme specifically onto the extracellular surface.

Interestingly, electron microscopic studies has provided an ample evidence that the α-dimer usually creates a **'deep-cleft'** in the Na^+, K^+-ATPase ; and that has been suggested as the most preferred binding site for the **cardiac steroidal glycosides** particularly.

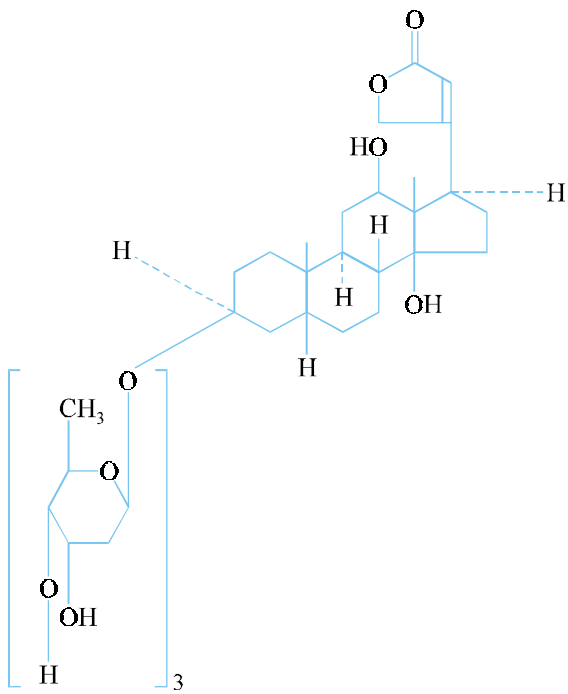
Digoxin and **digitoxin** are the two **cardiac glycosides** most frequently used nowadays and have obviously replaced digitalis in cardiac therapy.

A. Digoxin INN, BAN, USAN,

3β-[0, 2, 6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1 → 4)-0-2, 6-dideoxy-β-D-*ribo*-hexo-pyranosyl-(1 → 4)-2, 6-dideoxy-β-D-*ribo*-hexopyranosyl) oxy]-12β, 14-dihydroxy-5β, 14β-card-20(22)-enolide ; BP ; USP ; Eur. P., Ind. P., Int. P.,

Lanoxin$^{(R)}$ (Burroughs Wellcome) ; SK-Digoxin$^{(R)}$ (SK & F)

The side chain of **digoxin** is made up of three molecules of **digitoxose** in a glycosidic linkage, which upon hydrolysis yields the aglycone, **digoxigenin** (C_{23} H_{34} O_5).



Digoxigenin is obtained from the leaves of *Digitalis lanata* Ehrh. (Family : *Scrophulariaceae*).

Its cardiotonic actions are very much alike to those of digitalis. It is used in the *treatment of congestive heart failure.* It is administered to slow down the ventricular-rate *in the management and treatment of atrial fibrillation.* **Digoxin** enhances the force of myocardial contraction which in the case of heart-failure ultimately result in an improved cardiac output thereby reducing the size of the dilated heart. Concurrently, venous pressure is lowered as the heart is now in a position to accommodate an increased venous return of blood ; also an improvement in the peripheral circulation modifies renal function thereby causing diuresis and hence an apparent relief of oedema.

Dose : *Oral, adults and children more than 10 years of age : For rapid digitalization, 1 to 1.5 mg divided into 2 or more doses after 6-8 hours ; For slow digitalization and maintenance (0.125 to 0.5 mg) once a day.*

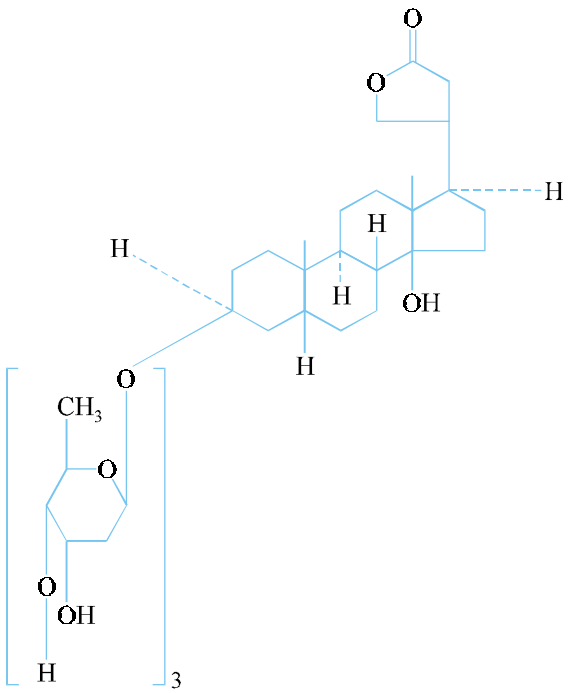
B. Digitoxin, INN, BAN, USAN,

3β-[0-2, 6-Dideoxy-β-D-*ribo*-hexopyranosyl-(1 → 4)-0-2, 6-dideoxy-β-D-*ribo*-hexopyranosyl-(1 → 4)-2, 6-dideoxy-β-D-*ribo*-hexopyranosyl) oxyl]-14-hydroxy-5β, 14β-card-20(22)-enolide ; BP ; USP ; Eur. P., Int. P., Ind. P.,

Crystodigin(R) (Lilly) ; Purodigin, Crystalline(R) (Wyeth)

Digitoxin is obtained from *Digitalis purpurea* Linne, *Digitalis lanata* Ehrh, and other suitable species of Digitalis.

Its side chain is comprised of three molecules of digitoxose in a glycosidic linkage. Hydrolysis affects removal of the side chain to yield the aglycone, **digitoxigenin** ($C_{23}H_{34}O_4$).



Digitoxin is the most potent of the digitalis glycosides besides possessing its inherent maximum cumulative action. *Though its onset of action is rather slower than that of the other cardiac glycosides, yet its effect persists much longer even extending up to 3 weeks.*

Dose : *Oral, intramuscular, or intravenous, adults, for digitalization ; initially 600 mcg folllowed by 200 to 400 mcg every 3 to 6 hours as needed.*

3.2. Mechanism of Action

The mechanism of action of **digoxin** and **digitoxin** are discussed as under :

3.2.1. Digoxin

The **'drug'** is mostly employed IV for extremely rapid **digitalization,** whereupon its action invariably becomes manifest in 15 to 30 minutes, while its effect ultimately attains its peak in 2 to 5 hours. In contrast, its action through the oral administration is usually manifested within a span of 1 to 2 hours, and reaches a peak in 6 to 8 hours. However, after accomplishing complete digitalization, the duration of action is about 6 days. In plasma it is normally protein-bound to the extent of 20 to 30%. It exhibits a high volume of distribution, having a v_d^{ss} of about 5.1 L kg^{-1} in normal healthy adults, neonates and even larger in infants ; whereas, patient with renal failure the value of v_d^{ss} is almost nearly 3.3 L. kg^{-1}. Interestingly, the observed large volume of distribution is exclusively by virtue of its *extensive intracellular binding*.

It has been duly observed that the biliary secretion and the enterohepatic recirculation usually account for almost 7 to 30% of the body burden. However, by the oral administration, approximately 50-80% of the drug gets absorbed from the solid dosage forms, but it may be extended upto 90-100% from the hydroalcoholic solutions in capsules. The overall outcome is the enhanced GI motility which gets diminished ; and hence, the lowered motility enhances the absorption of the drug.

3.2.2. Digitoxin

The '**drug**' after complete digitalization, shows duration of action extended upto 14 days. In fact, nearly 97% of the drug is protein-bound as found in plasma. The therapeutic level of the drug in plasma is optimum at a concentration ranging between 15-25 ng. m L^{-1} ; whereas, at a concentration varying between 35-40 ng. mL^{-1} or even more is regarded to be toxic. It has been observed that the *hepatic metabolism* usually accounts for 52-70% of its elimination. The β-half-life ranges between 2.4 to 9.6 (with an average of 7.6) days.

4. ANTIHYPERTENSIVE AND HYPOTENSIVE DRUGS

A plethora of substances are normally employed to lower the blood pressure, though their effect may be transient. A few of them are used for their hypotensive action. An arbitrary definition of normal adult blood pressure afforded by the **World Health Organization (WHO)-'is a systolic pressure equal to or below 140 mm Hg together with a diastolic pressure equal to or below 90 mm Hg.'**

Antihypertensive drugs are invariably employed in the treatment of hypertension, although a few amongst them, such as : **ganglionic blocking drugs,** do find their scattered applications in a variety of other therapeutic, diagnostic and surgical procedures.

Interestingly, a few of them are used as hypotensive drugs in nonhypertensive subjects. There exist two major categories of '*diastolic hypertension*', namely : (*a*) **primary hypertension** (*e.g.*, essential, idiopathic) ; and (*b*) **secondary hypertension.** However, the *malignant hypertension* is nothing but an acute and rather progressive phase of **primary hypertension.** It has been revealed that there is absolutely no universal therapy for the control and management of primary hypertension ; and, as such, most individual instances do vary widely in response to various therapeutic agents.

In fact, there are several glaring evidences available today that may attribute to certain types of hypertension previously known as **diastolic or essential hypertension,** for instances :

(*a*) Renin-angiotensin pathway,

(*b*) Angiotensin II receptor antagonists and

(*c*) Potential-dependent calcium channels.

4.1. Renin-Angiotensin Pathway

It has already been proved adequately that the prevailing **renin-angiotensin pathway** happens to be an extremely complex, highly regulated pathway which is intimately associated with the ultimate regulation of blood volume, electrolyte balance, and above all the arterial blood pressure. It essentially comprises of *two* cardinal enzymes, known as : *renin* and *angiotensin converting enzyme* (ACE). The most predominant and primary objective of these enzymes are to afford adequate release of angiotensin II from its endogenous precusror, usually termed as **angiotensinogen.** Importantly, angiotensinogen is an **α_2-globulin** having a molecular weight ranging between 58,000 – 61,000. It is essentially made up of 452 amino acids, is available abundantly in the plasma, and is continually replenished by synthesis and secreted by the liver.

In reality, the role of the **renin-angiotensin pathway** in the cardiovascular disorders is extremely vital and critical by virtue of the fact that it exclusively is responsible for the maintenance of blood volume, arterial blood pressure, and the electrolyte balance in the body. Therefore, any slightest abnormalities in this prevailing pathway, such as : excessive release of renin, overproduction of angiotensin II, may ultimately give rise to a plethora of **cardiovascular disorders**.

4.2. Angiotensin II Receptor Antagonists

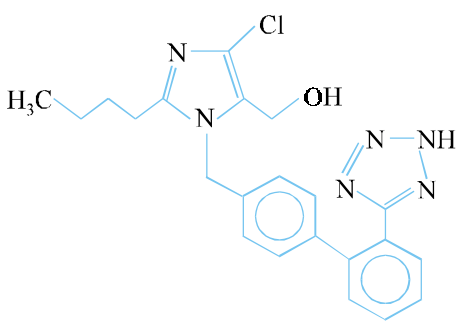
It is, however, pertinent to state here that **angiotensin II receptor** happened to be the first and foremost **'target approach'** towards the historical development of newer drug substances that could possibly inhibit the **renin-angiotensin pathway.** In early 1970s, a tremendous effort was geared into action to develop **angiotensin II receptor antagonists** that was solely based on the *peptide-linked structural analogues* of the **natural agonist.** Efforts in this direction gave birth to several drugs of which a few important ones are given below :

(*a*) **Saralasin**

Sar-Arg-Val-Tyr-Val-His-Pro-Ala

1-(N-Methylglycine)-5-*L*-valine-8-*L*-alanineangeotensin II. It is employed as antihypertensive and as a *diagnostic aid* (*i.e.,* renin-dependent hypertension).

(*b*) **Losartan**



2-Butyl-4-chloro-1-[2′-(1H-tetrazol-5-yl) [1, 1′-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol.

The wonderful drug **'losartan'** was developed in 1982 and since then being used as a potent antihypertensive agent. It specifically blocks the angiotensin II receptor.

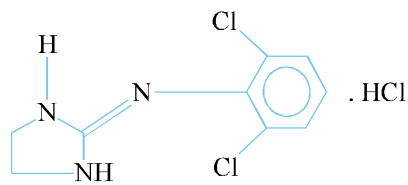
4.3. Potential-Dependent Calcium Channels

It has been well established and demonstrated that the *potential-dependent* Ca^{2+} *channels* are solely critical and important in modulating the influx of Ca^{2+} ; and hence, subsequent inhibition of Ca^{2+} flow through these specific channels results in both vasodilation as well as retarded cellular response to the prevailing contractile stimuli. Based on the proven facts that the *arterial smooth muscle* is found to be more sensitive than the *venous smooth muscle* ; besides, the *coronary and cerebral arterial blood vessels* are observed to be more sensitive in comparison to other *arterial beds**.

Consequent to these pharmacological actions, the calcium channel blockers are found to be profusely beneficial in the treatment of hypertension, and ischemic heart disease (IHD).

Examples. Clonidine hydrochloride, hydralazine hydrochloride, methyl-dopa, diaoxide and sodium nitroprusside.

A. Clonidine INN, Clonidine Hydrochloride BAN, USAN,



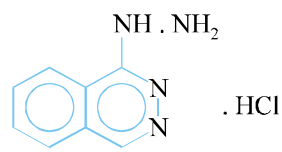
2-(2, 6-Dichloroanilino)-2-imidazoline hydrochloride ; 2-(2, 6-Dichlorophenyl-amino)-2-imidazoline hydrochloride ; 2, 6-Dichloro-N-(imidazolidine-2-ylidene) aniline hydrochloride ; BP ; USP ;

Catapres(R) (Boehringer Ingelheim)

The compound was initially investigated as a nasal vasoconstrictor but incidentally has shown to be an effective drug in the *treatment of mild to severe hypertension and prophylaxis of migraine headache.*

Dose : *0.15 to 0.9 mg daily in 2 or 3 divided doses.*

B. Hydralazine INN, BAN, Hydralazine Hydrochloride USAN,



1-Hydrazinophthalazine monohydrochloride ; Phthalazine, 1-hydrazino-, monohydrochloride ; BP ; USP ; Int. P. ;

Apresoline Hydrochloride(R) (Ciba-Geigy) ;

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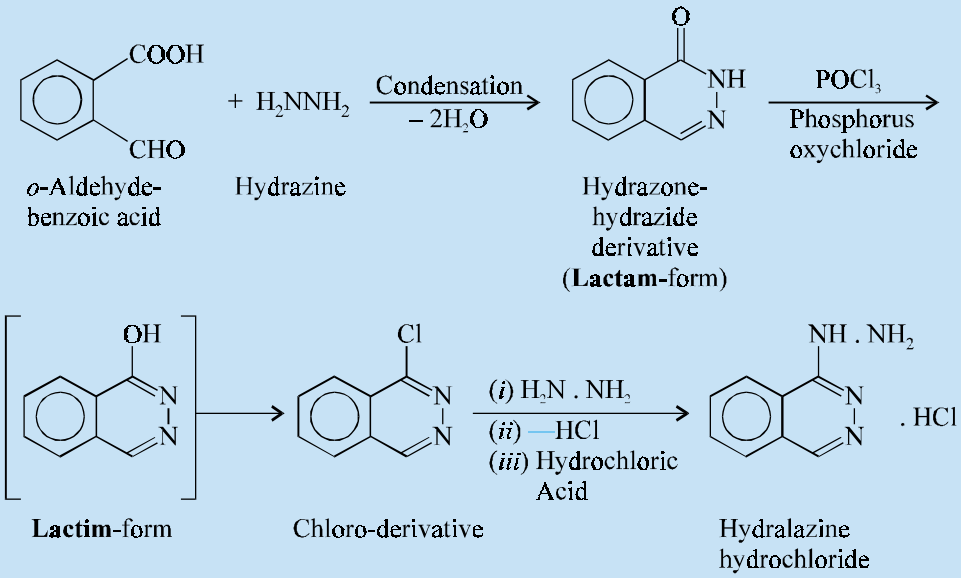
*Swamy VC and Triggle DJ. *Calcium Channel Blockers*, In : Craig GR, Stitzel RE, eds., **Modern Pharmacology with Clinical Applications**, Little Brown, Boston, 5th ed., 1997, 229-34.

Synthesis

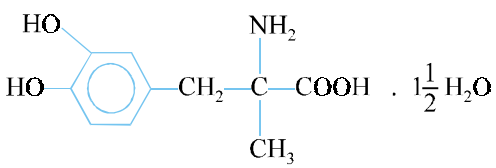


o-Aldehyde benzoic acid, *i.e.*, the half-aldehyde corresponding to phthalic acid, undergoes condensation with hydrazine to yield the **hydrazone hydrazide (lactam-form).** The **lactim-form** of this compound upon chlorination with phosphorus oxychloride gives the corresponding chloro derivative which on *first* treatment with a further mole of hydrazine and *secondly* with a calculated amount of hydrochloric acid affords the official compound.

It is a potent antihypertensive agent which exerts its action mainly by causing direct peripheral vasodilation. It has been observed that its effect on diastolic pressure is more marked and pronounced than on systolic pressure. It is employed in the *treatment of essential and early malignant hypertension usually in conjunction with thiazide diuretics or rauwolfia alkaloids.*

Dose : *Oral, initial, 10 mg 4 times daily for 2 to 4 days, then 25 mg 4 times per day for the rest of the week.*

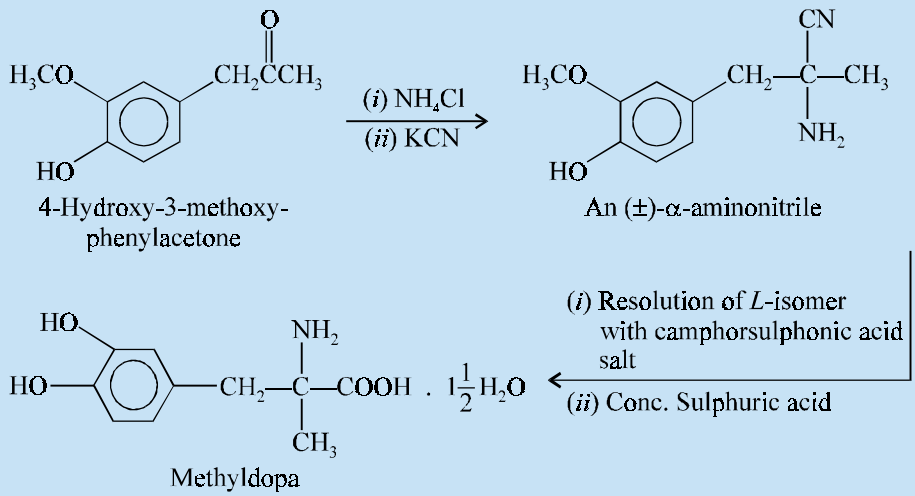
C. Methyldopa INN, BAN, USAN,



L-3-(3, 4-Dihydroxyphenyl)-2-methylalanine sesquihydrate ; L-Tyrosine, 3-hydroxy-α-methyl-, sesquihydrate ; BP ; USP ;

Aldomet$^{(R)}$ (Merck)

Synthesis

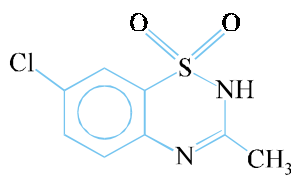


The reaction of 4-hydroxy-3-methoxy phenylacetone with ammonium chloride and potassium cyanide yields the corresponding racemic mixture of α-aminonitrile. The *L*-isomer is separated by means of camphorsulphonic acid salt which on treatment with concentrated sulphuric acid affords two processes simultaneously, namely : hydrolysis of the nitrile function to the acid function ; and cleavage of the methyl ether moiety, to yield the official compound in *its hydrated form.*

Methyldopa is a potent antihypertensive agent that acts centrally by stimulating α-adrenergic receptors. It also helps to minimise the tissue concentrations of adrenaline, noradrenaline and serotonin. It is widely employed *to treat patients having moderate to severe hypertension by reducing the supine blood pressure as well as the standing blood pressure.*

Dose : *Usual, initial dose, oral 250 mg of anhydrous methyldopa 2 or 3 times per day for 2 days ; usual maintenance dosage is 0.5 to 2 g of anhydrous methyldopa everyday.*

D. Diazoxide INN, BAN, USAN,

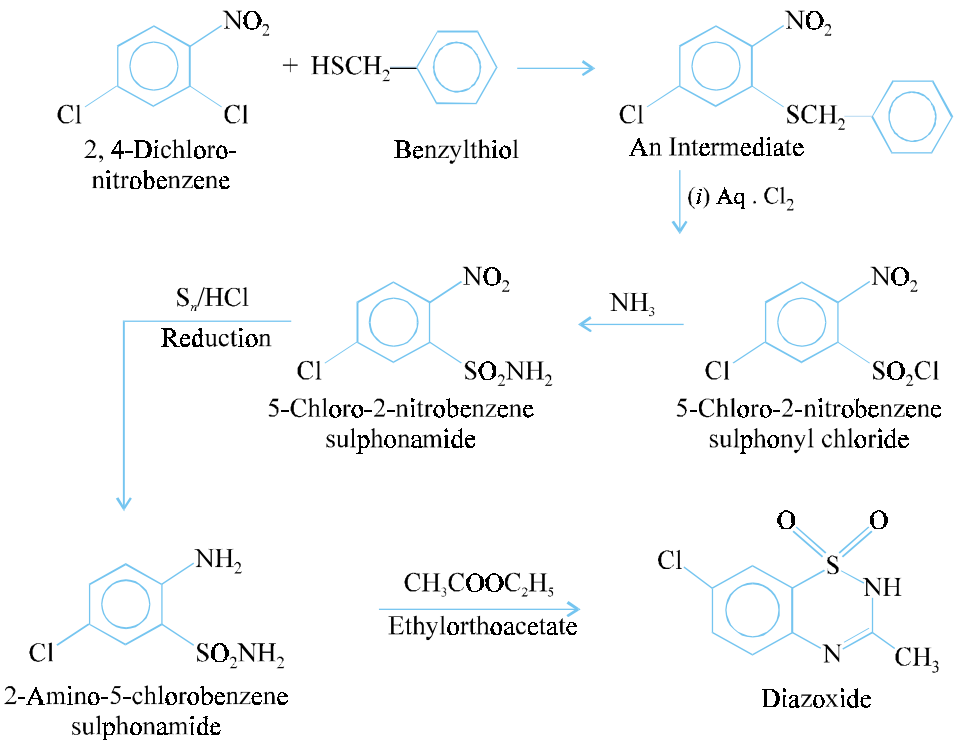


7-Chloro-3-methyl-2H-1, 2, 4-benzothiadiazine 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine, 7-chloro-3-methyl-, 1, 1-dioxide ; BP ; USP ;

Hyperstat(R) (Schering-Plough) ; Eudemine(R) (Allen and Hanburys, U.K.)

Synthesis

Interaction between 2, 4-dichloro-nitrobenzene with benzylthiol affords an intermediate thereby eliminating a mole of hydrogen chloride. The resulting product undergoes debenzylation with concomi-



tant oxidation in the presence of aqueous chlorine gives 5-chloro-2-nitrobenzene sulphonyl chloride which on subsequent treatment with ammonia and reduction yields the corresponding sulphonamide. This on condensation with a mole of ethyl *ortho* acetate yields the official product.

Diazoxide is employed intravenously for the *management and treatment of severe hypertensive crisis thereby lowering the blood pressure by a vasodilator effect on the arterioles.*

Dose : *0.4 to 1 g per day in 2 or 3 divided doses.*

E. Sodium Nitroprusside USAN,

$$Na_2\,[Fe(CN)_5NO]\,.\,2H_2O$$

Sodium nitroferricyanide ; Sodium nitrosylpentacyanoferrate (III) dihydrate ; B.P., U.S.P. ; Nipride(R) (Hoffmann-La Roche) ; Nitropress(R) (Abbott).

Synthesis

$$K_4Fe(CN)_6 \xrightarrow[(ii)\ Na_2CO_3\ (Neutralized)]{(i)\ 50\%\ HNO_3\ (Boiled)} Na_2[Fe(CN)_5NO]\,.\,2H_2O$$

Potassium ferrocyanide — Sodium nitroprusside

Potassium ferrocyanide is first dissolved in 50% HNO_3 and then the solution boiled for 1 hour. The resulting solution is cooled, filtered and neutralized with sodium carbonate, and finally evaporated to crystallization.

It is a short-acting hypotensive agent. It is mostly *employed as a vasodilator in the emergency treatment of hypertensive crises that normally do not respond to other antihypertensive measures.*

Dose : *By continuous infusion of a 0.005 or 0.01% solution in dextrose injection, normally at a rate of 0.5 to 8 mcg per kg body-weight per minute, under physician's observation.*

4.4. Mechanism of Action of Selected Antihypertensive and Hypotensive Drugs

The mechanism of action of certain selected antihypertensive and hypotensive drugs shall be discussed in the section that follows :

4.4.1. Clonidine

The antihypertensive actions are, in part, due to a central action. However, an observed retardation in the sympathetic activity gives rise to a variety of pharmacological actions, such as : vasodilation, bradycardia and occasional atrioventicular block, and a decrease in the release of renin from the kidney ; besides, an enhancement in the vagal activity also affords bradycardia.

Interestingly, the central activity, in part, seem to be the outcome of a specific stimulant action on the **α_2-adrenergic receptors** either located in the vasomotor and cardioinhibitory centres, or in the spinal cord on the preganglionic sympathetic neurons. Besides, it may also exert a peripheral action to reduce the release of norepinephrine from the sympathetic nerves. It has been found to cause stimulation of the **α_2-adrenergic receptors** on the sympathetic nerve terminals, which stimulation ultimately affords a feed back almost negatively to put an end to the release of the ensuing mediator.

4.4.2. Hydralazine

The drug acts on the vascular smooth muscle to afford definite relaxation. Its exact mechanism of action is still not quite vivid and clear. It is found to interfere with Ca^{2+} entry and Ca^{2+} release from the prevailing intracellular reserves ; besides, causing a specific activation of *guanylate cyclase* thereby giving rise to an enhanced levels of cGMP. In fact, the concerted effort of all these biochemical events may afford an apparent vasodilation.

It gets excreted rapidly through the kidneys, and within a span of 24 hours nearly 75% of the total quantum administered appears in the urine as its **'metabolites'** or absolutely unchanged form.

The drug invariably undergoes mainly *three* types of chemical transformations, namely : (*a*) **benzylic oxidation ;** (*b*) **glucuronide formation ;** and (*c*) **N-acetylation by the microsomal enzymes invariably found in the liver and tissues.** It has been observed that **'acetylation'** could pose as a main determinant factor of the rate of hepatic removal of the drug from the blood in circulation ; and, hence, of the prevailing systemic availability of the same.* Consequently, the rapid acetylation aids in an extremely high hepatic extraction ratio ensuing from the circulatory blood, which is virtually responsible for the greater portion of the **first-pass elimination.**

4.4.3. Methyldopa

The drug gets converetd to **α-methylnorepinephrine** that eventually helps in displacing norepinephrine, from the storage sites ; and thus, release as a **'false transmitter'** by means of the prevailing nervous impulses in the adrenergic nerves. Importantly, the **metabolite α-methylnorepinephrine** shows potent **α_2-agonist activity,** and this perhaps acts summararily to lower the blood pressure almost in the same manner as that of clonidine. However, in the spinal cord and the

*Zacest R and Koch-Wesres, *J. Clin. Pharmacol.*, 1972, **13**, 4420.

vasomotor centre, the ultimate results is an observed decrease in the vasomotor outflow, that ultimately is responsible for lowering blood pressure besides decreasing the plasma-renin activity.

4.4.4. Diazoxide

The **drug** at therapeutic dose levels, causes **vasodepression** which is primarily the outcome of arteriolar dilatation, in order that the ensuing orthostatic hypotension is normally minimal. However, certain extent of venous dilatation invariably occurs, which occasionaly is responsible to afford orthostatic hypotension. It has been duly observed that the smooth muscle-relaxing effects are usually caused due to the **hyper-polarization** of vascular smooth muscle by activating ATPase-sensitive K-channels. Hence, it is mostly used in IV as a **'hypotensive drug'** in situations arising from acute hypertensive crises.

Diazoxide is found to be 90% protein-bound ; however, fast and rapid IV administration allows quick-distribution to smooth muscle before it gets bound to protein intimately. Therefore, one may attain a greater and longer-lasting drop in blood pressure through faster rates of IV injection. Interestingly, the '*drug*' is found to persist in blood circulation much longer than the corresponding hypotensive effect. The plasma half-life is 20 to 60 hours in subjects having normal renal function, whereas the corresponding hypotensive effects lasts only 2 to 15 hours.

4.4.5. Sodium Nitroprusside

It happens to release nitric oxide (NO), which is also recognised as endogenous, endothelial-derived relaxing factor. Importantly, 'NO' progressively activated *guanylyl cyclase* strategically located in vascular smooth muscle to effect production of **vasodilatation.** However, its specific actions on the ensuing arterioles minimise the total systemic vascular resistance, and that perhaps is the major cause of the fall in blood pressure it evokes eventually. It has been observed to cause milder action on the *capacitance veins* ; and, therefore, with normal doses, venous return is impaired insignificantly in the *recumbent position.* But in the *upright position* there exists an appreciable *orthostatic hypotension.* Evidently, the observed cardiac output gets enhanced in the recumbent status ; whereas, lowered in the upright status distinctly. Besides, there prevails a variable effect particularly on the *renal plasma flow* and the **glomerular filtration rate,** but it is normally found to be enhanced in the recumbent position. One may also observe the **plasma-renin activity** to get enhanced within a range varying between slight to moderate.

5. ANTIARRHYTHMIC AGENTS

Certain diseases and the effect of some drugs are usually responsible for affecting the rhythm and the normal heart-rate. These cardiac arrhythmias may be caused from disorders in pacemaker function of the sinoatrial node thereby resulting into tachycardia, bradycardia, cardiac arrest, atrial flutter, atrial fibrillation and ventricular fibrillation. Hence, the antiarrhythmic agents are also termed as **'antidysrhythmic drugs'** or **'antifibrillatory drugs'.**

Antiarrythmic drugs may be defined as—**'drugs that are capable of reverting any irregular cardiac rhythm or rate to normal'.** In other words, an arrhythmic situation is that wherein either initiation or propagation of a heart-beat stimulus is found to be invariably abnormal.

At this juncture it is worthwhile to have a little in-depth knowledge with regard to a *normal sinus rhythm* and aspects of the **electrical characteristics** of the heart.

Salient Features. A few salient features are as follows :

(1) **Sinoatrial (SA) node*** is situated in the viccinity of the surface at the junction of the right atrium and the superior vena cava, which is solely responsible for the normal orderly maintenance of the sequence of events in the cardiac contraction profile being initiated by a pacemaker. **Automaticity** is one of its main characteristic features. SA-node essentially possesses a normal firing frequency ranging between 60-100 impulses per minute.

(2) Subsequently, the established rhythm is conducted to the atrioventricular (AV) node**, which critically serves to slow down the heart beat so that the atrial contraction may take place prior to the stimulation of the ventricle. The impulse is transmitted from the AV-node to the **'Bundle of His'** (*i.e.*, to a common bundle of fibers) which typically crosses the right atrium to the left ventricle. The branching of **'Bundle of His'** ultimately leads into the **Purkinje fibers** which essentially innevate the herat musculature of the ventricles.

The electrical activity produced by either the depolarization or the repolarization of myocardial tissue, specifically the nerve fibre cells, may be identified conveniently by the help of suitable electrodes ; and this may be plotted as a graph showing intensity (mV : millivolts) along the Y-axis and time (seconds) along the X-axis, as shown in Fig. 12.1(*a*), also known as the electro-cardiogram (ECG).

Explanations of Fig. 12.1(*a*) are as stated below :

(*i*) ECG-represents a *'cardiac cycle'* which could be either normal or abnormal.

(*ii*) P-wave specifically designates the electrical activity which passes over the atrial surface,

(*iii*) Q, R, S-waves, (*i.e.*, the QRS-complex) are produced by the ventricles.

(*iv*) T-wave is produced by the repolarization of the ventricular muscle fibres, and

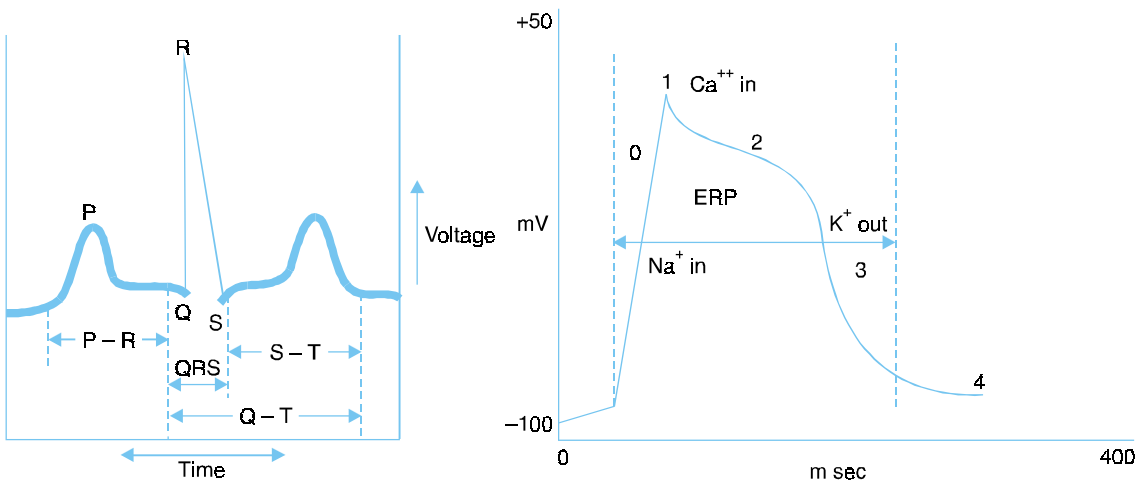


Fig. 12.1(*a*) Tracing of an Electrocardigram (ECG) **Fig. 12.1(*b*)** Schematic Sketch of Cardiac Electric Profile [Phases = 0 – 4 ; ERP = Effective Refractory Period]

[Adapted from : Gringauz A : An Introduction to Medicinal Chemistry, Wiley-VCH, New York, 1997]

*__SA-node__ : Sinoatrial node of the heart.

**__AV-node__ : Atrioventricular node of the heart.

(*v*) Irregular distances between the different peaks, such as : a **shortened ST-interval,** may be correlated to the particular rhythmic abnormalities. These vital information(s) could help a physician in the correct diagnosis *vis-a-vis* right choice of medicaments.

In short, any disturbance to the conductance of the electrical impulses in a perfect sequential and orderly manner ultimately forms the basis of an **arrythmia.**

Fig. 11.1(*b*) shows the schematic diagram of the cardiac electrical activity. It is, however, pertinent to state here that the electrophysiology of the heart is overwhelmingly governed by the prevailing **transmembrane resting potential.** Hence, the existing potential inside a **Purkinje fibre cell at rest,** with regard to the outside, is found to be almost equal to 90 mV. Interestingly, the potential difference is maintained by an **active transport system** (*i.e.*, a pumping device) which essentially sustains a higher extracellular Na^+ concentration in comparison to the intracellular K^+ level. It has been observed that upon excitation, the prevailing voltage quite rapidly gets reversed to a positive voltage, most probably spiking around + 30 mV. This situation gives rise to an extremely rapid spontaneous and simultaneous movement of Na^+ into the cell, just like a **gate** had all-of-a-sudden opened a channel (usually known as a **'gating mechanism'**). Therefore, the recovery from excitation status gives rise to the gradual restoration of the ensuing **'resting potential'** in various phases from 1 through 4.

Phase-4 : the resting potential is followed by the rapid depolarization and its reversal.

Phase-0 : gets started with a series of three repolarization phases, namely : Phase-1, 2 and 3.

Importantly, depending on the areas measured*, the distinct separation of phases are not quite feasible ; and the prevailing voltages invariably alter amongst the major cell types of the heart, *viz.*, Purkinje fibres**, AV-node, atrial cells, and the SA-node.

There are *two* types of influx, namely : (*a*) rapid influx ; (*b*) slow influx.

A. Rapid Influx. The rapid influx of Na^+ through the channels (or gates) during phase 0 results in the cell a rapid depolarization, which in turn **"closes"** the gate behind them to enable further influx to occur.

B. Slow Influx. The slow influx of Ca^{2+} gets triggered off to equalize (balance) the K^+ loss besides maintaining a proper relative voltage plateau as shown in Fig. 11.1(*b*). In fact, as the Ca^{2+} entry slows down, the membrane potential becomes low very swiftly to the predepolarization levels (*i.e.*, phase 4). Thus, in the heart muscle the **elcetrical activity** is coupled to a **mechanical activity** by Ca^{2+} as the potential trigger.

An effective refractory period (ERP) [See Fig. 11.1(*b*)]. Comprising of several hundred milliseconds follows during which no further stimulus may propagate an impulse effectively. However, the *'impulse initiation'* happens to be an inherent characteristic features of the cardiac fibres which evidently enables them to modulate action potentials almost spontaneously, and hence, the corresponding impulses.

Anti-arrhythmic agents may be classified on the basis of their different pharmacological actions as follows :

(*a*) membrane-stabilizing agents ;

(*b*) antisympathetic drugs ;

Measured*—with the aid of **intracellular microelectrode recorders ;

***A cardiac muscle cell beneath the endocardium of the ventricles of the heart. These extend from the bundle branches to the ventricular myocardium and form the last part of the cardiac conduction system.

(*c*) prolonging cardiac action ; and

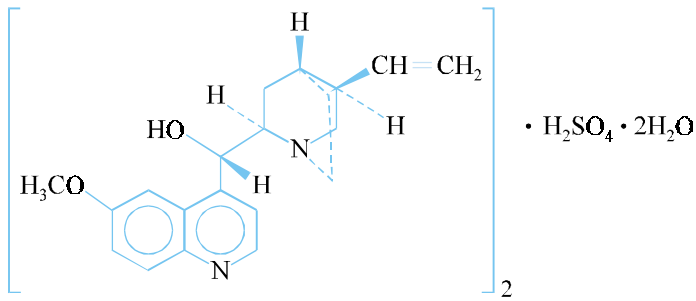
(*d*) interference with calcium conductance.

5.1. Membrane-Stabilizing Agents

These drugs are found to interfere directly with depolarization of the cardiac membrane. Quite often they also exhibit local anaesthetic properties.

A few important members of this category are discussed below :

A. *Quinidine Sulphate* BAN, *Quinidine Sulfate* USAN,



Quinidine sulphate (2 : 1) (salt) dihydrate ; Cinchonan-9-ol, 6′-methoxy-, (9S)-, sulphate (2 : 1) (salt), dihydrate ; BP ; USP ; Eur. P., Int. P., Ind. P. ;

SK-Quinidine Sulfate(R) (SK and F) ; Quinidex(R) (Robins)

Preparation

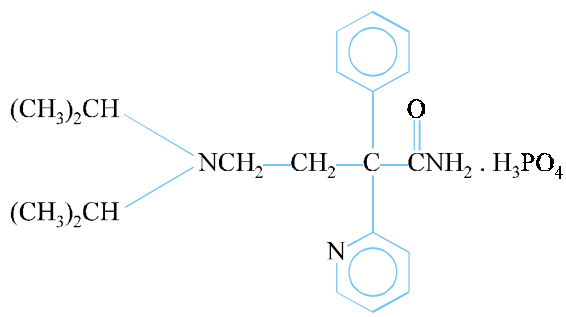
Quinidine sulphate may also be prepared from the mother liquors remaining after separation of quinine from the extracts of *Cinchona* by a known process.

It is very effective in the *suppression of atrial premature contractions and also in shielding the recurrences of atrial fibrillation.* However, it has been found to be effective moderately against ventricular premature systoles and paroxysmal atrial tachycardia.

Dose : *Initial, adult, oral, 200 to 800 mg after each 2 or 3 hours up to 5 g on the first day, followed by 100 to 200 mg 3 to 6 times per day.*

There are quite a few quinidine-like agents that are used frequently as membrane-stabilizing drugs. For instance

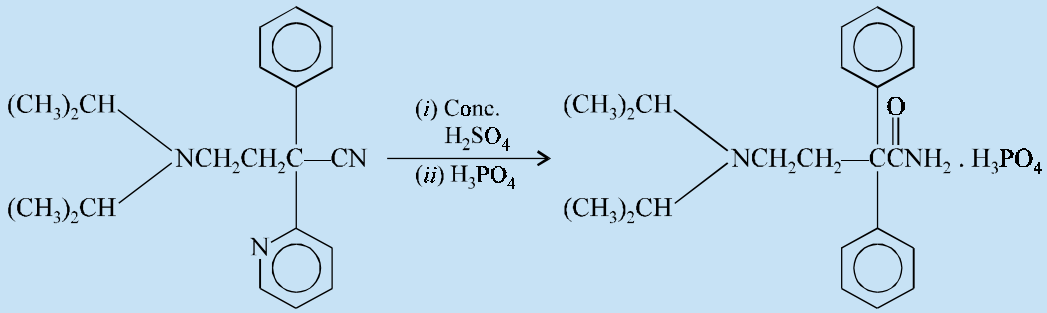
B. Disopyramide INN, Disopyramide Phosphate BAN, USAN



α-[2-(Diisopropylamino)-ethyl]-α-phenyl-2-pyridine-acetamide phosphate (1 : 1) ; 4-Diisopropylamino-2-phenyl-2-(2-pyridyl) butyramide phosphate (1 : 1) ; BP ; USP ;

Norpace(R) (Searle)

Synthesis



4-Diisopropylamino-2-phenyl-2-(2-pyridyl) butyronitrile

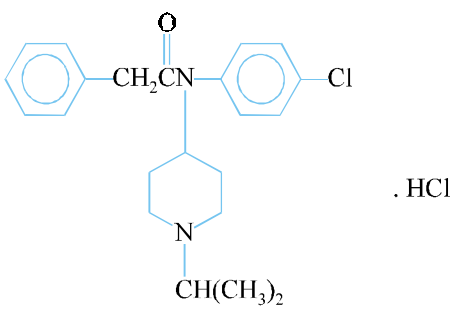
Disopyramide phosphate

Conversion of 4-diisopropylamino-2-phenyl-2-(2-pyridyl) butyronitrile to the corresponding amide is caused by heating with concentrated sulphuric acid which on treatment with phosphoric acid yields the official compound **disopyramide phosphate**.

Disopyramide phosphate is recommended orally as a prophylaxis of either unifocal or multifocal premature ventricular contractions and ventricular tachycardia. It also exhibits both anticholinergic and local anaesthetic properties.

Dose : *Initial, adult, oral, 200 to 300 mg followed by 100 to 200 mg after every 6 hours.*

C. Lorcainide INN, Lorcainide Hydrochloride BAN, USAN,

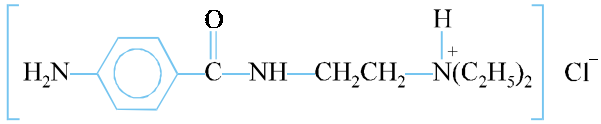


4′-Chloro-N-(1-isopropyl-4-piperidinyl)-2-phenyl-acetanilide monohydrochloride ; Benzeneacetamide, N-(4-chlorophenyl)-N-1-(1-methylethyl)-4-piperidinyl-, monohydrochloride ; Lorcainide Hydrochloride(R) (Janssen Pharmaceutica, Belgium)

It is very effective particularly during *chronic thearpy perhaps due to its inherent high first-pass metabolism orally.*

Dose : *100 mg 2 or 3 times per day.*

D. Procainamide INN, Procainamide Hydrochloride BAN, USAN,

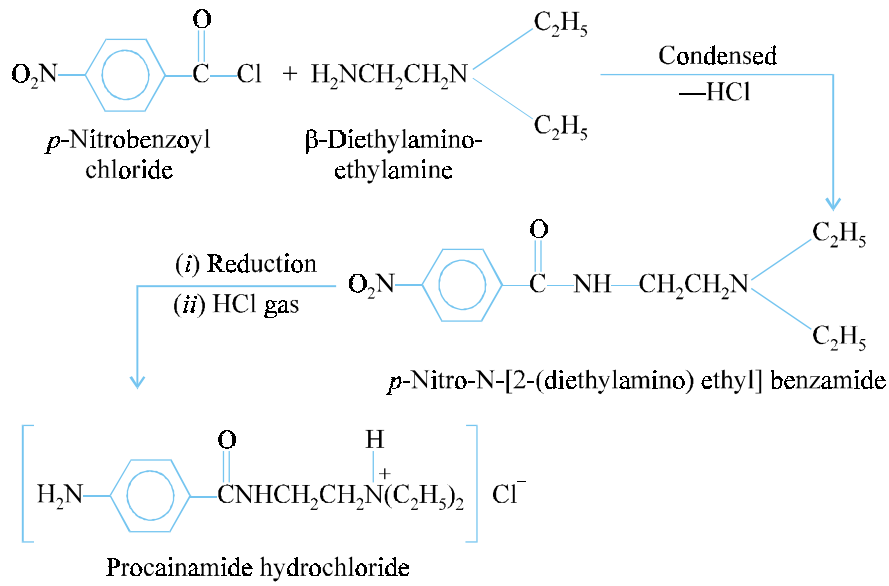


p-Amino-N-[2-diethylamino)-ethyl] benzamide hydrochloride ; Benzamide, 4-amino-N-[2-(diethylamino) ethyl]-, monohydrochloride ; BP ; USP ; Int. P., Ind. P. ;

Procan$^{(R)}$ (Parke-Davis) ; Pronestyl$^{(R)}$ (Squibb)

Synthesis

p-Nitro-N-[2-(diethylamino) ethyl] benzamide is obtained by the interaction of *p*-nitrobenzoyl chloride and β-diethylamino ethylamine. The resulting product on reduction with tin and hydrochloric acid gives the procainamide base which yields the official compound on passing a stream of hydrogen chloride gas.

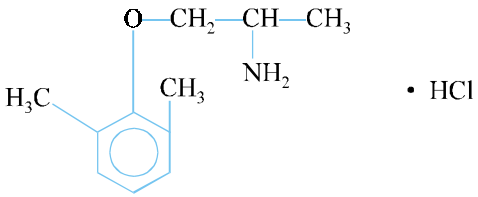


Procainamide is a class I anti-arrhythmic agent with actions similar to those of quinidine. It depresses myocardial automaticity and excitability and increases the effective refractory period of the atrium. It finds its application *towards the suppression of ventricular extrasystoles and paroxysmal ventricular tachycardia. It is also useful in the control and management of atrial fibrillation and premature atrial contractions.*

Dose : *Initial, adult, oral, for atrial dysrhythmias, 1.25 g, then 750 mg after 1 hour, followed by 500 mg to 1 g every 2 hours as required ; for ventricular dysrhythmias, 1 g followed by 250 to 500 mg every 3 hours.*

Lignocaine has already been discussed under **'local anaesthetics'** and it is also found to possess anti-arrhythmic actions. There are a few other synthetic compounds which exhibit **lignocaine-like properties,** *e.g.,* **mexiletine hydrochloride ; tocainide** which shall be discussed as under :

E. Mexiletine INN, Mexiletine Hydrochloride BAN

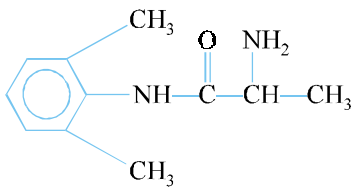


1-Methyl-2-(2, 6-xylyloxy) ethylamine hydrochloride ; Mexitil(R) (Boehringer Ingelheim, U.K.)

It belongs to the Class I anti-arrhythmic agent having properties very much alike to those of lignocaine. *Unlike* **lignocaine** *it may be administered orally. It is employed for the management and control of ventricular arrhythmias.*

Dose : *Initial, oral, 400 to 600 mg, followed by 200 to 250 mg 3 or 4 times per day, starting 2 hours after the loading dose ; maintenance dose 600 to 800 mg daily in divided doses.*

F. Tocainide INN, BAN, USAN,



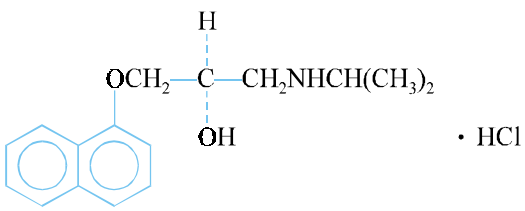
Amino-2′, 6′-propionoxylidide ; Propanamide, 2-amino-N-(2, 6-dimethyl-phenyl) ; Tonocard(R) (Merck)

It is used exclusively *for the prevention and treatment of ventricular arrhythmias.*

Dose : *500 to 750 mg administered slowly through* IV.

There are a few compounds which may be conveniently grouped together under the miscellaneous category.

G. Dexpropranolol INN, Dexpropranolol Hydrochloride USAN,



(+)-(R)-1-Isopropylamino-3-(1-naphthyloxy) propan-2-ol hydrochloride ; 2-Propanol, 1-[(1-methylethyl)-amino]-3-(1-naphthalenyloxy)-, hydrochloride ;

Dexpropranolol Hydrochloride(R) (ICI Pharmaceuticals, U.K.) ;

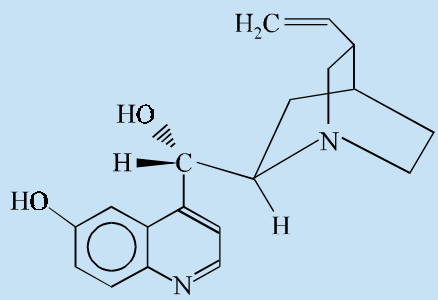
Besides possessing similar membrane-stabilizing effects like propranolol, it also exerts little beta-adrenoreceptor blocking activity.

5.1.1. Mechanism of Action of Membarne-Stabilizing Agents

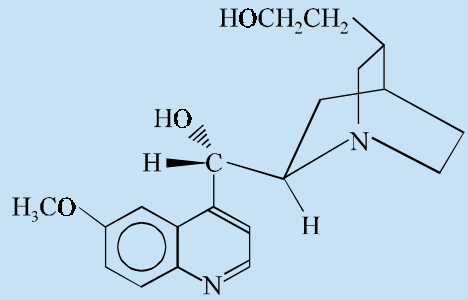
The mechanism of action of certain **membrane-stabilizing agents** are described here under :

5.1.1.1. Quinidine

The bioavailability of **quinidine** seems to be governed solely on a combination of metabolism and **P-gp*** efflux. It has been demonstrated that the bioavailabilities of **quinidine gluconate** and **quinidine sulphate** are 70-75% and 80-85%, respectively. Interestingly, once the **'drug'** gets absorbed, it is subjected to the **hepatic first-pass metabolism** and is found to be plasma-protein bound to the extent of almost 85%, having an elimination half-life of nearly 6 hours. The 'drug' is largely metabolized in the liver, and the renal excretion of the '*unchanged drug*' is also substantially appreciable *i.e.*, nearly 10%-15%. The *two* predominant metabolites are the corresponding hydroxylated derivatives, namely : (*a*) ***o*-Demethylquinidine ;** and (*b*) **Oxydihydroquinoline,** as given below :



o-Demethylquinidine (*a*)
[Obtained by hydroxylated structural analogues at the **'Quinoline Ring'**]



Oxydihydroquinidine (*b*)
[Obtained by oxidation of the '*vinyl*' *function* at the **'Quinuclidine Ring'**]

Interestingly, the aforesaid metabolites (*a*) and (*b*) essentially retain only about 33% of the pharmacological activity in comparison to that of **quinidine.** Furthermore, it has been observed that the quinidine, which being a **P-gp substrate**, invariably checks the renal tubular secretion of digoxin *via* the P-gp efflux pump route, thereby giving rise to an enhanced plasma concentration for **digoxin.**

5.1.1.2. Disopyramide

Though its antiarrythmic features are quite identical to those of **quinidine** and **procainamide,** yet there exist certain exceptions with regard to its specific antimuscarinic activities which are found to be much more marked and pronounced ; and strategically manifested at the two prominent extracardiac and intracardiac sites.

Salient Features. The various salient features of the **'drug'** are :

1. Minimises cardiac automaticity in non nodal cells.
2. Enhances the functional refractory period and minimises the relative refractory period in atrial as well as ventricular cells.
3. Lowers the responsiveness of particularly the myocardial cells to the electrical stimulation.
4. Minimises the ensuing conduction velocity and enhances the stimulus threshold.

***P-gp** : P-Glycoprotein ;

5. Both at the SA-node and AV-node, its inherent direct myocardial depressant pharmacological actions are adequately opposed by its antimuscarinic property. Hence, at a dosage regimen varying between low to intermediate doses, specfically, it can caused essentially *sinus tachycardia* in certain subjects ; besides, decreasing AV-nodal capability to afford a **second-degree block** of considerably high frequency atrial impulses that eventually pass through directly to the ventricle. Perhaps, that is why such patients that do have particularly *supraventricular tachyarrythmias*, are normally **digitalized** before being treated with disopyramide.

The drug is practically absorbed completely when administered orally, having the bioavailability extending upto 90%. About 50% of the drug gets usually excreted parctically unchanged in the urine having a biological half-life of 5 to 7 hours in subjects with both adequate cardiac output and almost normal renal function. A small fraction $\simeq$ 10% is usually secreted into bile. Its thereapeutic plasma levels normally vary between 2-4 mcg. mL^{-1}. Lastly, it has been demonstrated with adequate evidence that a substantial portion of a dose gets eliminated by N-monodealkylation.

5.1.1.3. Procainamide

The **'drug'** is found to depress myocardial contractility and hence, may produce hypotension ; it must be given to patients very cautiously those who are having a clear cut history of *heart-failure, valvular disease* or *aortic stenosis.* It possesses an antimuscarinic action on the atrioventricular node which may ultimately negate its direct depressant action on that node.

It is practically absorbed completely from the oral route, and the peak-plasma levels are accomplished within a span of 1-2 hours, where it is protein bound to the extent of 15%. Its volume of distribution is approximately 2 mL . g^{-1}. About 50 to 60% of the drug gets eliminated by the renal excretion (along with the tubular secretion). Importantly, it gets metabolized to **N-acetylprocainamide**, which is an **active metabolite,** and can be accumulated.

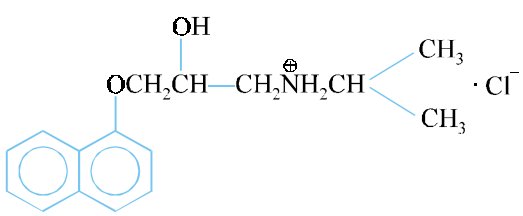
5.1.1.4. Tocainide Hydrochloride

It has been established that the total body clearance of **tocainide hydrochloride** stands at 166 mL. min^{-1} only thereby suggesting that the hepatic clearance is not to an appreciable extent. By virtue of the fact that the drug has very low hepatic clearance, the prevailing hepatic extraction ratio should be quite small ; and hence, the drug is most unlikely to afford a sizable first pass effect. It gets hydrolyzed in a manner very much akin to **lidocaine** ; and as such its metabolites are **active.**

5.2. Antisympathetic Drugs

The therapeutic agents that possess **antisympathetic characteristic features** is of the type propranolol.

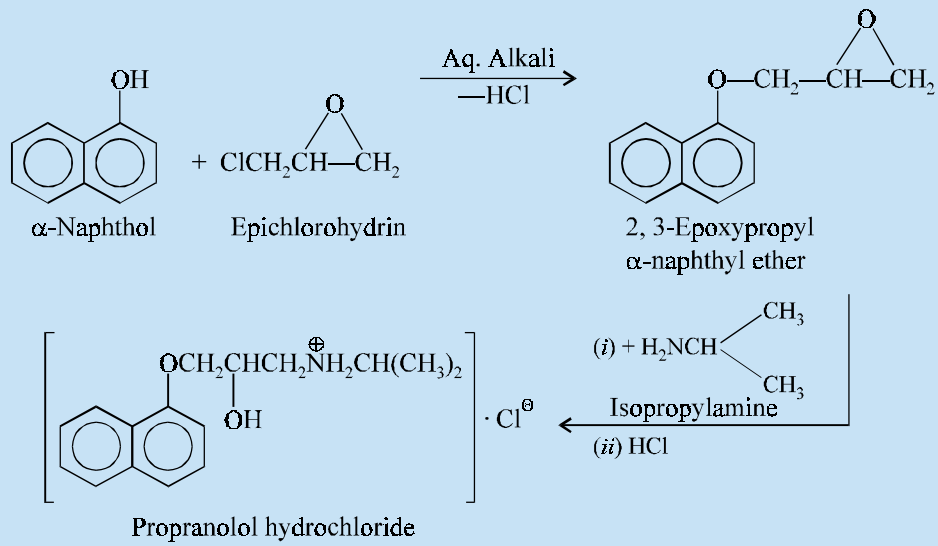
Propranolol INN, Propranolol Hydrochloride BAN, USAN,



1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride ; 2-Propanol, 1-[(1-methylethyl) amino]-3-(1-naphthalenyloxy-, hydrochloride ; BP ; USP ;

Inderal$^{(R)}$ (Ayerst)

Synthesis



The interaction of α-naphthol and epichlorohydrin in the presence of aqueous alkali gives 2, 3-epoxypropyl-α-naphthyl ether which upon treatment with isopropylamine affords the rupture of the epoxy ring thereby forming the **propranolol base** and this ultimately yields the official compound with HCl.

In addition to its prominent β-adrenergic blocking effect, it does possess independent quinidine-like anti-arrhythmic actions. Hence, it finds its utility *to minimise ventricular and atrial extrasystoles, digitalis-induced tachyarrhythmias, ventricular tachycardia and above all paroxysmal atrial tachycardia.*

Dose : *Adult, i.v., for arrhythmias, 1 to 3 mg at a rate not exceeding 1 mg per minute.*

5.2.1. Mechanism of Action

The **'drug'** exerts its actions by penetrating into the CNS and thereby causes the central effects. Though the precise mechanism for this specific action has not yet been established, it has been suggested that the **β-blockers** usually lower blood pressure in one of the following several methods, namely :

(*i*) a direct effect on the heart and blood vessels,

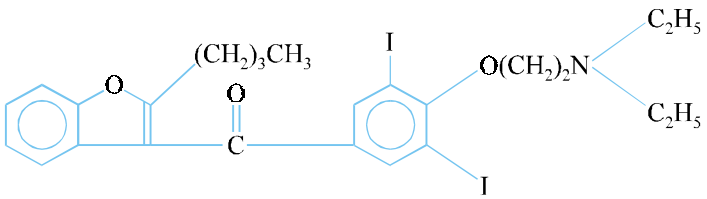
(*ii*) minimising sympathetic outflow from the CNS, and

(*iii*) affecting the renin-angiotensin-aldosterone system.

5.3. Prolonging Cardiac Action

These are a few compounds which specifically prolong the cardiac action potential, such as : **amiodarone** and **bretylium tosylate.**

A. Amiodarone INN, BAN,



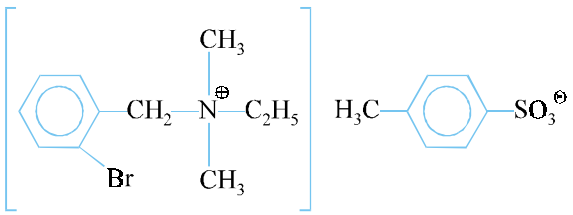
2-Butylbenzofuran-3-yl 4-(2-diethylaminoethoxy)-3, 5-diiodophenyl ketone ; 2-Butyl-3-benzofuranyl 4-[2-(diethylamino) ethoxy]-3, 5-diiodophenyl ketone ;

Cardarone X(R) (Labaz Sanofi, U.K.)

It is frequently employed *in the control and management of ventricular and supraventricular arrhythmias, and also in the treatment of angina pectoris.*

Dose : *Initial (as its hydrochloride salt), 200 mg 3 times per day for a week or more and then reduced to a maintenance dose of 200 mg daily.*

B. Bretylium Tosilate INN, Bretylium Tosylate BAN, USAN,

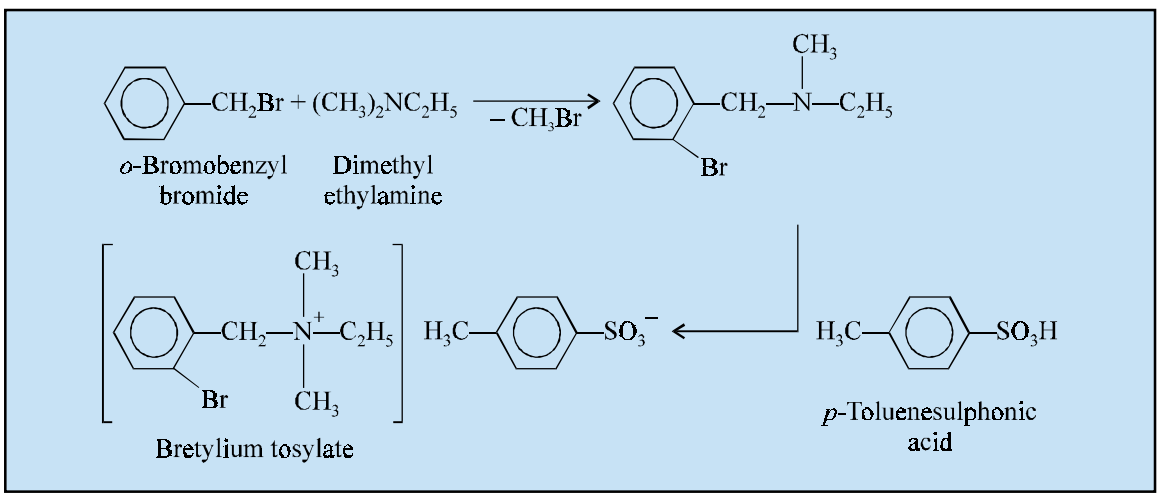


[2-Bromo-N-ethyl]-N, N-dimethylbenzene-methanaminium 4-methyl-benzene sulphonate ; (*o*-Bromobenzyl) ethyldimethyl-ammonium *p*-toluenesulphonate ;

Bretylol(R) (American Critical Care) ; Bretylate(R) (Wellcome, U.K.)

Synthesis

It may be prepared by the interaction of *o*-bromobenzyl bromide and dimethyl ethylamine and the resulting product on quaternization with *p*-toluenesulphonic acid yields the desired compound.



Bretylium tosylate is frequently used in the *treatment of ventricular arrhythmias which are refractory to other anti-arrhythmic drugs. It is specifically useful in the diagnosis of ventricular tachycardia.*

Dose : *Initial, adult, i.m., 5 to 10 mg per kg, repeated after 1 or 2 hours, then 5 to 10 mg per kg every 6 to 8 hours for maintenance.*

5.3.1 Mechanism of Action

The mechanism of action of **amiodarone** and **bretylium tosylate** are as stated below :

5.3.1.1. Amiodarone

It is categorized as **'class-III antidysrythmic drug'** that has been exclusively approved for *life-threatening recurrent ventricular arrythmias* which do not respond to other **antiarrythmic drugs.** It has a biological half-life ranging between 25 to 100 days. It inhibits metabolism of many drugs usually cleared by oxidative-microsomal enzymes.

5.3.1.2. Bretylium Tosylate

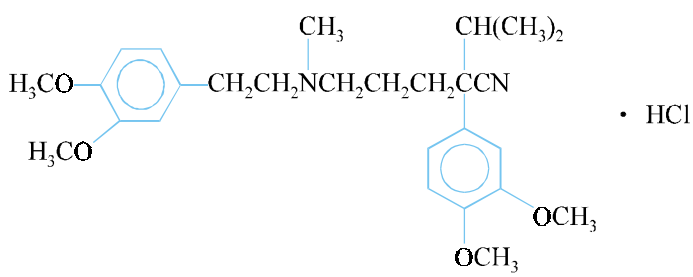
The **'drug'** is found to afford postural decrease in arterial pressure.* Nowadays, bretylium has been solely reserved for usage in the *ventricular arrythmias* which are observed to be resistant to other therapy. It fails to suppress phase-4-depolarization specifically, which action is generally found quite common in other antiarrhythmic agents. It is also categorized as a **'class-III antiarrythmic agent'** by virtue of the fact that it frequently prolongs the effective refractory period with respect to the action potential duration regardless the effect on conduction time.

However, the exact mechanism of antiarrhythmic action is still remain to be resolved.

5.4. Interference with Calcium Conductance

This particular class of compounds directly interfere with calcium conductance, such as **verapamil hydrochloride.**

Verapamil INN, Verapamil Hydrochloride BAN, USAN,



5-[N-3, 4-Dimethoxyphenethyl)-N-methylamino]-2-(3, 4-dimethoxy-phenyl)-2-isopropylvaleronitrile monohydrochloride ; Benzene-acetonitrile, α-[3-[[2-(3, 4-dimethoxyphenyl)-ethyl] methylamino] propyl]-3, 4-dimethoxy, [-α-(1-methylethyl)-. monohydrochloride ; BP ;
Calan(R) (Searle) ; Isoptin(R) (Knoll)

Verapamil hydrochloride is mostly advocated in the *control and management of supraventricular arrhythmias and angina pectoris. It also finds its usefulness in the treatment of supraventricular tachycardias.*

Dose : *Initial, oral, 40 to 120 mg 3 times per day according to the severity of the condition of the patient and his response.*

*Nadermanee K *et al. Circulation,* **66 :** 202, 1982

5.4.1. Mechanism of Action

The plasma half-life of this **'drug'** is unable to predict most precisely the actual duration of action on account of the presence of **active metabolites.** As it possesses an appreciably higher **first-pass metabolism,** nearly 100% of the **'drug'** gets ultimately excreted in the urine as its corresponding metabolites.

In general, the anti-arrhythmic drugs may be categorized judiciously into *four* distinct classes I through IV that may be described as given below :

Class I anti-arrhythmic drugs normally prolong the refractory period of cardiac muscle, reduce its excitability, and above all minimise the conduction velocity for example, quinidine sulphate, disopyramide phosphate, tocainide hydrochloride, procainamide hydrochloride, mexiletine hydrochloride, aprindine, etc.

Class II anti-arrhythmic drugs essentially improve myocardial cell responsiveness such as propranolol hydrochloride.

Class III anti-arrhythmic drugs usually prolong the cardiac action, for instance : amiodarone and bretylium tosylate. ***The latter depresses automaticity and increases the threshold with respect to fibrillation-inducing electrical stimulation in either normal or infarcted myocardium. It has also been found to enhance the functional refractory period thereby shortening the relative refractory period, thus the overall effect being to discourage re-entry.***

Class IV anti-arrhythmic drugs usually interfere with calcium conductance such as **verapamil** hydrochloride. Verapamil inhibits the action potential of the upper and middle nodal regions of the heart where the slow inward calcium-ion-mediated current contributes to depolarisation. This is responsible for the blockade of slow-channel conduction in the atrioventricular node. It has been found to inhibit one limb of the re-entry circuit which is assumed to underlie most paroxysmal supraventricular tachycardias, thereby causing the reduction of ventricular rate in atrial flutter and fibrillation.

6. VASOPRESSOR DRUGS

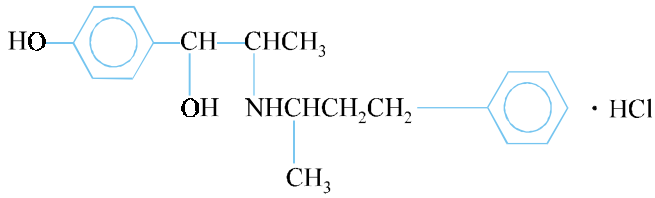
Vasopressor drugs (vasodilators) are chiefly those employed for angina pectoris, cerebral or peripheral vascular disorders. Besides, there are a plethora of **'drug substances'** belonging to certain other classes, treated elsewhere in this text, do also exert **vasoconstrictor** as well as cardiostimulator activity which may be judiciously and appropriately employed to increase the prevailing blood pressure under suitable conditions.

