6

Sedatives and Hypnotics

Chapter

6 Sedatives and Hypnotics

1. INTRODUCTION

Sedatives are drugs which exert a quietening effect accompanied by relaxation and rest but do not necessarily induce sleep. **Hypnotics** are drugs which induce sleep and are synonymous with somnifacient and saporific. Both hypnotic and sedative properties usually reside in the same drug ; a large dose of a drug may act as a hypnotic, whereas a small dose of the same drug would act as a sedative. It is pertinent to mention here that in a few exceptional cases a compound exerts only one specific effect, *e.g.,* **potassium bromide** is a good sedative and exhibits no hypnotic action ; likewise certain powerful hypnotics, *e.g.,* **thiopentone sodium** cannot be used as a sedative.

Dier and sudden unforeseen **'emotional crisis'** invariably create such clinical situations that exceptionally demand the essential use of **sedatives and hypnotics**. A plethora of insomnia (sleeplessness) inadvertently caused due to short-term **'situational stress'** is usually regarded as the most suitable and ideal circumstantial condition(s) which necessiates drug-treatment not only to facilitate but also to augment sleep. After a vigorous and intensive research the introduction of rather newer yet safer and definitely more efficacious **sedative and hypnotic drug** has always been greeted with great fervour and optimism.

In a broader perspective, therefore, an **'ideal sedative** and **hypnotic'** must fulfil the following essential pre-requisites and requirements, namely :

(*a*) Must exert transient decrease in the degree of consciousness for the purpose of inducing sleep without any lingering effects,

(*b*) Should possess no potential for either lowering or arresting respirations (even at relatively higher dose regimens), and

(*c*) Essentially cause absolutely little abuse, dependence, addiction, or tolerance.

Interestingly, an honest and dedicated attempt to circumvent the already discussed undesirable characteristic features of **'barbiturates',** have ultimately resulted to the synthesis of a host of **'nonbarbiturate'** structural analogue as **potential sedatives-hypnotics** in early 1950s, namely : **methaqualone**, **nitrazepam**, **glutethimide**, **methyprylon**, that are specifically noteworthy.

2. CLASSIFICATION

The sedatives and hypnotics are broadly classified into the following *two* categories, namely :

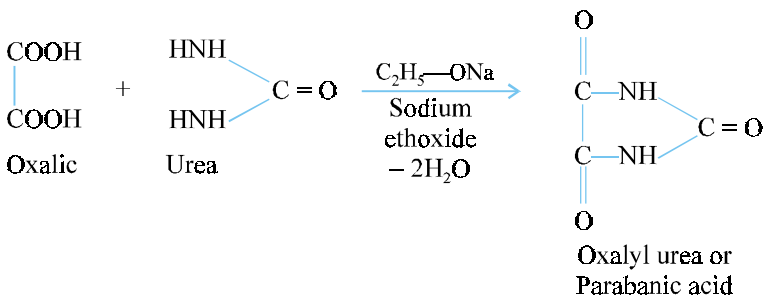
(*a*) Barbiturates ; and

(*b*) Non-barbiturates.

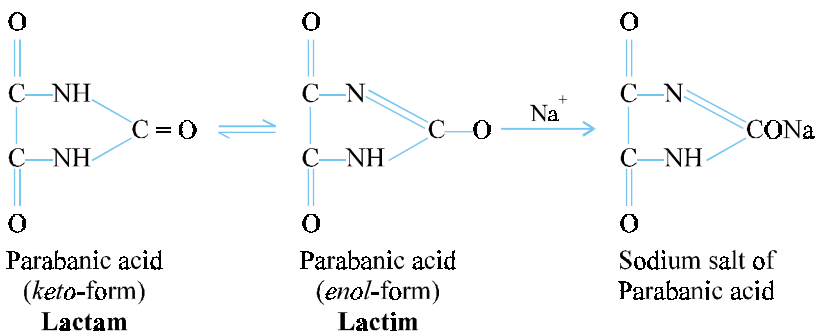
2.1 Barbiturates

In general, the barbiturates exert a significant **depressant** action on the cerebrospinal axis. The relative degrees of depression, sedation, hypnosis or anaesthesia are exclusively dependent on the nature of the barbiturate, its dose and route of administration.

Barbiturates are **cyclic ureides** and are formed when a dicarboxylic acid reacts with urea. The acids used are generally in the form of ester and are condensed in the presence of sodium ethoxide (*i.e.*, C_2H_5—ONa) *e.g.*,



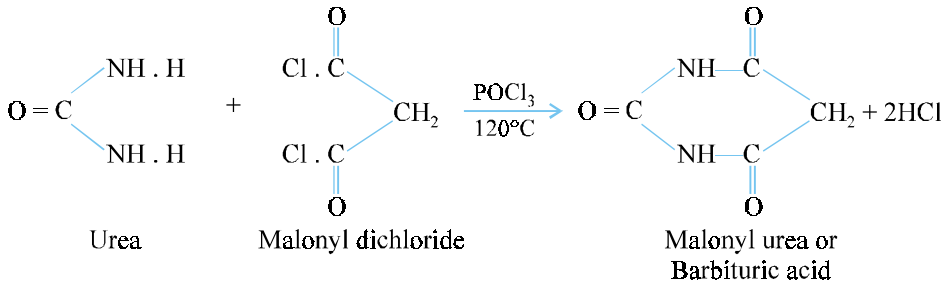
Parabanic acid is a **cyclic ureide** containing a five membered ring, which on hydrolysis by alkali may regenerate the corresponding acid and urea. The **cyclic ureides** are acidic owing to '**enolization**' and hence, they may form metallic salts by replacing the H atom of the –OH group as shown below :



Many **cyclic ureides** are derived from **malonic acid** or **malonic esters.** They are collectively known as **'barbiturates'** because of their **relationship of malonyl urea or barbituric acid**.

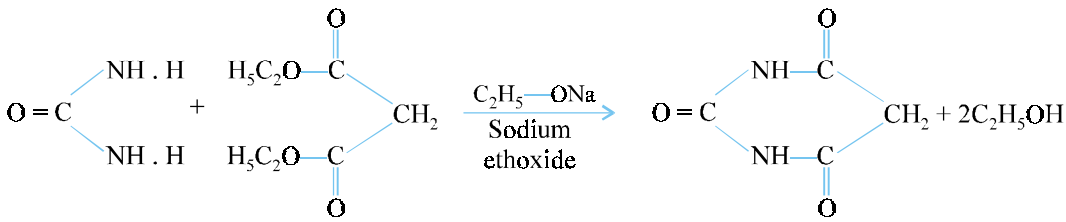
Barbituric acid is prepared by the following *two* methods :

(*a*) By the interaction of urea and malonyl dichloride,

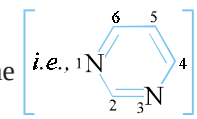


Urea — Malonyl dichloride — Malonyl urea or Barbituric acid

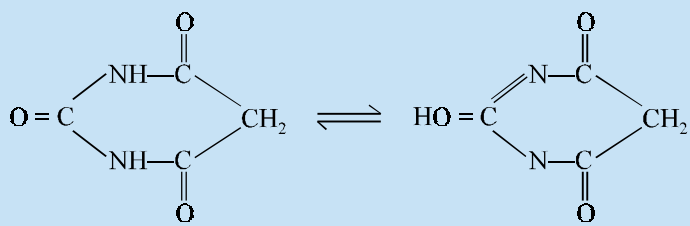
(*b*) By the interaction of urea and diethyl malonate,



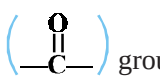
Urea — Diethyl malonate — Barbituric acid — Ethanol

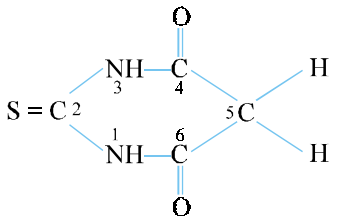
The **cyclic ureides** containing a six membered ring, are also regarded as derivatives of the fundamental type pyrimidine or 1 : 3-diazine 

Barbituric acid like **parabanic acid** exhibits **'keto-enol tautomerism'** as illustrated below :



Barbituric acid (*keto*-form) **Lactam** — Barbituric acid (*enol*-form) **Lactim**

In thiobarbiturate the oxygen of the  group of the urea residue is replaced by a sulphur atom *i.e.*,



Thiobarbituric acid

However, it is interesting to observe that the **barbituric acid** itself does not possess any hypnotic properties, but such a characteristic is conferred only when the hydrogen atoms at C-5 are replaced by organic groups (alkyl or aryl).

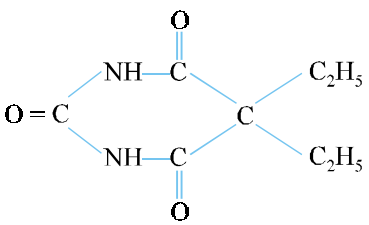
Classification of Barbiturates

Barbiturates are classified, rather arbitrarily, by the duration of their clinical effects. More than 50 derivatives are used in therapeutics. The more commonly used analogues of barbituric acid are recorded in Table 5.1.

A. Long Acting Barbiturates

The onset of action for **long acting barbiturates** is visible after an hour or so, and the duration of action lasts for 6–10 hours. They are largely excreted by the kidney. ***Examples*** **: Barbitone ; Barbital Sodium ; Phenobarbital ; Methyl-phenobarbital.**

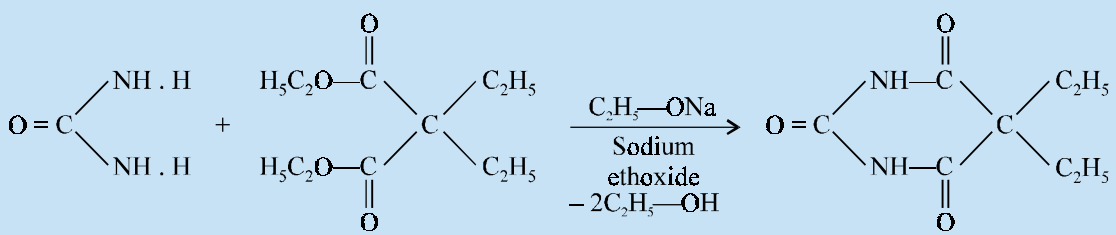
A1. Barbital INN, Barbitone BAN,



5, 5-Diethyl barbituric acid ; Diethylmalonyl urea ; Malonal ; B.P.C. 1963 ; Eur. P. ; N.F. XI

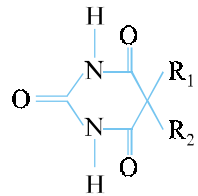
Veronal(R) (Winthrop)

Synthesis



Barbitone is prepared by the condensation of **urea** with **diethyl malonic ester** in the presence of sodium ethoxide with the elimination of two molecules of ethanol.

Table 6.1. Barbituric Acid and its Analogues



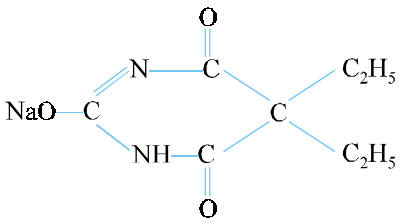
Name of Drug (Brand Name)	Chemcial Name (-barbituric acid)	Substitution at R_1	Substitution at R_2	Other Attachments	Duration of Action (hr.)
Barbitone (Veronal)	5, 5-Diethyl-	C_2H_5	C_2H_5		4—12
Phenobarbitone (Luminal)	5-Ethyl-5-phenyl	C_2H_5	C_6H_5		4—12
Methylphenobarbitone (Prominal)	5-Ethyl-1-methyl-5-phenyl	C_2H_5	C_6H_5	1-CH_3	1—4
Allobarbital (Dial)	5, 5-Diallyl	$CH_2 = CH—CH_2$	$CH_2 = CH—CH_2$		2—8
Amorbarbital (Amytal)	5-Ethyl-5-isopentyl	C_2H_5	$(CH_3)_2CHCH_2CH_2$		2—8
Butobarbitone (Soneryl)	5-Ethyl-5-n-butyl	C_2H_5	$CH_3CH_2CH_2CH_2$		2—6
Quinalbarbitone (Seconal)	5-Allyl-5 (1-methyl-butyl)	C_2H_5	$CH_3—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—CH_2—CH_2$		1—4
Hexobarbitone (Evipal)	5-Δ′-Cyclohexenyl-1-methyl N-methyl	CH_3	$(CH_2)_4CH = C—$ (ring)	1-CH_3	1—4
Thiopentone (Pentothal)	5-Ethyl-5-(1-methyl butyl)-2-thiobarbituric acid	C_2H_5	$CH_3(CH_2)_2CH(CH_3)$	2-S	1—4
Cyclobarbitone (Phanodorn)	5-Ethyl-5 (1-cyclohexen-1-yl)	C_2H_5	$(CH_2)_4CH = C—$ (ring)		2—8
Pentobarbitone (Nembutal)	5-Ethyl-5 (1-methyl butyl)	C_2H_5	$CH_3(CH_2)_2CH(CH_3)$		2—4

It is a powerful **hypnotic drug** and generally used in the treatment of epileptic seizures. It has the main drawback of having a **low therapeutic index.**

Dose : *0.3 to 0.6 g.*

The solutions are incompatible with ammonium salts and acidic substances.

A2. Barbital Sodium INN, Barbitone Sodium BAN :

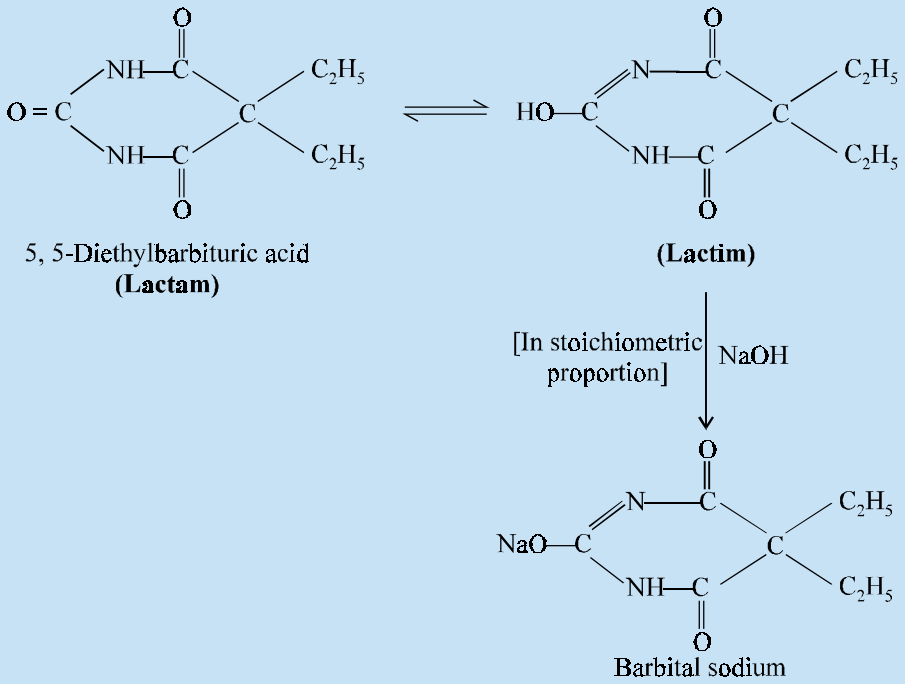


Sodium 5, 5-diethylbarbiturate ; Sodium derivative of 5, 5-diethylbarbituric acid ;

Soluble Barbitone, B.P. 1973 ; NF XI ; Int. P. ; Ind. P.

Somnylic Tablets(R) (Philip Harris)

Synthesis

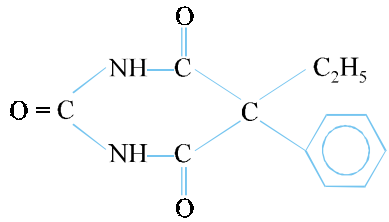


It is prepared by the neutralization of an aqueous solution of **barbital** with sodium hydroxide and then precipitating the salt by the addition of alcohol.

Being water-soluble, barbital sodium is more readily absorbed than its parent compound barbital. **Owing to its slow rate of excretion there exists an element of risk of a cumulative action.**

Dose : *0.34 to 0.6 g.*

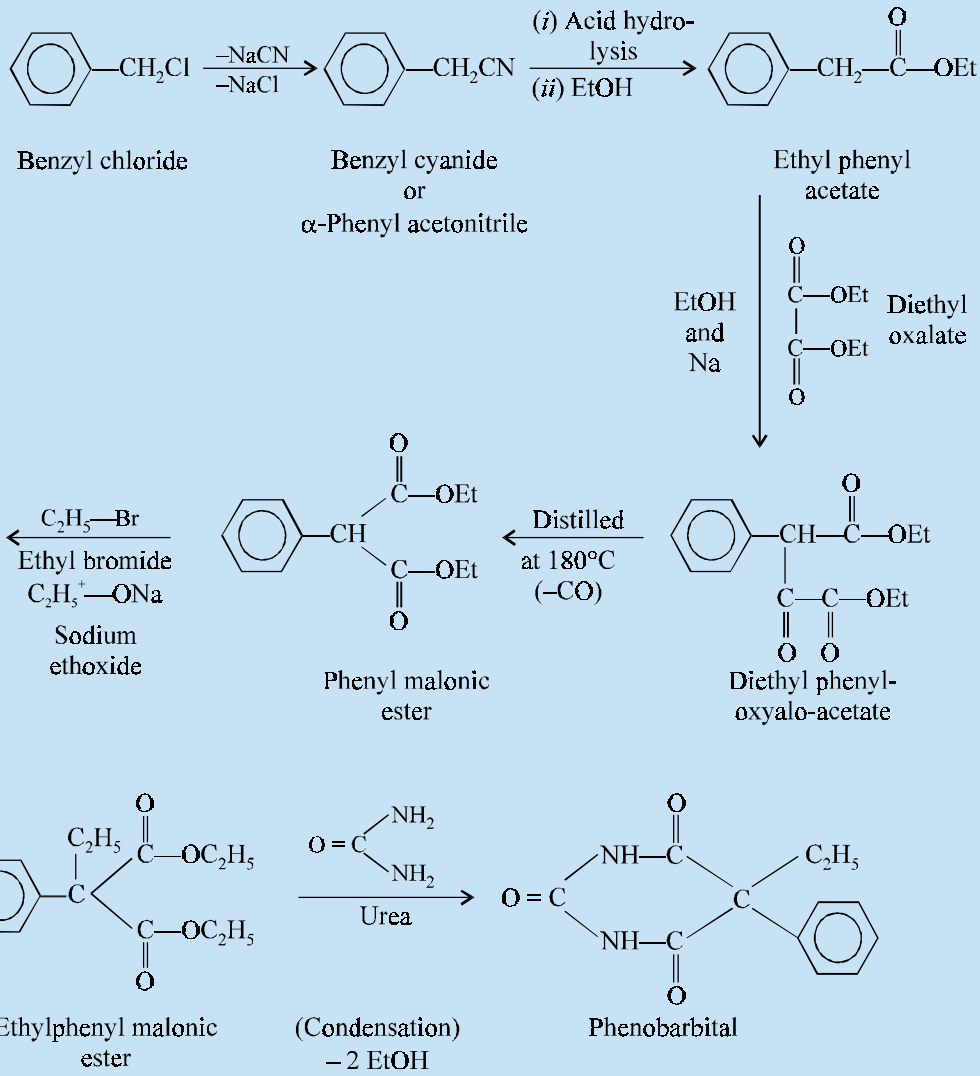
A3. Phenobarbital INN, USAN, Phenobarbitone BAN,



5-Ethyl-5-phenyl barbituric acid ; 2, 4, 6 (1H, 3H, 5H)-pyrimidinetrione, 5-ethyl-5-phenyl ; Phenylethylmalonylurea ; U.S.P. ; B.P. ; Eur. P. ; Int. P.

Eskabarb(R) (Smith Kline and French) ; Luminal(R) (Winthrop) ; Gardinal(R) (May and Baker) ; Stental(R) (Robins)

Synthesis

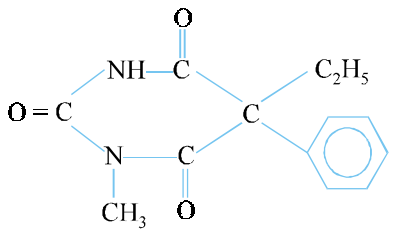


Phenobarbital is prepared by treating benzyl chloride with sodium cyanide when benzyl cyanide (or α-phenyl acetonitrile) is formed with the elimination of a molecule of sodium chloride. Benzyl cyanide, first on hydrolysis yields phenyl acetic acid which on subsequent esterification with ethanol forms the corresponding ester as ethyl phenyl acetate. This on reaction with diethyl oxalate in the persence of absolute ethanol and sodium metal gives diethyl phenyl oxalo acetate which on distillation at 180°C results into phenyl malonic ester. When it is treated with ethyl bromide and sodium ethoxide, the lonely active hydrogen atom gets replaced with an ethyl group thus forming ethyl phenyl malonic ester. Lastly, this on condensation with urea loses two molecules of ethanol and finally forms the desired compound phenobarbital.

It is used both as **sedative and hypnotic**. It is the drug of choice in the treatment of *grandmal and petitmal epilepsy.*

Dose : *30 to 120 mg.*

A4. Methylphenobarbital INN, Methylphenobarbitone BAN, Mephobarbital USAN,



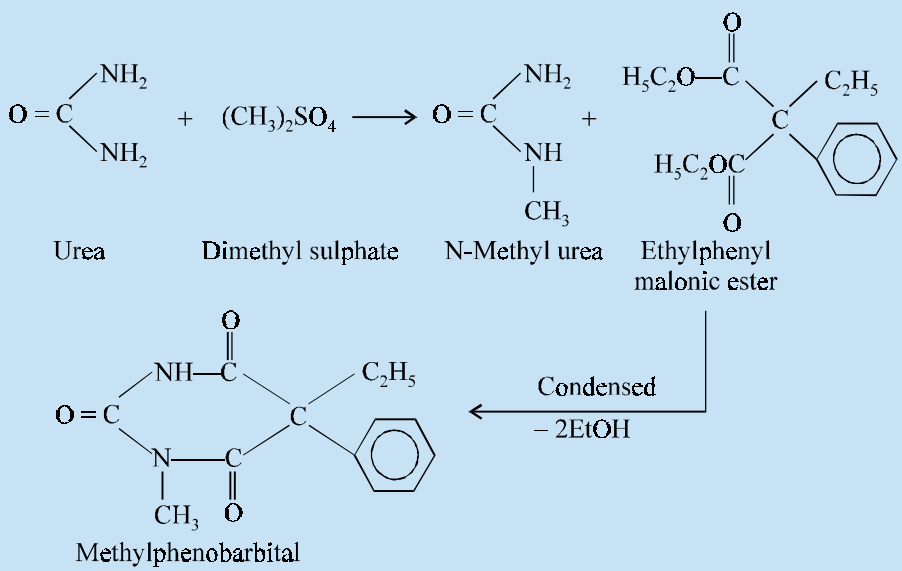
5-Ethyl-1-methyl-5-phenylbarbituric acid ; 2, 4, 6 (1H, 3H, 5H)-pyrimidinetrione, 5-ethyl-1-methyl-5-phenyl- ; U.S.P., B.P., Eur. P.

Prominal(R) (Winthrop, U.K.)

Methylphenobarbital can be prepared by the following *two* methods :

Method I : (From Urea)

Synthesis

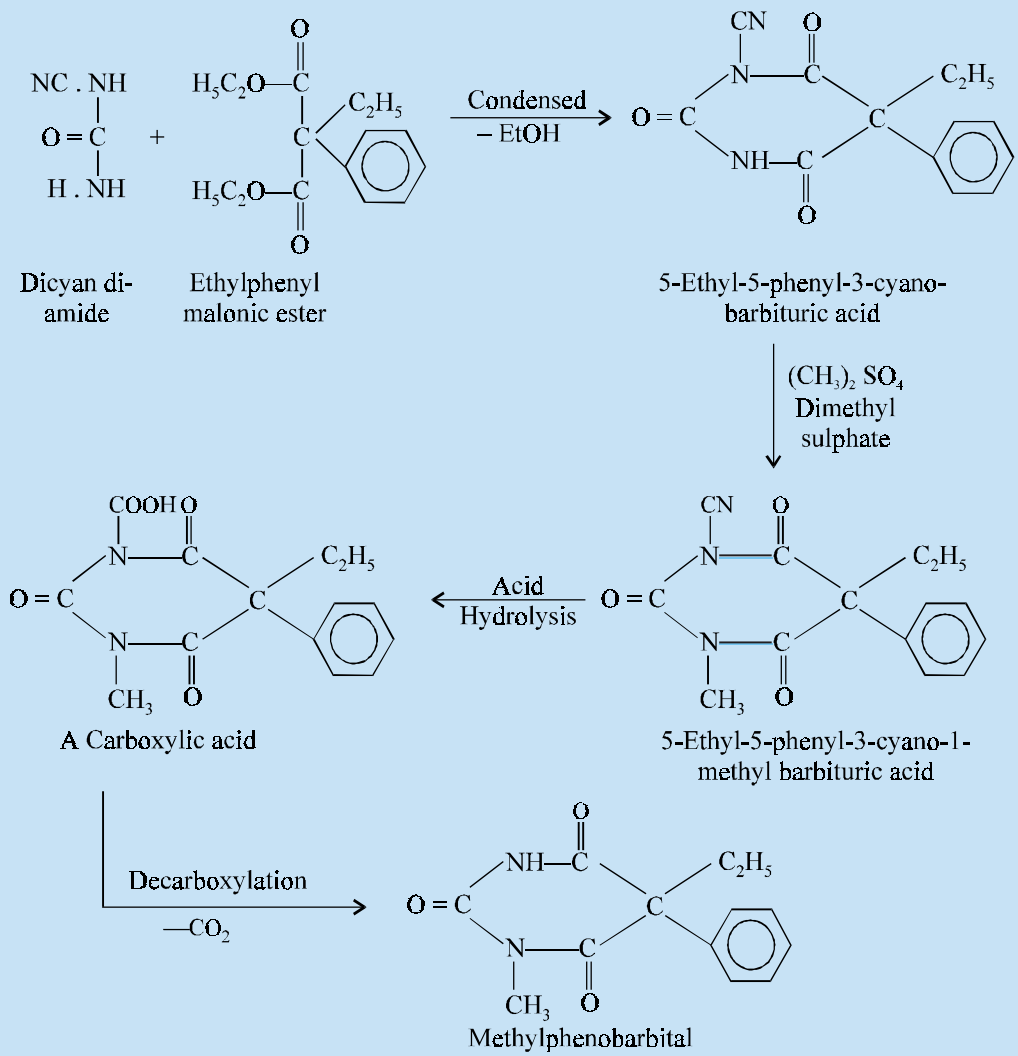


It may be prepared by the condensation of N-methyl urea, obtained from urea and dimethyl sulphate, and ethylphenyl malonic ester with the elimination of two molecules of ethanol.

Method-II : (From Dicyandiamide)

Methylphenobarbital can also be prepared by the interaction of ethylphenyl malonic ester and dicyandiamide when it results into the formation of 5-ethyl-5-phenyl-3-cyano barbituric acid, which on methylation with dimethyl sulphate yields 5-ethyl-5-phenyl-3-cyano-1-methyl barbituric acid. This on acid hydrolysis converts the cyano moiety at position 3 into a free COOH group which on decarboxylation finally gives methylphenobarbital.

Synthesis



It possesses hypnotic action, but in therapeutic doses they exert practically no effect on the medullary centre thereby allowing no appreciable change in the blood pressure or the rate of respiration.

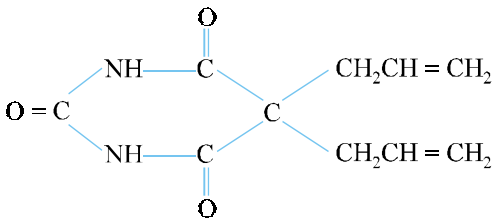
Dose : *As a sedative 30 to 100 mg 3 to 4 times per day ; as an anticonvulsant 400 to 600 mg daily.*

B. Intermediate Acting Barbiturates

The onset of action for **intermediate acting barbiturates** is 30 minutes and their hypnotic effect last for 2 to 6 hours. Most of them are first degraded by the liver and the metabolised product subsequently excreted by the kidney. They are generally used in insomnia and also as a pre-operative sedative. They also find their use in the treatment of convulsions when administered intravenously.

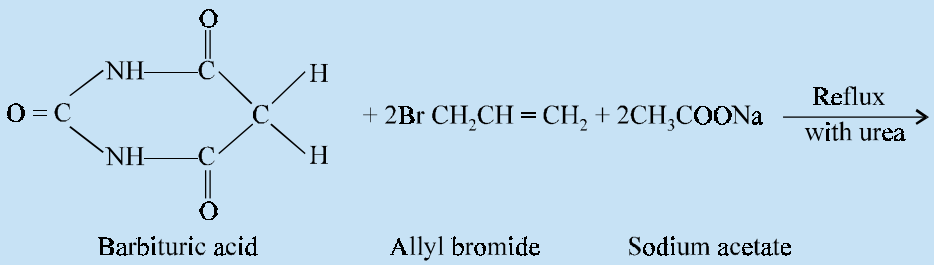
Examples : Allobarbital ; Butobarbitone ; Amobarbital

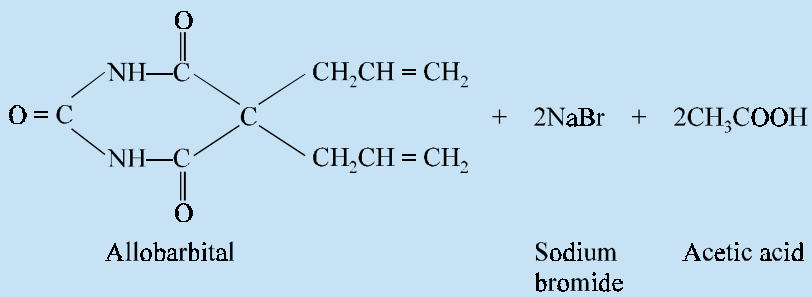
B1. Allobarbital INN,



5, 5-Diallylbarbituric acid ; 2, 4, 6 (1H, 3H, 5H)-Pyrimidinetrione, 5, 5-di-2-propenyl-; Allobarbital ; Diallylbarbitone ; Diallylmalonylurea ; Diallymalum ; Allobarbitone (BPC 1959)

Synthesis



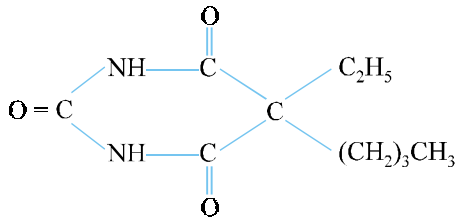


It may be prepared by the interaction of barbituric acid with an alcoholic solution of allyl bromide and sodium acetate and on being refluxed with urea.

It can be used both as a sedative and hypnotic at different dose levels.

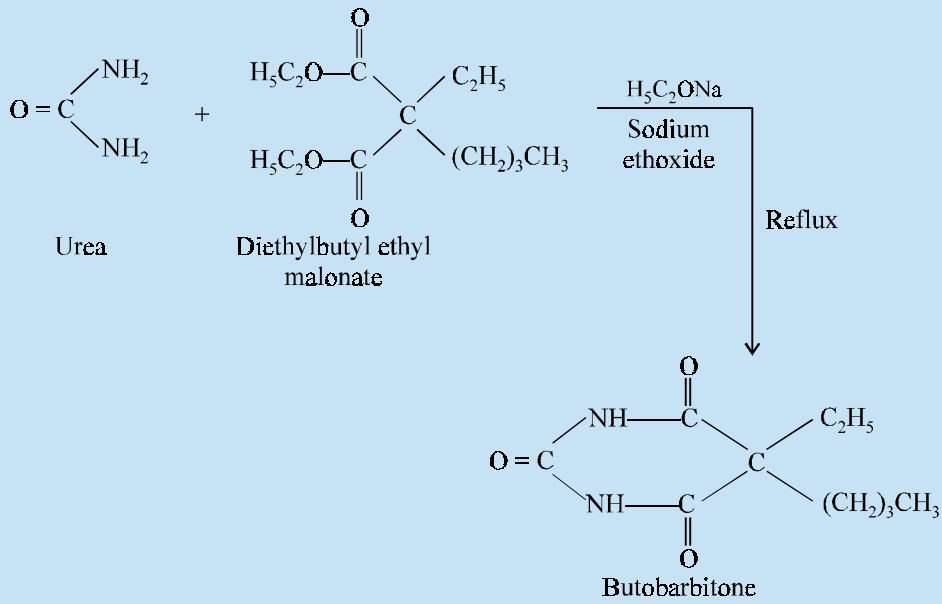
Dose : *As a sedative 30 mg 3 to 4 times a day ; as a hypnotic 100 to 200 mg at night.*

B2. Butobarbitone BAN,



5-Butyl-5-ethyl barbituric acid ; Butobarbital ; B.P., Eur. P., Butethal N.F. X Soneryl(R) (May and Baker, U.K.) ; Neonal(R) (Abbott) ;

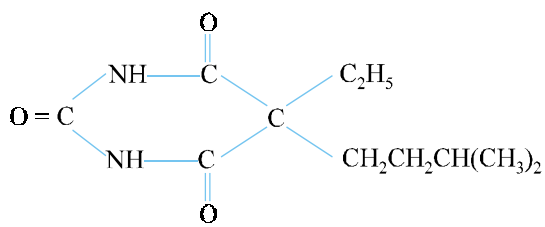
Synthesis



It is prepared by reacting together urea and diethyl butyl ethyl malonate in the presence of sodium ethoxide.

Dose : *30 to 120 mg as a sedative and 100 to 200 mg at night as a hypnotic.*

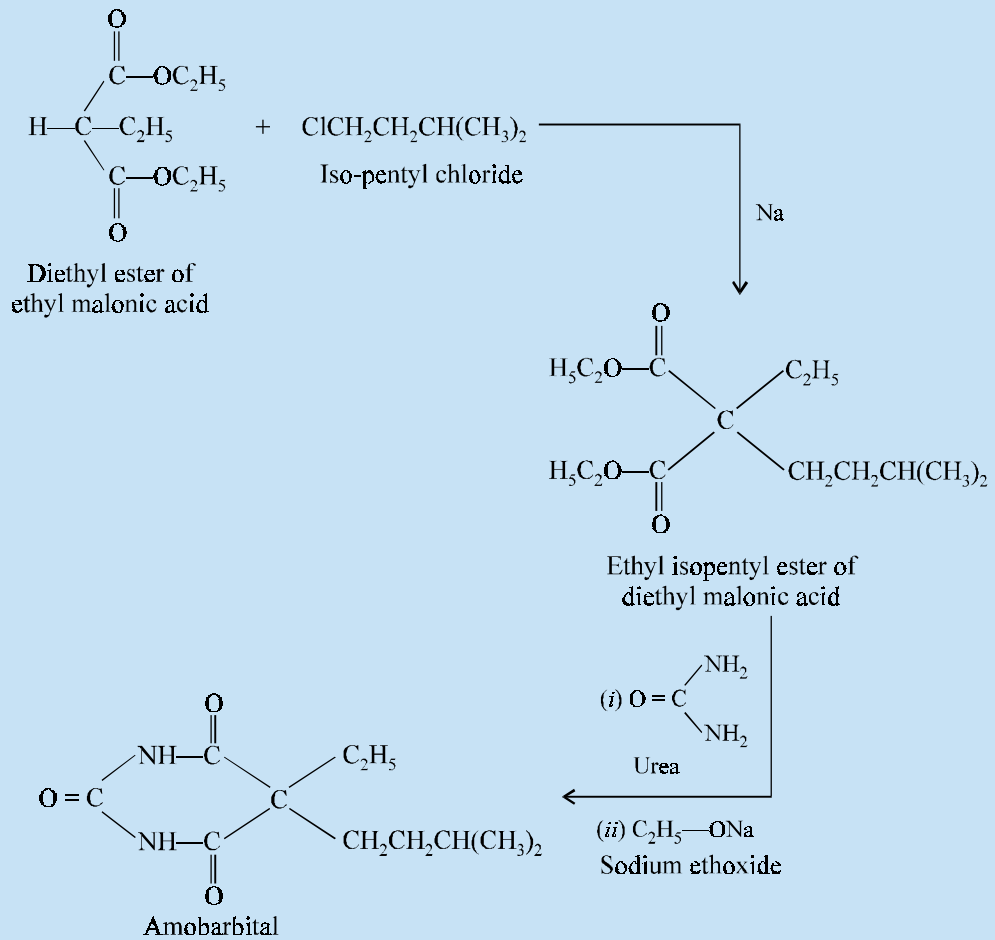
B3. *Amobarbital* INN, USAN, *Amylobarbitone* BAN ;



5-Ethyl-5-isopentylbarbituric acid ; 5-Ethyl-5-isoamylbarbituric acid ; 2, 4, 6 (1H, 3H, 5H)-Pyrimidinetrione, 5-ethyl-5-(3-methyl-butyl)- ; Amobarbital (U.S.P.), Amylobarbitone (B.P., Ind. P., Int. P.),

Amytal(R) (Lilly) ;

Synthesis



It is prepared by the interaction of diethyl ester of ethyl malonic acid and iso-pentyl chloride in the presence of sodium metal, when ethyl is isopentyl ester of diethyl malonic acid is obtained as an intermediate compound. This on condensation with urea in the presence of sodium ethoxide results into the formation of **amobarbital**.

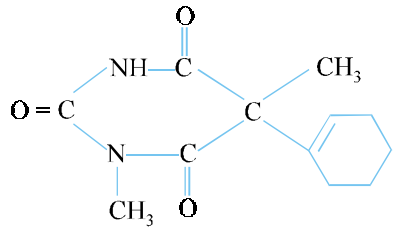
Dose : *300 mg*

C. Short-Acting Barbiturates

The onset of action for **short-acting barbiturates** falls within 15 minutes and their hypnotic action last for 1 to 2 hours. They are mostly metabolized in the liver. They are invariably used in the treatment of insomnia and pre-operative medication.

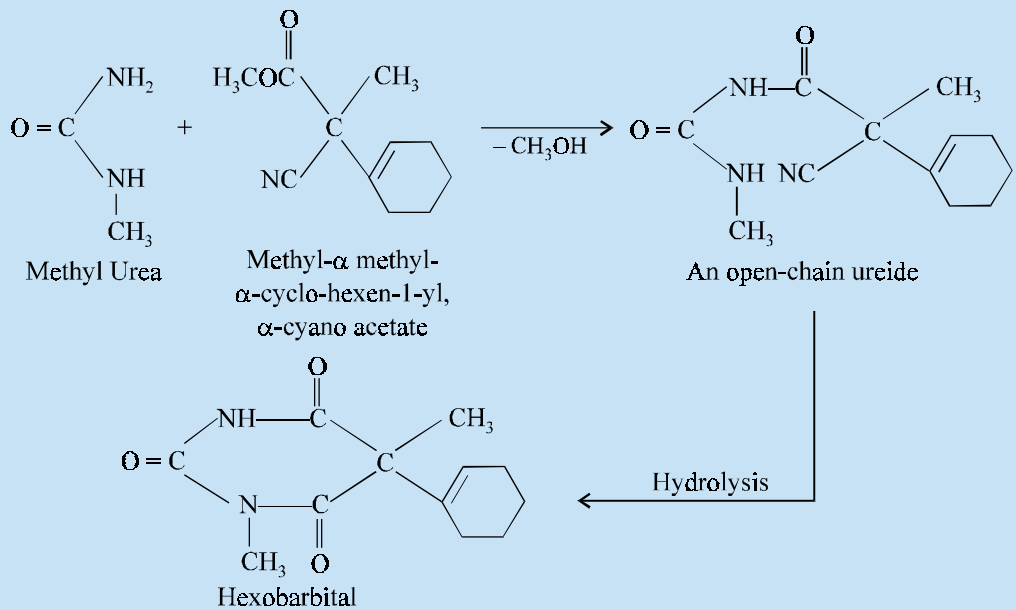
Examples : Hexobarbital ; Pentobarbital Sodium ; Quinalbarbitone Sodium ; and Cyclobarbital.

C1. Hexobarbital INN, USAN,



5-(1-Cyclohexen-1-yl)-1, 5-dimethyl barbituric acid ; 2, 4, 6 (1H, 3H, 5H)-Pyrimidinetrione, 5-(1-cyclohexen-1-yl)- 1, 5-dimethyl ; Enimal ; Methexenyl ; Hexobarbitone (Eur. P., Int. P., B.P.C. 1959) ; Hexobarbital (U.S.P.) Evipal(R) (Winthrop) ; Sombulex(R) (Riker)

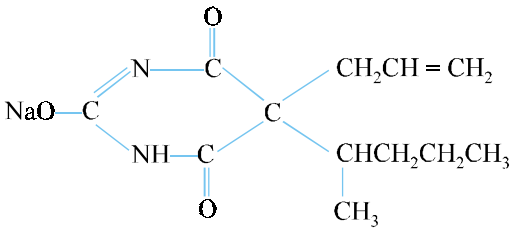
Synthesis



Hexobarbital is prepared by reacting together methyl urea and methyl-α-methyl-α-cyclo-hexen-1-yl-α-cyano acetate when an open-chain ureide is formed as an intermediate with the elimination of a molecule of methanol. This upon hydrolysis affords spontaneous closure of the ring thereby resulting into the formation of **hexobarbital.**

Dose : *Adult, oral, hypnotic, 250 to 500 mg.*

C2. Pentobarbital Sodium USAN, Pentobarbitone Sodium BAN,



Sodium 5-allyl-5-(1-methylbutyl) barbiturate ; 2, 4, 6 (1H, 3H, 5H)-Pyrimidinetrione, 5-ethyl-5-(1-methylbutyl), monosodium salt ; Ethaminal Sodium ; Soluble Pentobarbitone ; Pentobarbitone Sodium B.P., Eur. P., Ind. P.,

Nembutal Sodium(R) (Abbott) ; Palapent(R) (Bristol-Myers) ; Sodital(R) (American Critical Care) ;

Synthesis

It is prepared by :

(*i*) Synthesis of diethylester of ethyl-(1-methyl butyl) malonate ;

(*ii*) Condensation of (*i*) with urea ; and

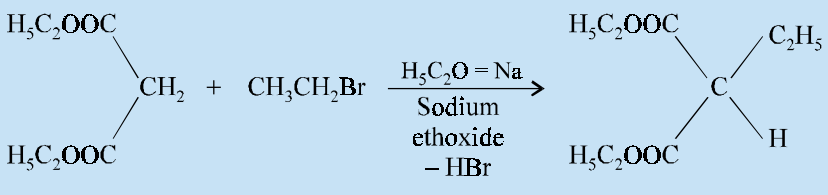
(*iii*) Conversion of Pentobarbital into its sodium salt.

In the first step the diethyl ester of malonic acid is treated with ethyl bromide in the presence of sodium ethoxide when one of the active hydrogen atoms in the former gets eliminated with bromine atom in the later as a molecule of hydrobromic acid resulting into the formation of the corresponding diethyl ester of ethyl malonic acid. This on subsequent addition of 2-monobromopentane and in the presence of sodium ethoxide gives rise to diethyl ether of ethyl-(1-methyl butyl) malonate with the elimination of one molecule of hydrobromic acid. Urea is made to condense with the product obtained from the previous step when **pentobarbital** is formed with the elimination of two moles of ethanol. Finally, the pentobarbital is treated with a calculated amount of sodium hydroxide when the required official compound is formed.

It is used mostly in the treatment of insomnia, as a basal anaesthetic and also in strychnine poisoning.

Dose : *100—200 mg*

(*i*) Preparation of Diethyl ester of ethyl-(1-methyl butyl) malonate :



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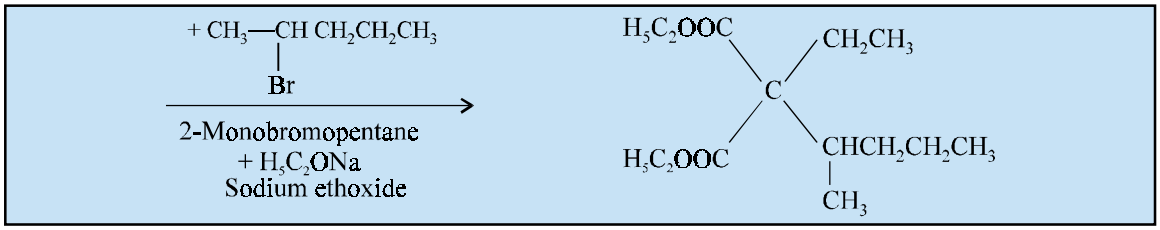
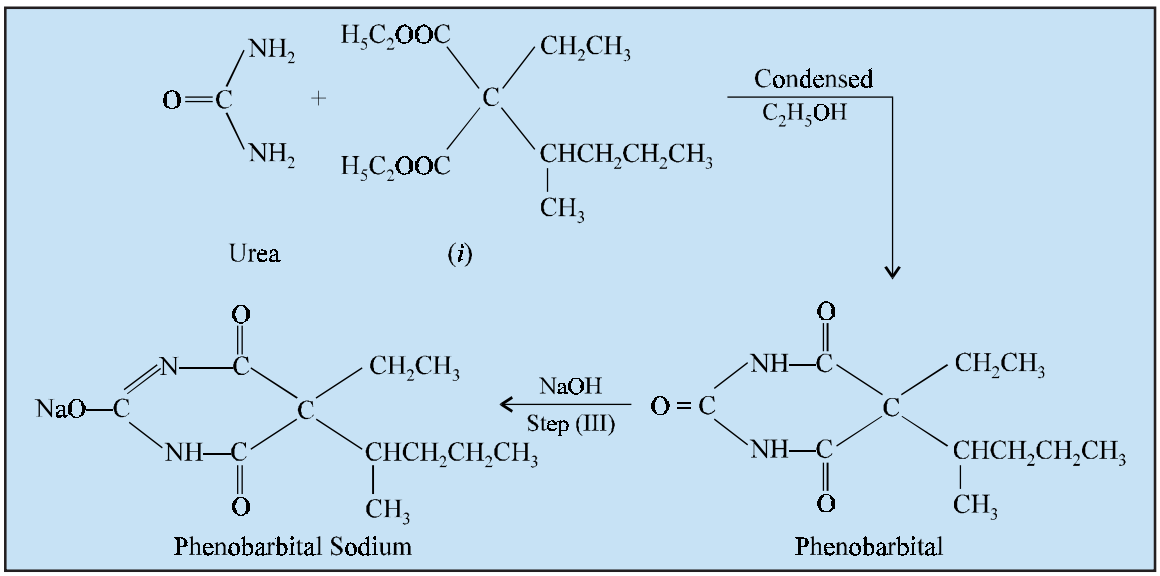
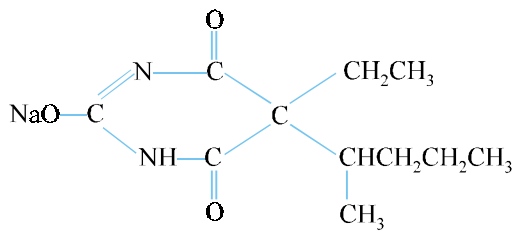


(*ii*) Condensation of (*i*) with urea ; and

(*iii*) Conversion of Pentobarbital into its sodium salt.



C3. Quinalbarbitone Sodium BAN, Secobarbital Sodium USAN,



Sodium 5-allyl-5-(1-methyl butyl) barbiturate ; 2, 4, 6 (1H, 3H, 5H)-Pyrimidine-trione, 5-(1-methyl butyl)-5-(2-propenyl)-, monosodium salt ; Secobarbitone sodium.

Quinalbarbitone Sodium, B.P., Eur. P., Ind. P., Int. P., Secobarbital Sodium U.S.P.

