16

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Chapter

16

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

1. INTRODUCTION

Inflammation may be defined as the series of changes that occur in living tissues following injury. The injury which is responsible for inflammation may be brought about by a variety of conditions such as : physical agents like mechanical trauma, ultra-violet or ionizing radiation ; chemical agents like organic and inorganic compounds, the toxins of various bacteria ; intracellular replication of viruses ; hypersensitivity reactions like reaction due to sensitized lymphocytes with antigenic material *viz.*, inhaled organic dusts or invasive bacteria ; and necrosis of tissues whereby inflammation is induced in the surrounding tissues.

Almost three decades ago, **steroids** namely : **prednisolone, dexamethasone, betamethasone, triamcinoline** and **hydrocortisone** were considered to be the **drug of choice as anti-inflammatory agents.** Owing to the several adverse effects caused by either short-term or long-term steroid therapy, these have been more or less replaced by much safer and better tolerated **non-steroidal anti-inflammatory drugs (NSAIDs).**

The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of non-steroidal anti-inflammatory drugs since the past three decades. A good number of these agents have been put into clinical usage widely and confidently thereby exhibiting positive therapeutic efficacy accompanied with fewer untoward reactions.

The mechanism of action principally responsible for most of the **NSAIDs** seems to be inhibition of prostaglandin synthesis by causing almost complete blockade of the activity of the precursor enzyme, *cyclogenase*. In fact, there are two *isozymes* that have been duly recognized for the **cyclo-oxygenase enzyme** (*viz.*, **COX-1** and **COX-2**). However, both **isozymes** practically perform the same reactions, but **COX-1** is the isozyme that is found to be *active* under normal healthy conditions. Importantly, in rheumatoid arthritis, **COX-2,** which is usually found to be quite dormant, gets duly activated and yields a substantial quantum of inflammatory prostaglandins. Based on these critical facts and observations a vigorous concerted effort is being geared up to develop such newer drug substances that are specifically selective for the **COX-2** isozyme, with a view to arrest particularly the production of the inflammatory prostaglandins.

In general, there exists virtually very little difference between the therapeutic efficacy of different **NSAIDs,** as certain patients would respond to one **'drug'** better than another. In reality, it is almost

difficult to predict the best suitable drug for a patient ; thus, it invariably necessitates to arrive at the **best-fit-drug** *via* trial and error only.

Keeping in view the innumerable adverse side effects caused by the **NSAIDs** their clinical usefulness are restricted drastically. Therefore, patients who are taking such drugs for a relatively longer periods should have periodic white-blood cell counts as well as determinations of serum creatinine levels, besides hepatic enzyme activities.

2. CLASSIFICATION

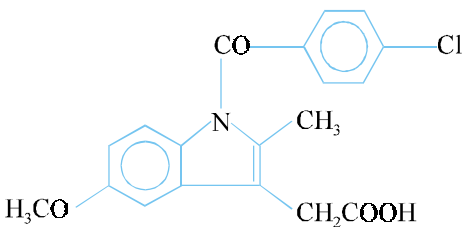
NSAIDs may be classified on the basis of their basic chemical structures as described below along with various classical examples belonging to each category, namely :

1. Heteroarylacetic acid analogues
2. Arylacetic acid analogues
3. Arylpropionic acid analogues
4. Naphthalene acetic acid analogues
5. Gold compounds
6. Miscellaneous anti-inflammatory drugs
7. Salicylic acid analogues and
8. Pyrazolones and pyrazolodiones.

2.1. Heteroarylacetic Acid Analogues

This constitutes an important class of **non-steroidal anti-inflammatory drugs** which have gained recognition in the recent past. A few classical examples of this group are, **indomethacin ; sulindac ; tolmetin sodium ; zomepirac sodium ;**

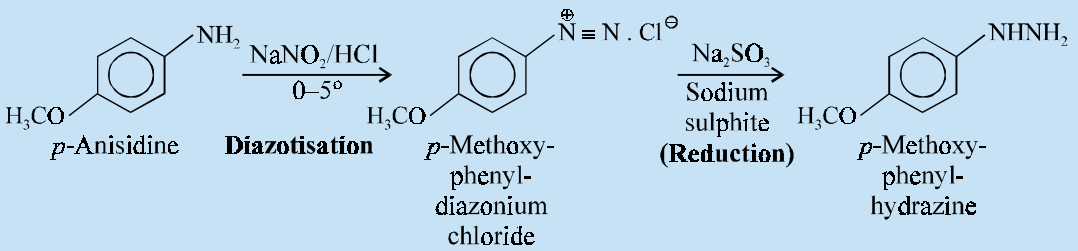
A. Indomethacin BAN, USAN, Indomethacin INN,



1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid ; 1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl- ; BP ; USP ;

Indocin(R) (MSD)

Synthesis



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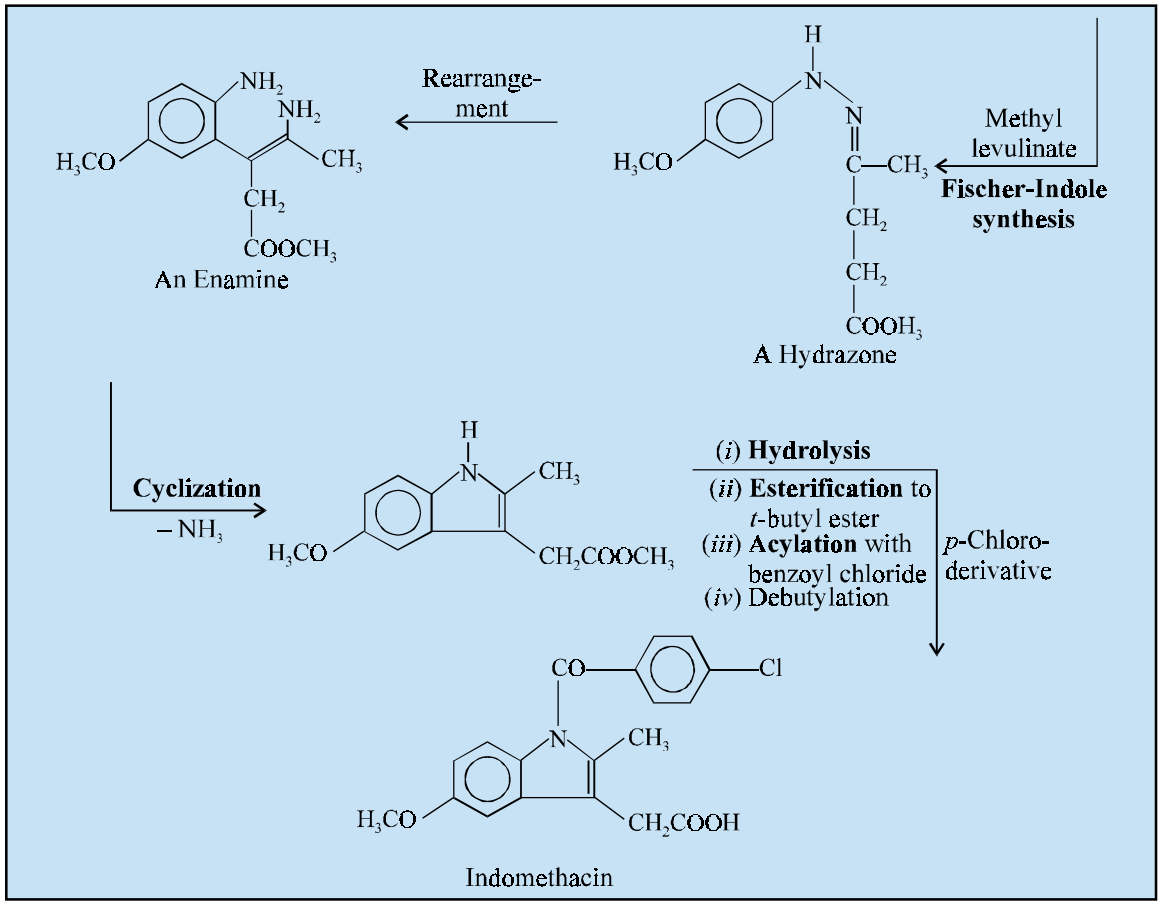
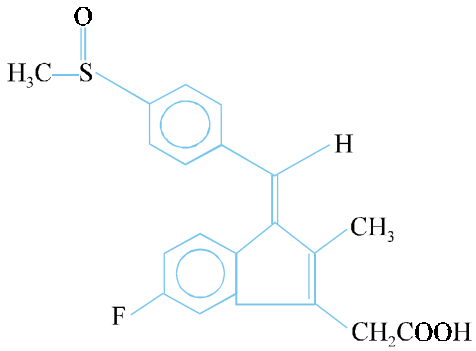


p-Methoxy phenyl diazonium chloride is obtained by the diazotization of *p*-anisidine which on reduction with sodium sulphite yields *p*-methoxy phenyl hydrazine. The resulting product undergoes the Fischer-indole synthesis in the presence of methyl levulinate to form a hydrazone which on intra-molecular rearrangement gives an enamine. This on cyclization loses a molecule of ammonia and forms an intermediate compound. It is then hydrolysed to the corresponding acid which is re-esterified *via* the anhydride to give the tert-butyl ester. Finally acylation with *p*-chlorobenzoyl chloride followed by debutylation gives rise to the official compound.

It is a non-steroid drug possessing anti-inflammatory, antipyretic and analgestic properties. *It is usually used for the treatment of rheumatoid arthritis, ankylosing (rheumatoid) spondylitis, gouty arthritis and osteoarthritis.* It is not an ordinary simple analgesic and owing to its reasonaly serious untoward effects should be used with great *caution.*

Dose : *In gout, usual, adult, oral, 100 mg initially, followed by 50 mg 3 times daily until pain is relieved ; As antirheumatic, oral, 50 mg 2 or 3 times daily ; As antipyretic, oral, 25 to 50 mg 3 times daily.*

B. Sulindac INN, BAN, USAN,



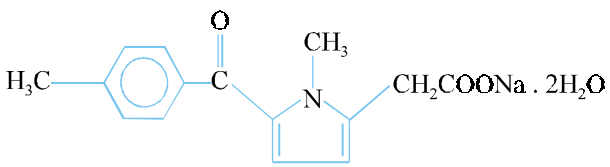
cis-5-Fluoro-2-methyl-1-[(*p*-methylsulfinyl) benzylidene] indene-3-acetic acid ; 1H-Indene-3-acetic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl) phenyl] methylene]-, (Z)-; USP ;

Clinoril(R) (MSD).