In typical physiological conditions wherein the **'plasma volume'** gets diminished sharply, as in *hypovolemic shock*, the immediate replacement tends to restore the blood pressure. The use of **'plasma-extenders'** in such conditions to restore the blood pressure are **not** regarded as the true **'vasopressor drugs'** for obvious reasons as they fail to affect vasoconstriction.

Over the years, there is much substantial evidence that explicitely prove that vasoconstriction particularly enhances the **ischemic damage** already caused on account of the improper and inadequate blood circulation prevailing in the body. As a result of these startling findings, the main emphasis got ligitimately shifted to the **α-adrenerging blocking drugs** in 1960s along with a host of **vasodilators,** and importantly to the **cardiostimulants.**

A few important members of this category shall be discussed in this section, such as : **Buphenine**, **Isoxsupurine** and **Prenylamine.**

A. Buphenine INN, Buphenine Hydrochloride BAN, Nylidrin Hydrochloride USAN,



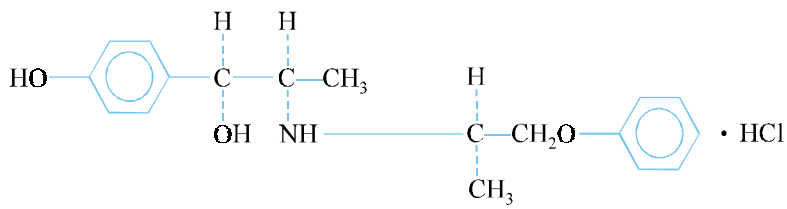
1-(4-Hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino) propan-1-ol-hydro-chloride ; *p*-Hydroxy-α-[1-[(1-methyl-3-phenylpropyl) amino] ethyl] benzyl alcohol hydrochloride ;

USP ; Arlidin(R) (USV Pharmaceutical)

Buphenine is used in the *treatment of peripheral vascular disease. It has also been employed in the treatment of Meniere's disease and similar disorders of the internal ear.*

Dose : *Usual, initial, oral 6 mg thrice daily, which may be enhanced to 36 or 48 mg per day in divided doses.*

B. Isoxsupurine INN, Isoxsupurine Hydrochloride BAN, USAN,



1-(4-Hydroxyphenyl)-2-(1-methyl-2-phenoxy-ethylamino) propan-1-ol hydrochloride ; Benzenemethanol, 4-hydroxy-α-[1-[(1-methyl-2-phenoxyethyl)-amino] ethyl]-, hydrochloride, stereo-isomer ; BP ; USP ;

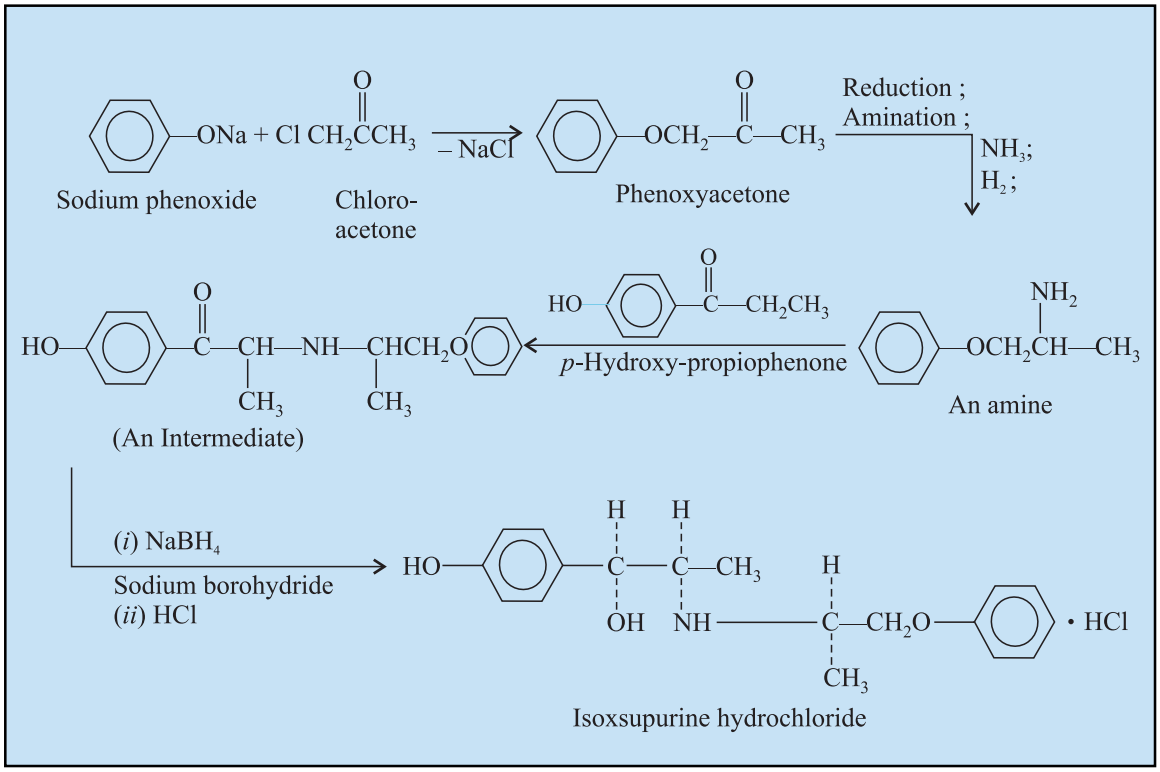
Vasodilan(R) (Mead Johnson)

Synthesis

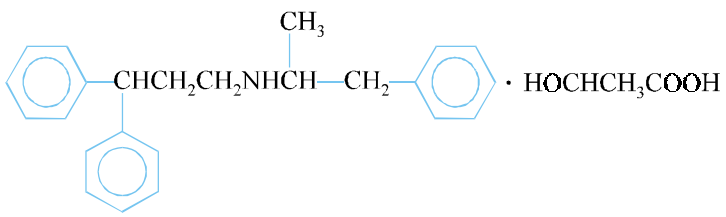
Sodium phenoxide and chloroacetone reacts to give a mole of phenoxyacetone with the elimination of a mole of NaCl, which on reductive amination in the presence of ammonia and hydrogen yields an amine. This amine on treatment with *p*-hydroxy-propiophenone gives an intermediate that on further treatment with sodium borohydride yields **isoxupurine** which when treated with hydrochloric acid affords the official compound.

It is used in the *treatment of cerebral and peripheral vascular disease.*

Dose : *Oral, 20 mg 4 times per day ; i.v. infusion as a solution containing 100 mg in 500 ml of sodium chloride solution.*



C. Prenylamine INN, USAN, Prenylamine Lactate BAN,



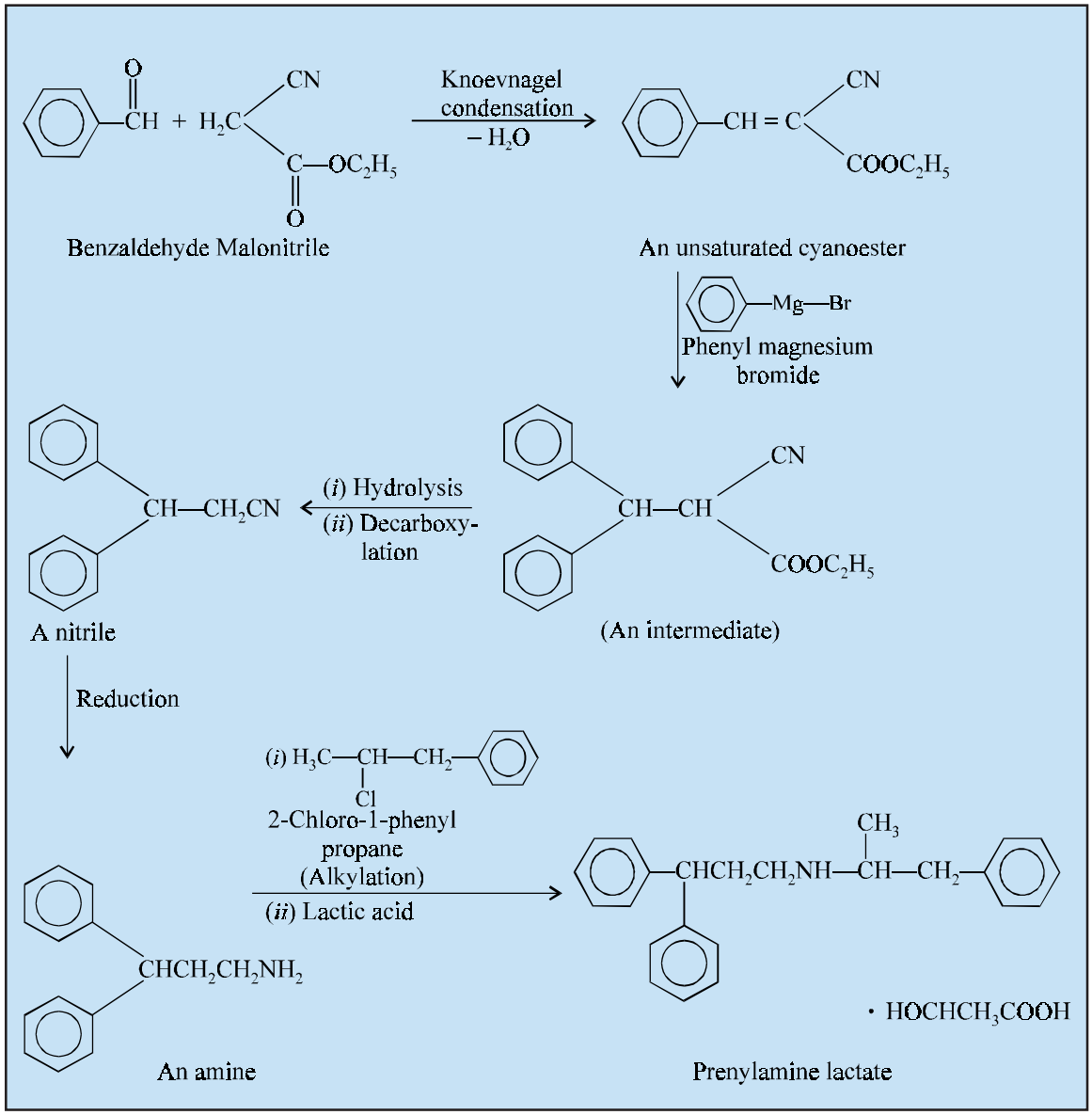
N-(2-Benzhydrylethyl)-α-methylphenethylamine lactate ; Benzenepropanamine, N-(1-methyl-2-phenylethyl)-γ-phenyl- ; BP ;

Synadrin(R) (Hoechst, U.K.)

Synthesis

Benzaldehyde and malonitrile undergoes **Knoevnagel Condensation** to give an unsaturated cyanoester which on reaction with phenyl magnesium bromide yields an intermediate. This on hydrolysis and subsequent decarboxylation yields a nitrile which on reduction gives an amine. The resulting amine on alkylation with 2-chloro-1-phenylpropane yields the **prenylamine** base which on treatment with lactic acid affords the official product.

It is used prophylactically in the *treatment of angina pectoris.*



Dose : *Usual, initial, 180 mg (of base) per day in 3 divided doses.*

6.1. Mechanism of Action

The mechanism of action of the aforesaid **'drug substances'** shall be described in the section that follows :

6.1.1. Buphenine (Nylidrin Hydrochloride)

It exhibits **β_2-activity** more predominantly for the skeletal muscle. It has been used extensively for the treatment of skeletal muscle with a vasospastic component.

6.1.2. Isoxsupurine

The **'drug'** is a vasodilator that also serves as a stimulator for **β-adrenergic receptors.** It has been found to exert direct relaxation of the vascular as well as uterine smooth muscle. Besides, its vasodilating action seems to be much higher and prominent upon the arteries supplying skeletal muscles in comparison to those supplying to skin. It has also been found to cause positive inotropic as well as chronotropic actions. It is observed to be absorbed adequately from the GI-tract. The peak plasma concentration is attained in approximately 1 hour after oral administration. Isoxsupurine exhibits a plasma half-life of 1.5 hours, and it gets excreted mostly in the urine as conjugates.

6.1.3. Prenylamine

It helps in the gradual depletion of myocardial catecholamine reserves ; besides, possessing certain extent of **Ca^{2+}-channel blocking activity**. Importantly, its administration has been largely associated with the development of ventricular arrythmias along with ECG abnormalities.

Probable Questions for B. Pharm. Examinations

1. Leaves of *Digitalis lanata* gave **two** important cardiac glycosides. Give the structure, chemical name and uses.
2. How would you classify the **'cardiovascular drugs' ?** Support your answer by providing the structure, chemical name and uses of **one** potent compound from each category.
3. Clonidine, hydralazine, methyl dopa and diazoxide and potent **'antihypertensive drugs'** used as cardiovascular drugs. Give the synthesis of any **two** named compounds.
4. Discuss the mode of action of some antihypertensive drugs being employed and **'cardiovascular drugs'.** Give their structures and chemical names.
5. Give a comprehensive account of **'antiarrythmic agents'** used as cardiovascular drugs. Support your answer with at least **one** example from each category.
6. Following are **two** important **'Vasopressor drugs'.**
   (*a*) Isoxsupurine hydrochloride and
   (*b*) Prenylamine lactate.
7. Describe the 'mode and action' of the following class of drugs used as **'cardiovascular drugs'** by citing typical examples :
   (*a*) Anti-arrythmic agents and
   (*b*) Vasopressor drugs
8. Discuss the synthesis of any **one** of the following membrane-stabilizing agents usually employed as **'cardiovascular drugs'.**
   (*a*) Disopyramide phosphate
   (*b*) Procainamide hydrochloride
9. Discuss the Antisympathetic drugs **Propranolol Hydrochloride.** Give its synthesis from alpha naphthol and epichlorohydrin.
10. Discuss the synthesis of Verapamil hydrochloride and describe its mode of action.

RECOMMENDED READINGS

1. DA William and TL Lemke : **Foye's Principle of Medicinal Chemistry**, Lippincott Williams and Wilkins, New York, 5th edn., 2002.
2. DLednicer and L A Mitscher **The Organic Chemistry of Drug Synthesis,** John Wiley and Sons, New York (1995).
3. EF Reynolds (ed.) **Martindale the Extra Pharmacopoeia,** 31st edn., The Pharmaceutical Press London (1997).
4. JH Block and JM Beale : **Wilson and Gisvold's Text book of Organic Medicinal and Pharmaceutical Chemistry,** Lippincott Williams and Wilkins, New York, 11th edn., 2004.
5. LS Goodman and A Gilman **The Pharmacological Basis of Therapeutics,** 9th edn., Macmillan Co. London (1995).
6. MC Griffiths (ed.) **USAN and the USP Dictionary of Drug Names,** United States Pharmacopeial Convention Inc. Rockville, (1985).
7. ME Wolff (ed.) : **Burger's Medicinal Chemistry and Drug Discovery,** 5th edn., John Wiley & Sons Inc., New York, (1995).
8. NV Costrini and W M Thomson **Manual of Medical Therapeutics,** 22nd edn., Little Brown and Co. Boston (1977).

13

Autonomic Drugs

Chapter

13

Autonomic Drugs

1. INTRODUCTION

The drugs which act on the **'autonomic nervous system' (ANS)** and control the vital internal processes which ordinarily, are not under volition, are known as **autonomic drugs**.

Noradrenaline is released particularly at the target organs and ultimately gives rise to the ensuing contraction of the cardiac muscles ; and ultimately an enhancement in the heart rate. Besides, it is also helpful in relaxing the smooth muscles and thereby causes a visible reduction in the contractions of the GI-tract as well as the urinary tract. It also minimises a distinct reduction in salivation and lowers dilatation of the peripheral blood vessels particularly.

Broadly speaking, the sympathetic (autonomic) nervous system aids categorically the *'fight or flight'* response by closing down the body's housekeeping mechanisms, such as : *digestion, defecation, urination* and the like, and thereby stimulating the heart ultimately. It has been observed that the '*adrenal medulla*' eventually helps in the release of the hormone **adrenaline,** that reinforces the action of noradrenaline finally.

It is, however, pertinent to mention here that the effects of autonomic (sympathetic) nervous system activation and, therefore, the effects of sympathomimetic drugs are evaluated mostly by the specific type and ultimately the localization of the post synaptic receptor to which the released neurotransmitter or exogenous sympathomimetic binds finally.

ANS is comprised of *two* divisions, namely : *sympathetic* and *parasympathetic.* Acetylcholine (ACh) invariably acts as a neurotransmitter at both sympathetic and parasympathetic nerve endings, postganglionic nerve fibers in the parasympathetic zone, and certain postganglionic fibers, such as : salivary and sweat glands, in the sympathetic division of **ANS**. Interestingly, **ANS** modulates the different types of activities of both the smooth muscle and the glandular secretions. Generally, all these activities, as a rule, exert their actions much below the level of consciousness, for instance ; *circulation, respiration, body temperature, digestion* and *metabolism.* It is worth while to mention here that the said two functional divisions afford almost contrasting effects upon the internal environment of the human body. Explicitely, the sympathetic division invariably shows its effect as a unit, particularly during conditions of fit, anger or shock (fright), and hence, expends energy. Interestingly, the parasympathetic division is organized for its absolutely localized and discrete discharge and, therefore, not only conserves but also stores energy as a potential reserve in the body.

2. CLASSIFICATION

The **autonomic drugs** may be classified into the following categories, namely :

(*a*) Sympathomimetic Drugs.

(*b*) Antiadrenergic Drugs.

(*c*) Cholinomimetic Drugs.

(*d*) Antimuscarinic Drugs.

(*e*) Ganglionic Blocking Agents.

(*f*) Adrenergic Neurone Blocking Agents.

The above categories of **autonomic drugs** have been treated separately, including typical examples from each group.

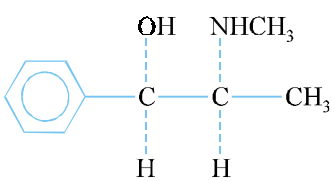
3. SYMPATHOMIMETIC DRUGS

Sympathomimetic drugs usually mimic stimulation of the peripheral endings of the sympathetic or **'adrenergic'** nerves, the action being exerted on the effector cells supplied by postganglionic endings. There is now enough evidence to show that the neurohormone directly concerned with such an action is **noradrenaline**.

It is, however, interesting to observe that a good number of sympathomimetics in fact do not really mimic the actions of noradrenaline or adrenaline at the effector receptor. They merely induce the release of noradrenaline from the sympathetic postganglionic adrenergic nerves. Such sympathomimetics which exert their action indirectly are comparatively less effective in patients treated with noradrenaline depleting drugs, for instance, the **rauwolfia alkaloids,** or other **adrenergic neuron blockers**.

A few important compounds used as **sympathomimetic drugs** are discussed below : **ephedrine : epinephrine; adrenaline; isoprenaline; methoxamine hydrochloride; metarminol bitartrate; naphazoline hydrochloride; oxymetazoline hydrochloride; phenylpropanolamine hydrochloride; xylometazoline hydrochloride, etc**.

A. Ephedrine BAN, USAN,

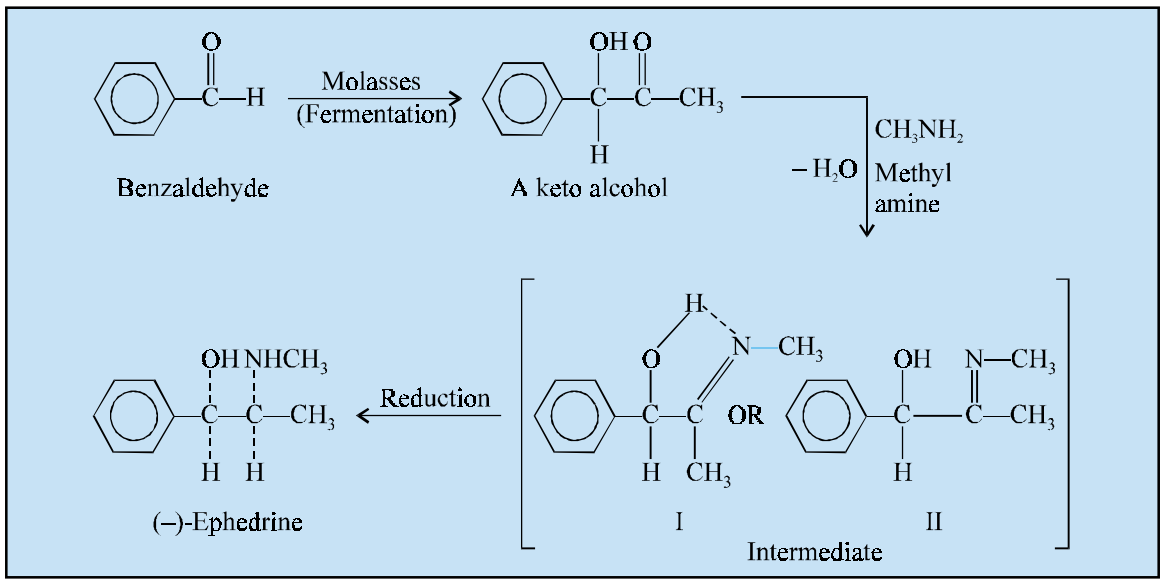


(–)-Ephedrine; Benzenemethanol, α-[1-(methylamino) ethyl)]-*R*-(*R**, *S**)- ; BP ; USP ; Eur. P., Ind. P.

Synthesis :

Nagai first isolated ephedrine in 1887 from a well-known Chinese herb, **ma huang** ; by moistening the powdered drug with either aqueous sodium carbonate or with lime water and subsequently extracting it with ethanol or benzene.

Neuberg's synthetic method is the most ideal one for the commercial production of **ephedrine :**

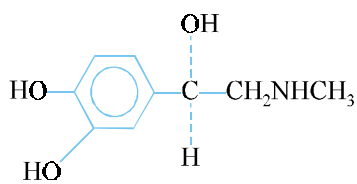


Fermentation of benzaldehyde with either molasses or a mixture of glucose and yeast yields a keto alcohol which on reaction with methyl amine gives rise to an intermediate which may be depicted either as I or II with the loss of a mole of water. This on reduction yields the official compounds.

Ephedrine helps to increase the blood pressure at a therapeutic dose level in *two* different ways ; first by enhancing peripheral vasoconstriction. It is found to exert a stimulant action on the respiratory centre. It shows a wide spectrum of actions, namely : ***reduction in the activity of the uterus, bronchodilatation and lowering of intestinal tone and motility. Ephedrine is also used in postural hypotension and in subjects having more or less complete heart block***.

Dose : *10 to 25 mg every 3 to 4 hours.*

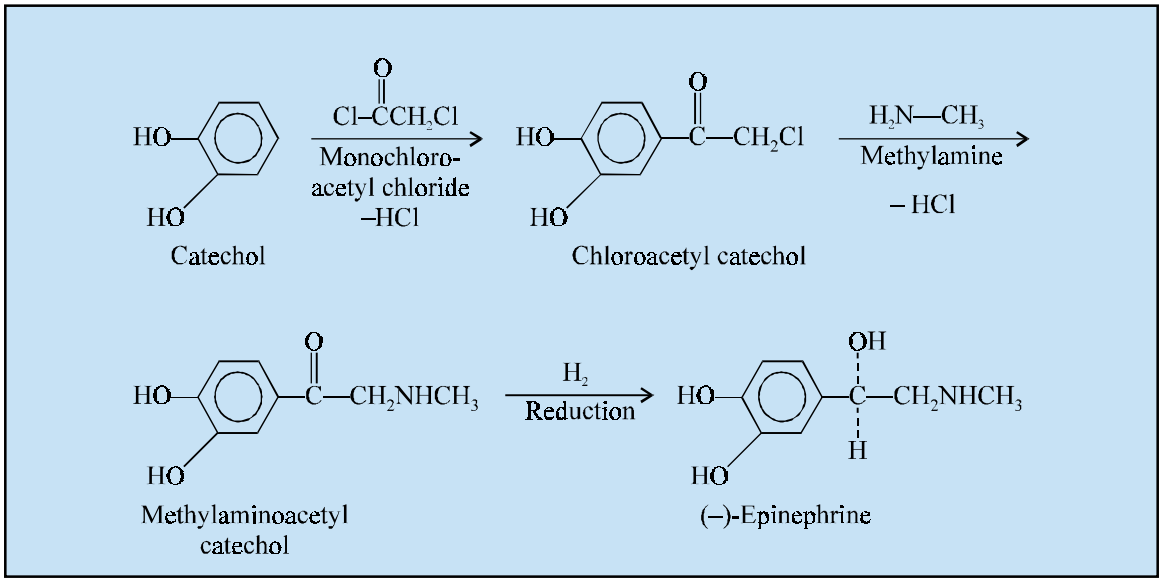
B. Epinephrine INN, USAN ; Adrenaline BAN,



(–)-3, 4-Dihydroxy-α-[(methylamino) methyl] benzyl alcohol ; 1, 2-Benzenediol, 4-[1-hydroxy-2-(methylamino) ethyl]-, (*R*)- ; Epinephrine (USP) ; Adrenaline BP ; Int. P., Ind. P., ; Adrenaline$^{(R)}$ (Parke-Davis).

Synthesis

Abel and Fuerth isolated independently the active principle from the *suprarenal glands* which were later on established as the same compound now known as **adrenaline.** It may be synthesized conveniently by several methods, but a very common process is described under :

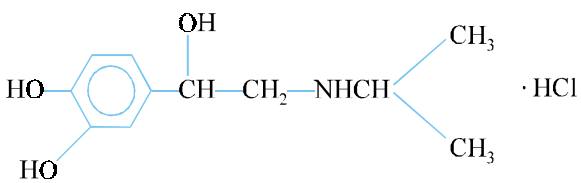


The interaction between **catechol** and **monochloracetyl chloride** gives **chloroacetyl catechol** with the elimination of a mole of hydrogen chloride which on subsequent reaction with methylamine yields **methylaminoacetyl catechol.** This on reduction gives rise to racemic **epinephrine,** which may be resolved conveniently with *d*-tartaric acid.

Epinephrine, the sympathomimetic adrenal hormone, is found to act on smooth muscles, heart and the gland cells thereby causing a similar pattern of actions as may have been produced by the stimulation of the respective adrenergic nerves. Hence, it had been invariably ***used to stimulate the heart, enhances the heart rate, tones up the blood pressure and above all affords relaxation of the musculature of the intestine and bronchi***. It is usually the drug of choice in acute allergic disorders and histamine reactions.

Dose : *Subcutaneous, 0.2 to 0.5 mg in 0.1% solution; intramuscular, 1 to 3 mg in a 0.2% oil suspension, repeated as required.*

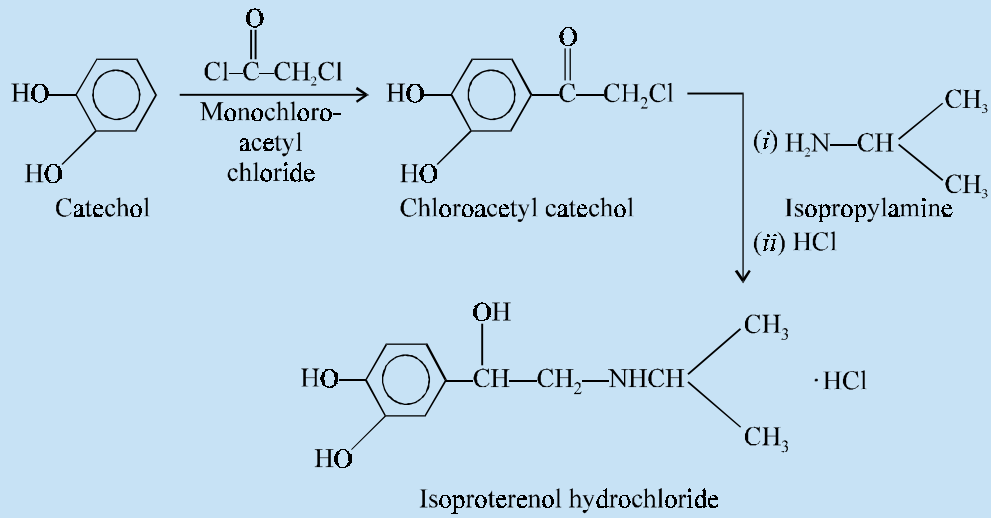
C. Isoprenaline INN, BAN, Isoproterenol Hydrochloride USAN,



3, 4-Dihydroxy-α-[(isopropylamino) methyl] benzyl alcohol hydrochloride ; 1, 2-Benzenediol, 4-[1-hydroxy-2-[(methyl-ethyl)-amino] ethyl]-, hydrochloride ; Isoprenaline Hydrochloride BP; Int. P., Isoproterenol Hydrochloride USP ;

Norisodrine Aerotrol$^{(R)}$ (Abbott) ; Vapo-Iso$^{(R)}$ (Fisons) ;

Synthesis

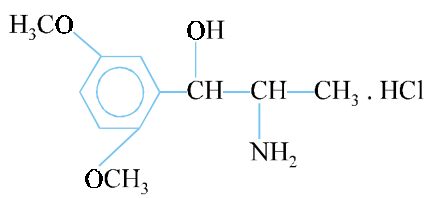


Chloroacetyl catechol may be prepared by the interaction of catechol and monochloroacetyl chloride, which on reaction with isopropylamine and hydrochloric acid yields the official product.

It exerts a stimulating action on the heart thereby enhancing cardiac output, rate and excitability. It is also ***employed in the management and treatment of bradycardia, as a stimulant following cardiac arrest and prevention for attacks of Strokes-Adams Syndrome. It is an effective bronchodilator in asthma.***

Dose : *Sublingual, 10 to 15 mg 3 to 4 times daily; intramuscular or subcutaneous, 0.01 to 0.2 mg; repeated as necessary; infusion, 1 to 2 mg per 500 ml of 5% dextrose infusion at such a rate so as to maintain blood pressure.*

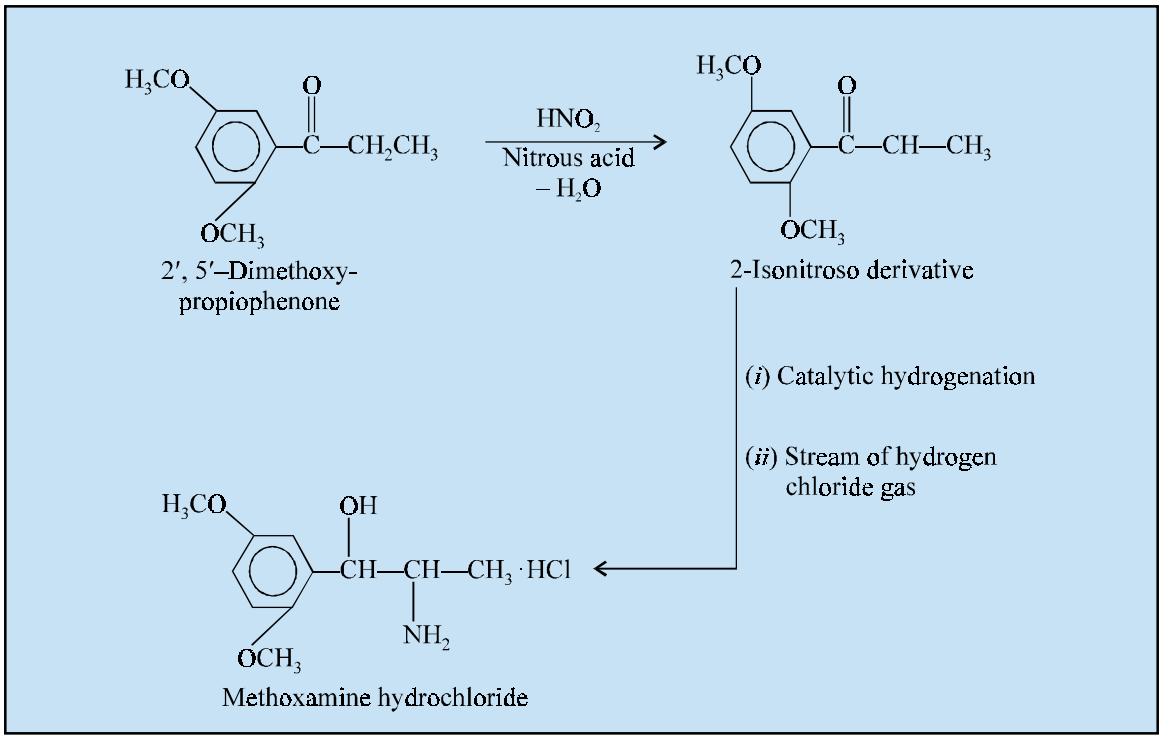
D. Methoxamine INN, BAN, Methoxamine Hydrochloride USAN,



(±)-α-(1-Aminoethyl)-2, 5-dimethoxybenzyl alcohol hydrochloride ; Benzene-methanol, α-(1-aminoethyl)-2, 5-dimethoxy-, hydrochloride ; Methoxamedrine Hydrochloride : BP ; USP ; Int. P. ; Vasoxyl$^{(R)}$ (Burroughs Wellcome).

Synthesis

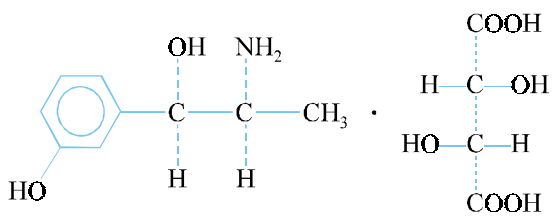
The reaction of 2′, 5′-dimethoxypropiophenone with nitrous acid gives the corresponding 2-isonitroso derivative, which on catalytic hydrogenation, *first* reduces the keto function, and *secondly* converts the nitroso group into an amino function. The methoxamine base when dissolved in an appropriate solvent and subjected to a stream of hydrogen chloride gas yields the official compound.



Methoxamine hydrochloride affords an increase in arterial blood perssure through peripheral vasoconstriction. It is the drug of choice for the treatment of hypotensive conditions when it is required to boost-up blood pressure without any cardiac stimulation.

Dose : *Usual, intramuscular, 5 to 20 mg ; intravenous, 3 to 10 mg administered slowly in divided doses.*

E. Metaraminol INN, BAN, Metaraminol Bitartrate USAN,



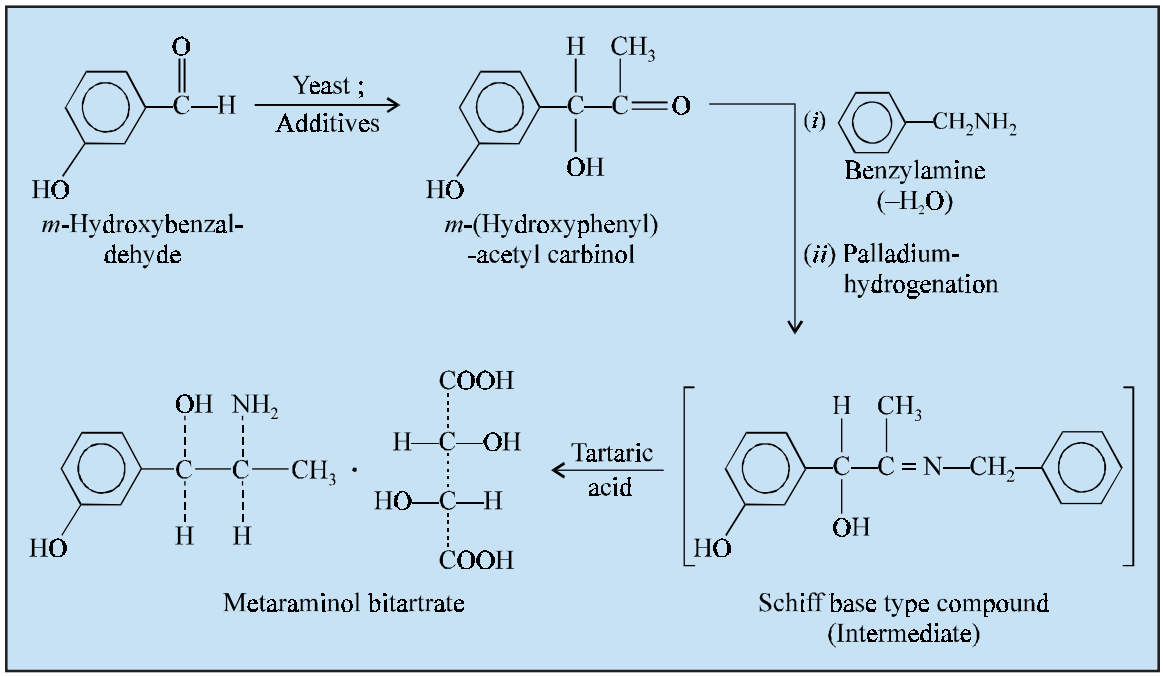
(–)-α-(1-Aminoethyl)-*m*-hydroxybenzyl alcohol tartrate (1 : 1) ; 1-*m*-Hydroxy-norphedrine Bitartrate ; Metaraminol Tartrate B.P., Metaraminol Bitartrate U.S.P. ;

Aramine(R) (Merck).

Synthesis

m-(Hydroxyphenyl) acetyl carbinol is obtained by the fermentation of *m*-hydroxy benzaldehyde in the presence of yeast and a few additives, which on subsequent treatment with benzyl amine followed by hydrogenation with palladium yields an intermediate which is considered to be a **Schiff's Base type**

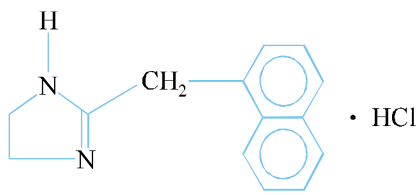
compound. This product undergoes cleavage at NH-CH_2, the hydrogenated residue of C—N linkage, to result the desired metaraminol base which on treatment with an equimolar proportion of tartaric acid in an alcoholic medium gives the official compound.



It enhances cardiac output, peripheral resistance, and blood pressure. It helps to increase the coronary blood flow thereby decreasing the heart-rate. The drug is *employed frequently in actue hypotensive states such as anaphylactic shock or shock secondary to myocardial infraction and trauma.*

Dose : *Intravenous, 0.5 to 5 mg in an emergency ; by infusion, 15 to 100 mg/500 ml of dextrose injection or sodium chloride injection ; intramuscular, 2 to 12 mg.*

F. Naphazoline INN, BAN, Naphazoline Hydrochloride USAN,

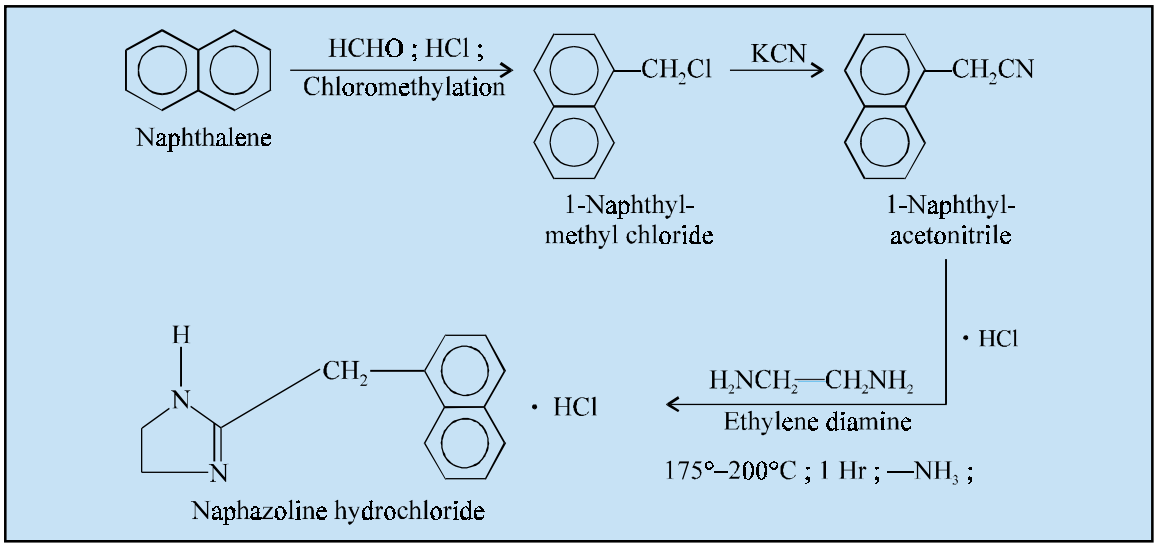


2-(1-Naphthylmethyl)-2-imidazoline monohydrochloride; 1H-Imidazole, 4, 5-dihydro-2-(1-naphthylmethyl)-, monohydrochloride; BP; (1968), USP;

Clear Eyes(R) (Abbott); Privine Hydrochloride(R) (Ciba-Geigy).

Synthesis

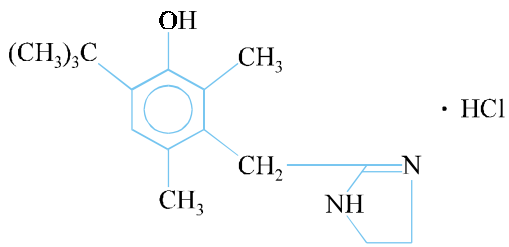
Chloromethylation of naphthalene with formaldehyde and hydrogen chloride yields 1-naphthyl methyl chloride, which on reaction with KCN gives 1-naphthyl acetonitrile. This product on condensation with ethylene diamine monohydrochloride between 175–200°C for 1 hour yields the desired official compound with the elimination of a mole of ammonia.



It is a directly acting sympathomimetic drug which is mostly *used as a local vasoconstrictor for the relief of nasal congestion due to allergic or infectious manifestations. It is also employed as an ophthalmic solution for the relief of ocular congestion and blepharospasm.*

Dose : *For nasal mucosa, 2 drops of 0.05% solution; for conjunctivita, 1 to 2 drops of a 0.1% solution after every 3 to 4 hours.*

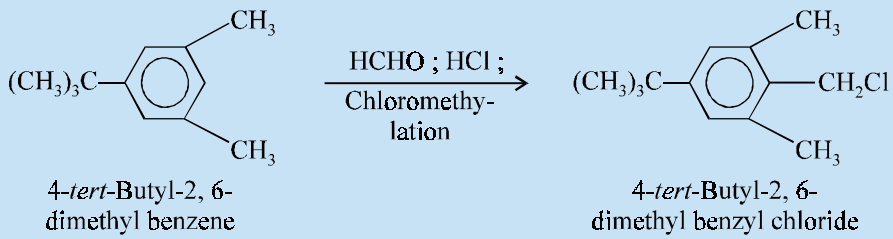
G. Oxymetazoline INN, BAN, Oxymetazoline Hydrochloride USAN,



6-*tert*-Butyl-3-(2-imidazolin-2-ylmethyl)-2, 4-dimethylphenol monohydrochloride; 2-(4-*tert*-Butyl-3-hydroxy-2, 6-dimethyl-benzyl)-2-imidazoline hydrochloride; USP;

Daricon(R) (Pfizer) ; Iliadin-Mini(R) (E. Merck, U.K.).

Synthesis



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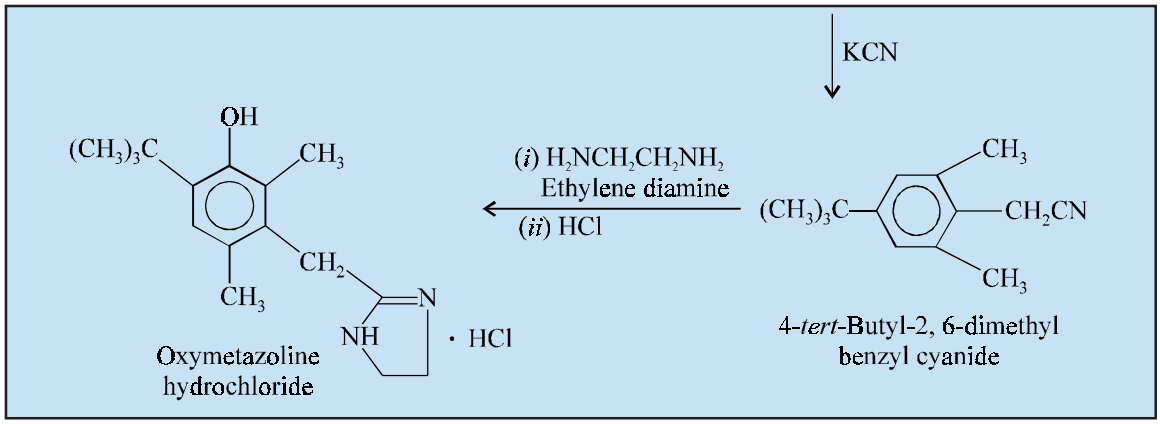
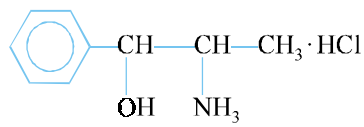


4-*tert*-Butyl-2, 6-dimethyl benzyl cyanide may be obtained by the chloromethylation of *4-tert*-butyl-2, 6-dimethyl benzene and treating this with KCN. The resulting product is reacted with ethylenediamine and the base thus obtained gives readily the official compound with an equimolar quantity of HCl.

It is employed exclusively topically to *decongest the nasopharyngeal membranes in sinusitis, rhinitis and otitis media. Its on-set of action is several minutes but its action lasts up to several hours.*

Dose : *Intranasal, 2 to 4 drops of a 0.05% solution.*

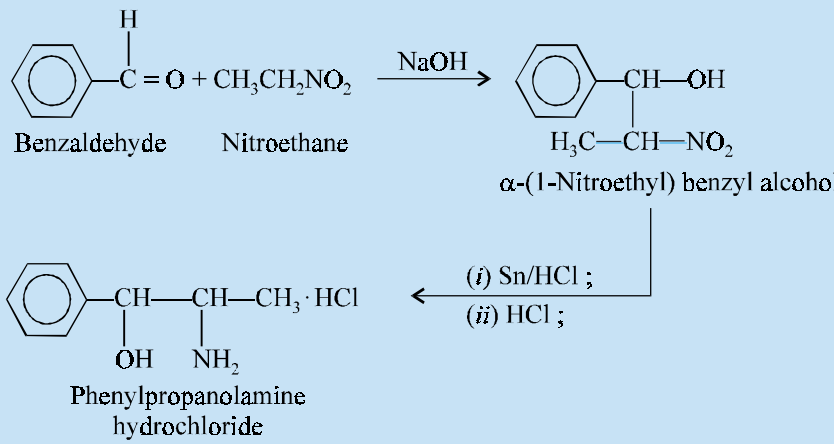
H. Phenylpropanolamine BAN, Phenylpropanolamine Hydrochloride USAN,



(±)-Norephedrine hydrochloride; Benzenemethanol, α-(1-amino-ethyl)-, hydrochloride, (R^*, S^*)-, (±) ; (±)-2-Amino-1-phenyl-propan-1-ol hydro-chloride ; BP ; USP ;

Propadrine Hydrochloride(R) (MSD).

Synthesis

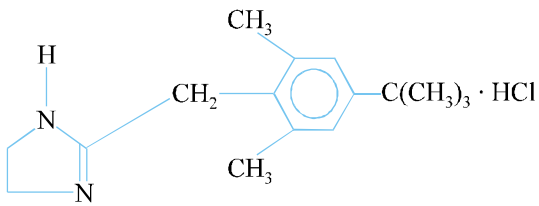


α-(1-Nitroethyl) benzyl alcohol is obtained by the interaction of benzaldehyde and nitroethane in the presence of sodium hydroxide. This product when subjected to reduction in the presence of tin and hydrochloric acid, followed by dissolution of the phenylpropanolamine base in an appropriate solvent and passing a stream of HCl gas yields the final product.

It is administered orally for the symptomatic relief of nasal congestion. It has also been used for the reduction of appetite and to monitor urinary incontinence. It also finds its use as a bronchodilator and bronchial decongestant in asthma.

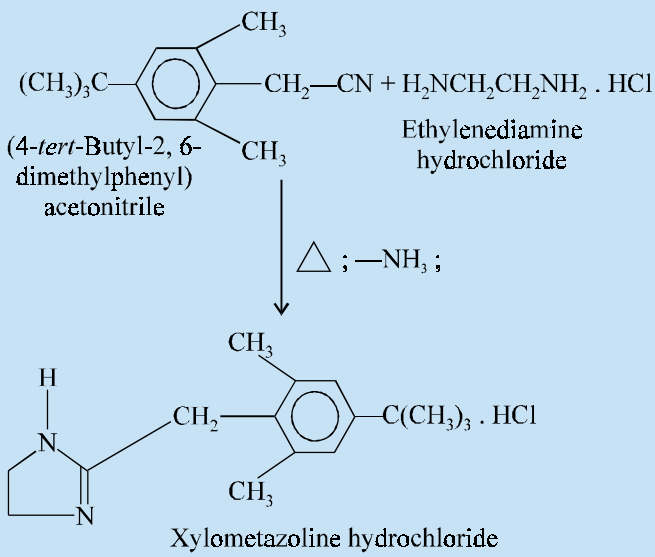
Dose : *Usual, oral, 25 to 30 mg three or four times per day; Topical, 0.1 to 3% aqueous solution.*

I. Xylometazoline INN, BAN, Xylometazoline Hydrochloride USAN,



2-(4-*tert*-Butyl-2, 6-dimethylbenzyl)-2-imidazoline monohydrochloride; 1H-Imidazole, 2-[[4-(1, 1-dimethylethyl)-2, 6-dimethylphenyl] methyl]-4, 5-dihydro-, monohydrochloride ; BP ; USP ; Otrivin Hydrochloride(R) (Ciba-Geigy).

Synthesis



It may be prepared by the interaction of (4-*tert*-butyl-2, 6-dimethyl-phenyl) acetonitrile with ethylenediamine hydrochloride at an elevated temperature with the loss of a mole of ammonia.

It is frequently employed as a *local vasoconstrictor for nasal congestion caused by sinusitis or rhinitis.*

Dose : *Intranasal, 1 drop of a 0.1% solution in adult; or a spray of 0.05% solution.*

3.1. Mechanism of Action

The mechanism of action of certain **'sympathomimetic drugs'** discussed under section 12.3 are dealt with in the sections that follows :

3.1.1. Ephedrine

The **'drug'** acts as a direct and indirect agonist *i.e.*, it helps in the release of **norepinephrine**. Besides, it also exerts CNS-stimulatory actions. It has been observed that the ephedrine stereoisomer having essentially the (1R, 2S) absolute configuration exhibits direct activity on the receptors, both α and β, as well as an indirect component. It is worthwhile to state here that the (1S, 2R) entantiomer has primarily an indirect activity.

3.1.2. Epinephrine

The '**drug**' happens to be predominant endogenous **catecholamine** released from the adrenal medulla in response to autonomic (sympathetic) nervous system **(ANS)** activation. It is believed that epinephrine acts on all the **α- and β-receptors,** although the affinity of **β-receptors** for it is found to be much higher as compared to the affinity of the α-receptors for **epinephrine**. As a result, with the administration of relatively low doses amalgamated with slow rates of infusion, **epinephrine** may minimise diastolic blood pressure by virtue of **β_2-receptor-regulated vasodilation** and a corresponding enhancement of heart rate through the **activation of β_1-receptors**. Besides, the systolic blood pressure may have been enhanced on account of enhanced cardiac output. Furthermore, it has been observed that with regular increment in doses, α_1-regulated vasoconstriction occurs promptly, having an overall net enhancement in vascular resistance followed by blood pressure.

3.1.3. Isoprenaline (Isoproterenol Hydrochloride)

Isoproterenol hydrochloride undergoes appreciable *o*-methylation by the aid of **catechol-*o*-methyl transferase (COMT)** in the humans. One may also observe a striking and pronounced identical structural features between **isoprenaline** and the endogenous **catecholamines**, namely : **dopamine** and **norepinephrine (NE)**.

It is a prototypic, non selective **β-agonist** invariably employed to stimulate heart rate in heart block, bradycardia, and *torsades de pointes.*

3.1.4. Methoxamine

The **'drug'** is a direct-acting **α_1-agonist** having a rather rapid and comparatively longer pressor action. It is found to possess certain extent of **β-receptor-blocking pharmacological characteristic features.** In fact, it gives rise to bradycardia, largely due to a reflex activation of the strategically located vagus nerve secondary to the increased blood pressure. It is invariably employed for the control and management of **critical hypotensive states** specifically when it is absolutely necessary to raise the blood pressure without causing any degree of cardiac stimulation. It is, however, pertinent to state here that this **'drug'** has very little effect upon the *capacitance veins* in particular, so as to accomplish a reasonable compromise with its usefulness, especially in the treatment of various types of shock. The reflex bradycardia produced by **methoxamine** is used juidiciously to terminate effectively *paroxysmal supraventricular tachycardia.* Besides, it is found to have very little effect on the bronchial muscles, thereby affording neither any central stimulation nor an enhancement of the irritability of the **anaesthetized-sensitized heart**.

3.1.5. Metaraminol

The **'drug'** essentially has the characteristic features, such as : *meta*—OH of a catechol, an α-CH_3 of an amphetamine, and the attenuating (3-OH for attributing the classic sympathomimetic activity. Thus, an overall pressor activity is predicted gainfully. It has an ability to enter the neuronal vescicles followed by displacement of NE gives rise to an indirect activity. Besides, it is also observed to stimulate the **α-adrenoreceptors** directly. Indeed, both of these activities are absolutely necessary for the pressor activity.

3.1.6. Naphazoline

The **'drug'** essentially has an imidazole nucleus and exhibits **peripheral α-adrenoceptor stimulant characteristic features ;** however, surprisingly no β-effects have been observed. Importantly, very much in contrast with other several direct and indiect agonists, there is no appreciable neuronal uptake mechanism involved. It is found to exert major action as decongestants upon the nasal mucosa particularly in addition to ocular membranes. It is, however, pertinent to mention here that a certain extent of α_2 central stimulation most likely puts forward a plausible explanation with regard to a certain degree of sedation encountered by this drug substance.

3.1.7. Phenylpropanolamine (PPA)

It is employed frequently as a nasopharynegeal and bronchial decongestant. It also finds its usage in the treatment of urinary incontinence and retrograde ejaculation. One may accomplish a partial success in the moderate release of histamine by coadministering sympathomimetic decongestant agents, for instance : **ephedrines** and **PPA,** that might relieve both nasal congestion as well as counteract drowsiness to a certain degree by virtue of their inherent CNS stimulant side effects.

3.1.8. Xylometazoline

It is a potent sympathomimetic agent having marked and pronounced α-adrenergic pharmacologic profile. However, it is found to act as a vasoconstrictor when applied topically to mucous membranes particularly ; and, therefore, retards both swelling and congestion to a considerable degree.

3.2. Structure Activity Relationships (SARs)

The **SARs** of the **sympathomimetic drugs** are as enumerated under :

(*i*) Aliphatic amines longer than *n*-butylamine [CH_3 $(CH_2)_3$] prove to be adequate for pressor activity.

(*ii*) Introduction of aromatic rings significantly increase potency.

(*iii*) Presence of one —OH group at C-3 or C-4 of the aromatic rings enhances vasoconstrictor activity, *e.g.*, metraminol bitartrate, oxymetazoline hydrochloride.

(*iv*) Introduction of two —OH groups at C-3 and C-4 invariably enhance the tendency to induce vasodilation in the presence of other preferred molecular substituents, *e.g.*, **adrenaline, isoprenaline hydrochloride,** etc.

(*v*) N-substituents favour vasodilation, *e.g.*, **epinephrine (—CH_3) ; isoprenaline** [**–$CH(CH_3)_2$**].

(*vi*) Enzymatic degradation of the drug molecule may be prevented by affording substitution on the side chain immediately adjacent to the amino function *e.g.*, **methoxamine hydrochloride, isoprenaline hydrochloride.** Such an innovation also accomplishes prolonged duration of action along with oral efficacy.

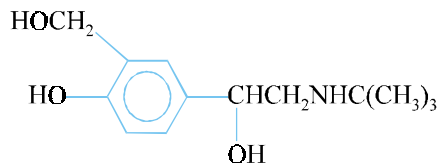
4. BETA ADRENERGIC RECEPTOR STIMULANTS

As stated earlier there are two types of beta-receptors, *viz :* **β_1 and β_2. Agents** that stimulates β_2-receptors selectively are very effective in relaxing the smooth muscles of the bronchi and uterus. They are, therefore, useful in asthma and in the management of uncomplicated premature labour in the trimester of pregnancy.

These are also known as the **β-adrenergic receptor agonists**.

A few typical examples are as stated below : **Salbutamol; Terbutaline; Pirbuterol hydrochloride; Salmetrol xinafoate;**

A. Salbutamol INN, BAN, Albuterol USAN,



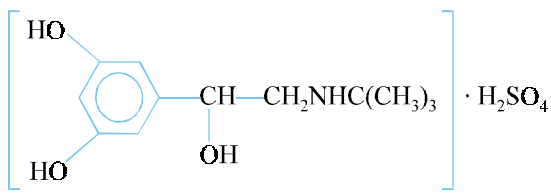
1, 3-Benzenedimethanol, α′-[[(1, 1-dimethylethyl) amino] methyl]-4-hydroxy-; α′-[(*tert*-Butylamino) methyl]-4-hydroxy-*m*-xylene-α-α′-diol ; BP ;

Ventolin Inhaler(R) (Glaxo, Inc.).

Salbutamol is used as *a bronchodilator.* Its bronchodilating property being relatively more marked and pronounced than its effect on the heart.

Dose : *Oral, inhalation, adult, 100 mcg, followed by a second dose after 5 minutes, if required.*

B. Terbutaline USAN ;

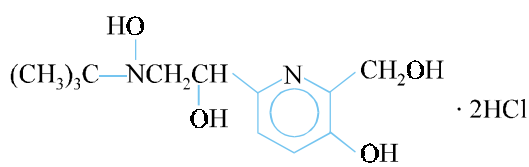


1, 3-Benzenediol, 5-[2-[(1, 1-dimethylethyl) amino]-1-hydroxy-ethyl]- ;

Bricanyl(R); Brethaire(R);

It is used for treating premature labour. It in indicated parenterally for the emergency treatment of *status asthmaticus*.

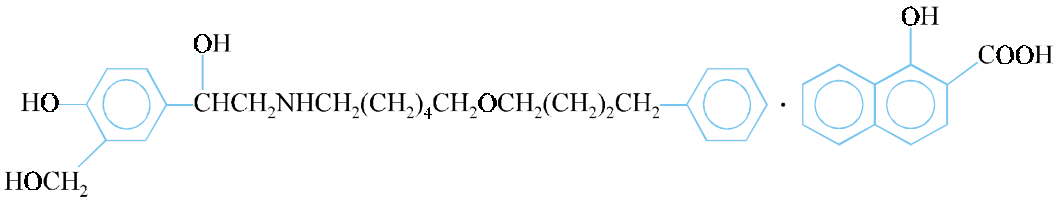
C. Pirbuterol Hydrochloride USAN;



2, 6-Pyridine dimethanol, α^6-[[(1, 1-dimethylethyl) amino] methyl]-3-hydroxy-, hydrochloride, Maxair$^{(R)}$;

It is employed as a **β_2-selective bronchodilator**.

D. Salmetrol Xinafoate USAN ;



1, 3-Benzenedimethanol, (±)-4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl] amino]-methyl-, 1-hydroxy-2-naphthalenecarboxylate (salt) ;

Serevent$^{(R)}$;

It is invariably used as a rather more lipophilic **β_2 agonist** recommended for long-term *bid* maintenance treatment of asthma; it has a duration of action even after inhalation of 12 hr.

4.1. Mechanism of Action

The possible **mechanism of action** of these drugs shall be described as under :

4.1.1. Salbutamol (Albuterol)

It is a **direct-acting sympathomimetic agent** with predominantly **β-adrenergic activity** together with a very selective action on the **β_2-receptors** (*i.e.*, **β_2-agonist**). It is pertinent to emphasize here that this preferential activity for the specific **β_2-receptor** stimulation gives rise to its spectacular bronchodilating action being comparatively more marked and pronounced than its effect on the heart in particular.

4.1.2. Terbutaline

The **'drug'** exhibits a direct-acting sympathomimetic agent having predominantly β-adrenergic activity plus a selective action on the **β_2-receptors** (*i.e.*, **(β_2-agonist)**. This is, therefore, recommended for the treatment of severe and acute forms of bronchospasm *via* IM, IV, sub-cutaneous routes.

4.1.3. Pirbuterol Hydrochloride

It is closely related structurally to **salbutamol,** the only difference being that the former has a basic-pyridine nucleus while the latter has a benzene ring (nucleus). It is also a direct-acting sympathomimetic agent having a most prominent **β-adrenoreceptor** stimulant action, and a selective action on **β_2-receptors**.

4.1.4. Salmetrol Xinafoate

Its mechanism of action is very much akin to **salbutamol, terbutaline** and **pirbuterol**.

5. ADRENERGIC RECEPTOR BLOCKING AGENTS

Adrenergic receptor blocking agents are broadly sub-divided into *two* heads, namely :

5.1. α-Adrenoceptor Blocking Agents

They usually exert a generalised direct vasodilator effect on all muscular walled vessels. They are found to reduce vasoconstriction and enhance tissue perfusion. They are also termed as either **α-adrenoreceptor antagonists or nonselective α-antagonists**.

However, it has been observed that the blockade of **α_1-adrenoreceptors** invariably produces prompt apparent actions ; whereas the blockade of **α_2-receptors** gives rise to rather subtle effects.

Effects of α_1-Antagonism. The various effects are as follows :

(*a*) The impulses to the arterioles minimises vascular resistance appreciably, which consequently tends to reduce blood pressure, produce a pink-warm skin, ptosis, and nasal, scleroconjunctival congestion.

(*b*) It not only enhances venous capacitance at the 'capacitance vessels (*i.e.*, venules) that essentially necessites fluids-loading, but also gives rise to postural hypotension.

(*c*) It produces mild to moderate miosis and serious interference with ejaculation (sexual debility).

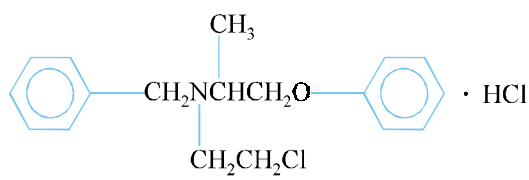
(*d*) It causes *palpitations*, *tachycardia*, and enhanced *secretion of renin.*

Note. The actions depicted in (d) above are essentially caused due to β_1-adrenoreceptor responses which are obviously not suppressable by α-blockade.

(*e*) It is now well established that there exists a simultaneous enhanced quantum of norepinephrine (NE) released from the adrenergic nerve-endings (*i.e.*, the transmitter **'overflow'**) on account of concurrent blockade of **α_2-adrenoreceptors** that subsequently affords a negative-feedback mechanism thereby to lower the release of transmitter significantly. As a result, *tachycardia, palpitations* and enhancement of **plasma-renin-levels** may take place even when BP falls to a very little extent. Furthermore, the aforesaid overflow/reflex actions are, in reality, counter productive with respect to the broad-spectrum applications of **non-selective α-blocking drugs**.

Only *three* non selective α-adreno receptor antagonists, such as : **phenoxybenzamine, phentolamine** and **tolazoline,** are presently being used in the US. These drugs shall now be discussed below :

A. Phenoxybenzamine INN, BAN, Phenoxybenzamine Hydrochloride USAN,

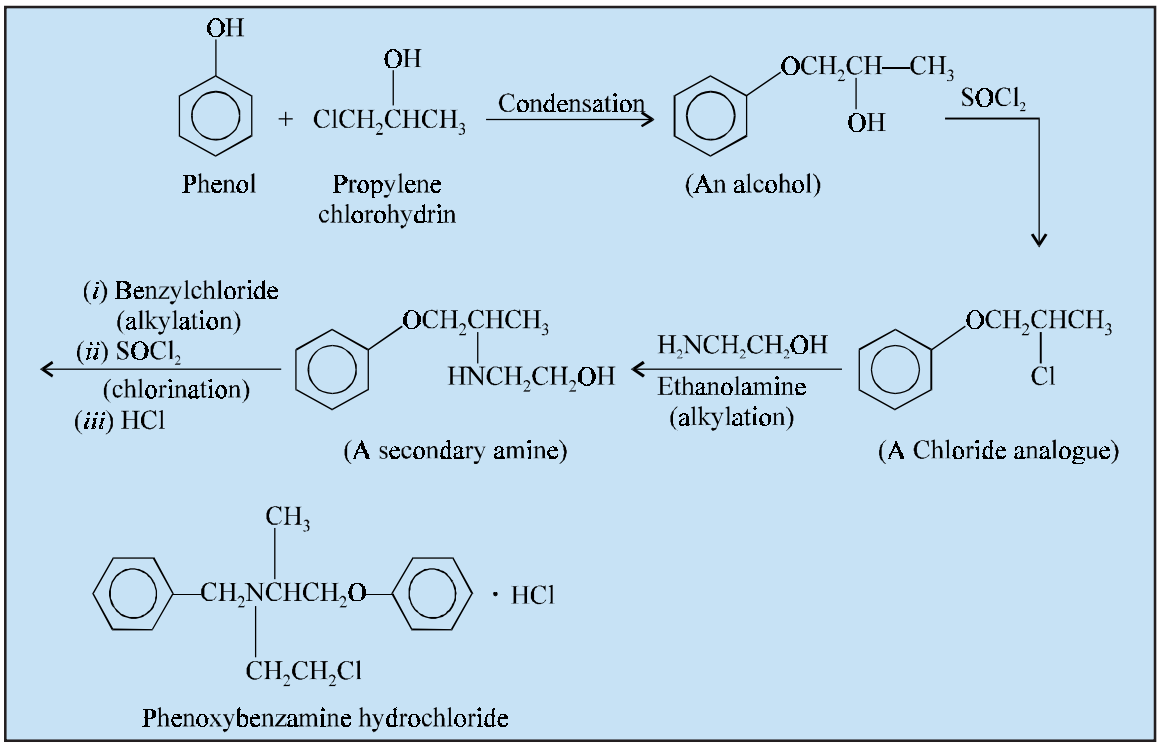


N-(2-Chloroethyl)-N-(1-methyl-2-phenoxyethyl)-benzylamine hydrochloride; Benzenemethanamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-, hydrochloride ; SKF 688A ; USP Dibenzyline$^{(R)}$ (Smith Kline and French).

Synthesis

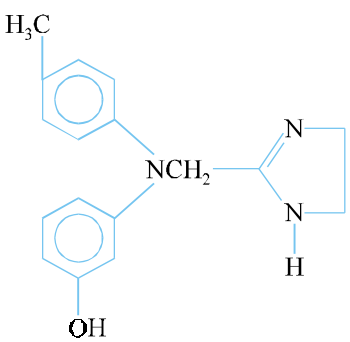
Condensation of phenol with propylene chlorohydrin gives an alcohol which upon treatment with thionyl chloride yields the corresponding chloride. This on alkylation with enthanolamine affords a secondary amine which on treatment with benzyl chloride followed by chlorination and lastly with hydrochloric acid yields the official compound.