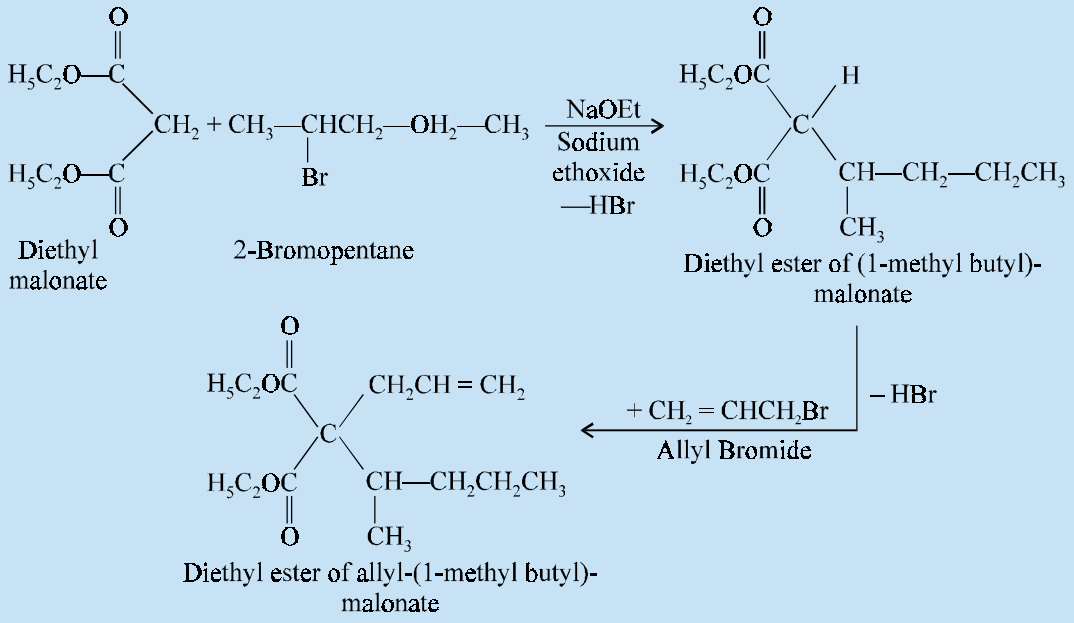
Seconal Sodium$^{(R)}$ (Lilly)

Synthesis

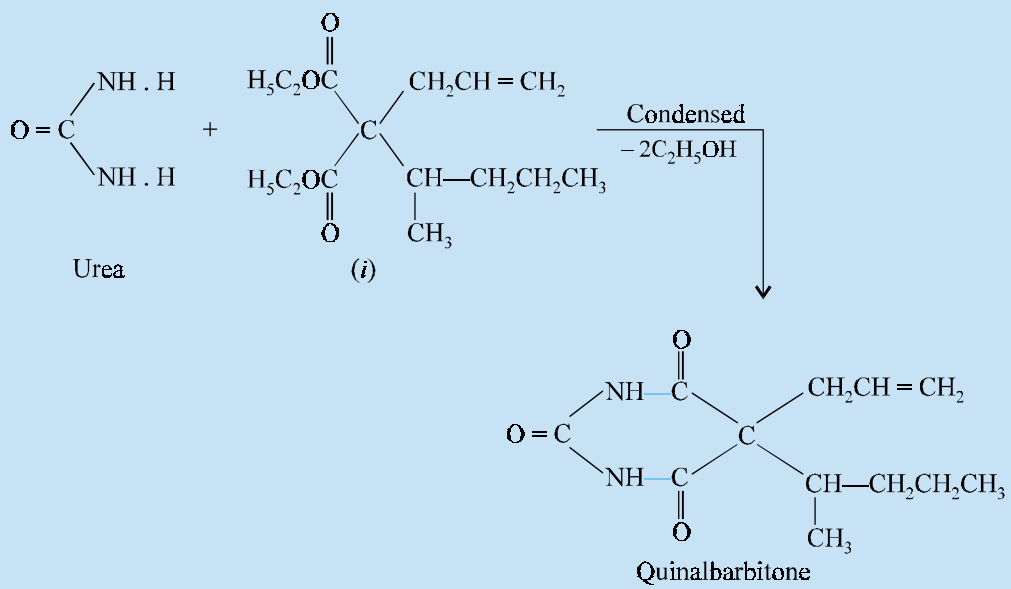
Quinalbarbitone sodium can be conveniently prepared by means of the follwoing *three* steps :

(*i*) Preparation of diethyl ester of allyl-(1-methyl butyl) malonate ; (*ii*) Condensation of (*i*) above with urea ; and (*iii*) Preparation of the sodium salt.

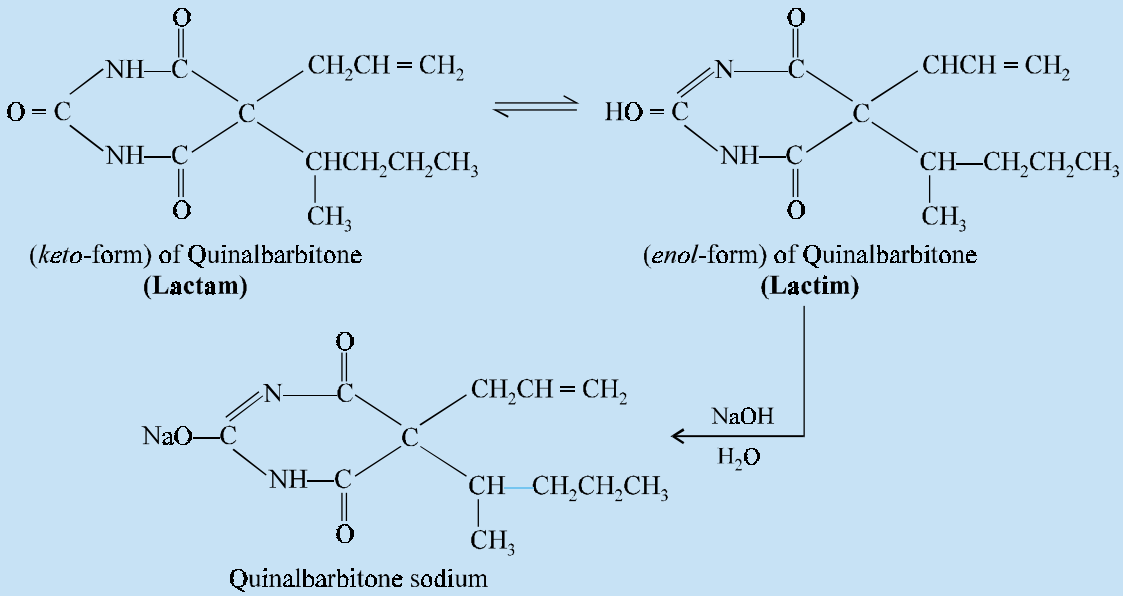
Step (*i*) Diethyl ester of allyl-1 (1-methylbutyl) malonate



Step (*ii*) Condensation of (*i*) above with urea



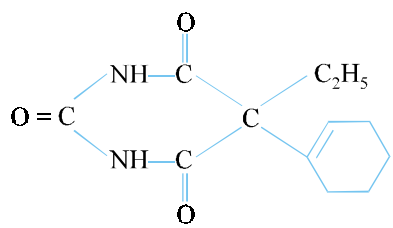
Step (*iii*) Preparation of Sodium Salt of Quinalbarbitone



First, diethyl malonate is reacted with 2-bromopentane in the persence of sodium ethoxide when one active hydrogen atom from the former and a bromine atom from the later gets eliminated as a molecule of hydrobromic acid and resulting into the formation of diethyl ester of (1-methyl butyl) malonate. On further treatment of this compound with allyl bromide, the lonely active hydrogen present in the malonate is abstracted with the bromine atom in the allyl halide as hydrobromic acid giving rise to the corresponding diethyl ester of allyl-(1-methyl butyl) malonate. *Secondly*, the resulting product on condensation with urea loses two moles of ethanol yielding **quinalbarbitone**. *Thirdly*, it undergoes *keto-enol* tautomerism and finally the *enol*-form of **quinalbarbitone** on reaction with a calculated amount of sodium hydroxide results into the sodium salt of **quinalbarbitone.**

Dose : *50—200 mg*

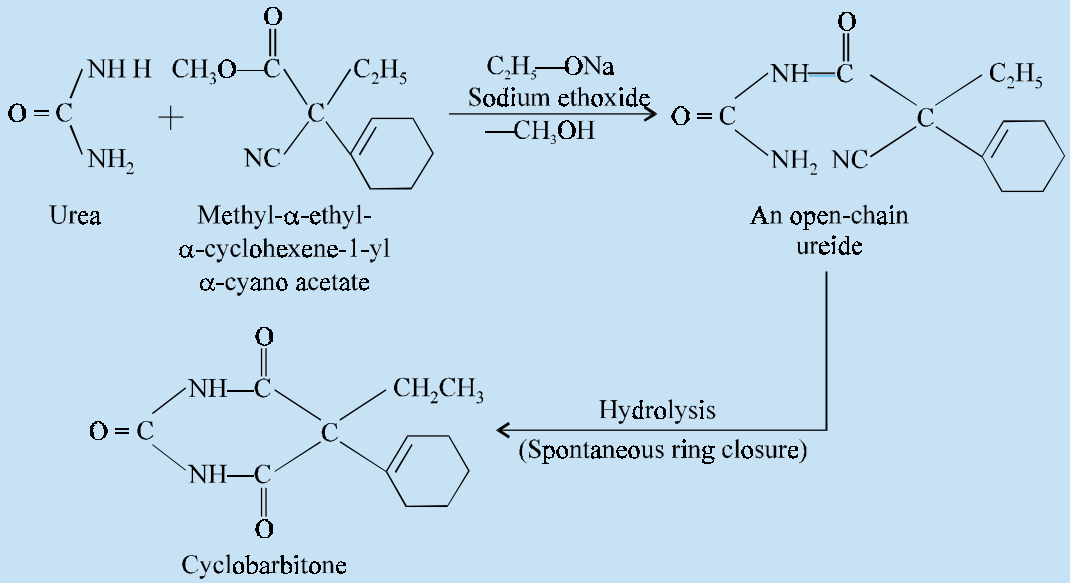
C4. Cyclobarbital INN, Cyclobarbitone BAN,



5-(1-Cyclohexen-1-yl)-5-ethyl barbituric acid ; Ethylhexabarbital ; Cyclobarbital N.F. X, Cyclobarbitone B.P., Ind. P.,

Phanodorn$^{(R)}$ (Winthrop)

Synthesis



It is prepared by the interaction of urea with methyl-2-ethyl-α-cyclo-hexene-1-yl-α-cyano acetate in the presence of sodium ethoxide when a molecule of methanol is eliminated with the formation of an **open-chain ureido ;** which upon hydrolysis results into spontaneous ring closure and gives rise to **cyclobarbital.**

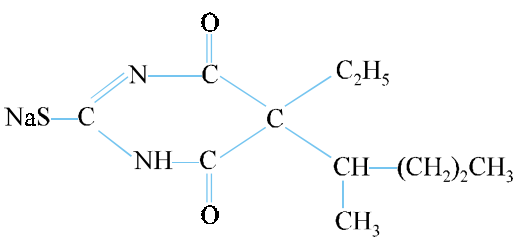
Dose : *200 to 400 mg*

D. Ultra-Short-Acting Barbiturates

These act almost instantaneously, *i.e.*, within a few seconds after administration. Because of this peculiar characteristics they are usually employed to produce general anaesthesia and to control convulsions. They may be used either alone or in conjunction with inhalation anaesthesia. After administration, they are first deposited in adipose tissues but are eventually dependent on the liver and kidney for their ultimate metabolic degradation and elimination.

Examples : Thiopental sodium, methohexital sodium.

D1. Thiopental Sodium INN, USAN,



Sodium 5-ethyl-5 (1-methyl butyl)-2-thiobarbiturate ; 4, 6 (1H, 5H)-Pyrimidinedione, 5-ethyldihydro-5-(1-methyl butyl)-2 thioxo-, monosodium salt ; Thiopental sodium U.S.P., Thiopentone sodium B.P., Eur. P., Ind. P., Int. P.

Pentothal sodium(R) (Abbott) ; Intraval sodium(R) (May and Baker)

Synthesis

It can be prepared by the following *three* steps, namely :

(*i*) Preparation of diethyl ester of ethyl-(1-methyl butyl) malonate ;

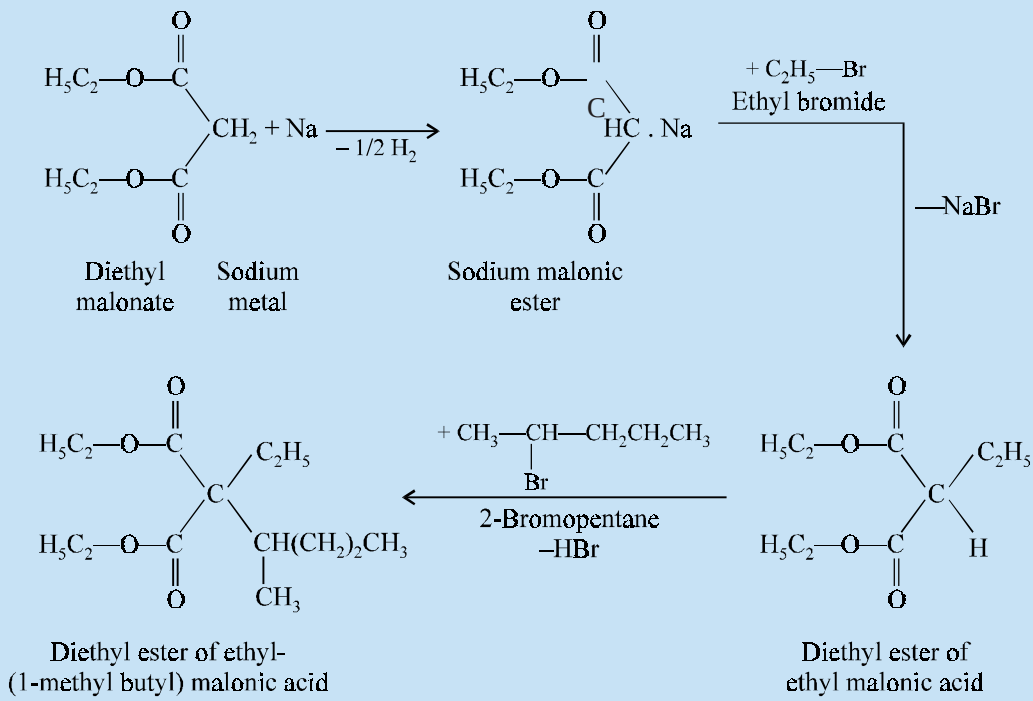
(*ii*) Condensation of (*i*) with thiourea ; and

(*iii*) Preparation of the sodium salt.

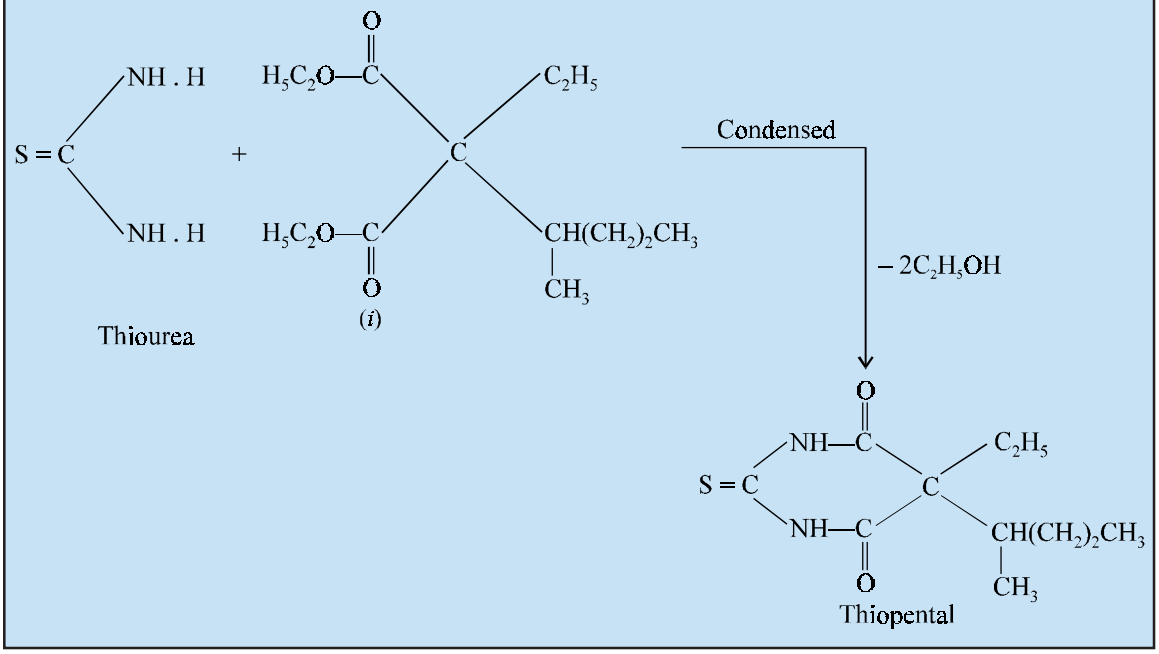
Diethyl malonate on reaction with sodium metal gives rise to sodium malonic ester which on treatment with ethyl bromide results into the formation of diethyl ester of ethyl malonic acid with the elimination of hydrobromic acid. The resulting ester on further reaction with 2-bromopentane gives the desired compound, *i.e.*, diethyl ester of ethyl (1-methyl butyl) malonic acid ; which on subsequent treatment with thiourea forms thiopental with the elimination of two moles of ethanol. Ultimately, the *enol*-form of thiopental when reacted with a calculated amount of sodium hydroxide, it gives **thiopental sodium**.

Dose : *100—150 mg (intravenous injection).*

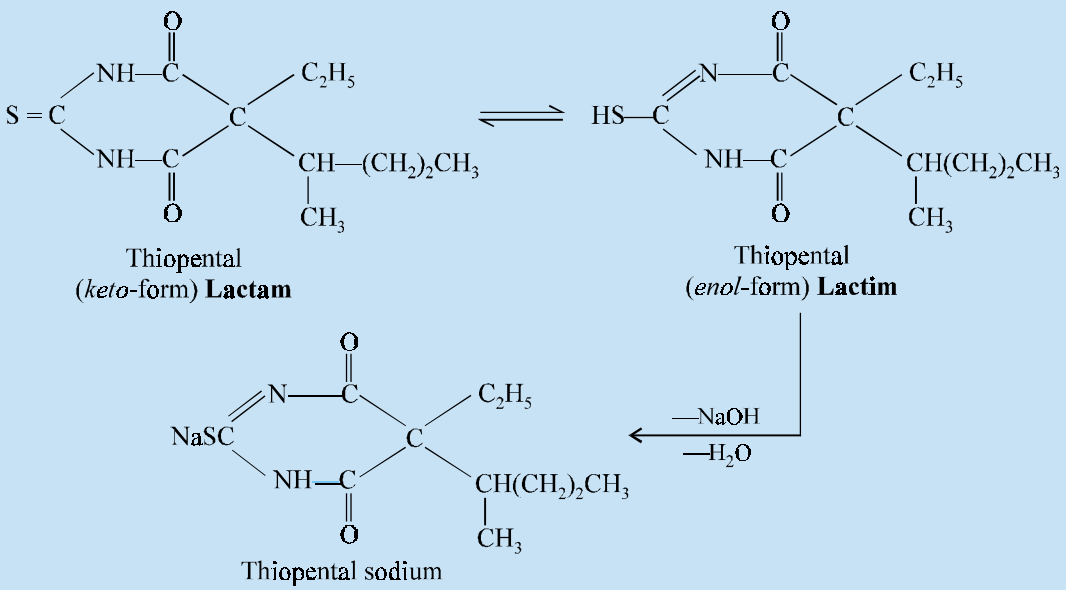
(*i*) Preparation of diethyl ester of ethyl-(1-methyl butyl) malonate :



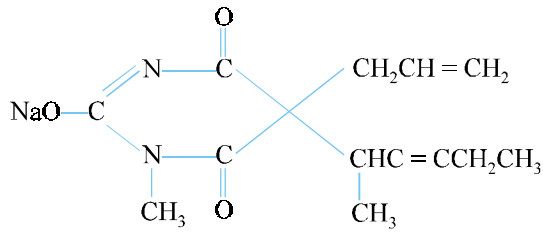
(*ii*) Condensation of (*i*) with thiourea :



(*iii*) Preparation of the sodium salt :



D2. Methohexital Sodium USAN,



Sodium 5-allyl-1-methyl-5 (1-methyl-2-pentynyl) barbiturate ; 2, 4, 6 (1H, 3H, 5H) Pyrimidinetrione, 1-methyl-5 (1-methyl-2-pentynyl)-5-(2-propenyl)- ± monosodium salt ;

Methohexital sodium U.S.P.

Brevital Sodium$^{(R)}$ (Lilly)

In the literature the two diastereoisomers of the barbituric acid have been designated as α- and β-forms, of which the α-form is the one employed medicinally whereas the corresponding β-form causes undesirable side-effects.

It is a barbiturate of choice for rapid action, administered intravenously, for causing anaesthesia, supplementing general anaesthetic agents, short surgical trauma and induction of hypnosis.

Dose : *5 to 12 ml of 1% solution (iv), at the rate of 1 ml every 5 sec., maintenance, 2 to 4 ml every 4 to 7 min as required.*

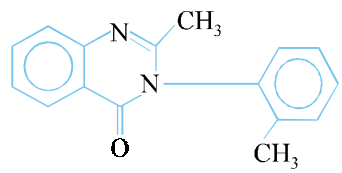
2.2 Non-barbiturates

There are a number of compounds which do not essentially possess the malonyl urea or barbiturate structure but exhibit marked and pronounced hypnotic-sedative activity very similar to that of the barbiturates. Like barbiturates these are habit-forming to varying degrees. They may be grouped together on the basis of their basic structures, namely :

Heterocyclics

A number of heterocyclics possessing significant hypnotic-cum-sedative activity have gained recognition in the therapeutic armanentarium. A few such compounds shall be discussed here briefly.

A. Methaqualone INN, USAN, BAN,



2, Methyl-3-*o*-tolyl-4 (3H)-quinazolinone ; 4 (3H)-Quinazolinone, 2-methyl-3-(2-methylphenyl) ;

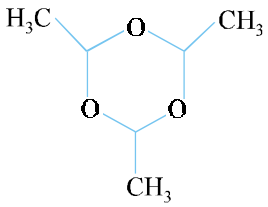
U.S.P., B.P.

Quaalude$^{(R)}$ (Lemmon) ; Tuazole$^{(R)}$ Pennwalt) ;

Its hypnotic action is similar to the **intermediate-acting barbiturate** which may be enhanced when administered along with an antihistaminic agent like **diphenylhydramine**. It may be used as a sedative at lower dose levels.

Dose : *50 to 150 mg*

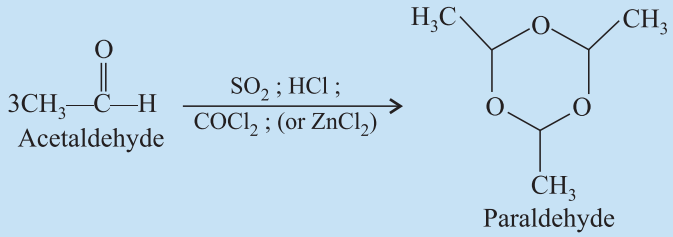
B. Paraldehyde USAN, BAN



2, 4, 6-Trimethyl-s-trioxane ; 1, 3, 5-Trioxane, 2, 4, 6-trimethyl- ; Paracetaldehyde ; The trimer of acetaldehyde ; U.S.P., B.P., Eur. P., Ind. P.

Paral(R) (O'Neal, Jones and Feldman) ;

Synthesis

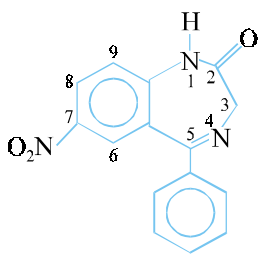


It is prepared by treating acetaldehyde with small quantities of sulphur dioxide, hydrochloric acid, carbonyl chloride, or zinc chloride. The resulting liquid is frozen and subsequent distillation of the crystallised material often yields paraldehyde.

It is one of the oldest hypnotics. The drug is usually employed in delirium tremens, status epilepticus and in patients undergoing withdrawal therapy for alcoholism. A certain portion of the administered drug is excreted through the lungs.

Dose : *Adult, oral : As sedative 5 to 10 ml ; as hypnotic 10 to 30 ml*

C. Nitrazepam INN, BAN,



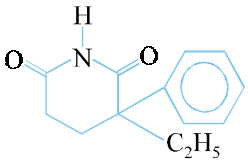
1, 3-Dihydro-7-nitro-5-phenyl-2H-1, 4-benzodiazepin-2-one ; 2H-1, 4-Benzodiazepin-2-one, 1, 3-dihydro-7-nitro-5-phenyl- ; B.P. Eur. P.

Mogadon(R) (Roche)

It is one of the members of the group **benzodiazepines** employed as sedatives and hypnotics. It is widely used in Canada and Europe as a sedative/hypnotic and also in the management of myoclonic seizures. It is extensively metabolized to inactive substances which are ultimately excreted through the urine.

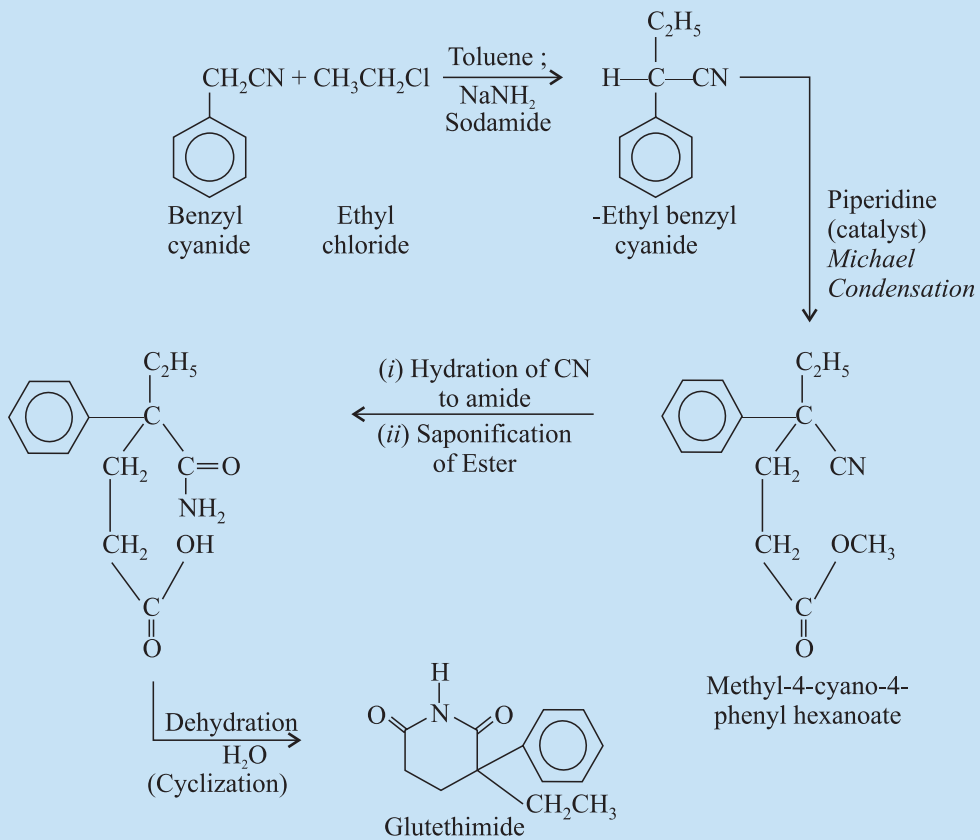
Dose : *Usual, oral, adult 2.5 to 10 mg.*

D. Glutethimide INN, USAN, BAN,



2-Ethyl-2-phenylglutarimide ; 3-Ethyl-3-phenylpiperidine-2, 6-dione ;
U.S.P., B.P., Int. P.
Doriden(R) (Ciba, UK) ; Glutril(R) (Roche)

Synthesis

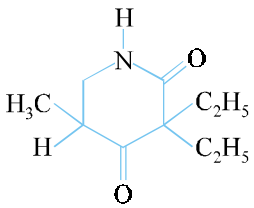


α-Ethylbenzyl cyanide is obtained from the reaction of benzyl cyanide and ethyl chloride in toluene as a medium and sodamide as a catalyst, which is then caused to undergo **Michael Condensation** in the presence of piperidine to yield methyl-4-cyano-4-phenyl hexanoate. This on hydration converts the free cyano moiety to an amide, which on saponification gives an intermediate. Cyclization of this intermediate is effected through dehydration between the amide and carbon groups. The pure product may be obtained by recrystallization from ethanol-water mixture (1 : 1).

It is safely used for inducing sleep in all types of insomnia without causing depression of respiration. Its hypnotic action is parallel to intermediate-acting barbiturates.

Dose : *250 to 500 mg*

E. Methyprylon INN, USAN, Methyprylone BAN



3, 3-Dimethyl-5-methyl-2, 4-piperidinedione ; 2, 4-Piperidine-dione, 3, 3-diethyl-5-methyl ;

Methyprylon U.S.P., N.F., Methyprylone B.P.

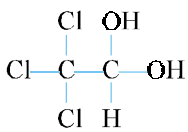
Nodular(R) (Roche) ;

It is an useful hypnotic agent employed in the management of insomnia of varied etiology. It may induce sleep within a span of 45 minutes and produce sleep ranging between 5 to 8 hours.

Like **glutethimide** it is also a piperidinedione derivative.

Dose : *Usual, sedative, 125 to 250 mg up to 3 times daily ; hypnotic, 500 mg to 1 g.*

F. Chloral Hydrate USAN, BAN,



1, 1-Ethanediol, 2, 2, 2-trichloro- ; Hydrated Chloral ; U.S.P., B.P., Eur. P., Int. P., Ind. P.

Noctec(R) (Squibb) ; SK-Chloral Hydrate(R) (Smith Kline and French) ; Somnos(R) (MSD)

It is mainly used for nocturnal and preoperative sedation. It is frequently administered in combination with barbiturates to allay anxiety in the first stage of labour. However, it finds an additional use as an adjunct to analgesics and opiates in post-operative medication. It must be avoided in subjects suffering from such diseases as : heat, kidney or liver complications. In patients having gastritis, chloral hydrate may be given through rectum in olive oil as a retention enema. **Chloral hydrate** is being replaced by new hypnotics with fewer side effects.

Dose : *As sedative 250 mg 3 times per day ; as hypnotic 500 mg to 1 g before going to bed.*

G. Carbromal INN, BAN,

2-Bromo-2-ethylbutyrylurea ; Bromodiethylacetylurea ; Bromadal ; Uradal ; Karbromal ;

B.P., N.F. XI.

Adalin(R) (Winthrop)

It is a weak hypnotic drug and is but infrequently used in modern therapeutics. On account of its inherent weak central depressant properties, its overall action is invariably disappointing and unreliable.

Dose : *Usual, oral, 500 mg*

3. MODE OF ACTION OF BARBITURATES

In general, the **hypnotics** may act in **two** different ways, namely ; *first* by exerting their action on the sensory cortex raising the threshold at which it responds to afferent stimuli ; *secondly*, they may interfere with the passage of impulses from the subsidiary centre or centres in the hypothalamus to the cortex. In other words, barbiturates act on the central synaptic transmission process of the reticular activating system.

In normal human being the cerebral electrical activity is directly proportional to anxiety, emotional excitement, or administration of a potent central nervous system stimulant (*e.g.*, **caffeine, dexamphetamine, lysergic acid diethylamide LSD** to name a few). At this juncture the administration of a reasonably overdose of **barbiturates** would cause a calming effect, which could be measured demonstrably with the help of an **electroencephalogram, (EEG).** Thus, **barbiturates** depress the reticular activating system by impairing the synaptic transmission.

In a broader perspective, the **excitatory synaptic transmission** is usually depressed appreciably by *barbiturates*, whereas the **inhibitory synaptic transmission** is normally either increased or unaffected absolutely. Interestingly, **barbiturates** are found to exert **antidepolarizing blocking action** that essentially check the causation of excitatory post synaptic potential not only by enhancing the threshold but also extending the refractory span of the post synaptic cell specifically. Paradoxically, however, the overall effect of **barbiturates** takes place whereby comparatively small doses bring about an unexpectedly marked and pronounced agitation and hyperexcitation rather than the expected sedative effect. This sepcific anomaly could be explained logically based on the fact the concentration of **barbiturate** is not enough to cause a depression in the reticular activating system, but is just capable of impedementing the inhibitory synapses usually present very much within the cortex. Besides, the **barbiturates** are also found to act on the hypothalamic, limbic, and thalamic synaptic systems.*

4. MECHANISM OF ACTION

The pharmacological effects of the **barbiturates** is invariably marked by a decrease with regard to the normal functional activities in the brain. It has been duly observed that at the prevailing therapeutic dose levels *in vivo* the barbiturates cause a distinct marked enhancement of the **GABAergic inhibitory response,** in a mechanism very much akin to that shown by the **benzodiazepines,** that is, by influencing conductance at the site of chloride channel. It is pertinent to mention here that at comparatively **higher concentration** barbiturates would display *six* marked and pronounced pharmacological actions :

(*a*) Potentiation of the **$GABA_A$-mediated chloride ion conductance**.

(*b*) Enhancement of binding between **GABA**** and **benzodiazepine**,

(*c*) Reduction in **glutaminergic transmission**,

(*d*) Uncoupling of **oxidative phosphorylation**,

*Richter JA *et al. Prog. Neurobiol.*, **18 :** 275-319, 1982.

****GABA :** Gamma-aminobutyric acid.

(*e*) Inhibition of cerebral carbonic anhydrase activity, and

(*f*) Inhibition of the electron-transport system.

Barbiturates, also effect the transportation of carbohydrates, and are observed to enhance the activity of liver microsomal enzymes, responsible for the regulatory mode of several drug substances *via* biotransformation.

5. BARBITURATES *Vs* BENZODIAZEPINES

The major glaring difference between the two entirely variant chemically structured compounds being that the **barbiturate binding site** happens to be altogether different from the **benzodiazepines**. The **'pharmaceutical elegance'** of **benzodiazepines** is believed to take place at the **picrotoxin-binding site** located on the **chloride channel**. These highly specific and high-affinity binding sites for the **benzodiazepines*** was adequately established by the aid of **radiolabeled benzodiazepines.** It was revealed that the benzodiazepines normally get bound at the specific **$GABA_A$ receptors** intimately involved in the regulatory function of the **chloride channel.** However, further extensive and intensive studies substantially suggested two additional subclasses of receptors, now known as BZ_1 and BZ_2 receptors. Interestingly, the presence of two distinct **structurally benzodiazepine receptor subclasses** were duly ascertained by making use of the **classical recombinant techniques** wherein $GABA_A$ receptor subclasses bearing variable subunit composition, very much similar to the BZ_1 and BZ_2 receptors, were coexpressed magnificently.**

In short, it has been advocated, though not yet proven experimentally, that the **BZ_2** subclass of the benzodiazepines is solely responsible for attributing the sedative-hypnotic activity ; whereas the BZ_1 subclass specific compounds would be **'non sedative'** in character.***

Barbiturates, in general, exert a distinct marked depresant activity on the cerebrospinal axis and depress the neuronal performance as well. Besides, these are found to retard the activities of smooth muscle, skeletal muscle and cardiac muscle. Perhaps, this could explain the spectrum of CNS-depression ranging from sedatives, hypnotics, anaesthetics, or even anticonvulsants.

6. STRUCTURE-ACTIVITY RELATIONSHIP

Barbituric acid itself does not possess any hypnotic properties. It is only when the two active hydrogen atoms at position 5 : 5 have the appropriate substituent (*e.g.,* alkyl or aryl groups) that the **'hypnotic activity'** is produced by the compound. The following cardinal points must be taken into consideration with respect to the **structure-activity relationship amongst the barbiturates**. These are :

(*i*) The total number of carbon atoms present in the two groups at carbon 5 must not be less than 4 and more than 10 for the optimal therapeutic results.

(*ii*) Only one of the substituent groups at position 5 may be a closed chain.

(*iii*) The branched chain isomer exhibits greater activity and shorter duration. The greater the branching, the more potent is the drug (*e.g.*, pentobarbital > amobarbital).

*Mohler H and Okada T, *Science,* **98** : 849-851, 1977.

Luddens H and Wisden W, *Trends Pharmacol-Sci.,* **12 : 49-51, 1991

***Muller WE, In : Kales A, ed, '**The Pharmacology of Sleep**', springer-verlag, Berlin, **116,** 211-242, 1995.

(*iv*) Double bonds in the alkyl substituent groups produce compounds more readily vulnerable to tissue oxidation ; hence, they are **short-acting**.

(*v*) Stereoisomers have more or less the same potencies.

(*vi*) Aromatic and alicyclic moieties exert greater potency than the corresponding aliphatic moiety having the same number of carbon atoms.

(*vii*) Short chains at carbon 5 resist oxidation and hence are **long-acting**. Long chains are readily oxidized and thus produce **short-acting barbiturates**.

(*viii*) Inclusion of a halogen atom in the 5-alkyl moiety enhances activity.

(*ix*) Inclusion of polar groups (*e.g.*, OH, CO, COOH, NH_2, *R*NH, and SO_3H) in the 5-alkyl moiety reduces potency considerably.

(*x*) Methylation of one of the imide hydrogens enhances onset and reduces duration of action (*e.g.*, the transition from 5, 5-disubstituted to 1, 5, 5-trisubstituted barbituric acid).

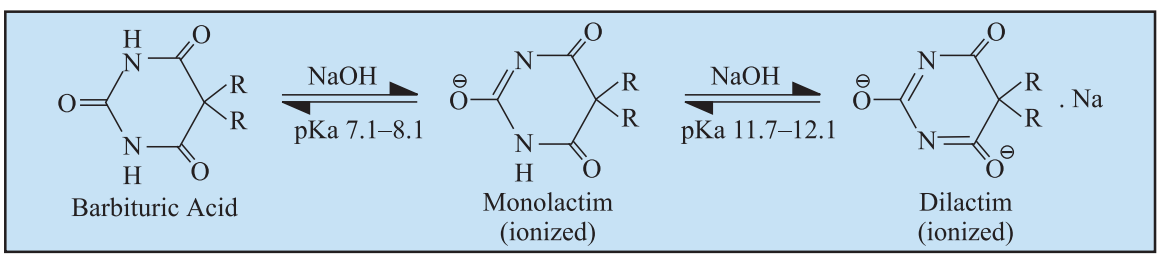
(*xi*) Replacement of sulphur for the carbonyl oxygen at carbon 2 results in thiobarbiturates which exhibit rapid onset and short duration of action because these are readily detoxified.

(*xii*) Inclusion of more sulphur atoms (*e.g.*, 2, 4-dithio ; 2, 4, 6-trithio) decreases activity. Likewise introduction of imino group(s) into the barbituric acids abolishes activity (*e.g.*, 2-imino ; 4-imino ; 2, 4-diimino and 2, 4, 6-triimino).

(*xiii*) Replacement of the hydrogen atom at carbon atoms 1 and 3 with an alkyl group increases the vulnerability of the molecule to tissue oxidation.

7. BARBITURATES *Vs* DISSOCIATION CONSTANT (pKa)

It has been adequately substantiated that the presence of 5, 5-disubstituted barbituric acid essentially comprises of **three lactam moities** which can be circumvented conveniently to pH dependent **lactim-lactam tautomerization** as given under :



Salient Features

The various **salient features** are as follows :

(1) 5, 5-Disubstituted barbituric acids* when subjected to UV-spectrophotometric investigations reveal the following facts, namely :

(*a*) The predominant-forms that usually exist in an aqueous medium are either the **trioxo tautomeric form** (*i.e.*, **barbituric acid configuration in an acid medium**) or the corresponding **dioxo tautomeric form** (*i.e.*, **monolactam in an alkaline medium**),

*Vida JA. In : Foye WO *et al.* **'Principles of Medicinal Chemistry'**, Williams and Wilkinson, Baltimore, 5th edn, 154-180, 2002.

(*b*) In an aqueous medium the '**acidity**' of the barbiturates is solely guided by the number of substituents attached at C-5 of barbituric acid,

(*c*) The following species, such as : 5, 5-disubstituted barbituric acids ; 5, 5-disubstituted thiobarbituric acids ; and 1, 5, 5-trisubstituted barbituric acids are relatively *weak acids.* Besides, the corresponding salts of these **barbiturates** are easily produced by interaction with appropriate bases.

(2) The pKa values of 5, 5-disubstituted barbituric acids usually range between 7.1 to 8.1*.

(3) It has been reported** that 5, 5-disubstituted barbituric acids are capable of undergoing a '**second phase of ionization**' that essentially possess pKa values falling within the range of 11.7 to 12.7.

(4) It has been observed that the **'sodium barbiturates'**, in general, exhibit extremely lipophilic property that may cause **distinct and rapid chemical incompatibility reactions**, such as : precipitation, when such compounds are inadvertently brought in contact with the acid salts of relatively weak basic amines.

8. SUBSTITUTIONS ON HETERO ATOMS IN BARBITURATES

The presence of hetero atoms, such as : N and O in the structure of **barbiturates** play an important role with regard to the wide spectrum of pharmacological activities.

(*a*) **Replacement of Oxygen at C-2.** The replacement of O-atom with an isostere, S-atom, at C-2 position of the barbiturates significantly enhances the lipid solubility profile. The resulting modified versions of the **barbiturates** thus obtained exert a rapid onset of activity by virtue of the fact that they attain **maximal thiobarbiturate-brain levels**. Therefore, such drugs as **'thiopental sodium'** find their profuse and abundant application as **'intravenous anaesthetics'.**

(*b*) **Alkyl group substitution on N^1, and /or N^3.** The careful replacement of one **imide-hydrogen atom** either on N^1 or N^3 by alkyl moieties enhances the lipid solubility profile appreciably. The ultimate outcome of such minor structural modification(s) usually give rise to a rapid onset of action but with a reasonable shorter duration of activity. Importantly, an increase in the size and magnitude of the N-alkyl substituent, for instance : **methyl, ethyl and propyl,** result into products with increasing lipid solubility and decreasing hydrophilic character. Furthermore, no sooner an alkyl functional moiety is attached to the N^1 or N^3 atom the resulting barbiturate gets converted into a non acidic drug molecule thereby rendering it drastically *inactive.* Therefore, focussed modifications at these two pivotal positions (N^1 and N^3) are normally of cardinal significance and enormous potential in the **design of barbiturates** intended to be utilized as **anaesthetics** and **anticonvulsants**.

9. OH^- CATALYZED DEGRADATION OF BARBITURATES

Importantly, **barbiturates** posed certain **serious hydrolytic problems** with regard to their incorporation in the liquid dosage formulations, such as : parenterals and elixirs. It has been duly observed

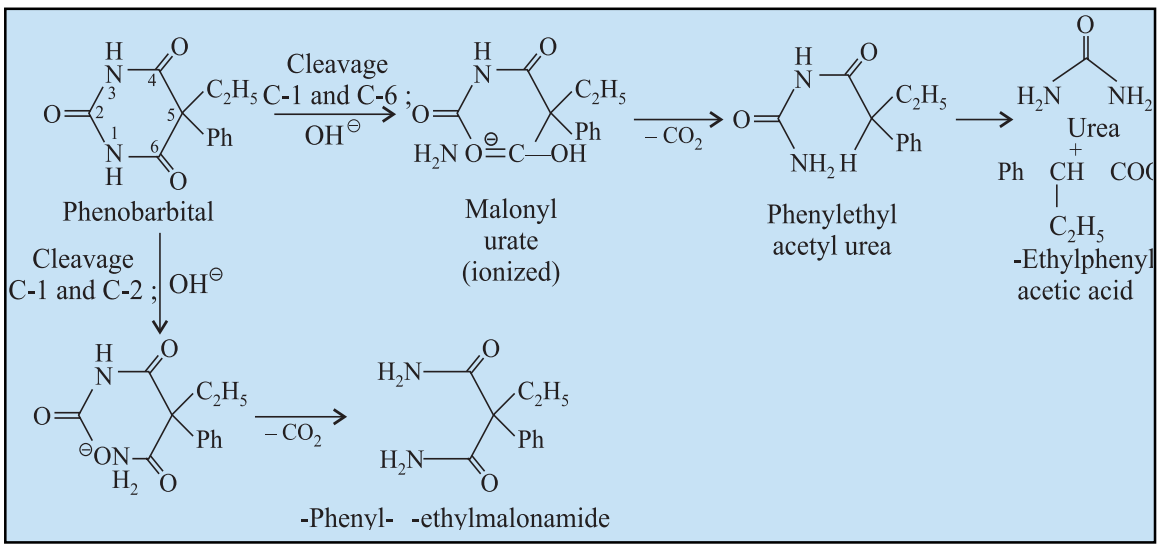
*Butler TC *et al. J. Am. Chem. Soc.*, **77 :** 1488-1491, 1955.

Drayton CJ, ed. In : Hansch C *et al.* eds, **Comprehensive Medicinal Chemistry, Pergamon Press, New York, 1990.

that **'acid solvolysis'** is not the root cause of such encountered problems : whereas the major culprit being the **OH^- catalyzed degradation of the ureide rings** imbedded in the barbiturates.

Example. Phenobarbital [Gardinal$^{(R)}$]. The following scheme vividly explains the base hydrolysis of phenobarbital wherein the cyclic ureide ring (in barbiturate) undergoes cessation. Besides, it may also be seen that the aforesaid cessation strategically takes place either between C-1/C-2 and/or C-1/C-6 locations in the structure of barbiturate. However, the cleavage between C-1 and C-6 is considered to be the most preferred pathway prevailing in the **'ionized barbiturates',** such as : aqueous solutions of sodium salts.

Therefore, to pervent the said cleavage between C-1 and C-6 in phenobarbital it is absolutely necessary to **'stabilize'** its liquid dosage forms (*e.g.*, elixir) at pH 6.0. At this specific pH the resulting **'hydroalcoholic solution'** remains fairly stable.*



A plethora of neutral organic solvents, for instance : sorbitol, glycerol, ethanol invariably employed as **'aqueous cosolvents'** do influence an enormous stabilizing effect on the barbiturate solutions. The most plausible and logical explanation to support the above observations could be due to the much lowered prevailing dielectric constants of the aforesaid *there* solvents that specifically checks the ensuing interactions between the similar charge existing on the **barbiturate anion** and the **hydroxyl ion.**

10. SPECIFIC MECHANISM OF ACTION OF SOME SEDATIVES AND HYPNOTICS

In this section the **'mechanism of action'** of certain drugs already discussed in this chapter shall be explained in *two* categories, namely : (*a*) **Barbiturates** ; and (*b*) **Non-barbiturates**.

[A] **Barbiturates.** The various barbiturates described are as under :

(1) **Phenobarbital.** It gets metabolized upto 65%, mostly to the inactive *para*-hydroxyphenyl derivative ; and upto 35% gets exerted by the kidney totally in unchanged form. However,, the plasma

*A 15-20% (*v*/*v*) ethanol exerts a **'stabilizing effect'.**

clearance is rather slow and generally approximates to 0.004 L kg^{-1} hr^{-1}. The apparent volume of distribution stands at 0.7 to 1 L kg^{-1} ; and the therapeutic plasma levels range between 10 to 30 mcg. mL^{-1}. Nearly 45 to 50% of **phenobarbital** is bound to plasma protein. Consequently, the plasma half-life varies from 50 to 120 hr in adults, whereas in children it ranges between 40 to 70 hr.

(2) **Methylphenobarbital (Mephobarbital).** It is anticonvulsant and sedative of the **barbiturate** class ; and in therapeutic dose levels it exerts practically no significant effect on the modullary centres thereby causing no appreciable alteration either in the blood pressure or the rate of respiration. Hence, the overall action is strong sedative and anticonvulsant actions but having a comparatively quite mild hypnotic activity.

(3) **Ammobarbital.** It has seven total C-atoms duly substituted on the C-5 position, which particularly enables, its ability to penetrate the liver microsomes. Besides, for such hydrophobic drug substance the legitimate partioning out of the brain to other relevant sites may also be involved.