It is a fluorinated indene with a structural resemblance to indomethacin. It has anti-inflammatory, analgesic and antipyretic properties. *It is usually employed in the treatment of rheumatic and musculoskeletal disorders ; and also for severe and long-term relief of signs and symptoms of acute painful shoulder, acute gouty arthritis and osteoarthritis.*

Dose : *Usual, adult, oral, 150 mg twice a day with food.*

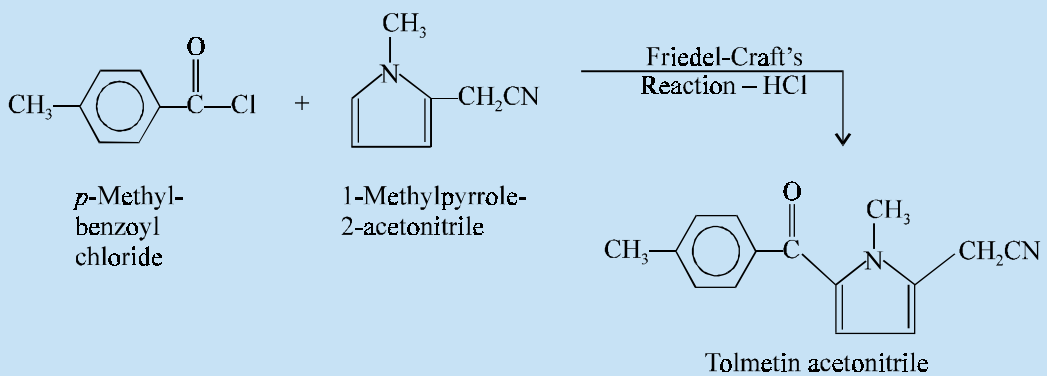
C. Tolmetin Sodium BAN, USAN, Tolmetin INN,



Sodium 1-methyl-5-*p*-toluoylpyrrole-2-acetate dihydrate ; 1H-Pyrrole-2-acetic acid, 1-methyl-5-(4-methylbenzoyl)-, sodium salt, dihydrate ; USP ;

Tolectin(R) (McNeil).

Synthesis



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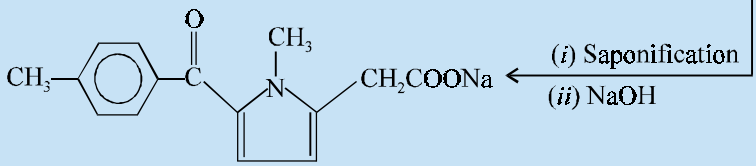


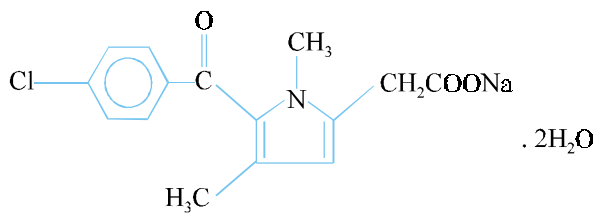
Tolmetin Sodium

Tolmetin acetonitrile may be prepared by the Friedel-Craft's reaction between *p*-methylbenzoyl chloride and 1-methylpyrrole-2-acetonitrile with the elimination of a mole of hydrochloric acid. The resulting product after appropriate separation from its 4-aroyl isomer is finally subjected to saponification followed by conversion to its sodium salt.

It has antipyretic, analgesic and anti-inflammatory actions. It is employed in the *treatment of rheumatic and other musculoskeletal disorders.* The drug is, however, comparable to indomethacin and aspirin in the control and management of disease activity.

Dose : *(Equivalent to tolmetin) Adult, oral, initial, 400 mg 3 times per day, subsequently adjusted to patient's response.*

D. Zomepirac Sodium BAN, USAN, Zomepirac INN,



Sodium 5-(*p*-chlorobenzoyl)-1, 4-dimethylpyrrole-2-acetate dihydrate ; 1H-Pyrrole-2-acetic acid, 5-(4-chlorobenzoyl)-1, 4-dimethyl-, sodium salt, dihydrate ; USP ;

Zomax(R) (McNeil).

It is an analgesic and anti-inflammatory drug structurally very similar to tolmetin sodium. It is normally used in mild to moderate pain, including that of musculoskeletal disorders.

Dose : *(Zomepirac sodium 1.2 g is approximately equivalent to 1g of zomepirac) ;* 400 to 600 mg of zomepirac daily.

2.1.1. Mechanism of Action

The **mechanism of action** of drugs discussed under Section 16.2.1. are as under :

2.1.1.1. Indomethacin

The **'drug'** exerts its pharmacologic activity by inhibiting the **enzyme *cyclo-oxygenase***. It has been observed that this aforesaid enzyme specifically involved in the biosynthesis of prostaglandins that are solely responsible for the pain and inflammation of rheumatoid arthritis ; and, therefore, inhibiting the '**enzyme**' decreases the prostaglandin levels and eases the apparent symptoms of the disease. Besides, it has been proved beyond any reasonable doubt that the *'drug'* also inhibits the synthesis of useful prostaglandins both in the GI-tract and kidney.

Indomethacin, is invariably absorbed quite rapidly after oral administration ; peak plasma levels are accomplished in just 2 hours ; and almost 97% of the drug is protein bound. It has a half-life of 2.6 to 11.2 hours ; and only 10-20% of the drug gets excreted practically unchanged in the urine.

Caution. The high potential for dose-related adverse reactions both restrains as well as makes it imperative that the smallest effective dosage must be determined for each individual patient carefully and meticulously.

2.1.1.2. Sulindac

The precise mechanism of action of the '**drug**' is still unknown. However, it is believed that the '**sulphide metabolite**' may perhaps inhibit the prostaglandin synthesis. Interestingly, it exerts appreciably much less effect on the platelet function and bleeding time in comparison to *'aspirin'*, it must be used with great caution in such patients who could be affected quite adversely by this sort of action.

The **'drug'** gets absorbed invariably to the extent of 90% after the oral administration. The peak plasma levels are usually accomplished in about 2 hour in the fasting patient and may be extended between 3-4 hours when given with food. It has been duly observed that the mean half-life of sulindac is 7 = 8 hours ; and the mean half-life of the corresponding sulphide-metabolite is 16.4 hour (almost double than the parent drug).

2.1.1.3. Tolmetin Sodium

The exact mechanism of action of the '**drug**' is not yet established, although inhibition of prostaglandin synthesis most probably contributes heavily to its anti-inflammatory activity. It has been observed adequately that in such patients having rheumatoid arthritis different types of manifestations of its anti-inflammatory and analgesic actions do occur, but there exists little distinct proof of alteration of the progressive course of the prevailing disease.

The **'drug'** is usually absorbed not only rapidly but also completely having peak-plasma levels being attained within a span of 30-60 minutes after an oral therapeutic after a dosage regimen (40 mcg. mL^{-1}) after a 400mg dosage). Besides, it gets bound nearly to 99% to the plasma proteins ; whereas, the mean plasma-life is almost 1 hour. Importantly, all of a dose gets excreted in the urine within 1 day, either as conjugates of the parent drug *'tolmetin'* or as an **inactive oxidative metabolite**.

2.1.1.4. Zomepirac Sodium

The **'drug'** happens to be the *chloro*-derivative of tolmetin ; and, therefore, it predominantly shows appreciably longer plasma levels nearly 7 hours*, thereby attributing much lesser dosing frequency. It has been demonstrated adequately that a dose ranging between 25-50mg of this *'drug'* gives relief almost equivalent to that produced by aspirin, 650mg. Interestingly, in advanced cancer subjects, oral doses of 100-200mg were as effective the moderate parenteral doses of morphine.**

Note. The *'drug'* is presently not marketed because of its severe anaphylactoid reactions.***

2.2. Arylacetic Acid Analogues

It has been observed that organic compounds which bear some sort of resemblance either with respect to their structural features or functionally often display similar biological actions. However, it may be noted with interest that by contrast there exists no such common goals between arylacetic and arylpropionic acids.

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*O' Neill PJ *et al. J Pharmacol Exp Therap.*, **209,** 366, 1979.

**Wallenstein SL, *Unpublished Report.*

***An agent producing anaphylactic reactions.

The early 1970s have withnessed the introduction of arylacetic acids into numerous beneficial antiarthritic-analgesic agents ; however, their various structural parameters are still being explored exhaustively. A few **salient features** are enumerated below :

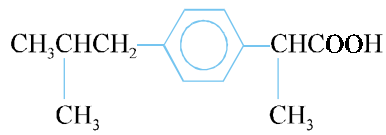
• Indole and pyrrole acetic acid, that are also aromatic in character, are regarded as a subgroup.

• Acidic heterocyclic sulphonamide compounds also afford clinically important **NSAIDs**.

Interestingly, all these compounds additionally show useful antipyretic activities. They all share a more or less common mechanism of action.

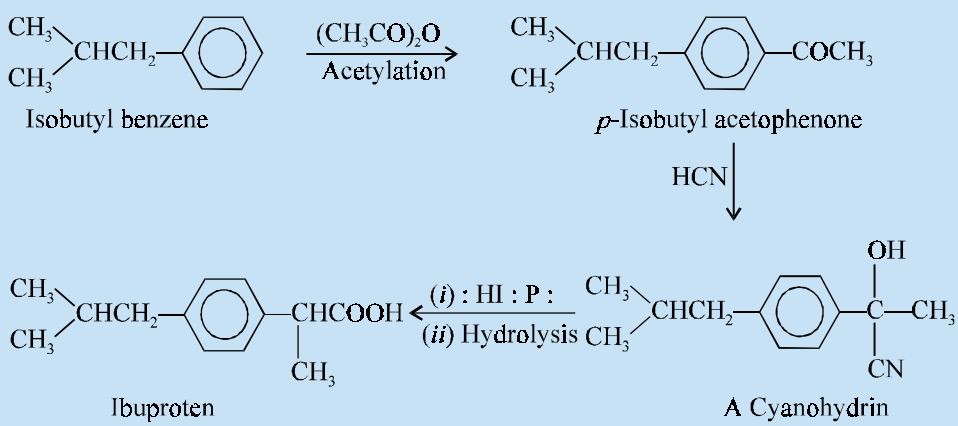
A few potent analogues belonging to this class of compounds are described below : **ibuprofen** ; **ibufenac** ; **diclofenac sodium**.