It is a potent **alpha-adrenoceptor (α_1 and α_2) blocking agent** with a prolonged duration of action. **Phenoxybenzamine hydrochloride** has been *employed intravenously in the treatment of shock. It also finds its application in the treatment of pulmonary oedema.*



Dose : *Usual, initial, 10 mg per day, increased gradually to 60 mg per day in divided doses.*

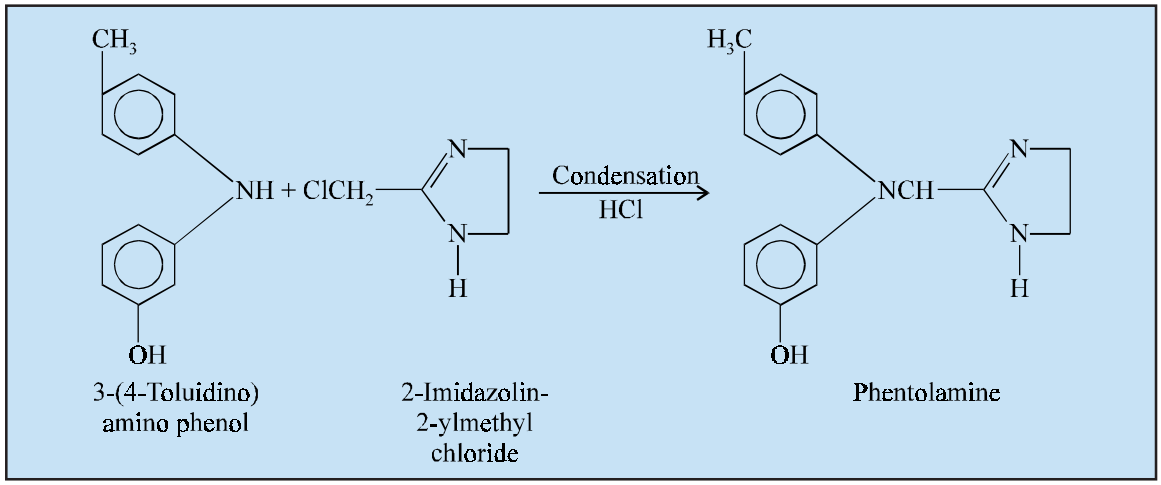
B. Phentolmine INN, Phentolamine Hydrochloride BAN,



3-[N-(2-Imidazolin-2-ylmethyl)-*p*-toluidino] phenol hydrochloride; BP, (1963), USP, Int. P.; Regitin(R) (Ciba, U.K.).

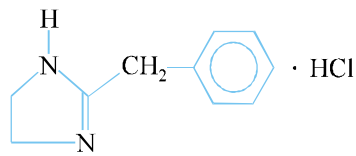
Synthesis

Phentolamine may be prepared by the condensation of 3-(4-toluidino) amino phenol and 2-imidazolin-2-ylmethyl chloride with the elimination of a mole of hydrogen chloride.



It is a short-acting α-adrenoceptor blocking agent which also possesses an overall direct vasolidator effect on all muscular walled vessels. *It is of great value as an adjunct in treatment of shock or heart failure.*

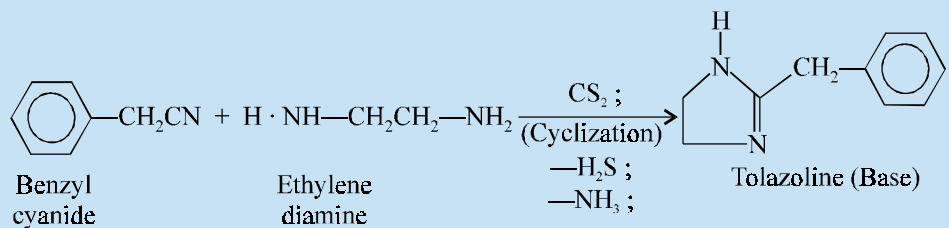
C. Tolazoline Hydrochloride USAN,



1 *H*-Imidazole, 4, 5-dihydro-2-(phenylmethyl)-monohydrochloride ;

Priscoline$^{(R)}$ (Ciba-Geigy).

Synthesis



The reaction between a mole each of benzyl cyanide and ethylene diamine in the presence of carbon disulphide as a medium gives rise to the formation of the desired **tolazoline (base)** through cyclization; and subsequent elimination of a mole each of hydrogen sulphide and ammonia that are liberated from the reaction mixture. The base thus obtained is treated with a HCl in molar concentration to obtain the corresponding salt.

It is mostly used as a vasodilator with **α-adrenergic blocking activity** and direct vasodilator actions. It exhibits a sympathomimetic effect to stimulate the heart, in doing so the BP sometimes gets increased moderately, despite vasodilation. It is found to be an effective α_2-antagonist having a free

access to the CNS; and, therefore, it has been employed efficaciously to antagonize the overdoses of clonidine besides other centrally acting **α_2-agonists**.

5.1.1. Mechanism of Action

The mechanism of action of the *three* aforesaid drug substances shall now be discussed in the sections that follows :

5.1.1.1. Phenoxybenzamine Hydrochloride

The **'drug'** exerts a quite unpredictable effectiveness and thereby produces an unduly excessive tachycardia ; besides, causing orthostatic hypotension in patients having essential hypertension because of its apparent competitiveness with newer breed of drugs. As an adjuvant with a **β-antagonist** it is specifically beneficial in the control and management of *inoperable pheochromocytoma** by virtue of its prolonged duration of action.

5.1.1.2. Phentolamine Hydrochloride

The **'drug'** is a non selective α-adrenoreceptor antagonist; and the blockade caused is reversible. Besides, exhibiting α-blocking activity it possesses a plethora of other pharmacological actions, namely :

- Mild to moderate sympathomimetic-like mydriatic as well as **'cardiostimulant'** (*viz*., rate, force of contraction and dysrythmias) activity,
- Weak **muscarinic activity** in the GI-tract, and weak to mild *histaminergic activity* in the stomach (*viz*., acid secretion), and
- Flushing and slight fall in BP due to **arterioles**.

5.1.1.3. Tolazoline Hydrochloride

Interestingly, **tolazoline** distinctly possesses a histamine-like effect to cause stimulation of the gastric secretion; and also on ACh-like activity to enhance GI-motility. It is also observed to produce mydriasis by means of a definite sympathomimetic action. It is found to be an excellent and effective **α_2-antagonist** having an easy access to the CNS; and, therefore, has been used judiciously to negate (antagonize) overdoses of clonidine and a host of other **centrally acting α_2-agonists**.

5.2. β-Adrenoceptor Blocking Agents

β-Adrenoceptor blocking agents or **antagonists** usually inhibit the actions of catecholamines at the β-adrenergic receptor sites competitively. They are also frequently termed as **β-adrenoreceptor** or **β-adrenergic blocking agents**. These agents normally retard the cardiac activity by preventing β-adrenoceptor stimulation. The effect on the heart may be viewed through different angles, *viz* : minimising its rate and force of contraction, reducing its reaction to stress and exercise and lastly, reducing the rate of conduction of impulses through the conducting system. All these remarkable characteristics are vital for their numerous applications in the therapeutic armamentarium, *e.g.*, in the treatment of angina pectoris and cardiac arrhythmias. These are also used in the control and treatment of hypertension.

The **β-adrenoceptor blocking agents** (or **β-blockers**) have received an overwhelming cognizance in the therapeutic armamentarium in the past four decades that they have been judiciously classified into the following *three* categories, namely :

*A chromaffin cell tumour of the sympathoadrenal system that produces catecholamines (*i.e.*, **EP** = epinephrine ; and **NE** = norepinephrine).

(*i*) First-generation β-blockers,

(*ii*) Second-geneartion β-blockers, and

(*iii*) Third-generation β-blockers.

These *three* specific types of β-blockers shall now be treated individually in the sections that follows :

5.2.1. First Generation β-Blockers

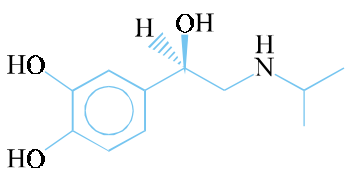
The first main objective towards the exploratory development of these agents was to accomplish selectivity for **β-receptors** with respect to α-receptors.

Salient Features for the Development of Propranolol

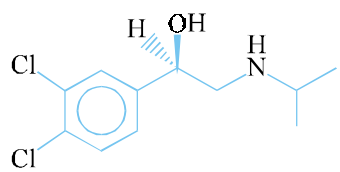
The various stages that were essentially followed in a sequential manner for the development of propranolol, a predominant candidate drug of this category are as stated under :

(1) **Isoprenaline [I]** (see section 12.3.C) was specifically picked up as the '**lead compound**', which was proved to be an **'agonist'*** and not an **'antagonist'**,** besides, being active at β-*receptors* and not α-*receptors*. Interestingly, the cardinal objective was to take advantage of the inherent specificity on one hand, and to modify the molecule meticulously to convert it from an **'agonist'** to an **'antagonist'** on the other.

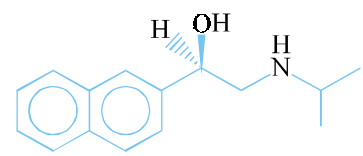
(2) **'Phenolic functional moieties'** are found to be absolutely necessary for the **'agonist activity'**-profile. Nevertheless, it does not imply that the **'phenolic groups'** are essential for antagonist activity, because antagonists mostly block receptors by binding in different manners from the agonist. Thus, the two phenolic functions in isoprenaline were skilfully replaced by chloro-functions to yield **dichloro-isoprenaline (DCI) [II]**, which proved to be a **'partial agonist'**. **Compound [II]** was capable of blocking the binding ability to the **'natural messangers'.** Thus, it could be regarded as an antagonist because it lowered the adrenergic activity appreciably.



[I]



[II]



[III]

Partial β-Agonists-Development

(3) The next vital and crucial step was to get rid of the partial agonist activity.

Medicinal chemists usually convert an **'agonist'** into an **'antagonist'** by introducing an additional **'aromatic ring'** *i.e.*, changing benzene with a naphthyl ring. The said proposed modification invariably give rise to an altogether different induced fit existing between the **ligand** and the **binding site**—, thereby without activating the receptor. Thus, the two adjacent **'chloro functional moieties'** of [II] were removed and an additional benzene ring introduced to obtain **pronethalol** [III]. Compound [III] was still acted as a partial agonist, but ultimately recognized as the very first and foremost

*Drugs that mimic the body's own regulatory function are known as **'agonist'**.

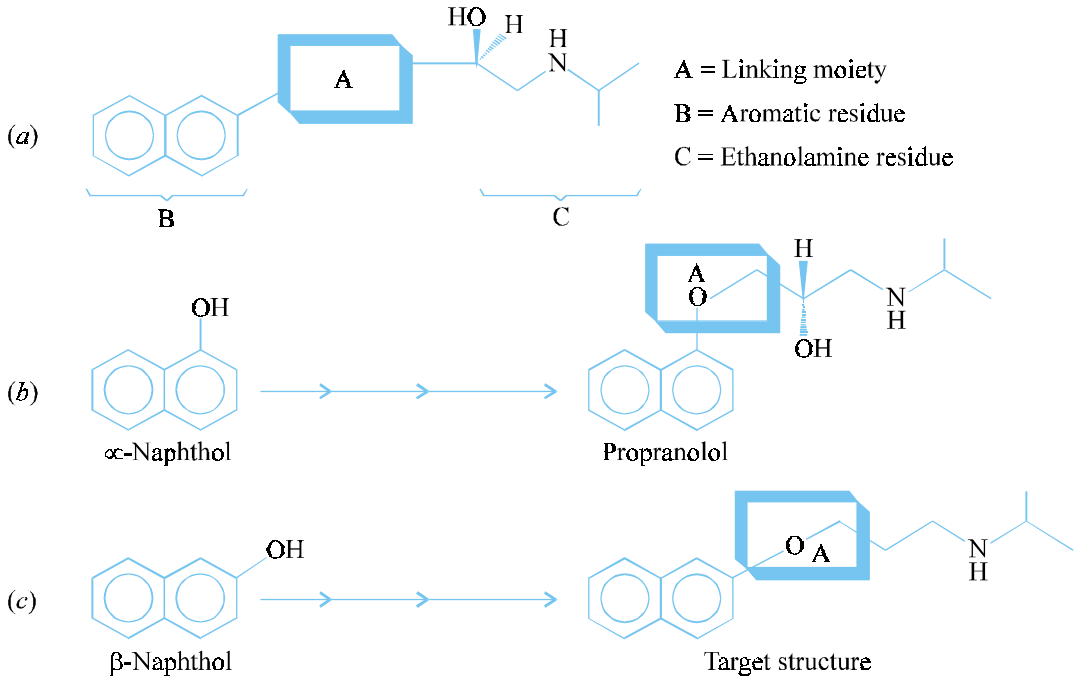
**That which counteracts the action of something else *e.g.*, drug substance.

β-blocker to be employed profusely as an wonderful drug for the control, management and treatment of angina, high BP, and arrythmias.

(4) Further structural modifications were carried out with respect to :

- Extension of the chain-length,
- Connection of the aromatic ring, and
- Joining to the amine function.

As evidenced profusely in the literature most of the **'drug discoveries'** were more or less accidental. The same was the fate in the synthesis of **propranolol**, for which α-naphthol was used in the reaction mixture instead of the β-naphthol, as the latter was not readily available in the laboratory to arrive at the predetermined **'target structure'** as illustrated below :



Explanations :

(*a*) It vividly displays the academic as well as the professional challenge adopted usually by the **'medicinal chemist'** in the accomplishment of **chain extension**.

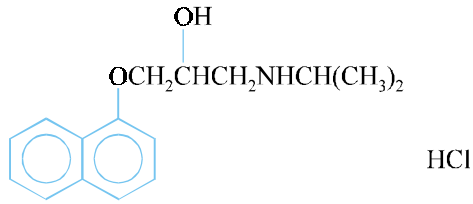
(*b*) **Propranolol** was synthesized by using α-naphthol, extending the linking moiety with an ether linkage (—O—), and an ethanolamine residue.

(*c*) The **'targetted drug molecule'** was synthesized by using β-naphthol, extending the residue with an ethereal linkage (—O), and an ethanolamine portion.

The net result of the entire exercise was the epoch-making discovery of **propranolol,** that was observed to be a pure *antagonist* and which was approximately 20 times more potent in comparison to **pronethalol** (*i.e.*, the original **'targetted-drug molecule'**).

The most potent drug substance belonging to the **first generation β-blockers,** propranolol, shall be discussed here under :

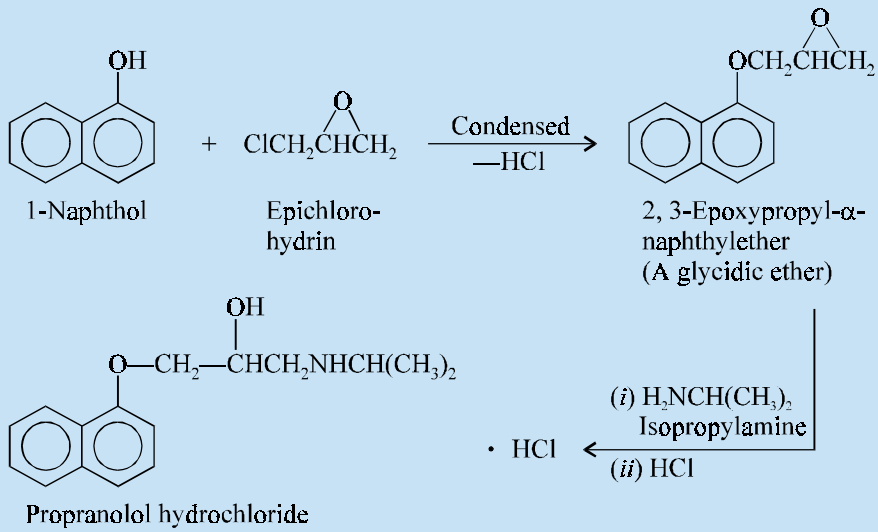
A. Propranolol INN, Propranolol Hydrochloride BAN, USAN,



(±)-1-Isopropylamino-3-(1-naphthyloxy) propan-2-ol-hydrochloride: 2-Propanol, -1-[(1-methylethyl) amino]-3-(1-naphthalenyloxy)-hydrochloride; BP., USP.;

Inderal(R) (Ayerst).

Synthesis



Interaction of 1-naphthol with epichlorohydrin affords a glycidic ether which upon treatment with isopropylamine aids in the opening of the oxirane ring yielding the propranolol base and this on being treated with a known quantity of hydrochloric acid gives the official compound.

Propranolol has been reported to exhibit quinidine-like antiarrhythmic actions which are quiet independent of beta-adrenergic blockade. Hence, these pharmacological properties are usually ***employed to suppress ventricular tachycardia, digitalis-induced tachyarrhythmias, paroxysml atrial tachycardia, and lastly ventricular and atrial extra-systoles. It is also currently receiving a lot of attention in the treatment and management of essential hypertension.***

Dose : *Oral, adult, for arrhythmias, 10 to 30 mg 3 to 4 times daily.*

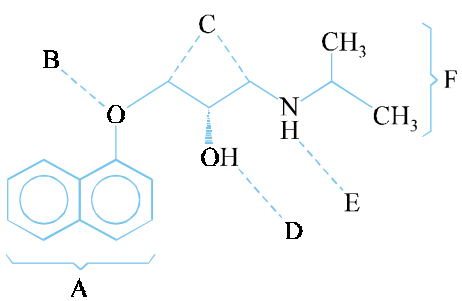
5.2.1.1. Structure Activity Relationships (SARs) of Aryloxypropanolamines

After the most successful synthesis of **propranolol,** a good number of **aryloxypropanolamines** have been synthesized in various laboratories; and, therefore, the SARs of these drug substances have been summarized as stated below :

1. The **'branched and bulky N-alkyl functional moieties',** such as : *tert*-butyl, *iso*-propyl etc., proved to be extremely vital for attributing the **β-antagonist activity,** thereby suggesting a possible interaction taking place with a hydrophobic pocket strategically located in the binding site.
2. It is, however, feasible to afford a variation of the aromatic ring system as well as heteroaromatic rings into the drug-molecules *e.g.*, **timolol, pindolol** etc.
3. The probable substitution of the *two methylene moieties* present in the **'side-chain'** enhances the **metabolic stability** at the expense of **therapeutic potency** (lowering of activity).
4. The **'alcoholic function'** on the side-chain is an absolute necessary requirement for its activity.
5. Isosteric replacement of the ethereal linkage (—O—) with such moieties as : CH_2, S or NCH_3 is found to be more or less detrimental; however, a tissue-selective β-blocker has been synthesized by replacing NH for O.
6. The introduction of relatively longer alkyl substituents in comparison to **'isopropyl'** or **'tert-butyl'** are found to be much less therapeutically potent and efficient.
7. The addition of an arylethyl functional moiety, for instance :

   $CH(CH_3)—CH_2—C_6H_5$ or $CH(CH_3)_2—CH_2—C_6H_5$ has proved to be useful in having better efficacious drug substances.
8. The **'amine nitrogen'** should always be a secondary in character with regard to the optimum activity.

The various aspects described under **SARs of aryloxypropanolamines** may be summarized in the following expression more categorically and rather explicitely :



A = Variable with heteroaromatic rings
B = Intimately engaged to H-bonding to receptor site
C = Substitution with functional groups lowers therapeutic efficacy
D = Absolutely essential for H-bonding interaction
E = Essential ionic-bonding interaction and must be **secondary in nature.**
F = Branching and extension both useful ; and fits into **hydrophobic pockets.**

5.2.1.2. Mechanism of Action

The **'drug'** penetrates into the CNS and thereby affords the predominant central effects. β-Antagonists are invariably employed in the treatment of *essential hypertension.* In reality, the exact and precise mechanism for this specific therapeutic effect has not yet been established, it has been adequately advocated that the **β-blockers** (*e.g.* **propranolol**) cause an effective decrease in BP by one of the *three* following manners, namely :

(*a*) Exerting a direct effect on the heart and the blood vessels.

(*b*) Minimising sympathetic outflow from the CNS, and

(*c*) Affecting the renin-angiotensin-aldosterone system.

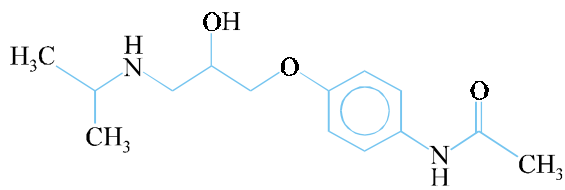
However, the probable best usage of propranolol shall be its combination with an antihypertensive vasodilators *e.g.* **hydralazine, minoxidil** etc., to preferentially check and prevent the **reflex tachycardia***.

5.2.2. Second Generation β-Blockers (Selective β_1-Blockers)

The genesis of the selective **β_1-blockers** or the **second generation β-blockers** received its legitimate cognizance by virtue of the stark reality that propranolol (see Section 12.5.2.1.A) happens to be a **non-selective β-antagonist** that eventually acts as an antagonist at both β_1*-receptors* and β_2*-receptors.* Hence, it does give rise to a very serious problem if the patient suffers from '*asthma*', because the very administration of **propranolol** (*i.e.*, **first-generation β-blocker**) would not only initiate but also precipitate an '*asthmatic attack*' by sharply antagonizing the prevailing **β_2-receptors** in the bronchial smooth muscle. Ultimately, it would give rise to sudden contraction of bronchial smooth muscle followed by an eventual closure of the airways.

A typical example of a potent drug belonging to this particular class is **practolol** which shall be described as given below :

A. Practolol INN



N-[4-[2-Hydroxy-3-[(1-methylethyl)-amino] propoxy] phenyl] acetamide ;

Eraldin$^{(R)}$.

Coleman (1979)** synthesized for the first time a series of twelve *para*-acylphenoxyethanol-and propanolamines ; of which, only one of them, **practolol**, was subjected to both extensive and intensive clinical trials.

Practolol was found to be less potent than propranolol. It also exhibited intrinsic sympathomimetic activity (ISA) to a certain extent. It is pertinent to state here that one particular property not earlier observed with the β-blockers : the ability predominantly to inhibit **isoproterenol (IPR)-induced tachycardia,** while exhibiting a minimal or no effect on the IPR-depressor (*i.e.*, hypotensive) response. In other words, **practolol** displayed cardioselectivity. Hence, for the first ever instance it was revealed and evidenced that the inhibition of β-adrenergic response may be confined significantly to certain sites.

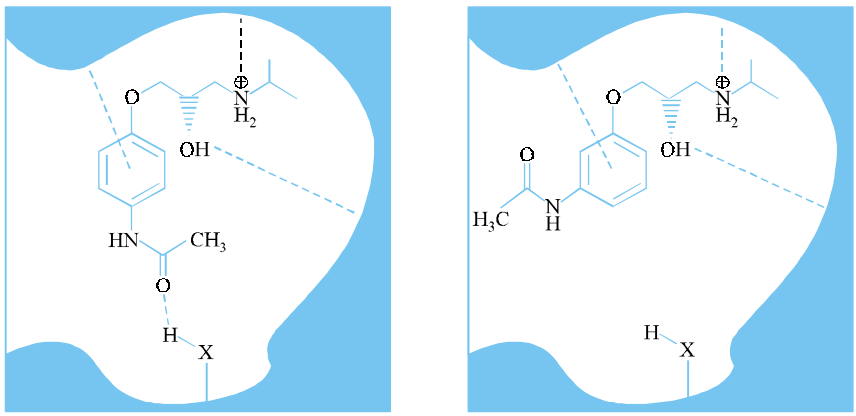
Note. Practolol was eventually withdrawn due to relatively rare, but of course extremely serious dermatologic as well as ophthalmic toxicological actions that ultimately led to total blindness and fatalities.

A comprehensive and intensive research of **practolol** was accomplished in a systematic manner, and it was proved amply that the **'acetamido functional moiety'** had to be strategically located at the *para* position of the aromatic phenyl ring rather than the correpsonding *ortho*- or *meta*-positions if the structure was to retain specifically the desired selectivity for the **cardiac β_1-receptors.** Fig. 13.1(*a*) and

*__Tachycardia__ (*i.e.*, an abnormal rapidity of heart action, usually heart rate more, than 100 beats per minute in adults) resulting from stimuli outside the heart, reflexly accelerating the heart-rate or depressing vagal tone.

Coleman AJ *et al. Biochem. Pharmacol.*, **28, 10, 1979.

(*b*) evidently depicts that in the particular instance of *para*-substitution **(practolol)** there exists an **extra H-bonding interaction** in the **β_1-receptors** but not the **β-receptors** ; whereas, in the *meta*-substitution the above mentioned criteria (*i.e.*, physical characteristic feature of an extra H-bonding interaction) is absolutely non-existence.



(*a*) *Para*-substitution (showing extra H-bonding interaction)

(*b*) *Meta*-substitution

Fig. 13.1. (*a*) and (*b*) Bonding Interactions with β_1-Receptors.

[Adapted from : Patrick GL, An Introduction to Medicinal Chemistry, Oxford University Press, Oxford UK, 2nd edn., 2001]

Special Note. The subsequent replacement of the acetamido functional moiety with other groups that are certainly capable of hydrogen bonding ultimately gave rise to the synthesis of a series of highly specific cardioselective β_1-blockers that were eventually employed as potent drugs, namely : Atenolol ; Betaxolol ; Metoprolol.

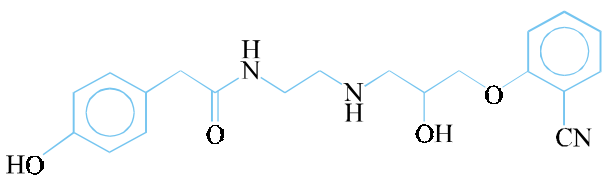
5.2.3. Third Generation β-Blockers

It has been stated earlier that the **first generation** and the **second generation** β-blockers essentially possess either **isopropyl** or *tertiary*-**butyl** functional moieties attached to the N-alkyl groups.

The wisdom and skill of the **'medicinal chemist'** further, promulgated the on-going research through the **'extension tactics'** that essentially incorporated the strategical addition of **arylalkyl functional moieties** attached to the terminal N-atom thereby producing a new series of **third generation β-blockers** that get ultimately bound to the β_1-receptor by means of an additional H-bonding interaction.

A few typical examples of the **third generation β-blockers** are discussed below ; namely : Epanolol :

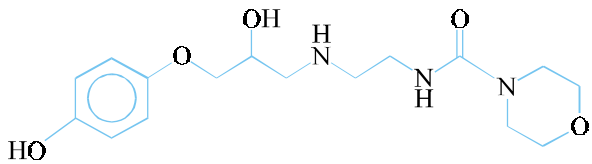
5.2.3.1. Epanolol



N-[2-[[3-(2-Cyanophenoxy)-2-hydroxy-propyl] amino] ethyl]-4-hydroxybenzeneacetamide ; Visacor(R).

Epanolol is a **cardioselective β-blocker.** It possesses intrinsic sympathomimetic activity to a certain extent. It finds its application as an antihypertensive as well as antianginal agent.

5.2.3.2. Xamoterol

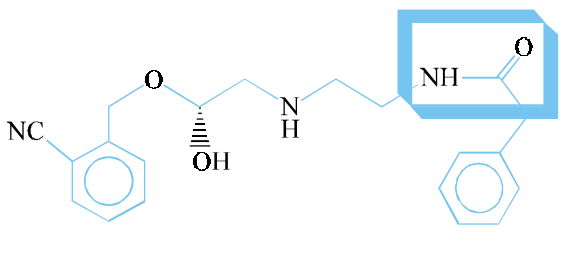


1-(4-Hydroxyphenoxy)-3-[2-(4-morpholinocarboxamido) ethylamino]-2-propanol.

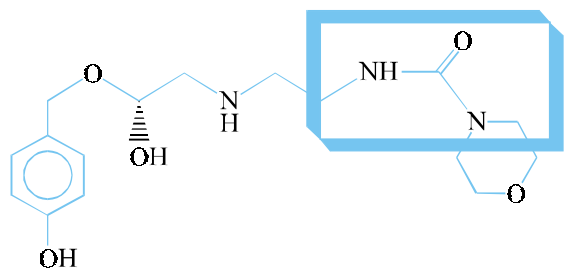
It is a **β-adrenoceptor partial agonist** having a selective action on the **β_1-receptors.** It has been observed that as a partial agonist it normally causes significantly agonist activity either at rest or under conditions of low sympathetic drive that may ultimately result in improved ventricular function and an obvious enhanced cardiac output. However, either during exercise or during conditions of enhanced sympathetic drive, for instance : that taking place in severe heart failure, **xamoterol** produces distinct **β-adrenoceptor antagonist activity.**

It is invariably employed as a cardiotonic.

The structures of **epanolol (I)** and **xamoterol (II)** are illustrated below respectively, wherein the specific moieties particularly involved in the additional hydrogen bonding have been demarcated explicitely as given below :



Epanolol (I)

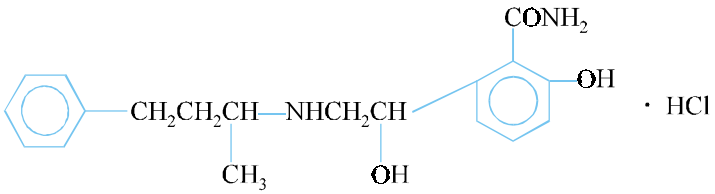


Xamoterol (II)

It has been observed that xamoterol is highly selective as a **β_1-partial agonist** ; and has been indicated largely in the control, management and treatment of mild heart failure. Interestingly, it emphatically acts as an **agonist** and it augments cardiac stimulation when the subject is usually taking rest ; however, (II) serves as a **β-blocker** in the course of a strenuous exercise *i.e.*, a situation when excessive quantum of **epinephrine (EP)** and **norepinephrine (NE)** are being produced simultaneously *in vivo*.

5.3. Alpha- and Beta-Adrenergic Receptor Blocking Agent

A. Labetalol INN, Labetalol Hydrochloride BAN, USAN,



2-Hydroxy-5 [1-hydroxy-2-(1-methyl-3-phenylpropylamino) ethyl] benzamide hydrochloride ; Trandate(R) (Glaxo Inc.).

It is an antihypertensive agent with β-adrenoceptor blocking actions similar to those of **propranolol hydrochloride.** Besides, it possesses α-adrenoceptor blocking properties which lower blood pressure by decreasing peripheral vascular resistance.

Dose : *Usual, initial, 100 or 200 mg twice per day with food.*

6. CHOLINOMIMETIC (PARASYMPATHOMIMETIC) DRUGS

The **cholinomimetic or parasympathomimetic or cholinergic drugs** are those which cause a muscarinic action on the receptors of the effector organs provided by the post-ganglionic cholinergic nerves. Invariably, these drugs exert their action in two different ways, namely : **direct action,** whereby they act on the **cholinoceptive receptors** like **acetylcholine; indirect action,** by rendering the cholinesterase enzymes inactive and preserving endogenously secreted acetylcholine, *e.g.*, **anticholinesterase drugs** like **physostigmine (naturally occurring neostigmine and pyridostigmine (synthetic)**.

Cholinomimetic drugs may be broadly classified under the following *two* categories. They are :

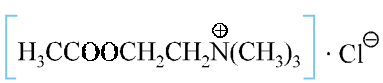
(*a*) Directly Acting

(*b*) Indirectly Acting (Anticholinesterase Drugs).

6.1. Directly Acting

A few typical examples of medicinal compounds bleonging to this category are discussed below : **acetylcholine chloride; bethanechol chloride; carbachol; methacholine chloride; pilocarpine nitrate,** etc.

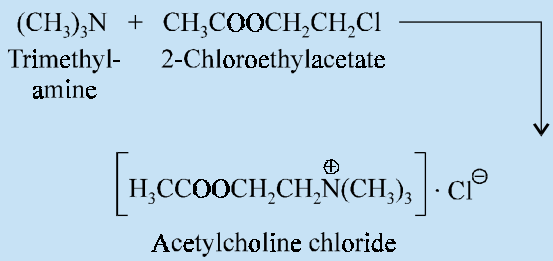
A. Acetylcholine INN, s BAN, USAN,



Choline chloride acetate ; (2-Acetoxyethyl) trimethyl-ammonium chloride ; (2-Hydroxyethyl) trimethylammonium chloride, acetate ; Ethanaminium, 2-(acetyloxy)-N, N, N-trimethyl-, chloride ; USP.

Miochol(R) (Cooper Vision Pharm.).

Synthesis

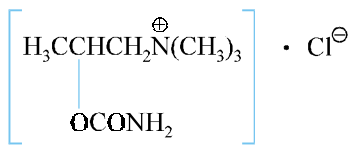


Acetylcholine chloride may be prepared by the interaction of trimethylamine and 2-chloroethyl acetate.

It is a potent quaternary ammonium parasympathomimetic agent. Its transient action is due to its destruction by **cholinesterase.** It is a vasodilator and cardiac depressant. The vasodilator action caused by acetylcholine is found to be most prominent in the peripheral vascular areas. It has been *used in a wide range of conditions such as cataract surgery, iridectomy, trophic ulcers, paroxysmal tachycardia, gangrene and Raynaud's disease.*

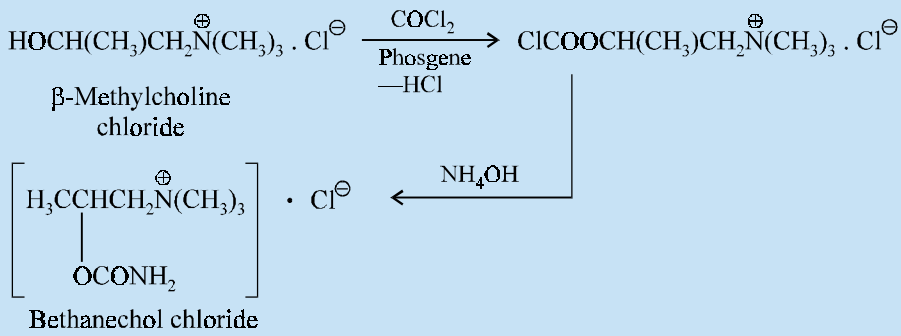
Dose : *Topical, as a 1% solution.*

B. Bethanechol Chloride BAN, USAN,



(2-Hydroxypropyl) trimethylammonium chloride carbamate ; Carbmylmethyl-choline chloride ; 1-Propanaminium, 2-[(aminocarbonyl) oxy]-N, N, N-trimethyl-, chloride ; USP. NF. ; Urecholine(R) (Merck) ; Myotonachol(R) (Glenwood).

Synthesis :



Bethanechol chloride is perpared by the interaction of β-methylcholine chloride with phosgene in chloroform solution followed by treatment of the resulting product with ammonium hydroxide.

It is not promptly inactivated by hydrolysis in the presence of enzyme cholinesterase, thereby enabling it to exert comparatively prolonged parasympathomimetic action. It is usually employed in the *treatment of functional urinary retention and postvagotomy gastric atony.*

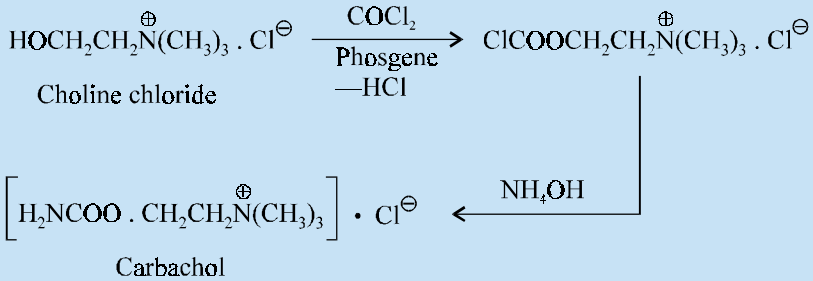
Dose : *Oral, 5 to 30 mg 3 or 4 times per day; subcutaneous, 2.5 to 10 mg 3 or 4 times daily.*

C. Carbachol INN, BAN, USAN,

$$[H_2NCOO \cdot CH_2CH_2N^{\oplus}(CH_3)_3] \cdot Cl^{\ominus}$$

Choline chloride carbamate; Carbamoylcholine chloride; Ethanaminium, 2-[(aminocarbonyl) oxy]-N, N, N-trimethyl-chloride ; BP. (1973), USP; Ind. P., Int. P. ;
Carcholin(R) (MSD); Moistat(R) (Alcon).

Synthesis

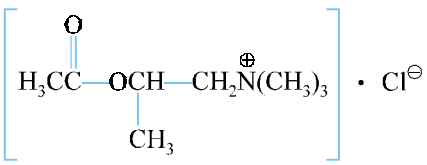


Carbachol may be prepared by reacting choline chloride with phosgene in chloroform solution followed by treatment of the product with ammonium hydroxide.

It possesses both muscarinic and nicotinic actions of acetylcholine. It is *used for its miotic actions in the treatment of primary glaucoma. It is employed invariably in urinary retention, peripheral vascular disease and intestinal paresis.*

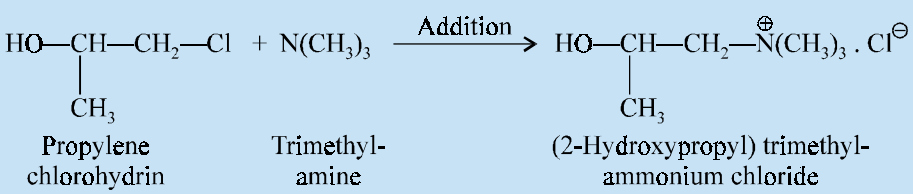
Dose : *Topical, 0.1 ml of a 0.75 to 3% solution.*

D. Methacholine INN, Methacholine Chloride BAN, USAN,



(2-Hydroxypropyl) trimethylammonium chloride acetate; Acetyl-β-methylcholine chloride; (2-Acetoxypropyl) trimethyl-ammonium chloride ; BPC. (1973) ; USP., Ind. P. ;
Provocholine(R) (Hoffman La Roche).

Synthesis



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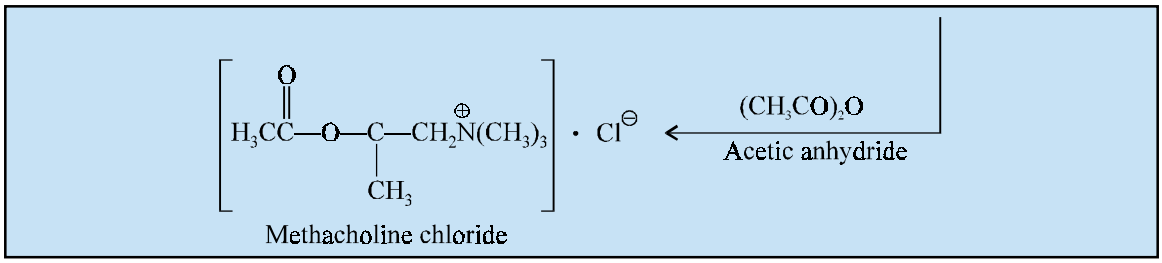
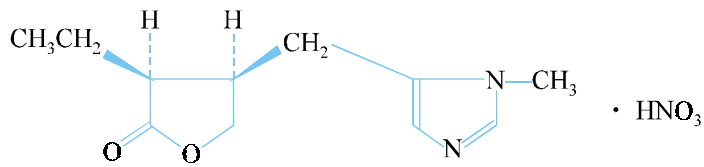


(2-Hydroxypropyl) trimethylammonium chloride may be prepared by the addition of propylene chlorohydrin to trimethylamine, which on acetylation with acetic anhydride yields the official compound.

Its actions on the cardiovascular system are more marked and pronounced than on the genitourinary and gastro-intenstinal systems. It has been *used successfully to terminate attacks of supraventricular paroxysmal tachycardia. It is found to be more muscarinic than nicotinic in its actions. It is frequently employed to afford vasodilation in vasospastic conditions, namely : chronic varicose ulcers, cold exposure and phlebits.*

Dose : *Usual paroxysmal tachycardia, 10 to 25 mg ; subcutaneous for peripheral vascular disease, 10 to 25 mg.*

E. Pilocarpine Nitrate BAN, USAN,



Pilocarpine mononitrate ; 2(3H-Furanone, 3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl) methyl]-, (3S-*cis*)-, mononitrate ; BP., USP., Eur. P., Ind. P., Int. P. ;

PV. Carpine(R) (Allergan).

Preparation

The dried and powdered leaves of *Pilocarpus microphyllus* is subjected to extraction for total alkaloids with ethanol acidified with hydrochloric acid. The solvent is removed under reduced pressure and the resulting aqueous residue is neutralized with ammonia and kept aside till all the resins settle down completely. It is subsequently filtered and the filtrate concentrated by evaporation to a small volume, made alkaline with ammonia and finally extracted with chloroform. The solvent is removed under reduced pressure and the contents dissolved in a minimum quantity of dilute nitric acid and the product is crystallized.

Pilocarpine nitrate is a parasympathomimetic agent possessing muscarinic effects of acetylcholine. *It is mostly used as a solution (1 to 5%) to exert an action on the eye to cause miosis and retard intraocular tension in the treatment of open-angle glaucoma.* **Pilocarpine nitrate** being less hygroscopic than its corresponding hydrochloride and hence it is more easy to handle.

Dose : *Topical, 0.1 ml of 0.5 to 6% solution into the conjunctival sac 1 to 5 times in a day.*

6.1.1. Mechanism of Action

The mechanism of action of certain **directly acting parasympathomimetic drugs** shall now be discussed in the sections below :

6.1.1.1. Acetylcholine Chloride

The **'drug'** is invariably employed as a main topical opthalmological agent to *induce miosis* during certain intraocular surgical operations, namely : cataract surgery, iridectomy, penetrating keratoplasty, and other anterior segment surgery. Importantly, when applied to the intact cornea, ACh penetrates rather too sluggishly to be a clinically efficient miotic. As ACh gets rapidly destroyed by acetylcholin-esterases; therefore, it has hardly any systemic usages.

6.1.1.2. Bethanechol chloride

It evidently possesses somewhat prominent and apparently stronger muscarinic activity for the GI-tract and the urinary tracts in comparison to the cardiovascular system ; and, therefore, is extensively used systemically exclusively for the *gasteroenterological* and *genitourinary* uses. It is found to be resistant to hydrolysis by the **cholinesterases**, and perhaps that is why it has a comparatively prolonged duration of action.

6.1.1.3. Carbachol

As on date, the **'drug'** finds its enormous use in ophthalmology, mostly for the control, management and treatment of narrow-angle glaucoma ; besides, to *induce miosis* just prior to ocular surgery. It is worthwhile to mention here that it does not undergo hydrolysis by **cholinesterase** ; and, hence, exhibits a much longer span of activity in comparison to ACh.

6.1.1.4. Methacholine Chloride

The '**drug**' shows a highly selective muscarinic activity. Interestingly, weak nicotinic actions are manifested usually at the neuromuscular junction specifically in *mysthenic patients*, and also at adrenal medullary tumours in pheochromocytoma*. However, it distinctly exhibits a tendency toward false positives amongst the nonasthmatic smokers and relatives of asthmatics ; there is also a relatively smaller percentage of **'false negatives'**. The *drug* is found to be contraindicated in the presence of **β-adrenoreceptor-blocking drugs**.

6.1.1.5. Pilocarpine Nitrate

The **'drug'** serves as a potential *muscarinic agonist* which is found to be totally devoid of the **nicotinic activity** but is found to be nonselective with regard to the **muscarinic targets. Pilocarpine nitrate** is observed to penetrate membranes in a much better and efficient manner than do **quaternary ammonium cholinomimetics** perhaps due to its basic tertiary amine characteristic feature.

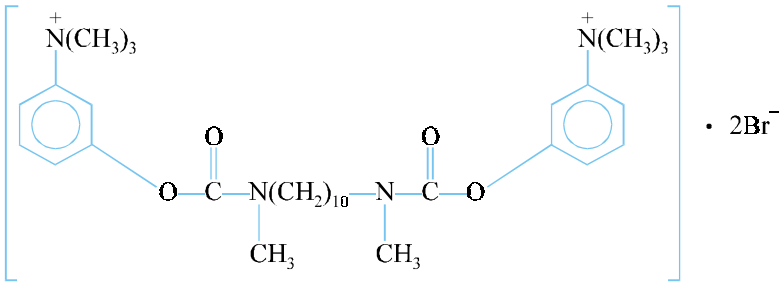
Interestingly, the free base, pilocarpine, is used frequently in the *ocular controlled-release system*, because the nonionized form may be able to diffuse readily and exclusively through the specific *hydrophobic* membrane.

6.2. Indirectly Acting (Anticholinesterase) Drugs

Following are a few examples of **indirectly acting cholinomimetics** (**anticholinesterase drugs**) : **demecarium bromide** ; **edrophonium chloride** ; **physostigmine salicylate** and **pyridostigmine bromide.**

*A well encapsulated, lobular, vascular tumour of chromaffin tissue of the adrenal medulla or sympathetic paraganglia.

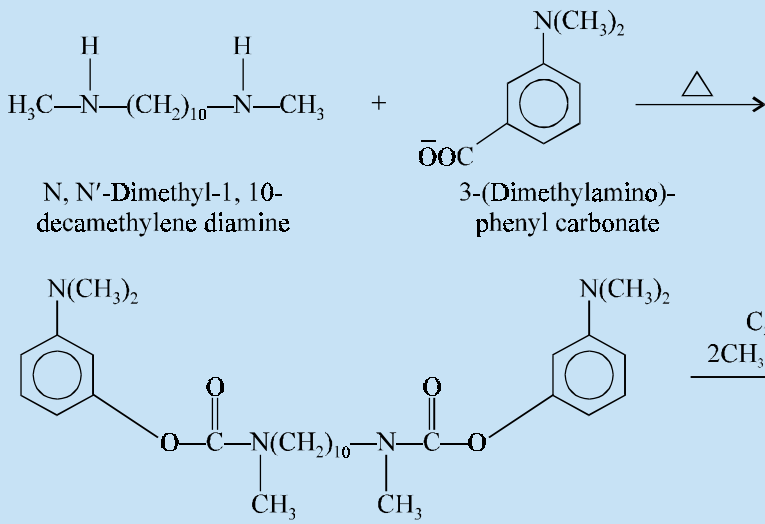
A. Demecarium Bromide INN, BAN, USAN,

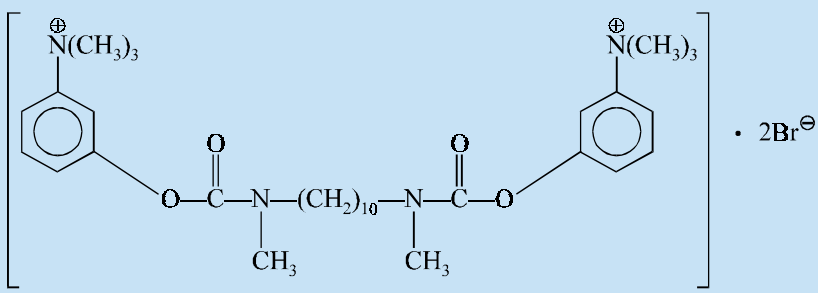


(*m*-Hydroxyphenyl) trimethylammonium bromide decamethylenebis (methyl-carbamate) (2 : 1) ; 3, 3′-[N N′-Decamethylenebis (methyl-carbamoyloxy] *bis*-(NNN-trimethylanilinium) dibromide ; USP.,

NF. Humorsol$^{(R)}$ (Merck).

Synthesis





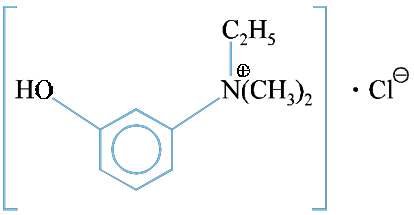
Demecarium bromide

The interaction of N, N′-dimethyl-1, 10-decamethylene diamine and molten 3-(dimethylamino) phenyl carbonate yields 1, 10-decamethylenebis [3-(dimethylamino)-phenyl N-methyl-carbamate] which on subsequent dissolution in ethanol and treatment with methylbromide in acetone gives the doubly quaternized official compound.

Demecarium bromide is a quaternary ammonium anticholinesterase drug which *possesses a very high degree penetrability in the eye. It is employed in the treatment of open-angle glaucoma and accomodative convergent strabismus (esotropia) by means of local instillation into the affected eye.*

Dose : *Topical, to the conjunctiva, 1 to 2 drops of a 0.125 to 0.25% solution twice weekly to 1 or 2 times per day.*

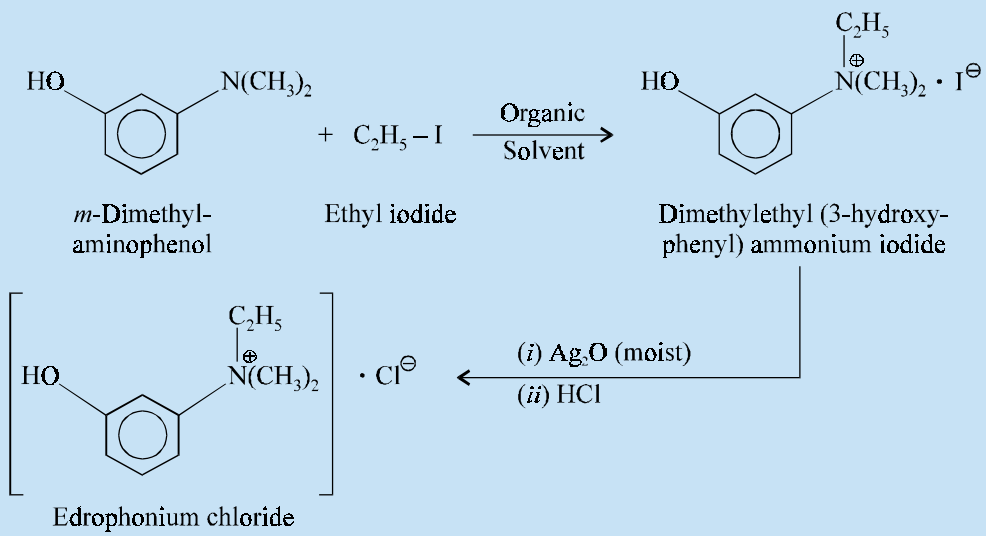
B. Edrophonium INN, Edrophonium Chloride BAN, USAN,



Ethyl-(*m*-hydroxyphenyl) dimethylammonium chloride; Benzenaminium, N-ethyl-3-hydroxy-N, N-dimethyl-, chloride; BP., USP., Int. P. ;

Tensilon(R) (Hoffmann La Roche).

Synthesis

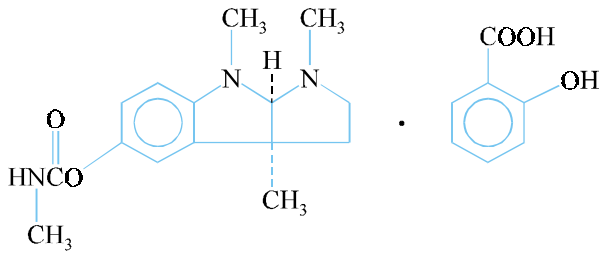


Dimethylethyl (3-hydroxyphenyl) ammonium iodide is prepared by quaternization of *meta*-dimethylaminophenol with ethyl iodide in a suitable organic solvent. **Edrophonium chloride** may now be obtained *via* treatment with moist silver oxide followed by neutralization with HCl.

It is of particular *utility in the diagnosis of myasthenia gravis.* It may also be *employed to make a clear distinction between a myasthenic crisis and a cholinergic crisis, because in the first instance an improvement of neuromuscular function is usually observed while in the second it worsens it further.*

Dose : *Intravenous, 2 to 10 mg ; usually 2 mg is injected initially and if no adverse reaction takes place within 30 seconds, the remaining 8 mg is injected.*

C. Physostigmine Salicylate USAN



Pyrrol [2, 3-*b*] indol-5-ol, 1, 2, 3, 3a, 8, 8a-hexahydro-1, 3a, 8-trimethyl-, methyl-carbamate (ester), (3a S-*cis*), mono (2-hydroxybenzoate) ; Eserine Salicylate ; BP ; USP ; Eur. P., Int. P., Ind. P. ;

Isopto-Eserine$^{(R)}$ (Alcon).

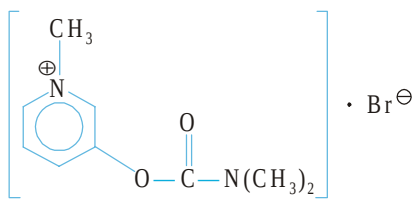
Preparation

The powdered seeds of *Physostigma venenosum* Balfour (*Family : Leguminoseae*) is extracted with hot alcohol. The excess of alcohol is distilled off under reduced pressure, the residue made alkaline with sodium carbonate and extracted with solvent ether. From the resulting solution **physostigmine** is removed with the aid of sulphuric acid. The base is liberated again from an alkaline medium. The official compound is now obtained by treating two parts of **physostigmine** with one part of salicylic acid in 35 parts of boiling distilled water and finally allowing it to crystallize out slowly.

It is *used chiefly as a miotic.* The constriction of pupil commences within 10 minutes of application and the effect lasts up to 12 hours. It is also *employed to decrease intra-ocular pressure in glaucoma.* The salicylate is comparatively less deliquescent than the sulphate. The drug is invariably *recommended for marginal corneal ulcers.* It also finds its seldom *use for atony of the urinary bladder.*

Dose : *Topical, for open-angle glaucoma, 0.1 ml of a 0.25 to 5% solution instilled into the conjunctival sac 2 or 4 times daily :*

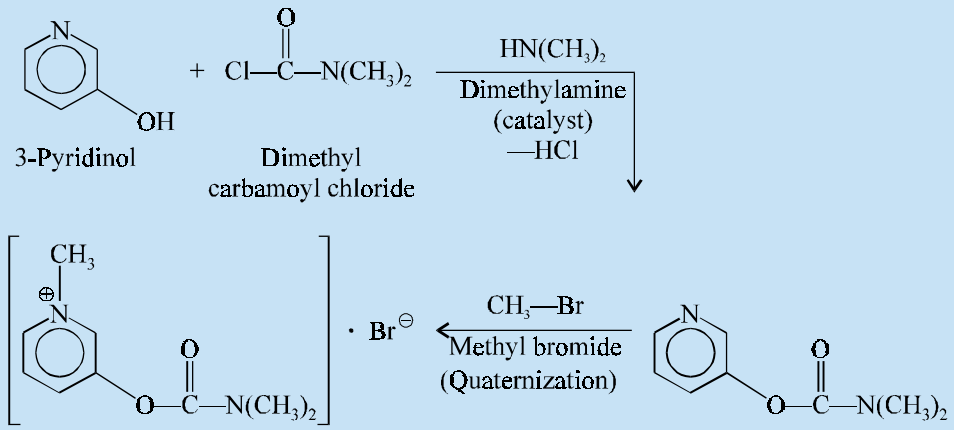
D. Pyridostigmine INN, Pyridostigmine Bromide BAN, USAN,



3-Hydroxy-1-methylpyridinium bromide dimethylcarbamate ; Pyridinium, 3-[[(dimethylamino)-carbonyl] oxy]-1-methyl-, bromide ; BP ; USP ; Int. P. ;

Mestinon(R) (Hoffmann La Roche) ; Regonol(R) (Organon).

Synthesis



3-Pyridyl dimethyl carbamate is prepared by the interaction of 3-pyridinol with dimethyl carbamoyl chloride in the presence of a basic catalyst like dimethyl amine with the loss of a mole of HCl. The resulting product is quaternized and methyl bromide to yield the official compound.

Pyridostigmine bromide is abundantly employed in the treatment of myasthenia gravis. It is also used in the *treatment of paralytic ileus or postoperative urinary retention.*

Dose : *Initially, 60 mg every 4 to 8 hours, but 120 to 300 mg 6 times daily is the usual dose.*

6.2.1. Mechanism of Action

The mechanism of action of the *four* **indirectly acting (anticholinesterase) drugs** discussed in the Section 13.6.2. are described below :

6.2.2. Demecarium Bromide

It is a **quaternary ammonium anticholinesterase 'drug'** which shows relatively high topical penetrability into the eye. Importantly, the inhibition of **acetylcholinesterase** has several consequences depending upon exactly where the enzymes are inhibited. It has, however, been observed that neither the **butyrylcholinesterase** located in plasma nor the acetylcholinesterase present in erythrocyets do possess any well-defined functions ; and, hence, their inhibition has no known physiological consequences. Interestingly, such an inhibition may ultimately result moderate increase in the plasma halflife and the concentration of ACh together with some other **hydrolyzable choline esters.** However, the most pivotal and critical effects accrue to inhibition at the specific sites of cholinergic neuroeffector transmission. Nevertheless, the actual and realistic preservation of ACh at such sites not only prolongs but also intensifies the cholinergic activity precisely and effectively.

Consequently, bradycardia, partial heart block, miosis, enhanced gastric secretion and motility and tendency to urinate all result from the appreciable anticholinesterase profile.

6.2.3. Physostigmine Salicylate

It enjoys the reputation of being one of the oldest **anticholinesterases.** It has been observed that the **'drug'** invariably combines with the said enzyme particularly at the *esteratic site* to give rise to the corresponding **methylcarbamoyl enzyme,** which is **inactive**. Importantly, it is found to share with neostigmine marked and pronounced stimulatory activities on the bowel but produces excessive functions, such as : secretion of glands, effect on BP, constriction of the pupil, and relatively lesser action on the skeletal muscle in particular. By virtue of its inherent characteristic feature as a tertiary amine, it gets penetrated into the nervous system, and, therefore, may cause central activities on being administered in sufficiently large doses. It is found to penetrate rapidly into the eye. Interestingly, the salicylate salt exerts a dual purpose *viz., first*, its specific action on CNS ; and *secondly*, its ability to cause ophthalmological activities.

6.2.4. Pyridostigmine Bromide

The **'drug'** is a quaternary ammonium salt which is observed to be a reversible inhibitor of cholinesterase activity having activities very much akin to those of **neostigmine,** but is definitely much slower in onset and of longer duration.

Physostigmine is very sluggishly absorbed from the GI-tract. The drug gets hydrolyzed by the enzymes cholinesterases, and is also metabolized in the liver. It is excreted mostly in the urine as its metabolites and partly as unchanged drug. The **'drug'** happens to cross the placental barrier and only very small quantum are usually excreted in the breast-milk. However, the penetration into the CNS is comparatively very slow.

Interestingly, the **'drug'** is approximately 1/4th as potent as neostigmine at the *neuromuscular junction*; and nearly 1/8th as potent on the *exocrine glands*, *bowel*, and *gentiurinary tract.* Finally, the **'drug'** is frequently employed to antagonize competitive **neuromuscular-blocking drugs.**

7. ANTIMUSCARINIC (ANTICHOLINERGIC) AGENTS

The term **'antimuscarinic'** is derived from the action of acetylcholine at the postganglionic synapse which is closely imitated by the alkaloid, **muscarine**.

Antimuscarinic agents like **atropine** chiefly exert their action by blocking the normal responses to excitation of postganglionic parasympathetic (cholinergic) nerves that stimulate both smooth muscle as well as exocrine glands. Sometimes they are also termed as parasympatholytic and as anticholinergic agents. They usually act by preventing the normal effect of acetylcholine on the receptor cells.

The antimuscarinic effects mainly include an elevation of heart-rate. Besides, a diminution in the production of bronchial, lachrymal, gastric, nasal, intestinal, sweat and saliva secretions are observed together with a reduction in intestinal motility.

It has been established beyond any reasonable doubt that specifically the cholinergic transmission invariably takes place either at the neuroeffectors innervated by the parasympathetic and some sympathetic postganglionic nerves or mostly at all autonomic ganglia *viz.*, the somatic neuromuscular junction, besides certain central synapses. Broadly speaking, the **'anti-muscarinic agents'** behave as **competitive antagonists** which exert their action exclusively upon the cholinergic receptors at smooth muscle, secretory cells, and some central synapses. There are several synonymous terminologies for the

anti-muscarinic agents, namely : **anticholinergic, cholinolytic, parasympatholytic, and para-sympathetic blocking drugs**.

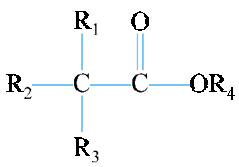
As a host of **cholinergic**, **ganglionic** and **neuromuscular blocking drugs** do commonly antagonize the activity of ACh ; it may, therefore, be expected that a few of these drug substances would help in blocking at more than one type of cholinergic receptor.

Antimuscarinic agents may be classified on the basis of their chemical structures under the following heads :

(*i*) Aminoalcohol Esters.
(*ii*) Aminoalcohol Ethers.
(*iii*) Aminoalcohol Carbamates.
(*iv*) Aminoalcohols.
(*v*) Aminoamides.
(*vi*) Diamines.
(*vii*) Miscellaneous Amines.

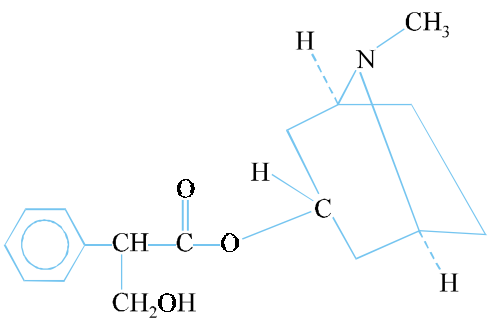
7.1. Aminoalcohol Esters

Aminoalcohol esters, having the following **general formula,** have emerged from the outstanding pharmacological actions displayed by atropine :



A follow-up from this generalised structure resulted into the formation of an altogether new breed of **'tropeines'** that possessed remarkable antimuscarinic activity. A few typical examples of this category of compounds are discussed below, namely :

A. Atropine BAN, USAN,



1 αH, 5αH-Tropan-3α-ol (±)-tropate (ester) ; (±)-Hyoscyamine ; (1R, 3R, 5S)-Tropan-3-yl (±)-tropate ; B.P.C. (1973) ; USP ; NF ; Ind. P. ;

Atropinol$^{(R)}$ (Winzer, Germany).

Synthesis

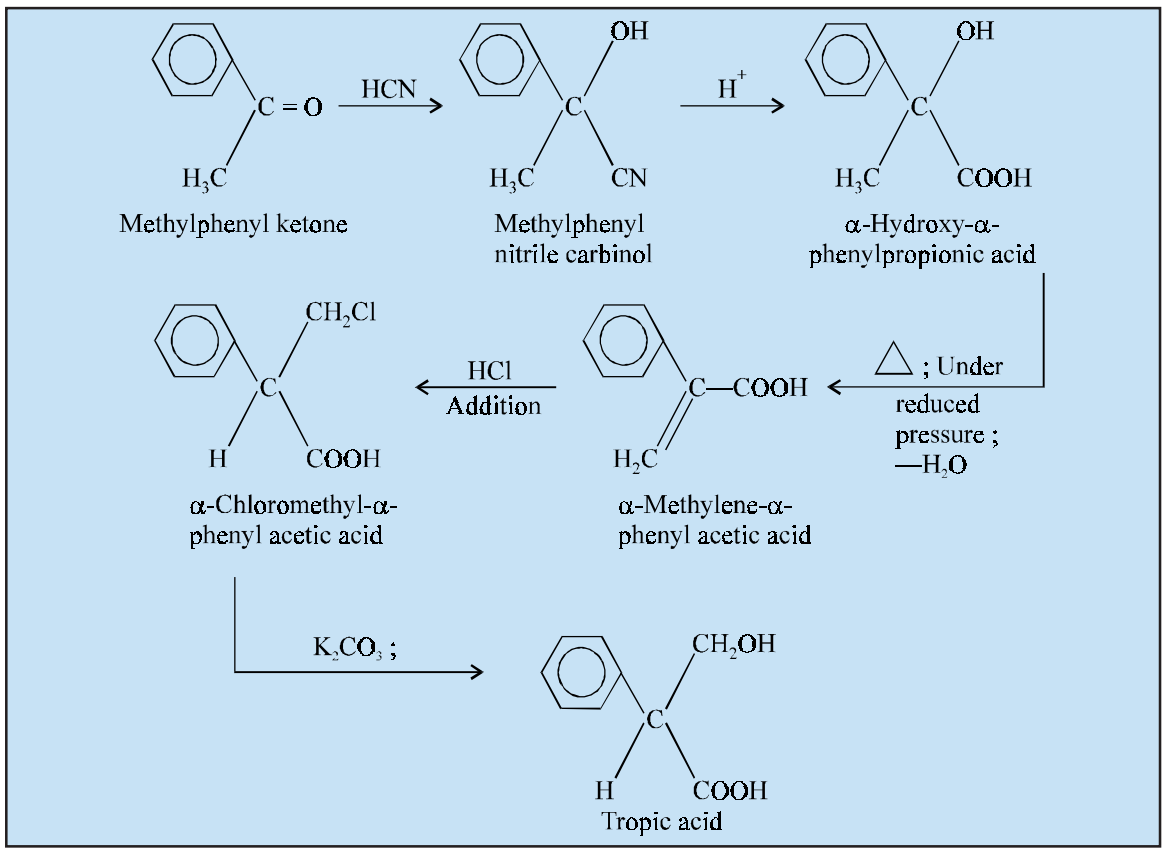
The synthesis essentially consists of the following *three* parts :
(*a*) Synthesis of tropic acid ;

(*b*) Synthesis of tropine ; and

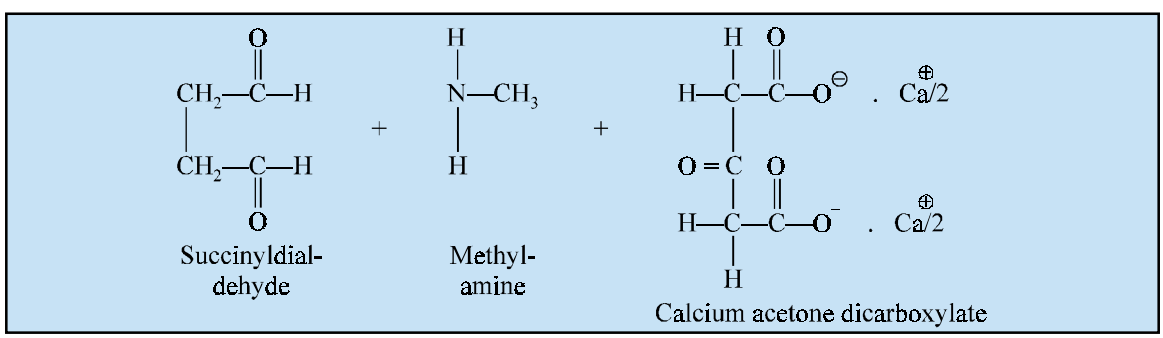
(*c*) Condensation of tropic acid and tropine.