(4) **Pentobarbital sodium.** This specific barbiturate is considered to effectively lower the cerebral blood flow, and thereby minimise substantially either oedema and/or intracranial pressure.

(5) **Quinalbarbitone sodium (Secobarbital Sodium).** It has been observed that within a short span of 2 hours after the oral administration, approximately 90% gets adequately absorbed from the GI tract. The elimination half-life is nearly 30 hours.

(6) **Methohexital sodium.** In this particular instance an induction dose of 1 mg kg^{-1} reliably causes unconsciousness in just 30 seconds. As a results pharmacological effect gets instantly terminated with quick distribution from the brain to the corresponding peripheral sites. Consequently, the recovery from the brain to the corresponding peripheral sites. Consequently, the recovery from methohexital is rather more rapid and there is less myocardial depression observed than with thiopental. Methohexital has been employed extensively to elicit spiking discharges on the EEG* in patients undergoing screening for seizure activity. It is exclusively metabolized in the liver thereby causing induction of **cytochrome enzymes**.

(7) **Thiopental sodium.** A single induction dose of 3 to 5 mg kg^{-1} may cause unconsciousness within a short span of 30 to 40 seconds. Its action is, however, terminated by the immediate redistribution of drug away from the brain. It has been observed that there exists a transient decrease in blood pressure (20%), and a simultaneous compensatory enhancement in the heart rate on injection. Thiopental is largely metabolized in the liver, although the kidney and muscle tissue may participate concurrently.

[B] **Non-Barbiturates :** The *five* **non-barbiturates** discussed are as stated below :

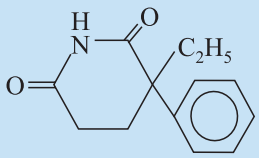
(1) **Methaqualone.** It may cause acroparesthesia (tingling and numbers in the extremities) just prior to the onset of the hypnotic activity, specifically in such situations when sleep does not ensue readily. Large doses of **methaqualone** do not give rise to significant respiratory and cardiovascular depression. **Mandrax**, a combination of **methaqualone** and **diphenylhydramine,** has been profusely abused by addicts in Australia, Canada and United Kingdom. In fact, **methaqualone** has now been banned altogether in several countries, including the United States (1984), by virtue of its abuse potential figured out to be much larger and dangerous to the '**society**' as compared to the corresponding short-acting barbiturates.

(2) **Glutethimide.** This particular **imide** essentially possess several structural relationships with the **'barbiturates',** and hence resembles the latter in many aspects pharmacologically. Based on its severe hydrophiobic nature the absorption from the GI-tract is found to be erratic to a certain extent. It

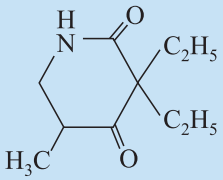
*__EEG :__ Electroencephalogram ;

exhibits an extensive metabolism, and the drug is established to be an **'enzyme inducer'.** Its oral absorption is quite variable, having peak plasma level lasting between 1 to 6 hours. It is observed to induce liver microsomal enzymes ; therefore, it is absolutely important and necessary for patients on coumarin-anticoagulant therapy for readjustment of the coumarin dose level both during and on discontinuation of such therapy. Its elimination half-life varies from 5 to 22 hours, having an average value of 11.6 hours.

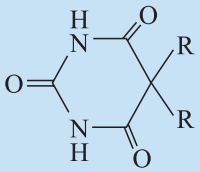
(3) **Methyprylon.** Interestingly, the two **piperidinediones** *viz.*, **glutethimide** and **methyprylon ;** and the **quinazolone** *viz.,* **methaqualone,** are of vital importance within the context of **non-barbiturate sedatives** and hypnotics. However, **glutethimide** and **methyl prylon** possess a striking resemblance to barbiturates as given below :



Glutethimide
[Doriden(R)]



Methyprylon
[Noludar(R)]



Barbiturate
[General Structure]

The **metabolism of methyprylon** is found to be extensive, and the drug is an enzyme inducer. Its pharmacological effects resemble to those of the **barbiturates**.

(4) **Paraldehyde.** It is chiefly detoxified by the liver upto 70–80% and is excreted by the lungs (exhalation) upto 11–28%. It has been observed that only a negligible amount is excreted in the urine. Because the drug has a peculiar strong characteristic smell invariably and prominently detectable in the exhaled air from the lungs along with an **'unpleasant palate'** its usage has been almost restricted exclusively to an institutional setting, such as : in the treatment of **delirium tremens.***

(5) **Nitrazepam.** Generally, the various aromatic nitro functional containing drug substances undergo enzymatic reduction to the corresponding *amines.* Therefore, **nitrazepam**, a 7-nitrodiazepine structural analogue gets metabolized extensively to their respective 7-amino metabolites in humans.**

Probable Questions for B. Pharm. Examinations

1. Explain how the '*cyclic ureide*' barbituric acid may by prepared from :
(*a*) Urea and malonyl dichloride
(*b*) Urea and diethyl malonate.

2. Keto-enol tautomerism exists in parabenic acid and barbituric acid. Explain.

3. Why the 'thiobarbiturates' get metabolized *in vivo* faster than the barbiturates ? Explain.

4. How the long-active barbiturate '*mephobarbital*' can be synthesized from :
(*a*) Urea, and
(*b*) Dicyandiamide

5. Introduction of two similar allyl functions at C-5 in the barbituric acid yields an intermediate acting barbiturate. Name the product and give its synthesis.

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*A dramatic complication of alcoholism.

Rieder J. and Wendt G. : In Garalini S. *et al.* (eds). **The Benzodiazepines, Raven Press, New York, p. 99, 1973.

6. A class of barbiturates find their usuage in the treatment of insomnia and preoperative medication. Name two potent drugs and discuss the synthesis of **one** compound.
7. A brand of barbiturates are usually employed to cause general anaesthesia and control convulsions. Discuss one potent member and explain how it is metabolised *in vivo.*
8. Based on Quinozolinone nucleus a potent hypnotic drug was introduced which subsequently was withdrawn because of its 'abuse'. Name the compound and give its structure.
9. Give the structure, chemical name and uses of a potent non-barbiturate drug having a benzodiazepin nucleus.
10. Explain the following with suitable examples :

    (*a*) Mode of Action of Barbiturates

    (*b*) Structure-activity relationship amongst barbiturates.

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7

Anticonvulsants

Chapter

7

Anticonvulsants

1. INTRODUCTION

Epilepsy is an age-long disease which often involves convulsive seizures. Hippocrates first coined the word **'epilepsy'** derived from the Greek word **epilambanein** (to seize). The common symptoms of epilepsy were not unfamiliar even in the earliest annals of medical lore. Because of the fact that these seizures are usually accompanied by both change in the rate and force of the electric pulsation of the cerebral cortex, epilepsy is supposed to be a condition of *paroxysmal cerebral dysrhythmia.* The principal types of epilepsy are as follows :

Grand mal is normally characterized by complete loss of consciousness, followed by transient muscular rigidity (tonic phase) and ultimately plunges into violent clonic convulsions embracing all voluntary muscles.

In epilepsy of the **petit mal** type usually momentary loss of consciousness prevails. This particular state is free of convulsions. However, occasionally blinking movements of the eyelids and jerking movements of the head or arms are observed. It is pertinent to mention here that this kind of epilepsy is more frequently seen in adolescence.

Psychomotor epileptic seizures normally display outbursts of temper, tantrums, mental apathy and sudden irrational and destructive attitude.

Myoclonic seizures is usually characterized by a rapid rhythmic movement of one side of the palate.

The **'anticonvulsants'** are also termed as **'antiepileptic drugs'** and **'antiseizure drugs'** that are used invariably in the adequate and impressive control and management of CNS disorders essentially characterized by recurrent transient attacks of disturbed brain function which ultimately give rise to motor (convulsive), sensory (seizure), and psychic sequence of events.

In fact, there are *two* school of thoughts who opined the **causes of epilepsy*,** namely :

(*a*) Epilepsy being a single disease entity ; and, therefore, all variants of it usually possess a common cause, and

(*b*) Different kinds of epilepsy originate from various anatomic, chemical, and functional imbalance (disorders).

*Forster FM (ed.) **Report on the Panel on Epilepsy,** WI Univ. of Winconsin Press, Madison, p. 91, 1961.

However, a generalized concerted opinion concluded at the **Symposium on Drug Therapy in Neurologic and Sensory Disease,** was that

"epilepsy is a symtom complex characterized by recurrent paroxysmal aberrations of brain functions, usually brief and self limited".

Jackson sometimes in early 19th century legitimately postulated and adequately substantiated the root cause or genesis of the **'seizures'**.* An intense discharge of **'gray matter'** inside the different portions of the brain virtually kicks off the epileptic seizures. Consequently, it is only a normal response of the brain to initiate the phenomenon of convulsive seizures. Precisely, the ensued discharge of an excessive electrical (nervous) energy has virtually been substantiated by an extensive and intensive brain-wave investigations that was made feasible ultimately by the aid of **electroencephalography (EEG)**.

Interestingly, the establishment of the '**Commission on Classification and Terminology of the International League Against Epilepsy**' in the year 1981 came up with an altogether **new proposal.**** In reality this proposal, advocates a classification of **'epileptic seizures'** exclusively based on *two* cardinal clinical seizure variants commonly observed in patients, namely :

(*a*) **ictal** (seizure induced) electroencephalographic (EEG) expression, and

(*b*) **interictal** (those taking place between attacks or paroxyms) EEG expression.

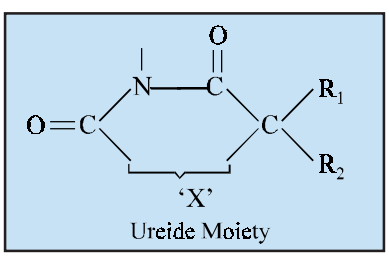
2. CLASSIFICATION

The various **anticonvulsant drugs**, containing essentially the ureide structure (Table 7.1), belong to the chemical categories of **barbiturates, hydantoins, oxazolidinediones** and **succinimides** and lastly the miscellaneous types of compounds possessing such characteristics.

2.1 Barbiturates

Barbiturates as a class of durgs mostly possess sedative and hypnotic properties. Surprisingly only a few of them really show anticonvulsant characteristics. Among the most common barbiturates generally employed as anticonvulsants in clinical use are namely : **phenobarbital**, **mephobarbital** and **methabarbital** (discussed in the chapter on **'Sedatives and Hypnotics'**); of which **phenobarbital** is the drug of choice and is used virtually in all the three types of epileptic seizures *viz*., grand mal, petit mal and psychomotor.

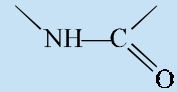
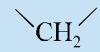
Table 7.1. Anticonvulsant Drugs Containing the Ureide Moiety



Ureide Moiety

*Jackson JH ; In : **Selected Writings of John Hughlings Jackson**, Vol.1., Taylor IJ, (ed). Hodder and Stoughton, London, 1931.

****Proposal for Revised Clinical and Electrocephalographic Classification of Epileptic Seizures, Epilepsia, 22**, 489 (1981).

Group of Compounds	'X'
Barbiturates	
Hydantoins	
Oxazolidinediones	
Succinimides	

Phenobarbital gets metabolized *in vivo* in two different stages ; *first*, by hydroxylation to 5-*p*-hydroxyphenyl-5-ethylbarbituric acid ; and *secondly*, this gets conjugated with either glucuronic acid or sulphuric acid. The metabolic product is ultimately excreted through the urine as its corresponding glucuronide or sulphate salts.

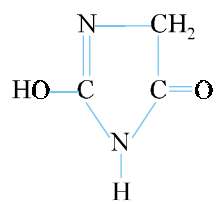
By virtue of its inherent liver-enzyme-inducing characteristic phenobarbital helps in enhancing the metabolism of such drugs that are usually metabolized by the microsomal enzymes.

Mephobarbital loses N-methyl group through metabolism and gets readily converted to **phenobarbital**.

Methabarbital is mostly demethylated to **barbital** *in vivo*. Also it possesses more sedating property than **phenobarbital,** it could be safely recommended for grand mal seizures.

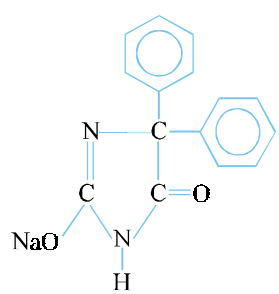
2.2 Hydantoin Derivatives

The following five-membered heterocyclic ring, **hydantoin** is present in the following *three* compounds, namely :



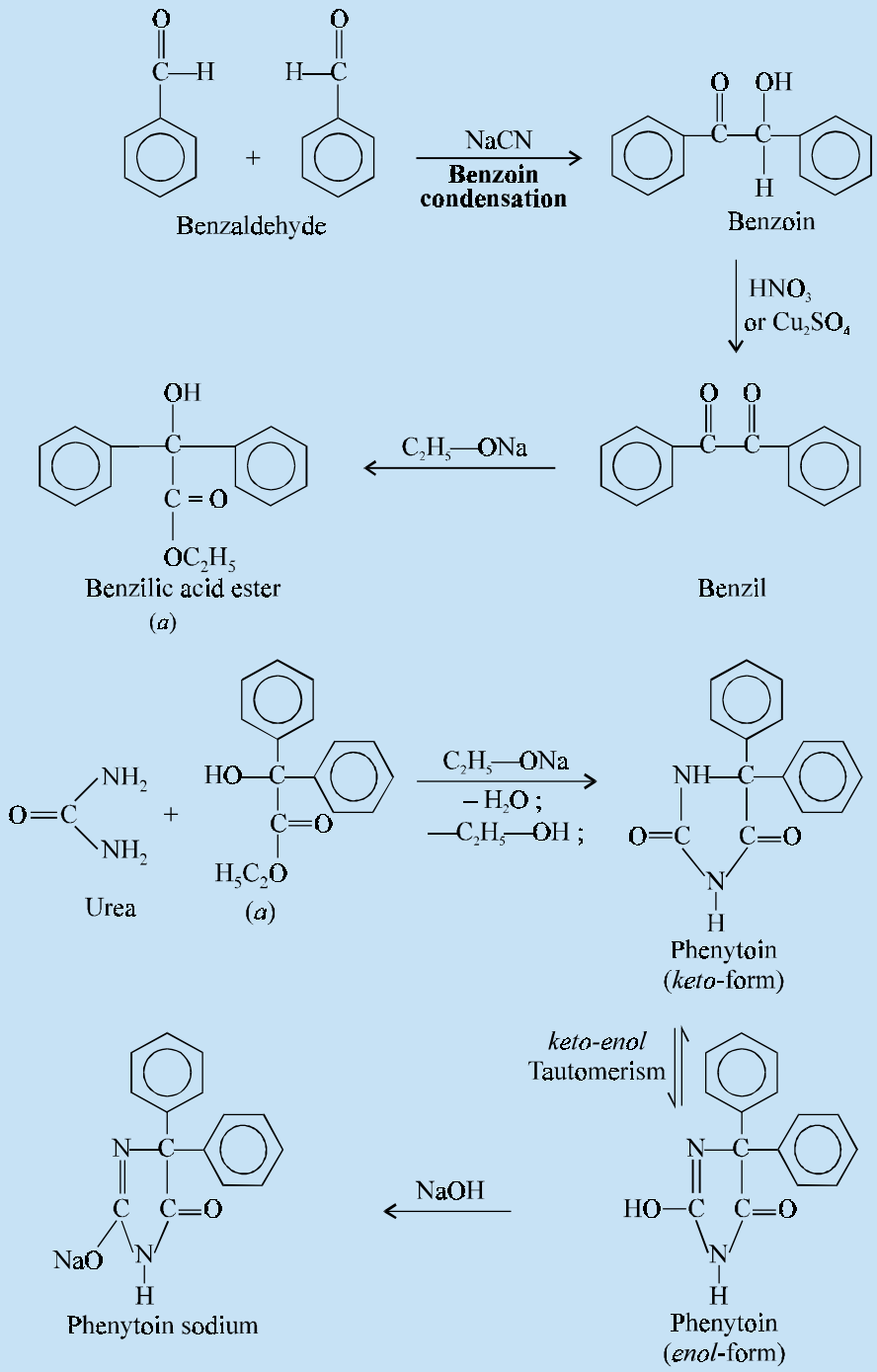
Phenytoin Sodium ; Ethotoin ; and **Mephenytoin.**

A. Phenytoin Sodium USAN, BAN,



5, 5-Diphenylhydantoin sodium salt ; 2, 4-Imidazolidinedione, 5, 5-diphenyl-monosodium salt ; Diphenylhydantoin Sodium ; Diphenin ; Soluble Phenytoin U.S.P., B.P., Eur. P., Ind. P. Diphentoin(R) (Beecham) ; Epanutin Infatabs(R) (Parke-Davis, U.K.) ;

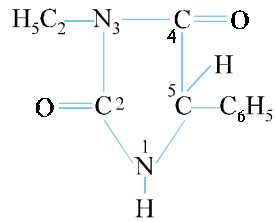
Synthesis



It is prepared by the condensation of two molecules of benzaldehyde with sodium cyanide to get benzoin, which on treatment with nitric acid or cupric sulphate forms benzil. In the presence of sodium ethoxide, benzil in hot condition yields benzilic acid ester. (*a*) The latter on condensation with urea in the presence of sodium ethoxide give rise to **phenytoin** ; the *enol*-form of which on neutralization with sodium hydroxide ultimately results into the formation of **phenytoin sodium.**

Dose : *50 to 100 mg*

B. Ethotoin INN, USAN, BAN,



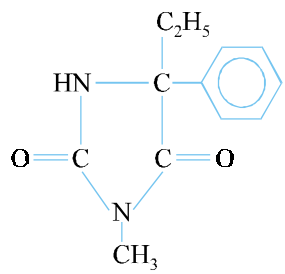
3-Ethyl-5-phenylimidazolidin-2, 4-dione ; 3-Ethyl-5-phenyl hydantoin ; B.P. 1973 ;

Peganone(R) (Abbott, U.K.)

It is an anticonvulsant having uses and actions very much similar to those of **phenytoin**, but comparatively it is less effective.

Dose : *Initial dose 1g per day ; maintenance dose increased by 500 mg at intervals of several days to 2 to 3g per day, given in 4 to 6 divided doses after meals.*

C. Mephenytoin INN, USAN, Methoin BAN,



5-Ethyl-3-methyl-5-phenylhydantoin ; 2, 4-Imidazolidinedione, 5-ethyl-3-methyl-5-phenyl ; Mephenetoin ; Methantoin ; Phenantoin ; B.P. 1973, U.S.P., Ind. P.

It is a **hydantoin anticonvulsant** with actions and uses resembling to those of **phenytoin** but it is found to be relatively more toxic. **On account of its high degree of toxicity it is exclusively given to such patients who do not response to other treatments.**

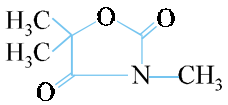
Dose : *Initial 50 to 100mg per day in divided doses ; increased at the rate of 50mg weekly until the optimum dose level ranging between 200 and 600mg per day is reached.*

2.3. Oxazolidinediones

The ureide function present in **oxazolidine-2, 4-dione** depicts a close resemblance to hydantoin, differing only in the replacement of NH moiety in the latter by an oxygen atom at C_1.

A few important members of this class of compounds are discussed below :

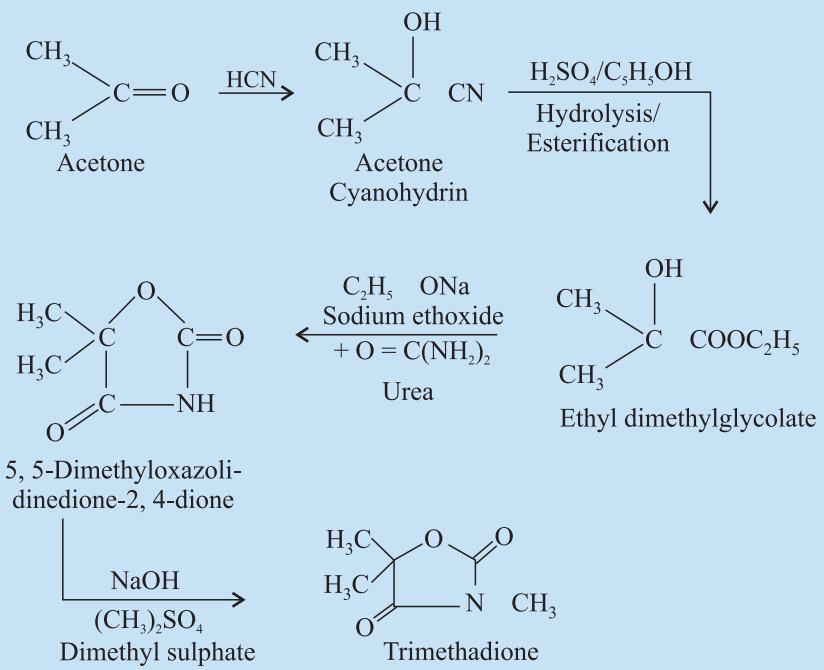
A. Trimethadione INN, USAN, Troxidone BAN,



3, 5, 5-Trimethyl-2, 4-oxazolidinedione ; 2, 4-Oxazolidinedione, 3, 5, 5-trimethyl ; B.P., U.S.P., Int. P., Ind. P.

Tridione$^{(R)}$ (Abbott) ;

Synthesis



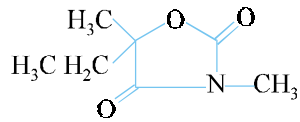
Acetone cyanohydrin is obtained from the interaction of acetone and hydrocyanic acid, which on subsequent hydrolysis followed by esterification with ethanol yields ethyldimethylglycolate. This is condensed with urea in the presence of sodium ethoxide to yield 5, 5-dimethyl-oxazolidinedione-2, 4-dione. **Trimethadione** is finally obtained by treating the resulting product with dimethyl sulphate in the presence of sodium hydroxide.

It is employed as an **anticonvulsant** in grand mal epilepsy to arrest status epilepticus and in petit mal epilepsy as a means of resisting control to other treatments. When administered alone trimethadione

may not be effective to contain the situation in petit mal epilepsy, but it may be useful when given in conjunction with phenytoin sodium and/or phenobarbital in petit mal seizures. It may be used occasionally in the treatment of behaviour problems encountered in children, status epilepticus and athetoses.

Dose : *900 mg to 2.4g per day ; usual, 300 to 600 mg 2 to 4 times daily.*

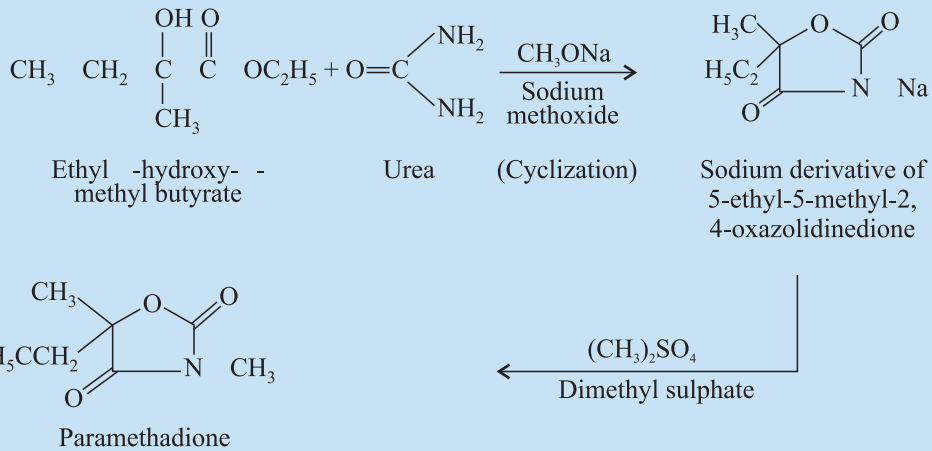
B. Paramethadione INN, BAN, USAN,



5-Ethyl-3, 5-dimethyl-2, 4-oxazolidinedione ; 2, 4-Oxazolidinedione, 5-ethyl-3, 5-dimethyl- ; Paramethad ; B.P. 1973, U.S.P., Ind. P.

Paradione(R) (Abbott) ;

Synthesis



Sodium derivative of 5-ethyl-5-methyl-2, 4-oxazolidinedione is obtained by refluxing urea and ethyl-α-hydroxy-α-methylbutyrate for 24 hours in the presence of sodium methoxide, due to condensation followed by cyclization. N-methylation is carried out by treatment with dimethyl sulphate.

It is usually used in the treatment of petit mal epilepsy and possesses similar actions to those of trimethadione. It is relatively less effective and does not exhibit *myasthenia-gravis-like syndrome* in patients.

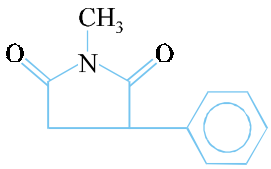
Dose : *300 mg to 2.4g daily ; usual, 300 mg 3 to 4 times per day.*

2.4. Succinimides

Due to the inherent high-level of toxicity attributed by the **oxazolidinediones** in prolonged therapy as **anticonvulsants a** vigorous attempt was made to replace them with better effective and less toxic drugs.

Three members of this class of compounds were introduced between early fifties to late fifties, namely ; **Phensuximide, Methsuximide** and **Ethosuximide.** All of them gained with acceptance for the treatment of petit mal seizures specifically.

A. Phensuximide INN, BAN, USAN,

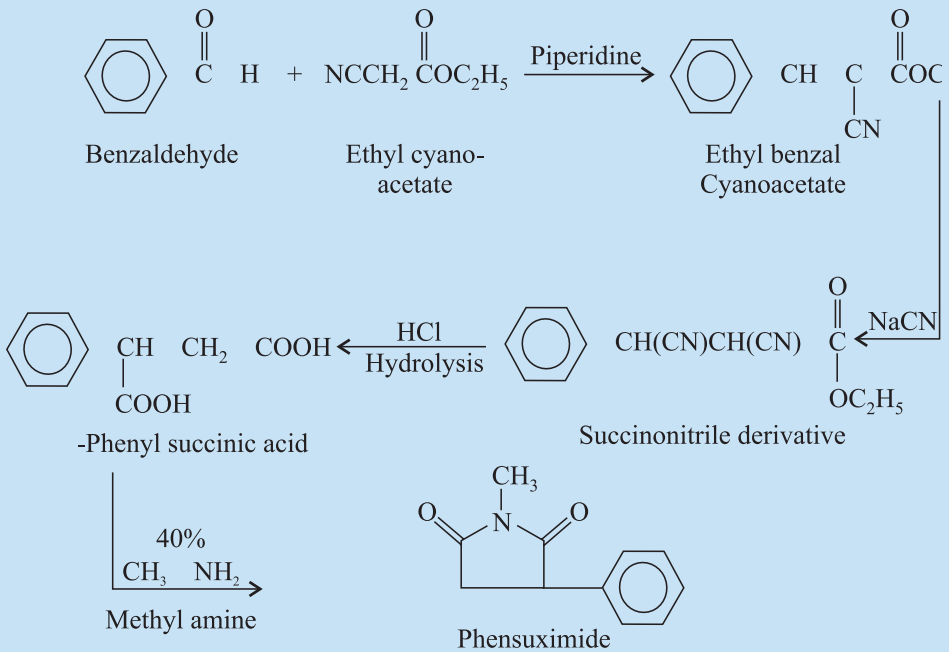


N-Methyl-2-phenylsuccinimide ; 2, 5-Pyrrolidinedione, 1-methyl-3-phenyl ; Fensuximid ;

B.C.P. 1973, U.S.P.

Milontin$^{(R)}$ (Parke-Davis)

Synthesis

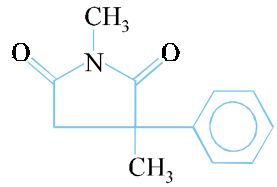


Ethylbenzal cyanoacetate is prepared by reacting together benzaldehyde and ethyl cyanoacetate in the presence of piperidine, which on treatment with sodium cyanide yields the corresponding succinonitrile derivative. This on hydrolysis in an acidic medium (HCl) gives rise to α-phenyl succinic acid which is dissolved in an excess of 40% methylamine to give **phensuximide.**

It is frequently employed in the treatment of petit mal epilepsy. The arrest of such convulsive seizures is normally caused by depression of the motor cortex together with significant elevation of the threshold of the central nervous system to convulsive stimuli. It is relatively less effectiev than **paramethadione** and **trimethadione.**

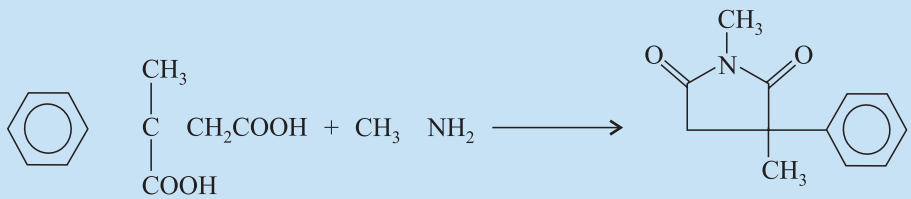
Dose : *500 mg to 1g 2 to 3 times per day for any age.*

B. Mesuximide INN, Methsuximide BAN, USAN,



N, 2-Dimethyl-2-phenylsuccinimide ; 2, 5-Pyrrolidinedione, 1, 3-dimethyl-3-phenyl-, U.S.P., Celontin(R) (Parke-Davis)

Synthesis



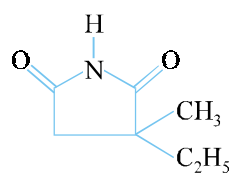
2-Methyl-2-phenyl-succinic acid | Methylamine (40%) | Mesuximide

It is conveniently prepared by the interaction of 2-methyl-2-phenyl succinic acid with excess of 40% methylamine. The excess of amine and water are distilled off under reduced pressure. The residue containing the dimethylamine salt of the acid is pyrolyzed at 250°C until no more distillate is obtained. The crude product is dissolved in an appropriate solvent, treated with activated charcoal and finally precipitated by the addition of water.

It is found to be more effective and potent than **phensuximide** in the cure of petit mal epilepsy and psychomotor seizures.

Dose : *Initial, 300 mg per day ; maintenance 0.3 to 1.2g daily.*

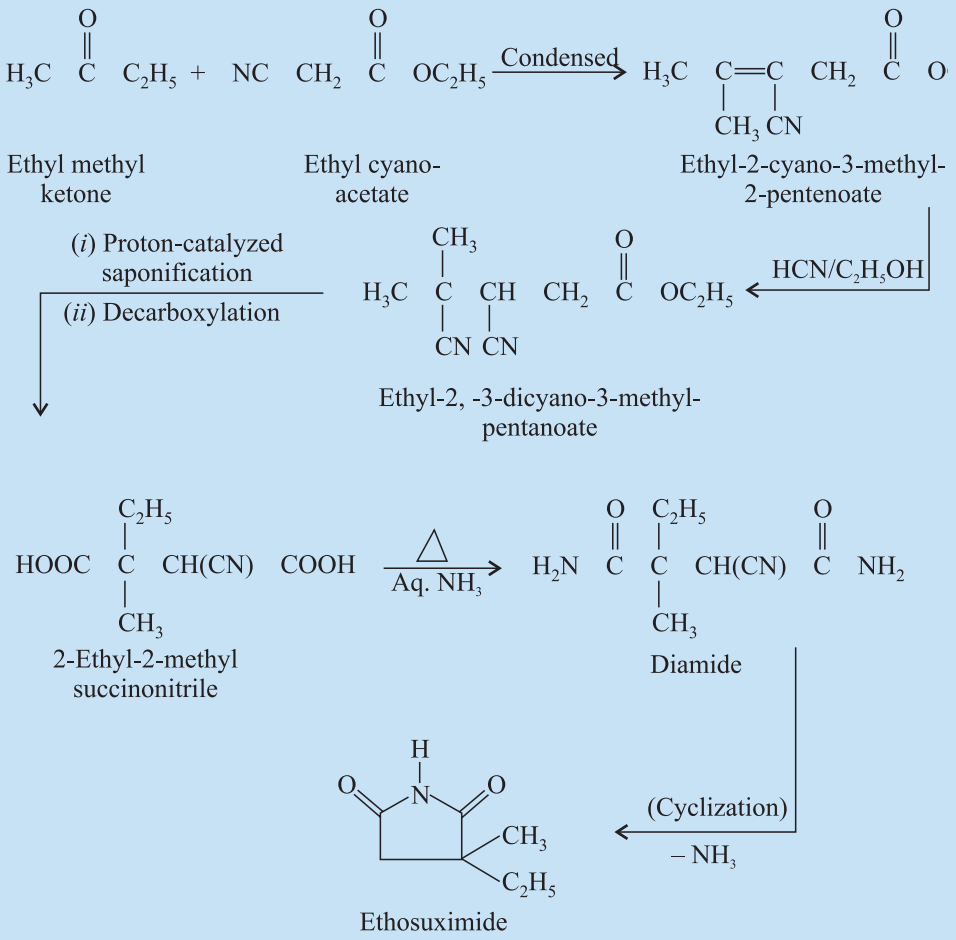
C. Ethosuximide INN, BAN, USAN,



2-Ethyl-2-methylsuccinimide ; 2, 5-Pyrrolidinedione, 3-ethyl-3-methyl ; B.P., U.S.P.

Zarontin(R) (Parke-Davis)

Synthesis



Ethyl 2-cyano-3-methyl-2-pentenoate is first prepared by the condensation of ethyl methyl ketone and ethyl cyanoacetate, which in ethanolic solution takes up a molecule of hydrogen cyanide according to **Markownikoff's Rule** to yield ethyl-2, 3-dicyano-3-methyl pentanoate. This upon protoncatalyzed saponification and subsequent decarboxylation gives rise to 2-methyl-2-ethyl succinonitrile, which on heating with aqueous ammonia produces the corresponding diamide. Finally, the diamide undergoes cyclization, through loss of ammonia to give **ethosuximide**.

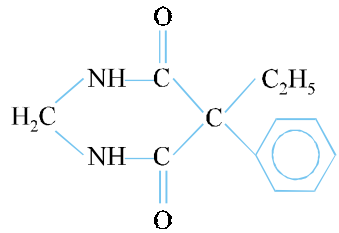
It has the reputation for being the most effective **succinimide analog** in petit mal therapy. It acts by suppressing the EEG pattern of petit mal epilepsy perhaps by depression of the motor cortex and raising the convulsive threshold. Combined drug therapy with either **phenobarbital** or **phenytoin** sodium is common in cases where petit mal co-exists with grand mal or other types of epilepsy.

Dose : *500 mg per day, in divided doses.*

2.5. Miscellaneous

A number of compounds bearing different miscellaneous basic chemical structures have been found to possess significant anticonvulsant properties. A few such compounds are dealt with in this section, namely ; **Primidione, Phenacemide, Carbamazepine, Sultiame, Valproic acid, Clonazepam.**

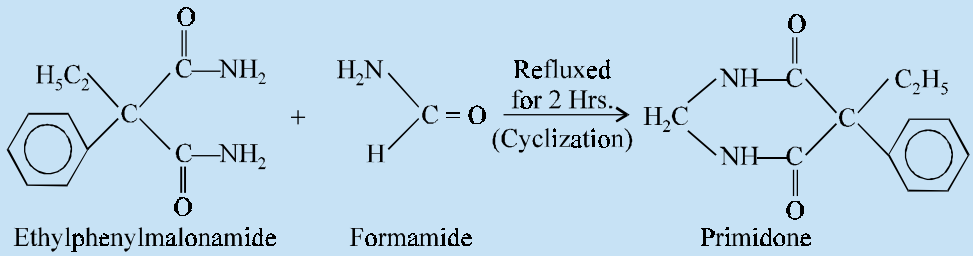
A. Primidone INN, BAN, USAN,



5-Ethyldihydro-5-phenyl-4, 6(1H, 5H)-pyrimidinedione ; 4, 6 (1H, 5H)-Pyrimidinedione, 5-ethyldihydro-5-phenyl- ; Primaclone ; B.P., U.S.P., Int. P. Ind. P.

Mysoline(R) (Ayerst)

Synthesis



It may be prepared by refluxing together a solution of ethylphenyl-malonamide with a large molar excess of formamide for 2 hours. The probable mechanism of this cyclization may be viewed to have taken place at three different stages, namely : Cannizzaro type of disproportionation of formamide, deammoniation and dehydration between ethylphenylmalonamide and the resulting highly virile methanolamine.

Primidone is a potent **anticonvulsant** which may be chemically regarded as a 2-deoxy analogue of phenobarbital. It is used either in conjunction with other antiepileptics or alone in the treatment and arrest of psychomotor, grand mal and focal epileptic seizures.

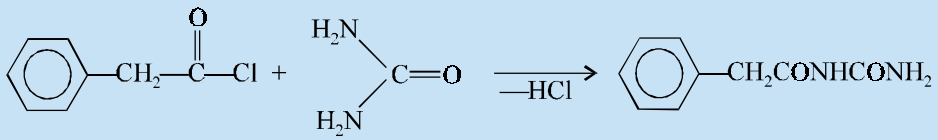
Dose : *500 mg per day, gradually increasing to a maximum of 2g daily.*

B. Phenacemide INN, BAN, USAN,

Phenylacetyl urea ; Benzeneacetamide, N-(aminocarbonyl)- ; U.S.P.

Phenurone(R) (Abbott)

Synthesis



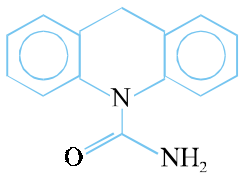
Phenylacetyl chloride Urea Phenacemide

It is readily prepared by reacting phenylacetyl chloride and urea with the elimination of a molecule of hydrogen chloride.

It is mainly used in the psychomotor type of seizure ; it is of relatively lesser therapeutic value in petit mal, grand mal and in mixed seizures.

Dose : *0.5 g, oral, 3 times daily with meals.*

C. Carbamazepine INN, BAN, USAN,



5H-Dibenz [*b, f*] azepine-5-carboxamide ; B.P., U.S.P.

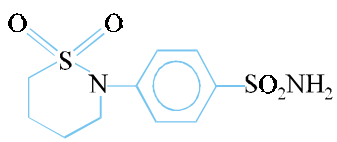
Tegretol(R) (Ciba-Geigy)

Carbamazepine essentially contains a dibenzazepine ring system with a carbamoyl moiety hooked on to the nitrogen atom.

It is an **anticonvulsant** employed in the treatment of grand mal and psychomotor epilepsy. It is considered to be one of the most vital drugs for the relief of pain associated with trigeminal neuralgia.

Dose : *200 mg per day, increasing to 1.2 g daily, in divided doses.*

D. Sultiame INN, Sulthiame BAN, USAN,



p-(Tetrahydro-2H-1, 2-thiazin-2-yl)-benzenesulphonamide, S, S-dioxide ; Benzenesulfonamide, 4-(tetrahydro-2H- 1, 2-thiazin-2-yl)-, S, S-dioxide B.P.

Conadil(R) (Riker) ; Ospolot(R) (Bayer)

It is a carbonic anhydrase inhibitor which is employed as an anticonvulsant in all types of epilepsy except petit mal seizures. However, it has been shown to elicit a favourable response in the management of myoclonic seizures, hyperkinetic behaviour and focal epilepsy than in controlling grand mal seizures.

Dose : *600 mg per day in divided doses.*

E. Valproic Acid INN, USAN, Valproate Sodium USAN, Sodium Valproate BAN,

Valproic acid Sodium Valproate

Sodium 2-propylvalerate ; Pentanoic acid, 2-propyl-, sodium salt ; Valproic acid U.S.P.,

Depakene(R) (Abbott) ; Abbott 44089(R) (Abbott) ; Sodium Valproate B.P., Abbott 44090(R) (Abbott)

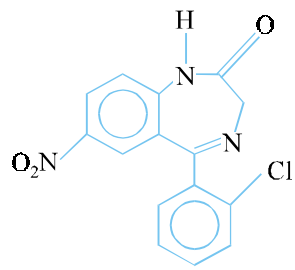
Valproate sodium was discovered when it showed moderately effective antagonistic property in experimental animal seizures induced chemically and electrically. It also possessed reasonably satisfactory margin of safety.

It is frequently employed as an **anticonvulsant** in the management and treatment of grand mal, petit mal, mixed and temporal lobe epilepsy.

Its mechanism of action may be related to increased brain levels of the inhibitory neurotransmitter **Gamma-aminobutyric acid (GABA).** This increase in brain content of **GABA** is probably due to the inhibition by valproate sodium of the enzymes that **metabolize GABA**.

Dose : *10 mg per day initially ; 20 to 25 mg daily maintenance dose.*

F. Clonazepam INN, BAN, USAN,



5-(*o*-Chlorophenyl)-1, 3-dihydro-7-nitro-2H, 1, 4-benzodiazepin-2-one ; 2H-1, 4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1, 3-dihydro-7-nitro ; U.S.P.

Clonopin(R) (Hoffman-La Roche)

Clonazepam a benzodiazepine is effective in all types of epilepsy *viz.*, grand mal, psychomotor, petit mal, myoclonic and *status epilepticus.* However, diazepam another **benzodiazepine** is preferred in *status epilepticus.* It possesses minor side effects.

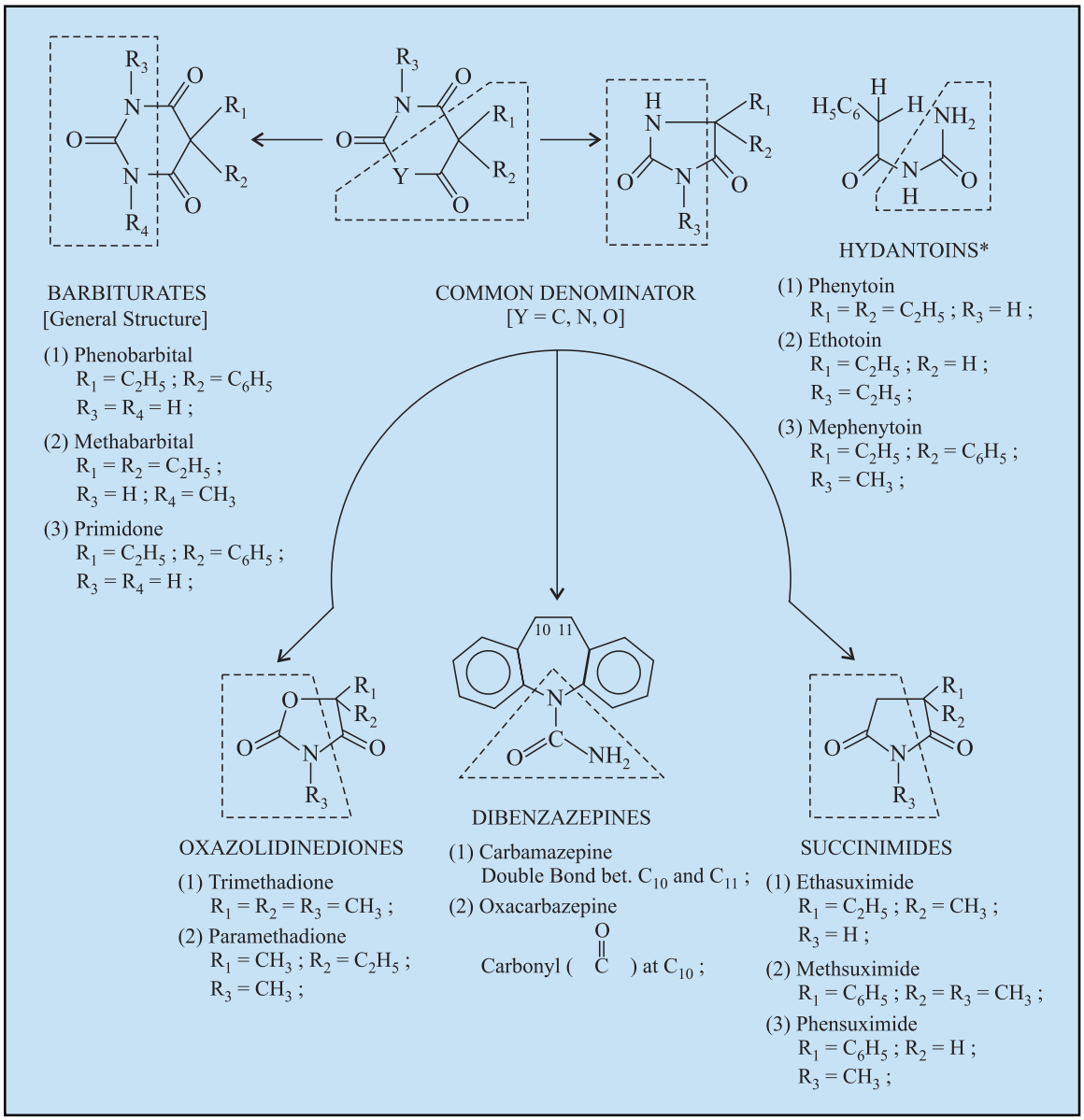
Dose : *Usual, adult, oral 4 to 8 mg daily in 3 or 4 divided doses.*

3. CHEMOTHERAPY* OF EPILEPSY

The actual **chemotherapy of epilepsy** dates back to 1850s with the introduction of **'inorganic bromides'.** It is, however, worthwhile to state here that the therapeutic gainful application of **'phenobarbital'** around 1920s virtually made an epoch making meaningful treatment of epilepsy. Almost within a span of two decades the wonderful contributions made by Merritt and Putman were recognized when they discovered that the **'5-substituted hydantoins'** successfully capable of suppressing the electrically induced convulsions in the laboratory animals. This ultimately paved the way towards the synthesis of **5, 5-diphenylhydantoin** (or **phenytoin**) which possessed the best as well as least sedative activity.

*__Chemotherapy :__ In the treatment of disease, the application of chemical reagents that have a specific and toxic effect on the disease-causing microorganism.

Interestingly, between 1940 and 1960 a plethora of structurally related chemical agents were synthesized based on the **'common denominator'** structure model as illustrated explicitely below :



Salient Features : The salient features with respect to the structural variants in chemical relationships amongst the **'anticonvulsants'** are as given under :

(1) The ketonic function strategically located in between the nitrogens is reduced to a methylene (—CH_2) function.

*__Hydantoins :__ Also known as Imidazole-2, 4-diones.

(2) **Hydantoins** essentially have the **'imidazole-2, 4-diones'** moiety.

(3) In dibenzazepines as **'epoxide-ring'** at C—10 and C—11 gives rise to an **active metabolite.**

(4) Based on the **'common denominator'** analogical structures, as shown earlier, quite a few chemically related **'anticonvulsants'** were meticulously designed, synthesized, tested and marketed. However, all these different categories of drug substances belonging to **barbiturates**, **hydantoins**, **oxazolidinediones**, **dibenzazepines**, and **succinimides** result into potential **'anticonvulsants'.** It is pertinent to state here that both **oxazolidinediones** and **succinimides** very much uphold this ideology and concept provided one take into cognizance the biosteric replacement of one of the N-atoms with O-atom and C-atom respectively. Furthermore, one should view **'phenacemide'** as an **open-chain (acyclic) hydantoin analogue**.

(5) The various structural variants having an **'uriedo-type moiety'** yield the following major class of **'anticonvulsants',** namely :

Class	Examples
Barbiturates	Phenobarbital ; Methabarbital ; Primidone etc.
Hydantoins	Phenytoin ; Ethotoin ; Mephenytoin etc.
Succinimides	Methsuximide ; Ethasuximide ; Phensuximide etc.
Oxazoldinediones	Trimethadione ; Paramethadione etc.
Dibenzazepines	Carbamazepine ; Oxacarbazepine etc.

4. MECHANISMS OF ACTION FOR THE ANTICONVULSANTS

A seizure is a sudden attack of pain, a disease or certain symptoms which could be due to bursts of **abnormal synchronous discharging** caused by a network of neurons. It is quite obvious that till date no exact mechanism(s) of seizure induction could be explained scientifically, but the following possible reasonings may be put forward, such as :

- ✦ Unusual triggering of the neuronal ion-channels
- ✦ Lack of balance existing between excitatory and inhibitory synaptic function
- ✦ Different antiseizure drugs (ASDs) or **anticonvulsants** usually display various combined activities on the neuronal function thereby exerting very specific and selective action against the broad range of prevailing seizures, such as :

(*i*) Ion Channels :

(*ii*) Synaptic Inhibition and Excitation, and

(*iii*) Aberrant Calcium Signalling.