A. Ibuprofen INN, BAN, USAN,



(±)-*p*-Isobutylhydratropic acid ; Benzeneacetic acid, α-methyl-4-(2-methyl-propyl), (±)-; BP ; USP ; Motrin(R) (Upjohn) ; Brufen(R) (Boots) ; Nuprin(R) (Bristol-Myers) ; Advil(R) (American Home Prod.).

Synthesis



p-Isobutyl acetophenone is prepared by the acetylation of isobutyl benzene which upon treatment with hydrocyanic acid yields the corresponding cyanohydrin. This on heating with hydrogen iodide in the presence of red phosphorous helps to reduce the benzylic hydroxyl moiety ; further hydrolysis of the nitrile groups gives the official compound.

It is an anti-inflammatory drug that possesses anti-pyretic and analgesic actions. It is indicated for the *treatment of rheumatoid arthritis and osteoarthritis.* It is also recommended *to arrest acute flares and in the long-term management of these diseases.*

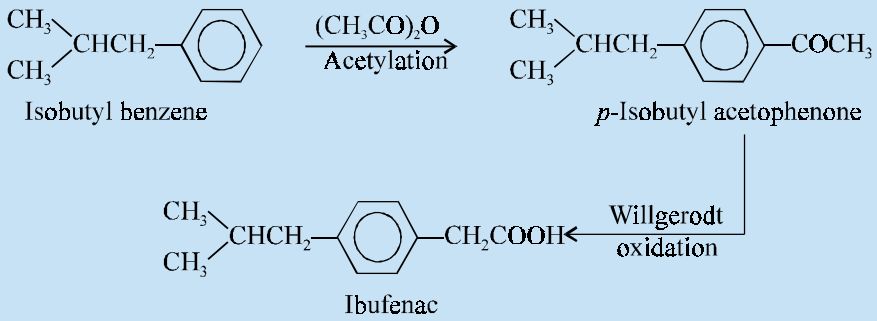
Dose : *Usual, oral adult, analgesia (dysmenorrhea), 200 to 400mg 4 to 6 times per day ; in rheumatoid arthritis, osteoarthritis, 300 to 400mg 3 or 4 times daily.*

B. Ibufenac INN, BAN, USAN,

(*p*-Isobutyl-phenyl) acetic acid ; Benzeneacetic acid, 4-(2-methylpropyl);

Dytransin(R) (Boots).

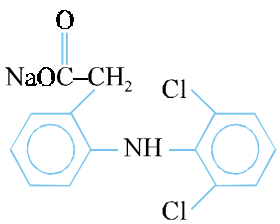
Synthesis



The *p*-isobutyl acetophenone obtained by the acetylation of isobutylbenzene is subjected to Wilgerodt oxidation to yield **ibufenac**.

It has anti-inflammatory, analgesic and antipyretic actions. It was formerly employed in the rheumatic conditions but was found to cause hepatotoxicity.

C. Diclofenac Sodium BAN, USAN, Diclofenac INN,



Sodium [*o*-(2, 6-dichloroanilino) phenyl] acetate ; Benzene-acetic acid, 2-[(2, 6-dichlorophenyl) amino]-, monosodium salt ; Dichlorophenac sodium ;

Voltaren(R) (Ciba-Geigy) ;

It is a phenylacetic acid derivative which has analgesic, antipyretic and anti-inflammatory actions. It is mostly employed in the *treatment of rheumatoid arthritis and other rheumatic disorders.*

Dose : *20 to 50 mg 3 times day. It is also given as a suppository.*

2.2.1. Mechanism of Action

The **mechanism of action** of compounds described under section 16.2.2 shall be dealt within the sections that follows :

2.2.1.1. Ibuprofen

The '**drug**' seems to be fairly comparable to '*aspirin*' in the control, management and treatment of rheumatoid arthritis having a distinct and noticeable lower incidence of side effects.* It has been amply proved and established that the pharmacologic activity of this '**drug**' exclusively resides in the S–(+)-isomer not only in **ibuprofen** but also throughout the arylacetic acid series. Nevertheless, these strategic isomers are exclusively responsible for causing more potent inhibition of the prostaglandin synthetase.

The '**drug**' gets absorbed quite fast after the oral administration ; and evidently the peak plasma serum levels generally are attainable within a span of 1 to 2 hour. It is usually metabolized rapidly and eliminated in the urine. The serum half-life is quite transient ranging between 1.8 and 2.0 hour.

Note. The inclusion of '*ibuprofen*' as an OTC-drug (*i.e.*, non prescription drug) in the United States is solely based on its lack of any serious untoward problems stretched over a decade of meticulous clinical observation and experience.

2.2.1.2. Ibufenac

The '**drug**' is a precursor in which the α-methyl benzeneacetic acid (ibuprofen) is replaced with simple benzeneacetic acid function, that was abandoned on account of its severe hepatotoxicity and was found to be less potent.

2.2.1.3. Diclofenac Sodium

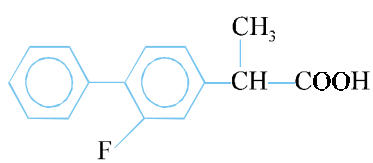
The '**drug**' is believed to exert a wide spectrum of its effects as a consequence of its ability to inhibit the prostaglandin synthesis noticeably. However, its anti-inflammatory activity is very much akin to other members of **NSAIDs** having a potency, *on weight basis*, which is nearly 2.5 times that of **indomethacin.** Likewise, *on weight basis*, its analgesic potency is about 8-16 times than that of **ibuprofen.**

Note. The corresponding potassium salt (Voltaren$^{(R)}$; Cataflam$^{(R)}$, which is proved to be faster acting, is invariably indicated for the management of acute pain and primary dysmenorrhea. It is also specifically recommended for patients having a history of high BP.

2.3. Arylpropionic Acid Analogues

Like the arylacetic acids the arylpropionic acid analogues also exhibit potent anti-inflammatory properties besides usual antipyretic and analgesic characteristics. A few examples of this category of compounds are discussed here, **flurbiprofen** ; **ketoprofen** ; **indoprofen** ; **fenoprofen calcium**.

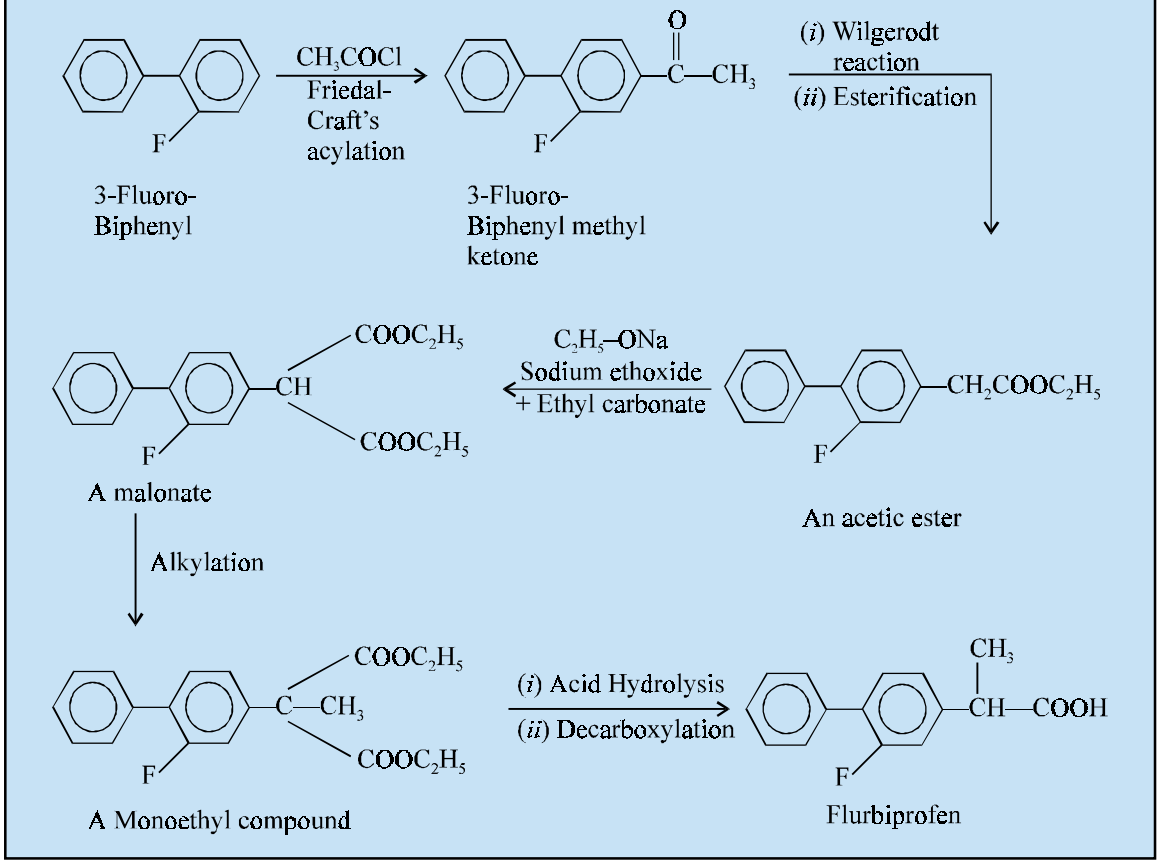
A. *Flurbiprofen* INN, BAN, USAN,



2-(2-Fluorobiphenyl-4-yl) propionic acid ; [1, 1′-Biphenyl]-4-acetic acid, 2-fluoro-α-methyl-, (±)-; (±)-2-Fluroro-α-methyl-4-biphenylacetic acid ; (±)-2-(2-Fluoro-4-biphenylyl) propionic acid ; Ansaid$^{(R)}$ (Upjohn).

*Dorman J *et. al. Can Med. Assoc J,* **110,** 1370, 1974.