(*a*) **Synthesis of Tropic Acid.** Methyl phenyl ketone on treatment with HCN yields methylphenyl nitrile carbinol which on acidification gives the corresponding α-hydroxy-α-phenyl-propionic acid. The resulting product loses a molecule of water upon heating under reduced pressure to give α-methylene-α-phenyl acetic acid which on treatment with HCl undergoes addition reaction according to the **Markownikoff's rule** and yields α-chloro-methyl-α-phenyl acetic acid. This product on reaction with K_2CO_3 gives **tropic acid.**

(*a*) **Synthesis of Tropic Acid**



(*b*) **Synthesis of Tropine**



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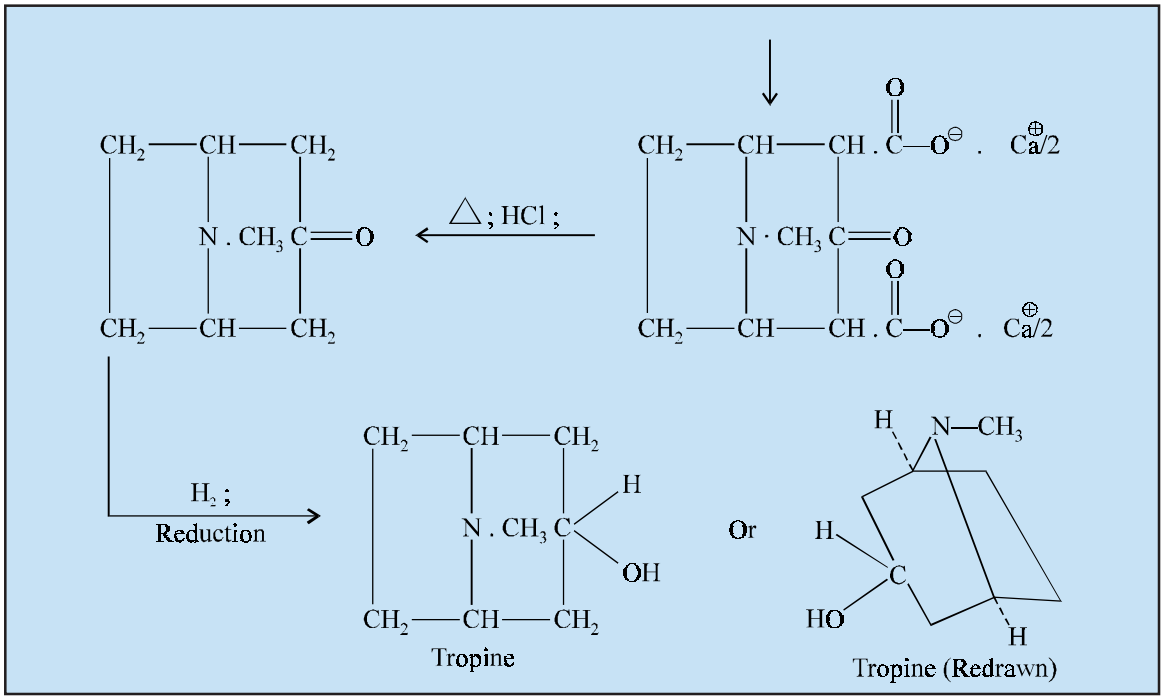
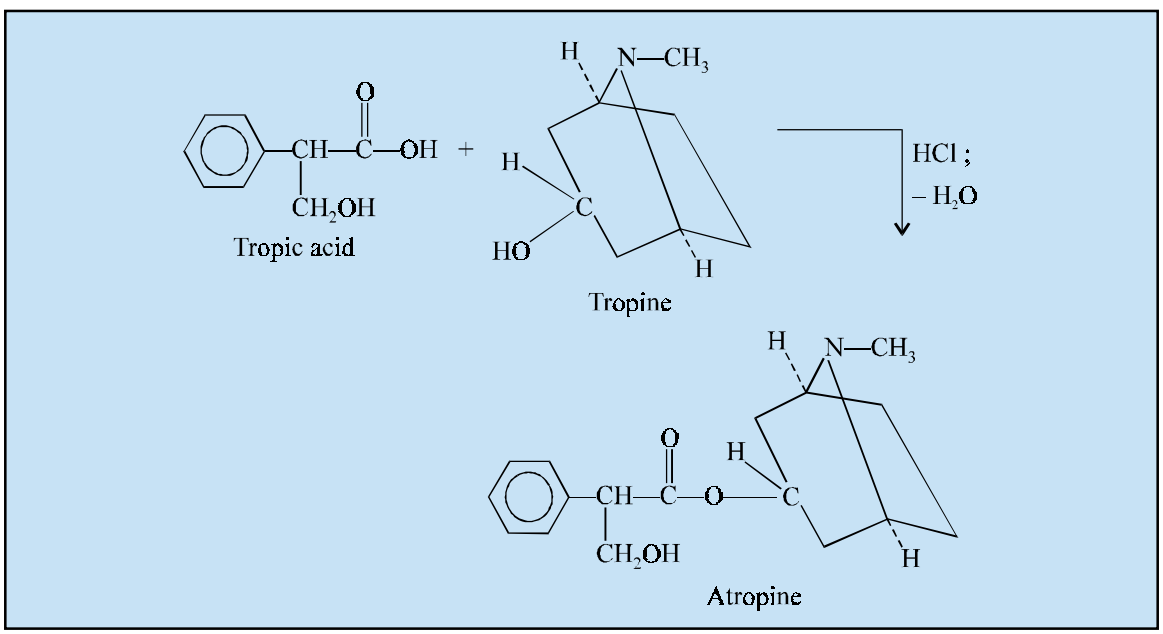


The interaction of succinyldialdehyde, methylamine and calcium acetone dicarboxylate yields the corresponding calcium salt which on treatment with HCl and subsequent reduction gives rise to **tropine**.

(*c*) **Condensation of Tropic Acid and Tropine**



A molecule each of tropic acid and tropine in the persence of HCl loses a molecule of water to yield the official product.

Atropine is an **antimuscarinic alkaloid** which possesses both central and peripheral actions. It exerts first a stimulating and then a depressing action on the central nervous system (CNS) and exhibits antispasmodic actions on the smooth muscle. On account of its broad spectrum of effects in the body the therapeutic applications are numerous, but unfortunately it lacks selectivity of action.

Its centrally potent actions are used in various conditions, namely : *postencephphalitic parkinsonism, paralysis agitans, respiratory stimulation, some types of spastic and rigid states and rarely in schizophrenia* (*at its toxic dose level*).

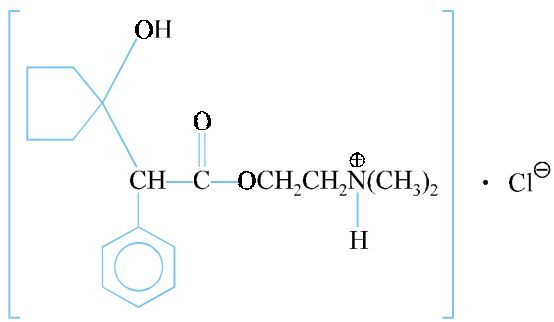
Its peripheral actions are so widespread as could be observed from the diversified therapeutic applications, *e.g., in ophthalmology to dilate the pupil and to paralyze accommodation, in bronchial asthma to dry up the bronchial secretions.*

In the diagnosis of heart diseases **atropine** finds its use to stop *extrasystoles and complete heart block.*

Atropine *helps to control the spastic conditions of the bowel, for instance, spastic colitis, cardiospasm and pylorospasm.*

Dose : *Usual, 0.25 mg thrice daily normally taken 30 minutes before meals.*

B. Cyclopentolate INN, Cyclopentolate Hydrochloride BAN, USAN,

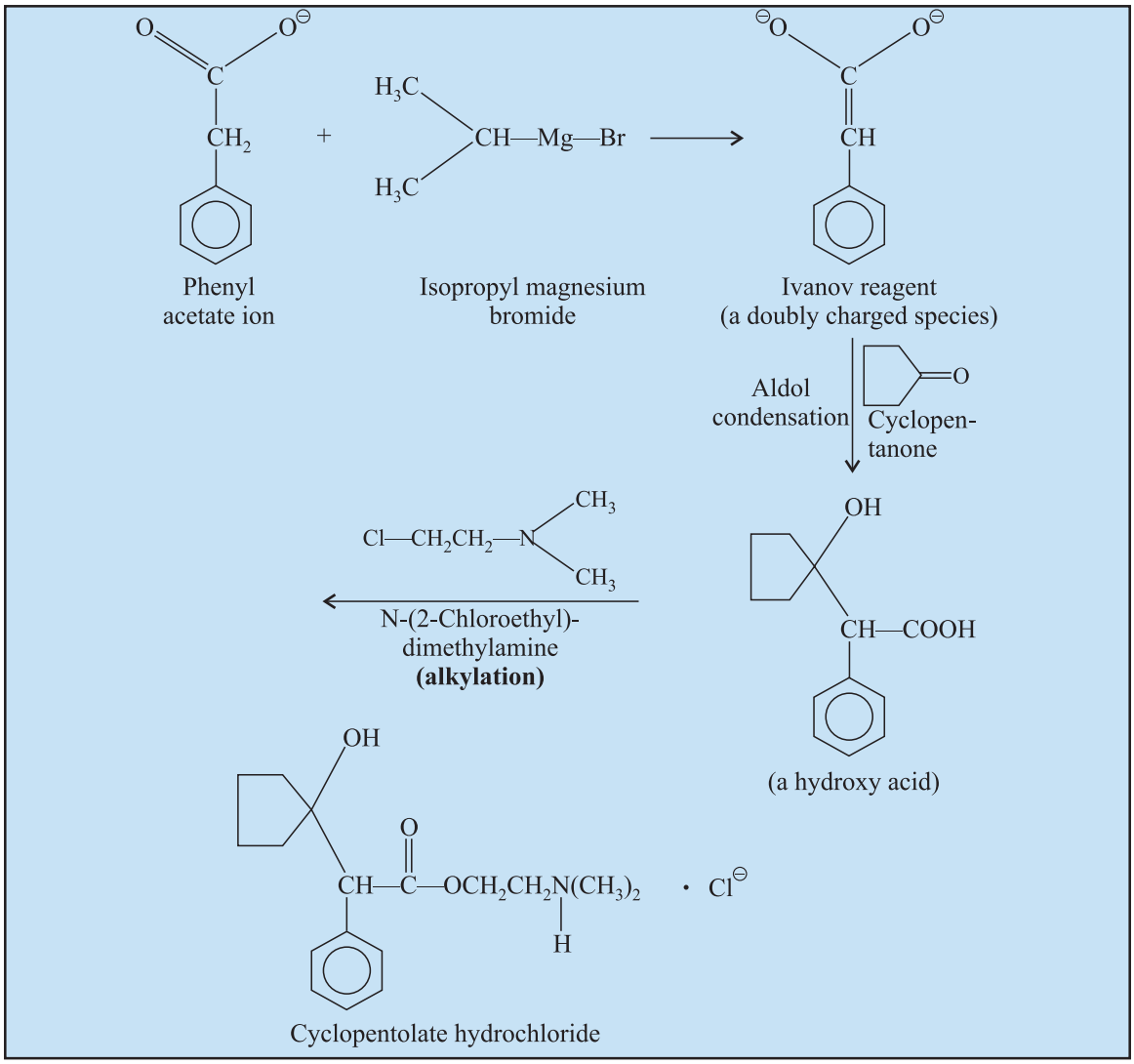


2-(Dimethylamino) ethyl-1-hydroxy-α-phenylcyclopentane-acetate hydrochloride ; Benzeneacetic acid, α-(1-hydroxy-cyclopentyl)-, 2-(dimethylamino) ethyl ester, hydrochloride ; BP ; USP ; Cyclogy(R) (Alcon).

Synthesis

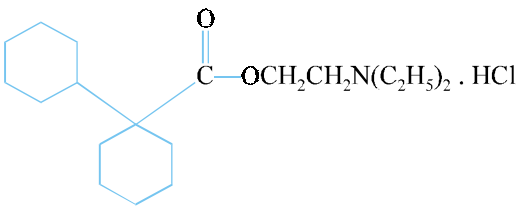
The interaction between the sodium salt of phenylacetic acid and isopropyl magnesium bromide results into a doubly charged species known as the *Ivanov reagent*. This product on treatment with cyclopentanone affords aldol condensation to yield the corresponding hydroxy acid. The resulting product on being subjected to alkylation with N-(2-chloro-ethyl)-dimethylamine gives the desired official compound.

Cyclopentolate hydrochloride is usually *employed as eye drops to cause cycloplegia and mydriasis. It acts much faster than atropine and possesses a relatively shorter duration of action.*



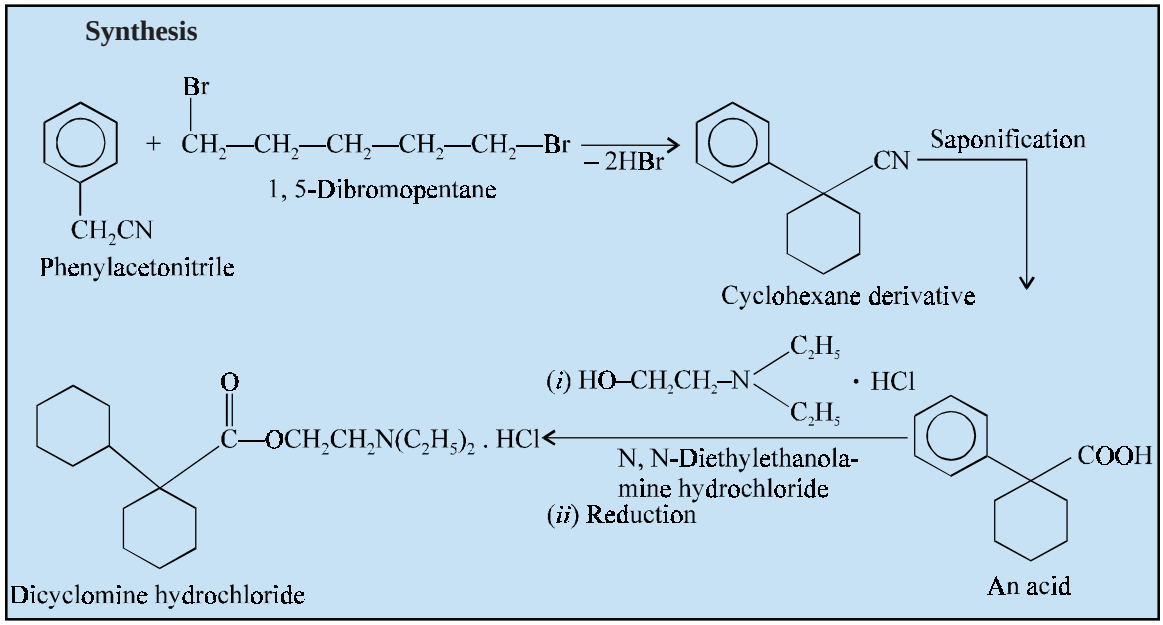
Dose : *Topical, adult, 1 drop of 1 or 2% solution to the conjuctiva ; for refraction, 1 drop of a 0.5% solution repeated after 5 to 15 minutes.*

C. Dicycloverine INN, Dicyclomine BAN, Dicyclomine Hydrochloride USAN,



2-(Diethylamino) ethyl [bicyclohexyl]-1-carboxylate hydrochloride ; Bicyclo-hexyl]-1-carboxylic acid, 2-(diethylamino) ethyl ester, hydrochloride ; BP ; USP ;

Bentyl$^{(R)}$ (Merrell Dow) ; Merbentyl$^{(R)}$ (Merrell, U.K.).

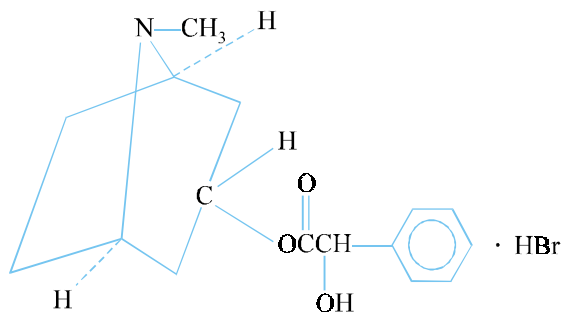


Double alkylation of phenylacetonitrile with 1, 5-dibromopentane yields the corresponding cyclohexane, with the elimination of two moles of hydrogen bromide. The resulting product on saponification gives the corresponding acid, which on *first* treatment with N, N-diethylethanolamine hydrochloride and *secondly* with catalytic reduction yields the desired official compound.

Dicyclomine hydrochloride behaves both as an antimuscarinic and a nonspecific antispasmodic agent. It is frequently employed in the *treatment of irritable colon, spastic colitis, mucous colitis, spastic constipation and biliary dyskinesia. It also finds its use in the diagnosis of peptic ulcer by delaying gastric emptying process.*

Dose : *Oral or intramuscular, 10 to 20 mg after 4 to 6 hours per day.*

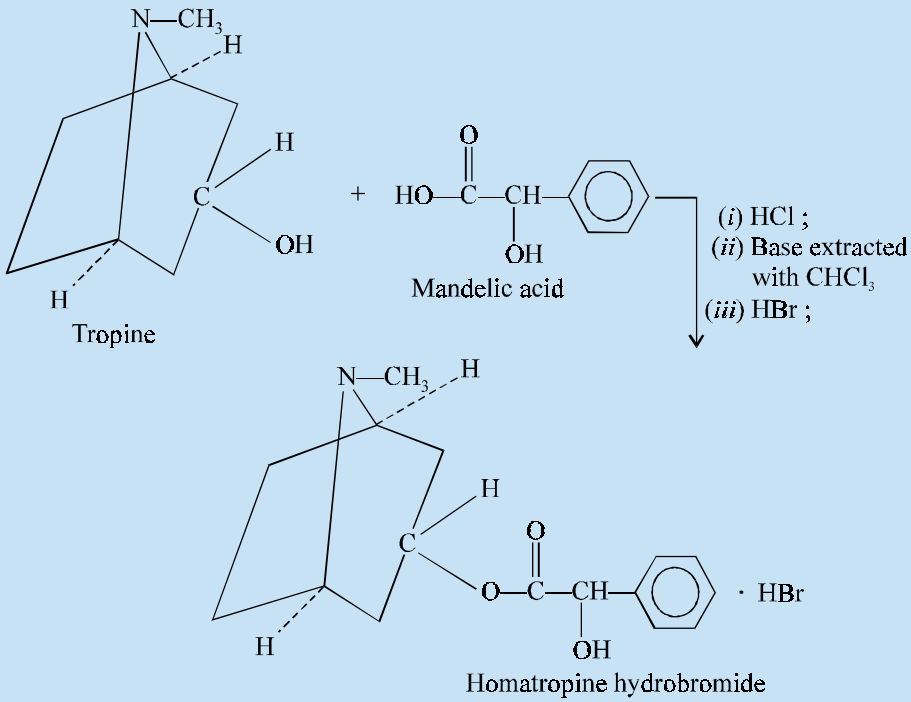
D. Homatropine INN, Homatropine Hydrobromide BAN, USAN,



1αH, 3αH-Tropan-3α-ol mandelate (ester) hydrobromide; Tropyl mandelate hydrobromide; Benzeneacetic acid, α-hydroxy-, 8-methyl-8-azabicyclol [3, 2, 1] oct-3yl ester hydrobromide, endo-(±) ; BP ; USP ; Eur. P., Int. P. ; Ind. P.,

Isopto Homatropine$^{(R)}$ (Alcon).

Synthesis

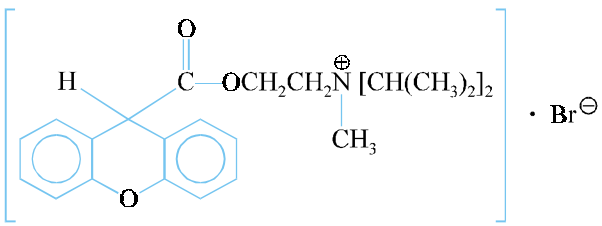


It may be prepared by the interaction of tropine and mandelic acid in the presence of hydrochloric acid. The base is liberated on alkalization with ammonia, extracted with chloroform, the solution is evaporated and treated with hydrobromic acid to obtain the desired compound.

Homatropine hydrobromide is employed as *a mydriatic. It is used preferentially to atropine because of its three vital reasons, namely ; more rapid action ; less prolonged action and conveniently controlled by physostigmine.*

Dose : *Topical, adult, to the conjuctiva, 1 drop of a 2–5% solution given 3 times at 10 minutes intervals.*

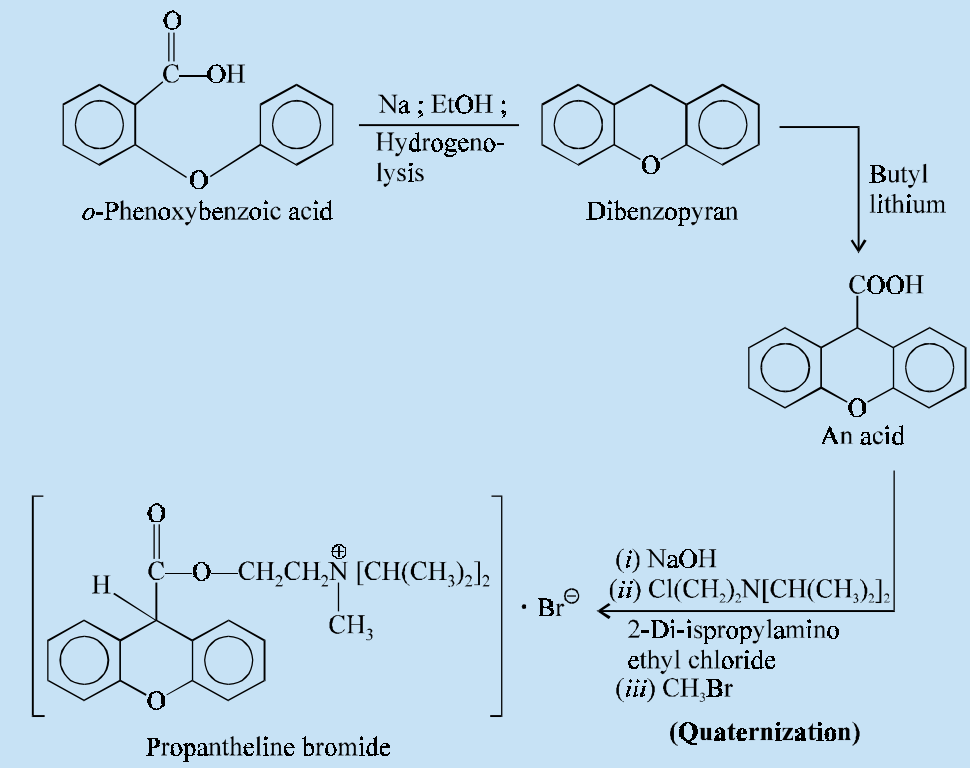
E. Propantheline INN, Propanetheline Bromide BAN, USAN,



Di-isopropylmethyl [2-(xanthen-9-ylcarbonyloxy) ethyl] ammonium bromide ; (2-Hydroxyethyl) diisopropylmethylammonium bromide xanthene-9-carboxylate; BP; USP; Int. P.;

Pro-Banthine(R) (Searle) ; SK-Propentheline Bromide(R) (SK and F).

Synthesis



o-Phenoxybenzoic acid undergoes Friedel-Crafts cyclization in the presence of sodium and alcohol to form dibenzopyran, which on treatment with butyl lithium gives acid products. The resulting compound *first* converted to its sodium salt, *secondly* treated with 2-di-isopropylamino ethyl chlroide, and *thirdly* subjected to quaternization with methylbromide to give the desired official compound.

Propantheline bromide is used in the treatment of acute and chornic pancreatitis, pylorospasm, gastritis, and ureteric and biliary spasm. It also finds its application as an adjunct *in the treatment of gastric and duodenal ulcer.*

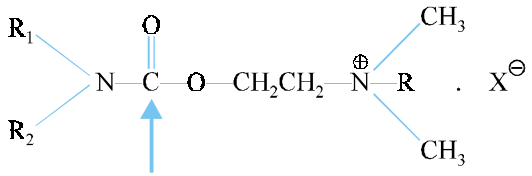
Dose : *Usual, initial, 15 mg 3 times per day before meals ; and 30 mg at bed-time.*

7.2. Aminoalcohol Ethers

Generally, the **aminoalcohol ethers** have been more widely employed as **anti-parkinsonism agents** rather than as usual **antimuscarinic drugs.** A few such compounds, namely ; **benztropine mesylate, chlorphenoxamine hydrochloride** and **orphenadrine citrate** have been adequately discussed under **anti-parkinsonism drugs.**

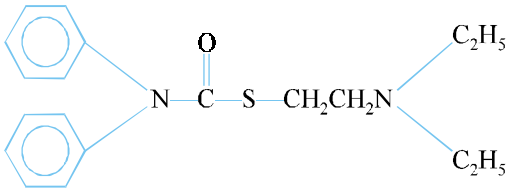
7.3. Aminoalcohol Carbamates

The concept of structural modification amongst the **aminoalcohol carbamates** has crept up due to the introduction of non-polar functions on the unsubstituted N of the carbamoyl moiety in the following general formula :



Only one such compound belonging to this category is discussed here.

A. Fencarbamide INN, Phencarbamide USAN,



S-[2-(Diethylamino) ethyl] diphenylthiocarbamate; Carbamothionic acid, diphenyl-1, S-[2-(diethylamino) ethyl] ester;

Escorpal(R) (Farbenfabriken Bayer A.G., W. Germany).

7.4. Aminoalcohols

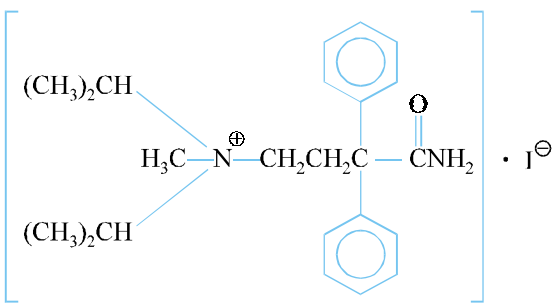
Most of the **aminoalcohols** have been developed in the past two decades. These compounds have gained their prominence as **antiparkinsonism agents,** such as **biperiden hydrochloride, procyclidine hydrochloride, trihexyphenidyl hydrochloride** etc., (see chapter on **'antiparkinsonism agents'**).

7.5. Aminoamides

The **aminoamides** essentially differ from the **aminoalcohols** whereby the polar hydroxyl group in the latter is replaced by the corresponding polar amide function. However, the bulky structural features found commonly at one terminal end of the molecule remain the same in both the species stated above.

Examples : Isopropamide iodide; Tropicamide.

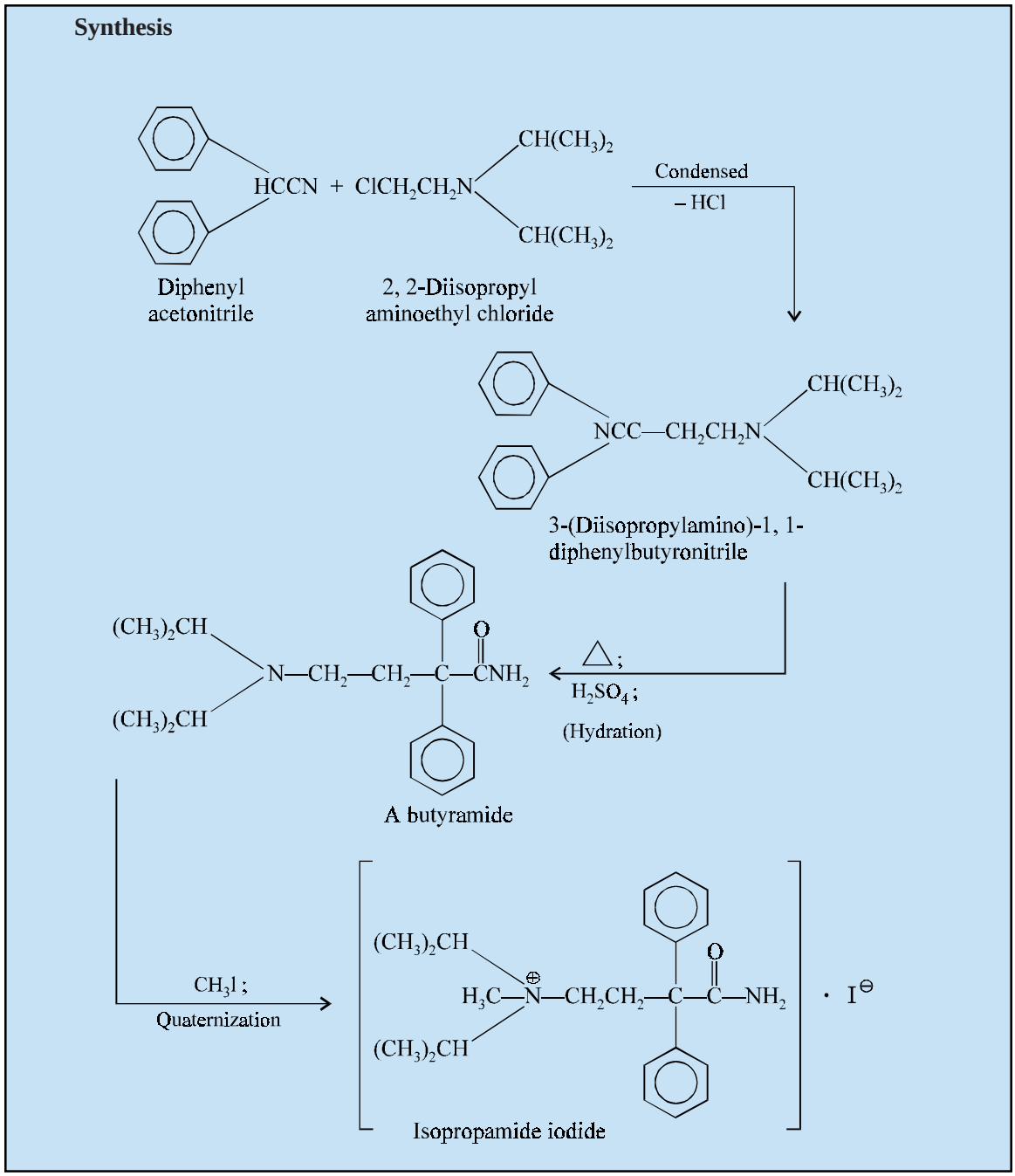
A. Isopropamide INN, Isopropamide Iodide BAN, USAN,



(3-Carbamoyl-3, 3-diphenylpropyl) diisopropylmethylammonium iodide; Benzenepropanaminium, γ-(aminocarbonyl)-N-methyl-N, N-*bis* (1-methyl-ethyl)-γ-phenyl-, iodide ; USP ;

Darbid(R) (SK and F).

Synthesis

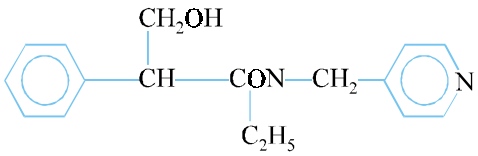


3-(Diisopropylamino)-1, 1-diphenylbutyronitrile is obtained by the condensation of diphenyl acetonitrile with 2, 2-diisopropylamino ethyl chloride, which undergoes hydration by heating in the presence of sulphuric acid to yield the corresponding butyramide. Quaternization of the butyramide with methyl iodide results into the formation of the official compound.

Isopropamide iodide is recommended for *use in the treatment of peptic ulcer and various other states of gastrointestinal hyperactivity. It has also been advocated as an adjunct in the therapy of duodenal and gastric ulcer and invariably in the relief of visceral spasms.*

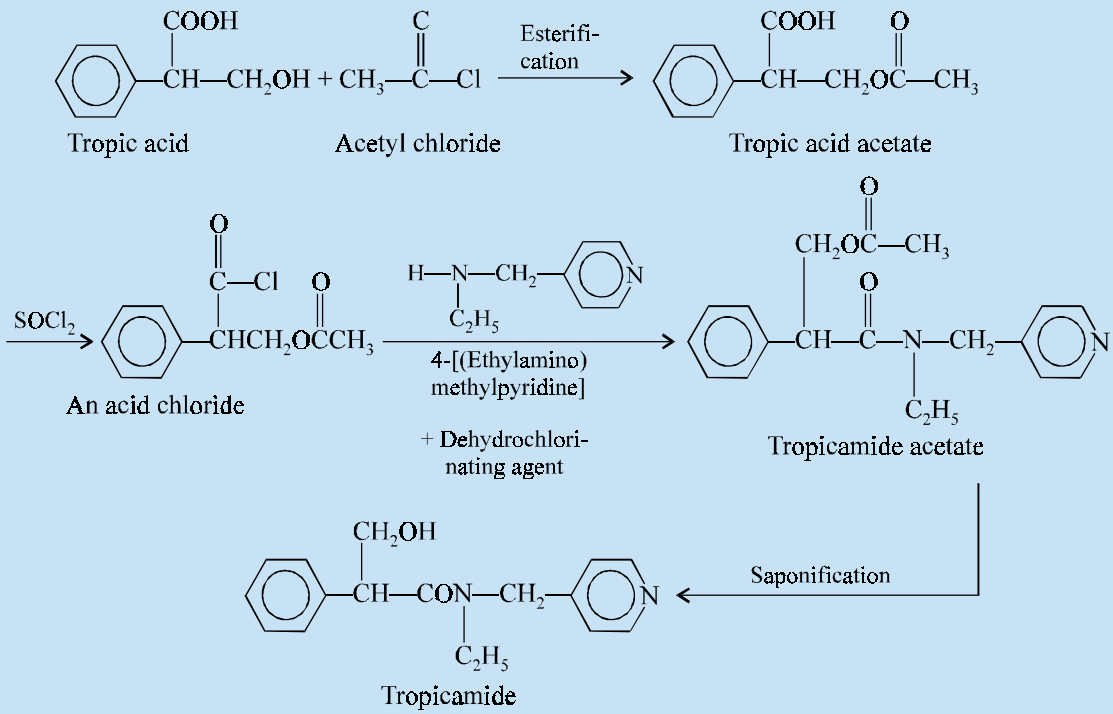
Dose : *Initial, adult, oral, 5 mg twice a day.*

B. Tropicamide INN, BAN, USAN,



N-Ethyl-2-phenyl-N-(4-pyridylmethyl)-hydracrylamide ; Benzeneacetamide, N-ethyl-α-(hydroxymethyl)-N-(4-pyridinyl-methyl)- ; N-Ethyl-N-(4-pyridyl-methyl) tropamide ; B.P. U.S.P., Mydriacyl(R) (Alcon).

Synthesis



Esterification of **tropic acid** with acetyl chloride gives tropic acid acetate which on chlorination with thionyl chloride yields the corresponding acid chloride. The resulting product on treatment with 4-((ethylamino) methyl-pyridine and subsequently with an appropriate dehydrochlorinating agent gives rise to **tropicamide acetate.** Saponification of this compound affords the desired official product.

Tropicamide is *frequently used in the ophthalmologic practice to induce mydriasis and cycloplegia.*

Dose : *Usual, adult, topical, 1 to 2 drops of a 0.5 or 1% solution to the conjunctiva ; for mydriasis 0.5% solution is employed and for cycloplegia 1% solution.*

7.6. Diamines

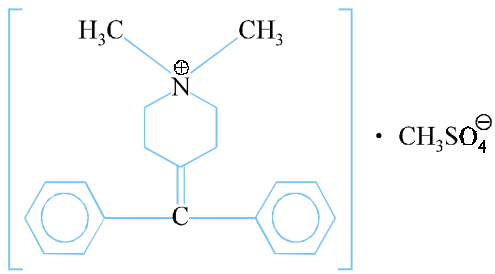
The *two* derivatives of **phenothiazine** belonging to the classification of diamines are **diethazine** and **ethopropazine hydrochloride** which are broadly grouped together under antiparkinsonism agents. The former being more toxic than the latter and hence has been withdrawn. The latter has been discussed under **'antiparkinsonism agents'**.

7.7. Miscellaneous Amines

The **miscellaneous amines** essentially consists of two potent compounds both of which possess characteristic bulky group that attribute to the typical features of the usual antimuscarinic molecule.

Examples : Diphemanil methylsulphate, Methixene hydrochloride, Glycopyrronium bromide and **Pirenzepine.**

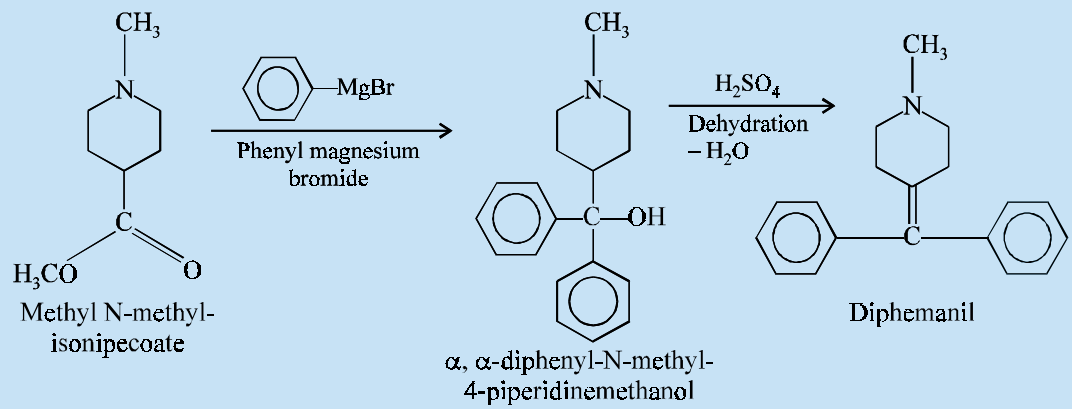
A. Diphemanil Metisulfate INN, Diphemanil Methylsulphate BAN ; Diphemanil Methylsulfate USAN,



4-(Diphenylmethylene)-1, 1-dimethylpiperidinium methyl sulphate ; 4-Benz-hydrylidene-1, 1-dimethyl piperidinium methyl sulphate ; Piperidinium, 4-(diphenylmethylene)-1, 1-dimethyl, methyl sulphate ; USP ;

Prantal[R] (Schering-Plough)

Synthesis



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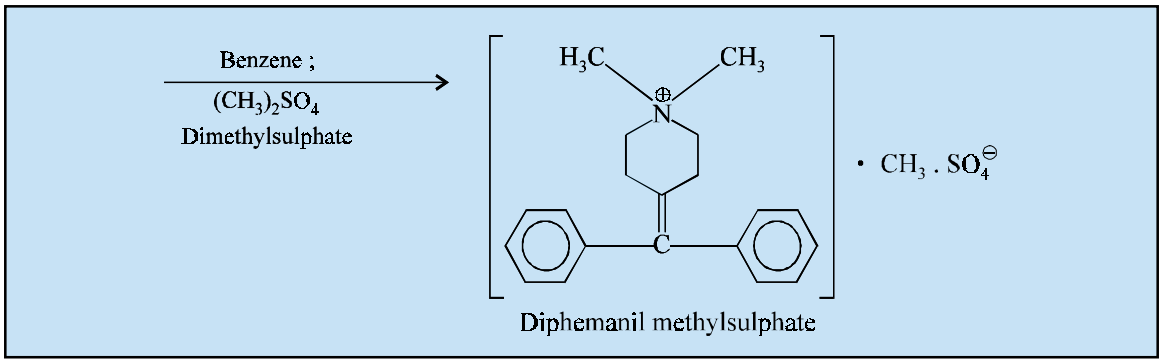
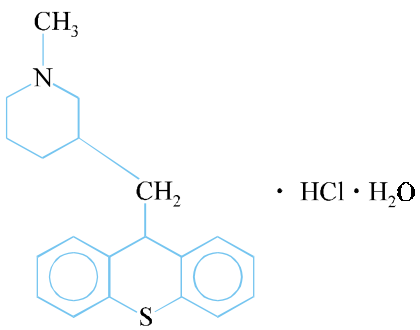


Grignardization of methyl N-methyl isonipecoate with phenyl magnesium bromide yields α, α-diphenyl-N-methyl-4-piperidine methanol which on dehydration with concentrated suplhuric acid gives the diphemanil base. **Quaternization** of the purified base in benzene with dimethyl sulphate yields the desired official compound.

Diphemanil methylsulphate is the drug of choice in causing the relief of pylorospasm. At comparatively low doses it exerts its action in two ways, namely, by effectively suppressing sweating and by causing bronchodilation. Hence, it finds its wide application in the *treatment of gastric hyperacidity, hypermotility, hyperhidrosis and peptic ulcer. It is also recommended for gastric and duodenal ulcer, and to relieve visceral spasms.*

Dose : *Initial, oral, 100 mg 4 to 6 times daily.*

B. Metixene INN, Methixene Hydrochloride BAN, USAN,



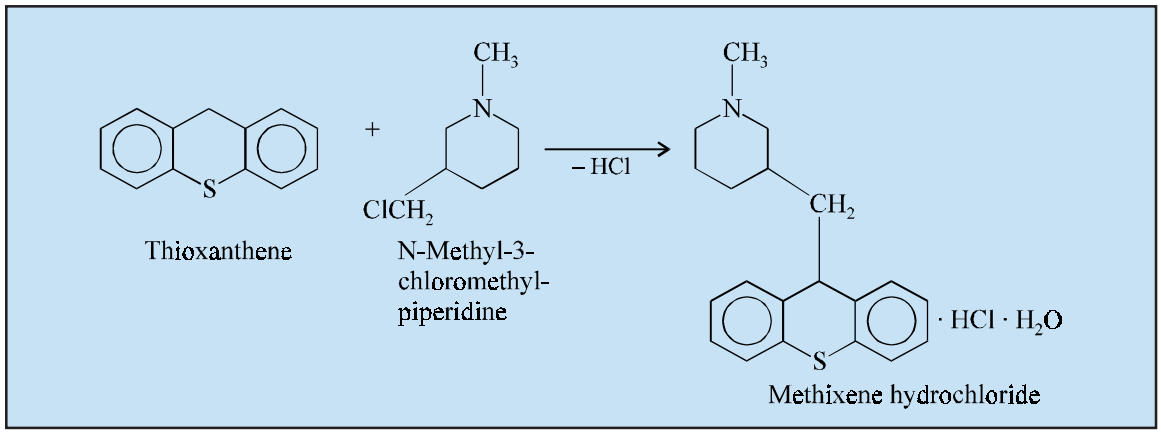
1-Methyl-3-(thioxanthen-9-ylmethyl)-piperidine hydrochloride monohydrate ; 9-(1-Methyl-3-piperidylmethyl) thioxanthene hydrochloride monohydrate;

Trest(R) (Dorsey Pharm.).

Synthesis

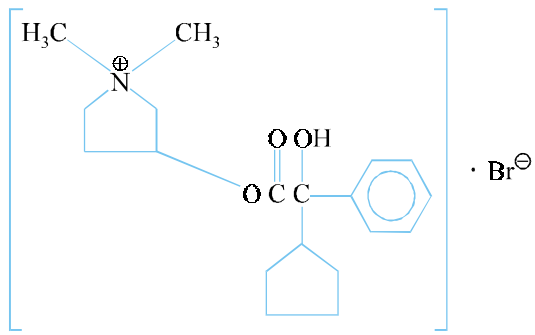
It may be prepared by the alkylation of the sodium salt of thioxanthene with N-methyl-3-chloromethyl piperidine.

Methixene hydrochloride besides possessing antimuscarinic properties also exhibit antihistaminic, local anaesthetic and antispasmodic actions. It is invariably employed in the *management of pylorospasm, biliary dyskinesia, spastic colon, gastritis and also in duodenal ulcer.*



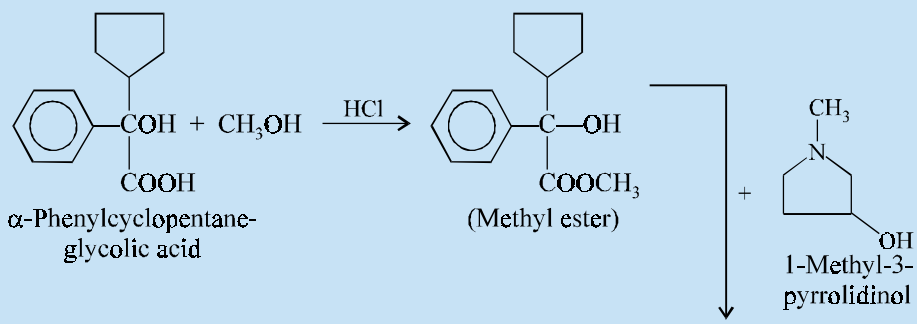
Dose : *1 to 2 mg 3 times daily.*

C. Glycopyrronium Bromide INN, BAN, Glycopyrrolate USAN,



3-Hydroxy-1, 1-dimethylpyrrolidinium bromide α-cyclopentyl-mandelate; Pyrrolidinium, 3-(cyclopentylhydroxyphenylacetyl) oxy-1, 1-dimethyl-, bromide ; U.S.P. ;
Robinul(R) (Robins).

Synthesis



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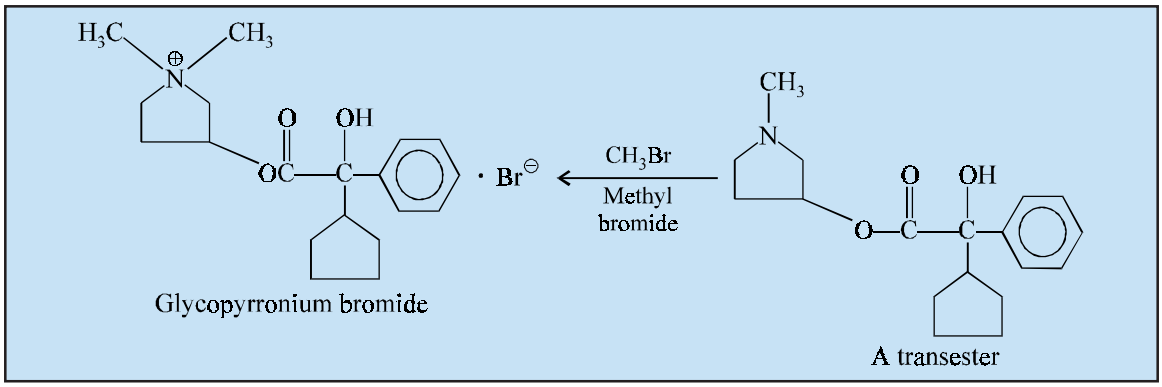
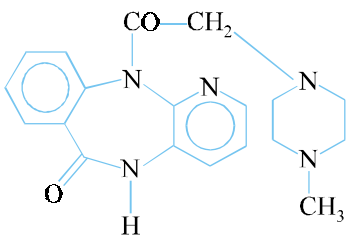


Esterification of α-phenylcyclopentane glycolic acid with methanol in the presence of hydrochloric acid yields the corresponding methyl ester which on further treatment with 1-methyl-3-pyrrolidinol undergoes transesterification and this on subsequent reaction with methyl bromide gives the desired official compound.

Glycopyrrolate is one of the four choicest drugs used in the management and control of gastric secretion. ***It exerts a two-fold action, first by prolonging the gastric emptying time and secondly by decreasing the gastric acid production. Thus it generously favours the retention of antacids in acute cases of peptic ulcer. Besides, it also finds its usefulness in the treatment of colitis, biliary spasm, spastic colon, spastic duodenum***.

Dose : *Initial, oral, 1 to 3 mg, 6 to 8 hours per day.*

D. Pirenzepine INN, BAN,



5, 11-Dihydro-11-[(4-methyl-1-piperazinyl) acetyl]-6H-pyridol [2, 3-β] [1, 4] benzodiazepine-6-one ;

Gastrozepin(R) (as dihydrochloride) [Boehringer Ingelheim] ;

Pirenzepine hydrochloride is found to retard gastric secretion appreciably with minimal systemic anticholinergic effects. Hence it has been successfully employed for the *management and treatment of hyperacidity and peptic ulcer.*

7.8. Mechanism of Action

The **mechanism of action** of the various categories of **'muscarinic agents'** described under Sections 7.1 through 7.7 shall be discussed individually in the sections that follows :

7.8.1. Aminoalcohol Esters

The *five* potent compounds discussed under Section 7.1 are as follows :

7.8.1.1. Atropine

The antimuscarinic activity of **atropine** largely resides in the ***l-isomer (l-hyoscyamine).*** It is absorbed rapidly from the GI-tract and is distributed rather speedily throughout the body. It also produces *mydriasis** for a longer duration and also *cycloplegia*** for more than upto 7 days. It gets metabolized solely in the liver. The plasma half life is found to be less than 4 hours.

7.8.1.2. Cyclopentolate Hydrochloride

Although, the **'drug'** does not seem to affect intraocular tension appreciably, yet it must be used with great care and percautions in patients having either very high intraocular pressure or with unrecognized glaucomatous changes. After being used to the cornea, the ensuing *cycloplegia* is almost complete in 25 to 75 minutes. A necessary neutralization with a few drops of **pilocarpine nitrate** (1–2%) solution, invariably affords almost complete recovery in a span of 6 hours ; otherwise it would take a relatively longer duration of nearly 6–24 hours for its complete recovery.

7.8.1.3. Dicyclomine Hydrochloride

It possesses approximately 1/8th the neurotropic activity of **atropine,** and nearly double the musculotropic activity of **papaverine.** It has substantially minimised the undesirable side effect intimately linked with the **atropine-type compounds.** It exerts its spasmolytic effect on various smooth-muscle spasms, specifically those associated with the GI-tract.

7.8.1.4. Hematropine Hydrobromide

The **'drug'** a tertiary amine hydrobromide, causes both *mydriasis* and *cycloplegia.* However, its duration of action seems to be much shorter and rapid when compared to those of **atropine**; and perhaps it may be the reason why it is preferred for such purposes.

7.8.1.5. SAR of Amino-Alcohol Esters

A plethora of extremely potent antimuscarinic medicinal compounds essentially possess an esteratic functional moiety, and this could perhaps be a major contributing feature for the effective binding. However, this explanation seems to be not only reasonable but also plausible by virtue of the fact that **acetylcholine (ACh)** the agonist essentially possesses an almost identical characteristic feature and function for getting strategically bound to the same site.

7.8.2. Aminoalcohol Ethers

The *three* medicinal compounds cited under this category, namely : **benzotropine mesylate, chlorphenoxamine hydrochloride** and **orphenadrine citrate** have been discussed under **'antiparkinsonism drugs'**.

7.8.3. Aminoalcohol Carbamates

The only compound dealt with in this section is **phencarbamide.**

7.8.3.1. Phencarbamide

The **'drug'** is reported to possess appreciable antimuscarinic activities. It finds its usage as its napadisylate salt (derivative) exclusively in the control, management and treatment of gastro-intestinal disorders.

---

*Pronounced or abnormal dilation of the pupil.

**Paralysis of the ciliary muscle.

7.8.3.2. SAR of Aminoalcohol Carbarmates

The introduction of non-polar bulky functional moieties *e.g.*, phenyl ring, on the unsubstituted N-atom of the carbamoyl group perhaps render the molecule capable of **van der Waal's interactions** to the receptor surface to a certain extent.

7.8.4. Aminoalcohols

The compounds stated under this specific section, such as : **biperiden hydrochloride, procyclidine hydrochloride, trihexyphenidyl hydrochloride,** have been dealt with under the chapter on **'antiparkingonism agents'**.

7.8.5. Aminoamides

There are *two* drugs discussed under this section *viz.*, **isopropamide iodide** and **tropicamide** which would be treated as under :

7.8.5.1. Isopropamide Iodide

The **'drug'** exerts a potent anticholinergic effect and causes atropine-like effects peripherally. It has been observed that only at high dose levels it affords sympathetic blockade at the ganglionic sites. It can provide a long extendable action lasting upto almost 12 hours to contain the antispasmodic and antisecretory effects.

7.8.5.2. Tropicamide

The **'drug'** possesses an obvious advantage over the **belladona alkaloids** in two aspects, namely : *first*, its evident **shorter duration of action ;** and *secondly*, the over homatropine in its ability to **induce cycloplegia.** It is found to cause little enhancement of the intraocular pressure in the normal subjects ; but it may do so in such patients having either glaucoma or suffering from some sort of structural deformities in the anterior chamber of the eye.

7.8.5.3. SAR-of Aminoamides

In fact, the aminoamide type of anticholinergic usually designates almost the same type of molecule as the **aminoalcohol** group ; however, it has an apparent and absolutely distinguishable characteristic feature duly represented by the replacement of the corresponding polaramide group with the corresponding polar hydroxyl moiety. Nevertheless, the **aminoamides** still retain the same bulky structural moieties as are commonly seen at one end of the molecule.

7.8.6. Diamines

The *two* drugs sited under this category *viz.*, **diethazine** and **ethopropazine hydrochloride** have been dealt with adequately under the chapter on **'antiparkinsonism agents'**.

7.8.7. Miscellaneous Amines

The *four* compounds discussed under this category, namely : **diphemanil methylsulphate, methixene hydrochloride, glycopyrronium bromide** and **pirenzepine,** will be described as under :

7.8.7.1. Diphemanil Methylsulphate

It acts as a potent parasympatholytic by blocking the nerve impulses at the site of parasympathetic ganglia; however, it fails to invoke a sympathetic ganglionic blockade. It has been observed to be highly

specific in its activity upon those innervations which categorically activate both functionalities, namely : (*a*) GI-motility ; and (*b*) gastric secretion. Interestingly, based on the extremely specific nature of its pharmacological activity on the gastric functions actually renders diphemanil particularly beneficial in the control, management and treatment of peptic ulcer. Besides, its inherent lack of atropine-like effects makes this specific usage relatively less painful in comparison to several other antispasmodic drugs.

Note. The methylsulphate salt is considered to be the best in terms of its stability in comparison to its corresponding halides e.g., Cl^- (hygroscopic) ; Br^- and I^- (toxic reactions).

7.8.7.2. Methixene Hydrochloride

The **'drug'** essentially exhibits both antihistaminic and direct antispasmodic activities. It has been duly observed that the drug is invariably absorbed from the GI-tract. It subsequently gets excreted through the urine, partly as its corresponding isomeric sulphoxides or their metabolites ; and a reasonable quantum as unchanged product.

Methixene hydrochloride has been profusely indicated in such preparations that may ultimately relieve gastro-intestinal spasms.

7.8.7.3. Glycopyrronium Bromide

It is a quaternary ammonium antimuscarinic agent having marked and pronounced peripheral effects that are quite akin to those of atropine. It has been found that approximately 10–25% of the **'drug'** gets absorbed from the GI-tract when administered orally. It penetrates the blood brain barrier (BBB) rather very poorly. It gets ultimately excreted in bile and urine.

7.8.7.4. Diphemanil Methylsulphate

The **'drug'** is quite active for the symptomatic management and subsequent control of visceral spasms. It may also cause enough relief from the ensuing painful and distressing spasms of the biliary and the genitro-urinary systems. Importantly, it also finds its adequate usage for the treatment of symptomatic bradycardia.

8. GANGLIONIC BLOCKING AGENTS

Langley first studied the action of drugs on the autonomic ganglia with the alkaloid nictoine obtained from *Nicotiana tabacum*. Subsequently, some other alkaloids were also found to possess similar effects, namely ; **coniine** from the poison Hemlock obtained from *Conicum maculatum*, **gelsemine** from the yellow **jasmine** and **lobeline** from the lobelia, a native of America.

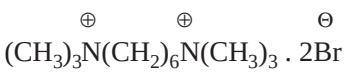
Generally, **ganglionic blocking agents** normally exert their action by competing with acetylcholine from the cholinergic receptors present in the autonomic postganglionic neurons. In fact, the ganglia of either of the sympathetic and parasympathetic nervous systems are cholinergic in character, these therapeutic agents interrupt the outflow through both these systems. Therefore, it is not practically possible to accomplish a complete therapeutic block of the autonomic outflow to a specific locus without encountering a few undesirable but unavoidable '**side effects**' that may arise as a consequence from the blockade of other ensuing autonomic nerves. Thus, the resulting blockade of the sympathetic outflow to the blood vessels may ultimately lead to either a distinct hypotension or an enhanced blood flow (having a pink or warm skin).

In general, the **ganglionic blocking agents** must be employed with great caution particularly when such drugs as : hypotensives, antihypertensives or anaesthetic drugs are used concomitantly, by virtue of the fact that the '*hypotension*' may be aggrevated to such an enormous degree that would cause complete jeopardization of normal blood flow through the brain, heart, or kidney.

The **ganglionic blocking agents** are usually used in hypertension, peripheral vascular disease, vasopastic disorders—thereby lowering the blood pressure and increasing the peripheral blood flow. Occasionally these agents are also employed for their interruption of parasympathetic nervous outflow, as is observed in peptic ulcer and intestinal hypermotility.

Such **ganglionic blocking agents** that interfere with the nervous transmission of sympathetic as well as para-sympathetic ganglia may include : **hexa-methonium bromide** ; **mecamylamine hydrochloride** ; **pempidine** ; **pentolinium tartrate, trimetaphan camsylate,** etc.

A. Hexamethonium Bromide INN, BAN,



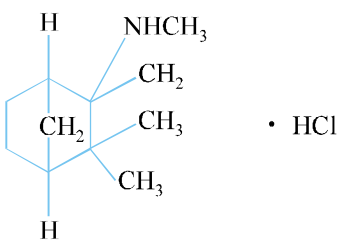
Hexamethylenebis (trimethylammonium bromide) ; Hexonium bromide ; BPC. (1968) ;

Bistrium Bromide(R) (Squibb).

Hexamethonium bromide is a quaternary ammonium ganglion blocking agent which inhibits the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. It is usually employed in the *treatment of severe or malignant hypertension.*

Dose : *Initial, subcutaneously or intramuscularly 5 to 15 mg ; administration after each 4 to 6 hours, if necessary.*

B. Mecamylamine INN, Mecamylamine Hydrochloride BAN, USAN,

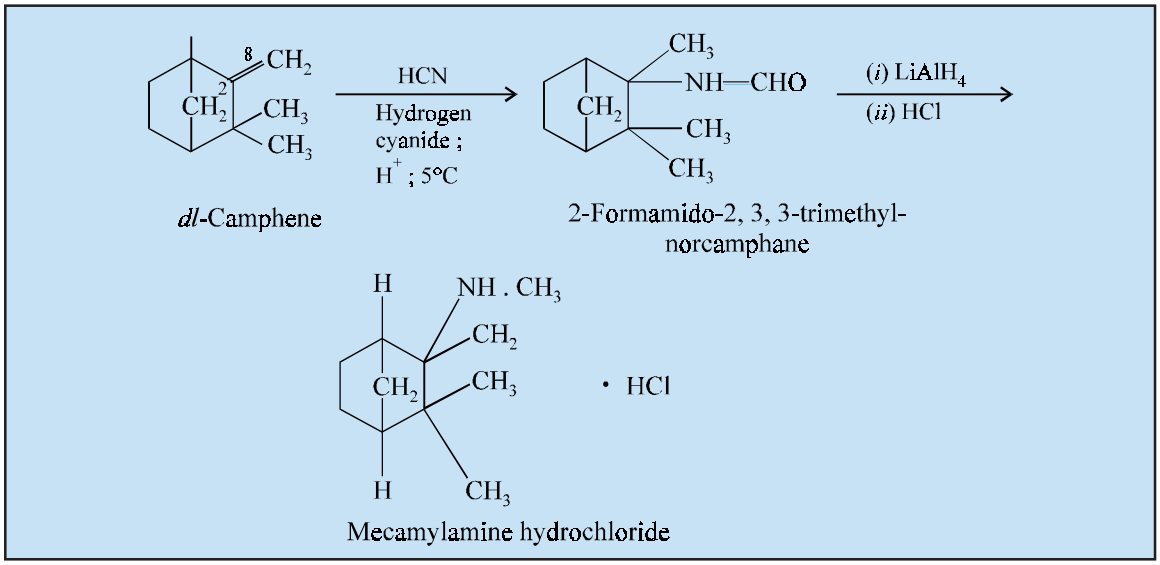


N, 2, 3, 3-Tetramethyl-2-norbornanamine hydrochloride ; Bicyclo [2, 2, 1] heptan-2-amine, N, 2, 3, 3-tetramethyl-, hydrochloride ; BP ; (1968), USP ; Int. P., Ind. P. ;

Inversine(R) (Merck).

Synthesis

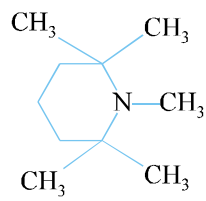
***dl*-Camphene** on treatment with an excess of hydrogen cyanide in a rather strongly acidic medium to 5°C gives rise to 2-formamido-2, 3, 3-trimethyl-norcamphane. The course of reaction may be considered as due to the addition of HCN to the 2, 8-double bond present in the camphene moiety to yield the corresponding 2-isocyanate which on subsequent hydration gives the formamido derivative. Mecamylamine base is obtained by the reduction of the formyl function in the formamido derivative with lithium aluminium hydride which may be converted into its hydrochloride salt by dissolving the base in an appropriate solvent and passing a stream of HCl gas.



A non-quaternary ammonium compound with very poor ionizability in the small intestine thus rendering it absorbable more easily. It gets excerted through the kidney comparatively slowly thereby enhancing its duration of action.

Dose : *Usual, initial, 2.5 mg twice daily ; maintenance, 7.5 mg thrice daily.*

C. Pempidine INN, BAN



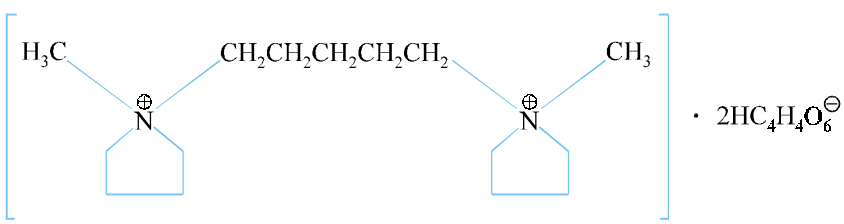
1, 2, 2, 6, 6-Pentamethyl-piperidine ; Pempidine Tartrate (BP ; 1968) ;

Perolysen(R) (May and Baker)

It is a tertiary amine ganglion-blocking agent which essentially blocks the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. It is used in the *managemnet and treatment of severe or malignant hypertension.*

Dose : *Usual, initial, 2.5 mg of pempidine tartrate orally 3 to 4 times daily ; maintenance dose, 10 to 80 mg per day in 4 divided doses.*

D. Pentolonium Tartrate INN, Pentolinium Tartrate BAN,

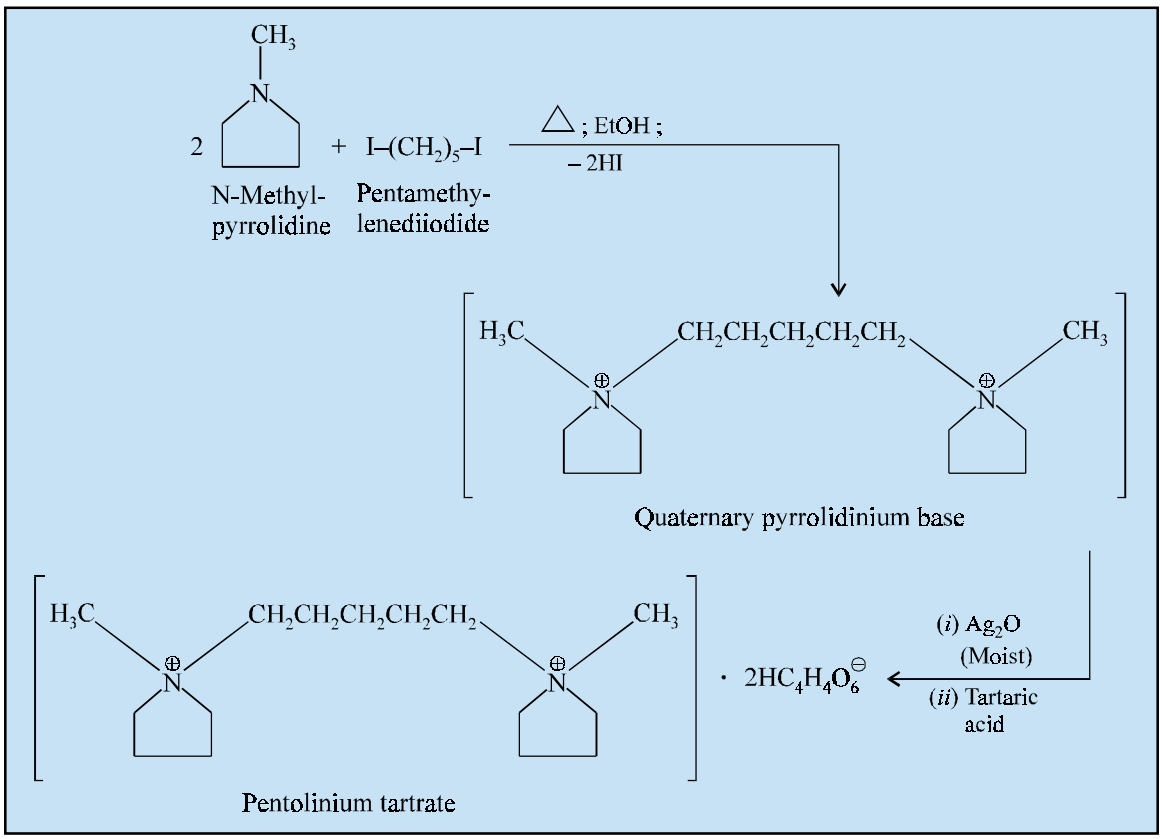


1, 1′-Pentamethylenebis [1-methylpyrrolidinium] tartrate (1 : 2) ; Pyrrolidinium, 1, 1-(1, 5-pentanediyl) *bis* [1-methyl- ; [*R*- (R^*, R^*)]-2, 3-dihydroxy butanedioate (1 : 2) NF ;

Ansolyson(R) (Wyeth).

Synthesis

N-Methylpyrrolidine and pentamethylene diiodide on heating with ethanol yields the quaternary pyrrolidinium base which upon treatment with moist silver oxide and double equimolar proportion of tartaric acid gives the official product.



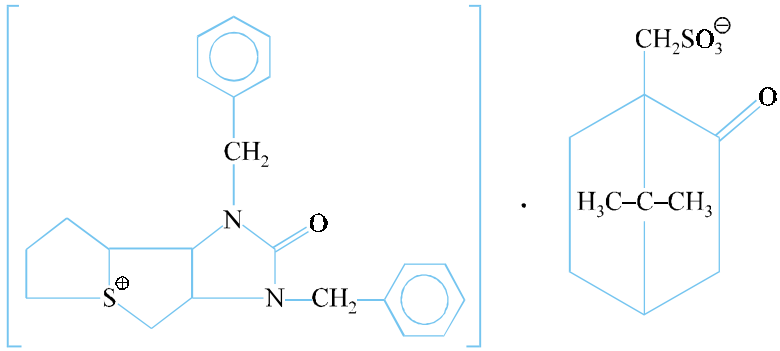
Pentolinium tartrate is mainly used in the *treatment of severe essential and malignant hypertensions and employed to produce controlled hypotension in patients undergoing surgical procedures.*

Dose : *Oral, initial 20 mg 3 times a day for 2 to 7 days, maintenance dose : 60 to 600 mg per day ; intramuscular or subcutaneous, initial, 2.5 to 3.5 mg, increased by 0.5 to 1 mg at 4- to 6- hour intervals till the desired effect achieved ; parenteral dose : 30 to 60 mg.*

E. Trimetaphan Camsilate INN, Trimetaphan Camsylate BAN, Trimethaphan Camsylate USAN,

(+)-1, 3-Dibenzyldecahydro-2-oxoimidazo [4, 5-*c*]-thieno [1, 2- α]-thiolium 2-oxo-10-boranesulphonate (1 : 1) ; BP ; (1968), USP ; Int. P. ;

Arfonad(R) (Roche, U.K.).