These *three* **mechanisms of action** for the **anticonvulsants** shall now be discussed briefly in the sections that follows :

[A] Ion Channels :

It has been observed that both the Na^+ and Cl^- ions are invariably present at much higher concentration **'outside the cell',** whereas K^+, charged proteins, and organic cations are more abundantly available very much **'inside the cell'.** It is an universal fact that only the smaller ions can permeate through the membrane, whereas the larger ions or proteins fail to do so ; therefore, the neuronal membranes

normally maintain and sustain the phenomenon of charge separation. Consequently, a **'resting potential'** having a range of – 50 mV to – 80 mV usually gets established between the inside and outside of the cell.

At this juncture *two* different situations may arise :

(*a*) **Enhancement in Interior Negativity :** It is also known as **'hyperpolarization',** which lowers the resting potential down to – 90 mV, thereby rendering it much more difficult for a neuron to accomplish the desired threshold and ultimately fire (*i.e.*, trigger its action), and

(*b*) **Reduction in Interior Negativity :** It is usually termed as **'depolarization',** that may essentially cause generation of an **'action potential',** in case, the extent of depolarization is just enough to accomplish a threshold value nearly – 40 mV. At this point in time the **'neuronal firing'** is commenced by an influx of Na^+ ions.

[B] Synaptic Inhibition and Excitation :

The actual requirement for a neuron, whether or not an **'action potential'** is accomplished exclusively governed by the achievable equilibrium (or balance) between the prevailing excitatory and inhibitory stimulation. It has been established beyond any reasonable doubt that **GABA** is solely responsible as the predominant inhibitory transmitter in the brain. The *modus operandi* are as stated below :

- synthesized by glutamic acid (an amino acid) and glutamic acid decarboxylase (GAD - an enzyme)
- inactivated by GABA-transaminase (GABA-T)
- GABA binds to two receptor types *viz.*, $GABA_A$ and $GABA_B$
- neuronal *'hyperpolarization'* is caused when $GABA_A$ receptors takes place on Cl^- ion channels, and subsequently the binding of GABA results into chloride influx.
- linkage of $GABA_B$ receptors with G proteins ; besides second messangers to Ca and K channel activity, — also meditating inhibition in the **CNS**.*
- the oscillation rhythms in certain types of epilepsy is solely caused by **$GABA_B$ receptors**.**
- plethora of antiseizure drugs (ASDs) are found either to potentiate GABA-mediated inhibition or to affect GABA concentration to a great extent.
- both barbiturates and benzodiazepines augment the activity of GABA precisely on the $GABA_A$ chloride channel.
- activation of such ligand-gated channels *viz.*, excitatory transmission of glutamic acid *via* **α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) ; N-methyl-D-asparate (NMDA)** ; and kainate receptors appreciably helps both Ca and Na *influx*, and K *efflux* thereby the phenomenon of depolarization gets facilitated.

[C] Aberrant Calcium Signalling :

It has been amply demonstrated that the T-type calcium currents, at low-threshold levels, play a pivotal role as **'pacemakers'** to maintain and sustain the usual normal brain activity. Furthermore, the thalamic oscillatory currents, believed to be intimately associated with the normal brain activity, help in the generation of **absence seizures**.***

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*Jones KA *et. al. Neuropsychopharmacology*, **23,** (4 suppl.) : S41-9, 2000.

Bal T *et al. J. Neuro Sci.*, **20, 7478-88, 2000.

***Browne TR *et. al.*, : In **Hand book of Epilepsy,** Lippincott Williams and Wilkins, New York, 2nd, edn, 1-18, 1999.

Examples : Oxazolidinediones and **ethosuximide** that specifically prevent and check T-type currents, are recognized to be very effective against the **'absence seizures'**, whereas absolutely ineffective against either partial or other seizure types.

5. SPECIFIC MECHANISMS OF SELECTED ANTICONVULSANTS

The **specific mechanism of actions** by which certain selected **anticonvulsants** dicussed in this chapter are enumerated below :

5.1. 5, 5-Diphenylhydantoin Sodium (Phenytoin Sodium)

It is found to exert its action on the motor cortex where it stabilizes the neuronal membrane and thereby inhibits the spread of the seizure discharge. Present evidence also suggests that it limits high frequency repititive firing by blocking Na^+-channels in a use and frequency dependent fashion. Besides, it enhances Ca- binding to the phospholipids present in neuronal membranes.

In fact, these effects collectively give rise to a more stable membrane configuration. Importantly, these critical findings are found to be in perfect harmony with the glaring and supportive fact that its most easily demonstrated characteristic features are by virtue of its ability to limit the development of maximal seizure activity and also to minimize the virtual extension of the seizure phenomenon from the active focus. Interestingly, both of these splendid features in phenytoin are very much related to the clinical usefulness beyond any reasonable doubt.

5.2. Ethotoin

It is N-dealkylated and *para*-hydroxylated *in vivo.* However, the N-dealkyl metabolite is most presumably the **'active compound' ;** it is similarly metabolized by *para*-hydroxylation, and the resulting hydroxyl function undergoes conjugation subsequently.

This particular **'drug substance'** is used against not-so-specific seizures, but invariably on an adjunctive basis on account of its **low potency.** In a broader perspective, such anticonvulsants which are *not* completely branched on the appropriate C-atom are of definite lower potency than their rather more fully-branched structural analogues.

5.3. Mephenytoin

It is metabolically N-dealkylated to the corresponding **5-ethyl-5-phenylhydantoin,** which is considered to be the **'active agent'.** Interestingly, the said metabolized product, happens to be the **'hydantoin counterpart'** of **phenobarbital [Gardinal$^{(R)}$]** as one of the first breed of hydantoins ever introduced into the therapeutic armamentarium. Furthermore, it may be assumed that *'mephenytoin'* is a *'pro-drug'*, that essentially ameliorates a part of its toxicity along with skin and blood disorders of serious nature of the delivered **'active drug'.** The metabolic inactivation of this drug and its corresponding dimethylmetabolite is caused due to the *para*-hydroxylation and subsequent conjugation of the free hydroxyl moiety.

5.4. Trimethadione

It is believed to get metabolized by N-demethylation to the much reputed **'active metabolite' dimethadione***, which is a water-soluble and slowly lipophilic **'drug substance'**. Dimethadione is usually excreted as such without any further metabolic degradation.

5.5. Paramethadione

Though it is closely related to trimethadione in its structural aspect yet it may be safer. It has been observed that the corresponding N-demethyl metabolite, that subsequently gets excreted very sluggishly and slowly, is actually considered to be the **'active drug'.**

*Spinks A and Waring WS. In : Ellis GP and West GB (eds) **Progress in Medicinal Chemistry,** Butterworth, Washington DC. Vol. 3, p. 261, 1963.

5.6. Phensuximide

It has been duly observed that to a certain extent nutrition **(trophism)** towards antiabsence activity may be caused by the imbedded **'succinimide system'.** Besides, the methylene ($-CH_2-$) function could be viewed very much like an ***'α-alkyl branch'*** condensed into the ring system. Particularly, the inherent phenyl substituent grants certain degree of activity against the generalized tonic-clonic and partial seizures. However, the resulting N-demethylation takes place to give rise to the formation of the **'putative active metabolite'.** Evidently, the parent drug, phensuximide, and the N-dimethyl metabolite are virtually inactivated by either conjugation and/or *para*-hydroxylation.

5.7. Methsuximide

The parent compound and the metabolite are both subjected to N-demethylation and *para*-hydroxylation.

5.8. Ethosuximide

A certain portion of the drug is excreted intact through the kidney. However, the major metabolite is actually produced by oxidation of the ethyl group. It conforms quite closely to the general structural pattern for the **'antiabsence activity'.** It is observed to be much more active and comparatively less toxic than trimethadione. Therefore, it has gained cognizance as a drug of choice for acute absence seizures.

5.9. Primidone

It gets metabolized to **phenylethyl malonamide (PEMA)** and **phenobarbital*** (an active long-acting barbiturate). The actual formation to phenobarbital varies between 15-25%. The plasma half-life of **PEMA** ranges between 24-48 hours, whereas that of phenobarbital is 48-120 hours. However, the two aforesaid metabolites have a tendency to exert a cumulative storage in the body particularly during chronic medication. **Primidone** is quite often described as a **2-deoxybarbiturate.**

5.10. Phenacemide

It gets metabolized by *para*-hydroxylation. It is pertinent to mention here that this *'drug'* must be employed *only* in such instances wherein the patients failed to respond to other anticonvulsant treatment (medication). However, one must exercise extreme caution in the treatment of patients who have a previous history (or record) displaying *liver dysfunction, personality disorder,* and *allergic manifestation.*

5.11. Sultiame

It exerts its action by inhibiting specifically the **carbonic anhydrase**.

5.12. Valproate Sodium

Importantly, its precise mechanism of its **anticonvulsant** action is still not fully understood. However, it has been duly advocated that its administration specifically inhibits **GABA-transaminase**, and thereby enhancing the concentration of cerebral **GABA.** It has also been observed that a few other straight-chain saturated fatty acids *i.e.*, lower fatty acids, such as : propanoic acid, butyric acid, and pentanoic acid which are devoid of **anticonvulsant** characteristic features are relatively more potent and efficacious inhibitors of **GABA-transaminase** than is valproic acid. Furthermore, it has been adequately substantiated that there exists a rather stronger correlation between the anticonvulsant potency of valproate and other branched-chain fatty acids ; besides, their capability to minimise the prevailing concentration of cerebral aspartic acid (an amino acid).

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*Spinks A and Waring WS. In : Ellis GP and West GB (eds) **Progress in Medicinal Chemistry,** Vol. 3. p. 261, Butterworth, Washington DC, 1963.

Further evidences reveal that **valproate sodium** may also decrease binding to certain serum proteins or block the hepatic metabolism of **phenobarbital.** Therefore, administration of the **'drug'** to patients in a steady state, while on **phenobarbital** concurrently (or **primidone**, which gets metabolized to **phenobarbital**) may enhance the plasma levels of **phenobarbital** from 35-200%, a quantum jump, thereby causing an excessive **somnolence.*** However, the present evidence amply substantiates that this is caused exclusively by an immediate lowering in the prevailing rate of elimination of **phenobarbital.**

5.13. Clonazepam

It is a partial against at **benzodiazepine allosteric binding sites on $GABA_A$ receptors.** The metabolism essentially invovles hydroxylation of the 3-position followed by glucuronidation and nitro group reduction, followed by acetylation ultimately. It has been observed that almost 87% of the drug is bound to plasma protein ; volume distribution is 3.2 $L.kg^{-1}$, and its half-life ranges between 19 to 46 hours in adults and from 13 to 33 hours in children. Its concomitant use with valproate may cause absence status.

Probable Questions for B. Pharm. Examinations

1. Classify the drugs used for convulsive seizures. Give the structure, chemical name and uses of one important compound from each class.
2. Explain '*Hydantoins*' as potent anticonvulsants. Give the synthesis of Diphentoin$^{(R)}$ (Beecham).
3. Discuss paramethadione as a therapeutic agent used in petitmal epilepsy.
4. 'Succinimides afford better tolerated and less toxic anticonvulsants'. Justify the statement with the help of a detailed account of one of the potent compounds belonging to this category.
5. Name the anticonvulsant drug obtained by replacing 'O' at C-2 of phenobarbital with 2H atom. Give its synthesis and uses.
6. Give an account of an anticonvulsant having a dibenzaepine ring system wtih a carbamoyl moiety hooked on to the N-atom.
7. Discuss the relative structural differences occuring amongst Phensuximide, Methsuximide and Ethosuximide. Give their chemical names, uses and advantages of one over the other.
8. Describe the mode of action of Hydantoins and Primidone inside the body.
9. How do the mode of action of oxazolidinediones and succinimides differ from hydantoins ?
10. Discuss a **Benzodiazepine based anticonvulsant** which possesses a broad-spectrum activity.

RECOMMENDED READINGS

1. DM Woodbury, J K Penry and R P Schmidt (ed.) **Antiepileptic Drugs**, Raven Press New York, (1972).
2. E Jucker, **Some New Developments in the Chemistry of Psychotherapeutic Agents** *Angew Chem* (*int* ed.) (1963).
3. Gennaro Alfonso R, Remington : **The Science and Practice of Pharmacy,** Lippincott Williams and Wilkins, New York, 20th end., 2000.

*Prolonged drowsiness or a condition resembling a trance that may continue for a number of days.

4. JA Vida (*Ed*), **Anticonvulsants, In : Medicinal Chemistry, A Series of Monographs,** Vol. 15, Academic Press, New York, (1977).
5. JEP Toman and J D Taylor, **Mechanism of Action and Metabolism of Anti-convulsants,** *Epilepsia* I (1952)
6. JEP Toman and L S Goodman, **Anti-convulsants** *Pharma Rev.* 28 (1948) 409.
7. JN Delgado and E I Issacson Anticonvulsants, In : **Burger's Medicinal Chemistry and Drug Discovery** M E Wolff (Ed.) (5th edn) Wiley-Interscience New york, (1995).
8. J Mercier (*Ed.*) **Anticonvulsant Drug In: Encycl Pharmac Therapeut** Pergamon Press, Oxford 2 Volumes (1973).
9. M Gordon, **Psychopharmacological Agents** Academic Press, New York, Vols. 1 and 2 (1964) and (1965).
10. Williams DA and Lemke TL, **Foye's Principles of Medicinal Chemistry,** Lippincott Williams and Wilkins, New York, 5th edn., 2002.

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8

Muscle Relaxants

Chapter

8 Muscle Relaxants

1. INTRODUCTION

Drugs which cause depression of motor function leading to relaxation of voluntary muscle are known as **muscle relaxants.**

The skeletal muscle may be relaxed by *two* different groups of drugs, namely : *first*, by those exerting an action on the **central nervous system (CNS)** and used mainly for the relief of painful muscle spasms of spasticity taking place either in neuromuscular or musculoskeletal disorders ; *secondly,* those affecting **neuromuscular transmission** that are employed as adjuncts in anaesthesia in order to modify the muscle relaxation ability.

Another school of thought suggests explicitely and with ample evidence that the skeletal muscle in particular could be relaxed by blocking the effect of **somatic motor nerve impulses.** Furthermore, this specific mode of action may be accomplished adequately by affording either substantial depression of the most suitable neurons within the CNS so as to negate the formation of *somatic motor nerve impulses,* or by minimising the availability of Ca^{2+} ions directly to the myofibrillar contractile system. Interestingly, a few local anaesthetics are duly responsible for the interruption of some specific *afferent reflex* pathways that may invariably effect the relaxation of circumscribed muscle groups.

In this chapter an emphasis shall be laid only on those drugs which exert their action at the **myoneural junction** *i.e.,* the **neuromuscular blocking drugs ;** and such other drug substances which solely act upon the **central neurons** *i.e.,* the **centrally acting muscle relaxants.**

2. CLASSIFICATION

In general, **skeletal muscle relaxants** may be classified as (*a*) Neuromuscular Blocking Drugs ; and (*b*) Centrally Acting Muscle Relaxants.

2.1 Neuromuscular Blocking Drugs

Skeletal muscle fibres are innervated by myclinated nerve fibres from the anterior horn cells of the grey matter of the spinal cord. The nerve fibre contains many axons and each axon extends uninterrupted from the spinal cord to the skeletal muscle where it forms many terminal branches. Each

branch ends close to a motor end-plate leaving a junctional gap (or cleft) of about 50 nm between nerve ending and the muscle fibre. By means of these branchings, an axon innervates one or more end-plates. The moror end-plate is a specialized zone of the muscle fibre whose surface is thrown into folds called **junctional folds.** It contains acetylcholine (cholinergic) receptors.

Neuromuscular blocking drugs exert their action by making the motor end-plate membrane of the myoneural junction incapable of reacting to acetylcholine, which functions as the neuro transmitter.

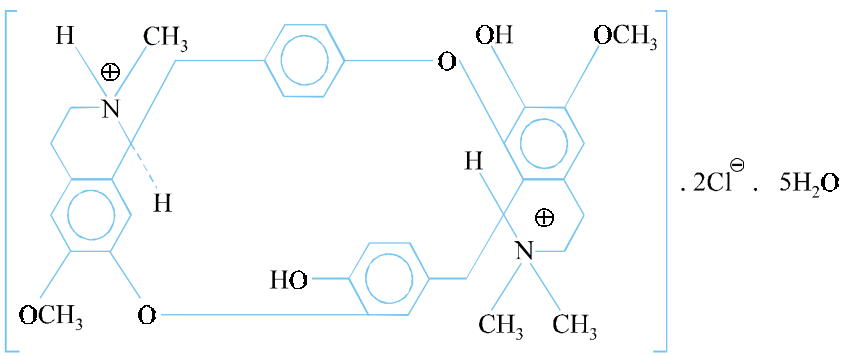
The **neuromuscular blocking agents** may be further sub-divided into *two* categories, namely :

A. Non-depolarizing Muscle Relaxants

Curare-type drugs containing essentially a bulky structure together with a minimum of one quaternary ammonium group, complete with acetylcholine thereby preventing a free access to the cholinergic receptors.

Examples :Tubocurarine chloride ; Metocurine iodide ; Gallamine triethiodide ; Pancuronium bromide ; Hexafluoronium bromide ; Fazadinium bromide ; Alcuronium chloride ; Dacuronium bromide and Stercuronium iodide.

A1. Tubocurarine chloride BAN, USAN, Tubocurarine, INN,

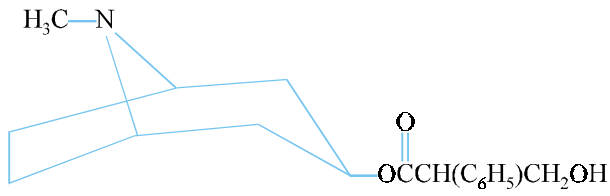


(+)-Tubocurarine chloride hydrochloride pentahydrate; Tubocuraranium,7′,12′-dihydroxy-6, 6′-dimethoxy-2, 2′, 2′-trimethyl-,chloride, hydrochloride, pentahydrate ; d-Tubocurarine chloride ;

B.P.; U.S.P., Eur. P., Int. P., Ind. P..

Tubarine(R) (Burroughs Wellcome) ; Jexine(R) (Duncan, Flockhart, U.K.)

d-Tubocurarine invariably blocks the stimulatory action of acetylcholine on skeletal muscles. It fails to produce any effect on involuntary muscles or glands. The fundamental basis of the activity of muscarinic stimulants as related to interatomic distances of vital functional moieties also holds good for this drug. It is interesting to observe that the distance between the three oxygen atoms residing on the same **tetrahydroisoquinoline residue** and the centre of one N-methyl function falls within a radius of 5-9 Å, which is more or less identical to the linear distances between the functional moieties present in acetylcholine. The average distance between the two quaternary nitrogen atoms is 13-15 Å and that of the two etherial oxygen atoms being 9 Å. Hence, configurationally every 'half-molecule' of **tubocurarine** is identical to atropine as shown below :



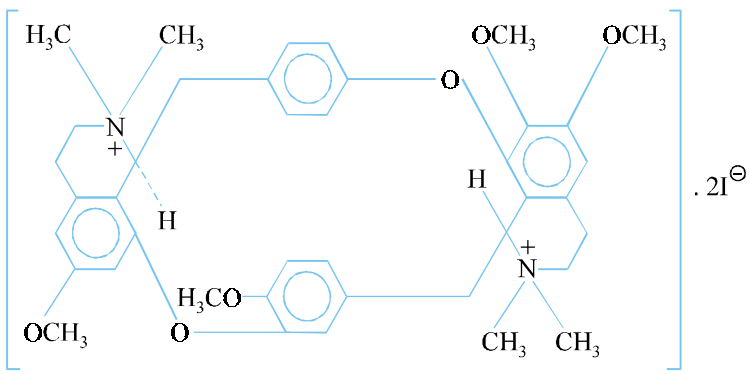
Atropine

However, a striking difference between tubocurarine and atropine exists ; in the former there are double rows of the O-N attachments, while in the latter only a single O-N row is prevalent. This fundamental difference between the two molecules perhaps may be put forward as a possible explanation of the specific action of **d-tubocurarine** on the neuromuscular junction which action atropine is devoid of.

It is a non-depolarizing muscle relaxant and when administered by injection produces paralysis of voluntary muscle by blocking impulses at the neuromuscular junction. It acts primarily by inhibiting the transmission of nervous impulses to skeletal muscle by competing with acetylcholine for cholinergic receptors. It causes muscular relaxation without producing any depression of the nervous system. It is often employed as an adjunct in surgical anaesthesia in order to achieve adequate skeletal muscle relaxation during surgery. **Tubocurarine** is also used to minimise the severity of muscle contraction during electroshock therapy.

Dose : *For paralysis of limb muscles, 6 to 10 mg in 30 to 90 seconds ; for profound abdominal relaxation and appnea, 15 to 20 mg; for shock therapy, 3 mg/18 kg of body weight ; for diagnosis of myasthenia gravis, 0.3 mg/18 kg.*

A2. Metocurine Iodide BAN, USAN,



(+)-*O, O′*-Dimethylchondrocurarine diiodide ; Tubocuraranium, 6, 6′, 7′, 12-tetramethoxy-2, 2, 2′, 2′-tetramethyl-, diiodide; Dimethyl Tubocurarine Iodide ; U.S.P., Dimethyl Tubocurarine Iodide N.F.; Metubine Iodide(R) (Lilly)

Synthesis

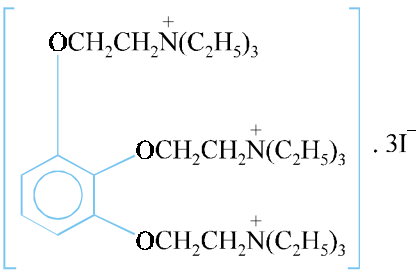
d-Tubocurarine $\xrightarrow[\text{(Methylation)}]{(i)\ CH_3\text{–}I}$ Metocurine Iodide
(*ii*) HI

Metocurine iodide may be prepared by the treatment of ***d*-tubocurarine** with methyl iodide to effect methylation, followed by reaction with bimolar concentration of hydroiodic acid to form the official compound.

Its actions and uses are almost the same as those of ***d*-tubocurarine**, however, in man it is found to be *three* times more potent than the latter with longer duration of action.

Dose : *Initial intravenous, 1.5 to 10 mg stretched over a 60 sec. period;maintenance, 500 μg to 1mg each 25 to 90 min.*

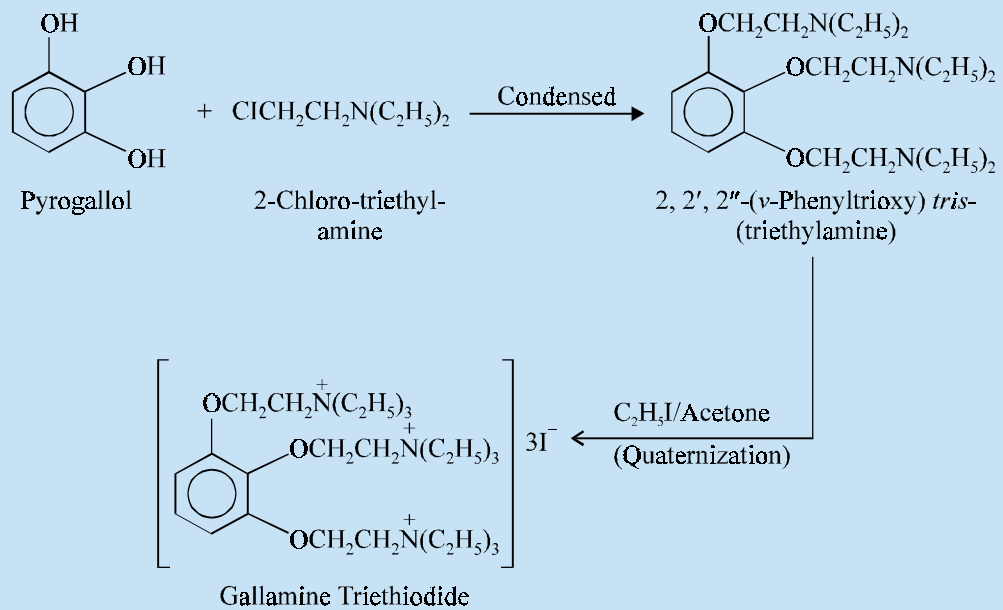
A3. Gallamine Triethiodide BAN, USAN, Gallamine INN,



[ν-Phenyl *tris* (oxyethylene)] *tris* [triethylammonium] triiodide ; Ethanaminium, 2, 2′, 2″-[1, 2, 3-benzenetriyltris (oxy) *tris* (N, N, N-triethyl]-, triiodide ; Bencurine Iodide ; B.P., U.S.P., Eur. P., Int. P., Ind. P.

Flaxedil$^{(R)}$ (Davis and Geck) ;

Synthesis

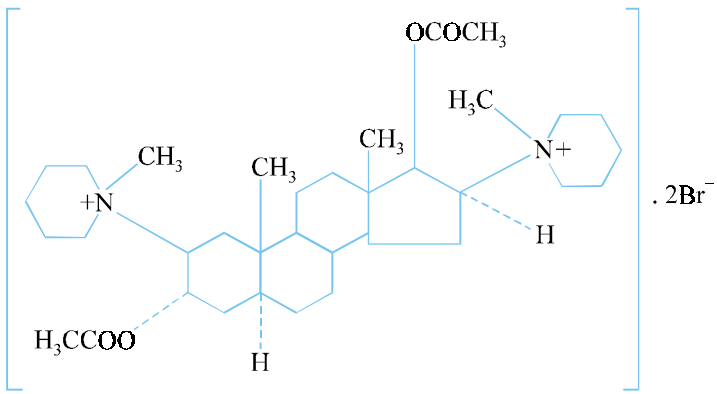


The triamine : 2, 2′, 2″-(*v*-pheneyltrioxy) *tris* (triethyl-amine) may be prepared by the condensation of pyrogallol and 2-chloro-triethylamine. This is then quaternized with ethyliodide in the presence of boiling acetone to yield the desired official compound.

Its actions are similar to those of **tubocurarine choride**. It is mostly employed as an adjunct to anaesthesia so as to achieve deeper muscular relaxation to facilitate surgical procedures.

Dose : *For limb muscle paralysis, initial i.v. or i.m. 1 mg/kg of body weight ; for abdominal surgery, 1.5 mg/kg of body weight; Maintenance dose, 500 mcg to 1 mg every 30 to 60 min. intervals if required. The dose must be reduced when used along with anaesthetics, like ether, cyclopropane, etc.*

A4. Pancuronium Bromide INN, BAN, USAN,



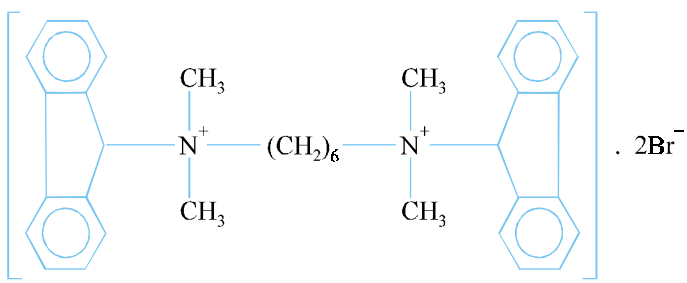
1, 1′-(3α, 17β-Dihydroxy-5α-androstane-2β, 16β-ylene) *bis* [1-methylpiperidinium] dibromide diacetate ; 2β, 16β-Dipiperidino-5α-androstane-3α, 17β-dioldiacetate dimethobromide :

Pavulon(R) (Organon) ;

It is a nondepolarizing muscle relaxant of choice with actions much alike to those of tubocurarine chloride. *It has been employed with greater margin of safety in patients having cardiovascular disease and in the management of status asthamaticus to facilitate artificial respiration (minimising oxygen demand) thereby relaxing the muscles, than other neuromuscular blocking drug.*

Dose : *For surgical relaxation, i.v., 20 to 100 mcg per kg, maintenance dose 10 mcg per kg ; For intubation, 60 to 100 mcg per kg.*

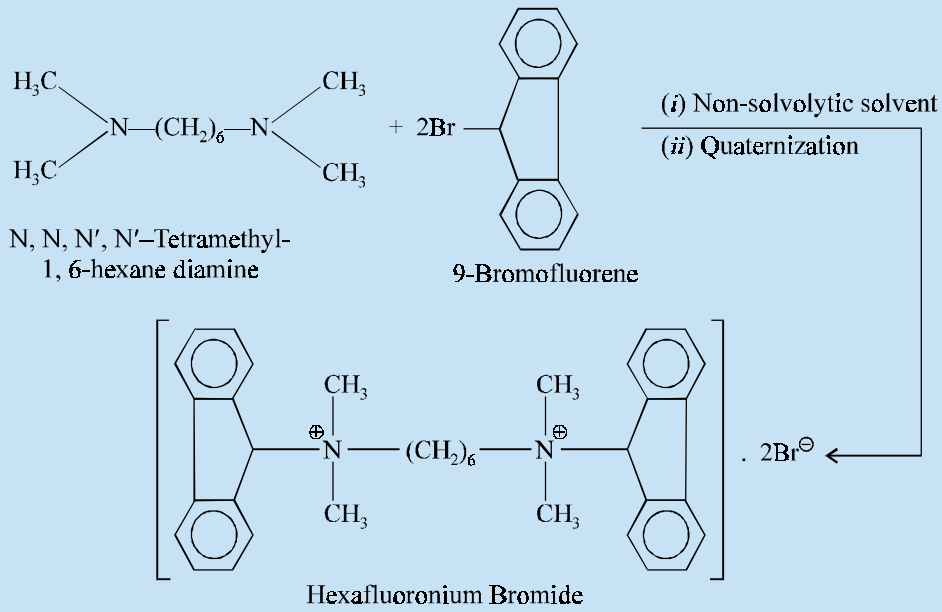
A5. Hexafluoronium Bromide INN, Hexafluorenium Bromide BAN, USAN,



Hexamethylenebis [fluoren-9-yldimethylammonium]-dibromide ; 1, 6-Hexanediaminium, N, N′-di-9H-fluoren-9-yl-N, N, N′, N′-tetramethyl-, dibromide ; U.S.P.

Mylaxen$^{(R)}$ (Carter-Wallace)

Synthesis

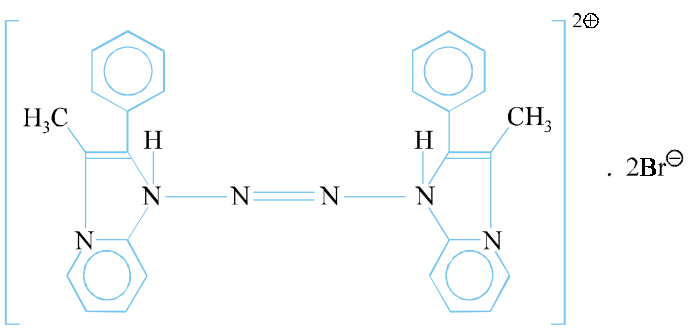


Hexafluoronium bromide may be prepared by dissolving N, N, N′, N′-tetramethyl-1, 6-hexane diamine in a nonsolvolytic solvent which is quaternized twice with 9-bromofluorene.

It exerts a weak and feeble neuromuscular blocking activity which fails to produce significant muscle relaxation except under deep ether anaesthesia. It has been found to potentiate the neuromuscular blockade caused by tubocurarine and to antagonize the action of **decamethonium**. Paradoxically, it has been used successfully to prolong and potentiate the relaxant effects of **suxamethonium chloride**. Besides, it has also been reported to decrease **suxamethonium-induced muscular fasciculations**.

Dose : *Initial, i.v. 300 to 400 mcg per kg ; maintenance dose 100 to 200 mcg at intervals of 80 to 100 min.*

A6. Fazadinium Bromide INN, BAN,



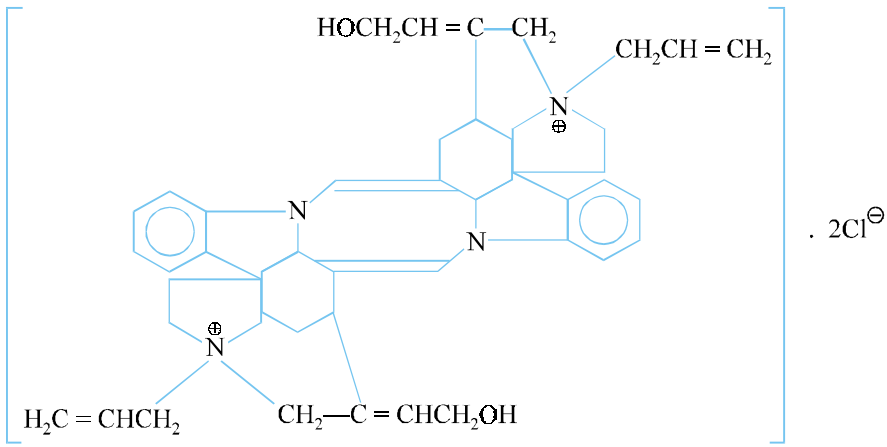
1, 1′-Azobis [(3-methyl-2-phenyl-1H-imidazo [1, 2-*a*] pyridin-4-ium] dibromide ;

Fazadon$^{(R)}$ (Duncan, Flockhart, U.K.) ;

It is a **muscle relaxant** possessing a dose-dependent rapid onset and prolonged duration of action. It is normally employed to aid endotracheal intubation and to produce muscular relaxation during surgical procedures.

Dose : *0.5 mg per kg body weight for effects lasting up to 30 minutes ; In surgery, usual, initial, i.v., 0.75 to 1 mg per kg.*

A7. Alcuronium Chloride INN, BAN,



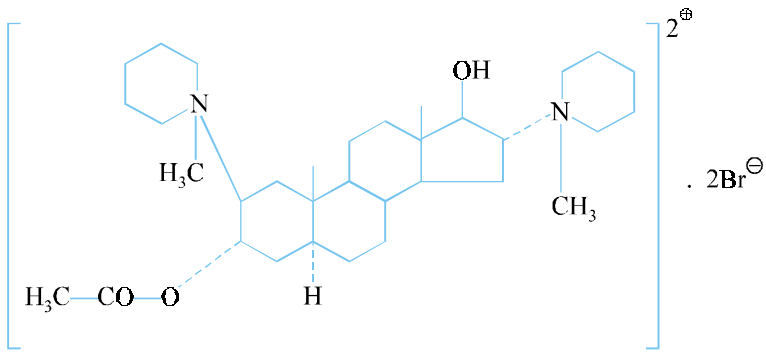
N, N′-Diallylnortoxiferinium dichloride; Toxiferine I, 4, 4′-didemethyl-4, 4′-di-2-propenyl-, dichloride;

Alloferin$^{(R)}$ (Hoffman-La Roche-International).

It is employed mostly as an adjuvant to anaesthesia.

Dose : *For neuromuscular blockade, usual, initial, i.v. 250 mcg per kg body weight.*

A8. Dacuronium Bromide INN, BAN, USAN,

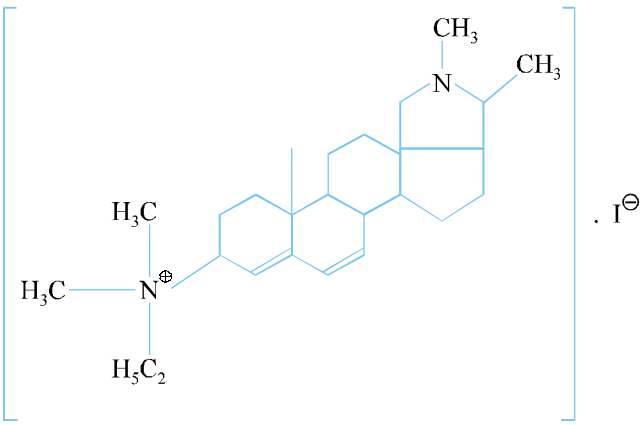


3α, 17β-Dihydroxy-5α-anadrostan-2β, 16β-ylene) *bis*-(1-methylpiperidinium) dibromide-3-acetate ;

NB68$^{(R)}$ (Organon) ;

It has anticholinesterase actions.

A9. Stercuronium Iodide INN, USAN,



(Cona-4, 6-dienin-3β-yl) dimethylethylammonium iodide; MYSC 1080 (Gist-Brocades) ;

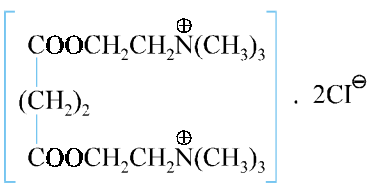
It also possesses anticholinesterase properties.

B. Depolarizing Neuromuscular Blocking Drugs

Decamethonium and **succinylcholine** possessing simple skeleton-like bisquaternary synthetic compounds usually show their presence in the initial phase of action by more or less mimicking acetylcholine and depolarizing the motor end-plate membrane. They produce persistent depolarisation responsible for the initial blockade by preventing the membrane from undergoing repolarisation in order to accept new stimuli. Repetitive doses with depolarizing blocking drugs usually change the initial depolarizing action on the motor end-plate to non-depolarizing type of blockade. Their blocking action is, therefore, rather difficult to antagonize because of the fact that either cholinomimetics or anticholinesterases can cause potentiation or antagonism depending on the blocking phase (depolarizing or non-depolarizing) of the drug at the time.

Examples : Suxamethonium chloride ; Suxethonium bromide ; Decamethonium bromide.

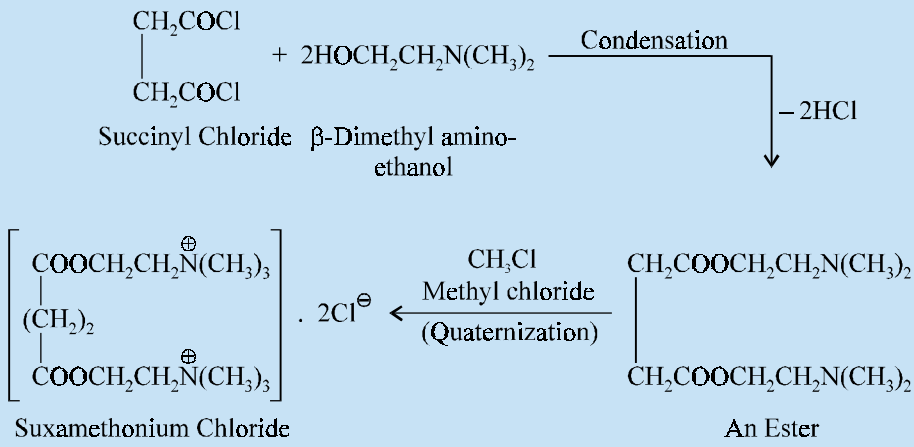
B1. Suxamethonium Chloride INN,BAN, Succinylcholine Chloride USAN,



Choline chloride succinate (2 : 1); Ethanaminium, 2, 2′-[(1, 4-dioxo- 1, 4-butanediyl) bis (oxy)] *bis*-[N, N, N-trimethyl]-dichloride ; Suxamethonium Chloride B.P., Eur. P., Int. P., Succinylcholine Chloride U.S.P.

Acectine(R) (Burroughs Wellcome) ; Quelicin(R) (Abbott) ; Sucostrin Chloride(R) (Squibb)

Synthesis

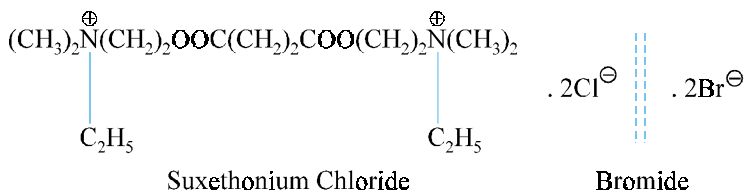


Condensation of succinyl chloride with β-dimethylamino ethanol yields an ester with the elimination of two moles of HCl. Further quaternization with two moles of methyl chloride forms the official compound.

Its depolarizing neuromuscular blocking effect is very transient because of its rapid hydrolysis by cholinesterases. It does not cause histamine liberation and hence it is well tolerated. Single-dose therapy of suxamethonium chloride is generally used to relax the skeletal muscle for orthopedic manipulation, endotracheal intubation, in laryngospasm and also to check the intensity of convulsions in patients receiving electroshock treatment (electroconvulsive therapy).

Dose : *Testing for sensitivity, initial i.v., 10 mg, then 10 to 75 mg ; alternative i.v. or 0.5 to 1 mg per kg ; Usual 20-80 mg i.v. or 0.5 to 10 mg per minute by i.v. infusion as a 0.1 to 0.2% solution.*

B2. Suxethonium Chloride INN, USAN, Suxethonium Bromide BAN,



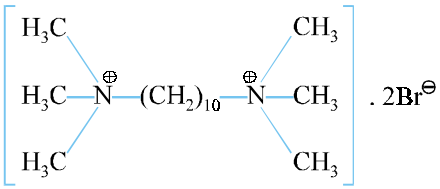
Ethyl (2-hydroxyethyl) dimethylammonium chloride (or bromide) succinate ; 2, 2′-Succinyldioxy-bis (diethyldimethylammonium) dichloride (or dibromide) ;

Brevidil(R) (May & Baker, U.K.) for Suxethonium Bromide.

Its actions and uses are similar to suxamethonium chloride but it possesses only about half the potency and a relatively shorter duration of action ranging between 2 to 4 minutes.

Dose : *Usual i.v., 1 to 1.25 mg of base per kg body weight (or 1.5 to 1.875 mg bromide).*

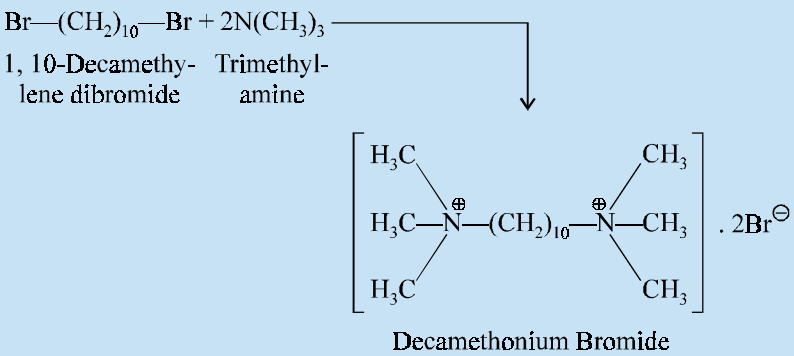
B3. Decamethonium Bromide BAN, USAN, Decamethonium INN,



Decamethylenebis [trimethylammonium] dibromide ; 1, 10-Decanediaminium, N, N, N, N′, N′ N′-hexamethyl-, dibromide ; U.S.P. ;

Syncurine(R) (Burroughs Wellcome)

Synthesis



It may be prepared by the condensation of one mole of 1,10-decamethylene dibromide with two moles of trimethylamine.

The two onium groups present in decamethonium bromide are situated at a distance of 15 Å which incidentally compares very closely to that of suxamethonium chloride. **Decamethonium** cannot be hydrolysed by chloinesterase and hence exerts a much more prolonged effect.

As it exerts an initial action of nicotinic depolarization at the motor end-plate membrane it is regarded as a depolarizing neuromuscular relaxant. It is used as a **muscle relaxant** especially for comparatively short surgical operations and, also for manipulative procedures.

Dose : *Initial, i.v., 2 to 3 mg administered at the rate of 1 mg per minute ; for maintenance of paralysis, 0.5 to 1 mg at 10-30 min intervals.*

2.2 Centrally Acting Muscle Relaxants

The discovery of centrally acting muscle relaxants dates back to 1910 when antodyne (3-phenoxy-1, 2-propanediol) first gained its entry into the therapeutic armamentarium as an analgesic and antipyretic ad later on as skeletal muscle relaxant. In 1946, Berger and Bradley* observed the **muscle relaxant** activity present in a large number of glycerol monoethers and analogues.

As of now practically all the centrally acting muscle relaxants seem to depress neuronal activity instead of stimulating the inhibitory nerves.

*F.M. Berger and W. Bradley, *Brit. J. Phannacol*., **1,** 265 (1946).

As stated earlier they are used to relieve painful muscle spasms and spasticity. They relax the muscle without impairing respiration centrally. They have sedative effects. Some have predominantly tranquilizing effect and are classified as such.

In the following sections some typical examples belonging to different categories of the above class of compounds are described, namely ;

(*a*) Glycerol Monoethers and Analogues

(*b*) Substituted Alkanediols and Analogues

(*c*) Benzoxazole Analogues

(*d*) Imidazoline Analogues

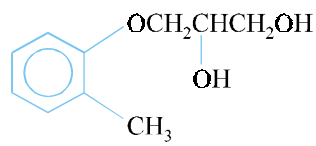
(*e*) Miscellaneous Drugs.

A. Glycerol Monoethers and Analogues

A number of α-substituted glycerol ethers possessing potent centrally acting muscle relaxant properties have been used clinically.

Examples : Mephenesin ; Chlorphenesin Carbamate ; Methocarbamol.

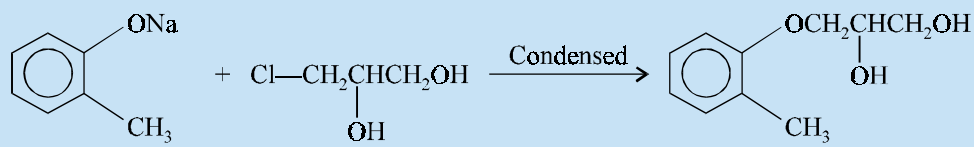
A1. Mephenesin INN, BAN, USAN,



3-(*o*-Methylphenoxy)-1, 2-propanediol ; 3-(*o*-Tolyloxy) propane-1, 2-diol ; Mephenes; Cresioxydiol ; B.P.C. 1973, N.F. XII

Tolserol(R) (Squibb) ; Tolyspaz(R) (Alcon)

Synthesis



Sodium-*o*-cresolate

3-Chloropropane-1, 2-diol (C-Chlorohydrin)

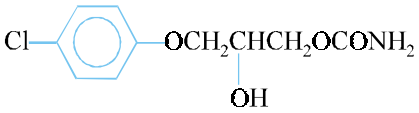
Mephenesin

It may be prepared by the condensation of sodium-*o*-cresolate with 3-chloropropane-1, 2-diol and the resulting product is recrystallized from alcohol.

Mephenesin relaxes hypertonic muscles, decreases response to sensory stimuli, and depresses superficial reflexes. It is used for the symptomatic relief of muscular spasm, and hyperkinetic conditions, such as parkinsonism, athetosis and chorea. It is also used in the treatment of anxiety and tension. Its action lasts up to 3 hours.