Synthesis

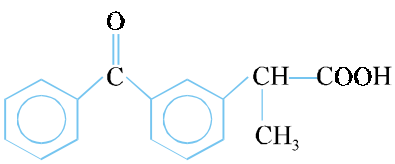


3-Fluoro biphenyl methyl ketone may be prepared by the Friedal-Craft's acylation of 3-fluorobiphenyl with acetyl chloride which upon Wilgerodt reaction followed by esterification yields the corresponding acetic ester. This on treatment with sodium ethoxide and ethyl carbonate yields a malonate which on alkylation forms a monoethyl compound. The resulting product on subsequent hydrolysis and concomitant decarboxylation yields **flurbiprofen**.

It is a phenylpropionic acid analogue which *possesses analgesic, anti-inflammatory and antipyuretic actions.* It is generally employed in the *treatment of rheumatoid arthritis and other rheumatic disorders.*

Dose : *Usual, adult, 150 to 200mg per day in 3 to 4 divided doses.*

B. Ketoprofen INN, BAN, USAN,



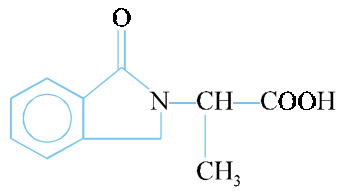
2-(3-Benzoylphenyl) propionic acid ; *m*-Benzoylhydratropic acid ; Benzeneacetic acid, 3-benzoyl-α-methyl- ; BP ;

Alrheumat(R) (Bayer, U.K.) ; Orudis(R) (May & Baker, U.K.)

It is used in the *treatment of rheumatoid arthritis and osteoarthritis.*

Dose : *50 to 100 mg twice daily with food.*

C. Indoprofen INN, BAN, USAN,



2-[4-(1-Oxoisoindolin-2-yl) phenyl] propionic acid ; *p*-(1-Oxo-2-Isoindolinyl) hydratropic acid ; Benzeneacetic acid, 4-(1, 3-dihydro-1-oxo-2H-isoindol-2-yl)-α-methyl- ;

Endyne(R) (Adria).

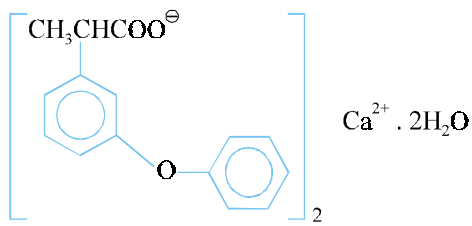
It is generally used for the relief of various types of pain. It is also employed in the treatment of rheumatoid arthritis and osteoarthrosis.

Dose : *600 to 800 mg per day in divided doses.*

D. Fenoprofen *Calcium* BAN, USAN, Fenoprofen INN,

Calcium (±)-2-(3-phenoxyphenyl) propionate dihydrate ; Calcium (±)-*m*-phenoxyhydratropate dihydrate ; Benzeneacetic acid, α-methyl-3-phenoxy-, calcium salt dihydrate, (±)- ; BP ; USP ;

Nalfon(R) (Lilly).



Fenoprofen calcium has *anti-inflammatory, (antiarthritic), and analgesic properties.* It has been shown to inhibit prostaglandin synthetase. It is known to *reduce joint-swelling, decrease the duration of morning stiffness and relieve pain.* It is also indicated *for acute flares and exacerbations and in the long-term management of osteoarthritis and rheumatoid arthritis.*

Dose : *(Fenoprofen equivalent) Usual, adult, oral, rheumatoid arthritis, 600mg 4 times daily ; osteoarthritis, 300 to 600mg 4 times per day.*

2.3.1. Mechanism of Action

The mechanism of action of the compounds discussed under Section 16.2.3. shall now be dealt with in the sections that follows :

2.3.1.1. Flurbiprofen

The '**drug**' is structurally and pharmacologically related to **fenoprofen**, **ibuprofen** and **ketprofen**. It is used for its specific ocular effects ; and therefore, is administered topically to the eye just before

certain ocular surgeries so as to prevent any intra operative miosis. However, the exact mechanism for the prevention and management of the postoperative ocular inflammation is yet to be established.

2.3.1.2. Ketoprofen

The '**drug**' is closely related to fenoprofen in its structure and properties. Besides, it has shown a very low incidence of side-effects and hence, has been approved as an OTC-drug in US.

2.3.1.3. Indoprofen

It is a **NSAID** now rarely used because of its adverse reactions. The **'drug'** shows carcinogenicity in *animal* studies ; and, therefore, it has been withdrawn from the market completely.

2.3.1.4. Fenoprofen Calcium

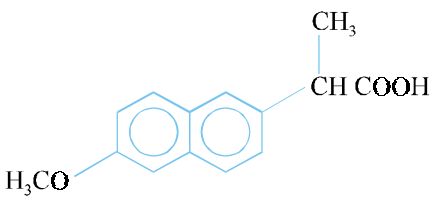
It is a propionic acid structural analogue closely related to **ibuprofen** and **naproxen**. The mechanism of action most probably relates to its inhibition of prostaglandin synthesis. The **'drug'** gets rapidly absorbed after the oral administration. Peak plasma-levels (of about 50 mcg. mL^{-1}) are attained within 2 hour after oral administration of a 600 mg dosage. The plasma half-life is nearly 3 hour. It is highly bound to albumin upto 90%.

It has been observed that nearly 90% of a single oral dosage gets eliminated within a span of 24 hours mostly as **fenoprofen glucoronide** and **4′-hydroxy fenoprofen glucuronide**, the obvious major-urinary metabolites of the **'drug'**.

2.4. Naphthalene Acetic Acid Analogues

The recent intensive quest for non-steroid anti-inflammatory drugs and arylacetic acids in particular offer a brighter scope that the naphthalene acetic acid analogues might turn out to be the leading compounds of an extensive series of promising clinical agents. **Example : Naproxen**.

A. Naproxen INN, BAN, USAN,

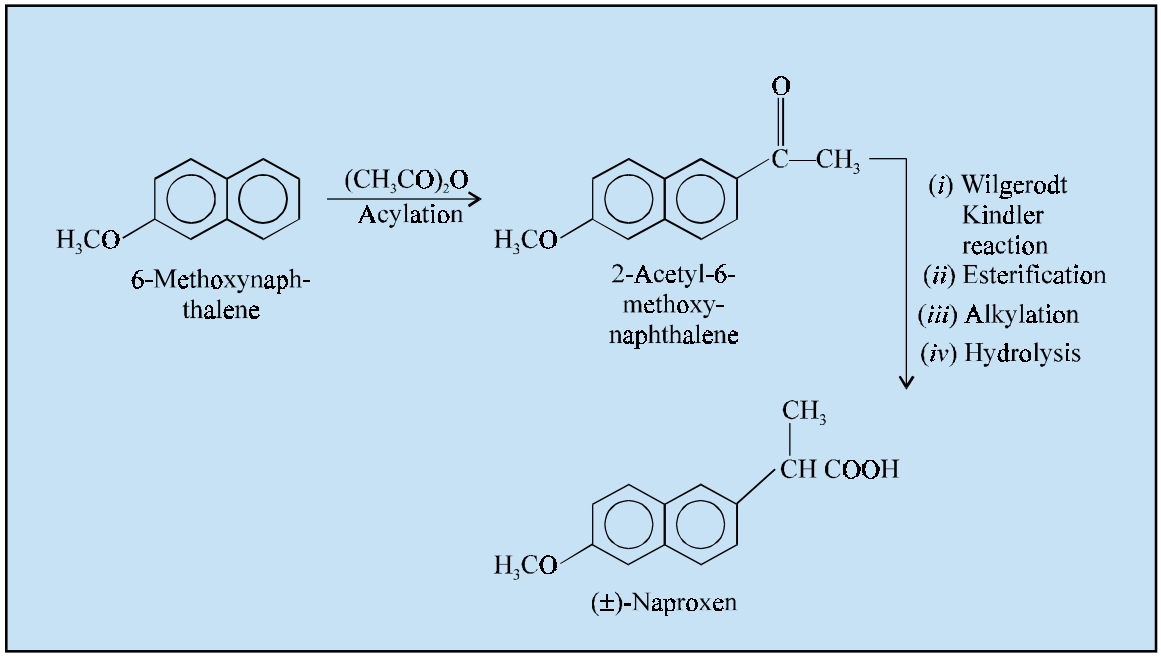


(±)-2-(6-Methoxy-2-naphthyl)-propionic acid ; (+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid ; 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (+)- ; BP ; USP ;

Naprosyn(R) (Syntex).

Synthesis

2-Acetyl-6-methoxy-naphthalene may be prepared by the acylation of 6-methoxynaphthalene. The resulting product is then subjected to a series of reactions, namely ; **Wilgerodt-Kindler reaction**, esterification, alkylation and hydrolysis ultimately yields *DL*-Naproxen. Resolution of the resulting racemic mixture is caused through precipitation of the more potent *D*-enantiomer as the cinchonidine salt.



It possesses analgesic, anti-inflammatory and anti-pyretic actions. It is normally used in the *treatment of rheumatic or musculoskeletal disorders, rheumatoid arthritis, dysmenorrhea, and acute gout.* However, the sodium salt is mostly employed as an analgesic for a variety of other painful conditions.

Dose : *Adult, in rheumatoid arthritis, 250 to 375mg as initial dose 2 times per day ; in acute gout, 750mg as loading dose followed by 250mg 3 times a day until relieved.*

2.4.1. Mechanism of Action

The **mechanism of action** of **naproxen** is described below :

2.4.1.1. Naproxen

It is a naphthalene acetic acid structural analogue available commercially as the acid and its sodium salt and is sold OTC. The '**drug**' is fairly comparable to **aspirin** both in the management and control of disease symptoms. Nevertheless, it has relatively lesser frequency and severity of nervous system together with milder GI-effects.