Trimetaphan is a **ganglionic-blocking agent** having a very brief duration of action. Hence, it is *chiefly used either for inducing controlled hypotension during surgical procedures or for certain diagnostic procedures.*

Dose : *Intravenous, by infusion, 0.2 to 5 mg/min. in 500 ml of isotonic solution at such a rate so that the blood pressure should not fall below 60 mm Hg.*

8.1. Mechanism of Action

The most probable mechanism of action of the various compounds described under Section 12.8. shall be dealt with in the sections that follows :

8.1.1. Hexamethonium Bromide

The **'drug'** blocks transition at the N_2 nicotinic receptors strategically positioned specifically in the autonomic ganglia. Hexamethonium bromide is both erratically and incompletely absorbed from the GI-tract; and therefore, the absorbed substance is invariably excreted almost completely through the urine in an unchanged form. However, it has been observed that the **'drug'** in a living system is largely confined to the extracellular fluid.

8.1.2. Mecamylamine Hydrochloride

The **'drug'** has an altogether different status from most other ganglionic blocking agents wherein it is not a quaternary ammonium compound; and, therefore, it usually gets very poorly ionized in the small intestine and thereby absorbed not only rapidly but also completely. It has been observed that its **non ionic status** (form) actually allows it to pass into the CNS that may obviously give rise to quite occasional bizarre central disturbances. The **'drug'** exhibits a low renal clearance, and gets absorbed from the GI-tract. It also gets diffused into the tissues, and gets across the placenta and the blood-brain barrier (BBB).

8.1.3. Pempidine

Pempidine exerts its actions in two ways : *first*, the sympathetic block causes peripheral vasodilation thereby affecting enhanced blood flow, raised skin temperature, and reduction blood pressure ; *secondly*, the parasympathetic block causes reduction of gastric and salivary secretion together with retarded motility of the gastro-intestinal tract and bladder.

8.1.4. Pentolinium Tartrate

The two quaternary N-atoms separated by a shorter distance *i.e.*, five CH_2 groups, caused primarily ganglionic blockade and a clinically appreciable fall in BP. Importantly, this *bis*-quaternary drug substance was much less satisfactory. Sympathetic blockade, however, did afford the well predicted pharmacological actions, such as : vasodilation and fall in BP. It is found to be absorbed from the GI-tract in an irregular and incomplete manner.

8.1.5. Trimethaphan Camsylate

Though the **'drug'** is usually classified as a **ganglionic blocking agent,** but it only blocks ganglia in the therapeutic dosage regimen not to an appreciable extent. It has been observed that to a certain extent its hypotensive activities are caused exclusively due to a direct peripheral vasodilator action.

Note. The '*drug*' very often causes the release of histamine ; and, therefore, its usage as a ganglionic blocking agent in subjects having a history of *allergy* and *asthma* should be avoided as far as possible.

9. ADRENERGIC NEURONE BLOCKING AGENTS

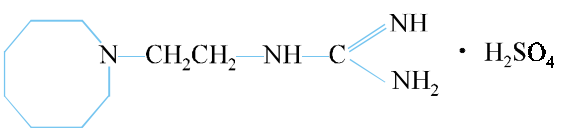
Adrenergic neurone blocking agents usually interfere with postganglionic sympathetic nervous transmission but they do not exert any effect on the parasympathetic nervous system.

It is, however, pertinent to state here that the adrenergic neurotransmitter, **norepinephrine (NE)** is invariably synthesized in the adrenergic neurons. Interestingly, **3, 4-dihydroxyphenylalanine (DOPA),** that is usually formed in the adrenergic neuron by means of the hydroxylation of tyrosine, subsequently undergoes decarboxylation (by the aid of aromatic amino acid decarboxylase) to yield the corresopnding **catecholamine dopamine (3, 4-dihydroxyphenylethylamine).** NE is produced normally within the adrenergic neuron in the viccinity of the nerve endings being *granular organelles* essentially comprising the enzyme **dopamine β-hydroxylase** that subsequently inducts the desired **side-chain-hydroxyl moiety** to dopamine and then to NE. Ultimately, the resulting NE thus generated gets stored in the *granular organelles.*

In short, the **adrenergic neuron blocking agents** help distinctly in reducing the delivery of catecholamines *viz.*, NE, to the adrenergic receptors genuinely, which may eventually take place by disallowing the synthesis of **catecholamines** and their subsequent storage or release.

The following *two* compounds belonging to this category shall be discussed, namely : **Guanethidine monosulphate ; Bethanidine sulphate :**

A. Guanethidine INN, Guanethidine Monosulphate BAN, USAN,

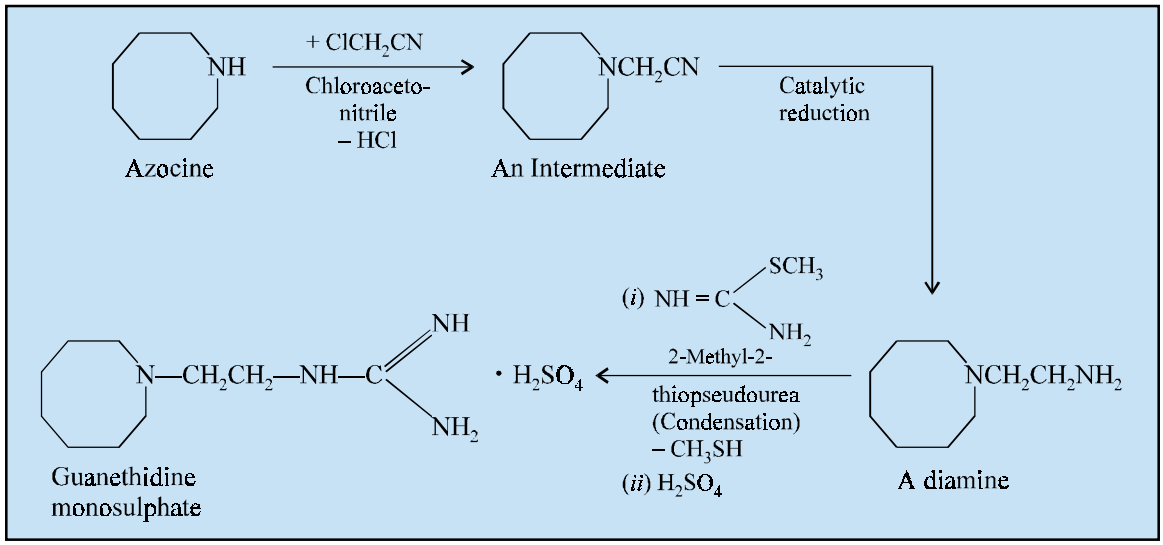


[2-(Hexahydro-1 (2H)-azocinyl) ethyl] guanidine sulphate (1 : 1) ; 1-[2-(Perhydroazocin-1-yl) ethyl] guanidine monosulphate ; BP ; USP ;
Ismelin$^{(R)}$ (Ciba-Geigy).

Synthesis

Alkylation of saturated azocine with chloroacetonitrile yields an intermediate and a mole of hydrogen chloride gets eliminated. Catalytic reduction of the intermediate affords the diamine. The

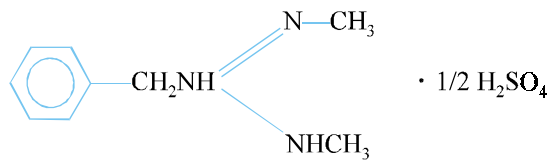
resulting product on condensation with 2-methyl-2-thiopseudourea (*i.e.*, S-methyl ether of thiourea) and the subsequent treatment with sulphuric acid yields the official compound by the elimination of a mole of thiomethanol.



It is an antihypertensive agent which is *frequently employed in the treatment of moderate and severe hypertension, or for mild hypertension. It has a rather slow onset of action, the full effect may range from several hours to 2 or 3 days, and its duration of action may extend from 4 or more days.*

Dose : *Usual, initial 10 to 20 mg per day ; usual maintenance dose 30 to 100 mg per day as a single dose but up to 300 mg daily may be given.*

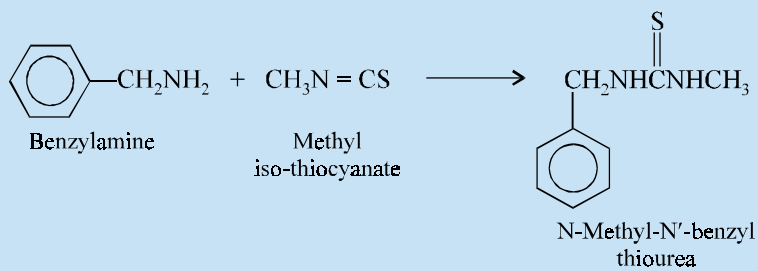
B. Bethanidine INN, Bethanidine Sulphate BAN, USAN,



1-Benzyl-2, 3-dimethylguanidine sulphate ; Guanidine, N, N′-dimethyl-N″-(phenylmethyl)-, sulphate ; BP ;

Esbatal(R) (Calmic, U.K.).

Synthesis



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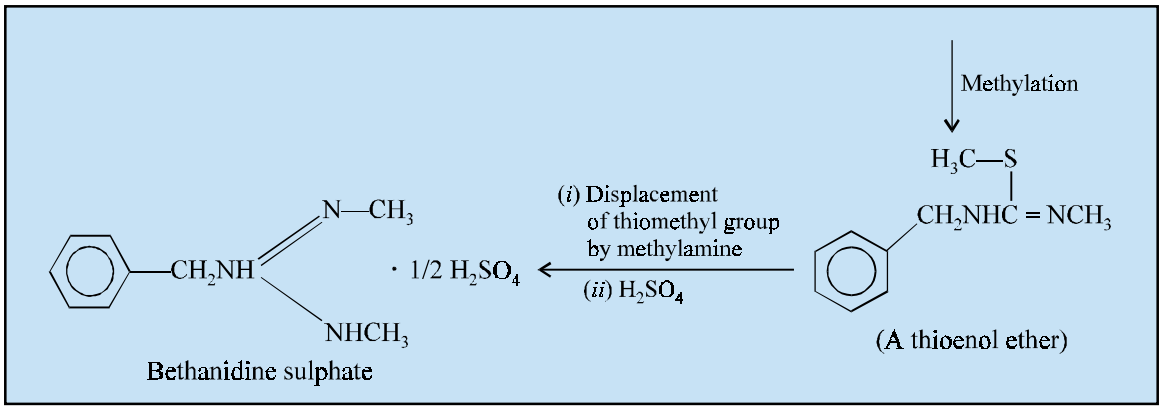

N-Methyl-N′-benzyl thiourea may be obtained by the interaction of benzylamine and methyl isothiocyanate, which on methylation yields a thioenol ether. Displacement of the corresponding thiomethyl group by methylamine *via* an addition elimination process affords **bethanidine** which on treatment with an aliquot of sulphuric acid gives the official product.

It is usually employed in the *treatment of moderate and severe hypertension or for the treatment of mild hypertension in patients.*

Dose : *Usual, initial dose 10 mg 3 times per day. Maintenance dose ranges from 20 to 200 mg per day.*

9.1. Mechanism of Action

The specific mechanism of action of the selected compounds under Section 12.9.1 are enumerated below :

9.1.1. Guanethidine Monosulphate

The **'drug'** inherently contains the **'guanido moiety'** that essentially inducts an appreciable degree of high basicity (pKa = 12) ; and hence, is 99.99% protonated at the physiologic pH. It is worthwhile to mention here that the drug does not pass through the BBB and, unlike reserpine, influences absolutely little CNS-mediated sedation.

Guanethidine distinctly produces vasodilation and positively enhances the venous capacitance significantly. It is observed to bring down the blood pressure to such a dangerously low levels in certain subjects, the drug invariably and importantly is used in *submaximal dose levels ;* and, therefore, administered in conjunction with either **thiazides** (*diuretics*) or **hydralazine** (*hypotensive*), to allow certain adrenergic function. Thus, the **'drug'** is **not** usually used in the treatment of mild to moderate hypertension, but exclusively moderately severe to severe hypertension.

9.1.2. Bethanidine Sulphate

The mechanism of action of the **'drug'** is very much akin to **guanethidine.** It has almost identical actions to the **ganglionic-blocking drugs,** but there is no **parasympathetic blockade** whatsoever.

Probable Questions for B. Pharm. Examinations

1. Classify the **autonomic drugs.** Give the structure, chemical name and use of one potent drug from each category.

2. Give the structure, chemical name and **uses** of of any **three** important sympathomimetic drugs and discuss the synthesis of one such compound selected by you.

3. Discuss the synthesis of **one** important medicinal compound used as an **'autonomic drug'** belonging to the following categories :

(*a*) Alpha-Adrenoreceptor blocking agent,

(*b*) Beta-Adrenoreceptor blocking agent.

4. Name **one** compound each belonging to the cateogry of **'chlinomimetic drugs'** that are either *directly acting* or *indirectly acting*. Describe their synthesis.

5. Give a comprehensive account of **'antimuscarinic agents'** by giving the structure, chemical name and uses of **one** important representative from each cateogry.

6. (*a*) Structure modification amongst the amino-alcohol carbamates by introducing non-polar functions on the unsubstituted N of the carbonyl moiety gave rise to **Phenyl carbamide.** Discuss this medicinal compound.

(*b*) Aminoalchols have gained their cognizance as **antiparkinson agents.** Discuss the synthesis of isopropamide iodide from diphenyl acetonitrile.

7. Give the structure, chemical name and uses of the following **'autonomic drugs'** :

(*a*) Diphemanil methylsulphate.

(*b*) Methixene hydrochloride.

(*c*) Glycopyrronium bromide.

Describe the synthesis of any **one** compound.

8. (*a*) Enumerate the importance of **'ganglionic blocking agents'** as autonomic drugs.

(*b*) Describe the synthesis of Mecamylamine hydrochloride.

9. Describe the **'mode of action'** of the following :

(*a*) Ganglionic blocking agents.

(*b*) Antimuscarinic agents.

10. Give a comprehensive account of the **'adrenergic neurone blocking agents'** with specific reference to :

(*a*) Bethanidine sulphate.

(*b*) Guanethidine monosulphate.

RECOMMENDED READINGS

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14

Diuretics

Chapter

14 Diuretics

1. INTRODUCTION

Diuretics are drugs that promote the output of urine excreted by the kidneys.

The increased excretion of water and electrolytes by the kidneys is dependent on three different processes, *viz.*, glomerular filtration, tubular reabsorption (active and passive) and tubular secretion.

Every normal human being essentially bears a daily rhythm in the excretion of water and electrolytes, being minimum during night and maximum in the morning. This may be a reflection of intra-cellular metabolism. Alteration prevailing in the diurnal rhythm is normally characterized by initial symptoms of disturbance of fluid balance of the body as evidenced in heart failure (Addison's disease), hepatic failure and renal diseases.

Diuretics are very effective in the *treatment of cardiac oedema, specifically the one related with congestive heart failure.* They are employed extensively in various types of disorders, for example, *nephrotic syndrome, diabetes insipidus, nutritional oedema, cirrhosis of the liver, hypertension, oedema of pregnancy and also to lower intraocular and cerebrospinal fluid pressure.* In some instances where oedema is not present, the diuresis may be specifically indicated and effected by certain highly specialized diuretics as in hypertension, epilepsy, migraine, glaucoma, anginal syndrome and bromide intoxication.

In its simplest explanation the formation of urine from the blood mainly comprises of *two* cardinal processes taking place almost simultaneously, namely : (*a*) **glomerular filtration ;** and (*b*) **selective tubular reabsorption, and subsequent secretion.** It has been duly observed that as the **'glomerular filtrate'** gets across through the tubules, substances that are absolutely essential to the blood and tissues, such as: water, salts, glucose, and amino acids are reabsorbed eventually.

However, under perfect normal physiologic circumstances the glomerular filtration rate is approximately 100 mL min^{-1}. And from this volume about 99 mL of the fluid is sent back to the blood pool, and thus only 1 mL is excreted as urine. From these critical and vital informations one may infer that the *'diuretics'* may enhance the rate of urine-formation by either of the *two* following phenomena, *viz.*,

(*a*) Increasing glomerular filtration, and

(*b*) Depressing tubular reabsorption.

2. CLASSIFICATION

Diuretics may be broadly classified under the following *two* categories :

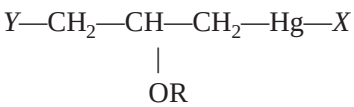
(*a*) Mercurial Diuretics,

(*b*) Non-mercurial Diuretics.

2.1. Mercurial Diuretics

The **mercurial diuretics** essentially contain Hg^{++} in an organic molecule. They usually inhibit sodium reabsorption in the proximal tubuler and ascending loop of Henle. There may be slight effect in the distal tubule where inhibition of chloride reabsorption also occurs. The mercurials have been found to enhance K^+ excretion though potassium loss is less than that produced by many other diuretics. However, the overall action of **mercurial diuretics** is invariably increased by acidification of urine. The mercurial diuretics are not very much used in clinical practices due to their pronounced and marked side-effects *viz.*, mercurialism, hypersensitivity and excessive diuresis which may lead to electrolyte depletion and vascular complications. Most of the **mercurials** are administered by intramuscular route and the availability of orally active diuretics has limited their use.

The **mercurial diuretics** has the following general formula :



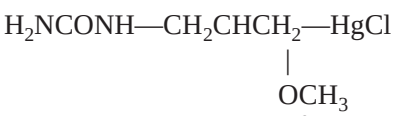
where *X* = OH, halide, or heterocyclic moiety,

Y = Subsituted side chain or substituted aromatic function,

and *R* = Methyl group.

Examples : Chlormerodrin Hg 197 ; Meralluride ; Mercaptomerin sodium ; Merethoxylline procaine ; Mersalyl ; and **Mercumatilin sodium.**

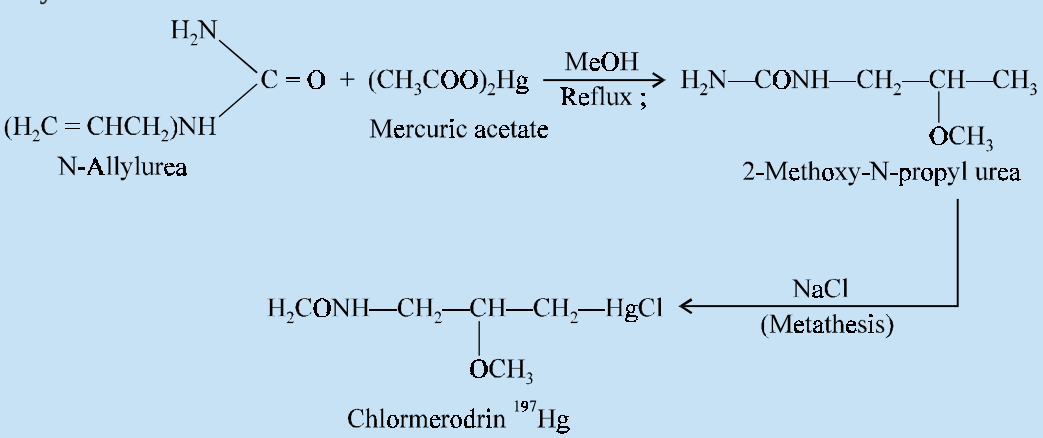
A. Chlormerodrin Hg 197 USAN. Chlormerodrin BAN, Chlormerodrin (197 Hg) INN,



Chloro (2-methoxy-3-uriedopropyl) mercury^{-197} Hg ; Mercury^{197} Hg, [3-(aminocarbonyl) amino] 2-methoxypropyl] chloro-USP ; BPC (1959) ;

Neohydrin-197$^{(R)}$ (Abbott).

Synthesis

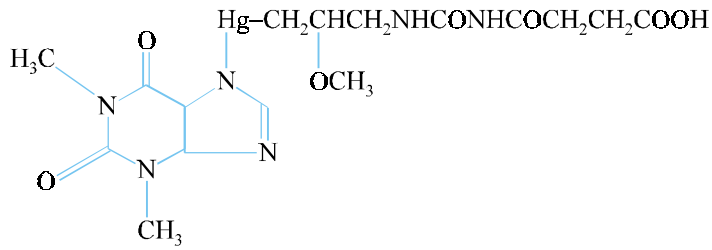


It may be prepared by the interaction of N-allyl urea with mercuric acetate in the presence of methanol when the former gets acetoxymercurated. The saturation also takes place simultaneously when the methoxy group is introduced at position 2. Metathesis occurs on the addition of aqueous NaCl resulting in the precipitation of **chlormerodrin** which is subsquently filtered, washed and dried.

Chlormerodrin[197] Hg is used in the *treatment of oedema of congestive heart failure. It has also been employed in the management of chronic nephritis, ascites of liver disease and nephrotic oedema.*

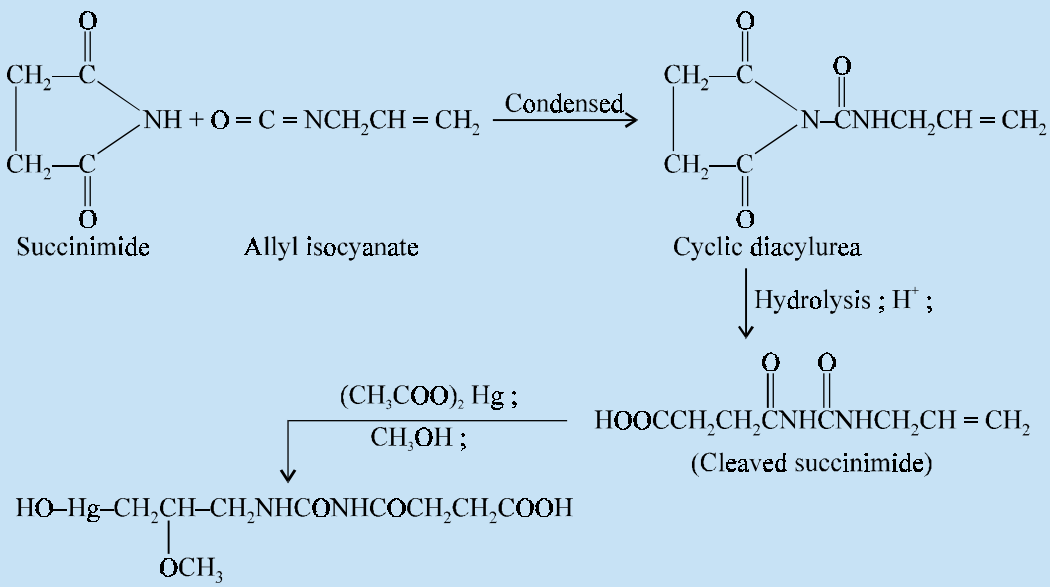
Dose : *Usual, oral, 18.3 to 73.2 mg per day* (≡ to 10 to 40 mg of mercury per day).

B. Meralluride INN, BAN, USAN,



[3-[3-(3-Carboxypropionyl) ureido]-2-methoxypropyl]-hydroxy-mercury mixture with theophylline ; Mercury [3[[[(3-carboxy-1-oxopropyl) amino] carbonyl] amino]-2-methoxypropyl] (1, 2, 3, 6-tetrahydro-1, 3-dimethyl-2, 6-dioxo, 7H-purin-7-yl)-; BPC (1959) ; NFXIV ; Mercuhydrin(R) (Merrell Dow).

Synthesis



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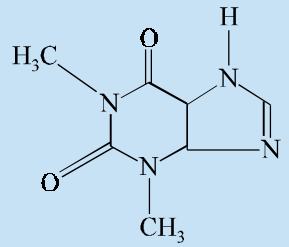
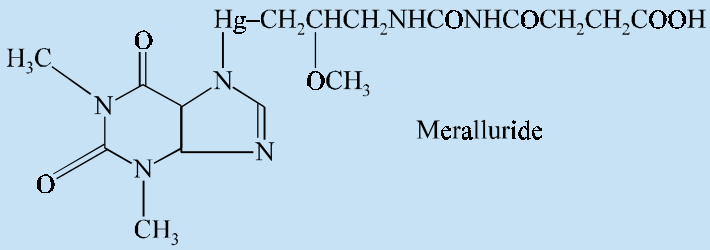
[3-[3-(3-Carboxypropionyl) Ureido]
-2-methoxypropyl]-hydroxy mercury



Theophylline



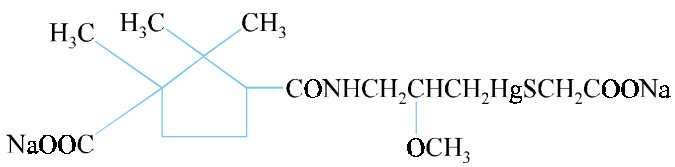
Meralluride

Cyclic diacylurea is prepared by the condensation of succinimide and allyl isocyanate which upon acid hydrolysis affords the cleavage of the ring of the succinimide. Oxymercuration of the terminal olefin bond in the presence of mercuric acetate in methanol solution gives [3-[3-(3-caboxy-propionyl ureido]-2-methoxypropyl]-hydroxy mercury. This on condensation with an equimolar portion of theophylline gives the official compound.

Meralluride is employed for the *treatment of oedema secondary to congestive heart failure, the nephrotic state of glomerulonephritis and hepatic cirrhosis.*

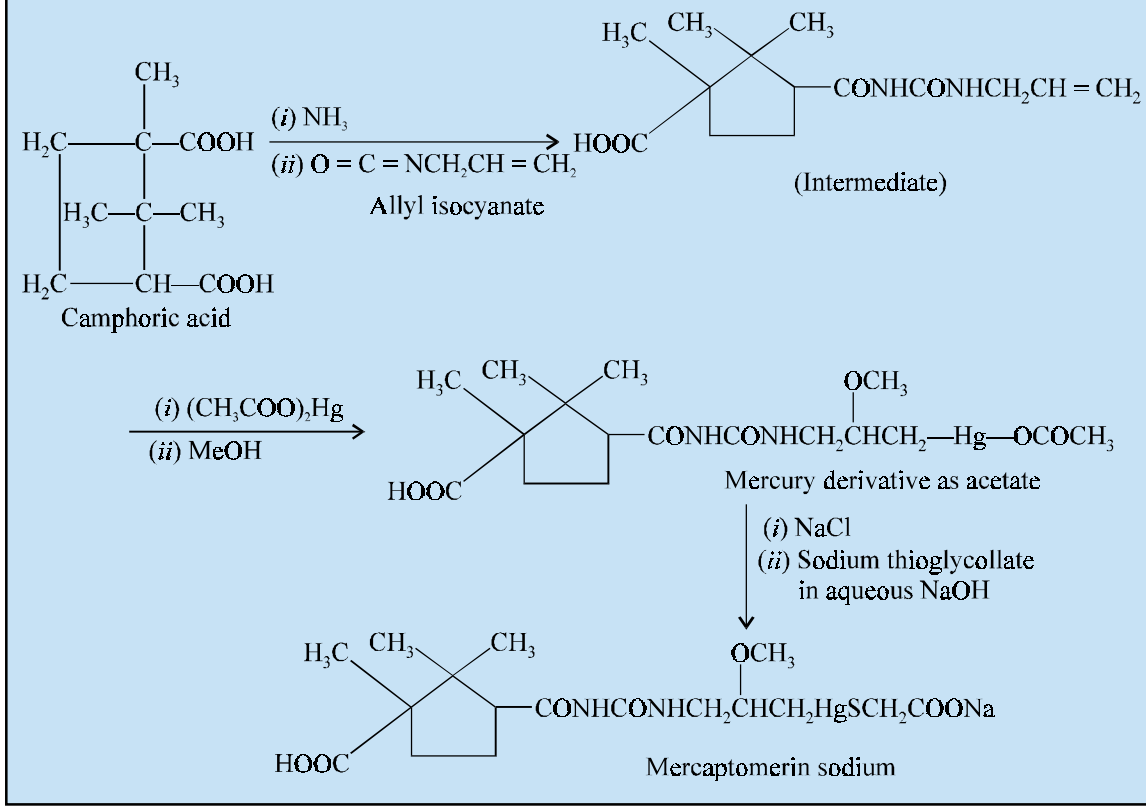
Dose : *Usual, 1 ml (≡ to 39 mg of Hg and 43.6 mg of anhydrous theophylline) 1 or 2 times a week, parenteral 1 to 2 ml.*

C. Mercaptomerin Sodium BAN, USAN, Mercaptomerin INN,



[3-(3-Carboxy-2, 2, 3-trimethylcyclopentane-carboxamide)-2-methoxypropyl] (hydrogen mercaptoacetate)-mercury disodium salt ; Mercury, [3-[[(3-carboxy-2, 2, 3-trimethylcyclopentyl) carbonyl] amino]-2-methoxypropyl] (mercapto-acetate-S)-, disodium salt ; USP. ; Ind. P. ; Thiomerin$^{(R)}$ (Wyeth).

Synthesis

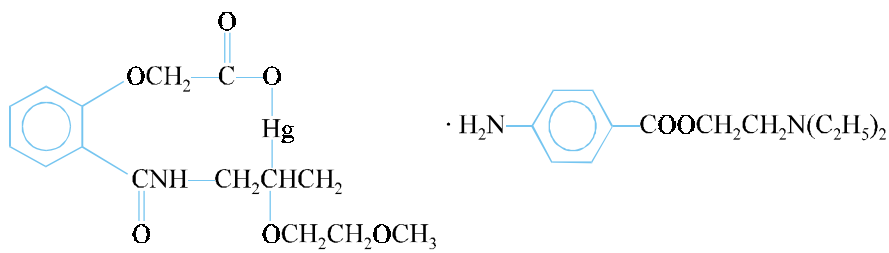


Camphoric acid on condensation with ammonia and subsequent treatment with allyl isocyanate affords an intermediate which on reaction with mercuric acetate in methanol gives rise to the corresponding mercury derivative as acetate. This on treatment with sodium chloride followed by sodium thioglycollate in aqueous NaOH solution yields the official compound which may be obtained either by evaporation or by precipitation with an appropriate solvent.

The uses of mercaptomerin sodium are similar to those of **meralluride.**

Dose : *Usual, 125 mg once daily ; parenteral 15 to 250 mg daily to weekly*

D. Merethoxylline Procaine BAN, USAN,

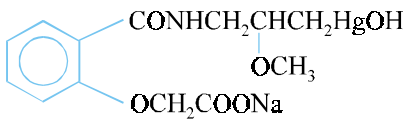


The **procaine merethoxylline** is an equimolar mixture of **procaine** and **merethoxylline,** the latter being the inner salt of [*o*-[[3-(hydroxymercuri)-2-(2-methoxyethoxy)-propyl]-carbamoyl] phenoxy] acetic acid. A mixture of the procaine merethoxylline and theophylline in the molecular proportion of 1 : 1.4 is available as a solution. **Dicurin Procaine(R) (Lilly, USA).**

It has been used effectively in the *treatment of oedema and ascites in cardiac failure and also in ascites due to cirrhosis of the liver. The procaine component helps in reducing the discomfort of local irritation which may be caused by the mercurial compound when injected into tissues.*

Dose : *Usual i.m., subcutaneous, daily 0.5 to 2.0 ml (containing 100 mg of merethoxylline procaine and 50 mg of theophylline per ml)*

E. Mersalyl INN, USAN, Mersalyl Sodium BAN,



Sodium salt of *o*-[(3-hydroxymercuri-2-methoxypropyl) carbamoyl]-phenoxy-acetic acid ; BPC. 1959 ; NF. XI ;

Salygran(R) (Winthrop).

Mersalyl is *used to increase the output of oedema fluid in such typical conditions as renal disease, heart failure etc. It is also employed in the treatment of nephrotic oedema and in ascites due to cirrhosis of the liver.*

Dose : *After assessing patient's tolerance by giving i.m. injection of 0.5 ml (10% m/v) ; 0.5 to 2 ml i.m. on alternate days.*

2.1.1. Mechanism of Action

The mechanism of action of the **'mercurial diuretics'** described under Section 13.2.1 are stated as under :

2.1.1.1. Chlormerodrin

Mercury-197 has been used in the form of **chlormerodrin (^{197}Hg)**, but has been largely superseded by other agents, such as : **Technetium-99 m.** It mainly survived as the **^{197}Hg isotope** ($t_{1/2}$ = 64 hr.) employed for the exact visualization of renal parenchyma.

2.1.1.2. Meralluride

Organic mercurial diuretics were widely employed prior to the introduction of ***'thiazides'*** and a host of other potent non-mercurial diuretics, but now have been virtually superseded by these orally active drugs that are found to be both potent and less toxic.

2.1.1.3. Mercaptomerin Sodium

The statement given under Section 2.1.1.2. also holds good for this *'drug'*.

2.1.1.4. Merethoxylline Procaine

The statement provided under Section 2.1.1.2. also holds good for this *'drug'*.

2.1.1.5. Mersalyl Sodium

The **'drug'** is a powerful diuretic that acts on the renal tubules specifically, thereby enhancing the excretion of Na^+ and Cl^- ions, in almost equal amounts, and of water.

Salient Features of Organomercurials : The exact mechanism of action pertaining to the *organomercurials* is still quite a mystery. However, a few important salient features are as stated under :

(1) They breakdown usually to ionic mercury at the acidic urinary pH.

(2) Bonding of a Hg-atom to the organic residue overwhelmingly lowered the degree of toxicity of the corresponding **'inorganic compounds'** to an appreciable **'acceptable'** levels *in vivo.*

(3) Besides, it may be suggested that as an **'organic ligand'** the chances of legitimate cellular penetration to the specific **sulfhydryl enzymes** present in the proximal tubules is significantly improved thereby inactivating the renal enzymes directly involved with the tubular reabsorption processes, causing *diuresis* ultimately.

2.2. Non-Mercurial Diuretics

The **non-mercurial diuretics** usually are predominant in terms of their significant clinical effectiveness and wider applications. They, in general, possess fewer side-effects and are much less toxic than the corresponding mercurial diuretics. They are used as adjunct specifically in the *treatment of either poisoning or drug over-dosage during which they increase the process of elimination of poisons or drugs through the kidneys. These diuretics are also employed to counter water and salt retention caused by various drug treatments.*

The most commonly used **diuretics** are invariably classified by their respective chemical class, mechanism of action, site of action, or effects on the *urine* contents. Nevertheless, these drugs normally exert their action rather widely with regard to their prevailing efficacy as well as their definite site of action located within the nephron. The real efficacy of a diuretic is often measured by its ability to enhance the rate of excretion of Na^+ ions filtered usually at the glomerulus (*i.e.*, the filtered load of sodium) and hence, must not be misunderstood with the potency, that is the actual amount of the *'diuretic'* essentially needed to cause a specific diuretic response. In other words, the efficacy of a diuretic is invariably estimated in portion by the site of action of the diuretic.

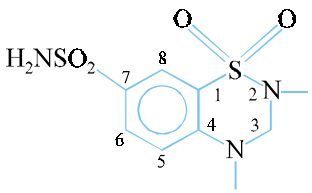
The **non-mercurial diuretics** may be classified on the basis of their chemical structures together with their physical characteristics as follows :

1. Thiazides (Benzothiadiazines),
2. Carbonic-Anhydrase Inhibitors,
3. Miscellaneous Sulphonamide Diuretics,
4. Aldosterone Inhibitors,
5. 'Loop' or 'High-Ceiling' Diuretics,
6. Purine or Xanthine Derivatives,
7. Pyrimidine Diuretics,
8. Osmotic Diuretics,
9. Acidotic Diuretics, and
10. Miscellaneous Diuretics.

2.2.1. Thiazides (Benzothiadiazines)

A major breakthrough in diuretic therapy was the introduction of **chlorothiazide** as a reliable, oral and non-mercurial diuretic in 1955 by Nouello and Spagne in the research laboratories of Merck,

Sharp and Dohme. A number of **benzothiadiazines (I),** having the following general chemical formula :



(I)

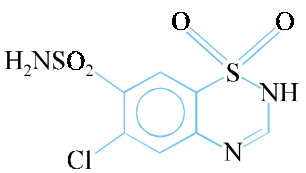
were subsequently synthesized and found to possess varying degree of diuretic actions. The **benzothiadiazines** are frequently known as **thiazides** or **benzothiazides.**

It has been amply observed that the **thiazide diuretics** enhance urinary excretion of both Na and H_2O by specifically inhibiting Na reabsorption located in the cortical (thick) portion of the ascending limb of Henle's loop* and also in the early distal tubules. Besides, they also progressively cause an increase in the excretion of Cl^-, K^+ and HCO_3^- (to a lesser extent) ions. However, the latter effect is predominantly by virtue of their mild carbonic anhydrase-inhibitory action. Importantly, due to their site of action, they invariably interfere with the dilution ; whereas, the concentration of urine is not affected appreciably.

In general, the **thiazide diuretics** minimise the glomerular filtration rate. Furthermore, this specific action fails to contribute to the diuretic action of such drugs, and this would perhaps put forward a logical explanation of their observed lower efficacy in instances having *impaired-kidney function.*

Examples : Chlorothiazide ; Hydrochlorothiazide ; Hydroflumethiazide ; Bendroflumethiazide ; Benzthiazide ; Cyclothiazide ; Cyclopenthiazide ; Methylclothiazide ; Trichlormethiazide ; Polythiazide ; Altizide

A. Chlorothiazide INN, BAN, USAN,



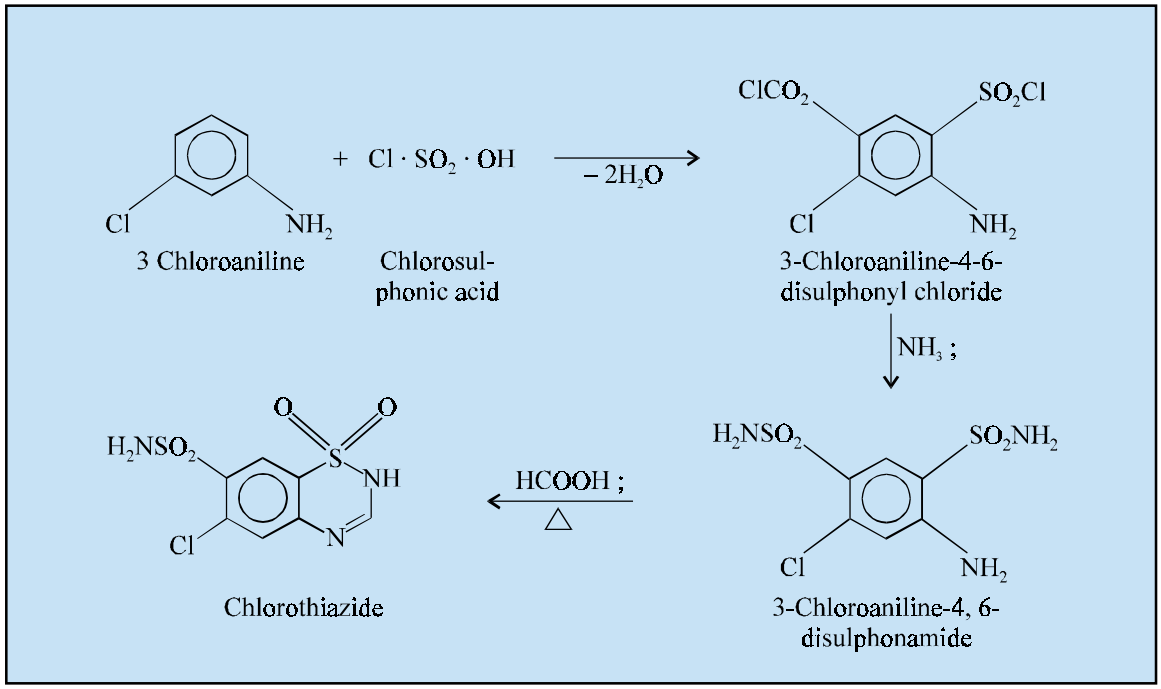
6-Chloro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-Chloro-1, 1-dioxide ; BP., USP., Int. P.

Diuril(R) (Merck Sharp and Dohme) ; SK-Chlorothiazide(R) (Smith Kline and French).

Synthesis

It may be prepared by the chlorination of 3-chloroaniline with chlorosulphonic acid to yield 3-chloroaniline-4, 6-disulphonyl chloride, which is then amidated with ammonia to give the corresponding 4, 6-disulphonamide analogue. This on heating with formic acid affords cyclization through double condensation.

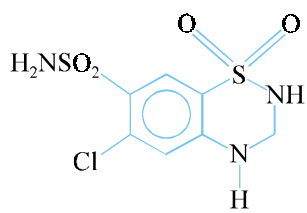
*The U-shaped portion of a renal tubule lying between the proximal and distal convoluted portions. It consists of a thin-descending limb and a thicker ascending limb.



Chlorothiazide is used in the *treatment of oedema associated with congestive heart failure and renal and hepatic disorders. It is also employed in hypertension, either alone or in conjunction with other antihypertensive agents. It is also used in oedema associated with corticosteroid therapy thereby increasing the potassium-depleting action of the latter.*

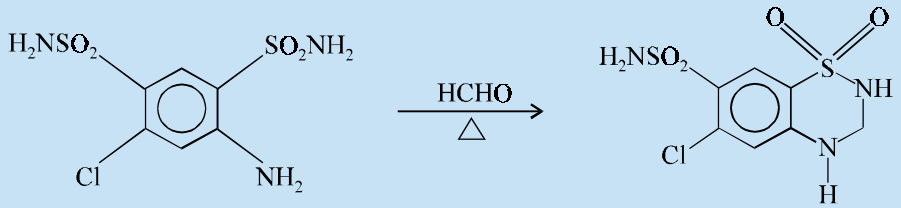
Dose : *Antihypertensive, 250 to 500 mg ; usual, antihypertensive, 250 mg 3 times per day ; diuretic 500 mg to 1g ; usual, diuretic, 500 mg 1 or 2 times per day.*

B. Hydrochlorothiazide INN, BAN, USAN,



6-Chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamine, 6-chloro-3, 4-dihydro-1, 1-dioxide ; BP ; USP ; Int. P ; Esidrix(R) (Ciba-Geigy) ; Hydro DIURIL(R) (MS and D) ; Thiuretic(R) (Parke-Davis) ; Oretic(R) (Abbott).

Synthesis



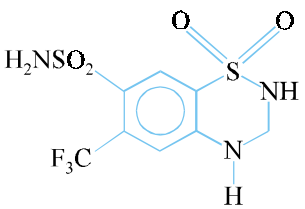
3-Chloroaniline-4, 6-disulphonamide — Hydrochlorothiazide

The route of synthesis is more or less identical with that for chlorothiazide described earlier except that formaldehyde is used instead of formic acid in the final cyclization step from 3-chloroaniline-4, 6-disulphonamide.

Its diuretic actions are similar to those of **chlorothiazide** but it is ten times more potent than the latter. However, when the treatment is prolonged loss of K^+ causes hypokalemia which may be prevented by supplementation with potassium salts.

Dose : *25 to 200 mg per day ; usual, 50 mg 1 or 2 times daily.*

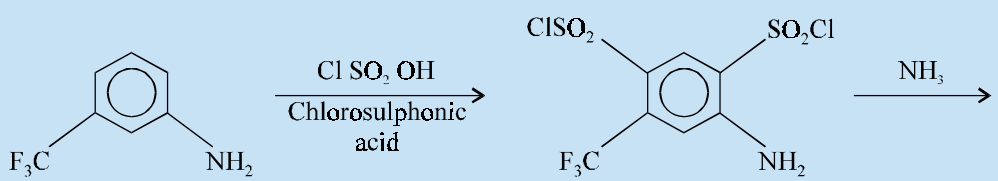
C. Hydroflumethiazide INN, BAN, USAN,



3, 4-Dihydro-6-(trifluoromethyl)-2H-1, 2, 4-benzothiadiazine-7-sulphonamide, 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 3, 4-dihydro-6-(trifluoromethyl)-1, 1-dioxide ; Trifluoromethylhydrothiazide ; BP. USP ; Int. P ;

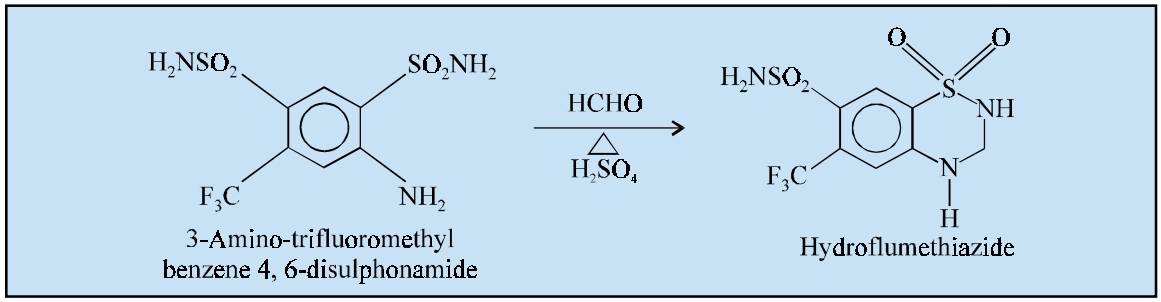
Diucardin(R) (Ayerst) ; Saluron(R) (Bristol).

Synthesis



3-Amino-trifluoro-methyl benzene — 3-Amino-trifluoromethyl benzene-4, 6-disulphonyl chloride

(*Contd...*)

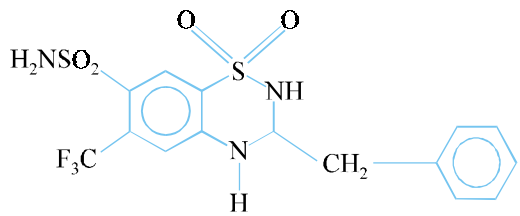


Treatment of 3-amino-trifluoromethyl benzene with chlorosulphonic acid yields the corresponding 4-disulphonyl chloride derivative which on reaction with ammonia gives rise to 3-amino-trifluoro methyl benzene 4, 6-disulphonamide. This on heating with formaldehyde in an environment of sulphuric acid affords a concomitant condensation and finally cyclization to the official compound.

Hydroflumethiazide is a potent diuretic employed in the management of oedema associated with cardiac failure, steroid administration, premenstrual tension and hepatic cirrhosis.

Dose : *25 to 200 mg ; usual, 50 to 100 mg daily.*

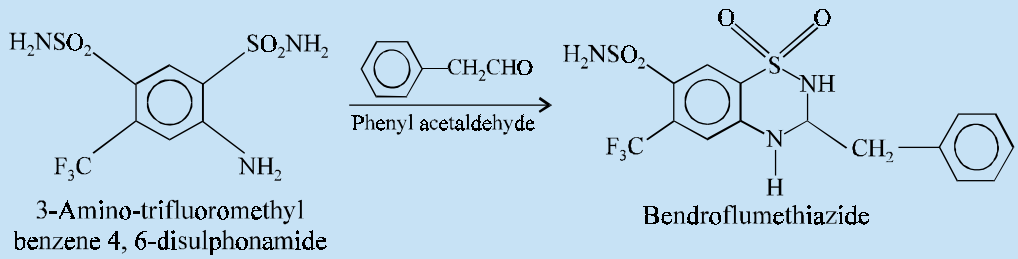
D. Bendroflumethiazide INN, USAN, Bendrofluazide BAN,



3-Benzyl-3, 4-dihydro-6-(trifluoromethyl)-2H, 1, 2, 4-benzo-thiadiazine-7 sulphonamide 1, 1-dioxide ; 2H, 1, 2, 4-Benzothiadiazine-7-sulphonamide, 3, 4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)-, 1, 1-dioxide ; BP., USP., Int. P. ;

Naturetin(R) (Squibb) ; Neo-Naclex(R) (Glaxo).

Synthesis

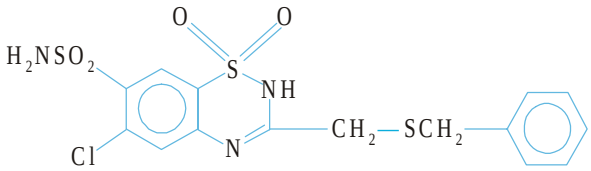


It consists of cyclization of 3-amino-trifluoromethyl benzene 4, 6-disulphonamide through condensation with phenylacetaldehyde.

Bendroflumethiazide is used in the *control and management of oedema, nephrosis and nephritis, cirrhosis and ascites, congestive heart failure, and other oedematous states. It is also employed as an antihypertensive agent.*

Dose : *Initial, diuretic, 5 to 20 mg per day ; maintenance, 2.5 to 5 mg daily ; as antihypertensive, initial, 5 to 20 mg per day, maintenance, 2.5 to 15 mg per day.*

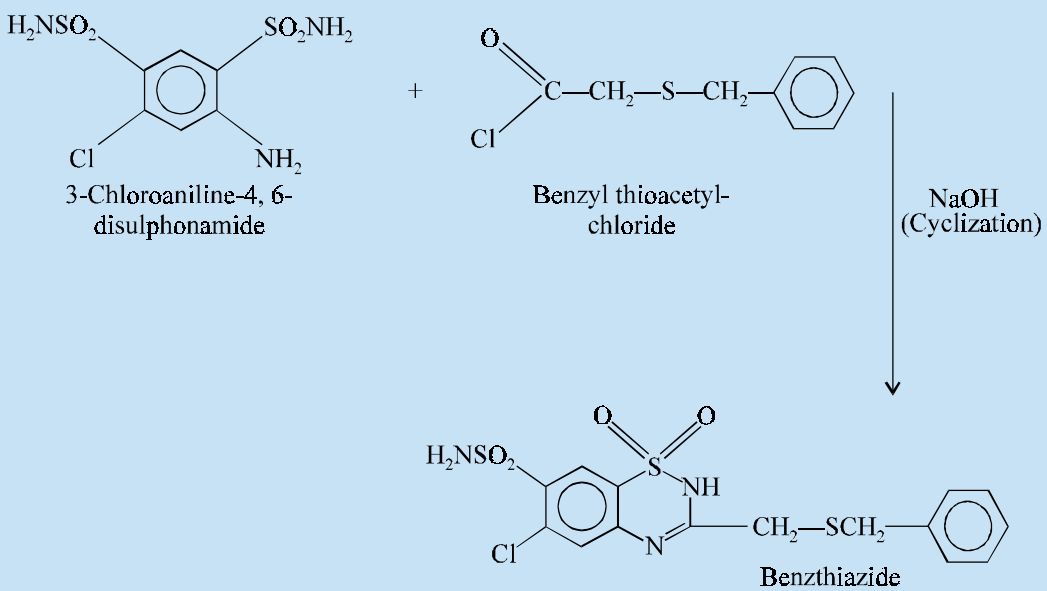
E. Benzthiazide INN, BAN, USAN,



3-[(Benzylthio) methyl]-6-chloro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide-6-chloro-3-[[(phenylmethyl) thio] methyl]-, 1, 1-dioxide ; BPC ; (1963), USP ;

Exna(R) (Robins) ; Aquatag(R) (Tutag).

Synthesis

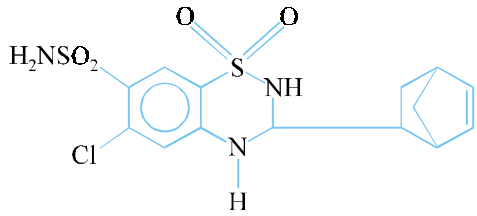


3-Chloroaniline-4, 6-disulphonamide is prepared in the same manner as described for **chlorothiazide** which is then made to condense and cyclize by treatment with benzyl thioacetyl chloride in the presence of sodium hydroxide to yield **benzthiazide.**

It is used as a diuretic and an antihypertensive agent with pharmacological actions similar to those of ***chlorothiazide.***

Dose : *Usual, diuretic, initial, 50 to 200 mg per day ; maintenance, 50 to 150 mg per day ; usual, antihypertensive, initial, 50 mg 2 times a day ; maintenance, maximal dose of 50 mg 3 times daily.*

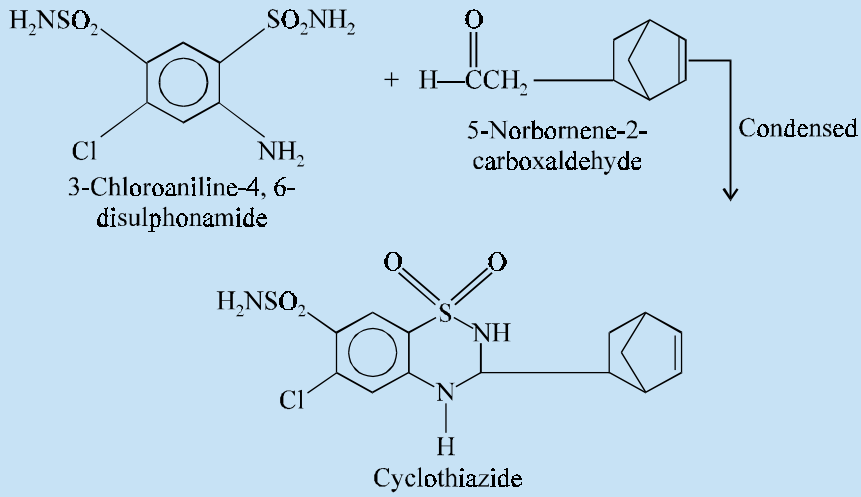
F. Cyclothiazide INN, BAN, USAN,



6-Chloro-3, 4-dihydro-3-(5-nor-bornen-2-yl)-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxides ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 3-bicyclol [2, 2, 1] hept-5-en-2-yl-6-chloro-3, 4-dihydro-, 1, 1-dioxide ; USP ; NF ;

Anhydron(R) (Lilly) ; Fluidil(R) (Adria).

Synthesis

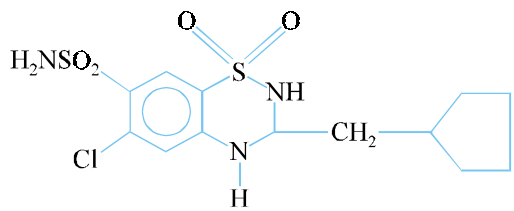


The synthesis of **cyclothiazide** is analogous to that for **chlorothiazide,** except that 5-nonbornene-2-carboxaldehyde is used in the cyclization process in place of formic acid.

It possesses both diuretic and antihypertensive actions. It is often *used as an adjunct to other antihypertensive drugs, such as reserpine and the ganglionic blocking agents.*

Dose : *Usual, initial, diuretic, 1 to 2 mg per day ; maintenance, 1 to 2 mg on alternate days, or 2 or 3 times per week ; usual, antihypertensive, 2 mg 1 to 3 times daily*

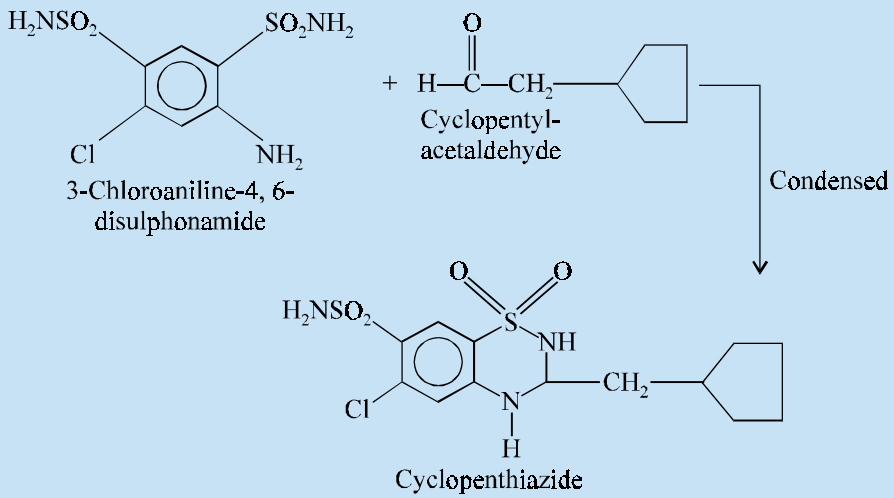
G. Cyclopenthiazide INN, BAN, USAN,



6-Chloro-3-(cyclopentylmethyl)-3, 4-dihydro-2H, 1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3-(cyclopentylmethyl)-3, 4-dihydro, 1, 1-dioxide ; BP ;

Navidrex-K(R) (Ciba, U.K.).

Synthesis

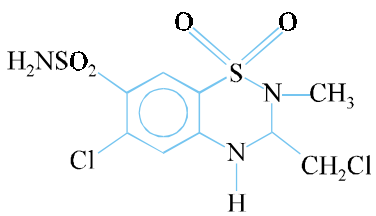


The process is similar to that for **chlorothiazide,** except that cyclopentyl acetaldehyde is used in the cyclization to yield the official compound.

Cyclopenthiazide possesses actions and uses similar to those of chlorothiazide.

Dose : *For oedema, usual, initial, 0.5 to 1 mg per day, reduced to 250 to 500 mcg per day or 500 mcg on alternate days ; For hypertension, usual, 250 to 500 mcg per day either alone, or in conjunction with other antihypertensive agents.*

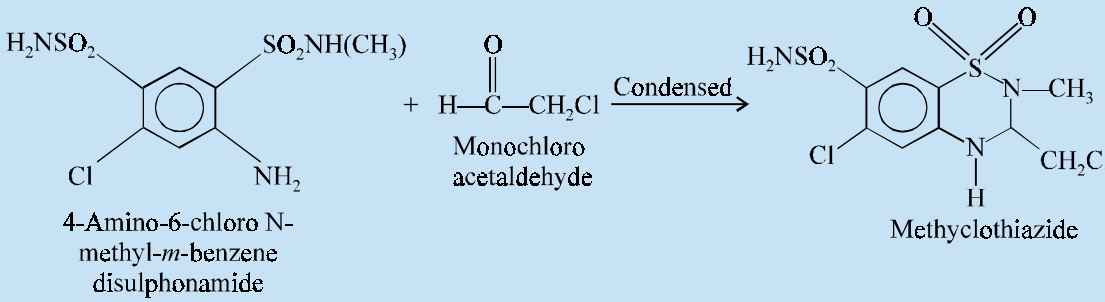
H. Methyclothiazide INN, BAN, USAN,



6-Chloro-3-(chloromethyl)-3, 4-dihydro-2-methyl-2H-1, 2, 4-benzothiadiazine-7-sulphonamide-1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3-(chloromethyl)-3, 4-dihydro-2-methyl, 1, 1-dioxide ; USP ;

Enduron(R) (Abbott).

Synthesis



It may be prepared by a method analogous to **chlorothiazide** when 4-amino-6-chloro-N^3-methyl-*m*-benzenedisulphonamide is caused to condense with monochloroacetaldehyde.

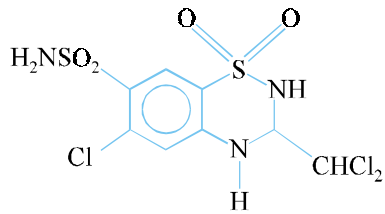
Methyclothiazide is effective both *as a diuretic and an antihypertensive agent. It is about 100 times more potent than chlorothiazide. In prolonged treatment it is absolutely necessary to supplement with potassium to avoid hypokalemia.*

Dose : *Usual, maintenance, as diuretic and antihypertensive, 2.5 to 10 mg once per day.*

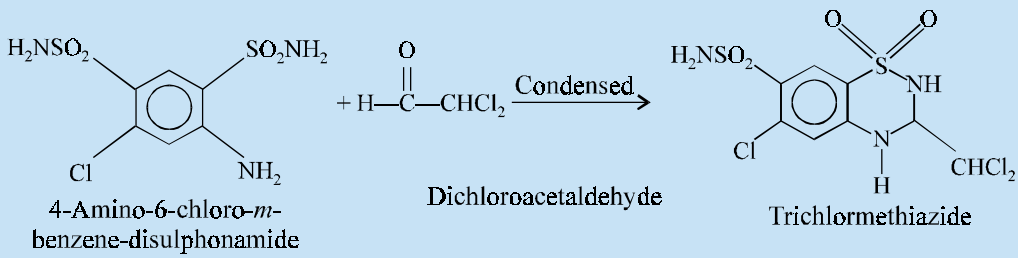
I. Trichlormethiazide INN, BAN, USAN,

6-Chloro-3-(dichloromethyl)-3, 4-dihydro-2H-1, 2, 4-benzo-thiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3-(dichloromethyl)-3, 4-dihydro-1, 1-dioxide USP ;

Metahydrin(R) (Merrell Dow) ; Naqua(R) (Schering)



Synthesis

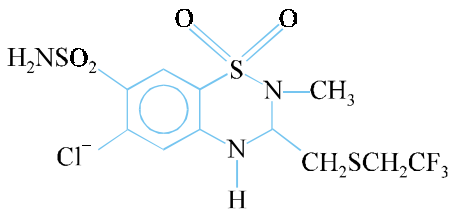


It may be prepared by the condensation of 4-amino-6-chloro-*m*-benzene disulphonamide with dichloroacetaldehyde.

Trichlormethiazide belongs to the class of *long-acting diuretic and antihypertensive thiazide.*

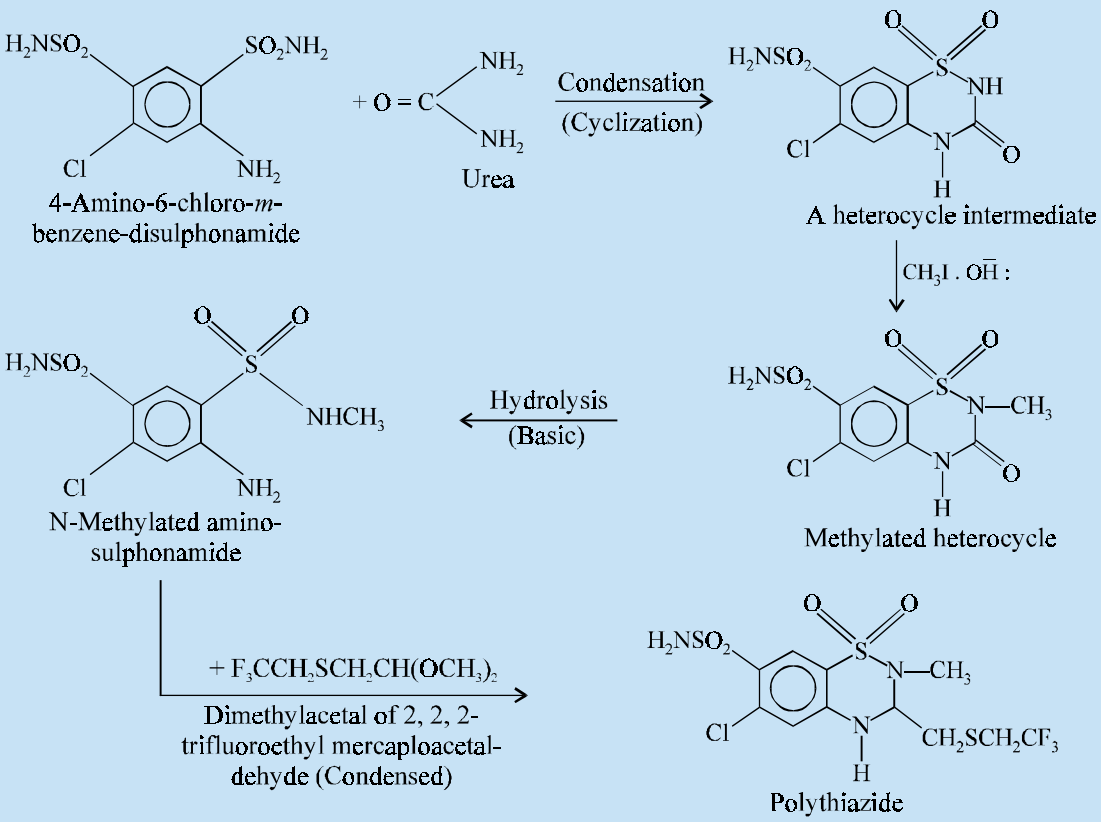
Dose : *Usual, 2 to 4 mg twice daily ; maintenance 2 to 4 mg once per day.*

J. Polythiazide INN, BAN, USAN,



6-Chloro-3, 4-dihydro-2-methyl-3-[[2, 2, 2-trifluoroethyl) thio] methyl]-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ; 2H-1, 2, 4-Benzothiadiazine-7-sulphonamide, 6-chloro-3, 4-dihydro-2-methyl-3-[[(2, 2, 2-trifluoroethyl) thio] methyl]-, 1, 1-dioxide ; BP ; USP ; NF ; Renese(R) (Pfizer).

Synthesis

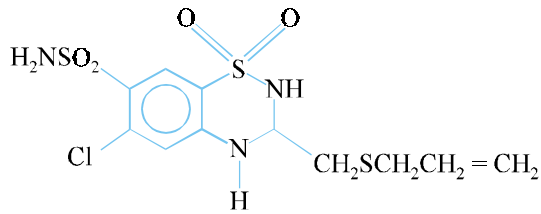


A heterocycle intermediate is prepared by the condensation of 4-amino-6-chloro-*m*-benzene disulphonamide with urea which on treatment with methyl iodide in a basic medium yields the corresponding methylated heterocycle. This on hydrolysis in the presence of a base affords N-methylated aminosulphonamide which on condensation with dimethylacetal of 2, 2, 2-trifluoroethylmercaptoacetaldehyde yields the official compound.

Polythiazide is a *potent long-acting diuretic and anti-hypertensive agent.*

Dose : *As diuretic, usual, 1 to 4 mg per day ; as antihypertensive, 2 to 4 mg as required.*

K. Altizide INN, Althiazide USAN,



3-[(Allythio) methyl]-6-chloro 3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide ;
Althiazide(R) (Pfizer).

2.2.1.1. Mechanism of Action

The mechanism of action of the **thiazide diuretics** shall now be discussed individually in the pages that follows :

2.2.1.2. Chlorothiazide

The epoch making era of wonderful **'drug discovery'** of **benzothiadiazines** commenced with the synthesis (1957) and the remarkable valuable diuretic characteristic features of this **'drug'** *i.e.*, **chlorothiazide (CTZ)**. It acts by depliting Na and followed by reduction in the plasma volume. Besides, it also reduces in the peripheral resistance. Refractoriness of the *'drug'* is comparatively uncommon, even after a prolonged span of continuous usage.

2.2.1.3. Hydrochlorothiazide (HCTZ)

Slightly more soluble in water than chlorothiazide, but its mode of action is practically the same as that of **chlorothiazide**.

2.2.1.4. Hydroflumethiazide

The replacement of the Cl-atom at C-6 with trifluoromethyl function (CF_3) renders the **'drug'** more potent in its therapeutic activity.

2.2.1.5. Bendroflumethiazide

Additional benzyl moiety at C-3 of **hydroflumethiazide** attributes far better potency than the parent drug in terms of its diuretic profile.

2.2.1.6. Benzthiazide

Additional benzyl thiomethyl group at C-3 of **chlorothiazide** renders the drug more broad-spectrum in its therapeutic values *i.e.*, it serves both as a diuretic and also as an antihypertensive agent.

2.2.1.7. Cyclothiazide

The only glaring difference between this **'drug'** and **chlorothiazide** is the presence of 5-norboren-2-yl lipid-soluble moieties strategically located at the C-3 position which renders the drug both orally effective as a diuretic and antihypertensive *i.e.*, the two pharmacological characteristics desirably present in the same drug molecule.

2.2.1.8. Cyclopenthiazide

The **'drug'** exhibits its activitiy quite similar to those of **HCTZ**. However, in suceptible patients potassium supplements or a potassium-sparing diuretic may be absolutely important and necessary.

2.2.1.9. Methyclothiazide

The dosage regimen of clinically used compounds invariably ranges between 1 to 2000 mg. Besides, there exists one more important and clinically useful variable within which a choice is obviously preferable is the duration of action. **Methyclothiazide** possesses a range of 24+ hours in comparison to **CTZ** having as much a low range of 6 hours.

2.2.1.10. Trichlormethiazide

The **'drug'** is an orally effective as well as long-acting thiazide diuretic and antihypertensive. It resembles **CTZ** with respect to its pharmacologic actions, therapeutic uses and untoward effects.