Dose : *Usual, oral, 0.5 or 1 g 1 to 6 times per day as per requirement.*

A2. Chlorphenesin Carbamate BAN, USAN, Chlorphenesin INN,



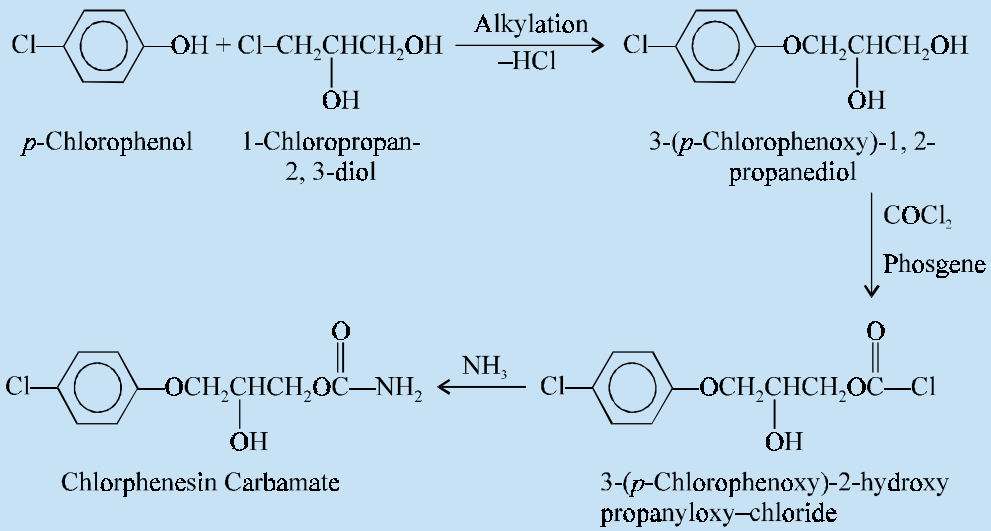
3-(*p*-Chlorophenoxy)-1, 2-propanediol 1-carbamate ; 1, 2-Propanediol, 3-(4-chlorophenoxy)-, 1-carbamate

Maolate(R) (Upjohn)

Synthesis

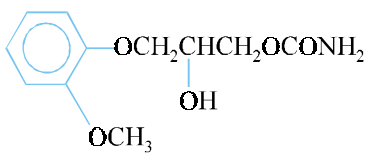
3-(*p*-Chlorophenoxy) 1, 2-propanediol is first prepared by the alkylation of *p*-chlorophenol with 1-chloropropan-2, 3-diol which on treatment with phosgene selectively forms the terminal carbamoyl chloride, namely, 3-(*p*-chlorophenoxy)-2-hydroxy propanyl oxychloride. The resulting product on amination yields chlorphenesin carbamate.

It is employed for the symptomatic relief of muscular spasm. **Chlorphenesin** also finds its use as an antifungal agent.



Dose : *Initial, usual 800 mg 3 times a day reduced to 400 mg 4 times daily or less as required.*

A3. Methocarbamol INN, BAN, USAN,



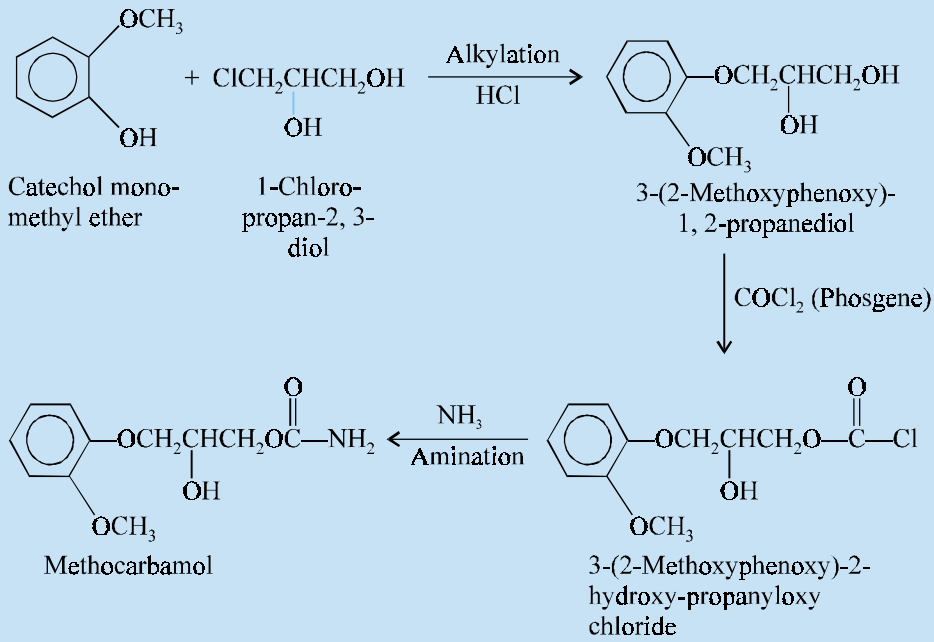
3-(*o*-Methoxyphenoxy)-1, 2-propanediol 1-carbamate ; 1, 2-Propanediol, 3-(2-methoxyphenoxy)-, 1-carbamate ; Guaiphenesin Carbamate ; U.S.P., N.F.

Robaxin(R) (Robins)

Synthesis

Application of the three-step sequence to catechol mono-methylether affords **methocarbamol** as shown below.

Owing to its poor solubility, as compared to mephenesin, its absorption through the gastrointestinal tract is rather slow, which is responsible for its longer onset and duration of action. It is employed in the treatment of muscle spasm caused by musculoskeletal disorders, tetanus and injury.



It is also used in the treatment of parkinsonism, cerebrovascular mishaps and cerebral palsy.

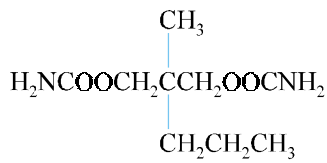
Dose : *Initial, oral, 1.5 to 2 g 4 times daily for the first 2 or 3 days followed by 2.25 to 4.5 g per day in 2 or 4 divided doses ; i.v., 1 to 3 g per day administered at a rate not exceeding 0.3 g per minute ; i.m., 1 g every 8 hours.*

B. Substituted Alkanediols and Analogues

A good number of 1, 3-alkanediols and their structural analogues have been reported to be reasonably potent muscle relaxant drugs. A few examples of this group of compounds are discussed below.

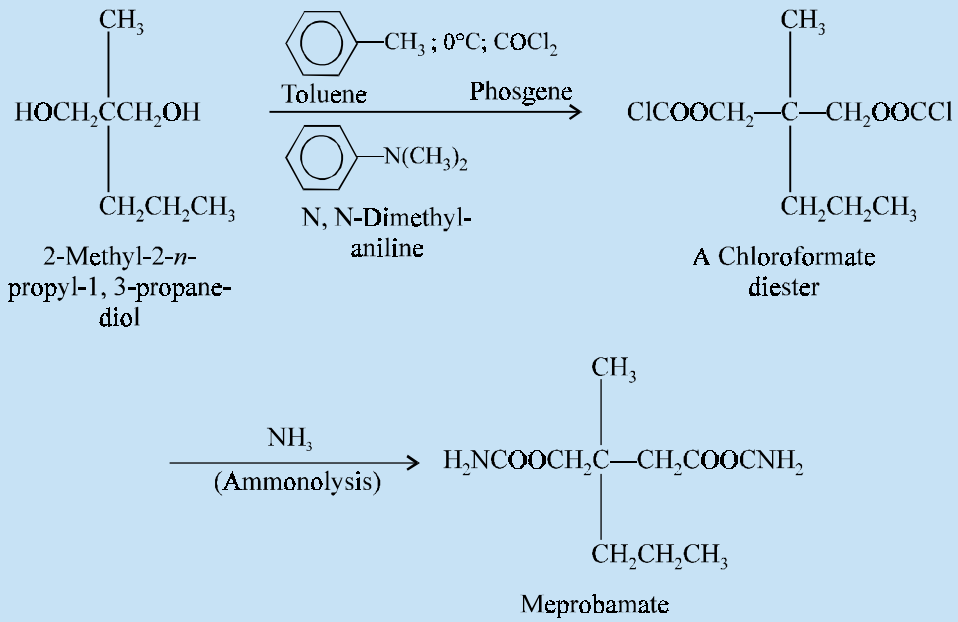
Examples : Meprobamate ; Carisoprodol ; Tybamate ; Metaxalone.

B1. Meprobamate INN, BAN, USAN,



2-Methyl-2-propyl-1, 3-propanediol dicarbamate ; 1, 3-Propanediol, 2-methyl-2-propyl-, dicarbamate ; 2-Methyl-2-propyl-trimethylene dicarbamate; B.P., U.S.P., Eur. P., Int. P., Ind. P.
Equanil(R) (Wyeth) ; SK-Bamate(R) (SK & F) ; Miltown(R) (Wallace)

Synthesis

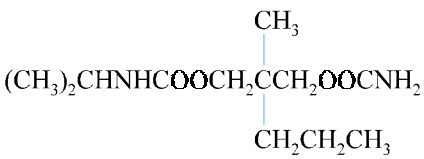


2-Methyl-2-*n*-propyl-1, 3-propane diol dissolved in toluene is condensed at 0°C with phosgene in the presence of dimethylaniline gives the chloroformate diester, which when subjected to ammonolysis yields meprobamate.

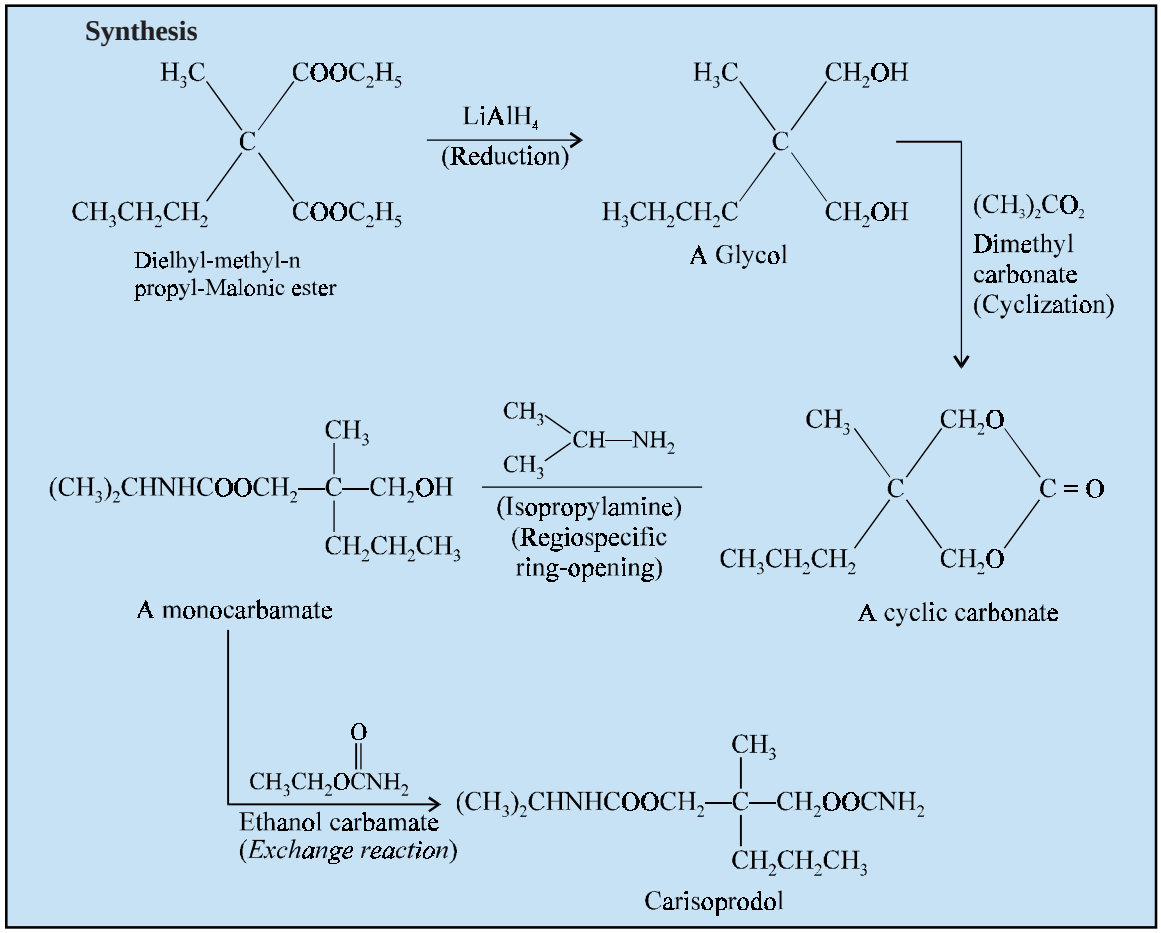
It possesses anticonvulsant and muscle relaxant properties. It has also been used as mild tranquilizer in the treatment of anxiety and tension but has now been more or less replaced by the benzodiazepines, *e.g.,* diazepam.

Dose : *Usual, oral, 400 mg 3 or 4 times per day ; usual, i.m., 400 mg every 3 or 4 hours ; children, 25 mg per kg body weight per day in divided doses.*

B2. Carisoprodol INN, BAN, USAN,



2-Methyl-2-propyl-1, 3-propanediol carbamate isopropylcarbamate ; N-Iso-propylmeprobamate.
Carisoma(R) (Pharmax, U.K.) ; Rella(R) (Schering-Plough)

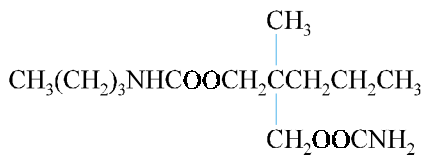


Reduction of diethyl-methyl-*n*-propyl malonic ester with lithium aluminium hydride yields the corresponding glycol, which on treatment with dimethyl carbonate undergoes cyclization and affords the cyclic carbonate. Ring cessation of the resulting product by the aid of isopropyl amine proceeds regiospecifically to afford the corresponding monocarbamate. Finally, the remaining hydroxyl group undergoes an exchange reaction in the presence of ethanol carbamate to yield **carisoprodol**.

Its actions are similar to those of mephenesin. The duration of action ranges between 4 to 6 hours. It is usually employed for the symptomatic relief of muscular spasm.

Dose : *Usual, adult, 350 mg 4 times a day.*

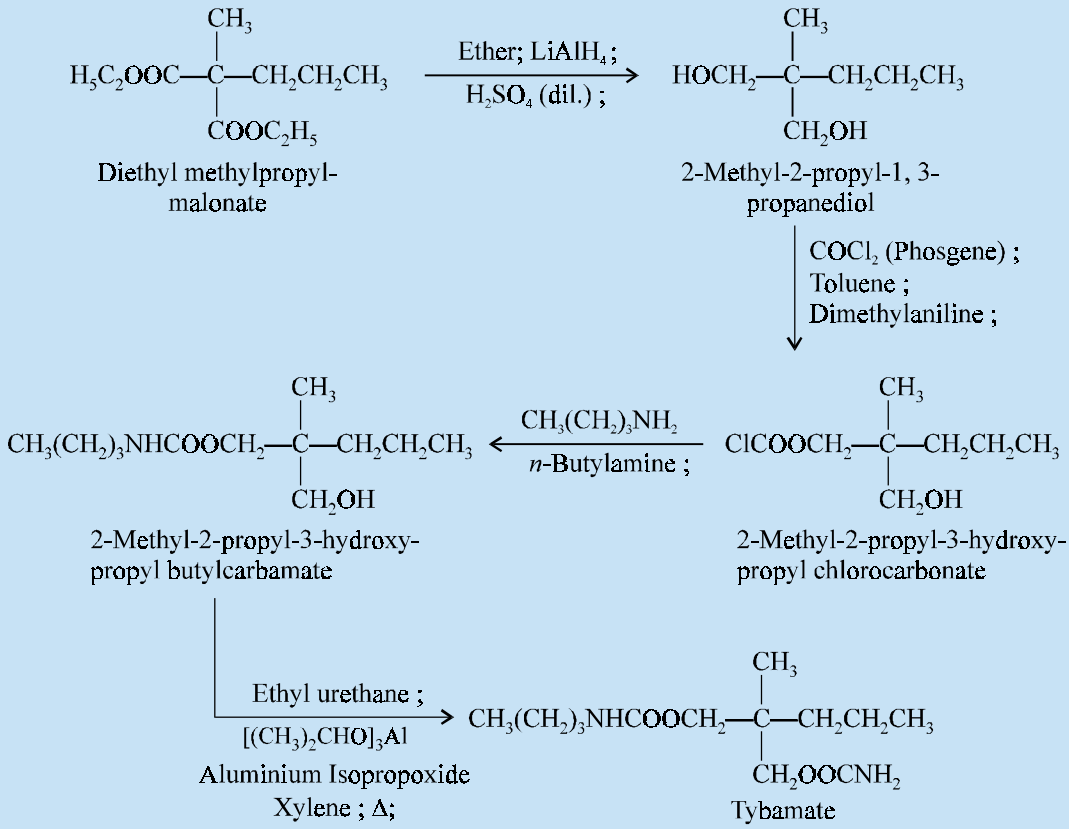
B3. Tybamate INN, BAN, USAN,



2-(Hydroxymethyl)-2-methylpentyl butylcarbamate ; Carbamic acid, butyl-, 2-[[(aminocarbonyl) oxy] methyl]-2-methylpentyl ester ; N.F. XIII

Tybatran(R) (Robins)

Synthesis

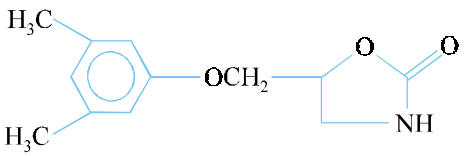


2-Methyl-2-propyl-1, 3-propanediol is prepared by reacting diethyl methylpropyl malonate in ether in the presence of lithium aluminium hydride and then treated with dilute sulphuric acid. This on treatment with phosgene in toluene by means of dimethylaniline yields 2-methyl-2-propyl-3-hydroxypropyl chlorocarbonate, which on reaction with *n*-butylamine forms 2-methyl-2-propyl-3-hydroxypropyl butylcarbamate. The resulting product on treatment with ethyl urethane in the presence of aluminium isopropoxide in boiling xylene yields ethanol during transesterification which is removed from the reaction mixture simultaneously and **tybamate** is obtained.

Its actions and uses are similar to its congener meprobamate. It has been used in the treatment of anxiety and tension states in patients having psychoneurotic disorders.

Dose : *250 to 500 mg 3 or 4 times per day.*

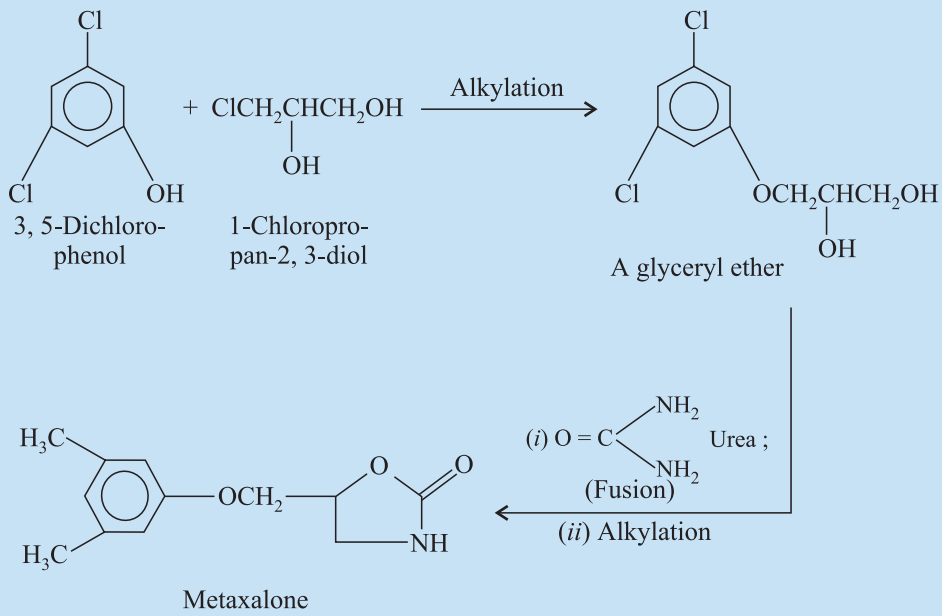
B4. Metaxalone INN, BAN, USAN,



5-[3, 5-Xylyloxy) methyl]-2-oxazolidinone ; 2-Oxazolidinone, 5-[(3, 5-dimethyl-phenoxy) methyl]-

Skelaxin(R) (Robins)

Synthesis



3, 5-Dichlorophenol on alkylation with 1-chloropropan-2, 3-diol affords a glyceryl ether which on treatment with urea and subsequent alkylation yields **metaxalone.**

Metaxalone is used for the relief of acute muscle spasm resulting from various injuries or strains. Because of its potential toxicity, it has been superseded by other drugs belonging to this class.

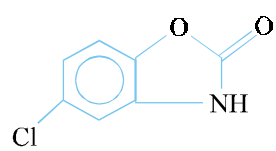
Dose : *Usual, 800 mg 3 or 4 times per day.*

C. Benzoxazole Analogues

Two **structural analogues of benzoxazole** have gained prominence as potent muscle relaxants.

Examples : Chlorzoxazone ; Zoxazolamine.

C1. Chlorzoxazone INN, BAN, USAN,

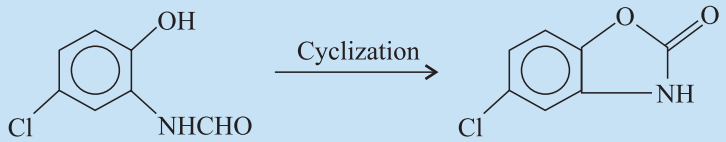


5-Chloro-2-benzoxalinone ; 2(3H)-Benzoxazolone, 5-chloro-; Chlorobenzoxazolinone.

U.S.P.

Paraflex(R) (McNeil)

Synthesis



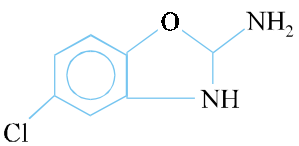
2-Hydroxy-5-chloro-benzformamide — Chlorzoxazone

Chlorzoxazone may be prepared by the cyclization of the 2-hydroxy-5-chlorobenzformamide.

It is used for the treatment of painful muscle spasm associated with musculoskeletal disorders, such as spondolytis, sprains and muscle strains. It is also recommended sometimes for vertebral disk disorders and cervical root syndrome.

Dose : *Usual, intial, 500 mg 3 or 4 times per day, maintenance dose 250 mg.*

C2. Zoxazolamine INN, USAN,



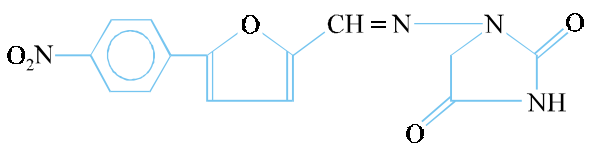
2-Amino-5-chlorobenzoxazole ; N.F. XI

Due to the significant hepatotoxicity properties of zoxazolamine it is no longer used in clinical therapy.

D. Imidazoline Analogue

Dantrolene, an imidazoline analogue has been found to possess muscle relaxant characteristics, *e.g.,* **Dantrolene Sodium.**

D1. Dantrolene Sodium BAN, USAN, Dantrolene INN,



1-[[5-(*p*-Nitrophenyl) furfurylidene] amino] hydantoin sodium salt hydrate ; 2-Imidazolidinedione, 1-[[[5-(4-nitrophenyl)-2-furanyl]-methylene] amino]-, sodium salt, hydrate (2 : 7).

Dantrium (R) (Eaton)

Dantrolene is a skeletal muscle relaxant which may possess either central or peripheral components of action. It is mostly employed for the symptomatic relief of muscular spasm caused by stroke, spinal cord injury and cerebral palsy.

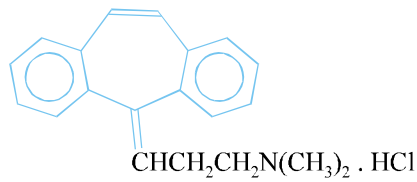
Dose : *Initial, oral, 25 mg per day, slowly increased over a period of 7 weeks to 100 mg 3 to 4 times per day.*

E. ***Miscellaneous Drugs***

There exist a few potent **muscle relaxants** that do not fall into any of the classifications discussed above (A-D) and hence it will be convenient to group them under this heading.

Examples : Cyclobenzaprine Hydrochloride ; Baclofen,

E1. Cyclobenzaprine Hydrochloride BAN, USAN, Cyclobenzaprine INN,

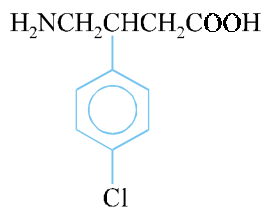


N, N-Dimethyl-5H-dibenzo [*a, d*] cycloheptane- Δ^5, γ-propylamine hydrochloride; 1-Propanamine, 3-(5H-dibenzo [*a, d*] cyclohepten-5-ylidene)-N, N-dimethyl-, hydrochloride ; Proheptatriene Hydrochloride.

Cyclobenzaprine hydrochloride belongs to the class of centrally acting muscle relaxant and is chemically related to the tricyclic antidepressants. It is mostly employed for the symptomatic relief of muscle spasm.

Dose : *Usual, oral, 10 mg 3 times a day and it must not exceed 60 mg per day.*

E2. Baclofen INN, BAN, USAN,



β-(Aminomethyl)-*p*-Chlorohydrocinnamic acid ; Butanoic acid, 4-amino-3-(4-chlorophenyl)-; Lioresal$^{(R)}$ (Ciba-Geigy) ;

Baclofen is an analogue of gamma aminobutyric acid. It is employed for the symptomatic relief of muscular spasm caused by either lesions of the spinal cord or multiple sclerosis.

Dose : *Initial 5 mg 3 times per day increased by 15 mg per day every 4th day to 20 mg 3 times a day.*

3. GENERAL MECHANISM OF ACTION OF MUSCLE RELAXANTS

The mechanism of action of the **'muscle relaxants'** shall now be discussed on a broader perspective under the following *two* major categories, namely :

(*a*) Neuromuscular blocking drugs, and

(*b*) Centrally acting muscle relaxants.

[A] Neuromuscular Blocking Drugs

In general, the **'drugs'** belonging to this category invariably check the somatic motor nerve impulses from initiating the contractile responses in the effector skeletal (striated) muscles, thereby causing a paralysis of the muscles.

However, this specific category of **'drugs'** may be further sub-divided into *two* heads, namely :

(*i*) Competitive (or stabilizing) paralyzants, and

(*ii*) Depolarizing paralyzants.

(*a*) **Competitive Paralyzants**

These are also known as the **competitive neuromuscular blocking drugs**. In a situation, when the impulses in the somatic nerve arrive at the specific region located in the nerve terminals in the motor end-plate, they eventually elicit the release of **acetylcholine (ACh)**, which in turn gets diffused to the post-synaptic motor end-plate membrane. Thus, **ACH** combines with **nicotinic cholinergic receptors** to activate them that ultimately leads to the opening of transmembrane ion channels, ion-flow, and as a result affords membrane depolarization. Importantly, end-plate membrane depolarization is usually accompanied by depolarization of the muscle membrane and ultimately leads to '*muscle contraction'*. In short, any plausible and feasible interruption of the aforesaid squence of events gives rise to the muscular paralysis.

Therefore, the **'competitive paralyzants'** normally found to combine with the nicotinic receptors and occupy them strategically without causing any activation. Furthermore, **ACH** cannot activate the already preoccupied receptors, consequently the motor nerve impulses are unable to evoke contractions, and, hence, paralysis takes place. A few of them, however, take shelter in the receptor-operated ionophore which subsequently minimise the prevailing activation of the **postsynaptic membrane.**

(*b*) **Depolarizing paralyzants**

These are also termed as **depolarizing neuromuscular blocking drugs.** They are **'nicotinic agonists'** that essentially interact **(just like ACH)** with the post synaptic nicotinic receptors to cause a depolarization of the membrane at the motor end-plate specifically. In reality, their **'temporary stay'** at the end-plate is a little longer **(unlike ACH)** and, therefore, the post synaptic membrane virtually remain depolarized. Because, the muscle membrane as well as the resulting contraction can only be excited by a fresh lease of depolarization, the muscle remains paralyzed ultimately. In other words, the virtual initiation for the conducted muscle impulse is due to the short-stayed fall in end-plate membrane potential, and not caused due to the ensued depolarization.

Ultimately, the motor end-plate membrane gets repolarized inspite of the continued presence of the **'drug substance'** by virtue of a shift in receptor conformation. Though the membrane is normally poised for a new lease of depolarization, yet **ACH** and the motor nerve impulses do not succeed to evoke an appreciable response. Perhaps, this could be due to the fact that the nicotinic receptor is not positioned in its desired configuration. It has also been observed that during this critical phase, the neuromuscular blockade usually occurs specifically on certain characteristic features of competitive blockade ; and this may even get antagonized partially by the aid of **anticholinesterases**.

An Ideal Neuromuscular Blocking Drug. The ultimate objective of an ideal neuromuscular blocking drug should essentially possess the following characteristic features, namely :

(1) A *bis*-quaternary chemical structure having a sufficient separation (gap), between the two N-atoms, so as to cause an effective and significant level of blockade. It has already been established that the distance between the said two N-atoms must be in the range of 10-11 Å (*i.e.*, about 10-12 atoms apart).

(2) Always the choice for a **'competitive antagonist'** is preferred. Experimental evidences have revealed that the presence of a **'bulky and large hydrocarbon environment'** (*i.e.*, causing steric hindrance) in the viccinity of the **'cationic nitrogens'** effectively prevents the access of ACH to the postsynaptic receptor areas located on the motor-end plate.

(3) There should be either minimal or absolutely negative action at the cholinergic receptors except those of the nicotinic subtypes at the neuromuscular junction. In this manner the **'quaternization'** prevents a free access to the centrally located receptors, and, therefore, the proper distance separating the **'cationic zones'** present in the '*drug substance'* decreases the activity on the ganglionic receptors significantly.

(4) It has been well established that the **'molecular drug designs'** which would ultimately pave its way to an efficient metabolic degradation and/or variable pattern of exretions absolutely not found to solely dependent on **enzyme catalysts**.* Interestingly, a **'drug substance'** having such characteristic qualification would certainly exhibit explicitely both a rapid recovery and a shorter-duration of action from the ensuing blockade whether it could be caused due to either *hepatic dysfunction or renal dysfunction* or *pharmacogentic effects.*

[B] Centrally Acting Muscule Relaxants

It is reasonably proven analogy that the **'cell bodies'** present in the somatic motor nerves invariably lie within the spinal cord and, therefore, very much within the CNS. It has been observed that the prevailing activity of motor neurons is mostly affected by a host of such cardinal factors, such as : facilitatory and inhibitory modulation through feedback from **contralateral**** and **ipsilateral***** stretch, besides other receptors ; various centres of the brain.

Therefore, **spasticity****** may arise from particularly the musculoskeletal injury, that invariably give rise to a duration from a standard with regard to the **observed afferent impulse traffic** into the spinal cord. In this manner an inflicted injury slowly leads to the disease related to either motor nerves, or interneurons within the cord, or sensory neurons located in the sensory ganglia ; and ultimately boils down to the **'brain disorders'** thereby changing the regular flow of suprasegmental impulses to the motor neurons. Thus, the virtual cause of impairment to the motor neurons in the brain leads to involuntary movement as could be seen in Parkinsonism, chorea and palsies.

In actual practice it is, however, difficult to make a clear-cut distinction between the disorder caused either within the spinal cord or due to musculoskeletal dysfunction *vis-a-vis* the selectivity of *drug substances'* which evidently remains at a low-ebb. This is perhaps on account of the collective neurons engaged intimately in the reflex arcs that are found to be insufficiently and qualitatively variant from the prevailing motor and sensory neurons with regard to the '*chemical sensitivity'* in order to allow a specific selective depression of the hyperactive influences on the motor neuron.

In short, the centrally acting muscle relaxants find their abundant application in a plethora of conditions, namely : strains and sprains, which may ultimately be responsible for causing acute muscle spasm. Besides, they also particularly possess interneuronal-blocking characteristics at the level of the spinal cord, which may give rise to the much desired **relaxation of the skeletal muscle**********. Interestingly, most of them exhibit a distinct general CNS-depressant activities.

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*A drug Albert (1985) suitably describes as '*self-canceling*'.

**Originating in or affecting the opposite side of the body.

***Affecting the same side of the body.

****Increased tone of contractions of muscles causing stiff and awkward movements.

*****Berger FM, In : Usdin E and Forrest IS (eds.) **Psychotherapeutic Drugs**, Pt II, Marcell Dekker, New York, p. 1089, 1977.

4. MODE OF ACTION OF SOME SPECIFIC MUSCLE RELAXANTS

The probable and proven mode of action of certain selected muscle relaxants discussed in this chapter shall be dealt with in the section that follows.

4.1. Tubocurarine Chloride

It is found to be not absorbed directly from the gut (intestine). After IV administration the drug simply gets disappeared so readily from the plasma, with a distribution half-life of approximately 12 minutes ; whereas, its terminal plasma half-life ranges between 1 to 3 hours. It is mostly excreted through urine upto 43%; and the remaining gets degraded subsequently either in the liver or in the kidneys. However, in instances where either hepatic failure or renal failure occur it may prolong the half-life of the drug appreciably.

4.2. Metocurine Iodide

It is found to be 2 to 4 times more potent than **tubocurarine** (+ TB). In man, it is eliminated chiefly by renal and biliary excretions ; the half-life is about 3.5 hour. It is observed that it can safely pass across the placental barrier.

4.3. Gallamine Triethiodide

It is a potent skeletal muscle relaxant which essentially works by blocking the neuromuscular transmission almost identical to that of (+TB). It markedly differs from ***d*-tubocurarine** (+TB) by virtue of its *two* inherent characteristic features, namely ; (*a*) possesses a reasonably strong **vagolytic effect***, and (*b*) it continues to lower the prevailing **'neuromuscular function'** after administration of successive doses which cannot be overcome by **cholinesterase inhibitors.** Besides, it has also been shown to exhibit **'muscarinic antagonistic characteristic features',** and gets bound intimately with greater affinity to the M_2-receptors than the corresponding M_1-receptors. However, the second characteristic feature is solely responsible for attributing its strong and prevalent vagolytic action.**

4.4. Pancuronium Bromide

Its mechanism of action normally is assumed to be almost similar to that of **d-tubocurarine** (+TB), but the '**dose-response curve'** is rather steeper in nature thereby suggesting a possible difference. The cardinal differences with respect to + TB are, namely : (*a*) it fails to block the autonomic ganglia (side-effect) ; and (*b*) it rarely releases **'histamine',** hence it fails to cause either bronchospasm or hypotension. It is found to have little effect on the circulatory system.

Interestingly, anticholinesterases, ACH and K^+ ion antagonize competitively pancuronium bromide effectively ; however, its activity is virtually enhanced by general anaesthetics, for instance : **halothane, ether, enflurane** etc. (see **Chapter 4**). Therefore, the latter substantial potentiation in pharmacological activity is particularly useful to the '**anaesthetist'** due to the fact that it is administered invariably as an '*adjunct'* to the anaesthetic procedure in order to cause simultaneous relaxation of the skeletal muscle.

4.5. Suxamethonium Chloride (Succinylcholine Chloride)

It usually has an extemely transient duration of action by virtue of the fact that it undergoes rapid hydrolysis by the help of serum butyryl (pseudo) cholinesterases. However, a prolonged muscular

*An agent, chemical or surgical, that prevents function of the vagus (cranial) nerves.

Benabe JE *et al. AM. J. Hypentens*, **6 : 701, 1993.

relaxation may be accomplished by continuous IV infusion, and the degree of muscle paralysis is controlled adequately by fine-tuning the rate of infusion precisely. It has been observed that the **'drug'** does not cause liberation of histamine, but may give rise to hypersensitivity reactions occassionally. It effectively produces contractions of motor units (*fasciculations*) and axon reflux-conducted impulses on account of its ability in depolarizing the motor end plate. An excessive dose may produce temporary respiratory-depression. Importantly, its action, just contrary to that of +TB, is not antagonized by such drugs as : **physostigmine, neostigmine** or **edrophonium chloride.**

4.6. Decamethonium Bromide

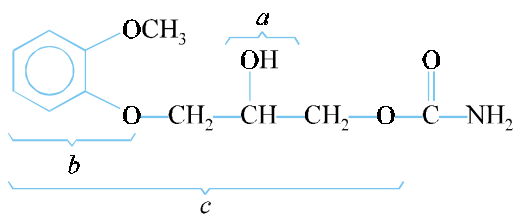
It cannot undergo hydrolysis in the presence of cholinesterase ; and, therefore, gives rise to an appreciable prolonged duration of action. It is usually considered to be a depolarizing neuromuscular relaxant by virtue of the fact that it initiates an action of **'nicotinic depolarization'** at the site of motor end-plate membrane.

4.7. Mephenesin

The **'drug'** exerts its action by causing relaxation of the hypertonic (*i.e.*, in a state of greater than normal tension) muscles minimise the response to the sensory stimuli, and also causes a significant depression of the superficial reflexes. Its weak activity and transient effect are on account of the facile metabolism of the primary hydroxyl function. In has been observed that the **'carbamylation'** of the said moiety enhances its activity. Importantly, the *para*-chlorination affords an appreciable increase in the prevailing lipid-water partition coefficient and helps in blocking the *para*-position from undergoing hydroxylation as far as possible.

4.8. Methocarbamol

The most probable site for the metabolic attack are the **secondary hydroxyl function 'a'** and the *two* **ring positions '*b*' and '*c*'** strategically located **opposite the ether moieties,** as shown below :



Methocarbamol

Its centrally acting muscle relaxant profile, after due parenteral administration is not only prompt but also intense enough to allow and facilitate orthopaedic procedures.

4.9. Meprobamate

It is also recognized as a potent sedative hypnotic drug ; and exerts a plethora of overall pharmacological characteristic features very much akin to **barbiturates** and **benzodiazepines.** However, the precise mechanism of action causing the anxiolytic effects is still not explicitely understood but it is believed that it may involve effects particularly on conductivity in certain specific areas of the brain.* It has already been shown that it does not seem to act by influencing the prevailing GABAergic systems. Interestingly, it is found to exhibit **interneuronal blocking activities** specifically in the area of the spinal cord ; therefore, it is said to be partially responsible for causing the much desired skeletal muscle

*Berger FM ; In : Usdin E and Forrest IS (eds.) **Psycliotherapeutic Drugs**, Pt. II, Mercel Dekker, New York, p-1089, 1977.

relaxation. Besides, the inherent general CNS-depressant activities possessed by it may also mainly attribute towards the skeletal muscle relaxant activity.

4.10. Chlorphensin Carbamate

The drug undergoes metabolism quite rapidly *via* the **'glucuronidation'** of the secondary hydroxyl function present in it. Its biological half-life in humans is 3.5 hours.

4.11. Carisoprodol

Its sedative and muscle relaxant activities specifically caused due to the reticulospinal depression. It has been established virtually that a certain portion of its **muscle relaxant** property is contributed due to analgesia, sedation and alleviation of anxiety status. Its on set of action occurs within a span of 30 minutes, while the duration of action lasts between 4 to 6 hours. The drug gets metabolized invariably in the liver ; and its elimination half-life is approximately 8 hours.

4.12. Tybamate

It is closely, related to **meprobamate**, wherein it has an additional *butyl moiety*, attached to the terminal amino function. It almost possesses the same spectrum of activity as that of **meprobamate**. Generally, the polyol compounds are not so effective and potent in *spasticity* on account of dyskinesia.

4.13. Metaxalone

This **drug substance** enjoys the reputation to exert muscle relaxant activities having a central nervous system focus of action. It gets metabolised by eliminated *via* hepatic metabolism ; and its half-life is between 2 to 3 hours. It attains peak blood levels within a span of 2 hours, while the duration of action lasts from 4 to 6 hours.

4.14. Chlorzoxazone

It acts by inhibiting the polysynaptic* reflexes both within the spinal cord and subcortical regions of the brain. It has been observed that more than 90% of it gets glucuronidated in the liver. The elimination half-life is about 60 minutes ; and the absorption time is from 3 to 4 hour.

4.15. Dantrolene Sodium

Its mechanism of action essentially differs from the classical neuromuscular blocking drugs, wherein its action is quite distal to either the neuro muscular junction or the nicotinic receptors. Alternatively, it has been amply proven that it suppresses the excitation-contraction coupling sequence by interfering with the corresponding release of calcium from the sarcotubular reticulum. In such a situation, the muscle fibres still very much give response to the nerve impulses ; however, the contractile response is decreased to a significant extent but never abolished completely. Hence, muscle weakness, rather than paralysis is normally accomplished as the ultimate outcome. Consequently, the **'fast muscle fibres'** (white) are affected more significantly in comparison to the **'slow muscle fibres'** (red). As the contractility of the intrafusal fibres present in the muscle spindles gets lowered appreciably, which in turn attenuate the spinal cord-mediated stretch reflexes ; and this provides a plausible explanation of the ability of dantrolene sodium to help in causing tremendous relief in certain types of acute muscular spasm. Furthermore, it is quite possible that perhaps a direct effect on the motor neurom may be involved in this rather narrow spectrum of activity, because the drug seems to exhibit CNS depressant activity to a certain degree.

*__Polysynaptic :__ Refers to nerve pathways involving multiple synapses.

4.16. Cyclobenzaprine Hydrochloride

The drug exerts its action by causing an appreciable depression in the suprasegmental (*i.e.*, upper) motor neurons in the brainstem. Besides, it also depresses to a certain degree the spinal motor neurons to lower the reflex skeletal muscle activity plus the tonus. Furthermore, it is found to cause inhibition to both the α- and γ-motor systems. It is employed invariably to afford substantial relief in spasm and pain that are linked with **musculoskeletal disorders.** It is intimately bound to plasma albumin. It has been observed to undergo conjugation and biotransformation to the corresponding glucuronides in the liver. It is excreted negligibly in its unchanged form into the urine, but to some extent excreted into milk. The elimination half-life ranges between 1 to 3 days.

4.17. Baclofen

The **muscle relaxant** actions of this drug invariably result from an action taking place within the *spinal cord*, which being the prime site where both monosynaptic and polysynaptic reflexes are usually prevented by it effectively. **Baclofen,** being a structural variant of **GABA (i.e., γ-aminobutyric acid)** which is an inhibitory transmitter within the CNS, the partial activity of it is attributed to its agonist characteristics existing at the site of $GABA_B$ receptor ; and that is subsequently coupled to a **G-protein-activated K^+ channel.** Nevertheless, the exact mechanism of its action is still not yet fully understood. Importantly, its inherent ataxis as well as sedative properties are very much consistent with a similar type of action prevailing in the brain. More than 80% of the drug gets excreted in the urine. The elimination half-life ranges between 3 to 4 hours. Its oral absorption period is nearly 2 hours.

Probable Questions for B. Pharm. Examinations

1. Explain with the help of structure that every 'half-molecule' of TUBOCURARINE is identical to ATROPINE. Discuss the striking different between the two drug molecules.

2. How would you classify the neuromuscular blocking drugs ? Give structure, chemical name and uses of **one** potent drug from each category.

3. Explain the following :

(*i*) The distance between the two onium groups present in decamethonium.

(*ii*) Why decamethonium bromide exerts a much more prolonged effect.

(*iii*) A non-depolarizing muscle relaxant having a steroidal moiety.

(*iv*) Various steps involved in the synthesis of gallamine triethiodide from pyrogallol.

4. Classify the centrally-acting muscle relaxants and give the structure, chemical name and uses of **one** important member of each class.

5. Discuss the synthesis of a potent glycerol monoether analogue prepared from :

(*i*) *p*-Chlorophenol, and

(*ii*) 1-Chloropropane-2, 3-diol.

6. How would you synthesize meprobamate ? Discuss the various steps sequentially.

7. Name an important member of benzoxazole analogue employed as muscle relaxant. Give its one-step synthesis.

8. Give the structure, chemical name and uses of Dantrolene Sodium.

9. Discuss the synthesis of the following important muscule relaxants.

(*i*) Chlorophenesin carbomate, and

(*ii*) Methocarbamol

10. Enumerate the mode of action of various types of muscule relaxants by giving specific examples.

RECOMMENDED READINGS

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2. Block JH and Beale JM (eds.) : **Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry,** Lippincott Williams and Wilkins, New York, 11th edn, 2004.
3. C.K. Cain and A P Roszkowski, **Psychopharmacological Agents,** Vol. I (ed.) M Gordon, New York, Academic Press (1967).
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9

Central Nervous System Stimulants

Chapter

9 Central Nervous System Stimulants

1. INTRODUCTION

Central nervous system (CNS) stimulants are drugs that produce generalized stimulation of the brain or spinal cord which may lead to convulsion. They are of limited therapeutic value because of their convulsant activities. There are, however, some that are used as respiratory stimulants (*e.g.*, **Nikethamide**) and others like the xanthine derivatives have many pharmacological actions and uses. Sympathomimetic amines like **amphetamines** and **ephedrine**, which are potent **CNS stimulants**, are discussed elsewhere.

A few **central nervous system stimulants** exhibit predominant central stimulant action, *e.g.*, **strychnine**, **nikethamide**, **leptazol**, **picrotoxine**, etc. ; others possess multiple side-effects, *.e.g.*, **ephedrine** and **atropine** act on the autonomic nervous system ; and finally a number of drugs do exert temporary stimulation of CNS in toxic doses, *e.g.*, **local anaesthetics**, **santonin**, **salicylates**. In usual practice, the central nervous system stimulants find their use in emergencies for prompt and short-term excitation of CNS, because **a prolonged stimulation may be followed by depression.**

CNS-stimulants may also be defined as : **'drug substances that most specifically afford an enhancement in excitability either very much within the different portions of the brain or the spinal cord'.** The most commonly observed, marked and pronounced stimulatory effects produced by a plethora of **CNS-stimulants** are essentially comprise of distinct wakening and enhanced motor function which give rise to a host of both covert and overt pharmacological actions, such as : individual feelings of increased mental alertness, lowered feeling of personal fatigue, enhanced concentration, apparent elevation in mood, and above all the increased energy and enthused motivation. It is, however, pertinent to state at this function that an excessive **CNS stimulation** may ultimately lead to serious and critical dose-dependent adverse effects, namely : mental anxiety, mental agitation, extreme nervousness, and sometimes epileptic seizures as well.

The suggested *modus operandi* of the ensued excitability of the **CNS** brings about a much so important and an intricate equilibrium between the excitatory and the inhibitory activity inside the brain. It has been established beyond any reasonable doubt that the **'excitatory transmitters',** such as : glutamic and aspartic acids, are considered to be the most important neurotransmitters prevailing at the excitatory synapses at which strategical location their activities are duly mediated through either **NMDA (N-methyl-D-aspartate)** or **non-NMDA (AMPA/quisqualate or Kainate) receptors.** Just contrary to the above

the predominant and extremely important *'inhibitory neurotransmitters'* are essentially **glycine (α-amino acetic acid) and GABA (γ-aminobutyric acid).** Besides, **adenosine-***a* neuromodulator serves as a major player in CNS excitation by exhibiting a distinct depresant action, by virtue of the fact that it has the ability : (*a*) **to minimise impulse-generated transmitter release ;** and (*b*) **to check excitation of post synaptic elements by direct hyperpolarization of the neuronal membrane.** Evidently, a plethora of clinically useful **CNS stimulants** cause excitation due to their proven antagonism prevailing at **glycine, GABA** and **adenosine** receptors. However, the host of **indirect-acting sympathomimetics** usually produce marked and pronounced CNS stimulation simply by increasing the actions of the **endogenous catecholamines** due to their inherent strong capability to either prevent or release adequately the uptake of endogenous **catecholamines.**

Salient Features : The important cardinal features of the **CNS stimulants** are enumerated below :

(1) **Amphetamine** the well-known **central sympathomimetic agent** and its close structural variants usually exhibit significant **alerting and antidepressant** activities but therapeutically find their abundant utility as *anorexiants.**

(2) Because of the immense abuse potential with **amphetamine** and particularly **methamphetamine,** the vigorous and intensive search is already on to suggest better and safer alternative medical treatments for the CNS stimulants to combat such critical disorders efficiently. **Modafinil,** after recent clinical trials, may prove to be a promising alternative candidate drug in treating **narcolepsy**.**

(3) The relatively older practice of employing **CNS stimulants** as respiratory stimulants particularly in instances of overdoses with depressant drugs. Recently their therapeutic usage in such critical conditions is no longer recommended on account of the following valid reasons and facts, namely :

(*a*) Antagonism of the **'depressant actions'** are found to be non-selective in nature.

(*b*) Both **epileptic seizures** and **cardiac arrythmias** may be inducted while making an attempt to reverse the process of respiratory depression.

(*c*) In order to provide a relatively safer and equally effective desired treatment of the patient the urgent and dire need of different supportive measures are an absolute necessity.

Interestingly, the proven ability of *caffeine*—a **methylxanthine** to enhance appreciably **'mental alterness'** is perhaps one of the main cardinal factors for the world-wide, high consumption of caffeine-containing beverages and natural **'drug-substances',** such as : tea, coffee, chickory, kola nut, areca nut etc. **Caffeine** is also found as an integral component in several analgesic drug formulations (dosage forms), including both prescription and non-prescription drugs (**OTC-drugs*****), although its exact efficaciousness in the control and management of pain is not yet well understood with concrete evidence.