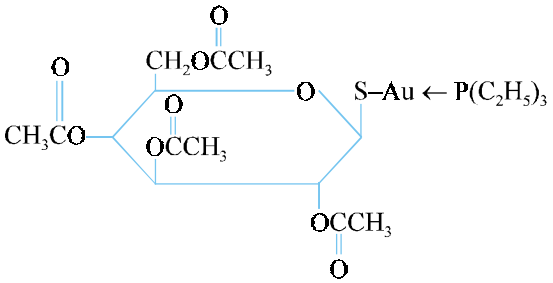
It is absorbed almost completely from the GI-tract after an oral administration. Peak plasma levels ($\simeq$ 55 mg.mL^{-1}) are accomplished after 4 to 5 doses at an internal of 12 hours. It has been observed that more than 99% gets bound to serum albumin. The mean plasma half-life is nearly 13 hour. About 95% of a dose gets excreted in the urine, largely as **conjugates of naproxen** and its corresponding **inactive metabolite 6-demethyl-naproxen**.

2.5. Gold Compounds

In general, gold compounds either suppress or prevent, but do not cure arthritis and synovitis. The use of organic gold derivatives for the treatment of rheumatoid arthritis was first reported in 1927.

However, the monovalent gold compounds bring symptomatic relief to rheumatoid arthritis in patients. A few classical examples of this class of compounds are discussed below. **Examples : auranfin** ; **aurothioglucose** ; **aurothioglycanide** ; **sodium aurothiomalate**.

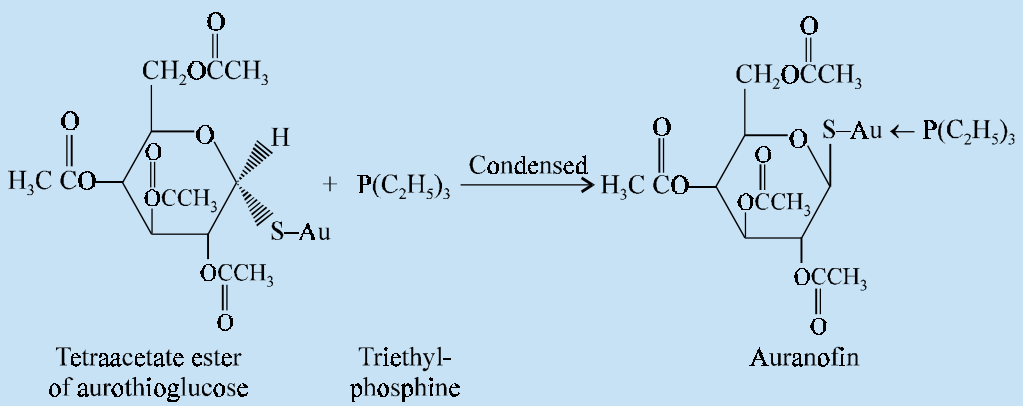
A. Auranofin INN, BAN, USAN,



(1-Thio-β-D-glucopyranosato) (triethylphosphine) gold 2, 3, 4, 6-tetra-acetate ; Gold, (2, 3, 4, 6-tetra-*o*-acetyl-1-thio-β-D-glucopyranosato-S) (triethylphosphine)- ;

Ridaura(R) (SK & F).

Synthesis

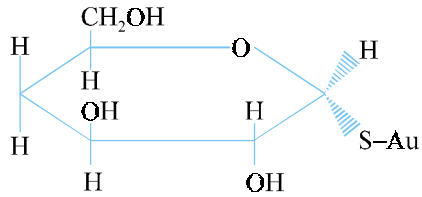


It may be prepared by the condensation of the tetraacetate ester of aurothioglucose with triethylphosphine to yield the co-ordination complex, auranofin.

Auranofin is administered orally and is used chiefly for its *anti-inflammatory action in the cure of rheumatoid arthritis.*

Dose : *Usual, adult, oral 3mg 2 times daily.*

B. Aurothioglucose BAN, USAN,

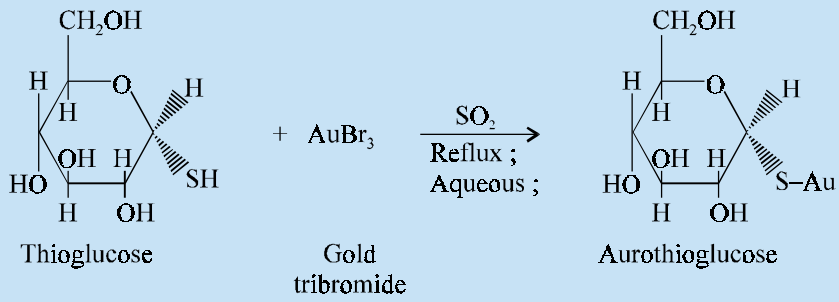


(1-Thio-D-glucopyranosato) gold ; Gold, (1-thio-D-glucopyranosato)- ; Gold Thioglucose ; (D-Glucosylthio) gold ; USP ;

Solganal$^{(R)}$ (Schering-Plough).

Synthesis

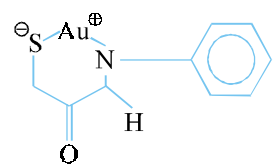
Aurothioglucose is prepared by refluxing together an aqueous solution of thioglucose and gold tribromide in the presence of sulphur dioxide. The resulting compound is precipitated, and is purified by dissolving in water and after which it is reprecipitated by the addition of alcohol.



It is an antirheumatic drug employed for *treatment of active and progressing rheumatoid arthritis and nondisseminated lupus erythematosus. It has been reported that no other antirheumatic drug possesses the capability of arresting the progression of the disease, as gold can do in some cases.*

Dose : *Intramuscular, administration as a suspension in oil for adult in an usual weekly dose of 10mg increasing gradually to 50mg ; children between 6 to 12 years, may be given one quarter the usual dose.*

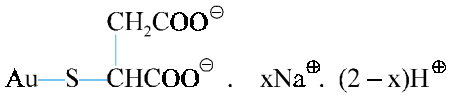
C. Aurothioglucanide INN, BAN, USAN,



S-Gold derivative of 2-mercaptoacetanilide ; α-Auromercaptoacetanilide ; 2-Aurothio-N-phenylacetamide ;

It is used mainly for its *anti-inflammatory effect in the treatment of rheumatoid arthritis.* Being practically insoluble in water it is more gradually released and subsequently absorbed than the other water-soluble gold compounds.

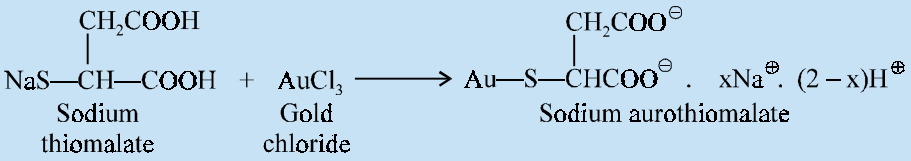
D. Sodium Aurothiomalate INN, BAN, Gold Sodium Thiomalate USAN,



Mercaptosuccinic acid, monogold (1+) sodium salt ; Butanedioic acid, mercapto-, monogold (1+) sodium salt ; (A mixture of the mono- and di-sodium salts of gold thiomalic acid) ; Gold Sodium Thiomalate USP ;

Myochrysine(R) (MSD).

Synthesis



It may be prepared by the interaction of sodium thiomalate with gold chloride.

It possesses anti-inflammatory actions and is used chiefly for the treatment of rheumatoid arthritis. It is extremely *effective in active pregressive rheumatoid arthritis.* It is, however, ineffective against other types of arthritis.

Dose : *Adult, intramuscular, initially, 10mg 1st week, 25mg in second week, 50mg per week for 20 weeks, and for maintenance 50mg every 2 weeks for 4 days.*

2.5.1. Mechanism of Action

The mechanism of action of compounds described under section 16.2.5 shall be dealt within the sections that follows :

2.5.1.1. Auranofin

The value of gold salts in the rheumatoid arthritis is fairly well established ; except for this drug, all available gold preparations should be IM administered. Nearly 25% of the gold content in the *'drug'* gets absorbed. The mean terminal body half-life varies between 21 to 31 days. It has been observed that nearly 60% of the '**absorbed gold**' gets excreted in the urine ; while the remainder is excreted in the faeces.

However, the exact mechanism by which this '**drug**' exhibits its therapeutic effect in rheumatoid arthritis is still not properly understood, although there are ample evidences whereby the *'drug'* does affect a plethora of cellular processes directly linked with inflammation. Importantly, in contrast to the parenteral gold preparations, it is not recognized as a potent inhibitor of sulphydryl moiety reactivity.

2.5.1.2. Aurothioglucose

It is, in fact, well known that once the **'adrenal steroids'** mostly displaced for the *'gold compounds'* from the therapeutic armamentarium for the treatment of active and progressive rheumatoid arthritis and disseminated *lupus erythematosus.** However, bearing in mind the recognition of the numerous hazardous dangers of **steroid therapy** and the potential curative properties has virtually restored the usage of gold

*A chronic autoimmune inflammatory disease involving multiple organ systems and marked by periods of exacerbation and remission.

compounds. It has been duly demonstrated that no other *'antirheumatic drug'* is as capable of arresting the progression of the disease, as gold compounds can do in certain instances.

The best therapy normally takes place when the **'drug'** is employed almost in the early active stages of the disease, and also it is solely based on the daily excretion rate of gold in an individual patient.

It has been observed that the **'drug'** invariably comprises of 50% gold, time to peak effect is 4-6 hours, almost 95-99% gets bound to plasma protein, plasma half-life after a single dose varies from 3 to 27 days ; and finally about 70% is excreted in the urine and 30% in the faeces.

2.5.1.3. Aurothioglycanide

It is one of the sulphur containing gold compounds with a heterocyclic moiety in which the gold (Au) is imbeded strategically. The **'drug'** gets absorbed *in vivo* rather slowly by virtue of its poor solubility in water.

2.5.1.4. Sodium Aurothiomalate

The **'drug'** gets absorbed rapidly after the intramuscular injection and 85 to 95% becomes bound to plasma proteins. It is widely distributed to body tissues and fluids, including synovial fluid, and hence accumulates in the body. The serum half-life of gold is nearly 5/6 days ; however, it increases after successive doses and after a complete course of treatment, gold may be seen in the urine even upto 1 year or more due to its presence in deep body compartments. It is mainly excreted in the urine, with similar quantum in the faeces.

2.6. Miscellaneous Anti-Inflammatory Drugs

There are a number of compounds which incidentally do not fall into any of the categories mentioned so far but they possess anti-inflammatory actions. A few such compounds are described here.