2.2.1.11. Polythiazide

It is also a long-acting diuretic and antihypertensive agent that causes diuresis within 2 hr, attains a peak in 6 hr and lasts 24 to 48 hr. The mean plasma half-lives for absorption and elimination are 1.2 and 25.7 hour respectively. It has been observed that nearly 20% of the drug gets excreted unchanged in the urine. On being compared on a milligram basis, 2 mg of **polythiazide** has almost nearly the same diuretic activity as produced by 500 mg of **CTZ**.

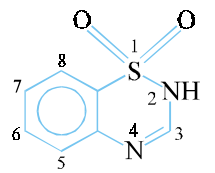
2.2.1.12. Altizide (Althiazide)

It is a **thiazide diuretic** having action very similar to **hydrochlorothiazide (HCTZ)**. It is invariably administered in combination with spironolactone.

2.2.1.13. SARs of Thiazide Diuretics

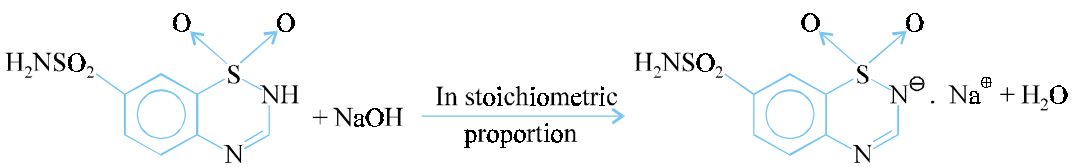
The SARs of these **benzene disulphonamide structural analogues** yielded a broad-spectrum of compounds having a relatively high degree of diuretic activity, which are summarized as stated under :

(1) **Thiazide diuretics** are found to be weakly acidic in nature having a benzothiadiazine 1, 1-dioxide nucleus.



Benzothiadiazine 1, 1-dioxide

(2) **Chlorothiazide (CTZ)** being the simplest member of this series of structural analogues having two pKa (dissociation constant) values of 6.7 and 9.5. The two acidic zones in **CTZ** are virtually due to the presence of : (*a*) presence of a H-atom at the 2-N that essentially attributes the most acidic character by virtue of the influence of the prevailing electron withdrawing effects of the neighbouring sulphone moiety ; and (*b*) presence of the sulphonamide ($-SO_2NH_2$) functional moiety strategically located at C-7 position which affords an additional environment (zone) of creating acidity in the molecule ; however, its acidic influence is much less than the 2-N proton. Importantly, these acidic protons enable the formation of the corresponding water-soluble sodium salt which may be gainfully used for IV-administration of the diuretics as shown below :



(3) Presence of an electron-withdrawing moiety at C-6 is an absoluble necessity for the diuretic activity. A few important and vital observations are as enumerated below :

(*a*) Practically negligible diuretic activity is obtained by having a H-atom at C-6 ;

(*b*) Substitution with a chloro or trifluoromethyl moiety at C-6 are quite active pharmacologically.

(*c*) Further, the CF_3 moiety renders the resulting diuretic compound more lipid-soluble and also with a much longer duration of action in comparison to its chloro-substituted derivatives ;

(*d*) Presence of electron-releasing moieties, namely : *methyl* or *methoxyl* at C-6 position attributes significantly reduced diuretic activity.

(4) Removal or possible replacement of the sulphonamide function at C-7 results into such compounds possessing either little or almost no diuretic activity.

(5) Saturation of the prevailing double-bond between 3 and 4 positions to give rise to a corresponding 3, 4-dihydro structural analogue which is observed to be having nearly 10 times more diuretic activity than the unsaturated analogue.

(6) Introduction of a lipophilic functional moiety at C-3 position renders a marked and pronounced enhancement in the diuretic potency. For instance : aralkyl, haloalkyl, or thioether substitution, enhances the lipoidal solubility of the molecule to a considerable extent thereby producing compounds with a much longer duration of action.

(7) Alkyl substitution on the N-2 position is observed to lower the polarity and ultimately enhancing the duration of the ensuing diuretic action.

2.2.2. Carbonic Anhydrase Inhibitors

In early 1940s, attempts were made towards the synthesis and subsequent screening of **sulphonamides** possessing carbonic anhydrase inhibitory characteristics of sulphanilamide which resulted in the production of a variety of heterocyclic sulphonamides. When the enzyme is inhibited, the generation of carbonic acid (H_2CO_3) that usually dissociated into HCO_3^- and H_3O^+, is also inhibited. Thus in glomerular filtrate, a deficiency of H_3O^+ which normally exchanges for Na^+ occurs. The Na^+ remains in the renal tubule together with the HCO_3^- plus an osmotic equivalent of water, which ultimately results in the excretion of a large quantity of urine and hence diuresis. These compounds which inhibit carbonic anhydrase, besides acting as diuretics, also cause acidosis because of the elimination of HCO_3^- and Na^+ ions. The acidosis tends to limit its diuretic activity.

A most logical H-bonding mechanism which is believed to act competitively perhaps explains the action of some sulphonamide carbonic anhydrase inhibitors which predominantly exhibit both diuretic and antiglaucoma activities. It is, however, assumed that carbonic acid being the normal substrate which not only fits into a cavity but also complexes with the corresponding enzyme **carbonic anhydrase (CA)** as illustrated in Fig. 14.1(*a*). Consequently, this complex is strongly stabilized by **four** H-bonds.

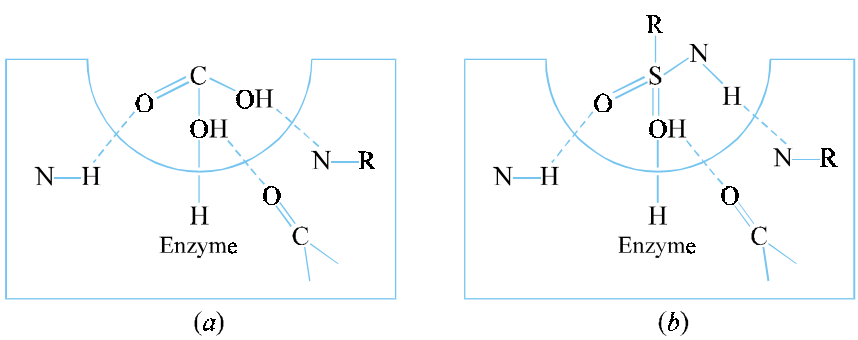


Fig. 14.1. Interactions Occurring at the Hypothetical Reactive Sites of Enzymes Carbonic Anhydrase.

Interestingly, the **sulphonamide moiety** which essentially possesses a **geometric structural entity** thus allowing an equally perfect fit compatible into the cavity of the enzyme CA also get bound quite securedly and effectively, perhaps to the same four areas by H-bonds as depicted in Fig. 14.1(*b*).

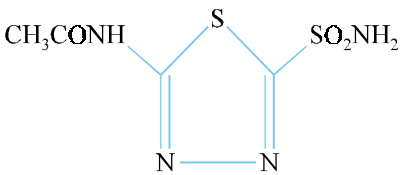
Therefore, one may safely draw an inference that these **sulphonamide structural analogues** competitively prevent the carbonic acid from getting bound at this specific site. Consequently, such an action shall obviously inhibit the prvailing action of the enzyme CA, thereby giving rise to an apparent acid-base imbalance that would ultimately cause diuresis.

It is, however, pertinent to state here that the **sulphonamides** of the type wherein the possibilities for H-bonding having been lowered from *four* to *three* usually render the compounds **inactive**.

A few typical examples of this class of **diuretics** are described here.

Examples : Acetazolamide ; Methazolamide ; Ethoxzolamide ; Diclofenamide ; Disulfamide

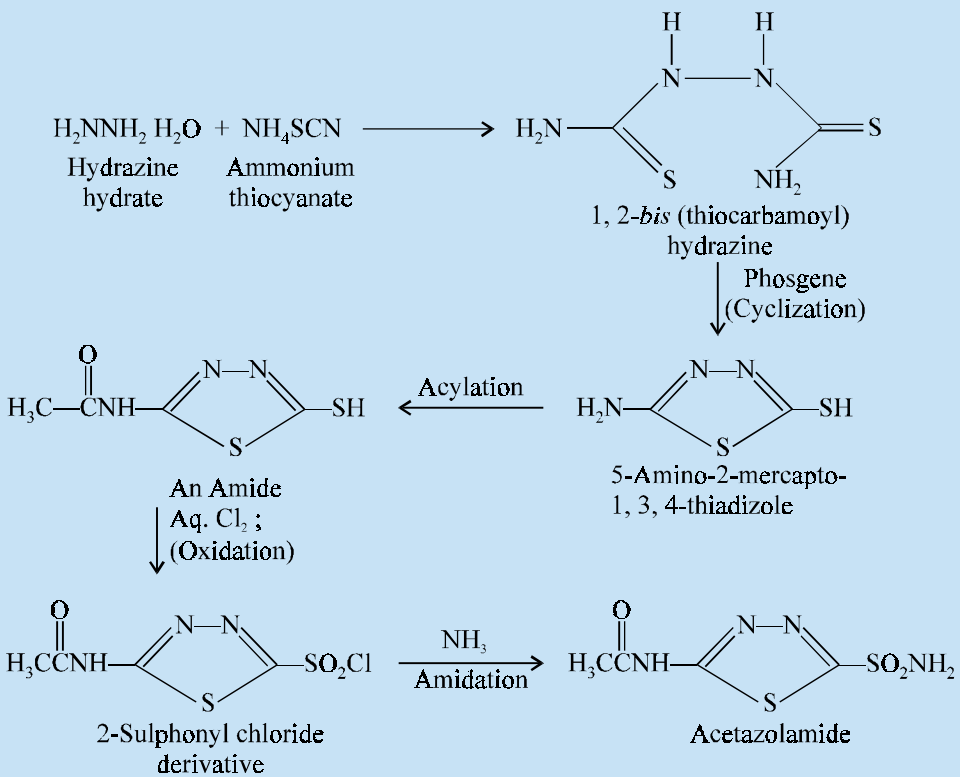
A. Acetazolamide INN, BAN, USAN,



N-(5-Sulfamoyl-1, 3, 4-thiadiazol-2-yl) acetamide ; Acetamide, N-[5-(amino-sulphonyl)-1, 3, 4-thiadiazol-2-yl]- ; BP ; USP ; Ind. P. ;

Diamox$^{(R)}$ (Lederle).

Synthesis

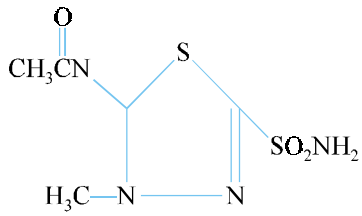


Reaction between hydrazine hydrate and ammonium thiocyanate yields 1, 2-*bis* (thiocarbamoyl) hydrazine which on treatment with phosgene undergoes molecular rearrangement through loss of ammonia to yield 5-amino-2-mercapto-1, 3, 4-thiadiazole. This on acylation gives a corresponding amide which on oxidation with aqueous chlorine affords the 2-sulphonyl chloride. The final step essentially consists of amidation by treatment with ammonia.

Acetazolamide *is employed effectively for adjunctive treatment of drug-induced oedema, oedema caused by congestive heart failure, petit mal and other centrencephalic epilepsies. It has also been used to lower the intraocular pressure prior to surgery in acute conditions of angle-closure glaucoma, besides open-angle and secondary glaucoma.*

Dose : *Usual, 250 mg 2 to 4 times per day.*

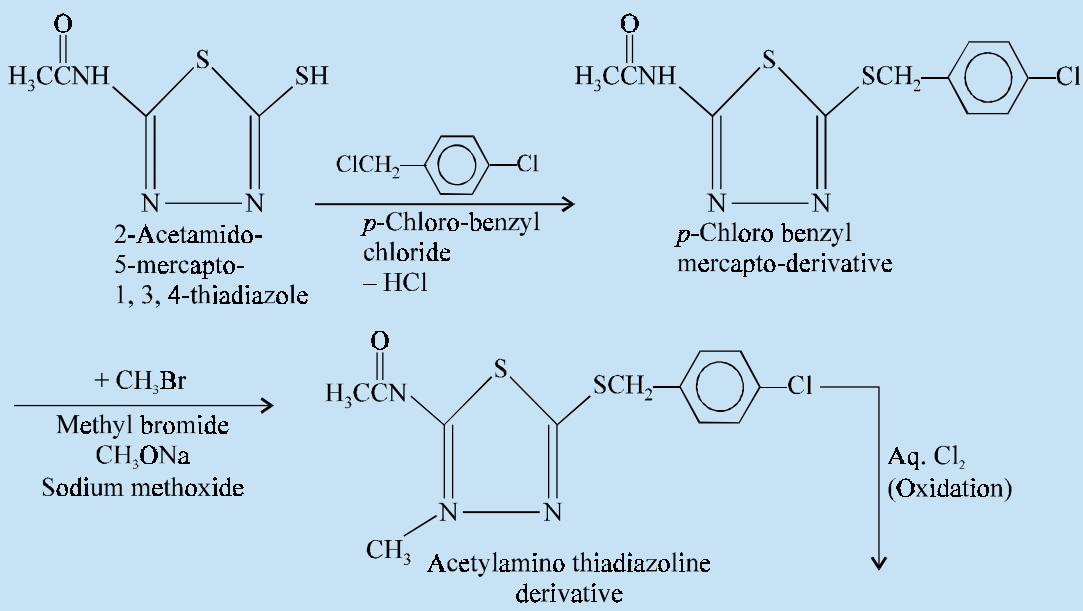
B. Methazolamide INN, BAN, USAN,



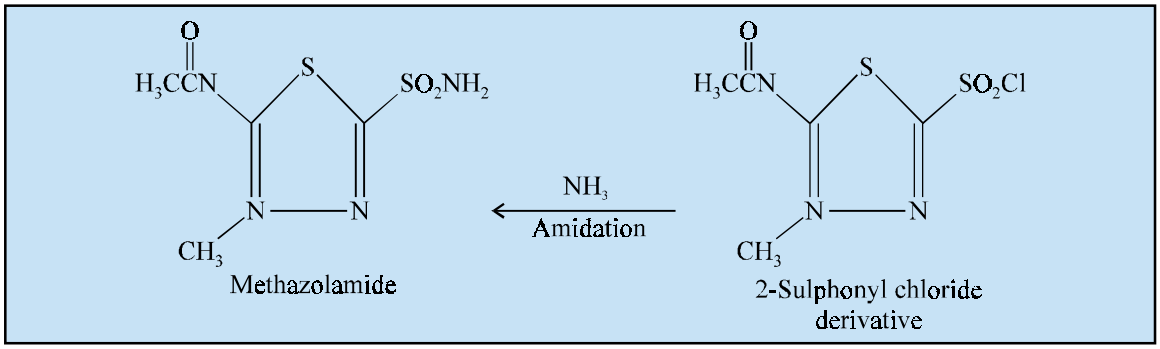
N-(4-Methyl-2-sulphamoyl-Δ^2-1, 3, 4-thiadiazolin-5-ylidene) acetamide ; Acetamide, N-[5-(aminosulphonyl)-3-methyl-1, 3, 4-thiadiazol-2 (3H)-ylidene] USP ;

Neptazane(R) (Lederle).

Synthesis



(*Contd...*)

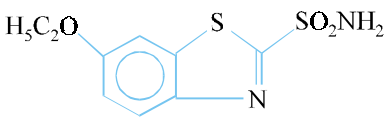


2-Acetamido-5-mercapto-1, 3, 4-thiadiazole is prepared as described under acetazolamide. This on treatment with *p*-chlorobenzyl chloride forms the corresponding *p*-chloro benzyl mercapto derivative, which when reacted with methyl bromide in the presence of sodium methoxide yields the acetylamino thiadiazoline derivative. On oxidation with aqueous chlorine it gives rise to the 2-sulphonyl chloride derivative which finally yields **methazolamide** on amidation with ammonia.

Its actions and uses are similar to those of **acetazolamide.** However, its action has been found to be *relatively less prompt but of definitely longer duration than that of the latter, lasting for 10 to 18 hours.*

Dose : *100 to 600 mg per day ; usual, 50 to 100 mg 2 to 3 times per day.*

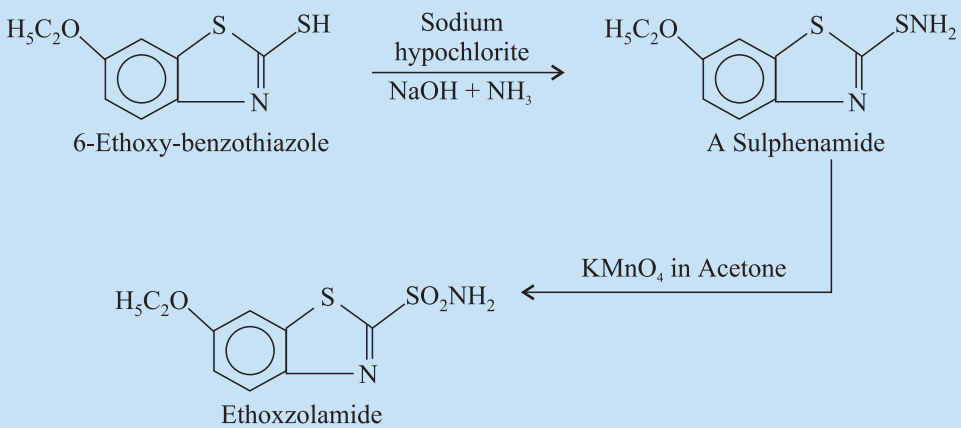
C. Ethoxzolamide BAN, USAN,



6-Ethoxy-2-bezothiazolesulphonamide ; 2-Benzothiazolesulphonamide, 6-ethoxy- ; Ethoxyzolamide ; USP ;

Cardrase (Upjohn).

Synthesis

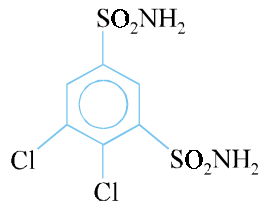


It may be prepared by the reaction of 6-ethoxy-benzothiazole with sodium hypochlorite in the presence of sodium hydroxide and ammonia to yield the corresponding sulphenamide, which upon oxidation with potassium permanganate in acetone forms the official compound.

Ethoxzolamide *is mainly used to lower the intraocular pressure prior to surgery in acute angle-closure glaucoma, besides its application in the treatment of chronic simple glaucoma and secondary glaucoma.*

Dose : *62.5 mg to 1g daily ; usual, 125 mg 2 to 4 times per day.*

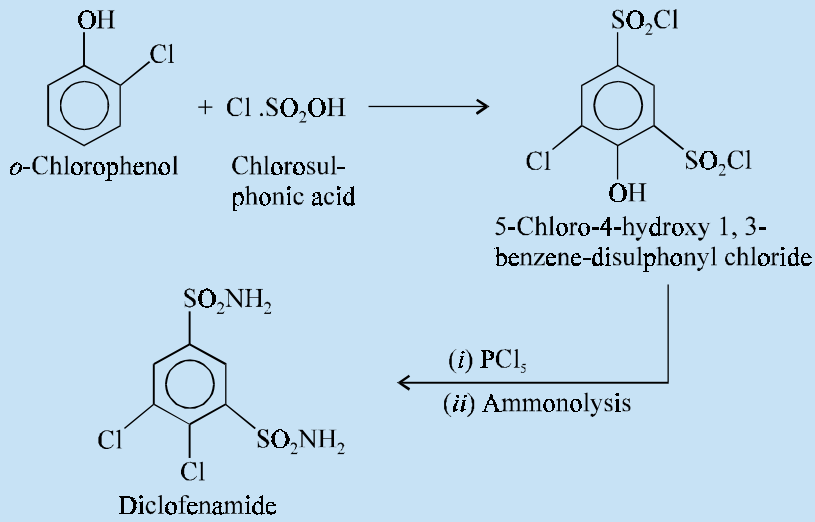
D. Diclofenamide INN, Dichlorphenamide BAN, USAN,



4, 5-Dichloro-*m*-benzenedisulphonamide; 1, 3-Benzenedisulphonamide, 4, 5-dichloro- ; 4, 5-Dichlorobenzene-1, 3-disulphonamide; BP ; USP ;

Daranide(R) (Merck Sharp and Dohme); Oratrol(R) (Alcon)

Synthesis

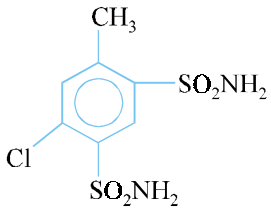


It may be prepared by the interaction of *o*-chlorophenol with chlorosulphonic acid to yield 5-chloro-4-hydroxy-1, 3-benzene-disulphonyl chloride. This on treatment with PCl_5 replaces the 4-hydroxy with chlorine and the subsequent ammonolysis gives the official compound.

Diclofenamide *is employed to lower intraocular pressure by reducing the rate of secretion of aqueous humor. It is recommended for the treatment of both primary and secondary glaucoma. Though it possesses inherent diuretic properties it is not promoted for this purpose. It produces less acidotic refractoriness to diuretic action than acetazolamide.*

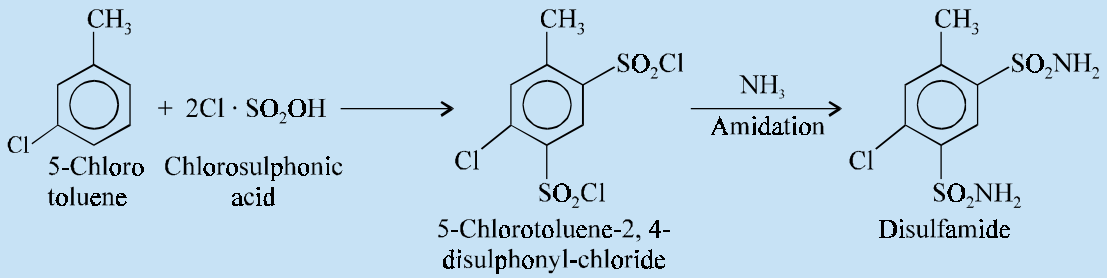
Dose : *50 to 300 mg per day ; usual ; 25 to 50 mg 1 to 3 times daily.*

E. Disulfamide INN, USAN, Disulphamide BAN,



5-Chlorotoluene-2, 4-disulphonamide ; BPC (1968) ;
Diluen(R) (Libra, Italy).

Synthesis



5-Chlorotoluene-2, 4-disulphonyl chloride is prepared by the interaction of 5-chlorotoluene and chlorosulphonic acid, which on amidation gives rise to **disulfamide.**

Its actions and uses are simialr to those of **chlorothiazide.** It is invariably employed for the *treatment of oedema.*

Dose : *For oedema, usual, initial, 200 mg per day for 5 days a week or on alternate days, reduced to 100 mg per day.*

2.2.2.1. Mechanism of Action

The mechanism of action of certain **carbonic anhydrase inhibitors** used as **diuretics** shall be discussed in the sections that follows :

2.2.2.1.1. Acetazolamide

The **'drug'** still remanis the most vital carbonic anhydrase inhibitor and being regarded as the prototype member of this specific category. It gets absorbed appreciably from the GI-tract, bound extensively to the plasma proteins, and does not undergo biotransformation. It is eliminated almost completely from the plasma by the kidneys within a span of 24 hr. The drug is subjected to filtration at the glomeruli, and viable tubular secretion in the proximal tubule. Importantly, it also invariably affords a varying range of pH-dependent non-ionic back diffusion taking place particularly in the distal segments of the nephron.

2.2.2.1.2. Methazolamide

If has been amply demonstrated *in vitro* that the **'drug'** is definitely has an edge over the prototype acetazolamide with regard to its potency as CA inhibitor. Besides, it is also observed to exhibit an improved penetration into the eye*, which action strongly recommends its usage in the treatment of glaucoma.

*Sprague JM : *Advances in Chemical Series,* American Chemical Society, Washington DC., **45,** 87–101, 1964.

2.2.2.1.3. Ethoxzolamide

The **'drug'** is a **carbonic anhydrase inhibitor** which is found to exert its action by lowering the intraocular pressure prior to surgery when employed preoperatively in acute angle-closure glaucoma.

2.2.2.1.4. Dichlorphenamide

The **'drug'** acts by lowering the intraocular pressure just like several other CA-inhibitors ; and hence, may be beneficial in the control, management and treatment of glaucoma *i.e.*, in primary as well as the acute phase of secondary glaucoma.

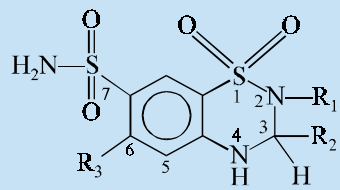
Interestingly, the major importance of this **'drug'** is that it ultimately served as stepping stone far away from the *'pure'* CA-inhibiting diuretics ; and, therefore, paved the way towards the development of the **'thiazides'** that proved to be extremely useful and effective Na^+ and Cl^- depleting agents having almost negligible CA-inhibitory activity.*

2.2.2.1.5. Disulphamide

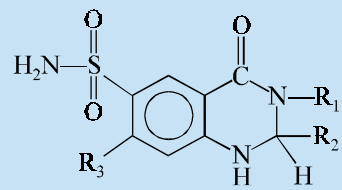
Its mechanism of action is almost similar to that of **chlorothiazide (CTZ)** in the relief of fluid retention in the body.

2.2.3. Miscellaneous Sulphonamide Diuretics

The actions of these drugs are very similar to the thaizide diuretics, except that these specifically possess longer duration of action.



Benzothiadiazines
(Thiazides)

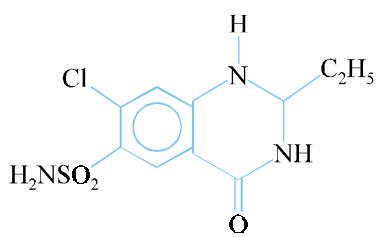


Thiazide Isosteres

In the above **benzothiadiazine (thiazides)** moiety the 'SO_2' at position 1 has been duly changed to (—C—, with O) carbonyl function *i.e.*, the sulphonyl moiety replaced with carbonyl moiety, thereby resulting into the formation of a series of *'thiazide isosteres'*, namely : **quinethazone, chlorthalidone, metolazone** and **indapamide.**

All these compounds grouped together under **'miscellaneous sulphonamide diuretics'** shall be treated individually as under :

A. Quinethazone INN, BAN, USAN,

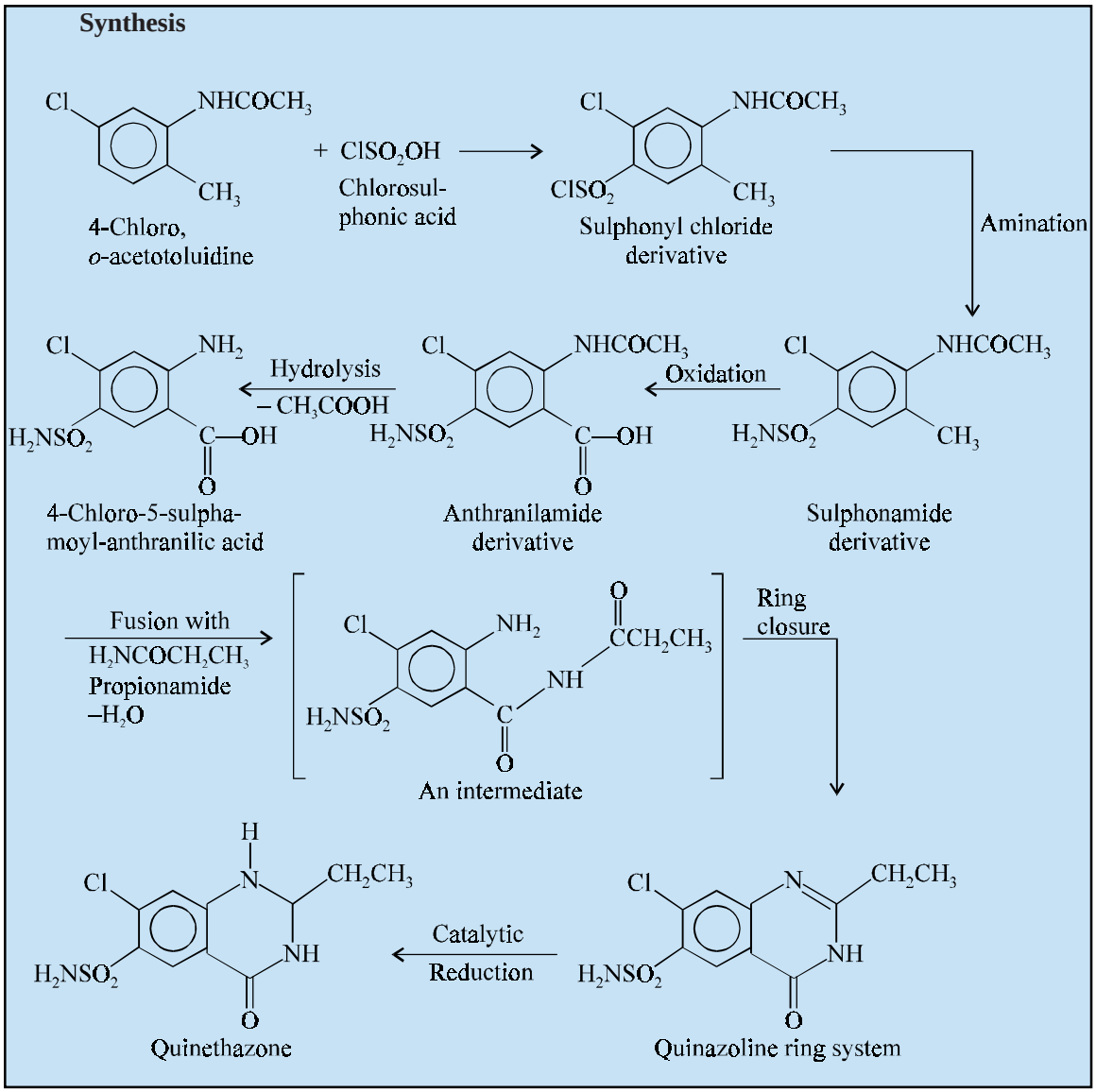


*Allen RC : In : Cragoe EJ (ed.) : *Diuretics-Chemistry Pharmacology and Medicine*, John Wiley and Sons, New York, pp-49–200, 1983.

7-Chloro-2-ethyl-1, 2, 4-tetrahydro-4-oxo-6-quinazolinesulphonamide ; 6-Quinazolinesulphonamide, 7-chloro-2-ethyl-1, 2, 3, 4-tetrahydro-4-oxo- ; USP. ;

Hydromox(R) (Lederle)

Synthesis



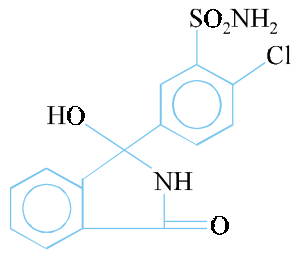
Chlorosulphonation of 4′-chloro-*o*-acetotoluidine yields the corresponding sulphonyl chloride derivative which on amination forms the sulphonamide derivative. Oxidation of the methyl moiety gives the respective anthranilamide derivative which on hydrolysis eliminates the acetyl group to yield the substituted anthranilic acid. Fusion of this amino acid with propionamide first gives rise to an intermediate by the loss of a mole of water and ultimately helps in the closure of the ring to generate the quinazoline ring system. Catalytic reduction of this finally produces the official compound.

Quinethazone essentially differs from the **benzothiazide type of diuretics** only in the replacement of a sulphur atom by a carbon at position 4.

It possesses both diuretic and antihypertensive properties similar to those of the thiazides.

Dose : *50 to 200 mg per day ; usual, 50 to 100 mg once daily.*

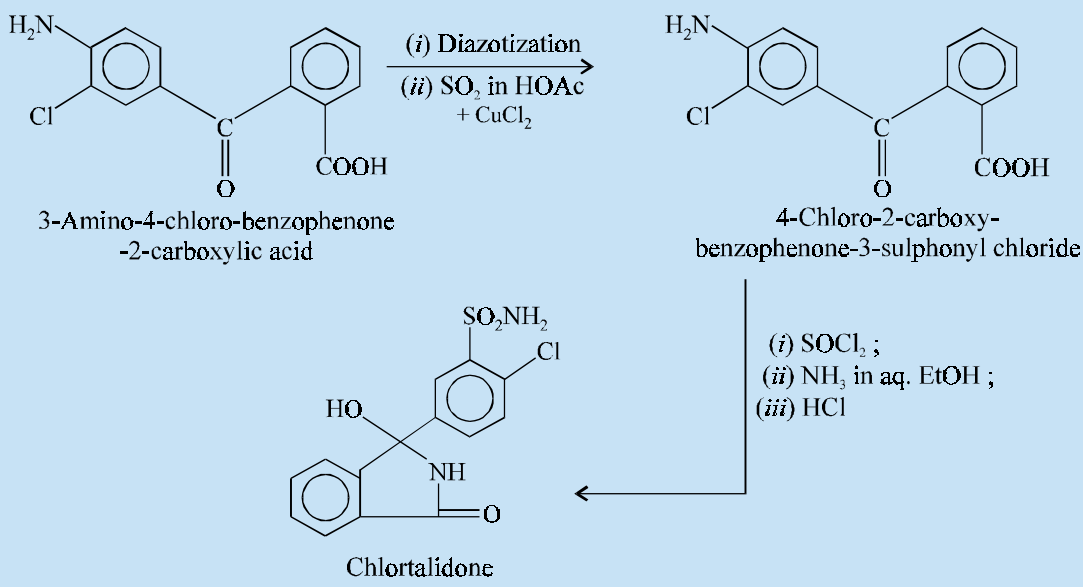
B. Chlortalidone INN, Chlorthalidone BAN, USAN,



2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulphonamide ; Benzene sulphonamide, 2-chloro-5-(2, 3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)- ; BP ; USP ;

Hygroton$^{(R)}$ (USV)

Synthesis



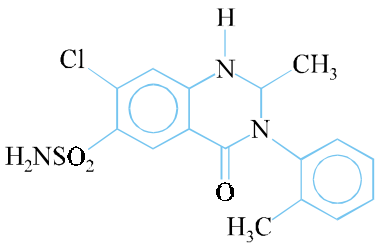
Chlortalidone is a thiazide-like diuretic agent *which essentially contains an isoindole ring.*

It may be prepared by the diazotization and subsequent treatment with sulphur dioxide in glacial acetic acid in the presence of cupric chloride of 3-amino-4-chloro-benzophenone-2-carboxylic acid to yield 4-chloro-2′-carboxy-benzophenone-3-sulphonyl chloride. This on treatment with thionyl chloride followed by amidation in aqueous ethanol and finally with HCl gives crude **chlortalidone** which is recrystallized from aqeous ethanol.

Chlortalidone *is employed in the treatment of oedema associated with obesity, pregnancy, renal disease, hepatic cirrhosis, premenstrual syndrome and above all the congestive heart failure.*

Dose : *As diuretic, 50 to 200 mg per day or alternate day ; usual, 100 mg once daily ; As antihypertensive, 100 mg alternate day or 50 mg every day.*

C. Metolazone BAN, USAN

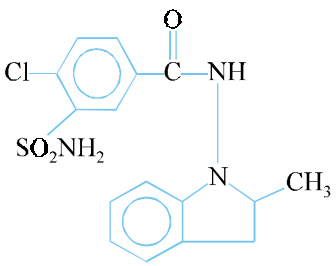


6-Quinazolinesulphonamide, 7-chloro-1, 2, 3, 4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo- ; Diulo(R) ; Zaroxolyn(R) ;

It is a **quinazoline-derived nonthiazide diuretic.** It is found to be more effective in comparison to the thiazide-like diuretics in the treatment of edema in such patients who have a history of compromised renal function. It is extensively indicated for *hypertension, edema accompanying congestive heart failure, renal disease* including the *nephrotic syndrome* and other *conditions of* retarded renal function.

Dose : *Usual, adult, oral, edema of cardiac failure, 5 to 10 mg once daily ; edema of renal disease, 5 to 20 mg once daily ; mild essential hypertension, 2.5 to 5 mg once daily.*

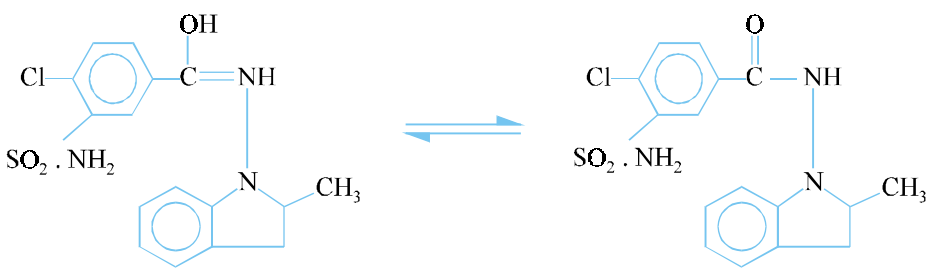
D. Indapamide BAN, USAN,



Benzamide, 3-(aminosulphonyl)-4-chloro-N-(2, 3-dihydro-2-methyl-1H-indol-1-yl)- ;

Lozol(R) (Rhone Poulenc Rorer) ;

It is an orally active and effective diuretic acid and anithypertensive drug closely related chemically to the **indolines.**



Indapamide (acid) (*enol*-form)

Indapamide (*keto*-form)

The **'drug'** undergoes ***keto-enol* tautomerism** and the *'acid form'* is the active one.

It is used for the control and management of edema associated with congestive heart failure and, alone or in combination with other such agents, in the treatment of hypertension.

Dose : *Usual, hypertension and edema of congestive heart failure, 2.5 mg as a single daily dose taken in the morning ; if the response is not satisfactory after one (edema) to four (hypertension) week, the dose is usually increased to 5 mg once daily.*

2.2.3.1. Mechanism of Action

The mechanism of action of the above **'drug'** shall be described individually as under :

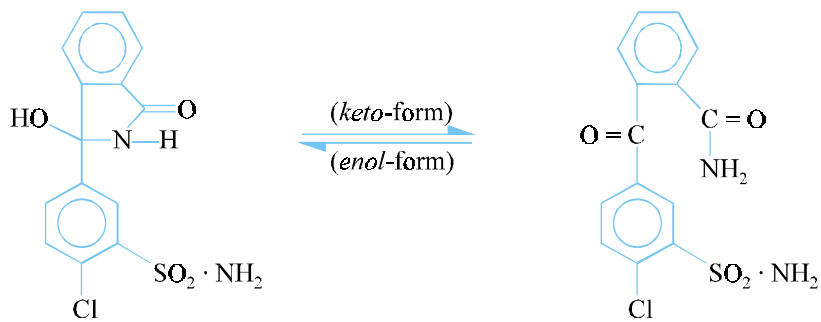
2.2.3.1. Quinethazone

The **'drug'** is a quinazoline derivative having 6-thiazide-like effect. Based on the available clinical evidence one may suggest that its site, mechanism of action, electrolyte excretion pattern and above all the therapeutic activities are very much similar to those of **CTZ.**

2.2.3.2. Chlorthalidone

The biochemical studies carried out with the **'drug'** suggest that the prolonged duration of action is solely on account of the slow gastrointestinal absorption, enterohepatic recirculation and above all the critical binding to RBCs in the body. It has been observed that nearly 30–60% of the **'drug'** gets excreted almost unchanged by the kidney.

SAR of Chlorthalidone. The *enol*-form (*i.e.*, the acid form) of chlorthalidone is the **'active drug'** as depicted below :



Predominant and Active Drug — Inactive form of Drug

It is not strictly speaking a thiazide.

2.2.3.3. Metolazone

The **'drug'** exerts its inhibition of Na^+ (and Cl^-) reabsorption in early *distal tubule* and the *ascending limb of loop of Henle.* It is also demonstrated to show its action primarily to inhibit Na^+ reabsorption both at the *cortical diluting site* and in the *proximal convoluted tubule.* Its long duration of action ranging between 12 to 24 hours is appreciably attributed to protein binding as well as enterohepatic recycling.

However, it may be more effective in comparison to the thiazide like diuretics in the usual treatment of edema in subjects having compromised renal function. About 95% of the plasma drug gets bound to plasma proteins in normal controls ; whereas, about 90% is bound in patients with severe renal failure.

2.2.3.4. Indapamide

The **'drug'** is taken up preferentially and reversibly by the erythrocytes in the peripheral blood. It has been observed that the whole blood/plasma ratio is about 6 : 1 at the time of peak concentration and reduces to 3.5 : 1 after a lapse of 8 hr. It has been found that 71 to 79% of the drug gets bound to plasma proteins. It gets metabolized extensively *in vivo* ; and only 7% of the unchanged form of the drug is excreted by the kidneys.

SAR of Indapamide. It apparently differs from the **thiazides** structurally. However, it may be viewed chemically as comprising of a **polar sulphamoylchlorobenzamide** and a highly **lipoidal methylindolyl** functional moiety.

2.2.4. 'Loop' and 'High-Ceiling' Diuretics

These are a group of diuretics which essentially contain carboxylic acid moietics. They usually produce an intense diuresis of relatively short duration (4-6 hrs) with rapid onset (30 min). They have been found to act mainly on the ascending limb of the loop of Henle (hence often referred to as **loop diuretics**), besides exerting some effect on both the proximal and distal tubules. They seem to act by inhibiting th reabsorption of Cl^- (and therefore of NaCl). They cause loss of Cl^-, Na^+ and K^+ ions to a considerable extent.

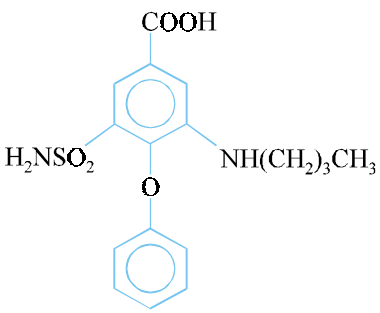
The **'loop diuretics'** usually possess a much greater diuretic profile in comparison to the **'thiazides' ;** and are observed to be even more potent and effective in a situation having electrolyte as well as acid-base disturbances concurrently. Besides, the time of onset and duration of action of the **'high-ceiling diuretics'** are emuch shorter than those with the *thiazides.*

Interestingly, there exists a little controversy with regard to the *relative superiority* of the **'loop diuretics'** in a specific situation of hypertension intimately associated with renal insufficiency than the *thiazides.* Furthermore, the former tend to *enhance* renal blood flow, whereas the latter tend to *minimise* renal blood flow, and thereby lead to further compromise to renal function.

As a point of caution it may, be added that a very **'close monitoring is absolutely warranted'** to avoid severe ensuing electrolyte imbalances in patients being treated with the *'loop diuretics'* by virtue of the fact that they normally possess much greater potency in comparison to the *thiazides.*

Examples : Bumetanide ; Furosemide ; Etacrynic acid.

A. Burmetanide INN, BAN, USAN,



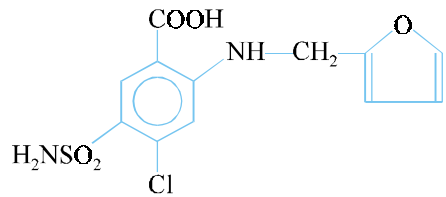
3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid ; Benzoic acid, 3-(amino-sulphonyl)-5-(butylamino)-4-phenoxy- ; Bumex(R) (Hoffman-La Roche) ;

Burinex(R) (Leo, U.K.)

Bumetanide *is used in the treatment of renal insufficiency and, in conditions which warrant forced diuresis regimens for the control and management of acute drug poisoning e.g., barbiturate poisoning in attempted suicide cases. It is also employed in the treatment of oedema.*

Dose : *For oedema, usual, oral 1mg once in the morning followed by another similar dose after 6–8 hours if necessary.*

B. Furosemide INN, USAN Frusemide BAN,

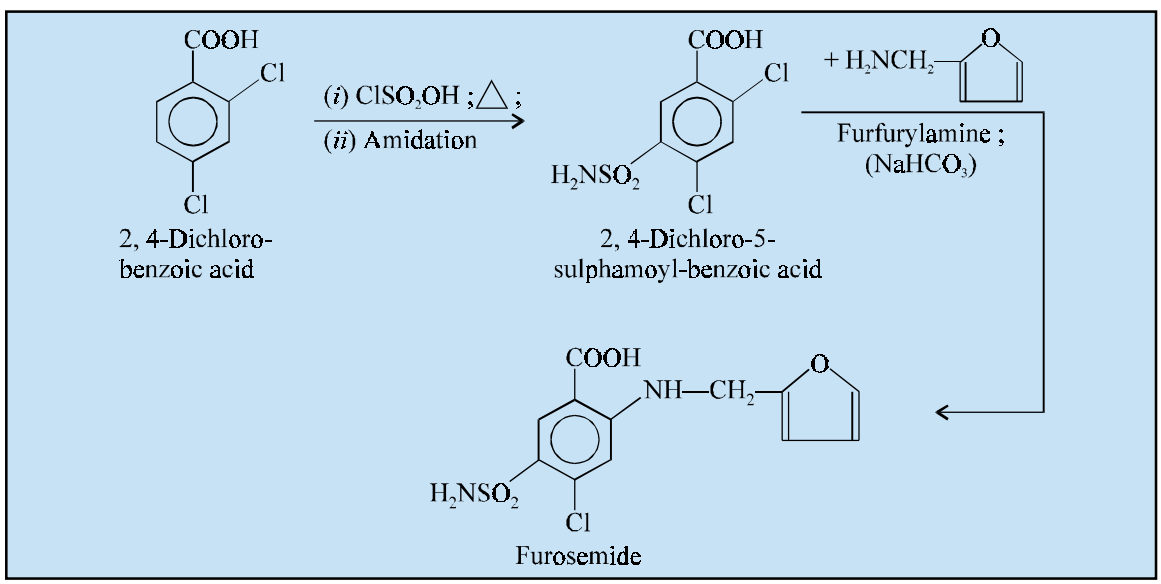


4-Chloro-N-furfuryl-5-sulphamoylanthranilic acid ; Benzoic acid, 5-(amino-sulphonyl)-4-chloro-2-[(2-furanylmethyl) amino]- ; Frusemide (BP ; Eur. P.,) ; Furosemide (USP.) ;

Lasix(R) (Hoechst) ; SK-Furosemide(R) (SK & F)

Synthesis

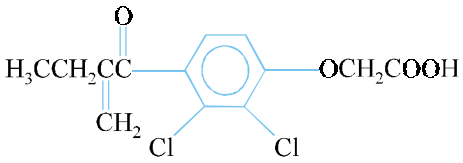
2, 4-Dichloro-5-sulphamoyl benzoic acid may be prepared by reacting 2, 4-dichlorobenzoic acid with chlorosulphonic acid at an elevated temperature and then carrying out the amidation. This on treatment with furfuryl amine in the presence of sodium bicarbonate, affords nucleophilic aromatic displacement of the highly activated chlorine at C-2, thereby yielding furosemide. However, the protection of the chlorine atom at C-4 may be achieved by regulating the temperature of the furfurylamination.



Furosemide possesses relatively high efficacy, rapid onset of action, short duration of action, and 1:10 ratio between the minimum and maximum diuretic dose. It is used for the *treatment of oedema associated with renal disease, nephrotic syndrome, cirrhosis of the liver and congestive heart failure. It has an edge over other commonly used diuretic agents specifically when a greater diuretic potential is required. It may also be employed towards the management of hypertension.*

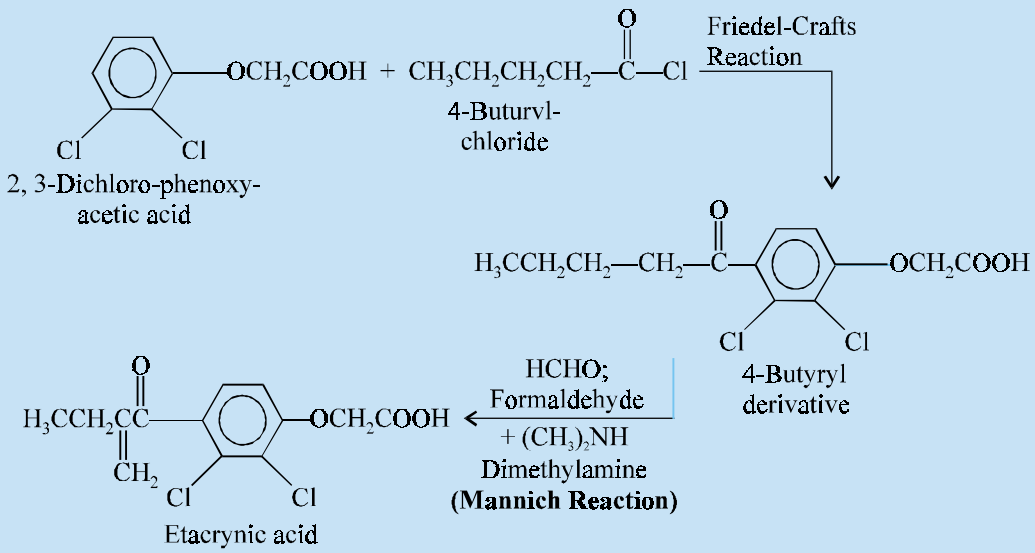
Dose : *Oral, 40 to 600 mg per day ; usual, 40 to 80 mg per day ; i.m. or i.v., 20 to 40 mg.*

C. Etacrynic Acid INN, Ethacrynic Acid BAN, USAN,



[2, 3-Dichloro-4-(2-methylenebutyryl) phenoxy] acetic acid ; Acetic acid, [2, 3-dichloro-4-(2-methylene-1-oxobutyl) phenoxyl]- ; Ethacrynic acid (BP., USP.) ; Etacrynic Acid (Eur. P.) ; Edecrin(R) (Merck Sharp & Dohme)

Synthesis



2, 3-Dichloro-phenoxy acetic acid undergoes **Friedal-Craft's reaction** with 4-butyryl chloride to yield the corresponding 4-butyryl analogue. This is subsequently subjected to **Mannich reaction** with formaldehyde and dimethylamino thereby introducing the methylene group caused by thermal decomposition, yields the official compound.

Ethacrynic acid is normally used in the *treatment of fluid retensive conditions due to congestive heart failure, cirrhosis of the liver, renal disease, and the nephrotic syndrome. It is invariably employed for the control and management of ascites due to lymphoedema, idiopathic oedema and malignancy. It is also recommended through i.v. in an emergency situation of acute pulmonary oedema.*

Dose : *50 to 200 mg per day ; 50 mg 2 times daily or 2 times every alternate day ; i.v. 100 mg per day in divided doses.*

2.2.4.1. Mechanism of Action

The mechanism of action of the various **'loop diuretics'** discussed in the previous section shall be dealt with in the sections that follows :

2.2.4.1.1. Bumetanide

The **'drug'** is found to inhibit both chloride and sodium reabsorption in the ascending limb of the loop of Henle. Besides, it is somewhat little more *chloruretic* than *natriuretic*. It markedly affords dilation

of renal vasculature and enhances the renal blood flow. It gets bound to protein to an extent of 95%, and the volume of distribution ranges between 12–35 L. Nearly 45% of an oral dose gets excreted almost unchanged. The biological half-life varies between 1–1.5 hr. and is usually prolonged in patients having renal failure.

SAR of Bumetanide. The presence of a 3-aminobenzoic acid along with the sulphonamido moiety at C-5 renders the drug significantly potent (1 mg ≡ 40 mg Furosemide). Furthermore, the presence of the phenoxy functional group at C-4 may substantially account for this portion through markedly enhanced lipophilicity. Interestingly, a rather newer structural analogue **azosemide,** is of great therapeutic advantage because of its logical as well as successful replacement of the COOH moiety with the corresponding isosteric tetrazolyl moiety.

2.2.4.1.2. Furosemide

The **'drug'** is found to be slightly more potent than the organomercurial agents (see section 13.2.1.), is orally effective ; and its diuretic action is independent of possible changes taking place in body acid-base balance. It has been demonstrated that it acts predominantly not only on the proximal and distal tubules but also on the ascending limb of the loop of Henle.

Furthermore, the renal excretion was observed to be the major channel of elimination and invariably averaged 92% of the administered dose levels, having a mean renal clearance of 149 mL. min^{-1}. Because, this quantum appreciably exceeds the prevailing glomerular filtrate rate, it is believed that the tubular secretion of this drug takes place, even though 95% of it gets bound to plasma protein.

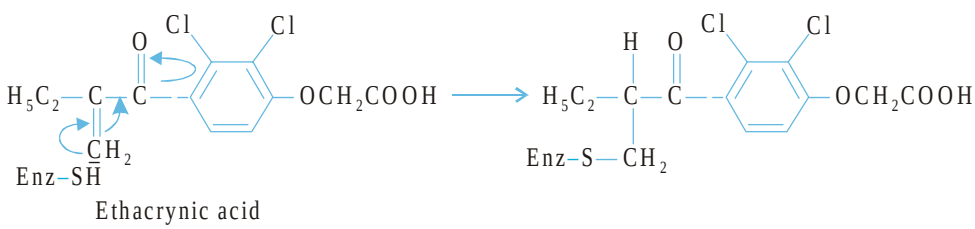
2.2.4.1.3. Ethacrynic Acid

The **'drug'** happens to be powerful loop diuretic whose exact molecular mechanism of action is not yet fully understood. Interestingly, it has been observed that it does possess marked pharmacodynamic similarities of the mercurial diuretics like *'mersalyl'*, which being a phenoxyacetic structural analogue. Besides, it exhibits both *in vivo* and *in vivo* compatibility in its reaction with SH moieties. Moreover, it logically competes with them for the same receptors.

Ethacrynic acid is an aryloxyacetic acid derivative which acts as a potent short-acting diuretic. It actually gives rise to the excretion of virtually an isoosmotic urine by altogether stopping Na^+ reabsorption from the loop of Henle ; however, the excretion of Cl^- is even greater than Na^+. It has been observed that nearly 95% of the **'drug'** gets bound to the plasma proteins. Plasma half-life stands at about 1 hr.

The maximum water as well as sodium diuresis is very much identical to that with **furosemide ;** but largely exceeds that with the thiazides.

SARs of Aryloylphenoxyacetic acids. The comparative study of nine aryloylphenoxyacetic acids revealed that the very presence of an activated double bond susceptible to a nucleophilic attack is almost imperative to cause an effective diuresis. Furthermore, the plausible reduction of the double bond, thereby making 1, 4-addition of an SH moiety practically impossible, ultimately lowered appreciably but failed to eliminate **saluretic activity.** It may be suggested that there exists no definite evidence to demonstrate the sulphhydryl binding in the mechanism of diuretic action of **ethacrynic-type drugs.**

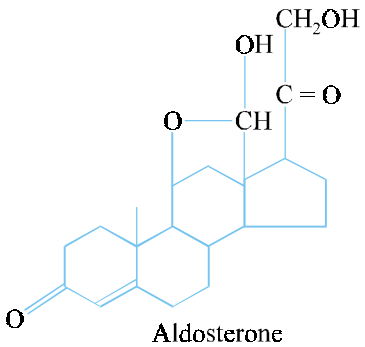


Ethacrynic acid

2.2.5. Aldosterone Inhibitors

Aldosterone is one of the most important members amongst the corticosteroids secreted by the adrenal cortex. It promotes the retention of Na^+, Cl^- and water *via* distal tubular reabsorption.

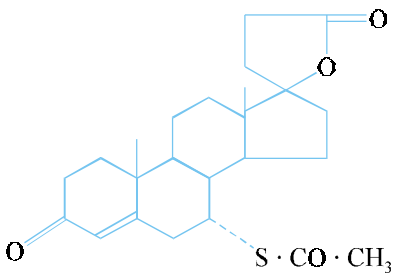
Aldosterone inhibitors (antihormone diuretics) are agents which particularly compete with aldosterone at the specific receptor site located in the distal tubule, thereby reversing the electrolyte



Aldosterone

actions of this naturally occurring hormone, and causing diuresis. The following are the two members of this class of compounds, namely ; **spironolactone** and **metyrapone.**

A. Spironolactone INN, BAN, USAN,

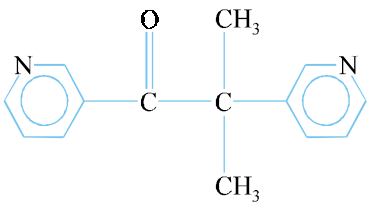


17-Hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone acetate ; Pregn-4-ene-21-carboxylic acid, 7-(acetylthio)-17-hydroxy-3-oxo-γ-lactone, (7α, 17α)- ; 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21, 17β-carbolactone acid γ-lactone ; Spirolactone ; BP ; USP ; Aldactone$^{(R)}$ (Searle)

It acts both as a diuretic and as an antihypertensive drug. It is mostly employed in the *treatment of refractory oedema associated with congestive heart failure, nephrotic syndrome or cirrhosis of the liver in which secretion of aldosterone plays a part. It has also been used successfully in the treatment of primary hyperaldosteronism.*

Dose : *Usual, initial, 100 mg per day in divided doses ; in hyperaldosteronism 400 mg per day.*

B. Metyrapone INN, BAN, USAN,



2-Methyl-1, 2-di-3-pyridyl-1-propanone ; 1-Propanone, 2-methyl-1, 2-di-3-pyridinyl- ; BP ; USP ; Metopirone(R) (Ciba-Geigy).

Metyrapone inhibits the synthesis of aldosterone which has been used in the treatment of some cases of resistant oedema. It is necessary to administer a glucocorticoid (cortisone) along with metyrapone because the latter also exerts an inhibitory effect on the former.

Dose : *2.5 to 4.5 mg per day in divided doses.*

2.2.5.1. Mechanism of Action

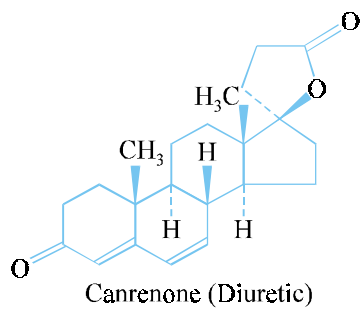
The mechanism of action of the two compounds discussed in the previous section shall be treated as under :

2.2.5.1.1. Spironolactone

It is a purely synthetic steroid which essentially exerts its action as a **'competitive antagonist'** of the potent, endogeneous **mineral-corticosteroid, aldosterone.** Its *natriuretic* action seems to be slightly more particularly in the long-term therapy. In other words, it reverses these electrolyte changes by blocking the renal tubular action of the hormone. Importantly, by critically inhibiting Na^+ reabsorption **spironolactone** produces diuresis and simultaneously minimises the K^+ excretion.

It has been duly observed that this **'drug'** blocks the sodium-retaining effects of aldosterone on the distal convoluted tubule, in doing so it particularly corrects one of the most cardinal mechanisms solely responsible for causing edema ; however, **spironolactone** is effective only in the presence of **aldosterone.**

It is metabolized rapidly after the oral administration. It is found that metabolites are excreted mostly in the urine, but also in bile. The primary metabolite is, *canrenone,* which attains the peak plasma levels within a span of 2–4 hr after oral administration of the drug.



Canrenone (Diuretic)

The half-life of canrenone, following multiple doses of the drug is 13 to 24 hour. It has been observed that both **spironolactone** and **carnenone** are usually get bound to the plasma proteins even more than 90%.

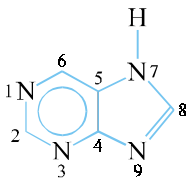
Note : The *'drug'* is particularly ineffective in such clinical situations that are known to have high circulating aldosterone levels (*e.g.*, cirrhosis with ascites).

2.2.5.1.2. Metyrapone

The **'drug'** is a purely synthetic compound which possesses a distinct unique characteristic feature of inhibiting 11-β-hydroxylation in the biosynthesis of cortisol, corticosterone and aldosterone. Therefore, it is invariably employed to test for *hypothalamic-pituitary* function. However, in the normal individual, the drug essentially blocks the specific enzymatic step that ultimately leads to the synthesis of **cortisol** and **corticosterone** (*in vivo*), causing an absolute intense stimulation of **adrenocorticotropic hormone (ACTH)** secretion and inducing thereby a marked and pronounced enhancement in the urinary excretion of 17-hydroxy-corticosteroids.

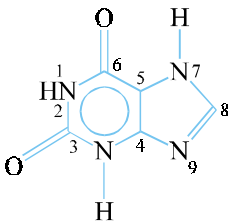
2.2.6. Purine or Xanthine Diuretics

These are the structural analogues of the parent compounds of unsubstituted **purine** (7-imidazo [4, 5-*d*] pyrimidine) and **xanthine.**



Purine

(7-Imidazo [4, 5-*d*] pyrimidine)



Xanthine

(3, 7-Dihydro-1H-purine-2, 6-dione)

Caffeine : 1, 3, 7-Trimethyl xanthine ;

Theophylline : 1, 3-Dimethyl xanthine ;

Theobromine : 3, 7-Dimethyl xanthine ;

Caffeine, theophylline and **theobromine** are the three important members of the xanthine diuretics, which are commonly found in the common beverages *viz.*, **coffee** (*Coffee arabica*), **coca-cola** (*Cola acuminata*) and **cocoa** (*Theobroma cacao*) contain **caffeine ; tea** (*Thea sinensis*) contains **caffeine** and **theophylline ;** and **cocoa** (*Theobroma cacao*) contains **theobromine.**

1. Caffeine BAN, USAN,

1, 3, 7-Trimethylxanthine ; 1H-Purine-2, 6-dione, 3, 7-dihydro-1, 3, 7-trimethyl- ; Guranine ; Methyl-theobromine ; Caffeine (BP ; USP ;) ;

Coffeinum (Eur. P.).

General Method of Extraction

The crude milled natural product is usually moistened with an aqueous alkali, for instance Na_2CO_3, $NaHCO_3$ or line so as to release the alkaloids from their respective salt and subsequently percolated with benzene, ether, or some other appropriate water-immiscible solvent. The solvent layer is extracted with dilute mineral acid to convert the alkaloids into their corresponding salts and also to push them into the aqueous phase. The free alkaloids may be precipitated by the addition of alkali and finally separated by suitable means.

The diuretic effects of **caffeine** are less than those of **theobromine** and **theophylline. Caffeine** may enhance renal blood flow and glomerular filtration rate, but its main action may be attributed to the reduction of the normal tubular reabsorption.

Dose : *100 to 300 mg.*

2. Theophylline BAN, USAN,

1, 3-Dimethylxanthine ; 3, 7-Dihydro-1, 3-dimethylpurine-2, 6 (1H)-dione ; BP ; USP ; Eur. P., Int. P., Ind. P. ;

Constant-T$^{(R)}$ (Ciba-Geigy) ; Duraphyl$^{(R)}$ (McNeil) ; Elixicon$^{(R)}$ (Berlex) ;

It may be extracted from the leaves of tea by the general method described under caffeine.

Dose : *Oral, 60 to 200 mg.*

3. Theobromine BAN, USAN,

3, 7-Dimethylxanthine ; 3, 7-Dihydro-3, 7-dimethylpurine-2, 6 (1H)-dione ; Santheose ;

It is extracted from cocoa by adopting the general method discussed under caffeine.

It possesses a weaker diuretic activity than **theophylline.**

Dose : *300 to 600 mg.*

2.2.6.1. Mechanism of Action

The mechanism of action of the three well-known **'purine diuertics'** shall be discussed as under :

2.2.6.1.1. Caffeine

It is a well-recognized **CNS-drug** which action is solely attributed on account of its inhibition of the enzyme phosphodiesterase in the brain and the ultimate accumulation and actions of cyclic 3′, 5′-adenosine monophosphate (C-AMP).

Caffeine stimulates the voluntary skeletal muscle, thereby enhancing the requisite force of contraction and minimising the ensuing muscular fatigue. Besides, it is found to stimulate parietal cells, increasing gastric juice (acid) secretion ; it also induces a mild diuretic action by aggravating renal blood flow and glomerular filtration rate and lowering proximal tubular reabsorption of Na^+ and H_2O significantly.

2.2.6.1.2. Theophylline

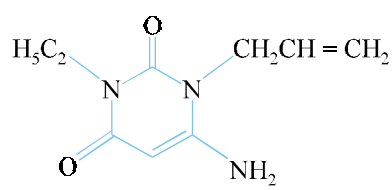
The **'drug'** produces **CNS stimulation** and **skeletal muscles** but to a much lesser extent as compared to caffeine ; however, it exhibits a greater effect on the coronary dilatation, smooth muscle relaxation, diuresis and cardiac stimulation than caffeine.

In general, it possesses relatively more pharmacologic activity practically in all categories than **'theobromine'.**

2.2.7. Pyrimidine Diuretics

The display of diuretic properties by the methylated xanthines, stimulated enough interest in research to establish and ascertain the fact whether or not the pyrimidine analogues, which incidentally are closely related biochemically to the purine derivatives *in vivo*, also possess diuretic activity, This paved the way towards the synthesis of two uracil analogues, namely : **aminometradine**-having 6-amino group and **amisometradine**-having 1, 3-diaklyl substituents.

A. Aminometradine INN, BAN, USAN,



1-Allyl-6-amino-3-ethyluracil ; 1-Allyl-6-amino-3-ethyl-pyrimidine-2, 4 (1H, 3H)-dione ; Aminometramide ; BPC (1959) ;

Minacard$^{(R)}$ (Searle)

It is a relatively weak diuretic which has been employed in the control of oedema in subjects having mild congestive heart failure. It is rarely used now.

Dose : *200 to 800 mg per day in divided doses on 3 days a week, or on alternate days.*

2.2.7.1. Mechanism of Action

The **'drug'** essentially has a pyrimidine nucleus that possesses an almost similar activity as those of the purine derivatives, such as : **caffeine, theophylline** etc. Besides, aminometradine happens to be intimately related biochemically to the xanthine analogues.

2.2.8. Osmotic Diuretics

The functional capacity and reabsorption capability of the renal tubule towards various electrolytes and nonelectrolytes are restricted to a limited extent only, and this vary with respect to each ionic species. A large intake of any of these substances by an individual, may enhance its concentration in the body fluids and will ultimately affect the glomerular filtration rate and the reabsorption capacity of the tubule. The substance will finally appear in the urine with an increased volume of water. Such a substance which increases the output of urine in this fashion is called **osmotic diuretics.**

Osmotic diuretics may be classified into *two* sub-groups, *viz.,*

(*a*) **Osmotic electrolytes,** *e.g.,* potassium and sodium salts, and

(*b*) **Osmotic nonelectrolytes,** *e.g.,* urea, sucrose, mannitol, trometamol.

A. Sodium Acid Phosphate BAN,

$NaH_2PO_4 . H_2O$

Sodium acid phosphate (BP ; Int. P ; Ind. P ;) ; Sodiumbiphosphate USP ;

It is used quite often as a urinary acidifier, for instance, during therapy with methenamine.

Dose : *500 mg to 1 g to 6 times daily ; usual, 600 mg 4 times per day.*

B. Potassium Acetate BAN, USAN,

CH_3COOK

Acetic acid, potassium salt ; BP ; USP ; Ind. P ;

It has been used as a diuretic.

C. Urea BAN, USAN,

H_2NCONH_2

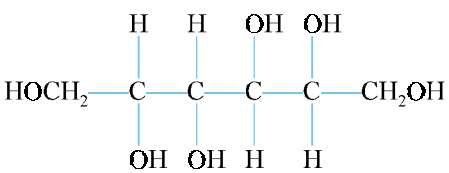
Carbamide ; BP ; USP ; Ind. P. ;

Ureaphil$^{(R)}$ (Abbott) ; Elaqua XX$^{(R)}$ (Elder)

It is an osmotic diuretic with a low renal threshold. It is also *administered to maintain the output of urine during surgical procedures. It is also recommended to decrease intra-ocular pressure in acute glaucoma.*

Dose : *Oral, up to 20 g from 2 to 5 times per day ; as a 40% solution in water or carbonated beverages, has been given as maintenance therapy after i.v. application for the relief of cerebral oedema.*

D. Mannitol BAN, USAN,



D-Mannitol ; BP ; USP ;

Osmitrol$^{(R)}$ (Travenol, U.K.)