2. CLASSIFICATION

The **central nervous system stimulants** may be classified into the following *three* categories, namely :

*Agents that produce loss of appetite.

**A chronic ailment consisting of recurrent attacks of drowsiness and sleep during day time.

***Over-the-counter drugs.

(*i*) Xanthine Derivatives

(*ii*) Analeptics

(*iii*) Miscellaneous Central Nervous System Stilmulants.

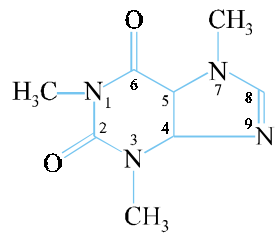
2.1. Xanthine Derivatives

The **xanthine derivatives** as stated earlier have a wide spectrum of therapeutic applications ranging from their stimulation of cardiac muscle, enhanced diuresis, stimulation of CNS and finally a soothing relaxation of bronchi and the coronary arteries.

A few typical examples of the members of this category are : **caffeine, theophylline, theobromine, aminophylline, etofylline** and **proxyphylline.**

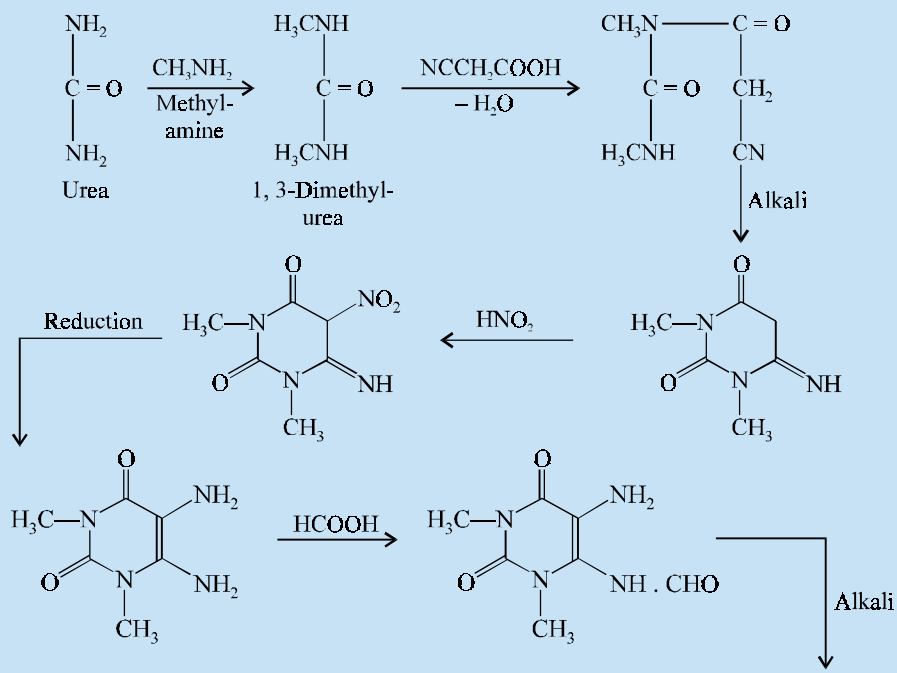
A. Caffeine BAN, USAN,

1, 3, 7-Trimethylxanthine ; 1H-Purine-2, 6-dione ; 7-Methyltheophylline ; B.P. ; U.S.P. ; Eur. P.



Caffeine is an alkaloid isolated from coffee, tea or the dried leaves of *Camellia sinensis* (*Theaceae*), or prepared synthetically.

Synthesis



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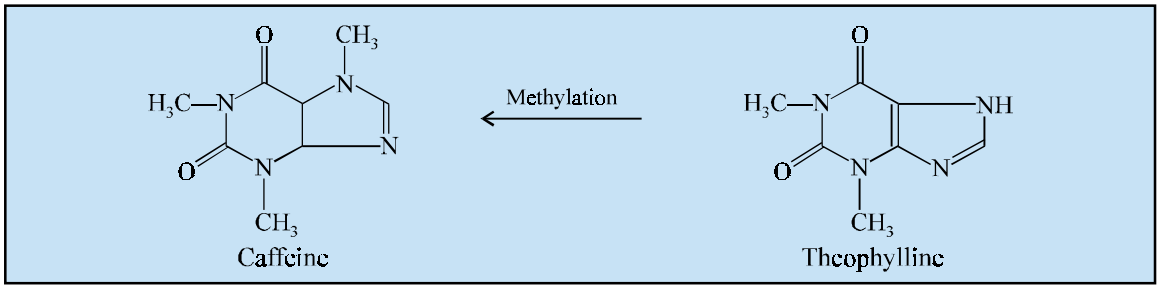
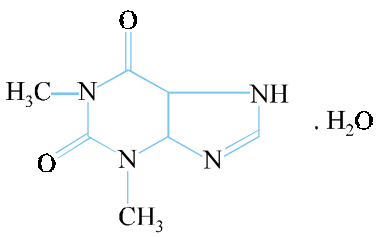


1, 3-Dimethyl urea is prepared by the interaction of urea and methylamine, which upon treatment with cyanoacetic acid yields an open-chain nitrite with the elimination of a molecule of water. This resulting compound undergoes cyclization in the presence of alkali. The cyclized compound on treatment with nitrous acid, followed by reduction, reaction with formic acid and subsequently with alkali gives rise to the formation of theophylline, which upon methylation finally yields **caffeine**.

Caffeine is a potent central stimulant. It also acts on the cardiac muscle and on the kidneys. It stimulates the higher centres of the CNS thereby causing enhanced mental alertness and wakefulness. **Caffeine** helps in the stimulation of respiratory centres. Its diuretic action is due to enhanced glomerular filtration rate, increased renal blood flow and above all the reduction of the normal tubular reabsorption.

Dose : *100 to 500 mg, usual 200 mg as required.*

B. *Theophylline* BAN, USAN,



1, 3-Dimethylxanthine ; 1H-Purine-2, 6-dione, 3, 7-dihydro-1, 3-dimethyl monohydrate ; B.P., U.S.P., Eur. P., Int. P., Ind. P.

Constant-T$^{(R)}$ (Ciba-Geigy) ; Elixophyllin$^{(R)}$ (Berlex) ; Theo-24$^{(R)}$ (Searle)

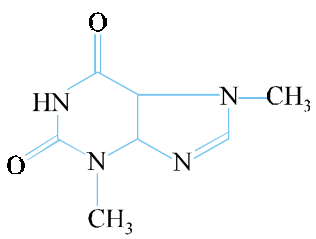
Synthesis :

Theophylline is prepared by the method described under caffeine.

Theophylline is widely used for the treatment and symptomatic relief of acute and chronic bronchial asthma, bronchospasm, cardiac dyspnea and angina pectoris.

Dose : *Usual, 200 mg 3 to 4 times per day.*

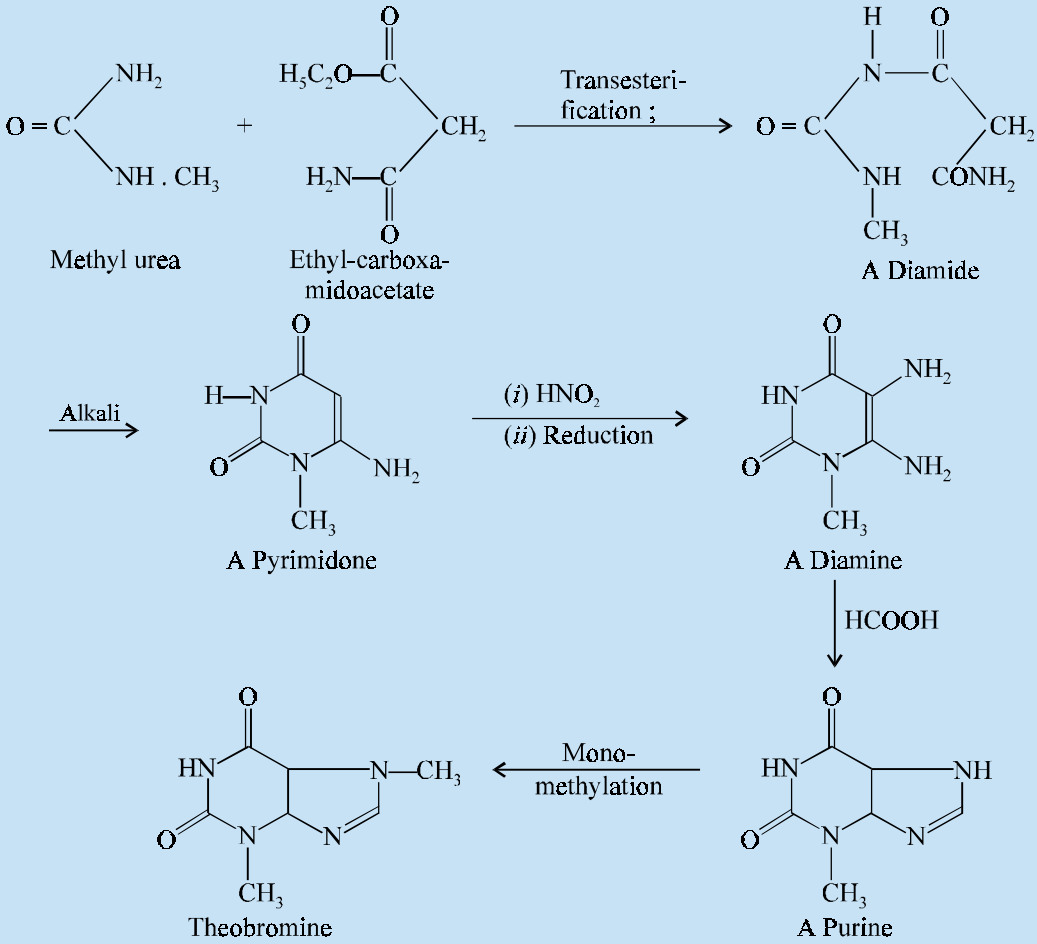
C : Theobromine BAN,



3, 7-Dimethylxanthine ; 3, 7-Dihydro-3, 7-dimethylpurine-2, 6 (1H)-dione ; B.P., Eur. P.

Theosalvose$^{(R)}$ (Techni-Pharma, Mon.)

Synthesis

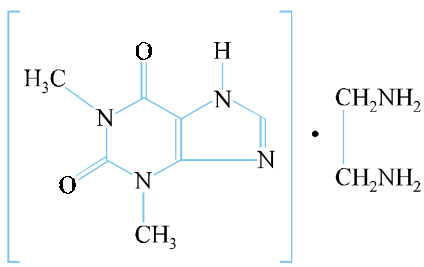


Methyl urea and ethyl carboxamido acetate undergoes transesterification to yield a diamide which on treatment with alkali gives rise to a pyrimidone. The resulting product on reaction with nitrous acid followed by reduction gives a diamine which on being treated with formic acid produces a purine and when subjected to monomethylation yields finally the **theobromine.**

The action of **theobromine** on the CNS is minimal and hence it may be employed for its other effects, namely, diuretic, effect on the coronary arteries, without showing significant side-action of central stimulation.

Dose : *Usual, 500 mg.*

D. Aminophylline INN, BAN, USAN,



1H-Purine-2, 6-dione, 3, 7-dihydro-1, 3-dimethyl-, compound with 1, 2-ethane-diamine (2 : 1) ; Theophylline compound with ethylene diamine (2 : 1) ; B.P., U.S.P., Eur. P., Int. P., Ind. P.

Aminophyllin(R) (Searle) ; Phyllocontin(R) (Purdue Frederick) ;

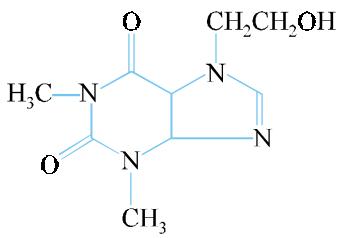
Preparation

Aminophylline is conveniently prepared by the vigorous shaking together of theophyline and ethylenediamine in stoichiometric proportions (2 : 1) in anhydrous ethanol.

Aminophylline is frequently used for the treatment and control of congestive heart failure, bronchial asthma, Cheyne-Stokes respiration, cardiac paroxysmal dyspnea. It is also a vital component in many cough mixtures so as to reduce the cough reflexes and to cause expectoration.

Dose : *Oral 300 to 800 mg per day ; usual, 200 mg 3 times daily. Intravenous, slowly, 250 mg to 1.5g per day ; usual, 500 mg slowly 1 to 3 times daily.*

E. Etofylline, INN, BAN,



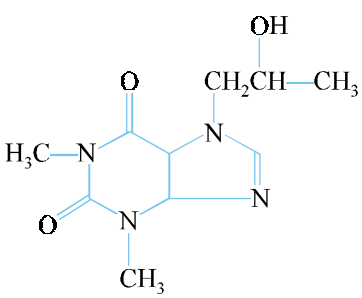
7-(2-Hydroxyethyl)-theophylline ; Hydroxyethyl-theophylline ; 7-(2-Hydroxyethyl)-1, 3-dimethylxanthine ; B.P., Eur. P ;

Bio- Phyllin(R) (Bio-Chemical Lab. Canada)

It is claimed to be a *better-tolerated drug than aminophylline* and may be administered orally, intramuscularly and intravenously.

Dose : *Up to 1.5g per day.*

F. Proxyphylline INN, BAN,



7-(2-Hydroxypropyl)-theophylline ; 7-(2-Hydroxypropyl)-1, 3-dimethylxanthine ; B.P., Eur. P.

It is a **theophylline derivative.** Its actions and uses are similar to those of **aminophylline.** It is found to be *better tolerated both orally and intravenously.*

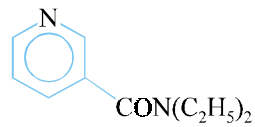
Dose : *Usual, oral, 300 mg 3 times per day.*

2.2. Analeptics

Analeptics counteract narcosis, with a specific stimulant action on the central nervous system. These are primarily employed to combat the drug-induced respiratory depression. An excessive dose of analeptics may result a wide-spread stimulation of the brain that may ultimately cause convulsions.

A few important drugs under this category are namely : **nikethamide, ethamivan, pemoline, pentetrazol, doxapram,** and **bemegride.**

A. Nikethamide INN,



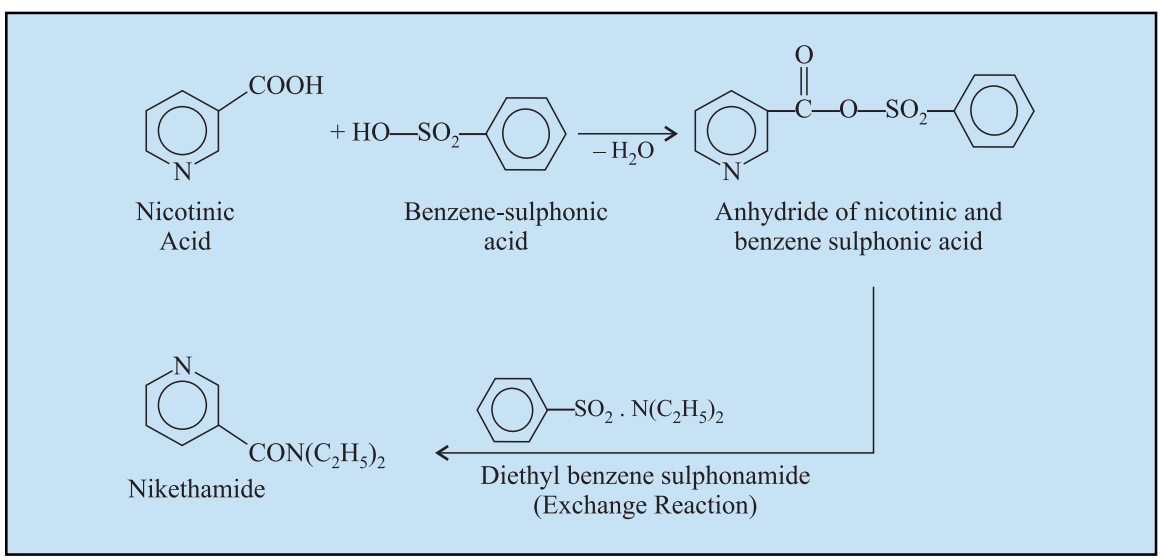
N, N-Diethylnicotinamide ; N, N-Diethylpyridine-3-carboxamide ; Diethylamide nicotinic acid ; B.P., Eur. P., Int. P., Ind. P., N.F. XIII

Coramine(R) (Ciba-Geigy) ; Corazon(R) (Grossmann, Switz)

Synthesis

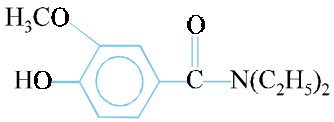
A molecule each of nicotinic and benzenesulphonic acid undergoes dehydration to yield a corresponding anhydride, which on contact with diethyl benzenesulphonamide affords an exchange reaction to give **nikethamide.**

Nikethamide is a weak analeptic employed as respiratory stimulant. It produces respiratory stimulation at doses that have only little CNS excitation. Its duration of action is very transient.



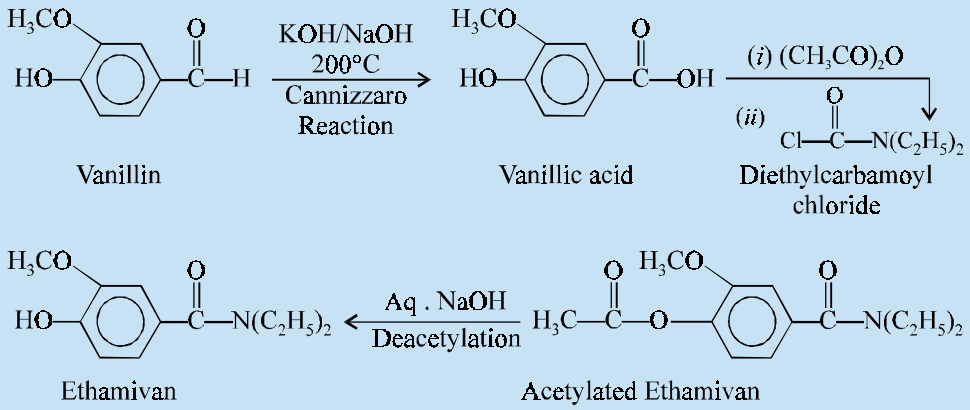
Dose : *Usual, 0.5 to 2g intravenously.*

B. *Etamivan* INN, *Ethamivan* BAN, USAN,



N, N-Diethylvanillamide ; Benzamide, N, N-diethyl-4-hydroxy-3-methoxy- ; B.P., U.S.P., N.F. ; Emivan(R) (USV)

Synthesis

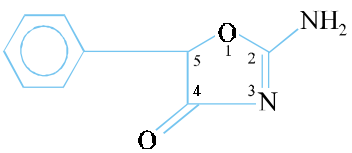


Vanillin subjected to **Cannizzaro Reaction** with KOH/NaOH at 200°C yields vanillic acid which upon treatment with acetic anhydride and diethyl carbamoyl chloride gives rise to acetylated ethamivan. This subsequently on deacetylation in aqueous NaOH yields the official compound.

Ethamivan is a respiratory stimulant having actions and uses similar to those of **nikethamide**. It can cause generalised CNS stimulation, but its action is short-lived.

Dose : *Usual, intravenous, 0.5 to 5 mg/kg.*

C. Pemoline INN, BAN, USAN,

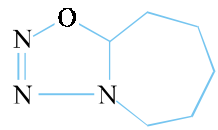


2-Imino-5-phenyloxazolidin-4-one ; 4(5H)-Oxazolone ; 2-amino-5-phenyl ; Phenilone ; Cylert(R) (Abbott) ; Ronyl(R) (Rona, UK)

It is a potent central nervous system stimulant which affects all parts of the nervous system to some extent. It has also been used for the *hyperkinetic states in children.*

Dose : *Usual, 20 mg twice daily.*

D. Pentetrazol INN, BAN,

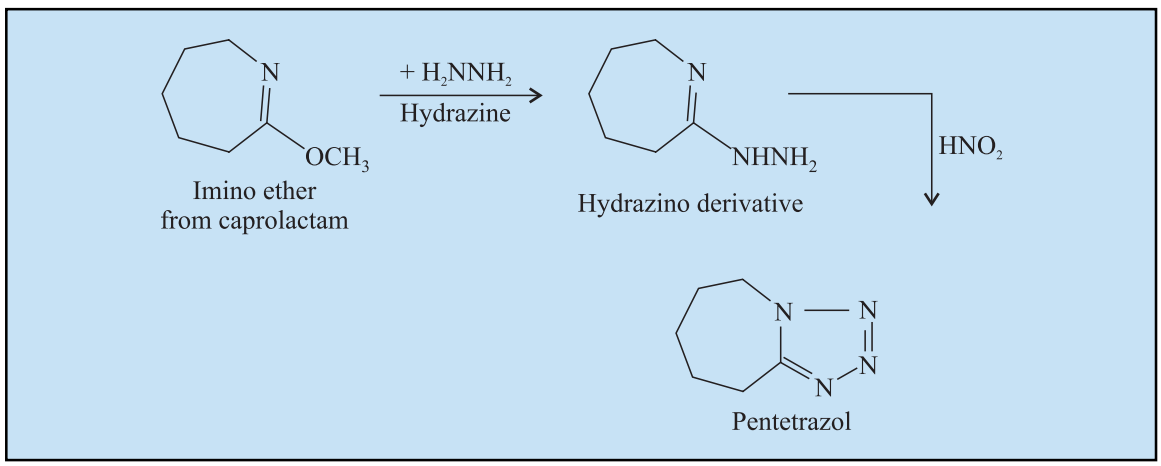


6, 7, 8, 9-Tetrahydro-5H-tetrazoloazepine ; 1, 5-Pentamethylene-tetrazole ; Laptazole ; Pentazol ; Pentylenetetrazol ; Corazol ; B.P., Eur. P., Int. P., Ind. P. ;

Metrazol(R) (Knoll, USA)

Synthesis

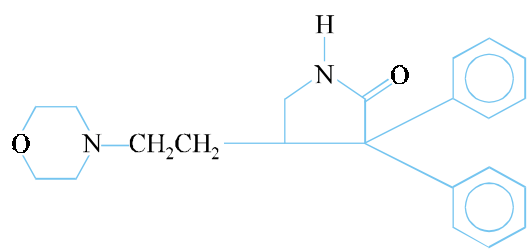
An amino ether obtained from caprolactam when reacted with hydrazine affords the corresponding hydrazino derivative which on treatment with nitrous acid yields the official article.



Pentetrazol is a CNS stimulant with actions and uses similar to those of nikethamide. It is used to induce convulsion in animals. It has been employed successfully in the elderly subjects to alleviate the symptoms of mental and physical activity.

Dose : *Oral, for treatment of senility, initially 100 or 200 mg 3 or 4 times daily, reduced to half for maintenance.*

E. Doxapram INN, Doxapram Hydrochloride USAN ;

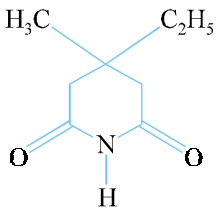


1-Ethyl-4-(2-morpholinoethyl)-3, 3-diphenylpyrrolidin-2-one hydrochloride monohydrate ; U.S.P. ; Dopram(R) (Robins)

It is a respiratory stimulant possessing slight vasopressor characteristics ; frequently employed in the treatment of respiratory depression following anaesthesia.

Dose : *Usual, IV., 0.5 to 1 mg/kg.*

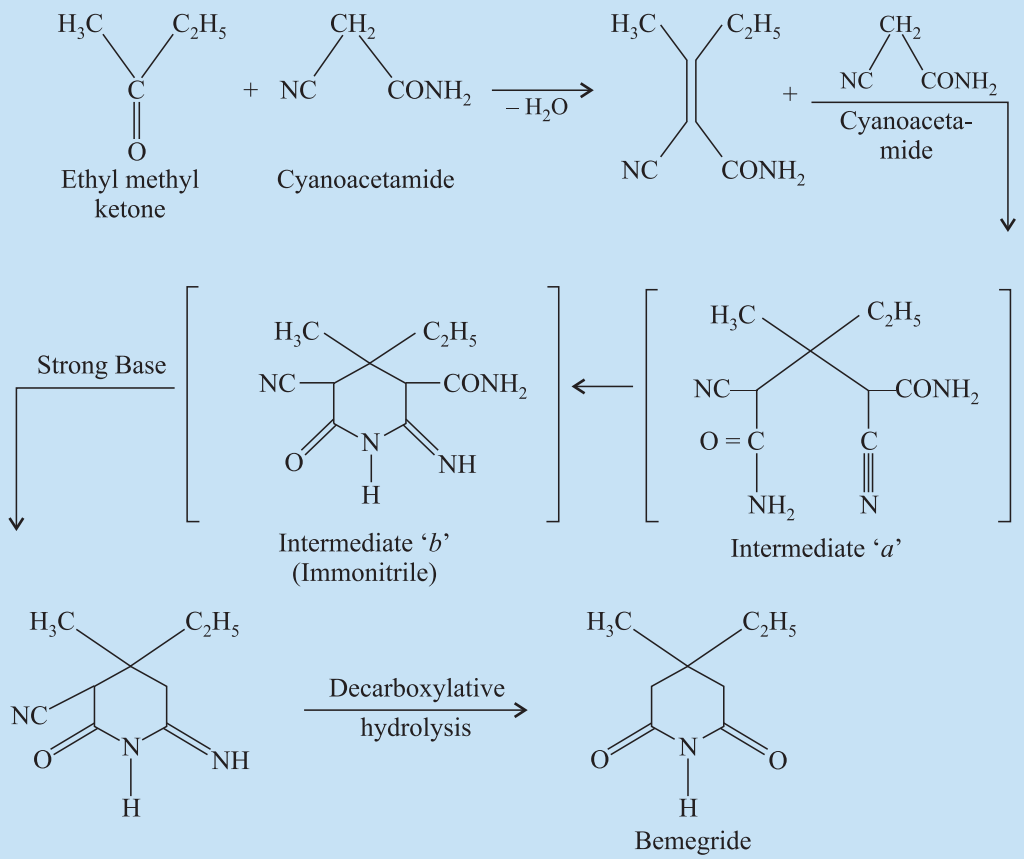
F. Bemegride INN, BAN,



3-Ethyl-3-methyl glutarimide ; 4-Ethyl-4-methyl piperidine-2, 6-dione ; B.P. (1968) ; U.S.P. (XVII) ; Int. P., Ind. P. ;

Megimide(R) (Abbott)

Synthesis :



An **Aldol Condensation** of ethyl methyl ketone with cyanoacetamide affords a loss of a molecule of water of yield an active methylene compound. Another molecule of cyanoacetamide undergoes congregate addition to give the *intermediate 'a'*. Addition of one of the amide amines to the nitrite will

subsequently give rise to the iminonitrile (*intermediate 'b'*), which on treatment with a strong base loses a carboxamide group. The resulting product on decarboxylative hydrolysis yields the official compound.

Bemegride is a respiratory stimulant with actions and uses similar to those of nikethamide.

Dose : *Usual, 25 to 50mg i.v.*

2.3. Miscellaneous Central Nervous System Stimulants

Several drugs specifically stimulate the central nervous system which are appropriately grouped together as anorexigenic or sympathomimetic agents.

Some drugs that act primarily on the central nervous system are discussed under this category, namely : **flurothyl, mazindol, phentermine** and **methylphenidate hydrochloride.**

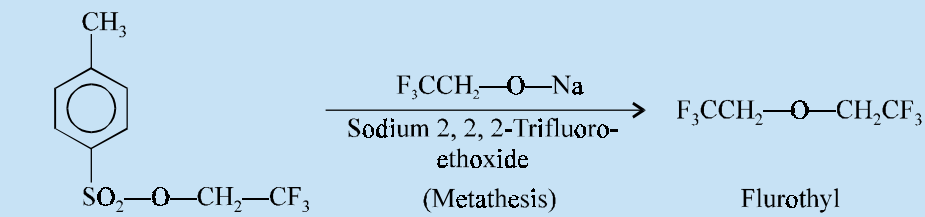
A. Flurothyl

$$F_3CCH_2—O—CH_2CF_3$$

Bis (2, 2, 2-trifluoroethyl) ether ; Ethane, 1, 1′-oxybis 2, 2, 2-trifluoro) ; U.S.P., N.F. ;

Indoklon(R) (Ohio Medical)

Synthesis



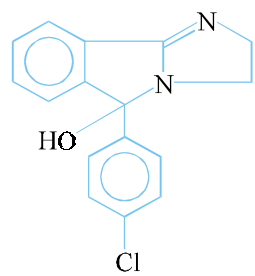
2, 2, 2-Trifluoroethyl *p*-toluenesulphonate

The interaction of 2, 2, 2-trifluoroethyl-*p*-toluenesulphonate and sodium 2, 2, 2-trifluoroethoxide causes metathesis thereby yielding flurothyl which is subsequently distilled and obtained in the purified state.

Flurothyl produces both clonic and tonic convulsions in experimental laboratory animals. It is frequently employed as an **alternative for electroconvulsive therapy** in the treatment of mental disorders. An inhalation or parenteral administration usually helps in the onset of action within 15 to 20 seconds, the initial myoclonic convulsions are immediately followed by a violent tonic phase which lasts from 30 to 90 seconds.

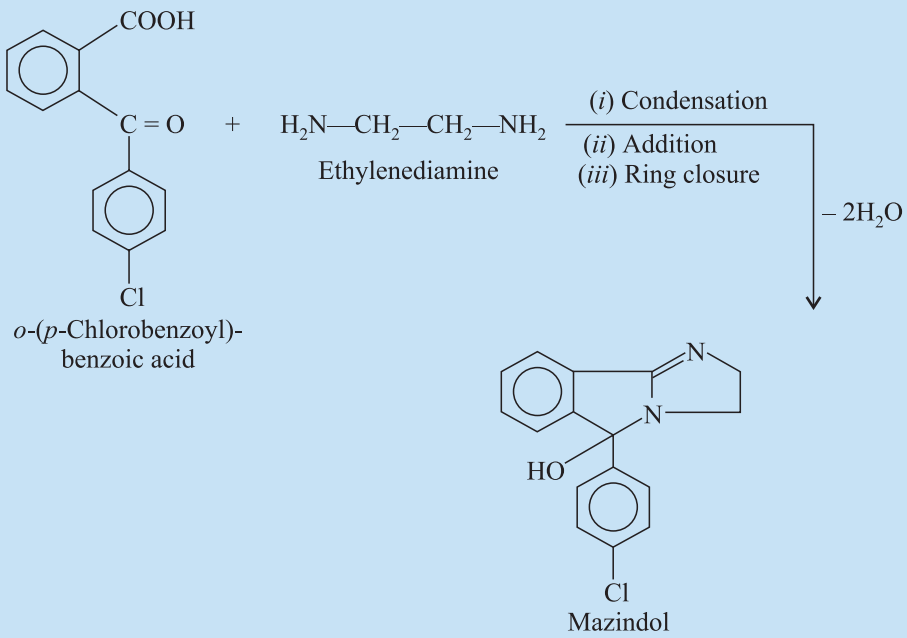
Dose : *Usual, up to 1ml by special inhalation.*

B. Mazindol INN, USAN, BAN,



5-(4-Chlorophenyl)-2, 5-dihydro-3H-imidazo 2, 1-*a* isoindol-5-ol ; U.S.P. ;
Mazanor(R) (Wyeth) ; Sanorex(R) (Sandoz)

Synthesis

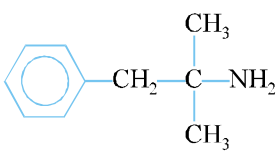


The interaction of *o*-(*p*-chlorobenzoyl)-benzoic acid with ethylenediamine affords condensation, addition and finally cyclization to yield the official product with the elimination of two moles of water.

It is an anorexiant used in the *treatment of obesity.* It also exerts a variable effect on the CNS thereby causing a **mild stimulation** in some subjects and **a mild depression** in others.

Dose : *2 mg once per day 1 hour before lunch.*

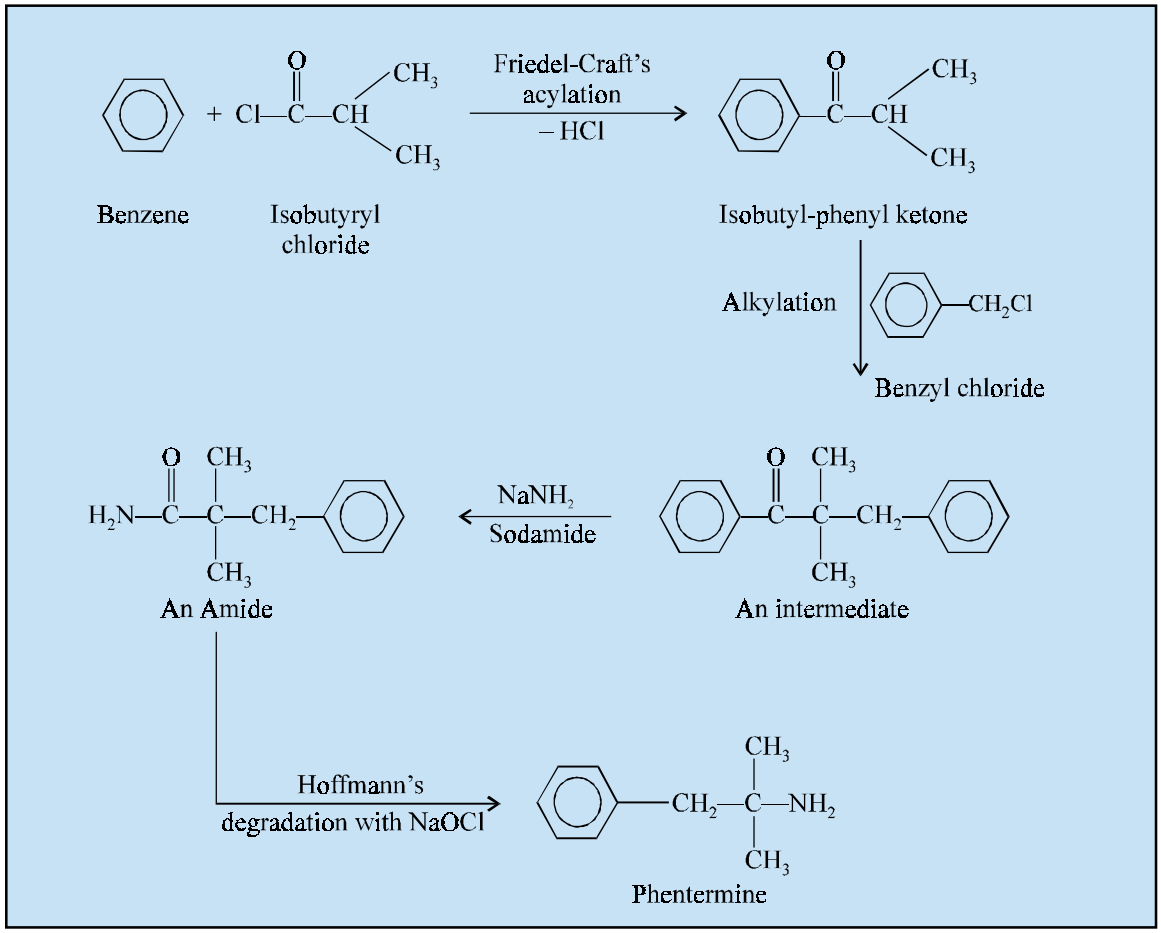
C. Phentermine INN, BAN, USAN,



α, α,-Dimethylphenethylamine ; Benzenethanamine, α-α-dimethyl ;
Ionamin(R) (Pennwalt)

Synthesis

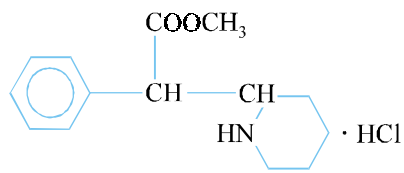
Friedel-Craft's acylation of benzene with isobutyryl chloride yields isobutylphenyl ketone which on alkylation with benzyl chloride gives rise to an intermediate. This intermediate, being a nonenolizable ketone, undergoes cessation at the amide linkage with a strong base like sodamide to yield the corresponding amide which when ultimately subjected to **Hoffmann's degradation** with sodium hypochlorite gives the desired product.



Phenetermine is a sympathomimetic agent employed as an anorectic in the *treatment of obesity*.

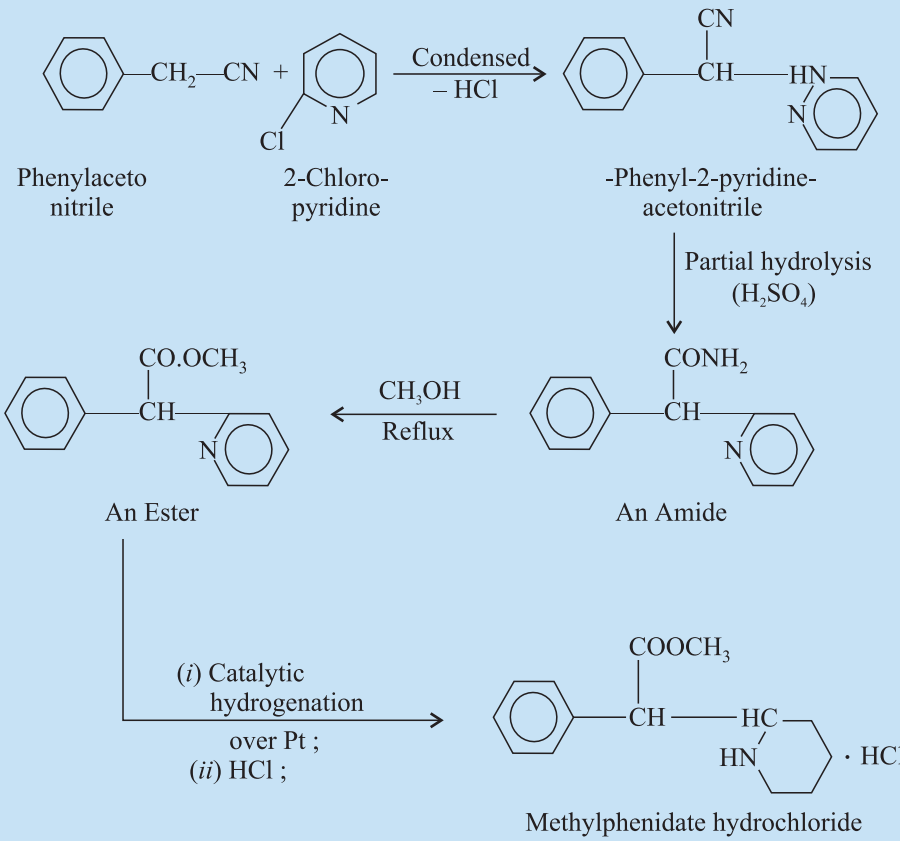
Dose : *Usual, adult 15 to 30 mg at breakfast.*

D. Methylphenidate INN, BAN, Methylphenidate Hydrochloride USAN,



Methylphenidate hydrochloride ; Methyl α-phenyl-α-(2-piperidyl) acetate hydrochloride ; U.S.P. ; Ritalin Hydrochloride$^{(R)}$ (Ciba-Geigy)

Synthesis



Condensation of phenyl acetonitrile and 2-chloro-pyridine yields α-phenyl-2-pyridine acetonitrile which upon partial hydrolysis with sulphuric acid gives an amide. Reflux of this amide with methanol gives the corresponding methyl ester which upon catalytic hydrogenation over platinum and subsequent treatment with a calculated amount of hydrochloric acid yields the official product.

It is a mild CNS stimulant having a therapeutic potency intermediate to caffeine and amphetamine. It is used in the **treatment and management of minimal brain dysfunction in children.**

Dose : *Oral or parenteral, 10 to 60 mg per day ; Usual, 10 mg 2 to 3 times per day.*

3. CNS-PEPTIDES, S-GLUTAMATE AND BLOCKADE OF NMDA-INDUCED RESPONSES

3.1. CNS-Peptides

It has been duly observed that the endogenous peptide sleep substances in particular seem to regulate the prevailing neuronal activity which are directly linked with the phenomenon of sleep. **Delta-sleep-inducing peptide (DSIP)** is regarded to be the most widely known **CNS-peptide** that has been proved to be directly associated with the sleep regulatory phenomenon. It has been established experimentally that the *'dialysate'** meticulously derived from the cerebral blood of rabbits, which were

*The product obtained after carrying out the **'dialysis'.**

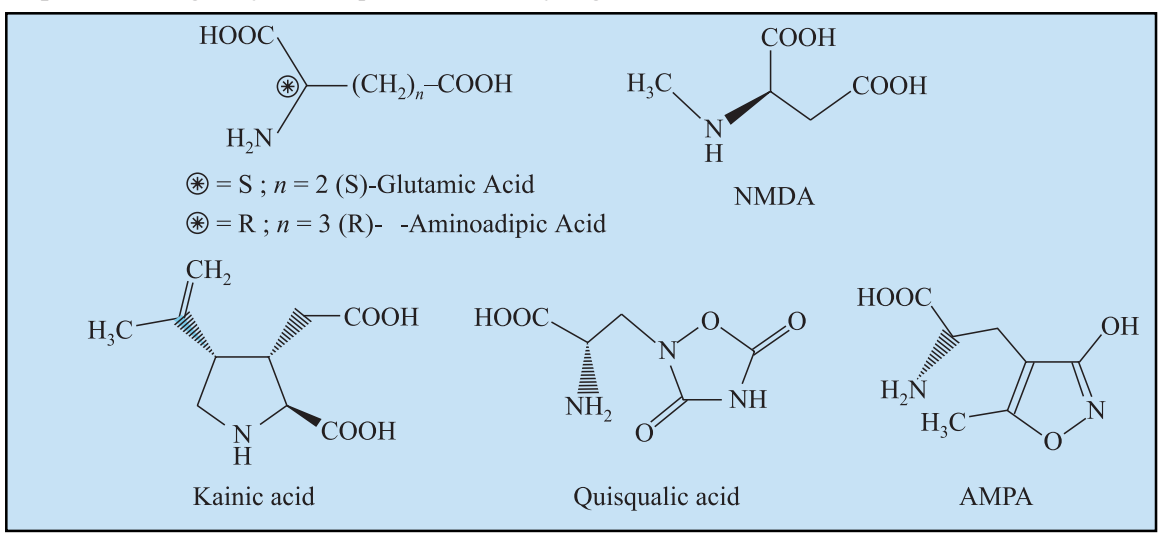
adequately maintained in a state of sleep by careful **'electrical stimulation of the thalamus',** could induce sleep efficaciously in normal rabbits. Therefore, the exact causative **'factor'** responsible might be the DSIP, which is a **non-apeptide entity.** The amino acid sequence is as given below :

Trp—Ala—Gly—Gly—Asp—Ala—Ser—Gly—Glu
1 2 3 4 5 6 7 8 9

Furthermore, it has also been proved substantially that P-DSIP, *i.e.*, the corresponding phosphorylated structural analogue of **DSIP** (having Ser at position 7), occurs and in rats it is found to at least five times more active than **DSIP.** Based scientifically and logically on the above clue it has been observed that prevailing ratio of **DSIP/P-DSIP** appears to play a vital role in modulating the circadian (*i.e.*, pertaining to events that occur at intervals of approximately 24 hours) time course of sleep and wakefulness in human beings. Besides, the two species of peptides increase **non rapid eye movement (NREM)** and **rapid eye movement (REM)** sleep. Interestingly, **DSIP** has also been employed gainfully for the control and management of insomnia and obstructive sleep apnea in patients.

3.2. S-Glutamate and Blockade of NMDA-Induced Responses

It is believed that the acidic amino acid (S)-glutamic acid happens to be the most prevalent and predominant excitatory transmitter in the CNS acting specifically at the **excitatory amino acid (EAA)** receptors.* The first and foremost scientific evidence with regard to the heterogeneity amongst the EAA-receptors was brought to light from the variable activity of a spectrum of agonists entirely based on the glutamic acid structure in various portions of the CNS.** Furthermore, rather concrete evidence surfaced from the wonderful observation suggesting that **(R)-α-aminoadipic acid (D-αAA)** eventually blocked the **N-methyl-(R)-aspartic acid (NMDA)**-induced and synaptic excitation prevailing in the spinal motor neurones ; but not caused due to depolarizations by either of the two natural products, *viz.*, **kainic acid and quisqualic acid** as illustrated below. However, the instance for **EAA-receptor subtypes** was adequately substantiated by the gainful knowledge of the selective blockade of **NMDA-induced responses** strategically on the spinal neurones by Mg^{2+} ions.***



*Watkins JC and Evans RH, *Ann. Rev. Pharmacol. and Toxicol.*, **21,** 165, 1981
Duggan AW, *Exp. Brain Res.*, **19, 522, 1974
***Evans RH *et al.*, *Experientia*, **33,** 489, 1977.

4. MECHANISM OF ACTION OF SELECTED CNS-STIMULANTS

The most plausible and logical explanations pertaining to the mechanism of action of certain selected **CNS-stimulants** are described as under :

4.1. Caffeine

It stimulates all levels of the CNS, particularly the cerebral cortex, distinctly producing a more rapid and clarity of thought, improved psychomotor coordination, wakefulness and augmentation of in spirit and feelings in fatigued patients. Its cortical effects are observed to be not only of shorter span but also are of milder nature in comparison to amphetamines. Interestingly, at higher doses it substantially stimulates vasomotor, medullary vagal and respiratory centres, thereby affording an induction of brady cardia, vasoconstriction, and an enhanced rate of respiration.

Caffeine exerts a noticeable **inotropic effect*** on the myocardium and a positive **chronotropic effect**** particularly on the sinoatrial mode which ultimately result into a transient observed heart-rate, force of contraction, working of the heart, and above all the cardiac output. However, it is largely belived that the vasoconstriction of the cerebral blood vessels by caffeine remarkably contributes a lot to its exceptional capability to relieve headaches.

It is found to cause stimulation of the voluntary skeletal muscle which is turn enhances the force of muscle contraction ; and, hence, the muscular fatigue.

Caffeine undoubtedly stimulates the **parietal cells***** which enhances the excretion of the gastric juice in the stomach (*i.e.*, causes acidity).

It is found to exert a mild diuretic action by increasing the renal blood flow, glomerular filtration rate and by minimising the proximal tubular reabsorption of Na and H_2O.

The metabolism of caffeine resolves around two major phenomena, namely : (*a*) **glycogenolysis :** and (*b*) **lipolysis.** Fortunately, the outcome of these two biochemical processes, leading to enhanced **blood-glucose** and **plasma lipids** do not cause any alarming consequences in relatively healthy human subejcts.

4.2. Aminophylline

It gets converted to almost 79% into its structural analogue **theophylline.** It has been found that the absorption from the GI tract after due oral as well as rectal administration is invariably incomplete, sluggish and variable. The optimal serum therapeutic levels achievable range from 10 to 20 mcg . mL^{-1}.

4.3. Theophylline

It is well absorbed after administration, which may be retarded in the presence of food. However, the rectal suppositories are absorbed slowly and very much erratically. The peak plasma levels for uncoated tablets and liquids are attained within a span of 2 hours ; the average volume of distribution stands at 0.5 $L.kg^{-1}$. A minimum of 10 to 20 mcg. mL^{-1} in plasma or serum levels is an absolute requirement to cause a maximum bronchodilator response. Generally, it exhibits relatively much more pharmacological response than theobromine in all aspects.

*Influencing the force of muscular contractility.

**Influencing the rate of occurence of an event *e.g.*, heart beat.

***A large cell on the margin of the peptic glands of the stomach that secretes HCl and the intrinsic factor.

4.4. Nikethamide

It has been advocated for the treatment of drug overdosage due to excessive CNS-depressants. It finds its occasional usage having potential **'emergency value'** as a respiratory stimulant prior to other modes of supporting respiratory devices.