2.6.1. Antimalarial Agents

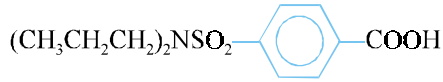
Chloroquine and **hydroxychloroquine** belonging to the class of **4-amino-quinoline anthmalarials** are being used in clinical practice in the cure and treatment of rheumatoid arthritis since 1957. However, the two important disadvantageous factors, namely : slow onset of therapeutic effect and significant ocular toxicity seemed to have shadowed the clinical supremacy of these drugs.

2.6.2. Uricosuric Agents

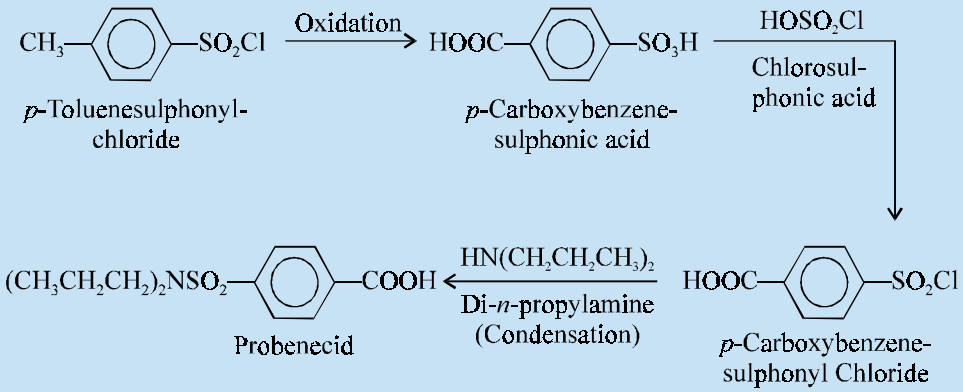
Such drugs that help in the enhanced excretion of excess uric acid through urination and thus reduce the urea concentration in the plasma are known as **uricosuric agents.** There are two important agents which are frequently used in hyperuricemia *viz.*, **sulfinpurazone** and **probenecid** both of which enhance the level of penicillin in plasma by inhibiting its secretion. The former agent has already been dealt under antipyretic analgesics in pyrazolones and pyrazolodiones ; the latter will be discussed here.

A. Probenecid INN, BAN, USAN,

p-(Dipropyl-sulfamoyl) benzoic acid ; Benzoic acid, 4-[(dipropylamino) sulfonyl]-; BP ; USP ; Int. P., Benemid$^{(R)}$ (MSD) ; SK-Probenecid$^{(R)}$ (SKF).



Synthesis

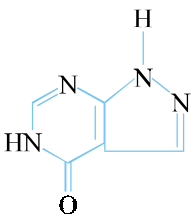


p-Carboxybenzenesulphonic acid is obtained by the oxidation of the methyl group present in *p*-toluenesulphonyl chloride which on further treatment with chlorosulphonic acid yields the corresponding *p*-carboxybenzene sulphonyl chloride. Condensation with di-*n*-propylamine gives rise to the official compound.

Probenecid inhibits renal tubular reabsorption of water and by this mechanism enhances the urinary excretion of uric acid. This lowers the level of urate in the serum. It thus serves as a potent uricosuric agent in the treatment of gout. Probenecid also blocks the renal tubular secretion of penicillins and cephalosporins. It is, therefore, used as *an adjuvant therapy with penicillin V or G, ampicillin, cloxacillin, oxacillin, methicillin and naficillin to increase and prolong their plasma levels.* Besides it also *enhances the plasma levels of anti-inflammatory agents like naproxen and indomethacin,* and a host of medicinal compounds such as sulphonamides, sulphonylureas, dapsone, etc.

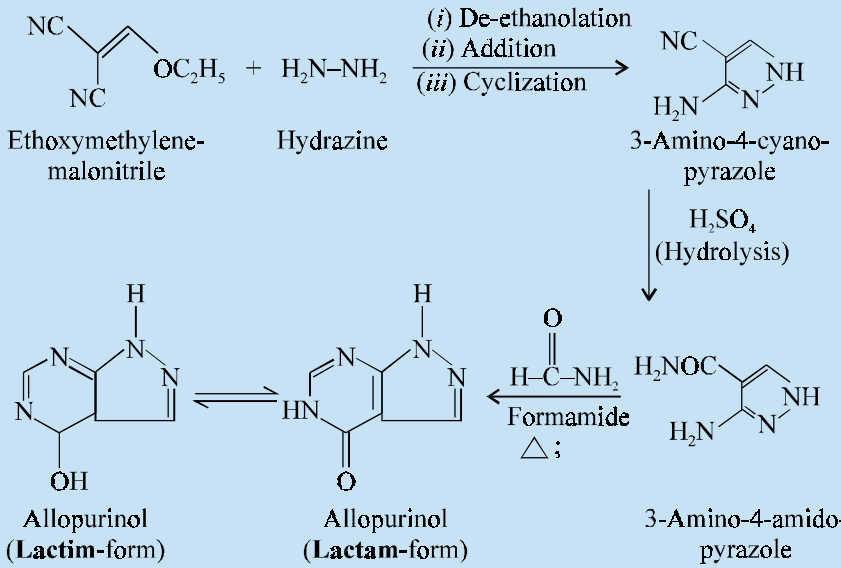
Dose : *Adult, oral, 500 mg to 2 g per day ; usual, 250 mg 2 times daily for one week, then 500 mg twice a day thereafter.*

B. Allopurinol INN, BAN, USAN,



1H-Pyrazolo [3, 4-*d*] purimidin-4-ol ; 1, 5-Dihydro-4H-pyrazolo [3, 4-*d*] pyrimidin-4-one ; BP ; USP ; Zyloprim$^{(R)}$ (Burroughs Wellcome).

Synthesis

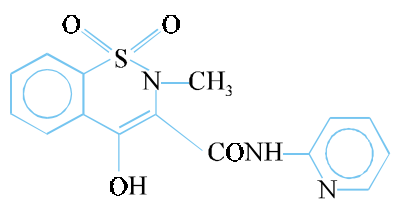


Condensation of ethoxymethylenemalonitrile with hydrazine *via* deethylation, addition and cyclization gives rise to 3-amino-4-cyanopyrazole which upon hydrolysis in the presence of sulphuric acid yields 3-amino-4-amino pyrazole. This on heating with formamide inserts the last carbon atom to afford allopurinol which exhibits tautomerism.

It is a structural analogue of hypoxanthine and is classified as xanthine oxidase inhibitor. It is administered for an indefinite duration in the *treatment of chronic gout.* It helps to decrease the concentration of uric acid in plasma by blocking the conversion of hypoxanthine and xanthine to uric acid and by reducing purine synthesis. Thus it *causes gradual resolution of tophi and minimises the risk of the formation of uric acid calculi.*

Dose : *Usual, adult, oral, antigout, 100 to 200mg 2 or 3 times a day.*

C. Piroxicam INN, BAN, USAN,



4-Hydroxy-2-methyl-N-2-pyridyl-2H-1, 2-benzothiazine-3-carboxamide 1, 1-dioxide ; 2H-1, 2-benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-2-pyridinyl-, 1, 1-dioxide ;

Feldene$^{(R)}$ (Pfizer)

It is employed for acute and long-term therapy for the *relief of symptoms of osteoarthritis and rheumatoid arthritis.* It also possesses uricosuric actions and has been used in the *treatment of acute gout.*

Dose : *Usual, adult, oral, 20 mg daily.*

2.6.2.1. Mechanism of Action

The mechanism of action of some of the typical compounds described under. Section 16.2.6.2. are treated in the sections that follows :

2.6.2.1.1. Probenecid

The **'drug'** is found to inhibit its tubular reabsorption of urate at the proximal convoluted tubule, thereby enhancing the urinary excretion of uric acid and mimising serum uric acid levels. Interestingly, with respect to the **'outward renal transport phenomenon'** the *'drug'* blocks the secretion of weak organic acids at the proximal as well as distal tubules. Therefore, it is overwhelmingly effective and useful as an '**adjuvant therapy**' with such drugs as : pencillin G, O, or V, or with ampicillin, methicillin, oxacillin, cloxacillin, or naficillin for the distinctive elevation as well as prolongation of penicillin plasma levels by whatever route the antibiotic is actually administered.

The **'drug'** get absorbed rather rapidly and completely after an oral administration. It has been observed that plasma levels of 100 to 200 mcg. mL^{-1} are almost necessary for an adequate and sufficient uricosuric effect ; whereas, an equivalent plasma levels of 40-60 mcg. mL^{-1} produce maximal inhibition of the pencillin excretion. The plasma half-life varies from 4 to 17 hour. However, at a plasma concentration of 14 mcg. mL^{-1}, about 17% of the drug invariably gets bound to the plasma protein.

SAR of Probenecid. In this **'drug'** the presence of its electron withdrawing carboxy and sulphonamido-moieties, has not been reported to undergo any aromatic hydroxylation, which explains its fast absorption after an oral administration.

2.6.2.1.2. Allopurinol

It has been observed that the **'drug'** is not uricosuric, but it does inhibit the production of uric acid by way of blocking categorically the biochemical reactions that are essentially involved immediately preceding uric acid formation. Hence, it also inhibits **xanthine oxidase** (enzyme), which is exclusively responsible for the conversion of hypoxanthine to xanthine and of xanthine ultimately to uric acid.

Besides, **allopurinol**, inhibits *de novo* purine synthesis *via* a feedback mechanism, that specifically provides another benefit to the subject. It is found to get metabolized by xananthine oxidase to *oxypurinol*, that also invariably inhibits xanthine oxidase. However, **oxypurinol** possesses a much longer half-clearance time from plasma than allopurinol.