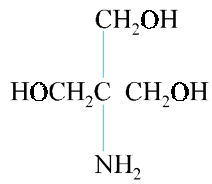
Preparation

On commercial scale it is produced by the catalytic or electrolytic reduction of certain monosaccharides, for instance, glucose and mannose.

It is a diuretic and a diagnostic agent for the kidney function test. The osmotic and diuretic is usually initiated by the administration of a hypertonic solution of mannitol. It is also employed to lower the intraocular pressure and cerebrospinal fluid pressure, before, during the after surgical procedures. Mannitol is considered to be superior to dextrose because of the fact that it is both metabolized in vivo and reabsorbed by the renal tubule to a negligible extent.

Dose : *Usual, i.v. infusion, 50 to 200 g per day ; as diuretic, 50 to 100 g, administered as a 5 to 20% solution.*

E. Trometamol INN, BAN, Tromethamine USAN,



2-Amino-2-(hydroxymethyl)-1, 3-propanediol ; 1, 3-Propanediol, 2-amino-2-(hydroxymethyl)- ; Trihydroxymethylaminomethane ; *Tris*-(hydroxymethyl) aminomethane ; 2-Amino-2-(hydroxymethyl) propane-1, 3-diol ; Tromethamine USP. ;

THAM$^{(R)}$ (Abbott)

It is an organic amine base that reacts with cations of fixed or metabolic acids and also combines with H^+ ions from H_2CO_3 to yield bicarbonate as well as a cationic buffer. *An intravenous infusion usually affords an osmotic diuresis.*

Dose : *Usual, 300 mg/kg body weight administered i.v. as a 0.3 M solution stretched over a period of not less than 60 minutes.*

2.2.8.1. Mechanism of Action

The mechanism of action of a few **osmotic diuretics** are enumerated in the sections that follow :

2.2.8.1.1. Sodium Acid Phosphate

The inorganic salt when employed in large doses usually cause short-term diuresis besides affording acidification.

2.2.8.1.2. Urea

Simply by employing large amounts (*e.g.,* 15 g or an adult) for the water-soluble and also nonmetabolizable compounds to afford a hypertonic condition *i.e.,* high osmolarity, water content is eventually withdrawn from tissues for instance, the eye-ball, thereby lowering pressure in it appreciably (*i.e.,* intraocular pressure). It also helps in reducing the intracranial pressure using almost the same mechanism.

2.2.8.1.3. Mannitol

The IV administration of the hypertonic solutions of the **'drug'**, which is a sugar alcohol, is usually employed to promote an **osmotic diuresis.** It invariably exerts its action because of the glaring

fact that the drug is not absorbed significantly from the GI-tract ; and if administered orally, it gives rise to definite osmotic diarrhea.

It is found that when this *'drug'* is administered parenterally it gets distributed adequately in the extracellular space. Furthermore, only a small portion ranging between 7–10% usually gets metabolized to glycogen ; and remaining quantity is excreted in the urine. Plasma half-life after single IV dose is only 15 minutes having normal renal function.

2.2.8.1.4. Tromethamine (Trometamol)

The **'drug'** happens to be a weak amine base having pKa value of 7.8 at the normal body temperature (98.4°F). Hence, it is almost very close to plasma pH (7.4) ; and, therefore, well-acceptable for the preparation of a buffer mixture for controlling the extracellular pH.

It is, however, pertinent to state here that at pH 7.4 (plasma pH) it is almost 30% non ionized ; and, therefore, it slowly penetrates the cells, where it would buffer the intracellular contents. Under the prevailing circumstances it is able to react with any proton donor, and the usual notion that it reacts first and foremost with carbonic acid (H_2CO_3) or CO_2 is absolutely erroneous. In this manner protons are removed from the H_3O^+ ions, whereby the ionization of H_2CO_3 is shifted so as to minimise pCO_2 and also to enhance the concentration of HCO_3^-. Thus, the excess quantum of HCO_3^- gets excreted slowly through the kidney. This is, therefore, an extremely beneficial manner by which the level of high pCO_2 may be managed conveniently in various conditions, namely : **respiratory acidosis** (*e.g.*, drug intoxication, asphyxia neonatorum, status asthmaticus etc.) wherein the pulmonary ventilation is quite insufficient.

2.2.9. Acidotic Diuretics

The **acidotic diuretics** are essentially the inorganic compounds having a cation function. Examples are-ammonium or calcium, combined with a fixed anion *viz.*, **chloride ion**, which causes two vital, actions, namely ; **systemic hyperchloremic acidosis** and **weak diuretic effect**. These compounds (*e.g.*, **ammonium chloride**, **calcium chloride**) invariably potentiate the diuretic action of mercurial diuretics and hence may be administered at least 48–72 hours prior to the treatment of a mercurial compound so as to facilitate hyperchloremic acidosis. Recently, insoluble **cation exchange resins** have been used to act as diuretics by this mechanism.

A. Ammonium Chloride BAN, USAN,

NH_4Cl

Sal ammoniac ; Muriate of ammonia ; BP ; USP ; Eur. P., Int. P ;

Expiger$^{(R)}$ (Pharmacia, Denm.)

Ammonium chloride causes diuresis by inducing mild acidosis. The acid-forming property is due to the conversion of NH_4^+ ion to urea, which leaves the Cl^- ion free to combine with the available cation, liberated from the elastic HCO_3^- ion. This eventually upsets the $BHCO_3 : H_2CO_3$ ratio thereby causing acidosis, thus :

$$2NH_4Cl + CO_2 \longrightarrow H_2NCONH_2 + H_2O + 2HCl$$

$$NaHCO_3 + HCl \longrightarrow NaCl + H_2CO_3$$

The liberated acid may be buffered by the phosphates as follows :

$$Na_2HPO_4 + H_2CO_3 \rightleftharpoons NaH_2PO_4 + NaHCO_3$$

Disodium hydrogen phosphate — Sodium acid phosphate

The net result in that Cl^- ion displaced HCO_3^- ion and the latter is converted to CO_2. This phenomenon appreciably enhances the Cl^- load to the kidneys thereby allowing a substantial amount of it to escape unabsorbed with a matching amount of Na^+ ion along with an isoosmotic amount of water. The overall effect being the net loss of extracellular fluid thereby helping the mobilization of oedema fluid.

Dose : *Oral, 4 to 12g per day ; usual, oral, 1 to 2 g 4 times daily ; i.v. 100 to 100 ml of 2% solution ; usual, i.v., 500 ml of a 2% solution infused over a period of 3 hours.*

2.2.9.1. Mechanism of Action

The mechanism of action of **ammonium chloride** is as follows :

2.2.9.1.1. Ammonium Chloride

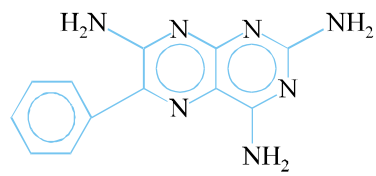
The **'drug'** is indeed a combination of a labile cation (NH_4^+) and a rather fixed anion (Cl^-). The ammonium ion on being converted to urea usually liberates H^+ that instantly reacts with HCO_3^- and other body buffers. The ultimate product is that the Cl^- ion displaces HCO_3^- ; and the latter is subsequently converted to CO_2. In doing so, the Cl^- load to the kidney is enhanced appreciably, and an adequate quantum escapes reabsorption together with an equivalent quantity of cation (mostly Na^+) and an isoosmatic quantum of water. In fact, this is the fundamental mechanism by which NH_4Cl brings forth a net loss of the extracellular fluid and thereby augments the actual mobilization of edema fluid from the body.

2.2.10. Miscellaneous Diuretics

There are a few potent diuretics which could not be accommodated conveniently into any of the classifications made so far (A-I), hence they have been grouped together under this head.

Examples : Triamterene ; Muzolimine.

A. Triamterene INN, BAN, USAN,

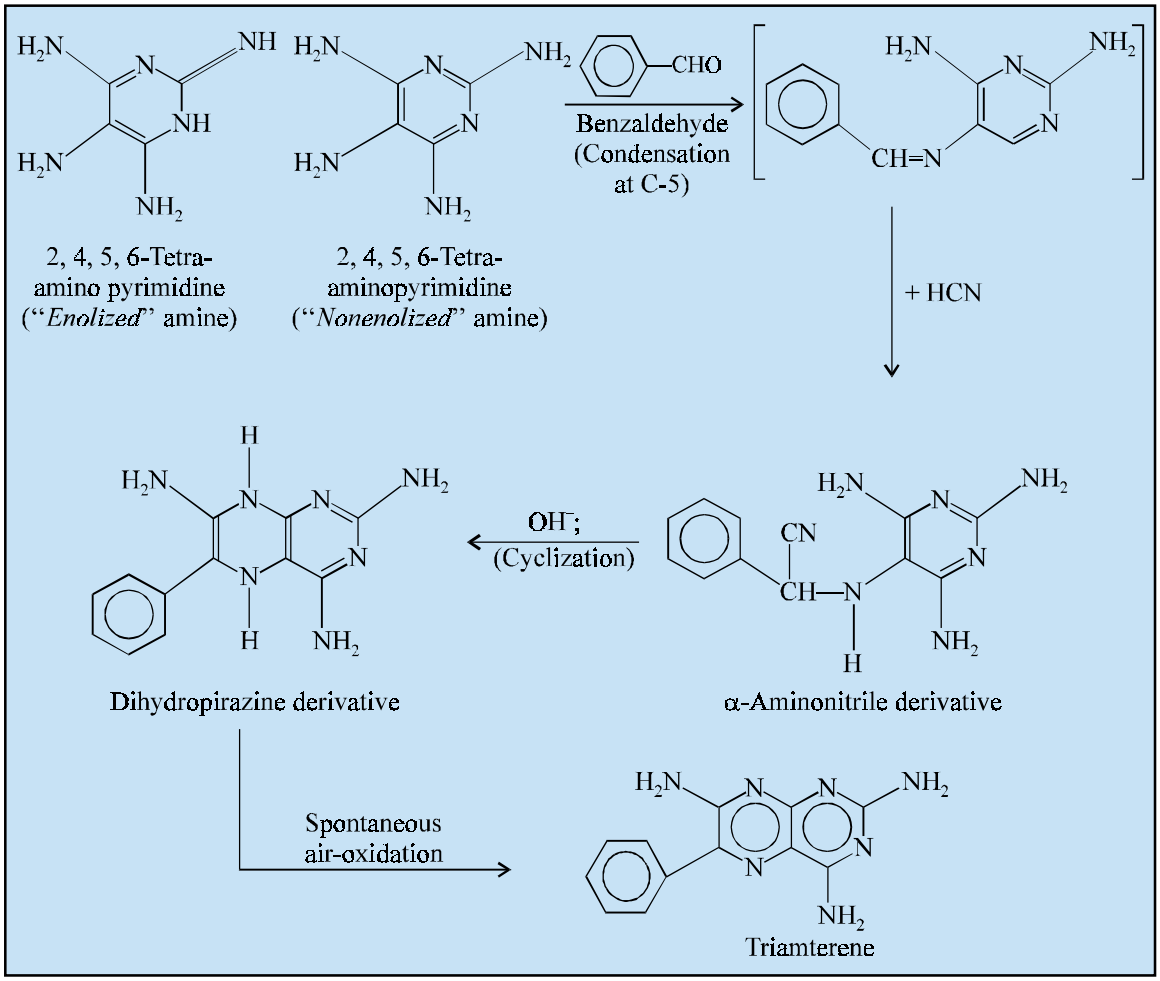


2, 4, 7-Triamino-6-phenylpteridine ; 2, 4, 7-Pteridinetriamine, 6-phenyl- ; BP ; USP ;

Dyrenium(R) (SK & F)

Synthesis

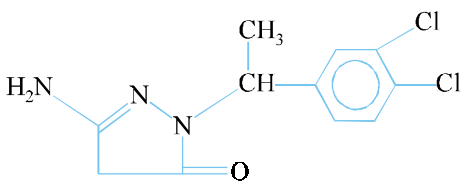
Tautomerism of 2, 4, 5, 6-tetraaminopyrimidine gives the ''nonenolized'' amine which renders the amino moiety at C-5 more basic in character as compared to the remaining amine functions. Therefore, on condensation with benzaldehyde, the union takes place at the most preferred basic nitrogen to form a benzylidene analogue as an intermediate with the loss of a mole of water. Treatment with hydrogen cyanide yields the corresponding α-aminonitrile derivative, which when subjected to a basic medium undergoes cyclization to form the dihydropirazine derivative. This undergoes spontaneous air-oxidation to yield the official compound.



Triamterene is usually recommended in the treatment of oedema associated with nephrotic syndrome, cirrhosis of liver, and congestive heart failure. It has also been used for the control and management of idiopathic oedema, steroid-induced oedema, oedema caused by hyperaldosteronism and in such oedematus patients who fail to respond to other therapy. It is usually used in conjunction with other diuretics like **thiazides.**

Dose : *100 mg every alternate day to 300 mg per day ; usual, 100 mg once daily.*

B. Muzolimine INN, BAN, USAN,



3-Amino-1-(3, 4-dichloro-α-methylbenzyl)-2-pyrazolin-5-one ; 3H-Pyrazol-3-one, 5-amino-2 [1-(3, 4-dichlorophenyl) ethyl]-2, 4-dihydro- ;

Its actions and uses have been reported to be similar to those of **frusemide.** It has a prolonged duration of action.

Dose : For oedema, 40 to 80 mg per day.

2.2.10.1. Mechanism of Action

The mechanism of action of the *'miscellaneous diurects'* are described as under :

2.2.10.1.1. Triamterene

The **'drug'** gets metabolized primarily by the liver in the form of **hydroxy triamterene sulphate,** which is an **active metabolite.** It has been observed that 3–5% of the drug gets usually excreted unchanged in the urine. Although it is known to promote the adequate excretion of Na^+ and Cl^-, it is also believed to conserve K^+ by significantly retarding the usual transport of this specific ion from the tubular cell to the tubular lumen.

In usual practice, however, it is given in conjunction with **hydrochlorothiazide (HCTZ)** particularly in the treatment of edema linked with *congestive heart failure, cirrhosis of the liver,* and the *nephrotic syndrome.*

2.2.10.1.2. Muzolimine. Muzolimine

Possesses diuretic activity on account of its action on the transport mechanism pertaining to the cells of the thick ascending limb of Henle's loop. However, the precise mechanism(s) by which muzolimine causes a diuretic action still remains to be established legitimately*. Furthermore, it has been proposed that **muzolimine,** in fact, inhibits the K^+/Cl^- *contransport system* specifically upon the basolateral membrane of the thick ascending limb cells, whereby it affords an inhibition of the 1 Na^+/1 K^+/2 Cl^- contransport system**.

Probable Questions for B. Pharm. Examinations

1. (*a*) What are **'diuretics'** ? Classify diuretics by citing the structure, chemical name and uses of at least **one** compound from each categroy.

(*b*) Why do the **'non-mercurical diuretics'** have an edge over the **'mercurial diuretics'** ?

2. Discuss **Benzothiadiazines (Thiazides)** as an important class of diuretics. Give the structure, chemical name and uses of any **four** official compounds.

3. Acetazolamide, Methazolamide, Diclofenamide and Disulfamide and potent carbonic anhydrase inhibitors employed as diuretics. Discuss the structural difference amongst these drugs and give the synthesis of any **two** compounds.

4. How would you synthesize **chlorthalidone,** a sulphonamide diuretic, from 3-amino-4-chloro benzophenone-2-carboxylic acid ?

5. 'High-ceiling diuretics exert an intense diuresis of relatively short duration (4-6 hours) with a rapid onset (30 mins)'. Justify the statement with the help of at least **two** important members of this class of drugs.

6. Write a brief note on the following :

(*a*) Aminometradine (*b*) Sapironolactone (*c*) Metyrapone (*d*) Caffeine.

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*Wangemann PH *et al. Pflugers Arch.* **410,** 674, 1987.

Landan RL *et al. Annu. Rev. Med.,* **41, 265, 1955.

7. How would you synthesize :
(*a*) Furosemide from 2, 4-dichlorobenzoic acid
(*b*) Disulphamide from 5-chlorotoluene
(*c*) Methixene hydrochloride from thioxanthene.

8. With the help of some specific examples give an account of the following :
(*a*) Osmotic diuretics (*b*) Acidotic diuretics.

9. **Trimterene** and **Muzoimine** are two diuretics belonging to the 'miscellaneous group'. Give their structures and the synthesis of the former drug.

10. Discuss the **mode of action** of the following class of diuretics :
(*a*) Thiazides
(*b*) Carbonic anhydrase inhibitors
(*c*) Mercurial diuretics
Support your answer with typical examples.

RECOMMENDED READINGS

1. D Lednicer and LA Mitscher **The Organic Chemistry of Drug Synthesis,** John Wiley and Sons, New York, (1995).

2. EF Reynolds (ed.) **Martindale the Extra Pharmacopoeia,** (31st edn.), Royal Pharmaceutical Society, London, (1996).

3. J M Spragne **"Diuretics : In : Molecular Modification in Drug Design"** (ed.) R F Gould *Adv Chem Ser* No. 45, American Chemical Society Washington, D.C., (1964).

4. JM Spragne Diuretics, in : **Topics of Medicinal Chemistry,** Vol. 2 (eds.) J L Rabinowitz and R M Myerson, Interscience Publishers, New York, (1968).

5. J Merrill, **Use and Abuse of Diuretics** *Med Clin N Amer,* **44,** 1155, (1960).

6. ME Wolff (ed.) : **Burger's Medicinal Chemistry and Drug Discovery** (5th edn.), John Wiley & Sons Inc, New York, (1996).

7. Nogrady T, **'Medicinal Chemistry : A Biochemical Approach',** Oxford University Press, New York, 2nd. edn, 1988.

8. RW Berliner and J Orlaff, **Carbonic Anhydrase Inhibitors,** *Pharmacy Rev,* June, (1956).

9. TC Daniels and EC Jorgensen, **Diuretics In : Text book of Organic Medicinal and Pharmaceutical Chemistry,** Eds. CP Wilson, O. Gisvold and RF Doerge (10th end.) J B Lippincott Co. Philadelphia, (1998).

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15

Antihistaminics

Chapter

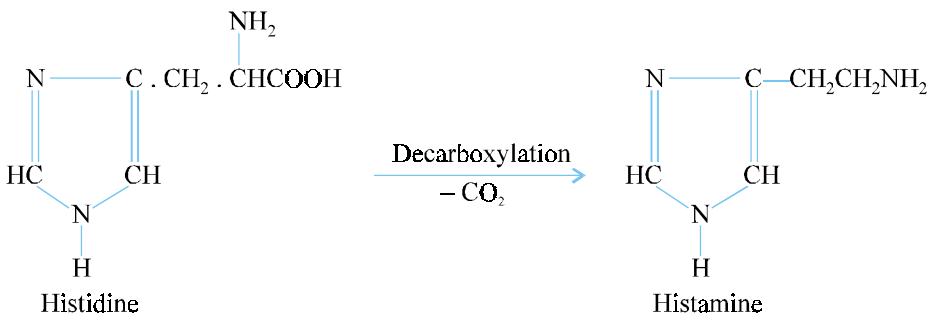
15

Antihistaminics

1. INTRODUCTION

Histamine, 4-(2-aminoethyl) imidazole, as such could not for many years attract enough attention from physiologists, pharmacologists and biochemists alike because of the absence of any therapeutic utility. It occurs in many storage sites in the body in varying amounts. It is present in the mast cells of many body organs, in blood basophils, the mucosal cells of the gastrointestinal tract especially the acid-secreting parietal cells, in the hypothalamus and area postrema in the central nervous system.

In the living organism, **histamine** is synthesized from the naturally occurring α-amino acid, histidine, by the loss of a carboxyl group through bacterial or enzymatic decarboxylation as stated below :

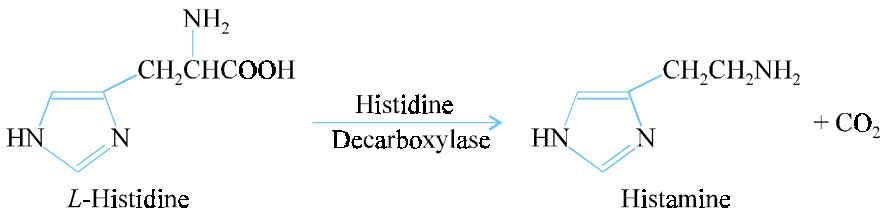


Histidine Histamine

A plethora of antigens (sensitizing substances) derived from food products, pollens, dust mite, house dust, human hair, sheep wool etc., may cause serious allergic and anaphylactic manifestations in human beings, due to the release of **histamine** with some other substances. The release of **histamine** gives rise to a number of physiological actions which are attributable to the activation by **histamine of histamine (H_1- & H_2-) receptors.** Some of the effects include dilation and enhanced permeability of the capillaries with oedema, vasodilation, reflex cardiac acceleration and bronchiole constriction. It also causes gastric acid secretion. A relatively mild release of **histamine** in the body leads to allergic reactions displayed by vivid skin rashes with itching, whereas in extreme instances it may result in an anaphylactic shock which may be fatal. The actions of **histamine** can be antagonized chemically using **histaminase** or formaldehyde but this is of no practical value. The actions are best modified by the use of substances that block competitively the **histamine sensitive receptors.** Such substances are known as **antihistamines (antihistaminics).** The term **antihistamine is** traditionally used to refer to drugs that block the **H_1-receptors.**

Best *et al.** (1927) made an epoch making observation that **'histamine'** was present in relatively high concentration in the lungs, which eventually gave rise to vasoconstriction, anaphylactic shock-like syndrome and acute respiratory distress in laboratory animals treated with IV administration. Subsequently, the histamine's specific role in the particular pathogenesis of the ensuing anaphylactic reaction was duly demonstrated and substantially established.

In the early 1930s, an amalgamation of sequential events and circumstancial evidences almost established the various deleterious and harmful effects caused by an excess of **'histamine'** ; and these findings were exclusively based on both *in vitro* and *in vivo* methods that were meticulously developed so as to screen the chemical effects upon the various physiological aspects, namely : bronchial, gastro-intestinal and other smooth muscle tissues. Thus, a broad platform was made available for the extensive as well as intensive screening of several synthesized drug molecules with respect to their possible viable **'histaminic activity'**, in addition to their anticipated *anticholinergic* and *antiserotoninergic* pharmacological profile.



L-Histidine Histamine

Antihistaminics are widely used in the *palliative treatment in allergic conditions like hay fever, urticaria, some forms of pruritus, rhinitis, conjunctivitis, nasal discharge, mild asthma etc. A few antihistaminics possess potent antiemetic action and hence are frequently employed in the prevention and treatment of irradiation sickness, motion sickness (air, sea, road), nausea in pregnancy and post-operative vomiting.*

In general, the most common side-effect of **antihistaminics** is sedation which may be followed by drowsiness, impaired alertness and retarded ability to perform jobs which need high precision and concentration.

2. CLASSIFICATION

The commonly used **antihistaminics** may be classified on the basis of their chemical structures and these all are of the type **histamine H_1-receptor antagonists.** They are :

2.1. Histamine H_1-Receptor Antagonists

(*i*) **Aminoalkylethers :** *Examples*-Diphenhydramine Hydrochloride ; Bromodiphenhydramine Hydrochloride ; Dimenhydrinate ; Doxylamine Succinate ; Diphenylpyraline Hydrochloride.

(*ii*) **Ethylenediamines :** *Examples*-Mepyramine Maleate ; Tripelennamine Hydrochloride, Thonzylamine Hydrochloride ; Zolamine Hydrochloride.

(*iii*) **Thiophene Derivatives :** *Examples*-Methapyrilene Hydrochloride ; Methaphenilene Hydrochloride, Thenyldiamine Hydrochloride ; Chlorothen Citrate.

(*iv*) **Cyclic Basic Chain Analogues :** *Examples*

(*a*) **Imidazoline Derivatives,** *e.g.*, Antazoline Hydrochloride ; (*b*) Piperazine Derivatives, *e.g.*, Cyclizine Hydrochloride ; Chlorcyclizine Hydrochloride ; Meclizine Hydrochloride ; Buclizine Hydrochloride ; (*c*) Piperidine Derivativs, *e.g.*, Thenalidine Tartrate.

*Best CH *et al. J. Physiol,* **62** : 397, 1927.

(*v*) **Phenothiazine Derivatives :** *Examples*-Promethazine Hydrochoride ; Promethazine Teoclate ; Trimeprazine Tartrate ; Methdilazine Hydrochloride.

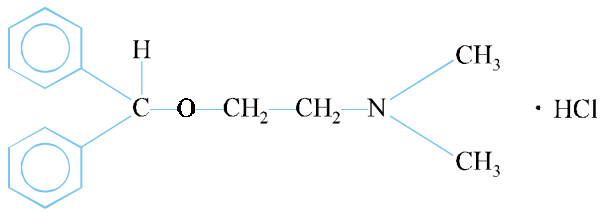
(*vi*) **Second-generation Non Sedating Antihistamines :** *Examples :* Terfenadine ; Astemizole ; Loratadine ; Acrivastine ;

(*vii*) **Miscellaneous Agents :** *Examples*-Phenindamine Tartrate ; Triprolidine Hydrochloride ; Chlorpheniramine Maleate ; Cyproheptadine Hydrochloride.

2.1.1. Aminoalkylethers

These are also referred to as basic ether group because of the presence of an alkyl amino function in the drug molecule.

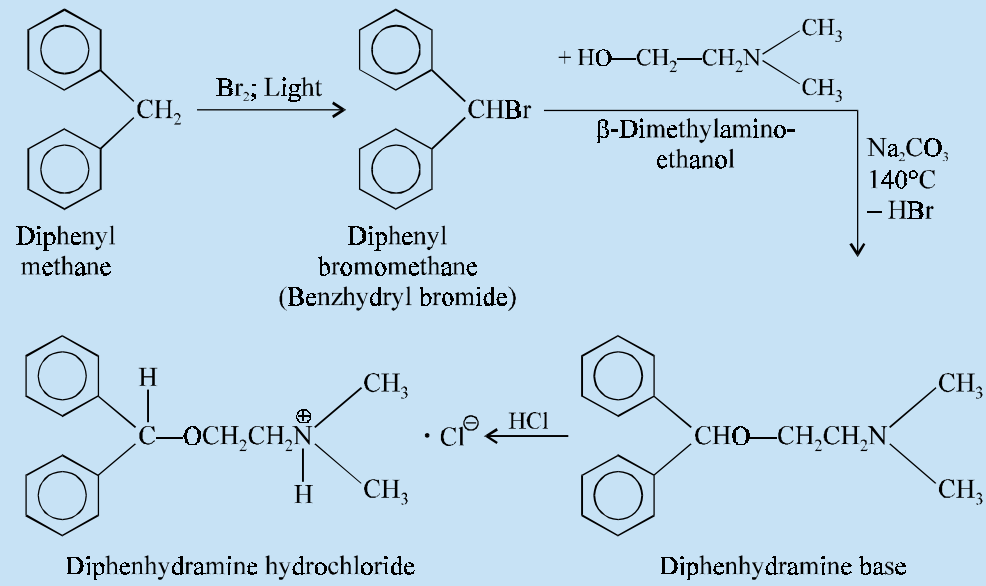
A. Diphenhydramine Hydrochloride BAN, USAN, Diphenhydramine INN,



2-(Diphenylmethoxy)-N, N-dimethylethylamine hydrochloride ; Ethanamine, 2-(diphenylmethoxy)-N, N-dimethyl-, hydrochloride ; BP ; BPC ; USP ;

Benadryl(R) (Parke-Davis) ; Bendylate(R) (Reid-Provident) ; SK-Diphenhydramine(R) (Smith Kline & French)

Synthesis

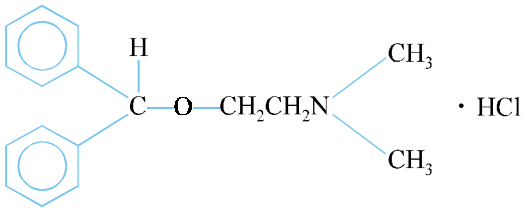


Diphenylbromomethane is first prepared by the bromination of diphenylmethane in the presence of light. Subsequently diphenhydramine base is obtained by heating diphenylbromomethane, β-dimethyl-amino-ethanol, and sodium carbonate is toluence. After distilling off toluene, the purified **diphenhydramine** is converted to the hydrochloride with hydrogen chloride.

It is *frequently used in mild, local allergic reactions due to insect bites. It possesses sedative, antiemetic and anti-tussive properties and can be used in seasonal allergic rhinitis, allergic manifestations due to urticaria and allergic conjunctivitis of inhalant allergens.*

Dose : *25–50 mg, usual, adult, oral dose 3 to 4 times a day, with maximum of 400 mg daily ; topical to skin 2% cream 3 or 4 times a day.*

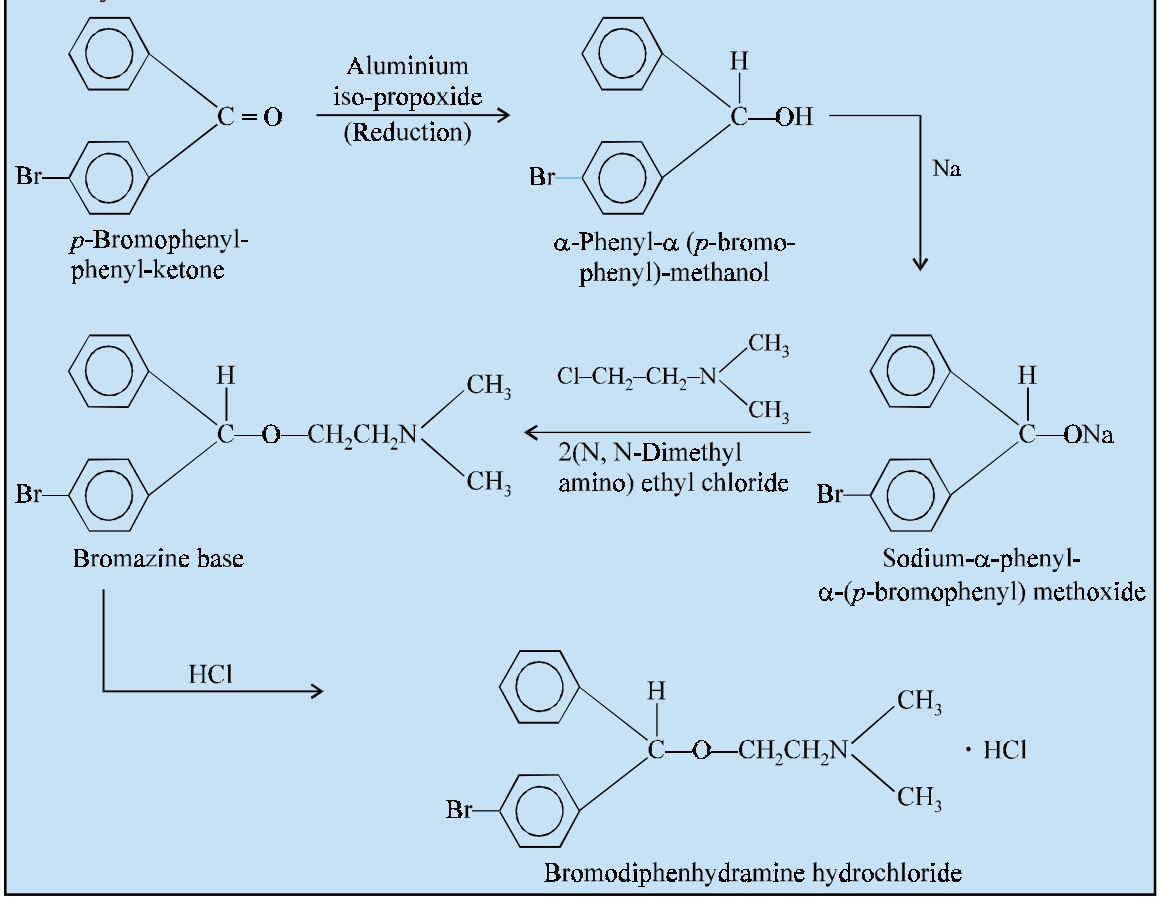
B. Bromodiphenhydramine Hydrochloride BAN, USAN, Bromazine INN,



2-[(*p*-Bromo-α-phenylbenzyl) oxy]-N, N-dimethylamine hydrochloride ; Ethanamine, 2-[(4-bromophenyl) phenylmethoxy]-N, N-dimethyl-, hydrochloride ; Bromazine hydrochloride ; BP ; USP ;

Ambodryl Hydrochloride(R) (Parke-Davis)

Synthesis

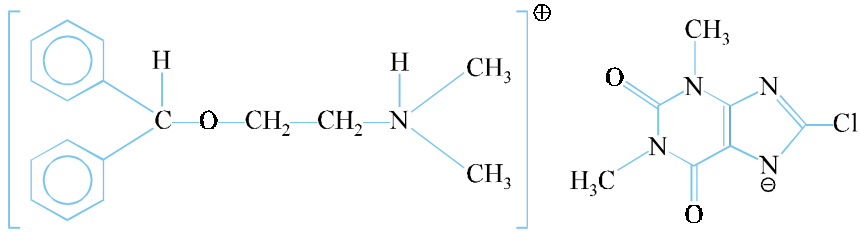


α-Phenyl-α-(*p*-bromophenyl) methanol is first prepared by the reduction of *p*-bromophenyl-phenyl ketone with aluminium isopropoxide, which on treatment with sodium metal results into the corresponding mono-sodium salt. This on reaction with 2(N, N-dimethyl amino) ethyl chloride loses a molecule of sodium chloride and provide the bromazine base which on neutralization with hydrogen chloride gives the **bromodiphenhydramine hydrochloride.**

It is probably effective for mild, local allergic reactions to insect bites, physical allergy, and *for minor drug reactions characterised by pruritis.*

Dose : *25 mg, usually 3 or 4 times daily.*

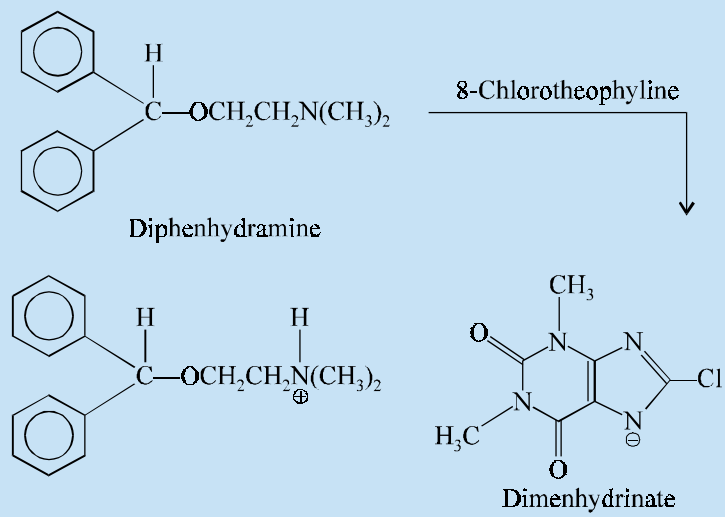
C. Dimenhydrinate INN, BAN, USAN,



8-Chlorotheophylline, compound with 2-(diphenylmethoxy)-N, N-dimethyl-ethylamine (1:1) ; 1H-Purine-2, 6-dioine, 8-chloro-3, 7-dihydro-1, 3-dimethyl-ethylamine (1:1) ; BP ; USP ; Int. P ; Ind. P ;

Dramamine(R) (Searle) ; Dommanate(R) (O'Neal, Jones and Feldman).

Synthesis

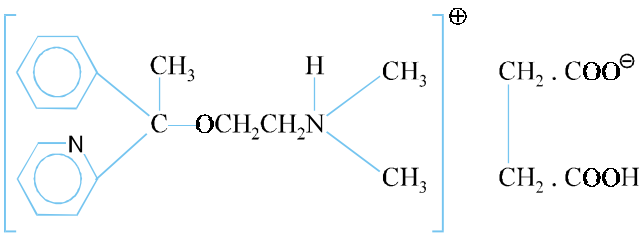


Dimenhydrinate is prepared from diphenhydramine and 8-chloro-theophylline in the stoichiometric proportion (1:1).

It is one and half time as potent as **diphenhydramine hydrochloride.** It is mostly used as an antinauseant, in motion sickness, radiation sickness and also in nausea of pregnancy.

Dose : *Usual, oral 50 mg thrice per day.*

D. Doxylamine Succinate BAN, USAN,



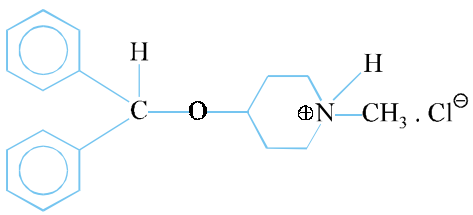
2-[α-[2-(Dimethylamino) ethoxy]-α-methylbenzyl] pyridine succinate (1:1) ; Ethanamine, N, N-dimethyl-2-[1-phenyl-1-(2-pyridinyl) ethoxy]-butanedioate (1:1) USP ;

Decapryn Succinate(R) (Merrell Dow) ; Unisom(R) (Pfizer)

It may be *used for allergic conjunctivitis due to inhalant allergens (like pollens and dust), seasonal and perennial allergic rhinitis, and uncomplicated allergic skin manifestations of urticaria.*

Dose : *12.5 to 25 mg ; Usual, adult, oral 4 to 6 times a day.*

E. Diphenylpyraline Hydrochloride BAN, USAN, Diphenylpyraline INN,



4-(Diphenylmethoxy)-1-methylpiperidine hydrochloride ; Piperidine, 4-(diphenylmethoxy)-1-methyl-, hydrochloride ; BP ; USP ;

Diafen(R) (Riker) ; Hispril(R) (Smith, Kline & French).

It may be employed for the *treatment of angioedema, dermographism and amelioration of reactions to blood or plasma. It is also effective for use in seasonal and perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods.*

Dose : *Usual, adult, oral 5 mg, 2 times a day.*

2.1.1.1. Mechanism of Action

The mechanism of action of aminoalkylethers dealt with in the previous section shall be discussed as under :

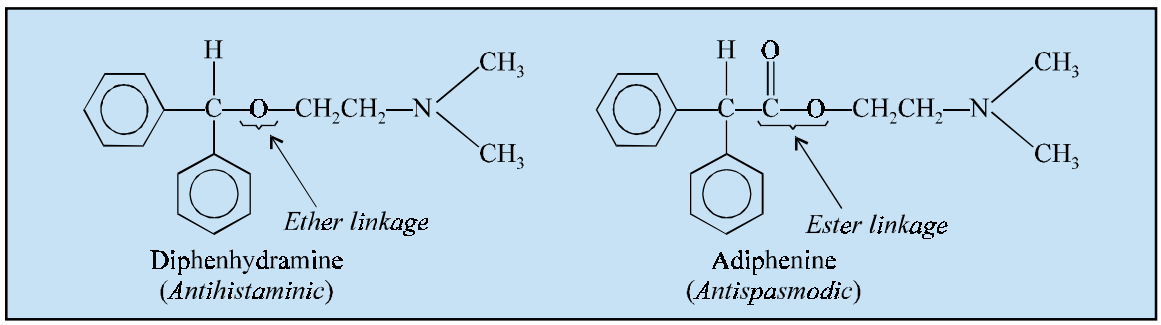
2.1.1.1.1. Diphenhydramine Hydrochloride

The **'drug'** is found to be well-absorbed after the oral administration ; and the first-pass metabolism is notedly so predominant that only 40-60% virtually reaches systemic circulation almost unchanged. It has been observed that the peak-plasma concentrations are invariably accomplished within a span of 1 to 4 hr, 80 to 85% gets bound to plasma protein and the elimination half-life varies between 2.4 to 9.3 hour.

As the **'drug'** has an atropine-like specific action, it needs to be administered with great caution and supervision in subjects having a history with asthma.

In reality, quite a few of the so called **'first-generation' H_1-antihistaminics** are believed to antagonize ACh. Nevertheless, the parasympatholytic activity could be regarded as the major undesirable side effects because it essentially gives rise to dry mouth and voiding difficulties. Interestingly, the ability to minimise nasal discharges (secretions) may be loohed upon as a positive clinical attribute, when included in *'hay fever'* and several *'cold'* medicaments.

SAR of Diphenhydramine. The **antihistaminic 'drug'** may be viewed as possessing an isosteric relationship with adiphenine an antispasmodic *i.e.*, the latter has an additional carbonyl moiety to give it the status of the *'ester'* compound as given below :



The **'etiology'** of this drugs anticholinergic activity may be explained explicity if one takes into consideration the two functional moieties *viz.*, ether and ester as isosterically related to one another.

2.1.1.1.2. Bromodiphenhydramine Hydrochloride

The **'drug'** is found to be more lipid soluble in comparison to **diphenhydramine.** It is observed to exert almost twice its effective activity particularly in the guinea pigs against the lethal effects of histamine aerosols.

2.1.1.1.3. Dimenhydrinate

It is an **ethanolamine antihistaminic agent** belonging to the **first-generation H_1-antagonist** drug classes causing appreciable sedation. Besides, it also exhibits significiant anticholinergic activity.

2.1.1.1.4. Doxylamine Succinate

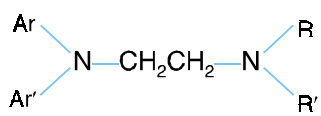
The **'drug'** is an ethanolamine antihistamine agent having appreciable sedative pharmacologic activity ; and, generally, listed in OTC* *sleep aids.* It also possesses significant anticholinergic activity.

2.1.1.1.5. Diphenylpyraline Hydrochloride

It exerts its antihistaminic properties along with antimuscarinic and central sedative pharmacologic activities. Though it may be applied topically but it has a risk of sensitization. Therefore, it finds its enormous application for the relief of hypersensitivity reactions, such as : *urticaria, angiodema, rhinitis, conjunctivitis,* and in pruritic skin disorders.

2.1.2. Ethylenediamines

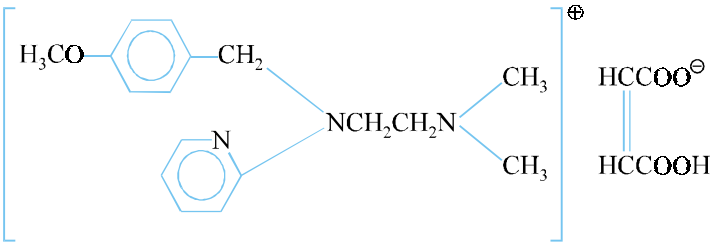
This class of compounds essentially have the following **general structure :**



*__OTC__ = Over the Counter.

where Ar and Ar′ are aromatic or heteroaromatic moieties, and *R* and *R*′ are small alkyl entities. A few classical members of this category shall be discussed here.

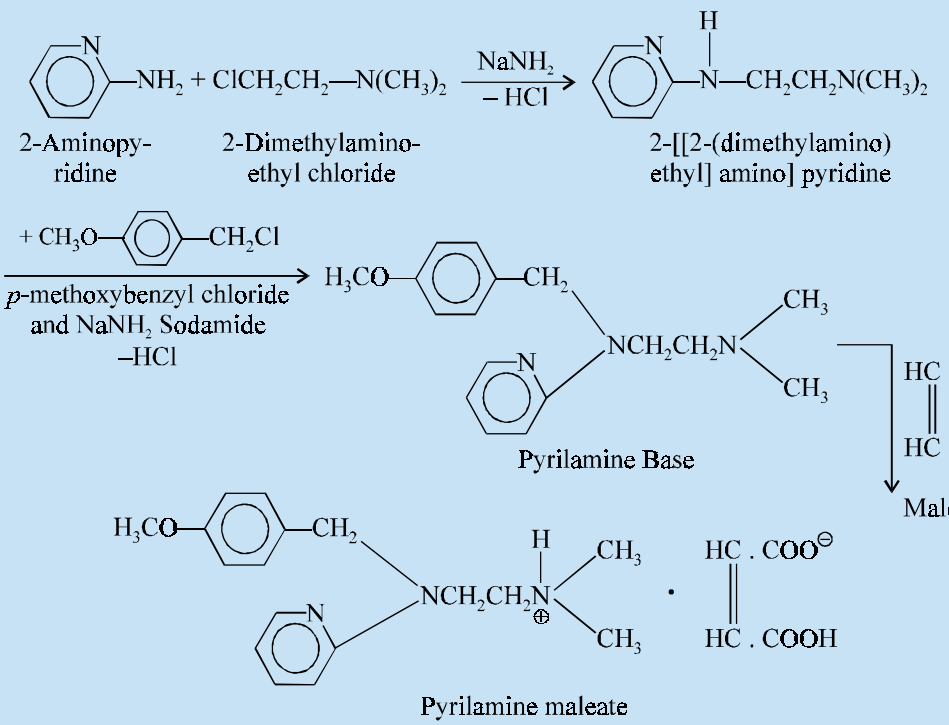
A. Mepyramine Maleate BAN, Pyrilamine Maleate USAN, Mepyramine INN,



2-[[(2-Dimethylamino) ethyl] (*p*-methoxybenzyl) amino] pyridine maleate (1:1) ; 1, 2-Ethanediamine, N-[(4-methoxy-phenyl) methyl]-N′, N′-dimethyl-N-2-pyridinyl-, (Z)-2-butanedioate ; Pyranisamine maleate ; Mepyramine Maleate BP ; Int. P., Ind. P. ; Purilamine Maleate U.S.P.,

Anthisan(R) (May & Baker) ; Dorantamin(R) (Dorsey Lab.) ; Minihist(R) (Ives) ; Pymafed(R) (Hoechst-Roussel)

Synthesis :



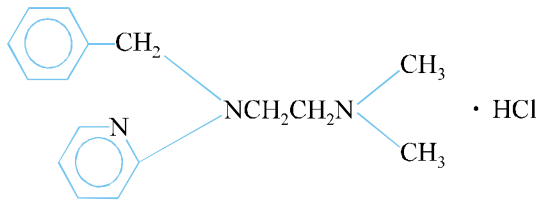
In the first step, 2-[[2-(dimethylamino) ethyl] amino] pyridine is prepared by the condensation of 2-aminopyridine with 2-dimethylamino ethyl chloride with the elimination of a molecule of hydrogen chloride in the presence of sodamide. The resulting product on further condensation with *p*-methoxy

benzyl chloride in the presence of sodamide yields the pyrilamine base which on neutralization with maleic acid gives rise to the desired product **pyrilamine maleate.**

It is a **potent antihistaminic agent with a low incidence of sedative effects.** It has acclaimed a legitimate entrance as component in a number of proprietary antitussive formulations.

Dose : *25 to 50 mg ; adult, oral, 3 to 4 times daily.*

B. Tripelennamine Hydrochloride BAN, USAN, Tripelennamine INN,



2-[Benzyl [2-(dimethylamino) ethyl] amino] pyridine monohydrochloride ; 1, 2-Ethanediamine, N, N-dimethyl-N′-(phenylmethyl)-N′-2-pyridinyl-, monohydrochloride ; BP 1963 ; USP ; Int. P., Ind. P. ;

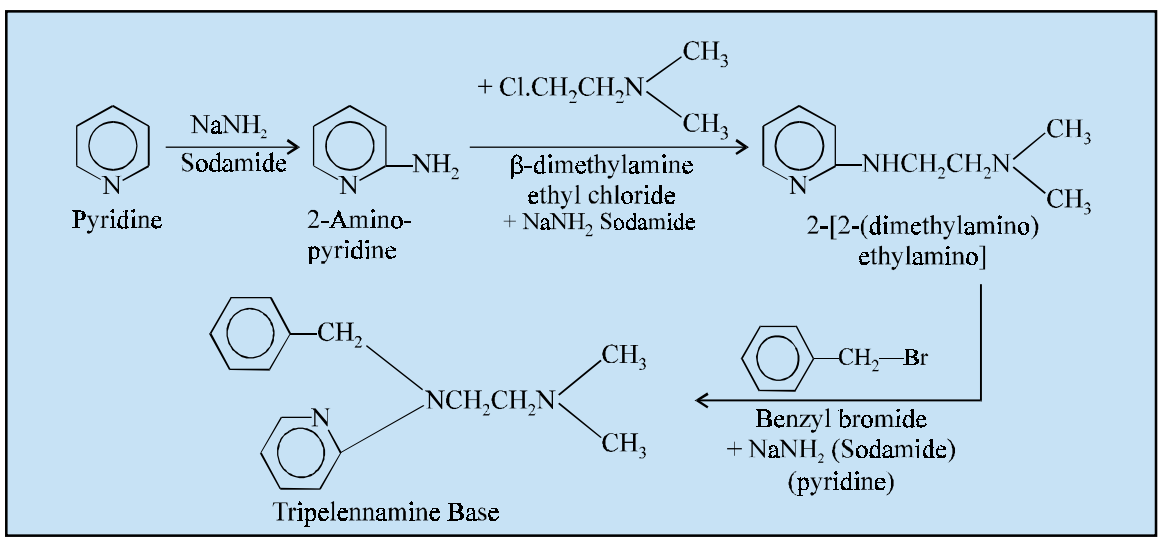
Pyribenzamine Hydrochloride(R) (Ciba-Geigy).

Synthesis

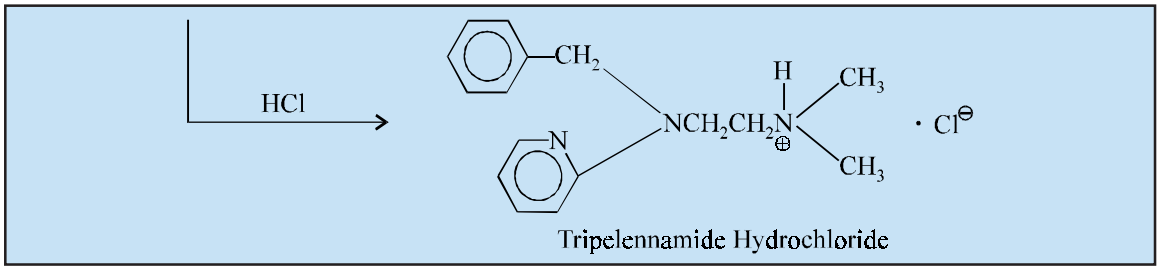
Tripelennamine can be prepared as follows : 2-aminopyridine, prepared by the action of sodamide on pyridine, is reacted with β-dimethylaminoethyl chloride in the presence of sodamide, and the resulting 2-[2-(dimethylamino) ethylamino] pyridine is subsequently condensed with benzyl bromide in the presence of sodamide. The corresponding hydrochloride salt is obtained from the base by treatment with hydrogen chloride in an organic solvent.

It is frequently employed in the *treatment of perennial and seasonal allergic rhinitis, allergic conjunctivitis due to inhalant allergens and foods, simple allergic skim manifestations of urticaria and angioedema, dermographism and anaphylactic reactions as an adjunct to adrenaline.*

Dose : *25 to 50 mg ; Usual, adult, oral 4 to 6 times a day.*

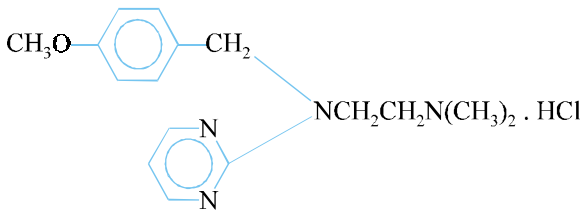


(*Contd...*)



Tripelennamide Hydrochloride

C. Thonzylamine Hydrochloride INN, BAN, USAN,

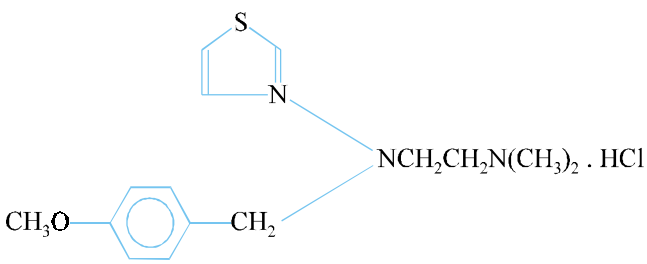


2-{[2-(Dimethylamino) ethyl]-(*p*-methoxybenzyl) amino} pyrimidine hydrochloride ; NF XII ; Resistab(R) (Bristol-Myers) ; Neohetramine Hydrochloride(R) (Nepera)

It is recommended for use with streptomycin in exudative human tuberculosis. It is used in treating the symptoms of hay fever, urticaria, drug reactions and other mild allergic conditions.

Dose : *50 mg ; Usual, adult, oral up to 4 times a day.*

D. Zolamine Hydrochloride USAN, Zolamine, INN,



2-[[2-(Dimethylamino) ethyl]-(*p*-methoxybenzyl) amino] thiazole monohydrochloride ; 1, 2-Ethanediamine, N-[(4-methoxyphenyl) methyl]-N′, N′-dimethyl-N-2-thiazolyl-, monohydrochloride.

It is used both as an antihistaminic and anaesthetic (topical) agent.

2.1.2.1. Mechanism of Action

The mechanism of action of some of the **ethylenediamines** are described as under :

2.1.2.1.1. Mepyramine Maleate (Pyrilamine Maleate)

The **'drug'** and **tripelennamine** are both pronounced clinically to belong to the category of less potent antihistaminics. It has been reported to be highly potent particularly in antagonizing the histamine-

*Casy AF : **Chemistry of H_1-Histamine Antagonists :** In : Rochae Silva M (ed.). **Handbook of Experimental Pharmacology,** Vol. 18.2, p-175, Springer-Verlag, New York. 1978.

induced contractions produced in guinea-pig ileum*. By virtue of this marked and pronounced local anaesthetic action, the **'drug'** is recommended to be taken along with food and **not be chewed prohibitively.**

SAR of Pyrilamine. It essentially differs structurally from **tripelennamine** by having a methoxy (OCH_3) functional moiety strategically positioned at the *para*-position of the benzyl radical.

2.1.2.1.2. Tripelennamine Hydrochloride

The **'drug'** (and its citrate) seem to be get metabolized almost completely to either quaternary ammonium N-glucuronide or *O*-glucuronides of the corresponding hydroxylated metabolites. The drug also undergoes several chemical modifications *in vivo*, namely : (*a*) ring hydroxylation ; (*b*) N-oxidation ; and (*c*) N-demethylation. In view of these glaring evidences the *'drug'* gets excreted principally in the urine as its conglomerate of metabolites.

Incidentally, **tripelennamine** enjoys the reputation of being the first and foremost **ethylenediamine** ever developed in the American Laboratories.

2.1.2.1.3. Thonzylamine Hydrochloride

The overall activity of this *'drug'* seems to be very much identical to **tripelennamine** but it is pronounced to have much less toxicity.

SAR to Thonzylamine. The only difference between this **'drug'** and tripelennamine is the presence of a **'pyrimidine nucleus'** instead of the **'pyridine nucleus'** in the latter, which perhaps retards its toxicity profile to an appreciable extent because of its comparatively faster metabolism *in vivo.*

2.1.2.1.4. Zolamine Hydrochloride

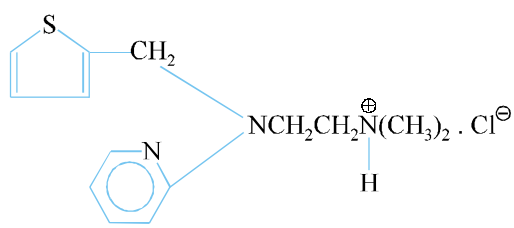
The **'drug'** possesses less toxicity in comparison to tripelennamine and thonzylamine. It exhibits both antihistaminic and anaesthetic pharmacological profile.

SAR of Zolamine. It essentially contains the **'thiazole moiety'** instead of the **pyridine** and **pyrimidine** groups present in tripelennamine and a 5-thonzylamine respectively. Being, a 5 membered ring (thiazole) which is certainly much more compact than the 6-membered heterocyclic ring present in the other two compounds.

2.1.3. Thiophene Derivatives

The **thiophene** moiety is an essential component of this group of compounds which exhibit significant antihistaminic properties. Though these compounds also possess an ethylene-diamine nucleus yet the presence of a **thiophene** group makes them belong to a separate category altogether.

A. Methapyrilene Hydrochloride BAN, USAN, Methapyrilene INN,



2-[[2(Dimethylamino) ethyl]-2-thenylamino] pyridine monohydrochloride ; 1, 2-Ethanediamine, N, N-dimethyl N′-2-pyridinyl-N′-(2-thenylmethyl)-, monohydrochloride ; USP ;

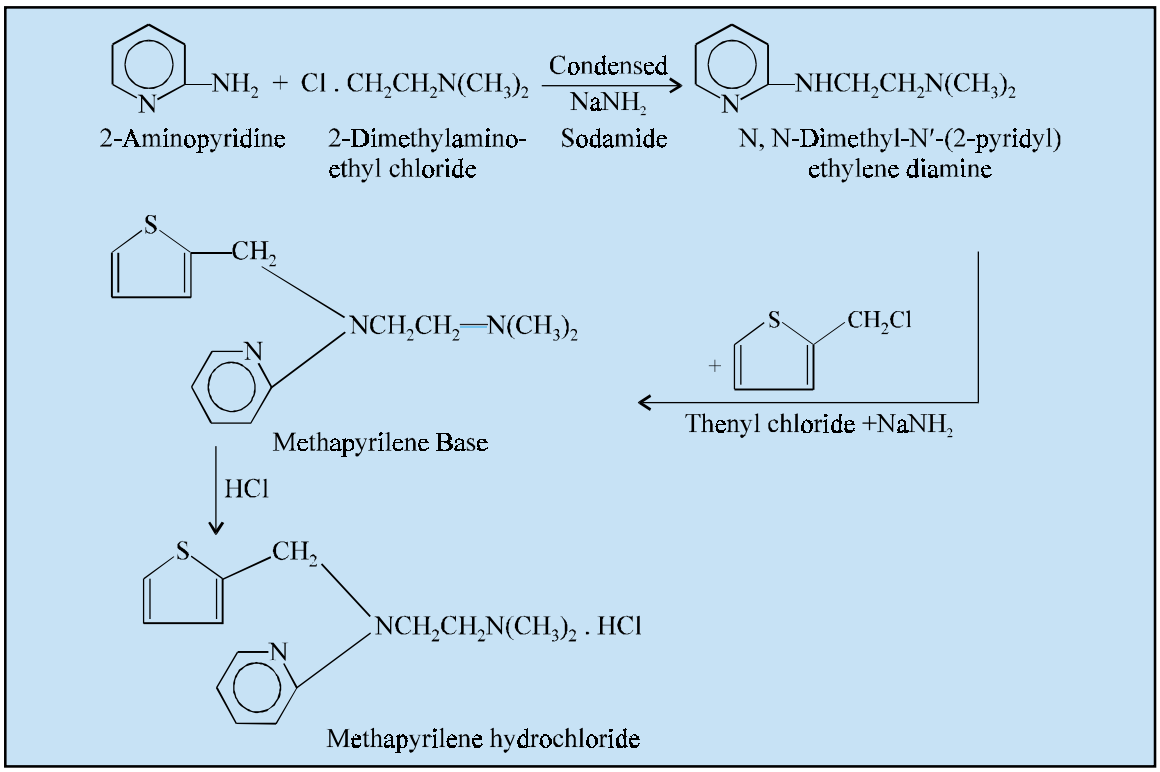
Histadyl$^{(R)}$ (Lilly) ; Semikon Hydrochloride$^{(R)}$ (Beecham) ; Thenylene Hydrochloride$^{(R)}$ (Abbott).

Synthesis

N, N-Dimethyl-N′-(2-pyridyl)-ethylene diamine is prepared by the condensation of 2-amino pyridine and 2-dimethylamino ethyl chloride in the presence of sodamide. The resulting product is

further condensed with 2-thenyl chloride, using sodamide as a catalyst, to obtain the methapyrilene base, which on neutralization with hydrogen chloride yields the methapyrilene hydrochloride.

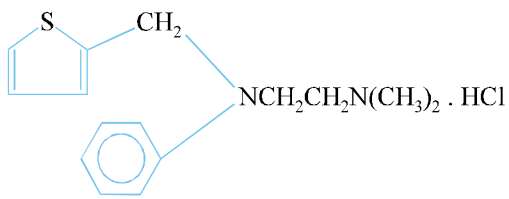
It essentially differs from tripelennamine in having a 2-thenyl (*i.e.*, thiophene-2-methylene) moiety instead of the benzyl group.



It possesses a low incidence of side-effects and may be employed in the treatment of all types of suspected allergies, namely—hay fever, chronic urticarias, allergic rhinitis and allergic dermatitis.

Dose : *50 to 100 mg, 3 to 4 times a day.*

B. Methaphenilene Hydrochloride USAN, Methaphenilene INN,



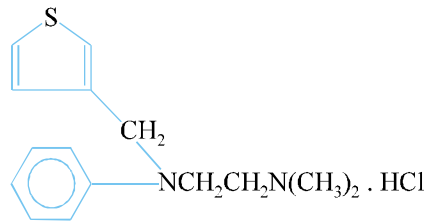
N, N-Dimethyl-N′-(α-thenyl)-N′-phenethylenediamine hydrochloride ; NF X ;

Diatrine Hydrochloride(R) (Warner Chilcott).

It is an effective antihistaminic agent. It induces slow incidence of side reactions but possesses a moderate tendency to cause gastro-intestinal irritation. It is a drug of choice for the symptomatic relief of upper respiratory infections.

Dose : *Usual, 25–50 mg 4 times per day.*

C. *Thenyldiamine Hydrochloride* BAN, *Thenyldiamine* INN, USAN,



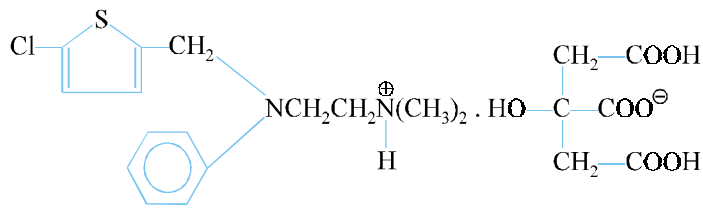
2-[[2-(Dimethylamino) ethyl]-3-thenylamino] pyridine-hydrochloride ; N, N-Dimethyl-N′-(2-pyridyl)-(3-thenyl)-ethylene-diamine hydrochloride ;

Thenfodil hydrochloride(R) (Winthrop) ;

It is an antihistaminic agent which is recommended in comparatively milder type of allergic conditions.

Dose : *Usual, oral, 15 mg up to 6 times per day.*

D. Chlorothen Citrate USAN, Chloropyrilene INN, Chloropyrilene Citrate BAN,



2-[(5-Chloro-2-thenyl [2-(dimethylamino) ethyl] amino] pyridine dihydrogen citrate ; Chloromethapyrilene citrate ; N.F. XIII ;

Panta(R) (Valeas, Italy).

Chlorothen is similar in structure to tripelennamine, the only difference being that the benzyl group in the latter is substituted by the 5-halothenyl moiety. It has been observed that the halogen-substitution enhances the antihistaminic activity and renders the compound less toxic than its corresponding non-halogenated version.

Dose : *25 mg ; every 3 to 4 hours.*

2.1.3.1. Mechanism of Action

The mechanism of action of the **thiophene structural analogoues** of histamine shall be discussed briefly as under :

2.1.3.1.1. Methapyrilene Hydrochloride

The FDA has declared it a potential carcinogen in 1979, and hence, it is no longer in use.

SAR of Methapyrilene. It essentially differs from **tripelennamine** in possessing a 2-thenyl (thiophene-2-methylene) moiety in place of the benzyl moiety. Besides, the thiophene ring is regarded to be isosteric with the benzene ring ; and, therefore, the isosteres found to display almost identical activity. An exhaustive study with respect to the **'solid-state conformation'** of this **'drug'** evidently showed that the geometrical *trans*-conformation is obviously the most preferred one for the two ethylene N-atoms.

2.1.3.1.2. Methaphenilene Hydrochloride

It is a potent antihistaminic agent that may give rise to rather mild type of gastro-intestinal irritation.

2.1.3.1.3. Thenyldiamine Hydrochloride

The *'drug'* is regarded as a traditional antihistaminic which action is usually associated with both troublesome sedative and antimuscarinic effects.

2.1.3.1.4. Chlorothen Citrate (Chloropyrilene Citrate)

It is invariably associated with an antibacterial formulation that is indicated mostly for the treatment of vasomotor rhinitis and other hypersensitivity reaction of the upper respiratory tract (URT) complicated by bacterial infections.

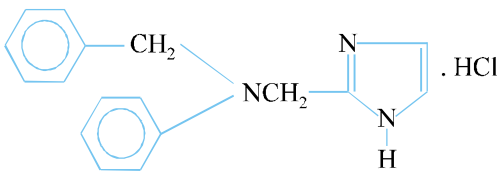
2.1.4. Cyclic Basic Chain Analogues

A variety of more potent and less toxic **antihistaminic agents** have been tailored by effecting molecular modifications of the general ethylenediamine structure whereby the dimethylamino function is essentially replaced by a small compact heterocyclic ring.

Thus, the cyclic basic chain analogs may be further sub-divided into **three** categories, namely :

(*a*) **Imidazoline Derivatives**

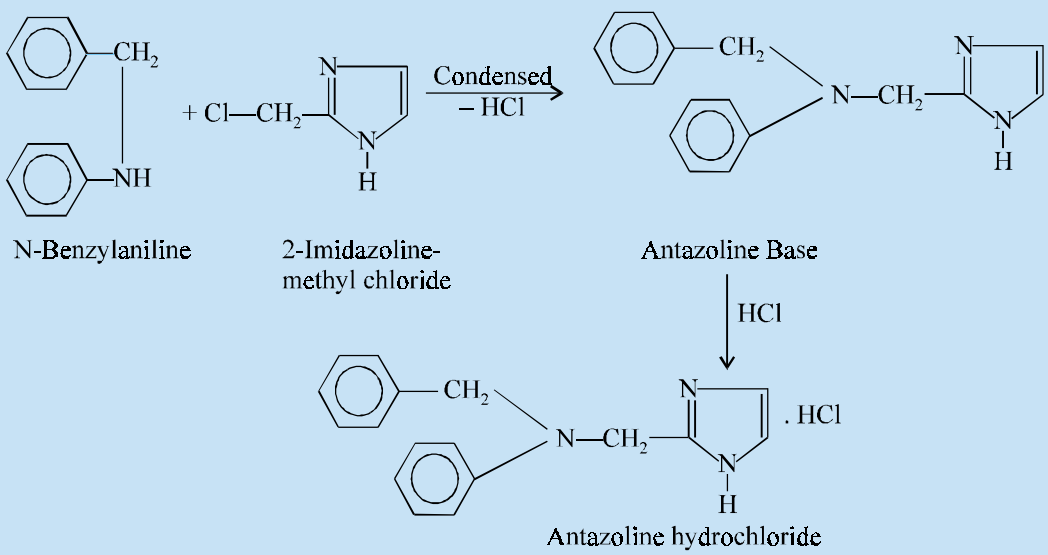
A. Antazoline Hydrochloride BAN, USAN, Antazoline INN,



2-(N-Benzylanilino) methyl-2-imidazoline hydrochloride ; N-Benzyl-N-(2-imdazoline-2-yl-methyl) aniline hydrochloride ; BP ; 1973, USP ; XV, Int. P., Ind. P.,

Antistine(R) (Ciba) ; Histostab(R) (Boots).