4.5. Pemoline

Though sufficient extensive and intensive laboratory studies have revealed that pemoline may exert its action through the **'dopaminergic mechanisms'** ; however, the exact and precise mechanism and site of action in humans are not yet established and known. It has been observed that about 75% of its oral dosage gets excreted through the urine in 24 hours, another 43% is excreted as *'unchanged'*, and the remaining 22% is excreted as **pemoline conjugates**.

4.6. Doxapram

It is found to exert its action by stimulating respiration by an activity directly linked with peripheral carodid chemoreceptors. Therefore, it is normally employed specifically as a respiratory stimulant postanaesthetically in such situations as, namely : (*a*) chronic pulmonary diseases ; (*b*) CNS-depressant drug overdose (inadvertently) ; and (*c*) apneas.

4.7. Bemegride

Its actions are very much akin to doxapram hydrochloride. It is, however, regarded to be absolutely unsafe in patients having acute **porphyria** because it has been associated with acute attacks.

4.8. Flurothyl

It causes stimulation of the CNS and also induces convulsions, which is why it was formerly employed as an alternative to **'electro-convulsive therapy'** in the treatment of severe depression either administered through IV injection or inhalation.

4.9. Mazindol

It is mainly absorbed from the GI-tract and is mostly excreted in the urine, partly unchanged and partly as its corresponding metabolites.

4.10. Phentermine

The drug is rapidly absorbed from the GI-tract. It is observed that a major portion gets excreted in the urine, partly unchanged and partly as its metabolities. Interestingly, phentermine has a quaternary C-atom with one methyl function exactly oriented like the methyl of **(S)-amphetamine** and one methyl oriented very much similar to the **(R)-amphetamine.** Therefore, it exhibits pharmacological characteristic features of both the **(R) and (S) isomers of amphetamine.** However, it has much less abuse potential in comparison to the not-so-famous **dextroamphetamine.**

4.11. Methylphenidate Hydrochloride

It is rapidly absorbed from the GI-tract. Approximately, 80% of an orally administered dose gets metabolized to the corresponding ritalinic acid and subsequently excreted in the urine.* In fact, its actions, like **cocaine**, seem to be regulated by blockade of **catecholamine** reuptake instead by the release of catecholamines as usually takes place with the **amphetamines** in general.

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*The **'urinary excretion'** is not pH dependent.

Probable Questions for B. Pharm. Examinations

1. Name any **eight** potent CNS stimulants, give their structures, chemical names and uses.

2. Why a drug having a short-term excitation of CNS is preferred over the one having a long term effect. Explain with specific examples.

3. Classify the CNS-stimulants and give the synthesis of one potent compound from each category.

4. Give the structures of *Propoxyphylline* and *Aminophylline*. Explain why the former has a better tolerance orally and intravenously than the later.

5. Xanthines represent an important class of CNS stimulants. Give the structure, chemical name and uses of any *Three* potent drugs from this category and discuss the synthesis of any *one* of them.

6. Discuss '*Analeptics*' as an important class of CNS stimulants. Give the synthesis of

(*i*) Etamivan, and

(*ii*) Nikethamide

7. Mazindol and Phentermine represents the miscellaneous CNS-stimulants. Give their structure, chemical name and uses.

8. Discuss the synthesis of the following CNS-stimulants :

(*i*) Phentermine (*ii*) Bemegride (*iii*) Fluorothyl (*iv*) Methylphenidate hydrochloride.

9. A constituent of coca-butter that acts as a CNS-stimulant may be obtained by the interaction of methyl urea and ethyl carboxamidoacetate. Explain.

10. Give a comprehensive account on the various CNS-stimulants used in the therapeutic armamentarium.

RECOMMENDED READINGS

1. D Lednicer and L A Mitscher **The Organic Chemistry of Drug Synthesis,** John Wiley and Sons, New York (1995).

2. H D Fabing, **The Newer Analeptic Drugs**, *Med Clin N.A.* 339 (1957).

3. M E Wolff, **Burger's Medicinal Chemistry and Drug Discovery** (5th edn.) John Wiley and Sons, New York (1995).

4. Patrick GL, **'An Introduction to Medicinal Chemistry',** Oxford University Press, Oxford (U.K.), 2001.

5. Remington's : **The Science and Practice of Pharmacy** Vol. I and II, (21st end.) Lippincott Williams and Wilkins, New York, 2006.

6 . W O Foye **Principles of Medicinal Chemistry,** (4th edn.) Lea and Febiger, Philedelphia, Philadelphia. (1996).

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10

Antipyretic Analgesics

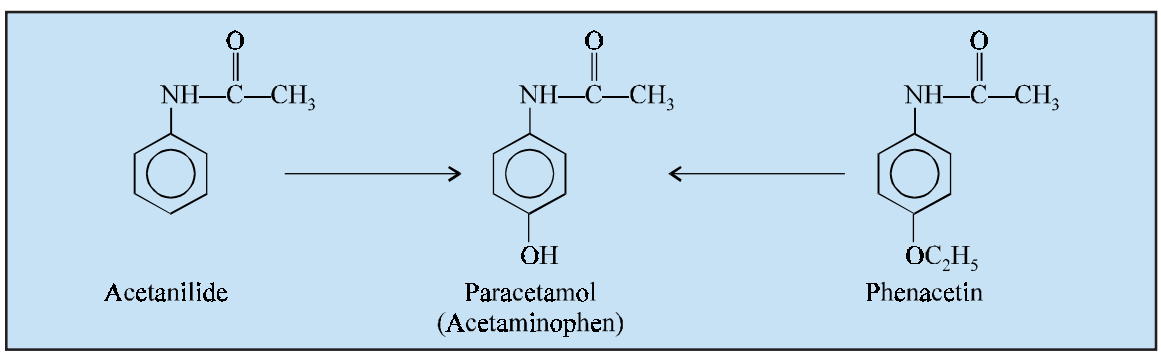
Chapter

10 Antipyretic Analgesics

1. INTRODUCTION

Antipyretic analgesics or **febrifuges** are remedial agents that lower the temperature of the body in pyrexia *i.e.,* in situations when the body temperatures has been raised above normal. In therapeutic doses they do not have any effect on normal body temperature. They exert their action on the heat regulating centre in the hypothalamus. These antipyretic agents also have mild analgesic activity. Amongst the most common group of compounds used as antipyretic analgesics are salicylates, aniline and aminophenol analogues, pyrazolones and quinoline derivatives. Though these heterogenous groups of compounds are analgesics, they have no addictive properties. Their analgesic use is limited to mild aches and pains like headache and backache.

Alternatively, **'antipyretic'** is the terminology quite frequently applied to drugs which essentially help to reduce fever to normal body temperature (*i.e.,* 98.4°F or 37°C). It is, however, worthwhile to mention here that the **'drug substances'** belonging to this particular category usually possess the ability to alleviate the sensation of pain threshold ranging from mild to severe status. These antipyretic agents are also found to be significantly effective in reducing fever to normal levels in humans. The '*drugs*' that are most commonly included here are, namely : acetanilide ; phenacetin (acetophentidin) ; and **paracetamol** [**acetaminophen** (known in US), *para*-acetaminophenol]. Interestingly, the aforesaid *three* drug entities are interrelated to one another *metabolically*, as illustrated below :



It is worthwhile to mention here that both acetanilide and phenacetin have has been withdrawn completely from being used because of its numerous toxic and undesirable effects, such as : skin

manifestations, jaundice, cardiac irregularities, and a relatively high incidence of methemoglobinemia* ; and quite seldomnly acute blood dyscrasias, for instance : hemolytic anemia. *Phenacetin* has also been dropped as a 'drug' since 1982 in US by virtue of the fact that it earned a bad reputation for causing nephrotoxicity due to its high-dose long-term abuse in several parts of the globle. It was also reported to cause kidney and liver cancer.

Paracetamol (acetaminophen) enjoys still the world-wide recognition as the only **'aniline-based analgetic-antipyretic'** for its abundant utility in controlling fever in most non-inflammatory conditions very much akin to **'aspirin'.** It has also been demonstrated adequately that both paracetamol and aspirin are **'equianalgetic'** at a dose of 650 mg.

Analgesics may be defined as–**'agents that relieve pain by elevating the pain threshold without disturbing consciousness or altering other sensory-modalities'. Besides, 'pain' may also be defined in psychological perspective as—'a particular type of sensory experience distinguished by nerve tissue from sensations, such as : touch, heat, pressure and cold'.** In the latest context '*pain*' essentially involves a major chunk of psychological factor which exclusively rests on perception. Therefore, more realistically '*pain*' may be defined introspectively in an exclusive manner.

Broadly speaking, the most probable and logical explanation for the '*mechanism*' by which certain analgesics specifically enhance the pain threshold has been caused solely due to the presence of the **'opiate receptors'** strategically located in selected parts of the CNS overtly and covertly associated with the pain regulation. It has been established that the **'opiate receptors'** are located in the following critical zones, namely :

(*a*) Medial thalamus which processes chronic, deep and burning pain that is usually suppressed by **narcotic analgesics only,**

(*b*) Brainstem's vagus nuclei which triggers the **'cough centres',** and

(*c*) Layers I and II in the spinal cord at the specific zone where the different nerves which solely hold the pain perception first synapse.

Importantly, **'endorphins'**** mostly logistically lower the intensity of pain by modulating particularly the pain threshold the critical material point at which one may commence to perceive a stimulus as **'painful'** sensation.

2. CLASSIFICATION

Antipyretic analgesics may be classified on the basis of their chemical structures.

2.1. Aniline and p-Aminophenol Analogues

In 1886, Cohn and Hepp first identified the powerful antipyretic activities residing in both aniline and acetanilid. The basic origin of this particular class of compounds from aniline has probably suggested these to be known as **'coal tar analgesics'.** However, the aminophenols (*o, m, p*) are reported to be

*The clinical condition in which more than 1% of haemoglobin in blood has been oxidized to the (Fe^{3+}) form. The principal symptom is *cyanosis.*

A generic name coined from **endogenous and **morphine** ; and commonly used for all native brain peptides having essentially the opiate-like action.

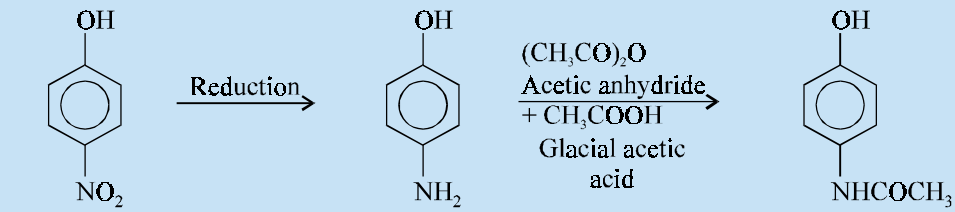
relatively less toxic than aniline. The *para*-isomer is claimed to be the least toxic of the three isomers of aminophenols and it also possesses a significant antipyretic action. A few examples belonging to this category of **antipyretics** are described below.

A. Paracetamol INN, BAN, Acetaminophen USAN,

4′-Hydroxyacetanilide ; Acetamide, N-(4-hydroxyphenyl)- ; Paracetamol B.P., Eur. P., Acetaminophen U.S.P.,

Tylenol(R) (McNeil Consumer) ; Tapar(R) (Parke-Davis) ; SK-Apap(R) (Smith Kline & French) ; Valadol(R) (Squibb)

Synthesis



It may be prepared by the reduction of *p*-nitrophenol and the resulting *p*-aminophenol is acetylated by a mixture of acetic anhydride and glacial acetic acid. The crude product can be purified by recrystallization from a water : ethanol mixture (1 : 1) or from other appropriate solvents.

It is a metabolite of **acetanilide** and **phenacetin** employed as an anti pyretic and analgesic. It may be used effectively in a broad spectrum of arthritic and rheumatic conditions linked with musculoskeletal pain, headache, neuralgias, myalgias, and dysmenorrhea. It is particularly useful **in aspirin-sensitive patients.**

Dose : *Usual oral, adult, 500 mg to 1 g 3 or 4 times per day.*

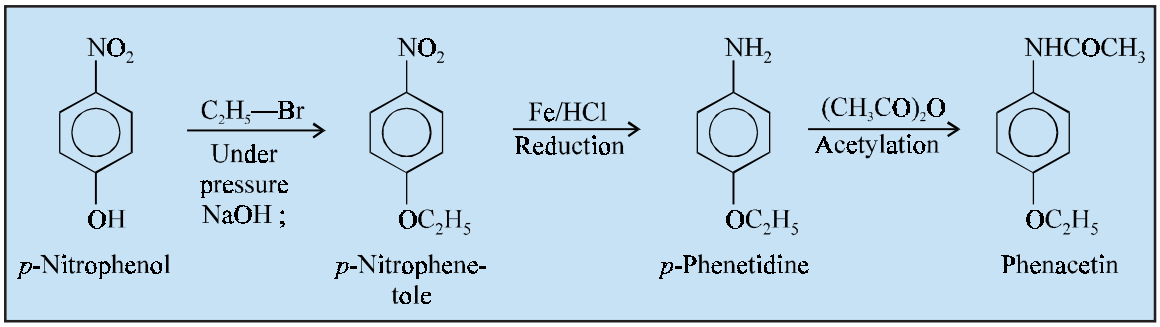
B. Phenacetin INN, BAN, USAN,

p-Acetophenetidide ; Acetamide, N-(4-ethoxyphenol)- ; Acetophenetidin ; *p*-Ethoxyacetanilid ; B.P. (1973), U.S.P., Eur. P., Int. P., Ind. P.

Synthesis

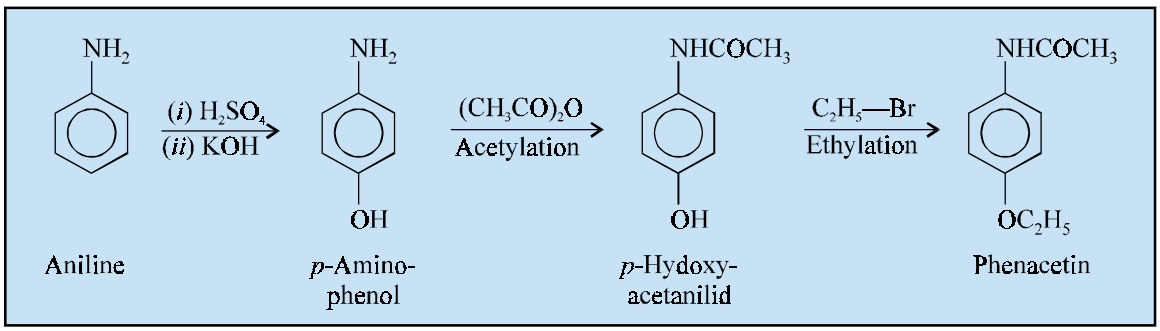
It may be prepared by any one of the following *three* methods, namely :

Method-I : From p-Nitrophenol



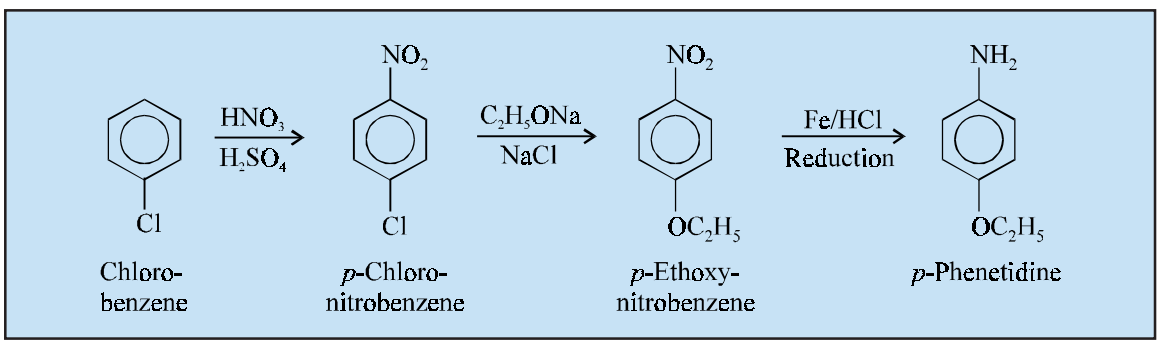
p-Nitrophenol, dissolved in sodium hydroxide solution, is subjected to condensation with ethyl bromide and the resulting *p*-nitrophenetole is reduced with suitable reductant. The *p*-phenetidine thus obtained is acetylated with acetic anhydride to yield the official compound.

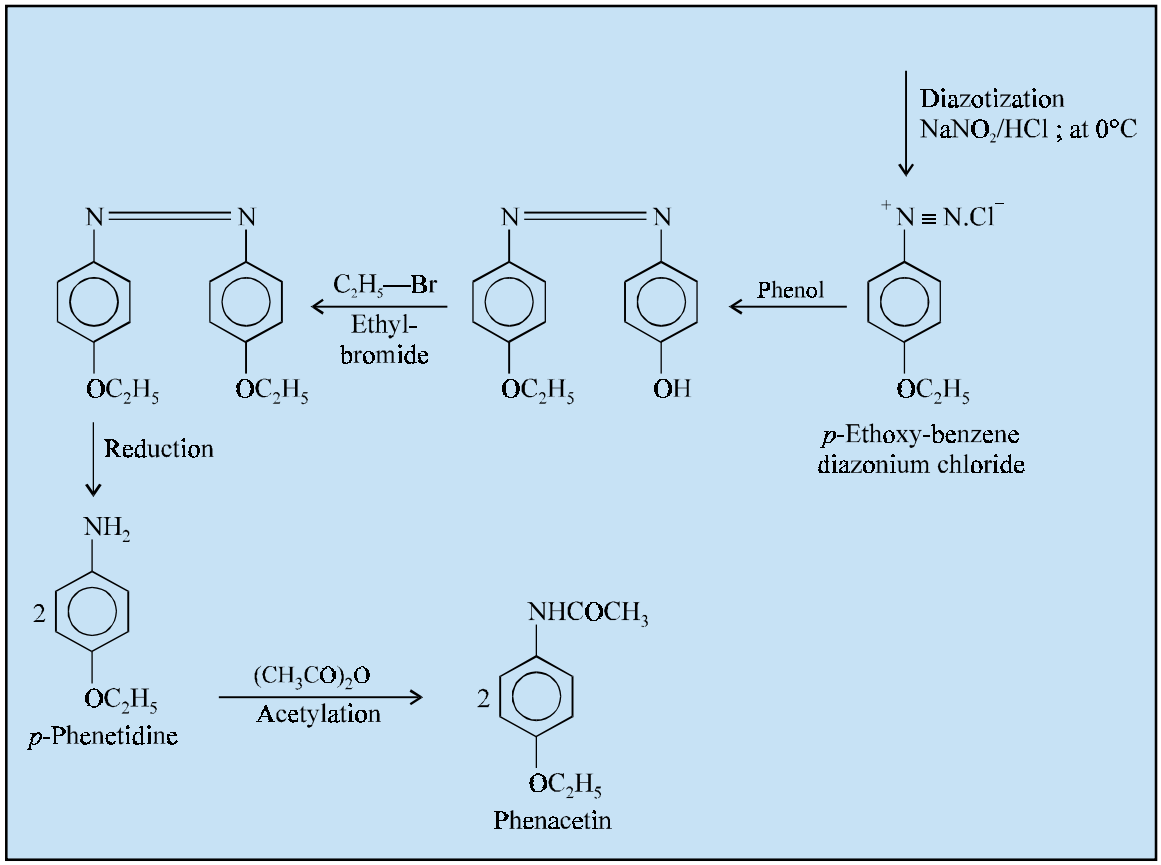
Method-II : From Aniline



p-Aminophenol is obtained by treating aniline with sulphuric acid and potassium hydroxide, which on acetylation with acetic anhydride yields the *p*-hydroxy acetanilide. The resulting product on ethylation with ethyl bromide forms **phenacetin.**

Method-III : From Chlorobenzene





p-Ethoxy nitrobenzene is prepared from chlorobenzene by its nitration followed by treatment with sodium ethoxide, which on reduction yields *p*-phenetidine. The resulting product is diazotised with nitrous acid at 0°C reacted with phenol, ethyl bromide and reduced to obtain two moles of *p*-phenetidine which upon acetylation with acetic anhydride yields two moles of **phenacetin**.

It is an analgesic and an antipyretic with similar effectiveness as **aspirin**. It has a greater potential for toxicity (hemolytic anemia and methemoglobinemia) than **paracetamol**. Irreversible kidney damage with prolonged ingestion of **phenacetin** has been established which ultimately resulted in complete withdrawal of this drug in many countries.

Dose : Usual, oral, adult, 300 mg to 2 g per day.

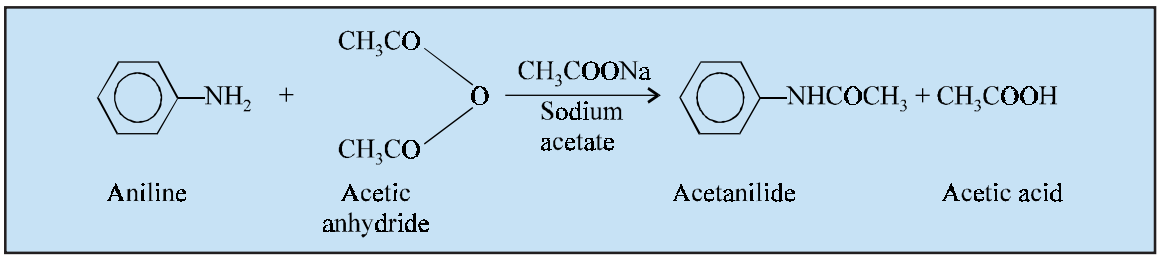
C. Acetanilide BAN, USAN,

N-Phenylacetamide ; Antifebrin ; B.P.C. 1949, N.F. X ;

Synthesis

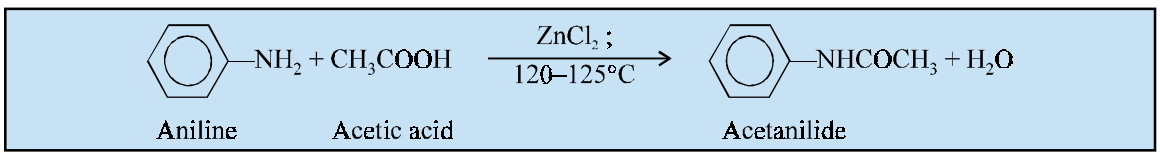
It may be prepared from aniline in two different ways, namely :

Method-I : From aniline and acetic anhydride



It may be prepared by the interaction of aniline and acetic anhydride in the presence of sodium acetate. The crude product may be recrystallized from alcohol.

Method-II : From aniline and acetic acid



It may also be prepared by reacting together redistilled aniline and glacial acetic acid in the presence of zinc chloride at an elevated temperature of 120-125°C.

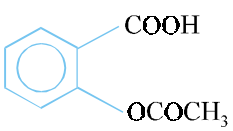
It is one of the cheapest antipyretic drugs. Owing to its high toxicity caused by liberation of free aniline *in vivo* it has been replaced by much safer antipyretics.

2.2. Salicylic Acid Analogues

Salicin was the first compound belonging to this category that exhibited medicinal value. It was employed as a substitute for quinine as a febrifuge. In 1838, Paria prepared salicyclic and whose structure was established by Hoffmann. Kolbe and Lautermann, (1860) introduced the commercial method of preparing salicyclic acid from sodium phenate. Acetylsalicylic acid or aspirin was first synthesized by Gerhardt in 1852, but unfortunately this wonder drug, more or less remained obscure until Felix Hoffmann studied its detailed pharmacodynamic properties in 1899. It gained entry into the world of medicine through Dreser, who coined a new name **'aspirin'** derived from "a" of acetyl and adding to it "spirin", an old name of **salicylic or spiric acid**, obtained from spirea plants.

A few classical of this series of compounds are discussed here.

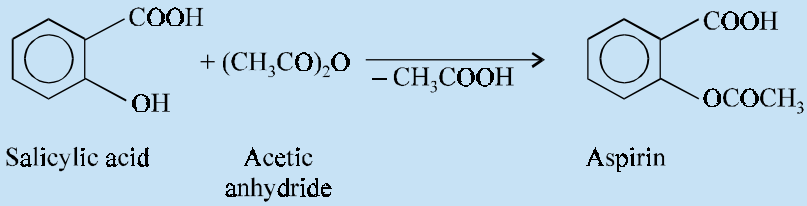
A. Aspirin BAN, USAN,



Salicylic acid acetate ; Benzoic acid, 2-(acetyloxy)- ; Acetylsalicylic acid ; *o*-Acetylsalicylic acid ; B.P., U.S.P., Eur. P., Int. P., Ind. P.,

Emipirin(R) (Burroughs Wellcome) ; A.S.A.(R) (Lilly) ; Bufferin(R) (Bristol-Myers)

Synthesis

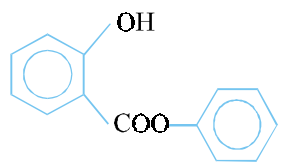


Acetylation of salicylic acid with acetic anhydride yields **aspirin**. The crude product may be recrystallized from benzene, mixture of acetic acid and water (1 : 1) or various other non-aqueous solvents.

It is used as an antipyretic anti-inflammatory and an analgesic in a variety of conditions ranging from headache, discomfort and fever associated with the common cold, and muscular pains and aches. **Aspirin** is regarded as the drug of choice in the reduction of fever because of its high degree of effectiveness and wide safety margin. As aspirin inhibits platelet function, it has been employed prophylactically to minimise the incidence of myocardial infarction and transient ischemic attacks.

Dose : *Usual, adult, oral 300 to 650 mg every 3 or 4 hours ; or 650 mg to 1.3 g as the sustained-release tablet every 8 hours ; Rectal, 200 mg to 1.3 g 3 or 4 times a day.*

B. Salol BAN, Phenyl Salicylate USAN.



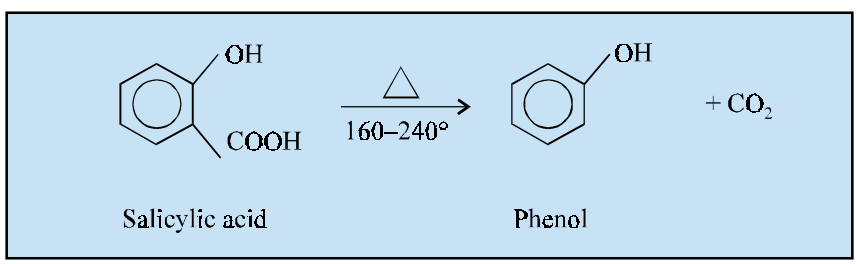
Sola-Stick$^{(R)}$ (Hamilton) ;

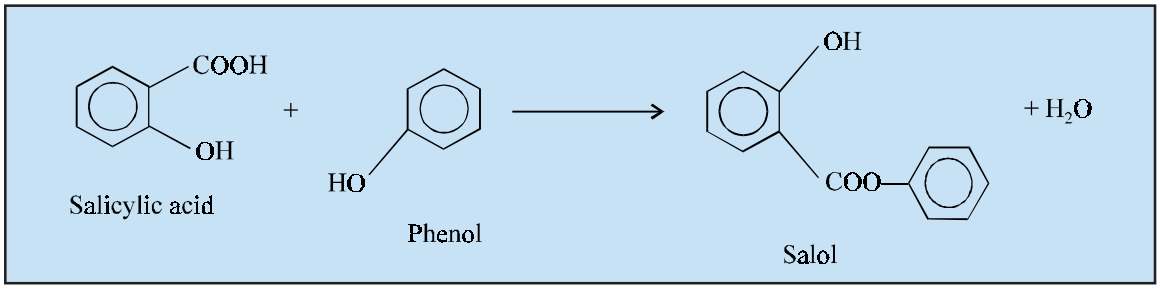
B.P.C. 1954, N.F. XI

Synthesis

It may be prepared by either of the *two* following methods :

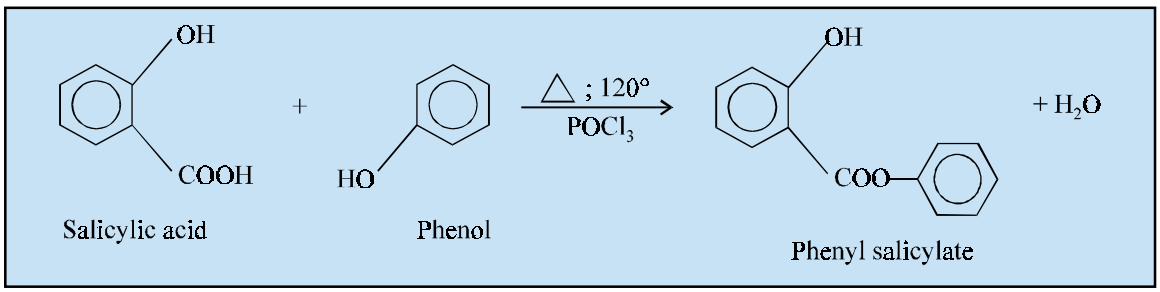
Method-I : By heating salicylic acid alone





It may be prepared by heating salicylic acid at 160–240°C under vacuum and distilling off the water formed as a by-product.

Method-II : By heating salicylic acid and phenol



It may be prepared by heating together salicylic acid and phenol at 120°C in the presence of phosphorus oxychloride or carbonyl chloride ($COCl_2$).

Salol was first introduced as a drug in 1886 by Nencki. It may be employed as an antipyretic and also as internal antiseptic, but effective doses were toxic owing to the liberation of phenol. It is not usually hydrolysed in the stomach but in the intestine it gradually gets hydrolysed into salicylic acid and phenol respectively. The liberated phenol exerts antiseptic action without any undue toxic effect. Thus the administration of drugs on the above criterion is commonly termed as **'salol principle'** or **'Nencki principle'.** Drugs used on salol principle are generally classified under *two* categories, namely : **true salols and partial salols.**

True Salols—are such compounds in which both the compounds *e.g.*, acid and phenol or alcohol are pharmacologically active. **Examples : Salol** and ; **betol (β-naphthyl salicylate).**

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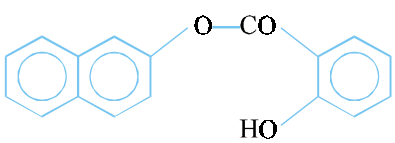
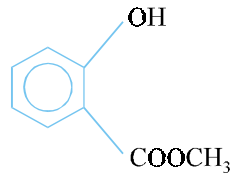


Betol

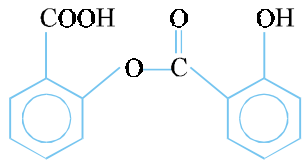
Partial Salols—are such compounds wherein either the acid or the hydroxylic moiety is active pharmacologically.

Example : Methyl salicylate (oil of wintergreen) in which the salicylic acid constitutes the active component.



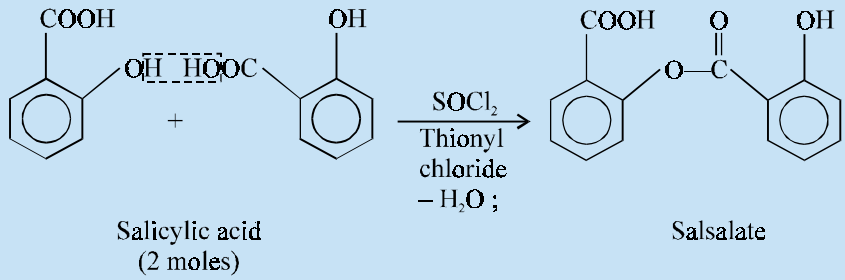
Methyl salicylate

C. Salsalate INN, BAN, USAN.



Salicylic acid, biomolecular ester ; Benzoic acid, 2-hydroxy-, 2-carboxyphenyl ester ; *o*-(2-Hydroxybenzoyl) salicylic acid ; Salicylosalicylic acid ; Sasapyrine ; Salicyl Salicylate ; Salysal ; Disalacid(R) (Riker) ; Saloxium(R) (Whitehall)

Synthesis

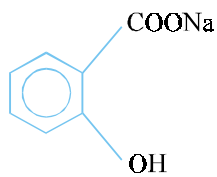


It is prepared by the condensation of two moles of salicylic acid in the presence of thionyl chloride.

It has antipyretic, analgesic and anti-inflammatory properties similar to those of aspirin. It is employed in the **treatment of rheumatoid arthritis and other rheumatic disorders.**

Dose : *Usual, adult, oral 325 to 1000 mg 2 to 3 times per day.*

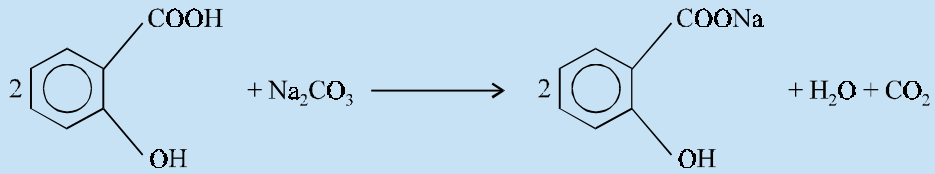
D. Sodium Salicylate BAN, USAN.



Monosodium salicylate ; Benzoic acid, 2-hydroxy-, monosodium salt ; B.P., U.S.P., Eur. P., Int. P., Ind. P.,

Entrosalyl (Standard)(R) (Cox Continental, U.K.)

Synthesis



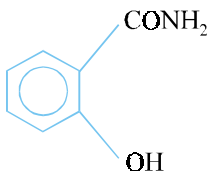
Salicylic acid — Sodium salicylate

It may be prepared by mixing together a paste of salicylic acid in distilled water with sufficient pure sodium carbonate in small lots at intervals. The reaction mixture is filtered through iron-free filter paper and evaporated to dryness under reduced pressure. Caution must be taken to avoid contact with iron which will alter the original white colour of the product.

It is generally used for the reduction of fever and the relief of pain. It also possesses anti-inflammatory actions similar to aspirin. It is recommended in acute rheumatic fever and in the symptomatic therapy of gout.

Dose : *In rheumatic fever, 5 to 10 g daily in divided doses.*

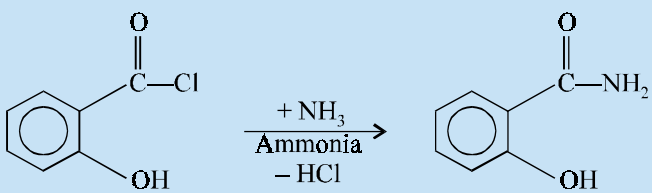
E. Salicylamide INN, BAN, USAN,



o-Hydroxybenzamide ; N.F. XIII ;

Salined(R) (Medo-Chemicals, U.K.)

Synthesis



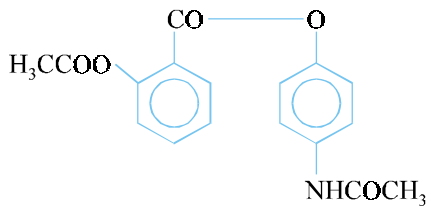
Salicyl chloride — Salicylamide

It is readily prepared from the interaction of salicyl chloride and ammonia.

Its antipyretic and analgesic activity is not more than that of **aspirin**. It may be used in place of salicylates where apparent sensitivity occurs with the latter.

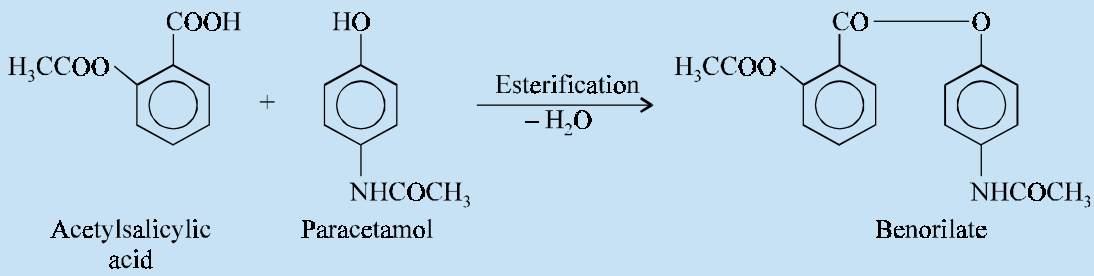
Dose : *300 mg to 1 g, 3 times per day.*

F. Benorilate INN, BAN, USAN, Benorylate BAN,



4-Acetamidophenyl salicylate acetate ; 4-Acetamidophenyl-*o*-acetyl-salicylate ;
Fenasprate ; Benoral(R) (Winthrop)

Synthesis

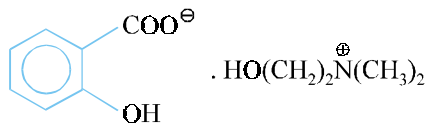


It may be prepared by the esterification of **acetyl salicylic acid** and **paracetamol** with the elimination of a mole of water.

It possesses antipyretic, analgesic and anti-inflammatory properties. It is employed in the treatment of rheumatic disorders and in moderate pain, and as an antipyretic.

Dose : *Rheumatic conditions 1.5 g, 3 times daily.*

G. Choline Salicylate, INN, BAN, USAN,

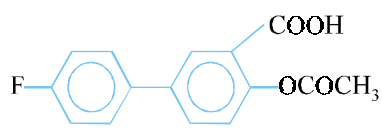


(2-Hydroxymethyl) trimethyl ammonium salicylate ;
Arthropan(R) (Purdue Frederick)

It possesses actions similar to those of **aspirin** but it is mainly used as a local analgesic by being applied to the painful area by gentle rubbing.

Dose : *Adult, usual 0.87 to 1.74 g, 3 or 4 times daily.*

H. Flufenisal INN, USAN,



Acetyl-5-(4-fluorophenyl) salicylic acid ; 4′-Fluoro-4-hydroxy-3-biphenyl-carboxylic acid acetate ; [1, 1′-Biphenyl]-3-carboxylic acid, 4-(acetyloxy)-4′-fluoro- ;

Flufenisal$^{(R)}$ (MSD).

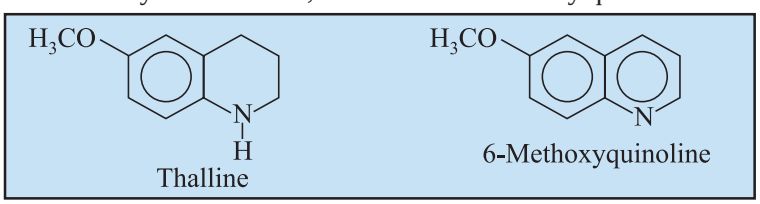
The search for a better drug than aspirin with increased potency, longer duration of action and having less effect on gastric secretion gave birth to flufenisal which essentially has a hydrophobic moiety at C_5. In man, it exhibits a two-fold increase in potency and duration of action than that of aspirin.

Dose : *150 to 300 mg every 3 or 4 hours.*

2.3. Quinoline Derivatives

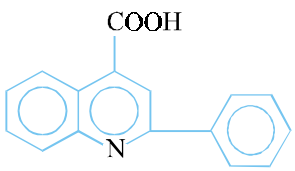
The historical importance and utility of quinine was known in the medical practice for a long time as a potent antipyretic in addition to its remarkable effect against the malarial fever. The basic quinoline nucleus, present in the **quinine** molecule, contributes to antipyretic activity to a certain extent. Therefore, an attempt was made to synthesize a number of quinoline derivatives which might exhibit better antipyretic activity.

Two quinoline derivatives first synthesized though possessed significant antipyretic action, yet could not gain cognizance as a drug because of their high toxic effects on the red blood corpuscles and damaging after-effect on kidneys. These were, thalline and 6-methoxy quinoline.



Thalline 6-Methoxyquinoline

A. Cinchophen INN, BAN, USAN,

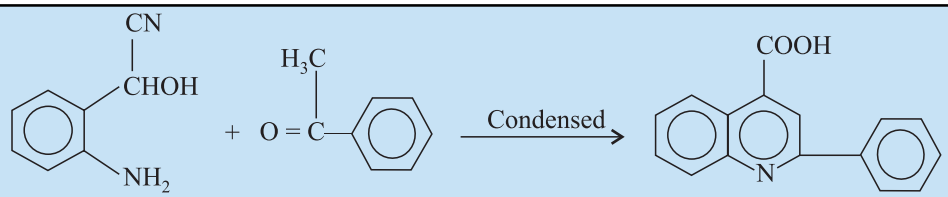


2-Phenyl-cinchoninic acid ; 2-Phenylquinoline-4-carboxylic acid ; Quinophan ; Atophan ; B.P. 1953, N.F. X.

Synthesis

It may be prepared by any one of the following *three* methods :

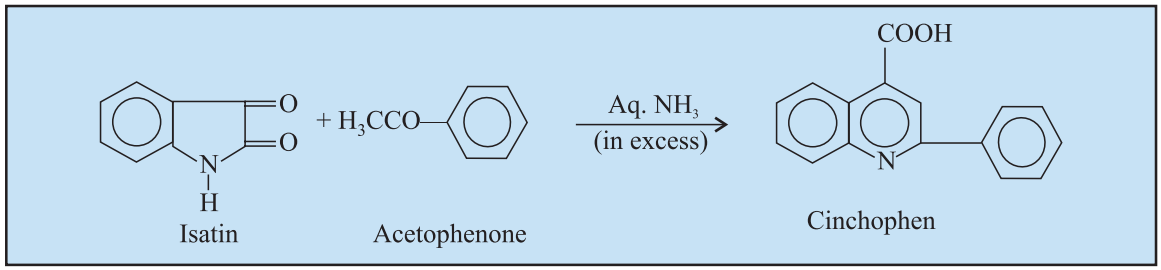
Method-I : From o-Amino benzaldehyde cyanohydrin



o-Aminobenzaldehyde cyanohydrin Methyl-phenyl ketone Cinchophen

Condensation of *o*-aminobenzaldehyde cyanohydrin and methylphenyl ketone yields **cinchophen.**

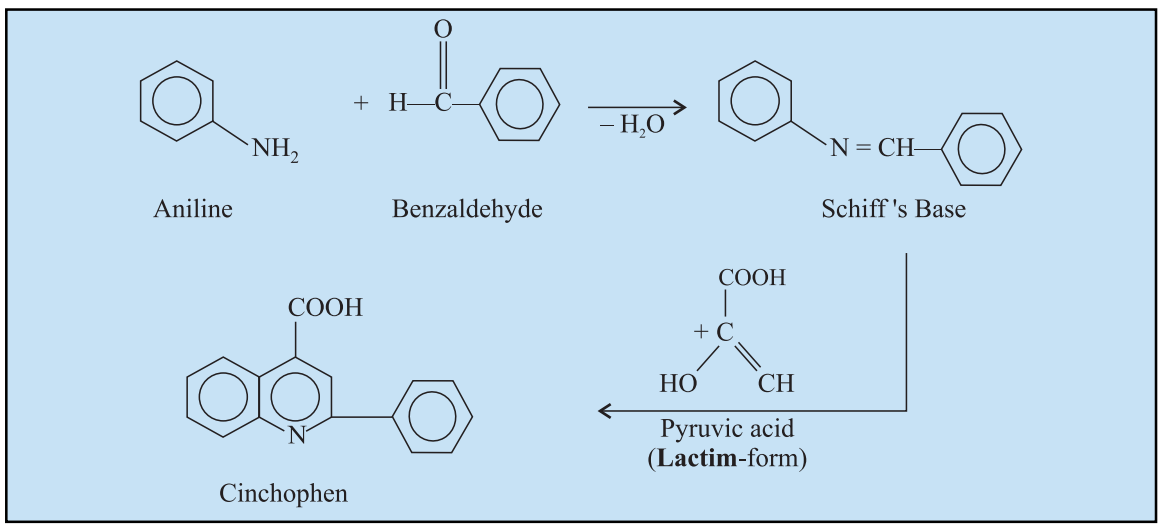
Method-II : From Isatin



Cinchophen may be prepared by the interaction of isatin and acetophenone in the presence of excess of aqueous ammonia.

Method-III : From Aniline

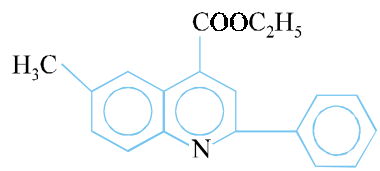
The **Schiff's base** is prepared by the interaction of aniline and benzaldehyde with the elimination of a molecule of water. The resulting base is treated with the *lactim*-form of pyruvic acid thereby resulting into the formation of **cinchophen.**



Cinchophen possesses antipyretic actions similar to those of the salicylates. It was chiefly used **in the treatment of chronic gout and rheumatic conditions but because of its high toxicity, e.g., liver damage resulting in acute jaundice, it has been completely withdrawn and replaced by safer drugs.**

Dose : *300 to 600 mg.*

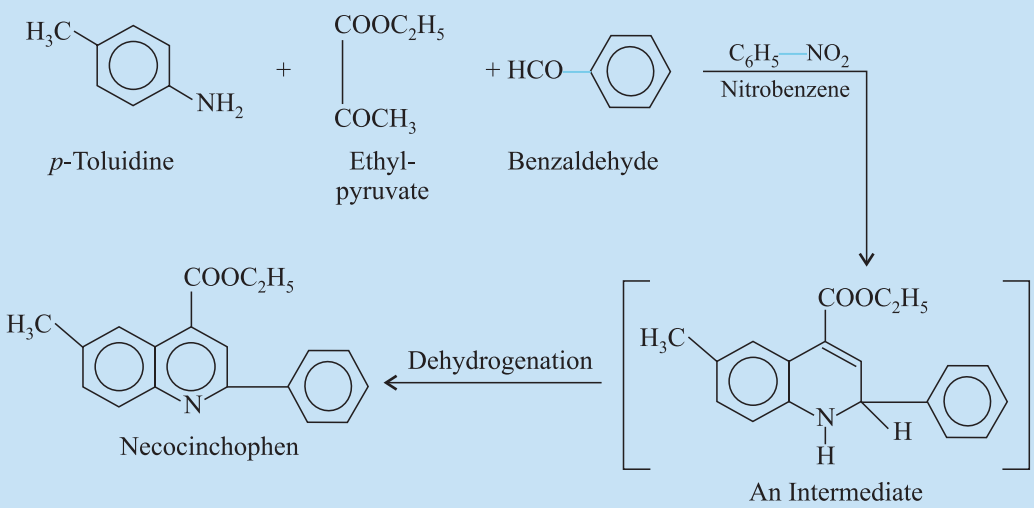
B. Neocinchophen INN, BAN, USAN



Ethyl-6-methyl-2-phenyl-4-quinolinecarboxylate ; N.F. XI ;

Tolysin(R) (Lederle)

Synthesis



It occurs through the reaction of *p*-toluidine, ethyl pyruvate and benzaldehyde in the presence of a small amount of nitrobenzene, when the products get condensed to form an intermediate compound. This when subjected to dehydrogenation yields **neocinchophen.**

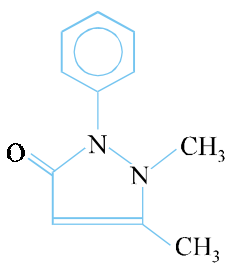
It has been used for the same purposes as **cinchophen**.

Dose : *500 mg.*

2.4. Pyrazolones and Pyrazolodiones

One of the first and foremost synthetic organic compounds which were successfully used as drugs was found to be a heterocycle. It is, however, worthwhile to mention here that the pharmacodynamic spectrum of both the above categories of heterocyclic compounds has a close resemblance to that of aspirin. A few such compounds belonging to either of the said classes are discussed here.