2.6.2.1.3. Piroxicam

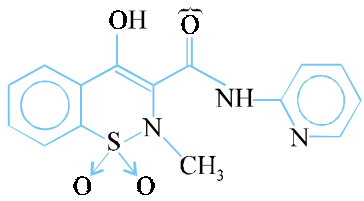
The **'drug'** represents a class of *acidic inhibitors* of **prostaglandin (PG) synthesis**, although it fails to antagonize PGE_2 directly.* It is found to be exerting a rather long duration of action having a plasma half-life of 38 hour, which remarkably pegs a dosage of only 20 to 30mg once daily. Besides, its overall pharmacologic activity has been determined to be almost equivalent to either 400mg of *ibuprofen* or 25mg of **indomethacin** 3-times daily.**

Like other **NSAIDs**, the ***'drug'*** inhibits **prostaglandin (PG) synthesis** chemotaxis and the release of liposomal enzymes (from liver). It has been observed duly that a chronic administration with 20mg per day causes steady state plasma levels of 3-5 mcg. mL^{-1} within a span of 7 to 12 days. The volume of

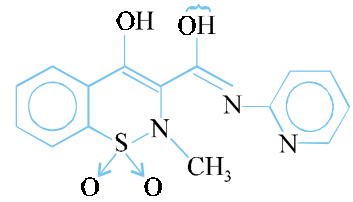
*Wiseman EH : *R Soc Med Int Congr Ser*, **1,** 11, 1978.

Balogh Z *et al. Curr Med Res Opin*, **6, 148, 1979.

distribution is found to be 0.12–0.14 L.kg^{-1} ; mean half life is ~ 50 hour (range, 30-86 hour). It gets metabolized mostly *via* hydroxylation and excreted in the urine ultimately.



Piroxicam
(*keto*-form)



Piroxicam
(*enol*-form) **(Acidic)**

2.7 Salicylic Acid Analogues

A good number of **salicylic acid analogues** have also been found to possess anti-inflammatory actions, *e.g.*, **aspirin**, **salol**, **salsalate**, **sodium salicylate**, **salicylamide**, **benorilate**, **choline salicylate**, **flufenisal** etc., in addition to their antipyretic analgesic property. These compounds have been individually treated in Chapter 9.

2.8 Pyrazolones and Pyrazolodiones

Drugs like **phenazone**, **aminophenazone** (**aminopyrine**), **dipyrone**, **phenylbutazone**, **oxyphenbutazone**, **sulfinpyrazone**, etc., belonging to this category, besides their antipyretic-analgesic action, have also been reported to exhibit anti-inflammatory properties. These compounds have been dealt separately in the chapter on '**antipyretic-analgesics**'.

Probable Questions for B. Pharm. Examinations

1. What are the advantages of NSAID(s) over the steroidal drugs used as anti-inflammatory drugs ? Support your answer with the suitable examples.
2. Classify NSAID based on their chemical structures. Give examples of **one** potent drug from each category.
3. Indomethacin and Tolmetin Sodium are two typical examples of heteroarylacetin acid analogue of NSAID. Give the synthesis of one of them while differentiating their chemical structures.
4. Give the structure, chemical name and uses of **three** important members of arylacetic acid analogues employed as NSAID. Discuss the synthesis of any **one** drug selected by you.
5. 'The arylpropionic acid analogue also exhibits potent anti-inflammatory properties besides analogesic and antipyretic activities'. Justify the statement with suitable examples of NSAID.
6. Naproxen derived from **naphthalene acetic acid analogue** proved to be the leading compound of an extensive series of promising clinical agents. Describe its synthesis from 6-methoxy naphthalene.
7. Discuss the monovalent gold compounds as NSAID. Give the synthesis of **auranotin** and **aurothioglucose** along with their usage.
8. Give the structure, chemical name and uses of the following uricosuric agents :

   (*a*) Allopurinol (*b*) Probenecid (*c*) Piroxicam

   Describe the synthesis of any **one** drug.

9. Give a comprehensive account of the following categories of drugs used profusely as NSAID(*s*) :

(*a*) Salicylic acid analogues,

(*b*) Pyrazolones and pyrazolodiones and

(*c*) Antimalarial agents

Support your answer with appropriate examples

10. Discss the mode of action of NSAID(*s*) by citing the examples of typical representative drugs.

RECOMMENDED READINGS

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17

Antiparkinsonism Agents

Chapter

17 Antiparkinsonism Agents

1. INTRODUCTION

Parkinson's disease or **Paralysis agitans** was first described as early as 1817 by James Parkinson, a London doctor, as consisting essentially of *'Involuntary tremulous motion with decreased muscular power in parts not in action and even when supported, with a propensity to bend the trunk forwards and to pass from a walking to a running pace, the senses and intellect being uninjured'*.

Parkinsonism is usually idiopathic but can arise from ischaemic changes in the brains as in arteriosclerotic and postencephatic parkinsonism.

Various drugs are invariably used in Parkinsonism for the following effects ; *first,* to lower abnormal reflex rigidity and tremor, and restore normal motor activity *e.g.*, natural atropine group of alkaloids, synthetic atropine substituted, antihistaminics ; *secondly,* to minimise mental depression-*e.g.*, analeptics ; and *thirdly,* to allay restlessness, tension and anxiety-*e.g.*, sedatives and tranquillizers.

Parkinsonism is a vivid example of a disorder that lends itself to such particular treatment as : disorders within separate nervous structures which essentially comprise of neurons predominately of one or two transmitter types. In reality, however, the *'antiparkinsonism agents'* are basically not interneuron depressants.

It has been duly demonstrated and established that the disorder in parkinsonism invariably occurs very much within the *substantia nigra** and *corpus striatum*.**

1.1. Etiology

It has been observed that although the neuropathology is well understood, the actual cause of Parkinson's disease is not yet known. In order to understand the etiology of the disease comprehensively one may have to take into consideration the development of both effective *pharmacotherapeutic* and *prophylactic therapy* adequately.

There are several *'theories'* that have been duly put forward with respect to the actual cause of the Parkinson's disease, namely :

(*a*) endogenous and/or environmental neurotoxicants,

***Substantia nigra :** The black substance in a section of the *erus cerebri.*

****Corpus striatum :** A structure in the cerebral hemispheres consisting of two basal ganglia and the fibres of the internal capsules that separate them.

(*b*) mitochondrial dysfunction, and

(*c*) oxidative metabolism : all of which may ultimately lead to a distinct *'oxidative stress'*.

(*d*) neurodegenerative disorders (*e.g.,* movement disorder Huntington's disease*) have been established genetically and that the researchers also proved a possible link and influence in the **Parkinson's disease**.

(*e*) epidemiological investigative researchers have adequately revealed that, besides the age-factor involved, — a family history of **Parkinson's disease** bears almost the strongest predictor of an enhanced possible risk of the ensuing disorder.**

(*f*) α-synucle in protein *i.e.*, a distinct mutation observed in the α-synuclein gene located on the choromosome 4*q*, happens to be a highly conserved and abundant 140-amino acid protein having quite unknown function (*modus operandi*) which is invariably expressed largely in the presynaptic nerve terminals in the brain.***

(*g*) there exists almost little evidence thereby suggesting that Parkinson's disease is virtually *autoimmune related*****; and it further proves that there exists neither a prevalent communicable infectious etiology nor a genetic etiology.

(*h*) the most striking and interesting characterized epidemiologic findings in Parkinson's disease is its remarkable *lower incidence in cigarrette smokers* than the corresponding nonsmokers.

(*i*) **dopamine** – implicates itself in the disease process by means of the production of *chemically reactive oxidation products* which suggest evidently that the endogenously liberated products may be the etiologic factors in **Parkinson's disease**.*****

(*j*) **MAO** – catalyzed oxidation of the **monoamine neurotransmitters** (*e.g.*, dopamine, norepinephrine, serotonin) produces H_2O_2 (Eqn. '*a*'), that may subsequently undergo a redox reaction with superoxide in the **Haber-Weiss reaction******** to give rise to the formation of the highly cytotoxic hydroxy radical as depicted in (Eqn. '*b*') below :

$$RCH_2CH_2NH_2 + O_2 + H_2O \longrightarrow RCH_2CHO + NH_3 + H_2O_2 \quad ...(a)$$

$$H_2O_2 + O_2 \bullet \longrightarrow O_2 + OH^{\ominus} + OH \bullet \quad ...(b)$$

Furthermore, the subsequent auto-oxidation of dopamine to the corresponding electrophilic **semiquinone** and **quinone** analogues has also received considerable cognizance because these '*oxidation products'* are also cytotoxic in nature.******* Besides, Mn^{2+}, is observed to catalyze oxidation of dopamine, and interestingly the resulting species *viz.*, semiquinone and quinone have been duly implicated in the **Mn-neurotoxicity**.********

---

*An inherited disease of the CNS that usually has its onset between ages 25 and 55. Degeneration in the cerebral cortex and basal ganglia causes chronic progressive chorea and mental deterioration, ending in dementia.

Semchuk KM *et al. Neurology,* **43, : 1173–1180, 1993.

***Kruger R *et al. Nature Genetics,* **18** : 106–108, 1998.

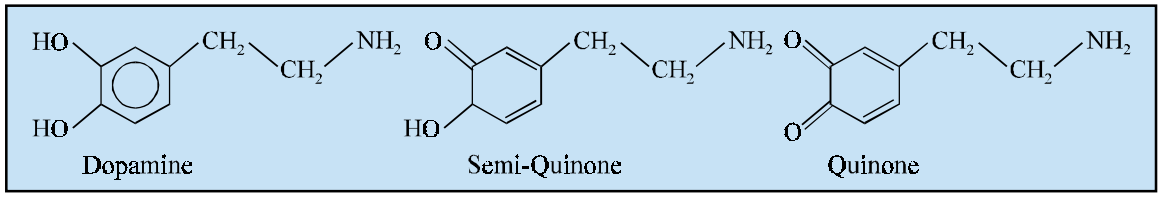
****Duvoisin RC : In Marsden CD, Fahn S eds., **Movement Disorders,** Butterworth Scientific London, 8–24, 1982.

*****Kessler II *et al. Am. J. Epidemiol,* **94,** 16-25, 1971.

******Haber F, Weiss J : *Naturwissenschaften,* **5,** 45-92, 1932.

*******Graham DG *et al. Mol. Pharmacol,* **14** : 644-653, 1978.

********Graham DG, *Neurotoxicology,* **5** : 83-95, 1984.



(*k*) various theories put forward till date suggest amply that the **Parkinson's disease** could be the consequence of normal aging phenomenon adequately superimposed on a lesion strategically located in the *substantia nigra* that might have occurred much earlier in one's life span.*

(*l*) symptoms of **Parkinson's disease** become distinctly apparant when the striatal dopamine levels invariably gets declined to about 80%.**

(*m*) imaginatively, the various apparent/visible symptoms of parkinsonism might be caused by *two* distinct phenomena, namely :

(*i*) a particular disease-linked episode amalgamated with certain observed pathological changes by virtue of normal aging process ; and

(*ii*) wonderful discovery of the selective as well as potent **dopaminergic neurotoxicant N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)** has largely helped scientists carrying out intensive and extensive researches to establish the etiology of Parkinson's disease.