Synthesis



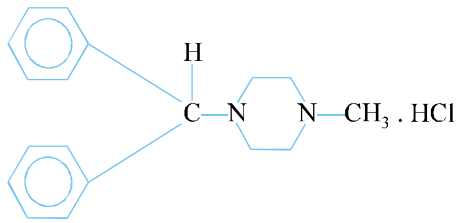
Antazoline base is prepared by the interaction of N-benzyl aniline with 2-imidazoline methyl chloride with the elimination of hydrogen chloride. The base is neutralized with hydrogen chloride to yield the desired **antazoline hydrochloride.**

It is less active than most of the other antihistaminic drugs, but has the advantage of being devoid of local irritant characteristics.

Dose : *50 to 100 mg.*

(*b*) **Piperazine Derivatives**

A. Cyclizine Hydrochloride BAN, USAN, Cyclizine INN,



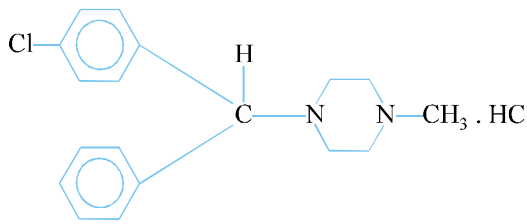
1-(Diphenylmethyl)-4-methylpiperazine monohydrochloride ; Piperazine, 1(diphenylmethyl)-4-methyl-, monohydrochloride ; BP ; USP ; Int. P., Ind. P.,

Marezine(R) (Burroughs Wellcome)

It is mostly employed as a prophylaxis and for treatment of motion sickness.

Dose : *25 to 50 mg.*

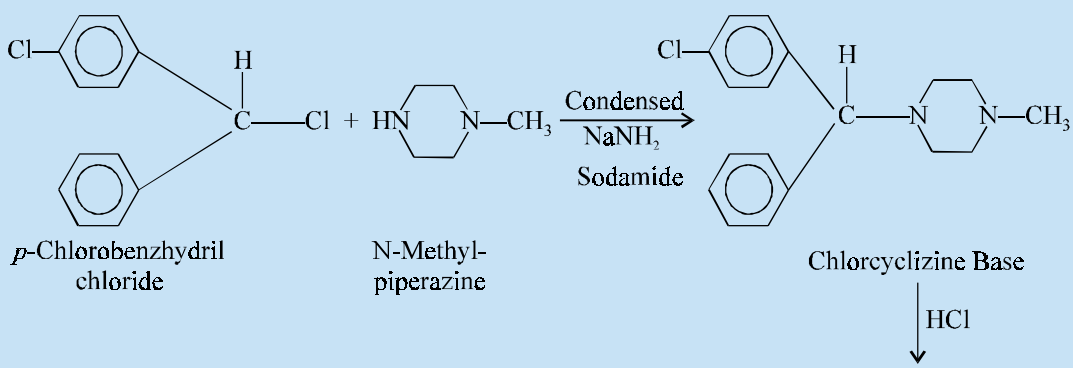
B. Chlorcyclizine Hydrochloride BAN, USAN, Chlorcyclizine INN,



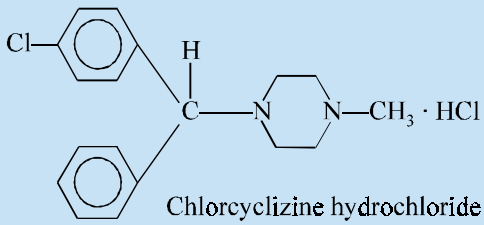
1-(*p*-Chloro-α-phenylbenzyl)-4-methylpiperazine monohydrochloride ; Piperazine, 1-[(4-chlorophenyl) phenylmethyl]-4-methyl-, monohydrochloride ; BP ; USP ; Int. P., Ind. P.,

Di-Paralene(R) (Abbott) ; Perazil(R) (Burroughs Wellcome)

Synthesis



(*Contd...*)



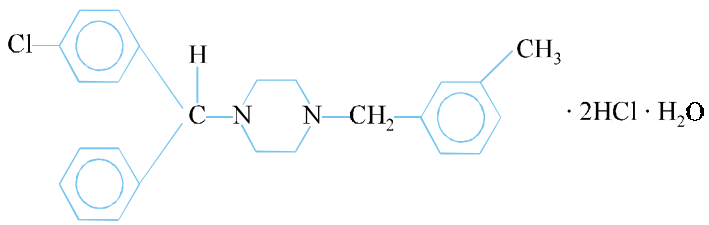
Chlorcyclizine hydrochloride

Chlorocyclizine base is first prepared by condensing together *p*-chlorobenzhydril chloride with N-methylpiperazine in the presence of sodamide. The resulting base is neutralized with hydrogen chloride to obtain the required chlorcyclizine hydrochloride.

Though it is less potent, it possesses a prolonged **antihistaminic action** of similar duration to that of **promethazine hydrochloride.** It has local anaesthetic, antiemetic and anticholinergic characteristics.

Dose : *50 to 200 mg.*

C. Meclizine Hydrochloride USAN, Meclozine INN, BAN,



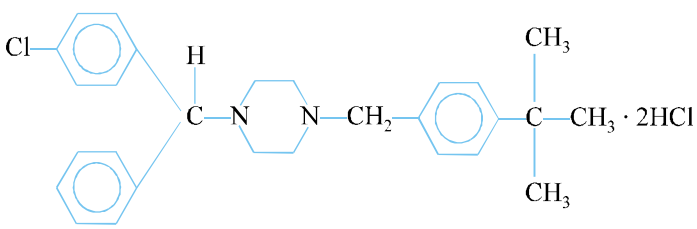
1-(*p*-Chloro-α-phenylbenzyl)-4-(*m*-methylbenzyl) piperazine dihydrochloride monohydrate ; Piperazine, 1-[(4-chlorophenyl) phenylmethyl]-4-[(3-methylphenyl)-methyl]-, dihydrochloride, monohydrate ; BP ; USP ; Int. P., Ind. P.,

Antivert(R) (Roerig) ; Bonine(R) (Pfizer).

It is mostly employed for its inherent antiemetic action which is quite marked and pronounced and lasts for up to 24 hours. It has also been used for the prevention and treatment of motion sickness and also for the relief of allergic conditions.

Dose : *25 to 50 mg.*

D. Buclizine Hydrochloride BAN, USAN, Buclizine INN,



1-(*p-tert*-Butylbenzyl)-4-(*p*-chloro-α-phenylbenzyl) piperazine dihydrochloride ; Piperazine, 1-[(4-chlorophenyl) phenylmethyl]-4-[(1, 1-dimethylethyl) phenyl] methyl]-, dihydrochloride ;

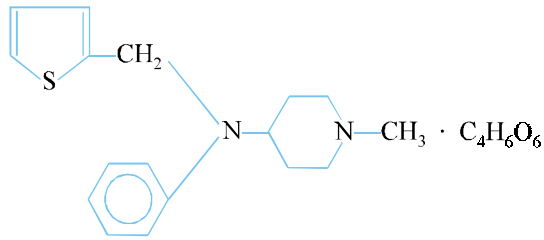
Bucladin-S(R) (Stuart) ; Vibazine(R) (Pfizer).

It is chiefly used for its antiemetic properties. It possesses less pronounced sedative effects than promethazine. *It is also recommended for the symptomatic treatment of allergic conditions and vertigo.*

Dose : *25 to 50 mg, 2 to 3 times a day.*

(*c*) **Piperidine Derivatives**

A. Thenalidine Tartrate BAN, Thenalidine INN,



1-Methyl-4-(N-then-2-ylanilino) piperidine tartrate ; Thenophenopiperidine Tartrate ; Thenopiperidine Tartrate ;

Sandosten(R) (Sandoz)

It is used for the prevention and treatment of allergic conditions.

Dose : *100 to 150 mg per day.*

2.1.4.1. Mechanism of Action

The mechanism of action of all compounds enumerated under sections (*a*) through (*c*) shall be treated individually in the sections that follows :

2.1.4.1.1. Antazoline Hydrochloride

The **'drug'** is less soluble than the corresponding phosphate salt and is mostly administered orally. It is found to be less active than a host of other antihistaminics ; however, it has been duly characterized by its predominant absence of local irritation.

Besides, it exhibits more than double than local anaesthetic potency of **'procaine'** and also exhibits the anticholinergic properties.

SAR of Antazoline. Just like the **ethylenediamines,** it also essentially comprises of an N-benzylamino function directly attached to a basic N-atom through a 2-carbon chain.

2.1.4.1.2. Cyclizine Hydrochloride

The **'drug'** is basically employed as a potent prophylaxis and also for the control, management and treatment of motion sickness.

2.1.4.1.3. Chlorcyclizine Hydrochloride

The **'drug'** is used invariably in the symptomatic relief of urticaria, hay fever, and a few other allergic manifestations.

SAR of Chlorcyclizine. It has been adquately demonstrated that the distribution or substitution of halogen either at the *ortho*-or at the *meta*-position of any of the two **'benzhydryl functional rings'** mostly gives rise to such compounds that do possess appreciably less potent acitivity.

2.1.4.1.4. Meclizine Hydrochloride

The **'drug'** is effective in vertigo intimately associated with such ailments that essentially affect the vestibular system. As the **'drug'** also exhibits anticholinergic activity, it may be employed in patients having a history of asthma, glaucoma, or prostatic enlargement.

SAR of Meclizine. It apparantly differs from chlorcyclizine by possessing an N-*m*-methylbenzyl functional moiety instead of the prevailing N-methyl moiety. Thus, it exhibits moderately potent antihistaminic profile.

2.1.4.1.5. Buclizine Hydrochloride

The **'drug'** acts by exerting appreciable anticholinergic and antihistaminic activities. Besides, it possesses CNS-depressant profile. Hence, indicated for the control and management of nausea, vomitting and dizziness closely related to motion sickness.

SAR of Buclizine. Importantly, buclizine-a member of the **piperazine class of antihistaminics** are very much structurally related to both the **ethylenediamines** as well as the **benzyhydryl ethers of ethanolamines.** Its structure essentially include the 2 carbon separation existing between the N-atoms, that forms a part of the piperazine ring.

2.1.4.1.5. Thenalidine Tartrate

The **'drug'** possesses the actions and uses of antihistaminics ; and has been employed parenterally for the symptomatic relief of hypersensitivity reactions.

2.1.5. Phenothiazine Derivatives

Since 1945, plethora of **antihistaminics** have come into existence as a consequence of bridging the aryl functional moieties of agents that were intimately related to the ethylene-diamines. **Phenothiazines** essentially possess S-atom as the bridging entity.

It is, however, pertinent to state here that the **phenothiazines** which predominantly exhibit therapeutically potential and useful antihistaminic activities should essentially contain the following characteristic features, namely :

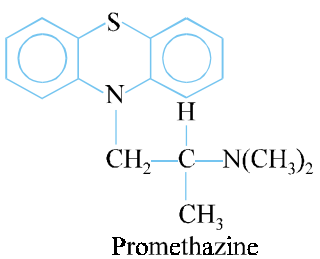
- at least 2 to 3 C-atom
- branched alkyl chain between the prevailing ring system
- terminal N-atom

Thus, the significant point of difference between the **phenothiazine antihistaminics** and the **phenothiazine antipsychotics** is that the latter should have an **unbranched propyl chain.** However, there are *two* most important aspects that are most essential for the phenothiazine antihistaminics, namely :

(*a*) 3 C-bridge between N-atoms are more potent *in vitro,* and

(*b*) heterocyclic ring of the antihistamines should be unsubstituted (*i.e.,* unlike the phenothaizine antipsychotics*.)

Toldy *et al.** (1959) resolved the two enantiomers of promethazine and observed identical antihistaminic and a number of other pharmacologic activities, such as : antiemetic, anticholinergic, and sedating agent. Importantly, this specific feature in **promethazines** is found to be in absolute contrast with regard to investigative studies carried out with **pheneramines** and **carbinoxamines,** wherein the strategically located chiral centre is located quite closer to the aromatic feature of the drug molecule.

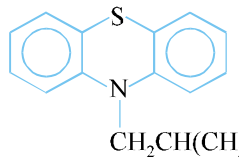


Promethazine

A number of **phenothiazine** derivatives have evolved into potent antihistaminic agents ; a few important ones are described below :

*Toldy L *et al. Acta. Chim. Acad. Sci. Hung.*, **19 :** 273, 1959.

A. Promethazine Hydrochloride BAN, USAN, Promethazine INN,

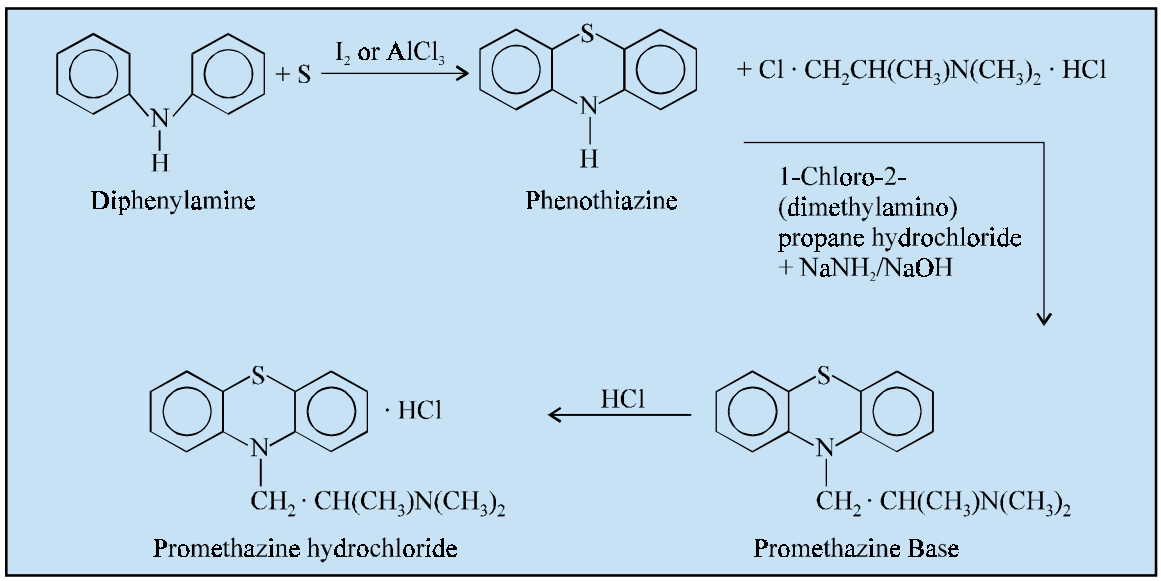


10-[2-(Dimethylamino) propyl] phenothiazine monohydrochloride ; 10H-Phenothiazine-10-ethanamine, N, N, α-trimethyl-, monohydrochloride ; BP ; USP ; Eur. P., Int. P., Ind. P ;

Phenergan(R) (Wyeth) ; Remsed(R) (Endo) ; Zipan(R) (Savage) ; Ganphen(R) (Reid-Provident) ; Fellozine(R) (O'Neal, Jones & Feldman) ; Tixylix(R) (May & Baker, U.K.)

Synthesis

Phenothiazine is first prepared by fusing together diphenylamine and sulphur in the presence of iodine or aluminium trichloride. Promethazine base may be prepared by reacting the resulting phenothiazine

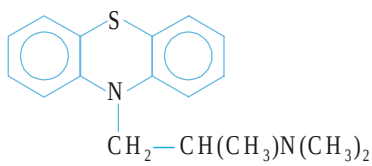


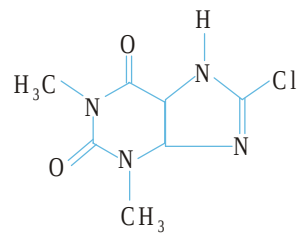
with 1-chloro-2-(dimethylamino) propane hydrochloride in the presence of sodamide and sodium hydroxide in xylene. The corresponding base is extracted, purified and converted to the hydrochloride.

It has a prolonged duration of action. It may be used effectively in perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods ; and certain milder type of skin manifestations of urticaria. It also possesses some anticholinergic, antiserotoninergic, and marked local anaesthetic properties.

Dose : *20 to 50 mg per day (B.P.) ; 12.5 to 150 mg per day (USP).*

B. Promethazine Teoclate INN, USAN, Promethazine Theoclate BAN,





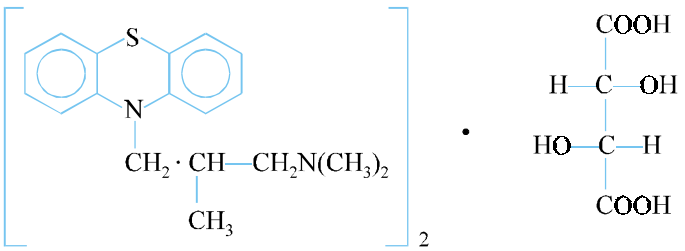
10-(2-Dimethylaminopropyl) phenothiazine compound of 8-chlorotheophylline ; Promethazine chlorotheophyllinate ; BP ; BPC ; USP ;

Avomine(R) (May & Baker)

It is mainly used as an antiemetic in the prevention and treatment of motion sickness. It may also be used in post-operative vomiting, the nausea and vomiting of pregnancy, drug-induced nausea and vomiting and in irradiation sickness.

Dose : *25 to 50 mg per day.*

C. Trimeprazine Tartrate BAN, USAN, Alimemazine INN,



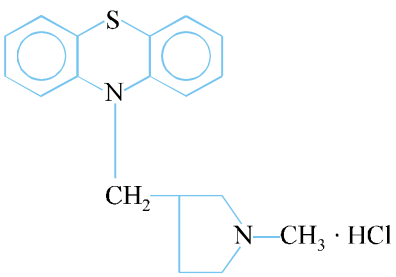
10-[3-(Dimethylamino)-2-methylpropyl] phenothiazine tartrate (2:1) BP ; USP ;

Temaril(R) (Smith, Kline & French)

It is used mainly for its marked and pronounced effect in the *relief of pruritus.* Its overall pharmacological characteristic lie between that of promethazine and chlorpromazine.

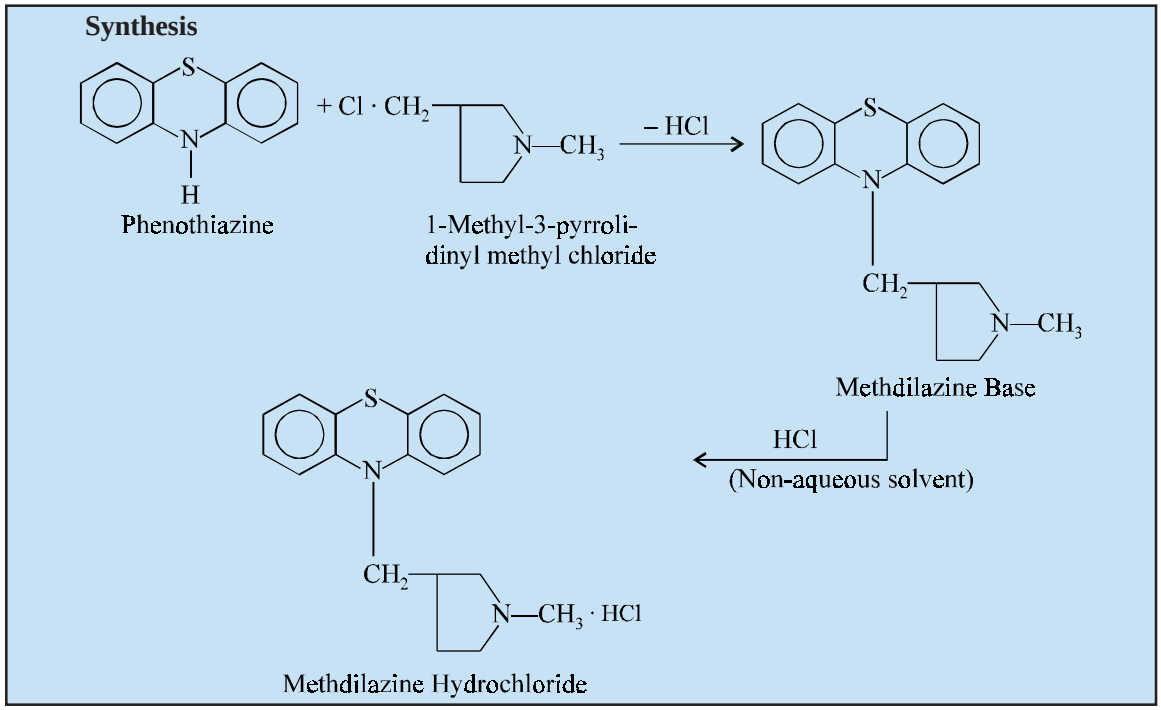
Dose : *10 to 40 mg ; adult, oral per day.*

D. Methdilazine Hydrochloride BAN, USAN, Methdilazine INN,



10-[(1-Methyl-3-pyrrolidinyl)-methyl phenothiazine monohydrochloride ; 10H-Phenothiazine, 10-[(1-methyl-3-pyrrolidinyl) methyl]-, monohydrochloride ; USP ;

Tacaryl Hydrochloride(R) (Westwod)



Methdilazine is prepared by reacting together phenothiazine and 1-methyl-3-pyrrolidinyl methyl chloride ; the resulting base is treated with equimolar quantity of hydrogen chloride in a non-aqueous solvent.

It may be used for the symptomatic relief of urticaria. It has also been used successfully for the treatment of migraine headache.

Dose : *8 mg usual, adult, oral 2 to 4 times a day.*

2.1.5.1. Mechanism of Action

The mechanism of action of certain members of this particular category of **antihistaminics** shall be discussed below :

2.1.5.1.1. Promethazine Hydrochloride

The **'drug'** is found to be well absorbed, and the peak optimum effects invariably take place very much within a span of 20 minutes after adequate oral, rectal, or IM administration. It is also observed to get bound to the plasma proteins to an extent of 76-80%. However, the **'drug'** gets excreted gradualy both in the urine and faeces, primarily in the form of its corresponding **inactive metabolites** *viz.*, **sulphoxides,** and **glucuronides.**

2.1.5.1.2. Trimeprazine Tartrate

The **'drug'** has an additional methylene (–CH_2–) unit in the side-chain of **promethazine,** which renders it more active than the latter, and interestingly less active than **CPZ** in histamine-induced bronchospasm in the guinea pigs. Hence, it is mainly used as an antipuritic drug.

2.1.5.1.3. Methdilazine Hydrochloride

The replacement of the moderately longer side chain of **promethazine (PMZ)** at position 10 has been meticulously substituted by a methylene-linked N-methyl pyrrolidine nucleus, which being rather

compact and small in its dimensions, enables the **'drug'** to exert its effect solely for the symptomatic relief of *urticaria.* It is also indicated invariably in very seriously ill or dehydrated children on account of the significantly greater susceptibility of *dystonias** with the **phenothiazines.**

2.1.6. Second-generation Nonsedating Antihistamines

Since 1980s an enormous impetus has been geared towards the development of improved H_1 selectivity so that the new breed of antihistaminics should bear practically no sedative properties, and may also possess adequate antiallergic activities. In fact, the outcome of such an overwhelming rigorous concerted research activities towards producing an altogether new class of antihistaminics have been baptised as the **second generation antihistamines.**

It has been critically observed that most of these newer compounds belonging to this category do possess a wide variation in their structural profile ; however, their pharmacologic characteristic features are not so variant in nature, as they invariably exert their action principally in the periphery. It is pertinent to mention here that the structural resemblance to the **first generation H_1-antogonists** (see Section 2.1) is not strictly adhered to by virtue of the fact that most of these drug substances came into existence first in the normal process of investigation pertaining to several other diversified pharmacologic targets.

In general, the **second-generation non-sedating antihistamines** essentially possess selective peripheral H_1-antagonism activities, and the specifically exhibit much less anticholinergic activity. Besides, they are associated with lowered affinity for adrenergic and serotonergic receptors, and usually possess very limited CNS-effects.

The mechanism of action of these agents show that they do not penetrate the blood brain barrier (BBB) appreciably most probably on account of the following cardinal factors, such as :

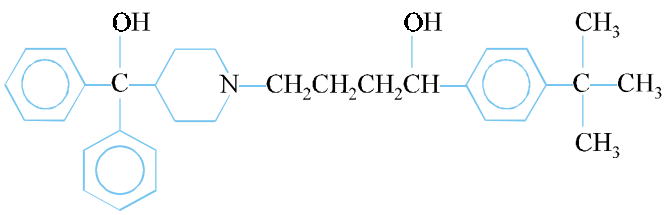
(*a*) Amphoteric nature (*i.e.*, majority of them are usually zwitter ionic at the prevailing physiologic pH) ;

(*b*) Partitioning properties ; and

(*c*) Behave as substrates for the drug efflux of either **P-glycoprotein transporter** or organic anion transporter protein.**

A few typical members of this category of **antihistaminics** shall now be discussed as under :

A. Terfenadine USAN, BAN,



Alpha-[4-(1, 1-Dimethylethyl) phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol ;

Seldane(R) ;

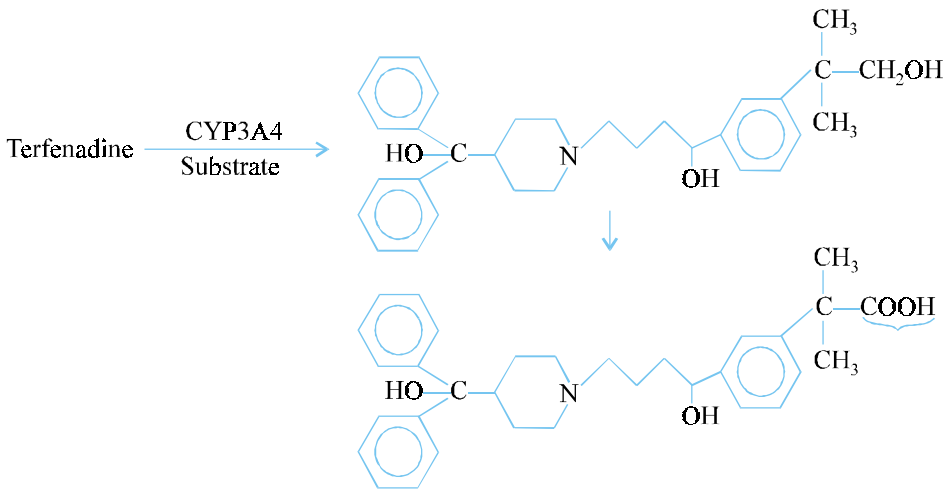
SAR : Terfenadine was discovered in the course of an extensive and intensive search for new **butyrophenone antipsychotic drugs** as could be seen by the presence of the N-phenylbutanol substituent. It is also studded with a **diphenylmethyl piperidine group structural analogous** as is normally observed in the **piperazine antihistaminics.**

*Prolonged muscle contractions that may cause twisting and repititive movements or abnormal posture.

Cvetkovic M *et al. Drug Metab. Dispos.* **27, 866–871, 1999.

Although **terfenadine** once enjoyed the very popular nonsedating antihistamines, but the extensive clinical experience pronounced it to be an altogether dangerous drug causing serious cardiac arrythmias, taking place very often in the event when certain other drugs were administered concomitantly. Such effects are caused due to the blockade of delayed rectifier K^+ channels in cardiac tissue, and hence are intimately related to the parent molecule.

Mechanism of Action. The **'drug'** undergoes rapid oxidation *in vivo* that finally gives rise to the formation of the corresponding carboxylic acid metabolite,* which is presently marketed as **fexofenadine** as given below :

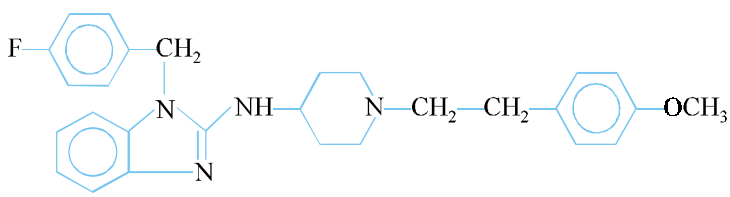


Fexofenadine

In fact, the acid metabolite is ultimately responsible for the antihistaminic properties of *terfenadine* in humans because the parent compound is readily metabolized *via* CYP3A4 substrate catalyzed processes in due course.

Nevertheless, the **histamine receptor** affinity of terfenadine are supposed to be associated primarily to the presence of the respective diphenylmethyl piperidine functional group. The actual cause of its prolonged action is solely on account of its slow dissociation from these receptors**.

B. Astemizole BAN, USAN,



1H-Benzimidazol-2-amine, 1-[4-fluorophenyl] methyl]-N-[1-[2, 4-methoxyphenyl) ethyl]-4-piperidinyl- ;

Hismanal$^{(R)}$;

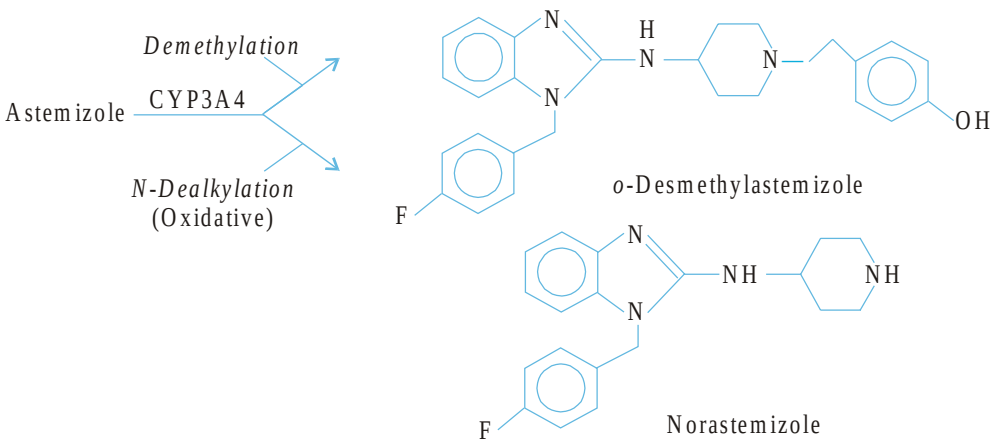
*Lalonde RL *et al. Pharm. Res.* **13,** 832–8, 1996.

**Facts and Comparison pp. 188-194C, 1993.

Astemizole is the creative product by the medicinal chemists of an extensive as well as intensive search of a series of **benzimidazoles.*** These new breed of the synthesized products may be regarded as the 4-aminopiperidines wherein the *para*-amino functional moiety essentially holds the *two aromatic rings viz.*, *first*, present in the benzimidazol structure itself ; and *secondly*, as the *para*-fluorophenyl moiety linked at one of the N-atoms.

The **drug** is found to be more potent and possesses longer duration of action than the terfenadine. It is a slow-onset, long acting and nonsedating **piperidine antihistaminic** having practically little anticholinergic activity. It is indicated for seasonal allergic rhinhitis and chornic urticaria.

Mechanism of Action. At least two **active metabolites,** namely : (*a*) **o-desmethylastemizole ;** and (*b*) **norestemizole,** as shown below are obtained :



Kamei *et al.*** (1991) confirmed the presence of a **'third metabolite'** that may also contribute to the effects of **astemizole** to a certain extent.

Astemizole gets largely distributed in the peripheral tissues having the highest concentration found in the *liver, pancreas,* and *adrenal glands.* The **'drug'** is observed to undergo substantial first-pass metabolism involving such processes as : oxidative dealkylation, aromatic hydroxylation, and glucuronidation. Interestingly, one of the active metabolites *i.e*, *o*-desmethylastemizole essentially possesses antihistaminic activity comparable to the parent drug, and hence helps to enhance the therapeutic activity.

Besides, **astemizole** is highly protien bound (96%) and has a plasma half-life of 1–6 days. However, the metabolite **desmethylastemizole** shows a half-life ranging between 10 to 20 days, that solely depends on the dosage regimen and its frequency.

SAR of Astemizole. The piperidino-amino-benzimidazol group seems to be absolutely an essential requisite for the H_1-receptor affinity ; besides, helping appreciably to the persistent receptor binding which ultimately gives rise to the prolonged action.

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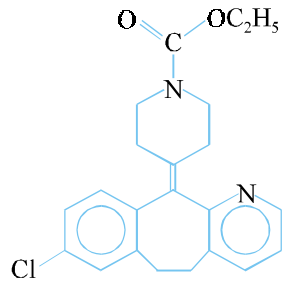
*Janssens F *et. al. J. Med. Chem.,* **28,** 1943–7, 1985.

Kamei C *et. al Arzneim Forsch,* **41, 932–6, 1991.

C. Loratadine BAN, USAN,

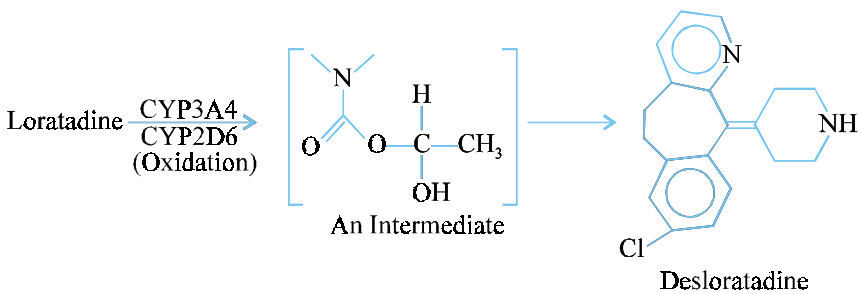


1-Piperidinecarboxylic acid, 4-(8-chloro-5, 6-dihydro-11H-benzo [5, 6]-cycloheptal [1, 2-*b*] pyridin-11-ylidene]- ;

Claritin$^{(R)}$;

It is a long-acting, nonsedating tricyclic antihistaminic drug. It possesses practically little anticholinergic activity. It shows potency that is fairly comparable to **astemizole** and significantly greater than **terfenadine.***

Mechanism of Action. Loratadine undergoes metabolic conversion to the corresponding major metabolite **decarboethoxyloratadine (desloratadine)** that specifically occurs *via* an **oxidative process** rather than *via* a direct means of **hydrolysis** as depicted below :



It has been observed that both CYP2D6 and CYP3A4 seem to be the perspective CYP450 isoenzymes that particularly help in the process of catalysis of this oxidative metabolic phenonomenon**. Interestingly, the ensuing metabolite **(desloratadine)** fails to gain its entry into the CNS in appreciable concentrations. It is, however, pertinent to state here that apparently among the **nonsedating second-generation antihistaminics,** this specific metabolite is found to be the only **nonzwitterizonic species.** Simons *et al.**** (1999) made a critical observation that while on one hand the failure of zwitterionic concentrations to have an easy access to the respective CNS sites in reasonably appreciable concentrations may be rationalized promptly, while on the other an identical explanation is not probably apparant for either the parent drug *loratadine* or its corresponding metabolite **desloratadine.*****

*Ahn HS *et. al. Eur. J. Pharmacol*, **127,** 153, 1986.

Yumibe N *et. al. Biochem Pharmacol*, **51 : 165–72, 1996.

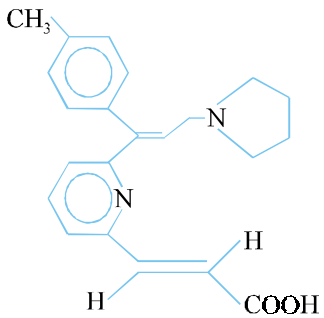
***Simons FE and Simons KJ, *Clinical Pharmacokinetics*, **36,** 329–52, 1999.

****Smith SJ, *Cardiorascular toxicity of antihistamines : Otolaryngol Head Neck Surg*. **III,** 348–54, 1994.

Besides, the competitive substrates for **CYP3A4** do not significantly give rise to drug-drug interaction, as could be seen with **astemizole** and **terfenadine,** by virtue of the fact that the parent molecule **(loratadine)** overwhelmingly lacks effect on K^+ rectifying channels located in the cardiac tissue.

SAR of Loratadine. The *'drug'* is intimately related to the **first generation tricyclic antihistaminics** and also to the **antidepressants.**

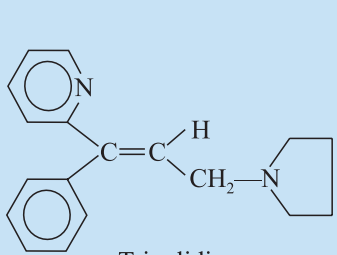
D. **Acrivastine** BAN, USAN,



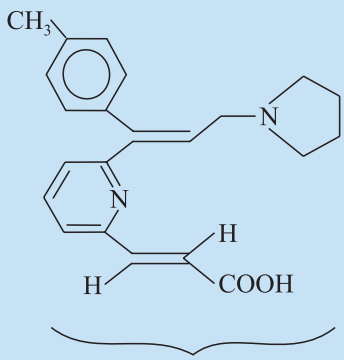
(E, E)-3-[6-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl-2-puridinyl]-2-propenoic acid ; (Semprex)$^{(R)}$;

Acrivastine displays antihistaminic potency as well as the duration of action fairly comparable to *tripolidine* ; however, unlike latter the former fails to exhibit appreciable anticholinergic activity at the therapeutic concentrations. Besides, the obvious increase in the polarity of **acrivastine** on account of the strategically positioned carboxyethyl actually limits the BBB penetration significantly which ultimately allows this *'drug'* to cause less sedation in comparison to **tripolidines.**

SAR of Acrivastine. The **'drug'** is of specific interest solely from a **'drug design'** standpoint. In fact, making an intensive search for new molecular entities, it does not bring forth any **'new chemistry'.** Interestingly, the already known old compound, **tripolidine,** has been restructured by enhancing the hydrophilicity *via* strategically introducing an acrylic acid functional moiety that ultimately yielded acrivastine as shown below :



Tripolidine
[Actidil$^{(R)}$]
(An 'Alkenylamine')



Acrylic acid
Acrivastine
[Semprex$^{(R)}$]

The lowering of the lipoidal solubility characteristic feature in the drug molecule still retained an effective H_1-antagonism peripherally. It also drastically squeezed in the $t_{1/2}$ to 1.7 hours only when compared to 4.6 hours for the parent molecule tripolidine.

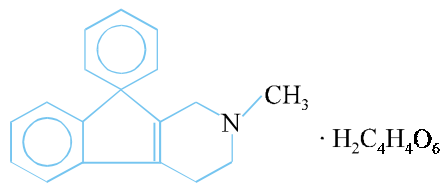
Mechanism of Action. The **'drug'** has a mean peak plasma concentration varying too widely ; and it seems to penetrate the CNS quite sluggishly. However, the metabolic fate of the **'drug'** is yet to be established.

Usual adult dose *:* Oral, 8 mg/60 mg/3–4 times per day.

2.1.7. Miscellaneous Agents

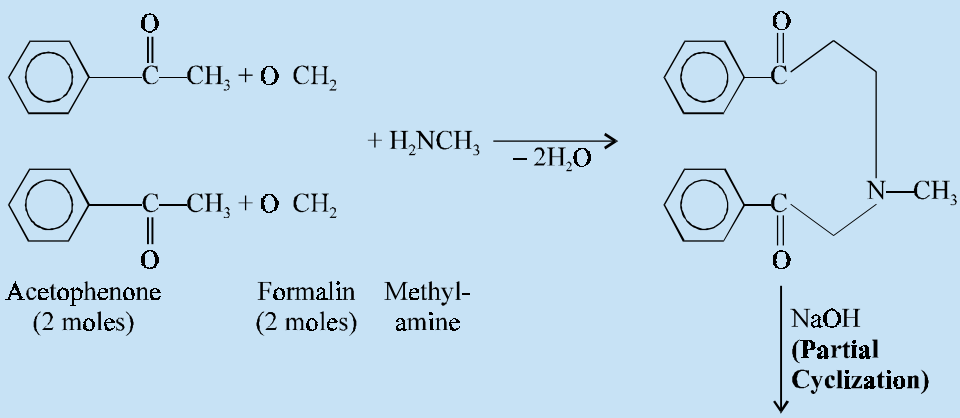
A few medicinally potent **antihistaminics** that cannot be conveniently accommodated under the above-mentioned categories (*viz* : *A* to *E*), but possess one or two nitrogen atoms in a heterocyclic system are discussed below :

A. Phenindamine Tartrate BAN, USAN, Phenindamine INN,

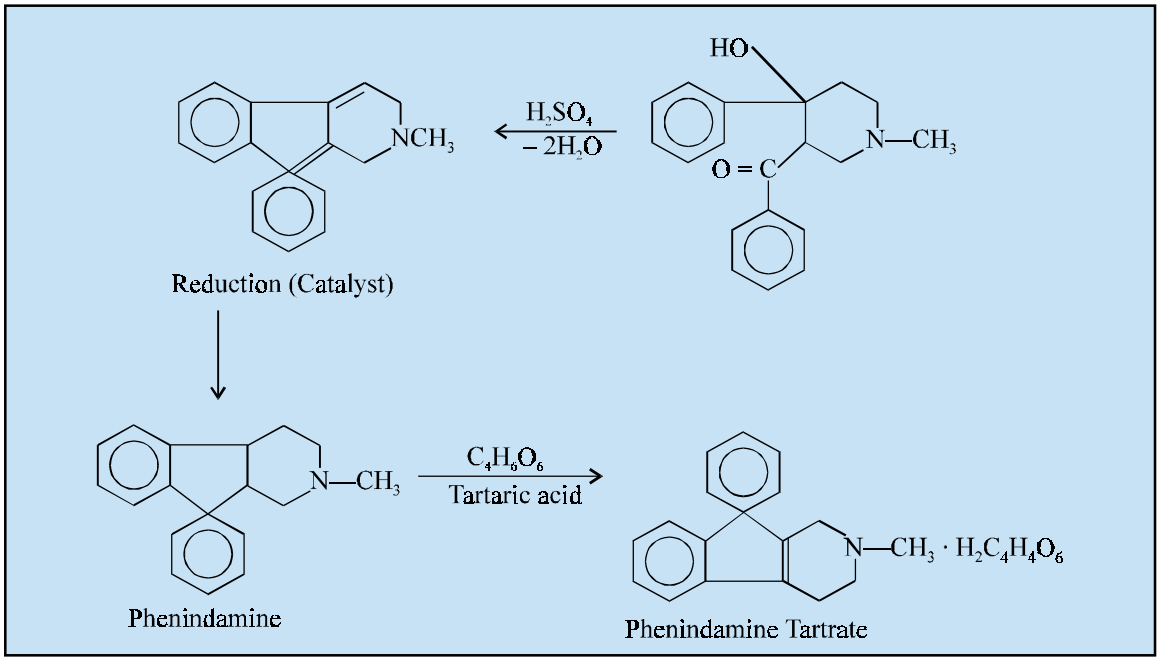


1, 2, 3, 4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate ; 2, 3, 4, 9-Tetrahydro-2-methyl-9-phenyl-1H-indenol [2, 1-C] pyridine hydrogen tartrate ; BP ; NF XIV, Int. P., Ind. P., Theophorin(R) (Hoffmann-La Roche)

Synthesis



(*Contd...*)

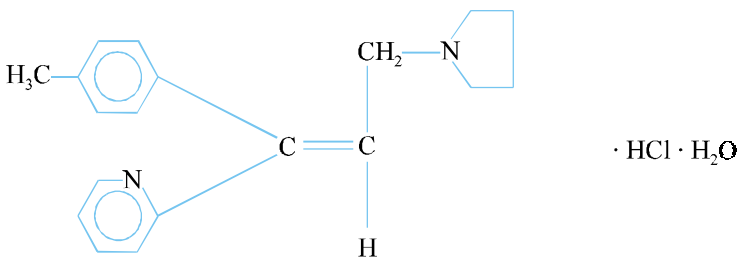


Two moles each of acetophenone, formaldehyde and one mole of methylamine are condensed to form an intermediate compound with the loss of two moles of water. This intermediate product on treatment with sodium hydroxide undergoes partial cyclization. On further treatment of the resulting product with concentrated sulphuric acid the complete cyclization takes place thereby losing two moles of water. This compound on catalytic reduction yields phenindamine which on treatment with an equimolar proportion of tartaric acid yields **phenindamine tartrate.**

It is less effective than promethazine but it does not generally produce drowsiness and may even cause a mild stimulation.

Dose : *75 to 150 mg per day.*

B. Triprolidine Hydrochloride BAN, USAN, Triprolidine INN,

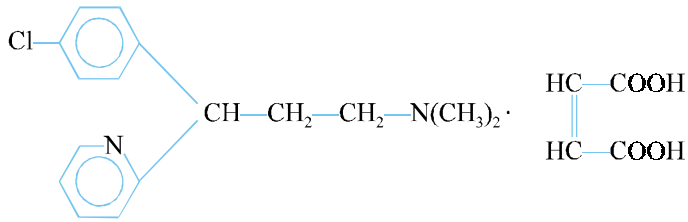


(E)-2 [3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl] pyridine monohydrochloride monohydrate ; BP ; USP ; Actidil$^{(R)}$ (Burroughs Wellcome)

It is one of the more potent of the antihistaminics and its action last for up to 12 hours.

Dose : *5 to 7.5 mg per day.*

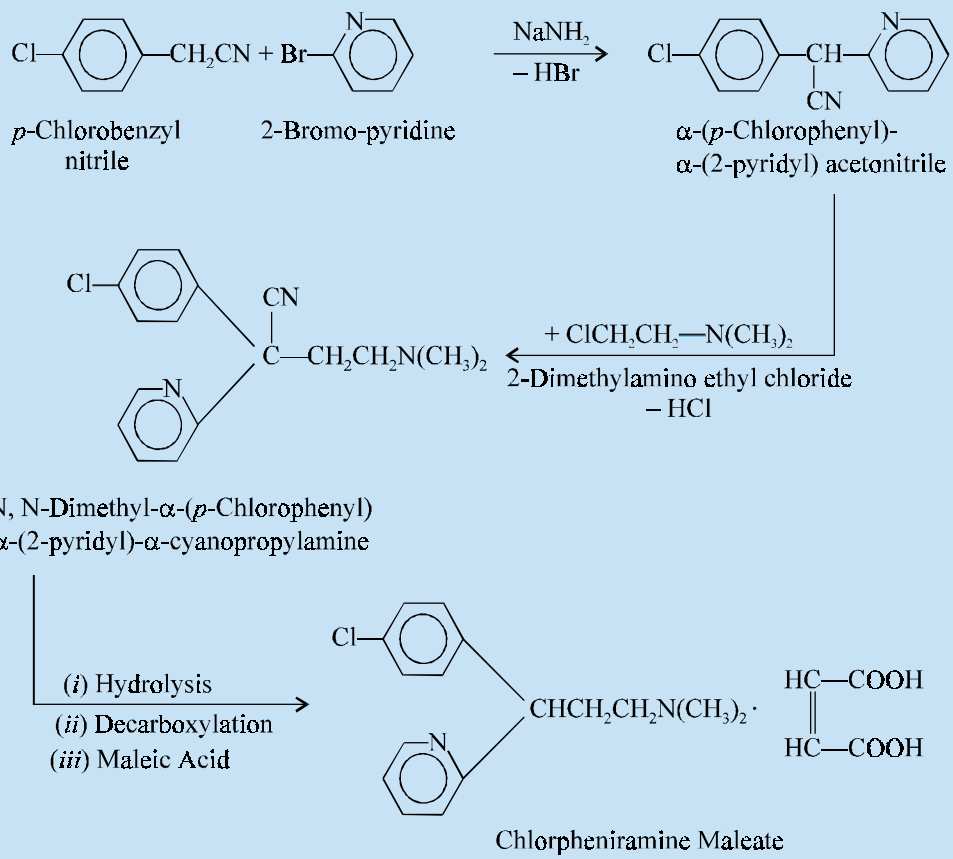
C. Chlorpheniramine Maleate BAN, USAN, Chlorphenamine INN,



2-[*p*-Chloro-α-[2-(dimethylamino) ethyl] benzyl] pyridine maleate (1:1) ; 2-Pyridinepropanamine, γ-(4-chlorophenyl)-N, N-dimethyl-, (Z)-2-butenedioate (1:1) ; Chlorphenamine Maleate ; Chlorprophenpyridamine Maleate ; BP ; USP ;

Piriton(R) (Allen & Hanburys U.K.) ; Chlor-Trimeton(R) (Schering-Plough) ; Alermine(R) (Reid-Provident).

Synthesis

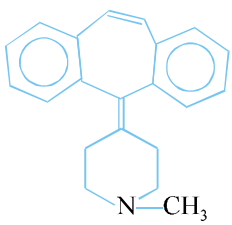


α-(*p*-Chlorophenyl)-α-(2-pyridyl) acetonitrile is prepared by the interaction of *p*-chlorobenzyl nitrile and 2-bromopyridine in the presence of sodamide with the elimination of a molecule of hydrogen bromide. This on treatment with 2-dimethylamino ethyl chloride abstracts the lonely active hydrogen atom present in the acetonitrile function as hydrogen chloride and yields N, N-dimethyl-α-(*p*-chlorophenyl)-α-(2-pyridyl)-α-cyano-propyl amine. The resulting product when subjected to hydrolysis, followed by decarboxylation and finally heated with maleic acid gives rise to the official compound.

It is one of the most potent of the antihistaminics which generally causes less sedation than promethazine.

Dose : *Usual, oral, 4 mg 3 or 4 times per day.*

D. Cyproheptadine Hydrochloride BAN, USAN, Cyproheptadine INN,



4-(5H-Dibenzo [*a, d*] cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride sequihydrate ; Piperidine, 4-(5H-dibenzo [*a, d*]-cyclohepten-5-ylidene)-1-methyl-, hydrochloride, sesquihydrate ; BP ; USP ;

Periactin(R) (Merck Sharp & Dohme)

It possesses antiserotonin, anticholinergic and antialdosterone characteristics. It is *highly potent and is effective in smaller doses than* **promethazine hydrochloride** *though the effect lasts for a short duration. It helps to stimulate the appetite in under-weight patients and those suffering from anorexia nervosa.*

Dose : *Usual, adult, oral, 4 mg 3 to 4 times a day.*

2.1.7.1. Mechanism of Action

The mechanism of action of certain important members of this particular class of compounds shall now be discussed as under :

2.1.7.1.1. Phenindamine Tartrate

The **'drug'** exerts its action by temporarily relieving running nose and also sneezing related to the common cold. However, it may cause drowsiness sleepiness, just similar to most of the antihistaminics ; but at the same time it may also give rise to a mild stimulating action in patients and may cause insomnia when taken prior to going to bed.

SAR of Phenindamine. Phenindamine may be structurally related to an unsaturated propylamine analogue wherein the rigid ring system essentially embedded with a distorted *trans*-alkene system. The presence of either oxidizing substances or an exposure to heat may render this compound to undergo *isomerization* which ultimately leads to an **inactive** form.

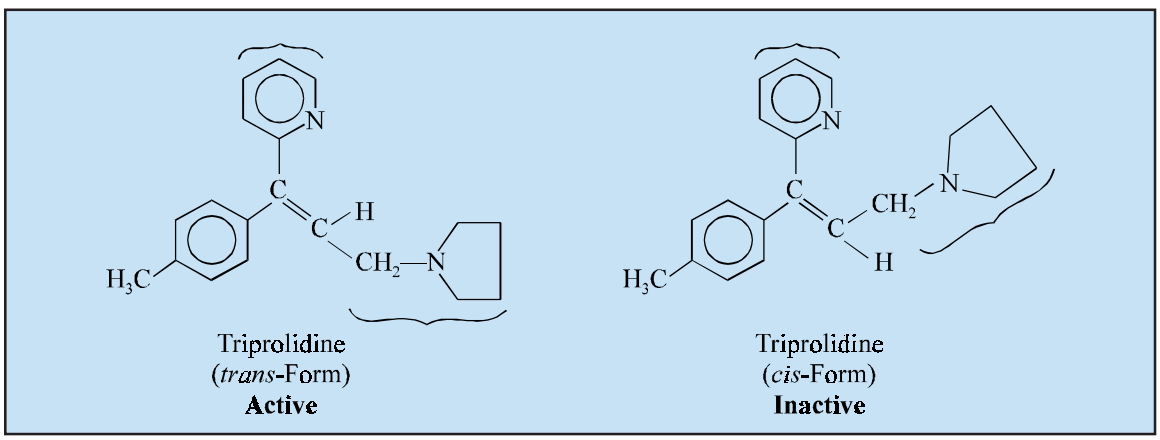
*Ison RR *et. al. J. Pharm. Pharmacol*, **25,** 887, 1973.

2.1.7.1.2. Triprolidine Hydrochloride

The **'drug'** is shown to exhibit both high *activity* and *superiority* of its **(E)-isomer** with respect to its corresponding **(Z)-isomer** as the **H_1-antagonists.*** It has been adequately demonstrated using the guinea pig ileum sites that the actual prevailing affinity of **triprolidine** for the **H_1-receptors** was found to be higher more than 1,000 times the affinity exhibited

by its (Z)-isomer. However, the overall relative potency of this *'drug'* is very much comparable to that of **dexchlorpheniramine.**

SAR of Triprolidine. It has been established that the pharmacoligic activity solely resides in the geometric isomer wherein the pyrrolidinomethyl moiety is present as *trans*-to the corresponding 2-pyridyl functional moiety as given below :



2.1.7.1.3. Chlorpheniramine Maleate

The **'drug'** is widely used as an essential component of a plethora of **antitussive formulations.** It is found to attain appreciable first-pass metabolism ranging between 40–55%. The peak plasma levels of 5.9 and 11 ng. mL^{-1} are accomplished within a span of 2–6 hours.

SAR of Chlorpheniramine. The presence of the strategically positioned chloro moiety at the *para*-position of the benzene ring affords a 10-times enhancement in its potency without making an significant alteration in its toxicity. Besides, it has been observed that the maximum activity of the **'drug'** resides in the *dextro*-enantiomorph exclusively.

2.1.7.1.4. Cyproheptadine Hydrochloride

The **'drug'** is an antihistamine having serotonin-antagonist, and calcium channel blocking activities. Besides, it also exhibits antimuscarinic and central sedative actions.

2.1.7.2. Structure Activity Relationships (SARs) Amongst H_1-Receptor Blockers

The large number of potent **antihistaminic agents** used in the therapeutic armamentarium belong to various defined chemical categories, namely : **aminoalkylethers, ethylenediamines, thiophene analogs, cyclic basic chain analogs and phenothiazine derivatives**. However, it is now possible to derive some important conclusions with respect to their structural requirements for optimal activity and pharmacological actions, namely :

1. In all derivatives the terminal N atom must be tertiary amine so as to exhibit maximum activity.

2. The terminal N atom may constitute part of a heterocyclic structure, *e.g.*, **pyribenzamine hydrochloride, thenylene hydrochloride,** etc.
3. For maximum activity the carbon-chain between the O and N atoms or the N and N atoms must be the ethylene moiety, *i.e.*, —CH_2CH_2—. However, a long or branched chain combination gives rise to a less potent analog.
4. It is interesting to observe that in the promethazine hydrochloride molecule the two carbon chain is linked with an iso-propyl moiety, but the presence of the phenothiazine group might exert better therapeutic effect on the molecules as such.
5. Introduction of a halogen atom *viz*, Cl, Br at the *para*-position of the phenyl function improves the antihistaminic activity of the parent molecule, *e.g.*, **pheniramine** compared with, **chloropheniramine** and **brompheniramine**.
6. Amongst the ethylenediamine analogs many potent compounds have evolved due to the inclusion of various groups on the second N of the chain. Such groups may be either heterocyclic aromatic rings or isocyclic group. Hydrogenation of such ring(s) leads to loss in activity.
7. The nucleus of an antihistaminic must bear a minimum of two aralkyl or aryl functions or an equivalent embeded in a polycyclic ring.
8. Antihistaminics exhibiting optical isomerism revealed that the *dextro*-isomer supersedes the *levo*-in their potency, *e.g.*, **dexchlorpherniramine**, **dexbrompheniramine**, **triprolidine** etc.
9. For enhanced effectiveness is antihistaminics it is essential that one of the aromatic moieties is α-pyridyl while the second substituent on the N atom could be either a benzyl function of a substituted benzyl group or one of the isosteres of the benzyl moiety, *e.g.*, **thenyldiamine**, **pyrilamine**, etc.
10. Introduction of basic-cyclic ring system by altering the position of dimethyl amino group also enhances the antihistaminic activity, *e.g.*, **cyclizine**, **chlorcyclizine**, **meclizine** etc.

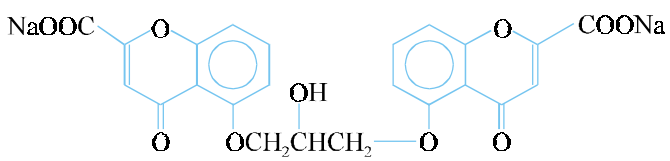
2.2. Prevention of Histamine Release

The release of **histamine** *in vitro* may be prevented by the aid of certain medicinally acive compounds. Such substances are not usually absorbed by the gastro-intestinal tract. An attempt has been made to find a similar substance which might be absorbed when administered orally and which possesses anti-allergic properties. Two such compounds are disucssed below namely : **Sodium cromoglycate** and **Ketotifen fumarate.**

A. Sodium Cromoglycate BAN, Cromolyn Sodium USAN, Cromoglicic Acid INN

Sodium 5, 5′-(2-hydroxytrimethylenedioxy) *bis* (4-oxo-4H-chromene-2-carboxylate ; Disodium 4, 4′-dioxo-5, 5′-(2-hydroxytrimethylenedioxy) di (4H-chromene-2-carboxylate) ; Sodium Cromoglycate BP ; BPC ; Cromolyn Sodium USP ;

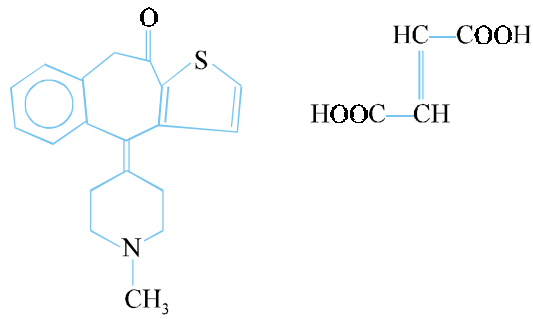
Intal$^{(R)}$ (Fisons ; U.K.) ; Aarane$^{(R)}$ (Syntex)



Sodium cromoglycate is a chromono derivative which inhibits the release of histamine and SRS-A in allergic reactions. It is mostly employed in the prophylactic treatment of asthma. It is administered only by inhalation, either alone or in conjunction with a small quantity of **isoprenaline** to prevent bronchospasm caused by the inhalation of the fine powder.

Dose : *20 mg, by inhalation 2 to 6 times a day.*

B. Ketotifen Fumarate USAN, Ketotifen INN, BAN,



4, 9-Dihydro-4-(1-methyl-4-piperidylidene)-10H-benzo [4, 5] cycloheptа [1, 2-*b*] thiophen-10-one fumarate (1:1) ; 10H-Benzo [4, 5]-cycloheptа [1, 2-*b*] thiophen-10-one, 4, 9-dihydro-4-(1-methyl-4-piperidinylidene)-, (E)-2-butenedioate (1:1) ; USP ;

Zaditen$^{(R)}$ (Sandoz).

It possesses anti-allergic properties similar to those of sodium cromoglycate and is used in the prophylactic treatment of asthma.

Dose : *Usual, oral, equivalent to 1 mg of ketotifen 2 times per day.*

2.2.1. Mechanism of Action

The mechanism of action of these compounds shall be described as under :

2.2.1.1. Sodium Cromoglycate

Though the precise mechanism of action of this **'drug'** remains uncertain, it is believed to exert its action primarily by preventing the release of mediators of inflammation from the sensitised mast cells through the stabilization of mast-cell membranes.

2.2.1.2. Ketotifen Fumarate

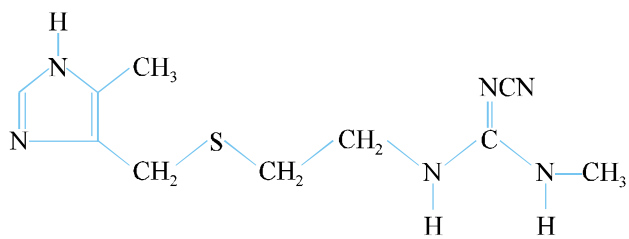
The **'drug'** is an antihistamine which also inhibits release of inflammatory mediators. It also exerts stabilizing action on the mast cells analogous to that of sodium cromoglycate.

2.3. Histamine (H_2) Receptor Blockers

As stated earlier, histamine activates two types of receptors *viz.*, **H_1 and H_2 receptors.** The activation of **H_2 receptors** leads to increased gastric acid secretion, increased contraction of the isolated atria and inhibition of isolated uterus. These effects are blocked by **H_2-receptor antagonists** which are now being used for the treatment of peptic ulcer.

Examples : Cimetidine ; Ranitidine ; Oxmetidine Hydrochloride

A. Cimetidine INN, BAN, USAN,



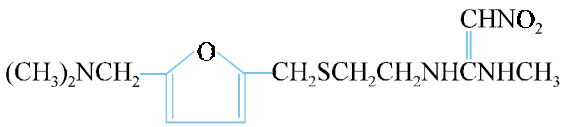
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl) methyl]-thio] ethyl] guanidine ; Guanidine, N″-cyano-N-methyl-N′-[2-[[(5-methyl-1H-imidazol-4-yl) methyl] thio] ethyl]- ; SKF 92334 ; BPC ; USP ;

Tagamet(R) (Smith Kline & French)

Cimetidine being a **histamine H_2-receptor antagonist** not only inhibits gastric acid secretion but also prevents other actions of **histamine mediated by H_2-receptors.** *It is employed in gastric and duodenal ulcer, and in all other situations where an inhibition of the secretion of gastric juice is considered to be useful.*

Dose : *Usual, oral, 200 mg 3 times per day with meals and 400 mg at night.*

B. Ranitidine INN, BAN, USAN,



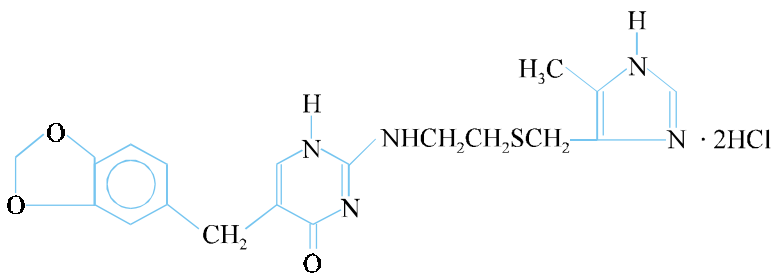
N-[2-[[5-[(Dimethylamino) methyl] furfuryl] thio] ethyl]-N′-methyl-2-nitro-1, 1-ethenediamine ; 1, 1-Ethenediamine, N-[2-[[[5-[(dimethylamino) methyl]-2-furanyl] methyl] thio] ethyl]-N′-methyl-2-nitro ;

Zantac(R) (Glaxo, U.K.)

The actions and uses of ranitidine are similar to **cimetidine.**

Dose : *Usual, 150 mg (as the hydrochloride) 2 times a day.*

C. Oxmetidine Hydrochloride BAN, USAN, Oxmetidine INN,



2-[[2-[[(5-Methylimidazol-4-yl) methyl] thio] ethyl] amino]-5-piperonyl-4-(1H)-pyrimidinone dihydrochloride ;

SK & F 92994-A_2(R) (Smith Kline & French)

It is reported to have **histamine H_2 receptor blocking activity.**

2.3.1. Mechanism of Action

The mechanism of action of the compounds enumerated under Section 15.2.3. are described as under :

2.3.1.1. Cimetidine*

The **'drug'** is observed to minimise the hepatic metabolism of such drugs that are eventually biotransformed by the **cytochrome P-450** mixed oxidase system by way of either delaying the elimination or enhancing the serum levels of these pharmacologic agents.

*Introduced in 1977 and enjoyed the reputation of being one of the most profusely prescribed drugs in history for several years.

Importantly, it exhibits relatively higher oral bioavailability (60–70%), and a plasma half-life of – 2 hour that gets enhanced particularly either in agedsubjects or those having a renal and hepatic impairment. However, it has been observed that nearly 30 to 40% of a cimetidine dose gets metabolized either as **S-oxidation** or a **5-CH_3 hydroxylation.** Finally, the parent drug and the metabolites are virtually eliminated primarily by the renal excretion.

2.3.1.2. Ranitidine

Zantac gives rise to *three* known metabolites, namely : (*a*) **ranitidine N-oxide ;** (*b*) **ranitidine S-oxide ;** and (*c*) **desmethyl ranitidine.** It is observed to be only a weak inhibitor of the **hepatic cytochrome P-450** mixed function oxidation system. The plasma half-life ranges between 2 to 3 hours ; and it usually gets excreted together with its metabolites in the urine.

Note : It is established that some 'antacids' may afford a reduction in the ranitidine absorption ; and, therefore, must not be taken at least within a span of one hour of the administration of this H_2-blocker particularly. In fact ranitidine is a stronger base (pKa 8.44).

2.3.1.3. Oximetidine Hydrochloride

The **'drug',** which being a 3-pyridyl structural derivative soon gained recognition by virtue of the fact that it predominantly exhibited certain **H_1-antagonism.**

SAR of Oximetidine. It essentially possesses a 5-substituted isocytosine functional moiety and also shows the latitude and complexitiy of digression from the urea permitted that renders the **'drug'** to become a potent **selective H_2-antagonist.**

Probable Questions for B. Pharm. Examinations

1. What are allergens ? What is the importance of **'antihistaminics'** in combating various types of allergic conditions ? Give suitable examples to support your answer.
2. Classify the Histamine **H_1-Receptor Antagonists.** Give the structure, chemical name and uses of **one** compound from each cateogry.
3. Name any **three 'aminoalkylethers'** being used as antihistaminics. Discuss the synthesis of **one** of them.
4. Give the structure, chemical name and uses of :
   (*a*) Mepyramine maleate and
   (*b*) Tripelenamine hydrochloride
   Describe the synthesis of any **one** drug.
5. **'Thiophene** derivatives have low side-effects and may be employed in the treatment of all types of suspected allergies'. Justify the statement with the help of at least **two** typical examples.
6. Cyclic basic-chain analogues essentially having
   (*a*) Imidazoline,
   (*b*) Piperazine and
   (*c*) Piperidine
   the above **three** types of heterocyclic nucleus give rise to potent 'antihistaminics'. Explain.
7. Discuss the synthesis of :
   (*a*) Promethazine hydrochloride

(*b*) Methdilazine hydrochloride

Elaborate their applications separately.

8. Phenindamine tartrate and chlorpheniramine mealeate are two important antihistaminics. Describe the synthesis of **one** drug in detail.

9. Give a brief account of :

(*a*) Drugs used in the 'Prevention of Histamine Release'

(*b*) Histamine (H_2) Receptor Blockers

10. Give a comprehensive account of :

(*a*) SAR-amongst H_1-receptor blockers

(*b*) Mode of action of antihistaminics.

RECOMMENDED READINGS

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9. RP Orange, MA Kaliner and KF Austen In : **Biochemistry of the Acute Allergic Reaction** (eds.) KF Austen and EL Becker, Blackwell Oxford (1971).

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