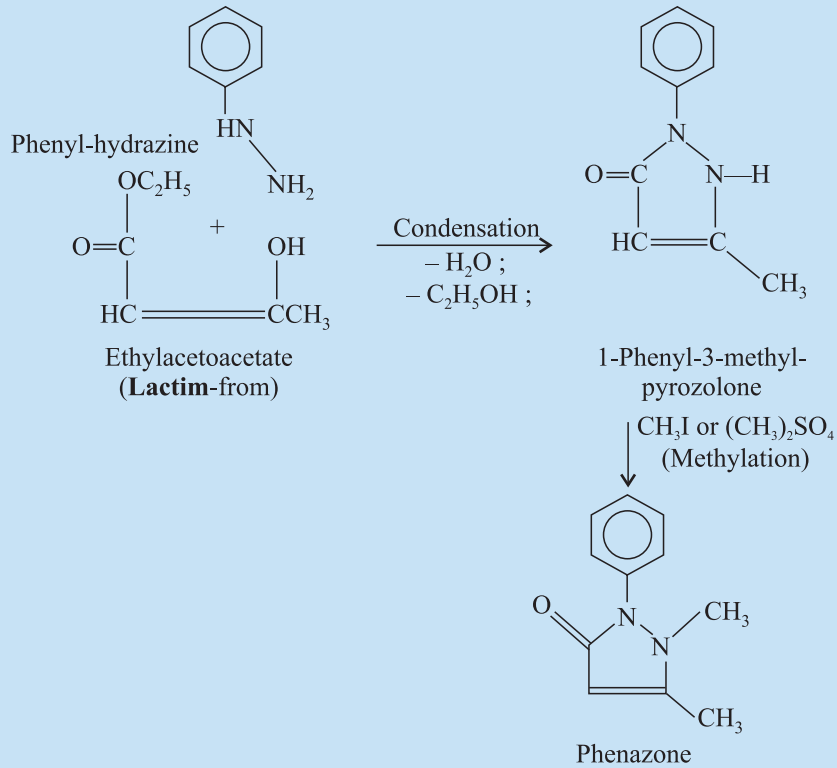
A. Phenazone INN, BAN, Antipyrine USAN,



2, 3-Dimethyl-1-phenyl-3-pyrazolin-5-one ; 1, 2-Dihydro-1, 5-dimethyl-2-phenyl-3H-pyrazol-3-one ; Antipyrin ; Phenazone B.P., Eur. P., Int. P., Antipyrine U.S.P.

Component of Auralgan(R) (Ayerst) ; Areumal(R) (as Gentisate ; Ecobi. Italy)

Synthesis

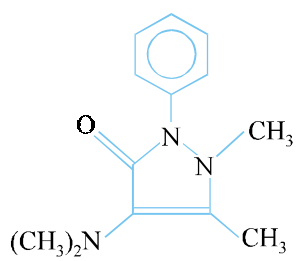


It may be prepared by the condensation of one mole each of phenyl-hydrazine and the *lactim*-form of ethylacetoacetate when 1-phenyl-3-methyl-pyrazolone is obtained by the elimination of a mole each of water and ethanol. The resulting product is subjected to methylation either with methyl iodide or dimethyl sulphate to yield **phenazone.**

As antipyretic, it possesses local anaesthetic and styptic actions and solutions containing 5% are used locally as ear drops. It has now been replaced by relatively more effective and safer drugs.

Dose : 300 to 600 mg.

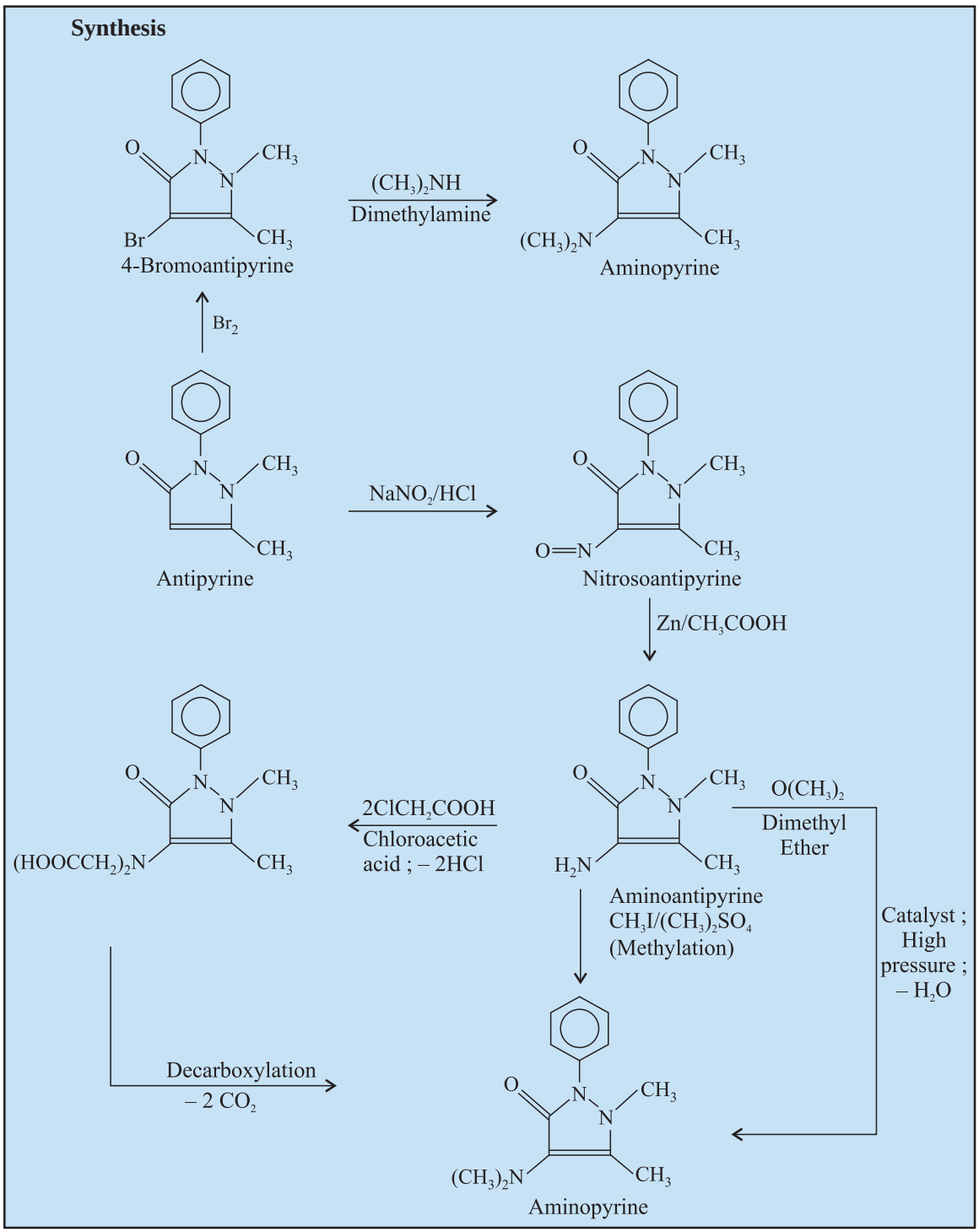
B. Aminophenazone INN, Amidopyrine BAN, Aminopyrine USAN,



4-Dimethylamino-2, 3-dimethyl-1-phenyl-3-pyrazolin-5-one ; 4-Dimethyl-amino-1, 5-dimethyl-2-phenyl-4-pyrazolin-3-one ; Dimethylaminoantipyrine ; Dimethylaminophenazone ; Amidopyrine B.P.C. 1954, Eur. P., Int. P., Aminopyrine N.F.X. ;

Piramidon$^{(R)}$ (Hoechst, Spain)

Synthesis



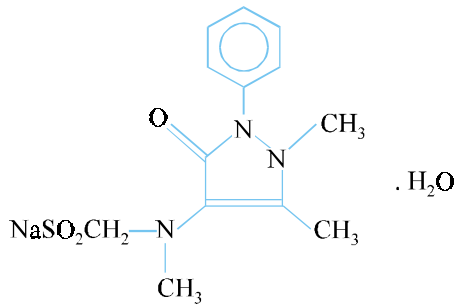
Aminopyrine (amidopyrine) may be prepared commercially first by treating **antipyrine** with nitrous acid to yield nitrosoantipyrine. The resulting product can now be routed through two different course of reactions, namely : (*a*) treatment with two moles of chloroacetic acid followed by decarboxylation

producing thereby aminopyrine ; and (*b*) treatment with dimethyl ether in the presence of catalyst and at high pressure eliminates a mole of water to give aminopyrine. However, aminopyrine can be prepared conveniently in the laboratory by first treating antipyrine with bromine partially to obtain 4-bromo-antipyrine which on subsequent treatment with dimethylamine yields the official compound.

It has antipyretic actions similar to those of phenazone but owing to the risk of agranulocytosis its use is discouraged and mostly abandoned. However, the gentisate has sometimes been used. **Aminopyrine** is often employed in drug metabolism studies.

Dose : *300 to 500 mg ; max in 24 hours 3 g.*

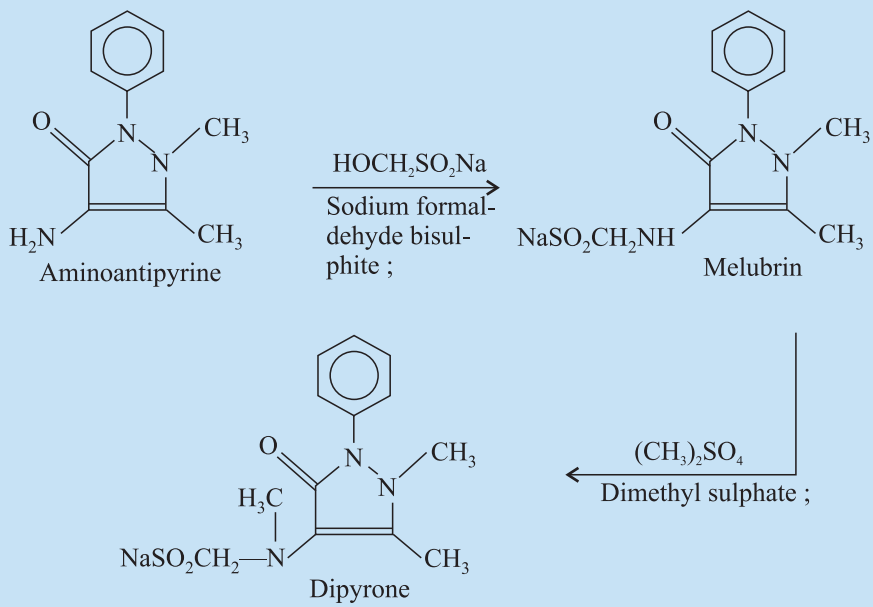
C. Dipyrone BAN, USAN, Noramidopyrine Methanesulfonate Sodium INN,



Sodium (antipyrinylmethylamino) methanesulfonate monohydrate ; Methane-sulfonic acid, [(2, 3-dihydro-1, 5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl) methylamino]-, sodium salt, monohydrate ; Analginum ; Metamizol ; Amino-pyrine-sulphonate sodium ;

Novalgin(R) (Hoechst) ; Novaldin(R) (Winthrop)

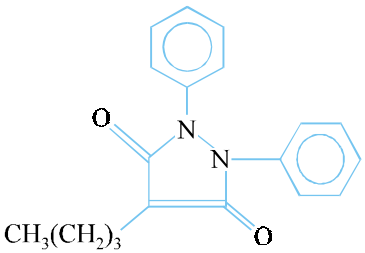
Synthesis



It possesses similar properties to that of amidopyrine. Its use is really justified only in serious or life-threatening situations where no alternative antipyretic is available or suitable. Its use is restricted in some countries.

Dose : *Usual, 0.5 to 1 g, 3 times per day.*

D. Phenylbutazone INN, BAN, USAN,

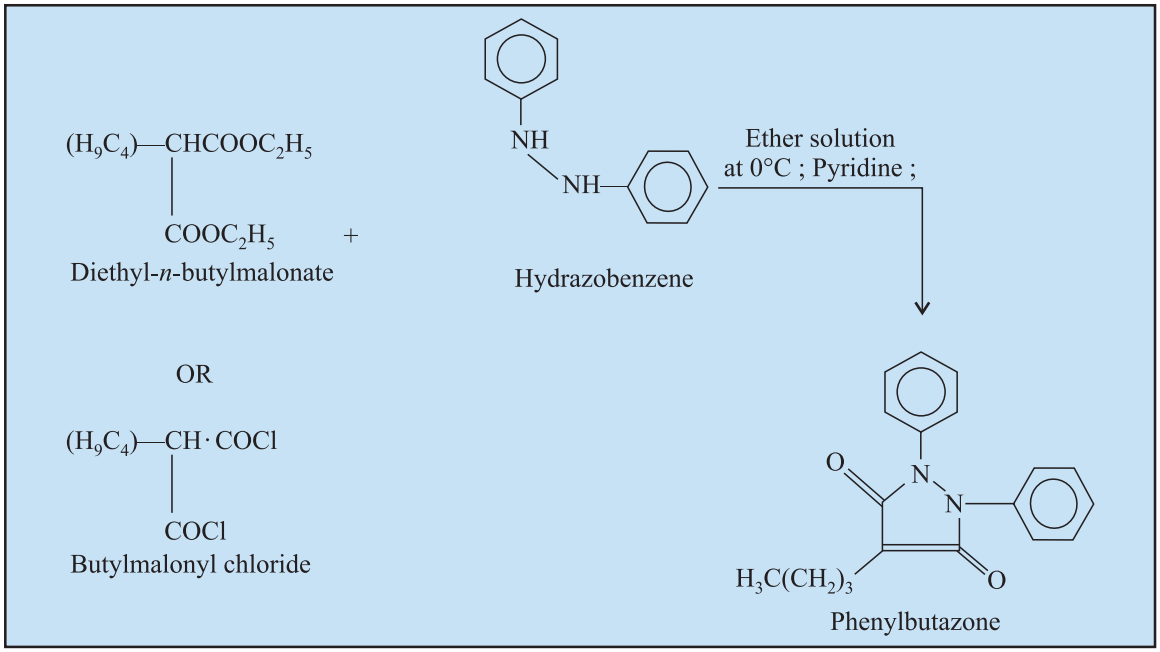


4-Butyl-1, 2-diphenyl-3, 5-pyrazolidinedione ; 3, 5-Pyrazolidinedinedione, 4-butyl-1, 2-diphenyl- ; Butadione ; B.P., U.S.P., Eur. P., Int. P.,

Butazolidin(R) (Ciba-Geigy) ; Busone(R) (Reid-Provident)

Synthesis

Phenylbutazone may be prepared by condensation either from diethyl-*n*-butyl malonate or *n*-butyl malonyl chloride with hydrazobenzene in either solution at 0°C with the aid of pyridine. Subsequently, the pyridine is extracted with aqueous hydrochloric acid, the phenylbutazone is extracted with aqueous sodium bicarbonate and finally precipitated by addition of hydrochloric acid.

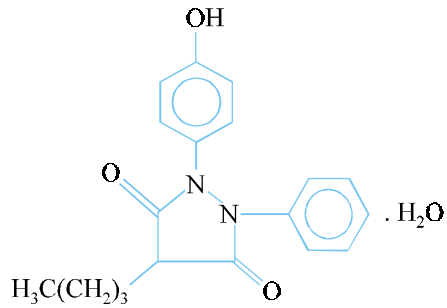


It is a pyrazole derivative which has antipyretic, analgesic and anti-inflammatory actions, because of its toxicity it is not used as a general antipyretic or analgesic. It is, an usual practice, reserved for use in the treatment rheumatic disorders, such as : osteoarthrosis, rheumatoid arthritis, ankylosing spondylitis, arthritis, acute superficial thrombophlebitis, painful shoulder and Reiter's disease, where less toxic drugs have failed.

In some countries, its use and that of oxyphenbutazone are now restricted to only ankylosing spondylitis.

Dose : *100 to 600 mg per day.*

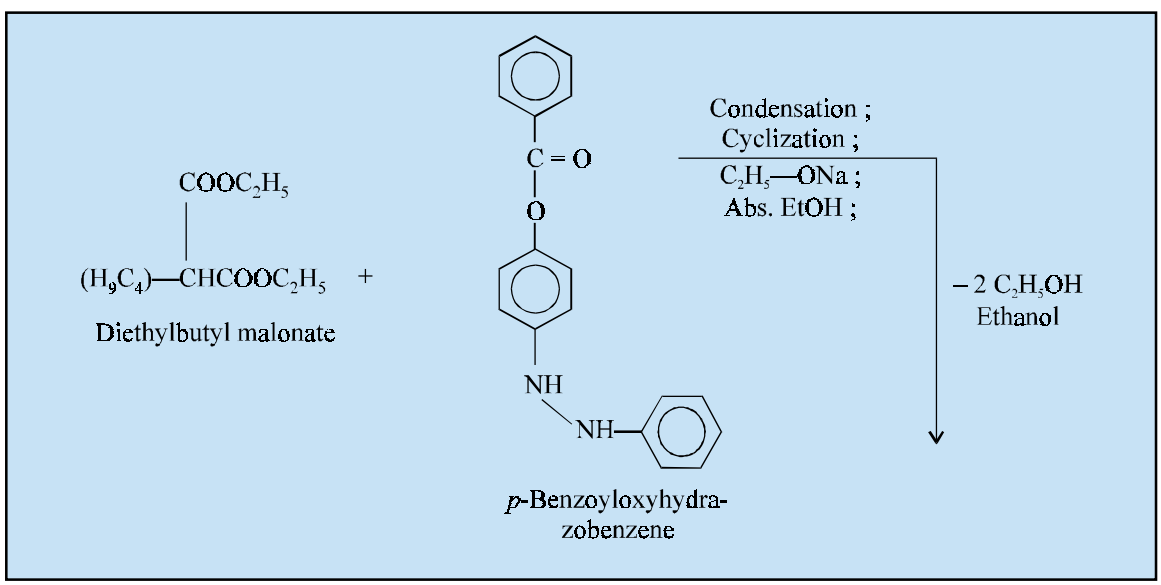
E. Oxyphenbutazone INN, BAN, USAN,



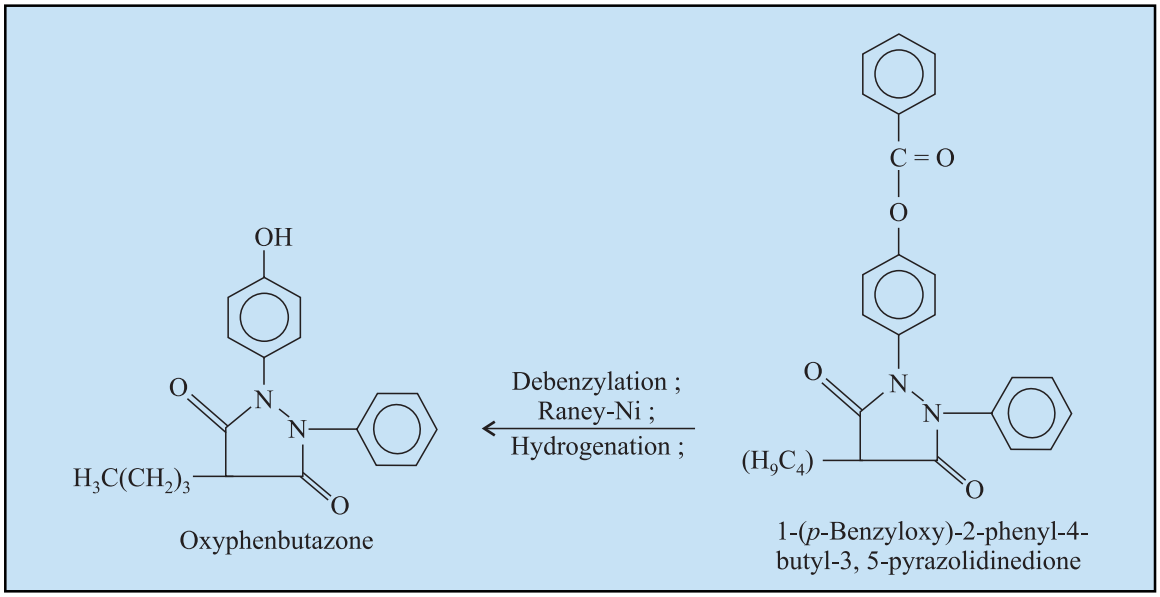
4-Butyl-1-(*p*-hydroxyphenyl)-2-phenyl-3, 5-pyrazolidinedione monohydrate ; 3, 5-Pyrazolidinedione, 4-butyl-1-(4-hydroxyphenyl)-2-phenyl, monohydrate ; B.P., U.S.P., Tandearil$^{(R)}$ (Ciba-Geigy) ; Oxalid$^{(R)}$ (USV).

Synthesis

Condensation of diethyl butyl malonate and *p*-benzyloxyhydrazo-benzene is done in the presence of sodium ethoxide in anhydrous ethanol to yield 1-(benzyloxy)-2-phenyl-4-butyl-3, 5-pyrazolidinedione. The reaction mixture is heated with xylene to about 140°C for several hours which aids in the removal ethanol eliminated by cyclization. The resulting product is debenzylated by the aid of Raney Nickel hydrogenation at an ambient temperature and pressure. The crude product may be recrystallized from ether/petroleum ether.



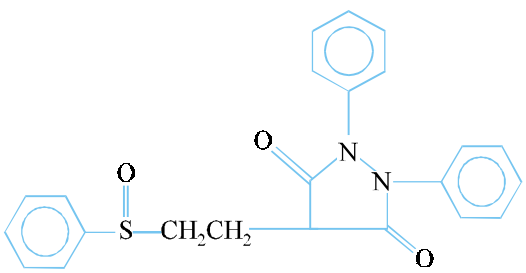
(*Contd...*)



It is a metabolite of **phenylbutazone** and possesses the same antipyretic, analgesic, anti-inflammatory and mild uricosuric actions as the parent compound. It also finds its use in rheumatic and other musculo-skeletal disorders. It has also been recommended in the management of thrombophlebits.

Dose : *Usual, oral, adult, antirheumatic, 100 or 200 mg 3 times daily ; maintenance 100 mg 1 to 4 times daily ; antigout, 400 mg initially as a loading dose, then 100 mg every 4 hours.*

F. Sulfinpyrazone INN, USAN, Sulphinpyrazone BAN.



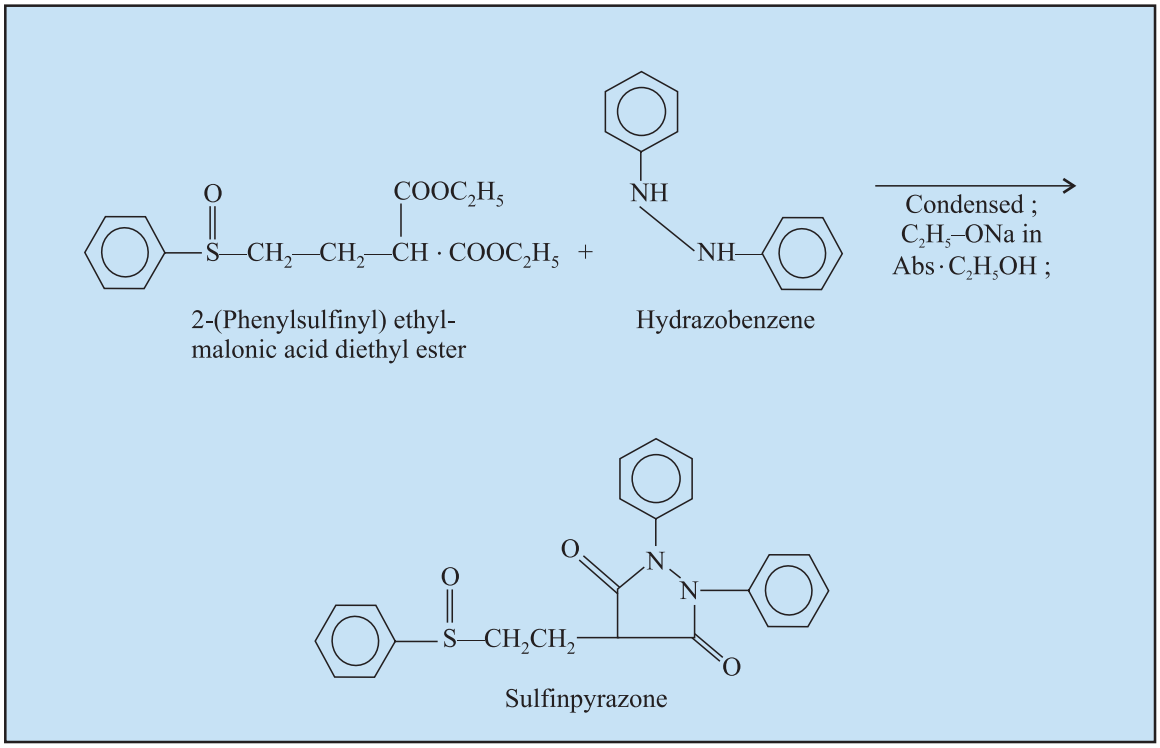
1, 2-Diphenyl-4[2-(phenylsulfinyl) ethyl]-3, 5-pyrazolidinedione ; 3, 5-Pyrazolidinedione, 1, 2-diphenyl-4-[2-(phenylsulfinyl) ethyl]- ; B.P.,

U.S.P., Anuturane$^{(R)}$ (Ciba-Geigy)

Synthesis

It may be prepared by the condensation of [2-(phenylsulfinyl) ethyl]- malonic acid diethyl ester with hydrazobenzene in the presence of sodium ethoxide in absolute ethanol. Completion of reaction is achieved by the addition of xylene and subsequent heating at about 130°C whereby the ethanol liberated as a product of condensation is removed completely. The crude product is extracted with a suitable solvent and finally recrystallized from ethanol.

It is a **uricosuric agent** structurally related to phenylbutazone. It is normally employed for the long term **treatment of chronic gout where it effects slow depletion of urate tophi in the tissues.**

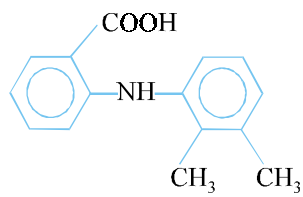


Dose : *Initial oral dose 100 to 200 mg per day, taken with meals or milk.*

2.5. The N-Arylanthranilic Acids

The structural analogues of **N-arylanthranilic** acid opened an altogether new horizon of antipyretic, analgesic and anti-inflammatory compounds which have recently gained recognition in the therapeutic armamentarium. A few compounds belonging to this category are discussed here.

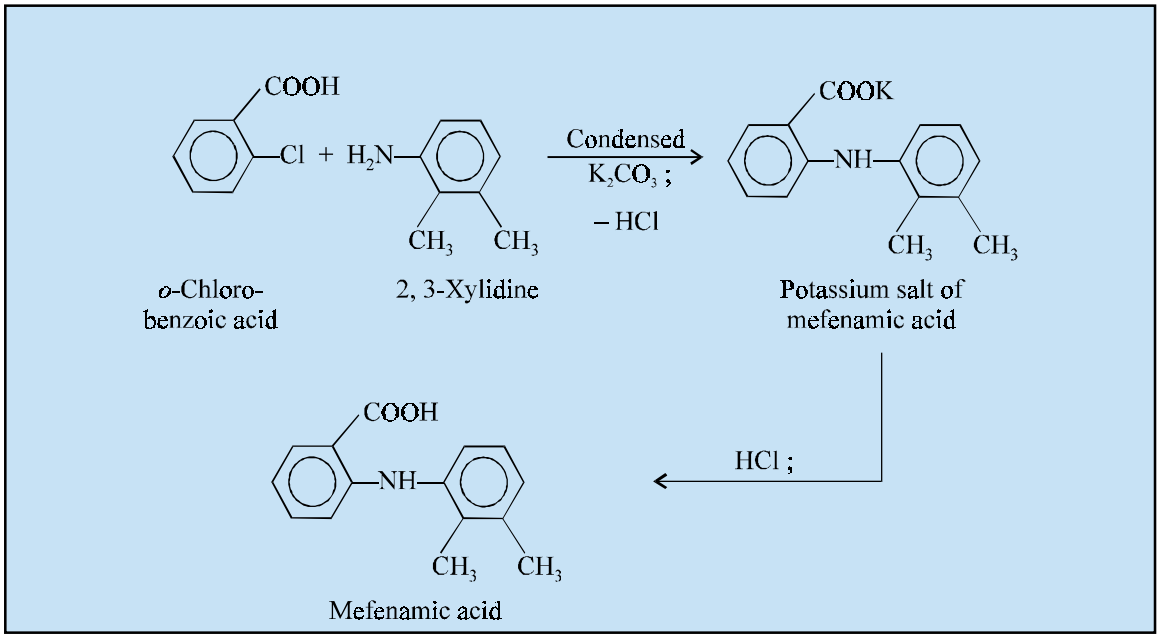
A. Mefenamic Acid BAN,



N-(2, 3-Xylyl) anthranilic acid ; Benzoic acid, 2-[(2, 3-dimethylphenyl) amino]- ; B.P., Ponstel$^{(R)}$ (Parke-Davis).

Synthesis

It may be prepared by the condensation of *o*-chlorobenzoic acid with 2, 3-xylidine in the presence of potassium carbonate to give the potassium salt of mefenamic acid, which on treatment with hydrochloric acid yields the official compound.

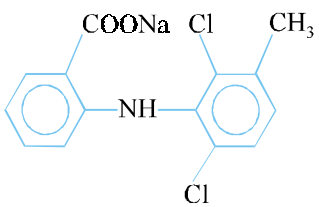


It is an analgesic drug usually indicated for the treatment of primary dysmenorrhea, mild pain and for pain due to dental extractions.

Dose : *Usual, adults, children over 14 years of age, oral, 500 mg, followed by 250 mg 4 times daily.*

(Caution : Must not be used for more than 7 days).

B. Meclofenamate Sodium BAN, USAN, Meclofenamic Acid INN.



Monosodium N-(2, 6-dichloro-*m*-tolyl) anthranilate monohydrate ; Benzoic acid, 2-[2, 6-(dichloro-3-methylphenyl) amino]-, monosodium salt ; U.S.P.,

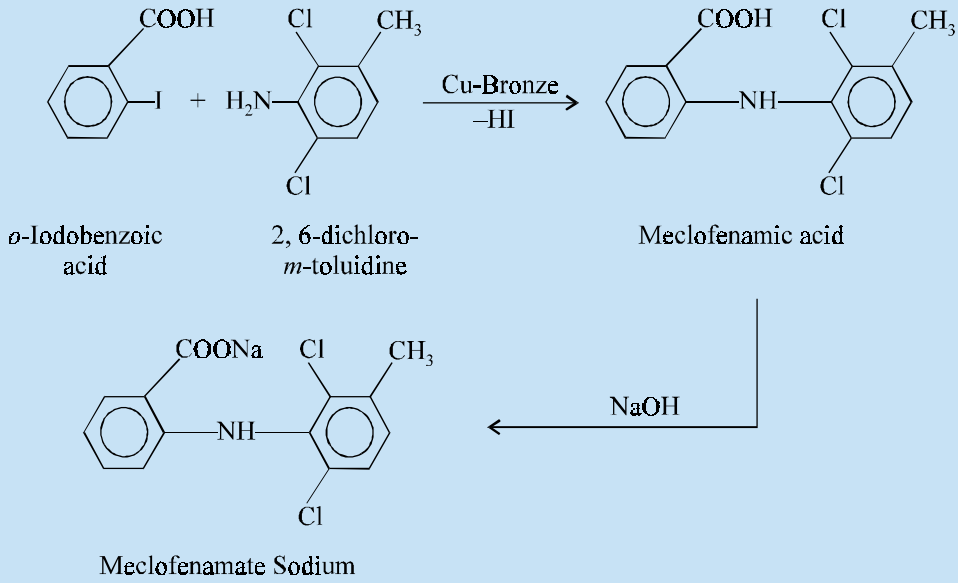
Meclomen$^{(R)}$ (Parke-Davis).

Synthesis :

It may be prepared by the **Ulman Condensation** of *o*-iodobenzoic acid with 2, 6-dichloro-*m*-toluidine in the presence of copper-bronze resulting into the formation of meclofenamic acid which on neutralization with equimolar proportion of sodium hydroxide yields **meclofenamate sodium.**

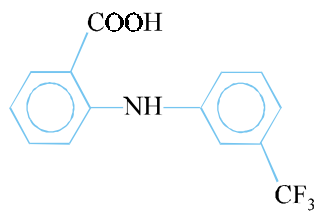
It possesses analgesic, anti-inflammatory, and antipyretic properties. It is used for the **treatment of acute and chronic rheumatoid arthritis and osteoarthritis.**

Synthesis



Dose : *Usual, oral, 200 to 400 mg daily in 3 or 4 equal doses.*

C. Flufenamic Acid INN, BAN, USAN.



N-(α, α, α-Trifluoro-*m*-tolyl)-anthranilic acid ; Benzoic acid, 2-[[3-(trifluoro-methyl) phenyl] amino]- ; B.P., U.S.P.,

Meralen(R) (Merrell, U.K.)

It has analgesic, anti-inflammatory and antipyretic actions. It is employed in the **treatment of rheumatic disorders** and dysmenorrhoea.

Dose : *400 to 600 mg per day in divided doses.*

3. MECHANISM OF ACTION

The **'drugs'** included in this chapter essentially possess solely the **'antipyretic and analgesic'** pharmacological actions but specifically lack anti-inflammatory effects.

Interestingly, the **'antipyretic'** activity is exclusively caused due to the direct interferences, with such phenomena with the aid of which **'pyrogenic factors'** give rise to **fever** ; however, they are found

absolutely unable to bring-down the elevated body temperature (>> 98.4°F) specifically in a febrile subjects. It has already been established beyond any reasonable doubt that the **'antipyretics',** in general, exert their activities very much within the CNS. These pharmacological actions are significantly located at the **'hypothalamic thermoregulatory centre'** ; however, recent studies categorically advocates the **'peripheral actions'** may also contribute enormously and positively.

In fact, there are *two* different school of thoughts that have been suggested to explain the modalities of antipyretic action :

(*a*) **Endogenous leukocytic pyrogens** are presumably released from the cells that have been duly activated by a host of stimuli, and '*antipyretics*' do exert their action by inhibiting the corresponding activation of these cells by an exogenous pyrogen, and

(*b*) Inhibition of the release of **'endogenous leukocytic pyrogens'** from the cells as soon as these have been adequately activated by the exogenous pyrogen.

Clark* (1979) put forward substantial evidences to prove that there exists a **'central antipyretic mechanism'** which specifically affords an **'antagonism'** that may be caused on account of :

(*i*) A direct competition ensuing of a pyrogen and the antipyretic drug pervailing at the CNS-receptors, and

(*ii*) An inhibition of prostaglandin (PG) synthesis occurring in the CNS.

More logistically, the experimental pharmacologists usually determine the *analgesic activity* in laboratory animals (rat/mice) by measuring the **'pain threshold'** in terms of certain reflex actions essentially produced by noxious stimuli, for instance : pressure, heat and electric shock. There are several, known methods to determine the exact **'analgesic profile'** in **'synthetic'** as well as **'natural plant products',** such as : rat tail-flick test ; mouse hot-plate test ; and usage of electricity to tooth-pulp thereby giving rise to almost reproducible results (*i.e.*, end-points) whose appearance may be delayed with respect to '*time*' by **'analgesic drugs'** under examination virtually with a direct relationship to both the **potency** and **efficacy**.

Hughes and Kosterlitz** (1975) isolated (from pig-brain) and identified **'enkephalins'** produced in the body having narcotic-like substances so as to react judiciously with receptors for the narcotic drugs. Thus, the two identified and characterized **'brain-peptides'** essentially differed only in the nature of their N-terminal amino acids, for instance : (*a*) **methionin-enkephalin**-having a tyrosine-glycine-glycine-phenylalamine-methionine sequence ; and (*b*) **leucine-enkephalin**-having a tyrosine-glycine-glycine-phenylalanine-leucine sequence.

4. MECHANISM OF ACTION OF SELECTED ANTIPYRETIC-ANALGESICS

The mechanism of action of certain selected **antipyretic-analgesics** included in this chapter (section 10.2) are discussed in the sections that follows :

4.1. Paracetamol (Acetaminophen)

It causes antipyresis by exerting its action on the **hypothalamic heat-regulating centre,** and analgesia by enhancing the pain threshold profile appreciably. It is found to lack the anti-inflammatory

*Clark WG, **Mechanisms of Antipyretic Action**, *Gen. Pharmacol.*, **10** : 71–77, 1979.

Hughes J and Kosterlitz, *Nature*, **258 : 577, 1975.

activity of the salicylates ; therefore, its therapeutic usefulness in inflammatory disorders is very much limited, and hence is not regarded as an NSAID agent. In contrast to the action of **'aspirin',** paracetamol possesses little affect in antagonizing the actions of uricosuric agents (*i.e.,* increases the urinary excretion of uric acid). It has also been observed that its large doses usually help in potentiating the action of the anticoagulants, whereas the normal therapeutic dose regimens exert hardly any effect on the **'prothrombin time'** (*i.e.,* coagulation time).

Nearly, 2% of the **'drug'** is excreted almost unchanged in the urine, while approximately 95% is found as its corresponding **glucuronide and sulphate-conjugates** that are absolutely devoid of any toxicity. Furthermore, the remaining 3% gets oxidized *via* the *hepatic cytochrome P-450 system* into a respective chemically reactive intermediate which eventually combines specifically with the **liver glutathione** to give rise to the formation of a **'nontoxic'** entity.

4.2. Phenacetin

Its toxic effects are very much comparable to those of **paracetamol (acetaminophen),** the '*active form*' to which it gets converted *in vivo.* The earlier findings revealed that it may cause a damage to the kidneys when used either in excessive dosage or for a longer duration. However, certain interesting recent evidences strongly suggest that phenacetin may *not* be responsible for causing nephritis to any greater extent when compared to **'aspirin'***. Importantly, it has been strongly demonstrated in causing carcinogenesis in rats and associated with the growth of tumours in abuses of **phenacetin****.

4.3. Acetanilide

It is considered to be relatively safer drug in the doses recommended for analgesia. Hence, it may be administered in intermittent periods, not exceeding a few days in any circumstances. The analgesic effect is quite selective for pharmacological action(s) ranging from simple headache to the pain associated with many muscles and joints.

4.4. Aspirin

It has been well established that **'aspirin'** inhibits platelet function ; therefore, it prophylactically minimises the incidence of **myocardial infarction** and **transient ischemic attacks** particularly in men and also postmenopausal women. Interestingly, **aspirin** is *not* hydrolyzed significantly when it happens to be in contact with the weakly acidic digestive juice present in the stomach (*i.e.,* gastric juice) ; however, as soon as it gains its passage into the intestinal canal it undergoes hydrolysis to a certain extent. A large portion of it usually gets absorbed unchanged. Garrett*** (1959) put forward a logical explanation with regard to the gastric mucosal irritation of aspirin to the formation of **salicylic acid** *i.e.,* the natural inherent acidity of **aspirin** ; besides, the intimate adhesion of undissolved **aspirin** to the gastric mucosa. Subsequently, Davenport**** (1967) demonstrated that **aspirin** affords an irreversible modification in the degree of permeability in the mucosal cell, thereby permitting the **'back-diffusion'** of gastric acid (in stomach) that ultimately is responsible in causing permanent damage to the capillaries.

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*Brown DM and Hardy TL., *Brit J. Pharmacol. Chemother.,* **32**, 17, 1968.

Tomatis L. *et. al. Cancer Res.* **38, 877, 1978.

***Garrett ER, *J. Am. Pharm. Assoc. Sci.,* **48**, 676, 1959.

****Davenport HW, *N. Engl. J. Med.,* **276**, 1307, 1967.

4.5. Sodium Salicylate

It is considered to be one of the **'choicest drug'** specifically for salicylate medication ; and is usually administered with either sodium bicarbonate to minimise effectively the **'gastric distress'** or as **enteric-coated dosage forms.** However, the usage of $NaHCO_3$ is not advisable as it is found to retard the plasma levels of **'salicylate'** and enhances the elimination of **'free salicylate'** in the urine.

4.6. Salicylamide

It is believed to exert a moderately faster and deeper analgesic effect in comparison to **'aspirin'**. It has also been established that its long term usage in rats no abnormal and untoward physiological and symptomatical reactions observed. Salicylamide gets metaboilized in a manner altogether different from that of other **'salicylates'** ; and, importantly it hardly gets hydrolyzed to the corresponding salicylic acid.*

4.7. Salsalate

The ester is usually hydrolyzed following its immediate systemic absorption. It is believed to afford much less gastric irritation and discomfort in comparison to **'aspirin'**, by virtue of the fact that the **'drug'** is virtually insoluble in the *stomach* ; and, therefore, never gets absorbed unless and until it happens to gain its access into the **small-intestine.** It is found to be as effective as **'aspirin'** and definitely possess fewer side effects.

4.8. Choline Salicylate

It is observed to be absorbed much more swiftly in comparison to **'aspirin',** thereby giving rise to faster peak blood levels.

4.9. Fluferisal

It is found to be more potent, long acting and possesses much less gastric irritation. All these characteristic features have been duly accomplished, by strategically introducing a hydrophobic functional moiety (4-fluorophenyl) at C-5. Just like other aryl acids the '**drug**' is most intimately bound to plasma proteins in the shape of its deacylated metabolite. However, in human beings it seems to be at least twice as effective *i.e.*, having almost twice the duration of activity.

4.10. Cinchophen

Its antipyretic actions are very much akin to those of the salicylates. Its major pharmacological action was in the control and management of **chronic gout and rheumatic** conditions, but by virtue of its relatively high level of toxic effects, such as : hepatic dysfunction ultimately leading to acute jaundice.

4.11. Phenazone (Antipyrine)

The drug is found to exert an appreciable paralytic action exclusively upon the sensory and the motor nerves which eventually give rise to certain degree of anaesthesia and vasoconstriction. Somatically (*i.e.*, systemically), it is observed to afford pharmacological activities which are very similar to those of **acetanilid** ; evidently these are normally quite fast and rapid. After due oral administration, it undergoes a free circulation within the system, and finally gets excreted through the kidneys in an **'unchanged form'**. It remarkably helps in reducing the abnormally high temperature in an exceptionally rapid man-

*Smith PK, *Ann. N.Y. Acad. Sci.*, **86**, 38, 1960.

ner *via* an altogether not-so-explicite (unknown) mechanism. Perhaps it is normally caused by a direct effect upon the **serotonin-regulated thermal controlling centre** of the nervous system. Besides, it remarkably minimises certain kinds of perception to pain, without any change in the prevailing central or motor functions, that essentially varies from the effects of **morphine**.

4.12. Aminopyrine

Though its overall antipyretic and analgesic effect is much more powerful and its effect last longer, yet it possesses a major disadvantage because of its ability to produce agranulocytosis* (granulocytopenia). It has been further demonstrated to be caused by drug therapy with a plethora of drug substances *e.g.*, **aminopyrine.**

Note. Several countries have either banned or adequately restricted its administration.

4.13. Dipyrone

Its pharmacological actions are very much akin to **aminopyrine**. Because of its high degree of toxicity its usage has been banned or restricted in several countries.

4.14. Phenylbutazone

The **'drug'** is absorbed quite rapid after oral administration, and subsequently gets bound to plasma protein very intimately. Its usual time to attain peak serum concentration level is nearly 2.5 hrs. However, the normal span for the overset of antigout activity ranges between 1 to 4 days, and that for antirheumatic activity varies between 3 to 7 days. It has been duly observed that the therapeutic serum concentrations average approximately 43 mg. mL^{-1} ; and the elimination half-life is nearly 84 hours. Interestingly, its major metabolite (oxyphenbutazone, 2%) and the unchanged drug (1%) are both excreted by the kidneys.

Note. The 'drug' must preferably be taken either with cold milk or with meals to avoid the possible gastric irritation.

4.15. Oxyphenbutazone

It happens to be the **'active metabolite'** of **phenylbutazone**. It has more or less the same effectiveness, side-effects, indications and contraindications. Undoubtedly, it affords a distinct less frequent incidence of acute gastric irritation.

4.16. Benorylate

The **acetaminophen (paracetamol)** ester of **aspirin**, **benorylate**, is an interestingly novel example of a prodrug where both the individual entities represent active agents. The **'drug'** seems to be free from the most undesirable **ulcerogenic characteristic features ;** and, therefore, soonafter the usual absorption, it gets split into its two active components once again by the aid of **serum esterases.** It has been duly reported to serve as an effective analgesic-anti-inflammatory drug.

4.17. Sulfinpyrazone

It belongs to the class of a pyrazone structural analogue having potent uricosuric activity together with some antirhombotic and platelet inhibitory activity. It is invariably employed to minimise **the serum-urate concentration** in the specific instances of chronic and intermittent gouty arthritis. It is ob-

*An acute disease marked by a deficit or absolute lack of granulocytic WBC (neutrophils, basophils, and eosinophils).

served to get adequately absorbed after the oral administration ; 98 to 99% is bound to plasma protein, plasma half-life is almost nearly 2.2 to 3 hours, and finally 50% of the administered '*drug substance*' is usually gets excreted practically unchanged in the urine.

4.18. Mefenamic Acid

The precise mechanism of action of this **'drug'** is assumed to be related to its ability to block **prostaglandin (PG) synthetase** almost completely. It has also been observed that it does not bear any relationship whatsoever with respect to partition coefficient, dissociation contant (pKa), and lipid-plasma distribution. Besides, there are several evidences in literature(s) with regard to its **anti-UV erythema activities,** and **antibradykinin activities*.** It definitely shows much decreased incidence of **gastrointestinal bleeding,** a prominent drawback of such drugs, when compared to **'aspirin'**.** Besides, it has been duly approved for the control and management of primary dysmenorrhea, that is believed to be caused by an overwhelming concentrations of endoperoxides as well as prostaglandins (PG).

4.19. Meclofenamate Sodium

This is the 2, 6-dichloro derivative of mefenamic acid, as its sodium salt ; and exerts its most predominant side effects, such as : diarrhea, and gastro intestinal disorders.

4.20. Flufenamic Acid

It is a trifluoromethyl analogue of anthranilic acid, that exerts its three-in-one pharmacological actions *viz.*, antipyretic, analgesic, and anti-inflammatory. It finds its abundant usage in dysmenorrhoea and various types of rheumatic disorders. However, the exact and precise mechanism of antipyretic action of the N-aryl anthranilic acid structural variants has not yet been established. There exists no relationship to lipid plasma distribution, partition coefficient or pKa values of these types of drugs *vis-a-vis* their antipyretic activity.

Probable Questions for B. Pharm. Examinations

1. Classify the **'febrifuges'** and give the structure, chemical name and uses of at least ONE compound from each category.
2. Give the names of **three** drugs belonging to the category of **'aniline and para aminophenol analogues'.** Discuss the synthesis of **one** of them.
3. Discuss **'Salicylic Acid Analogues'** as potent antipyretic analgesics. Give suitable examples of support your answer.
4. What is the structure difference between **Cinchophen** and **Neocinchophen ?** Give the synthesis of any **one** of them.
5. The metabolite of **Phenylbutazone** is a better effecitve drug. Discuss its synthesis and is important uses.
6. Name a Sulphur containing **pyrazolodione drug** used as an antipyretic analgesic and describe its synthesis.

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*Scherrer RA, In : Scherrer RA and Whitehouse MW (eds.) **Antiinflammatory Agents**, Academic Press, New York, *p*-132, 1974.

Lane AZ *et al*, *J. New Drugs.*, **4, 333, 1964.

7. 'Structural analogues of N-arylanthranilic acid yielded some potent antipyretic, analgesic and anti-inflammatory compounds'. Justify the statement with **two** important examples along with their synthesis.

8. Discuss the **'mode of action'** of antipyretic analgesics by citing the examples of some typical drugs, which you have studied.

9. What are Salol, Partial Salol and True Salol ? Give the structure, chemical name and uses of **one** typical examples from each type.

10. Give a comprehensive account of **antipyretic-analgesics**.

RECOMMENDED READINGS

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2. CO Wilson, O Gisvold and FR Doerge, **Textbook of Organic Medicinal and Pharmaceutical Chemistry,** (11th edn.) JB Lippincott Company Philadelphia (2002).
3. D Lednicer and LA Mitscher **The Organic Chemistry of Drug Synthesis,** John Wiley and Sons New York (1995).
4. HC Churchill-Davidson, **Hypothermia,** *Anaesth* June (1954).
5. JEF Reynolds (ed.) **Martindale The Extra Pharmacopoeia,** (31st edn.) The Pharmaceutical Press London (1997).
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7. PAJ Janssen and CAM van der Eycken in : A. Burger (ed.) **Drugs Affecting the Central Nervous System,** Marcell Dekker, New York (1968).
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