1.2. Parkinsonism Produced by MPTP

It has been reported that the **cyclic tertiary amine MPTP** *i.e.*, N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, has caused an induction of a specific type of **parkinsonism** both in humans as well as monkeys that are found to be virtually identical equally in *neuropathology* and *motor abnormalities* to the resulting idiopathic **Parkinson's disease**.***

Interestingly, MPTP was actually obtained during the course of synthesis of MPPP (as *by-products*) *i.e.*, the reverse ester of the narcotic analgesic meperidine termed as **'MPPP'** (N-methyl-4-propionoxy-4-phenylpiperidine), also commonly known as **'designer-heroin'** or **'synthetic heroin'.** ***MPPP***-is invariably regarded as a structural analogue of another narcotic analgesic **α-prodine.** The *three* vital phenylpiperidine synthetic analgesics. *viz.*, **MPPP**, **α-prodine**, and **meperidine** are illustrated as under :

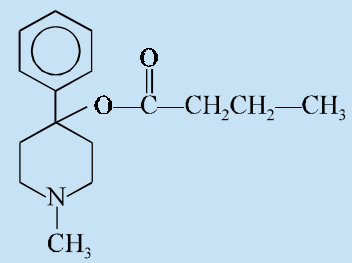
Importantly, the neuropathological and clinical characteristic features of **MPTP-induced parkinsonism** invariably resemble idiopathic Parkinson's disease rather more intimately than anyother previous human or experimented animal disorder exhibited by toxins, viruses, metals, or other modes. In short, the molecular pathophysiology of the ensuring **MPTP neurotoxicity** has virtually decephered the mystery surrounding the *neurodegenerative mechanisms* particularly associated with the **idiopathic parkinsonism.**

---

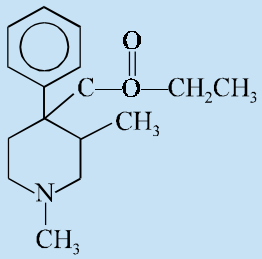
*Calne DB *et al. Nature,* **317** : 246-248, 1985

Riederer *et al. J Neural Transmission,* **38 : 277-301, 1976.

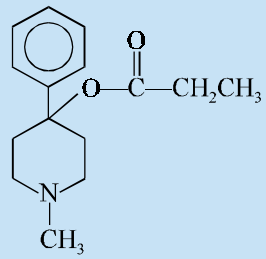
***Davis GC *et al. Psychiatric Res.* **1** : 249-254, 1979. ; Burns RS *et al. Proc Natl Acad Sci* USA, **80** : 4546-4550, 1983.



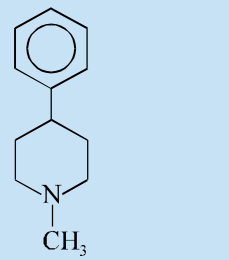
"Designer Heroin"
(MPPP)



α-Prodine
[Nisentil(R)]



Meperidine
[Demerol(R)]



N-Methyl-4-phenyl
1, 2, 3, 6-tetrahydropyridine
(MPTP)

2. CLASSIFICATION

Antiparkinsonism agents may be classified on the basis of their chemical structures as follows :

1. Piperidine analogues
2. Pyrrolidine analogues
3. Phenothiazine analogues, and
4. Miscellaneous drugs.

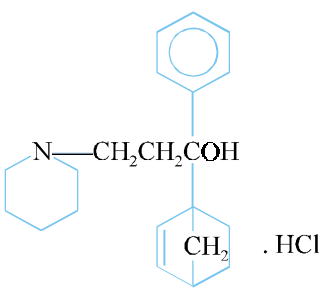
2.1. Piperidine Analogues

A few structural analogues of piperidine proved to be potent **antiparkinsonism agents**. A few examples belonging to this class of compound is given below, namely : **Biperiden hydrochloride ; Cycrimine hydrochloride** and **Trihexyphenidyl hydrochloride**.

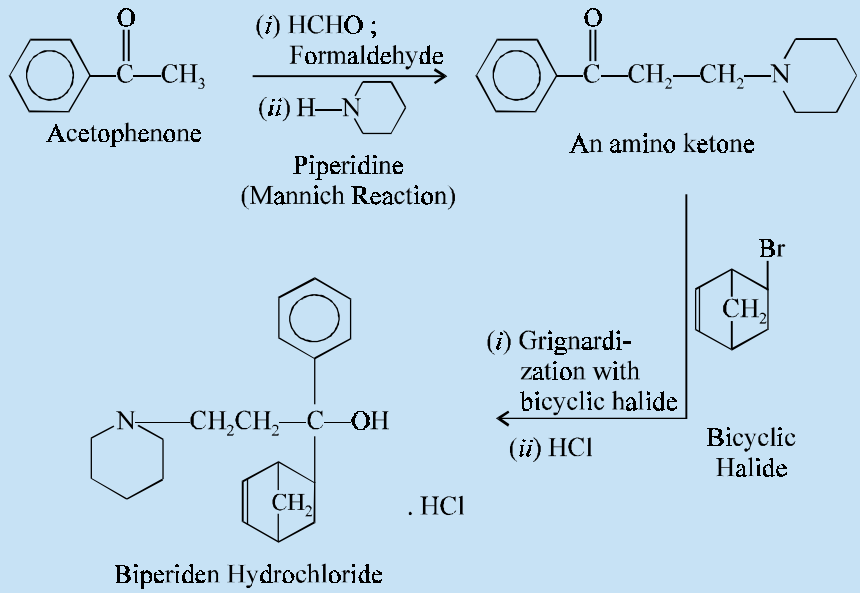
A. Biperiden Hydrochloride BAN, USAN, Biperiden INN,

α-5-Norbornen-2-yl-α-phenyl-1-piperidinepropanol hydrochloride ; Piperidinepropanol, α-bicyclo [2, 2, 1] hept-5-en-2-yl-α-phenyl-, hydrochloride ; USP ; NF ;

Akineton Hydrochloride(R) (Knoll).



Synthesis

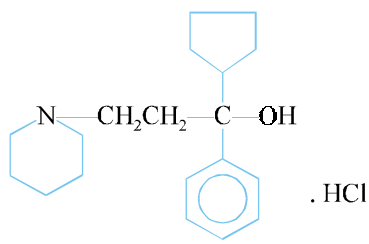


Mannich reaction of acetophenone with formaldehyde and piperidine results into the formation of an aminoketone, which on grignardization with bicyclic halide and subsequent neutralization with HCl affords the official compound **biperiden hydrochloride**.

Biperiden is used in the *treatment of parkinsonism, muscle rigidity, akinesia and drooling.* It is also employed in the *acute crises due to oculogyration (movement of eyeball).* It also finds its use in lowering spasticity in pyramidal tract disorders.

Dose : *For parkinsonism, 2mg 3 or 4 times daily.*

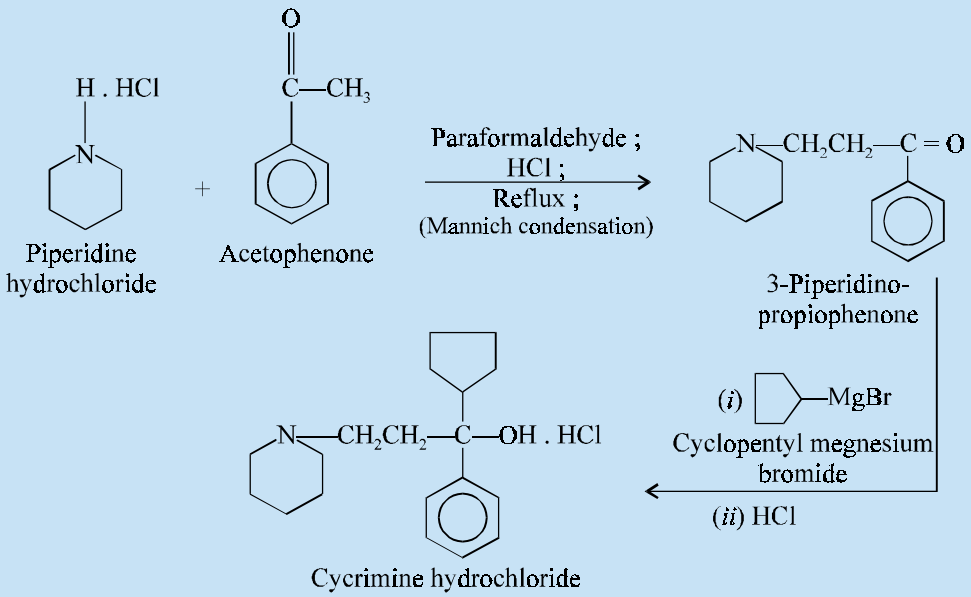
B. Cycrimine Hydrochloride BAN, USAN, Cycrimine INN,



α-Cyclopentyl-α-phenyl-1-piperidinepropanol hydrochloride ; 1-Piperidine-propanol, α-cyclopentyl-α-phenyl-, hydrochloride ; USP ; NF ;

Pagitane Hydrochloride(R) (Lilly).

Synthesis

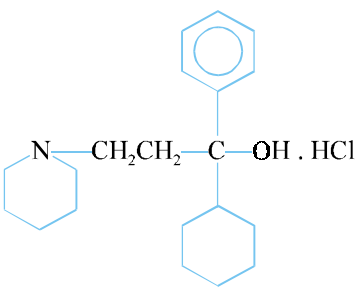


Mannich condensation takes place when piperidine hydrochloride, acetophenone, paraformaldehyde and HCl are refluxed for several hours to yield 3-piperidino propiophenone, which upon grignardization with cyclopentyl magnesium bromide followed by neutralization of the **cycrimine base** forms the official compound.

It is mostly employed in *all forms of paralysis agitans (parkinsonism).*

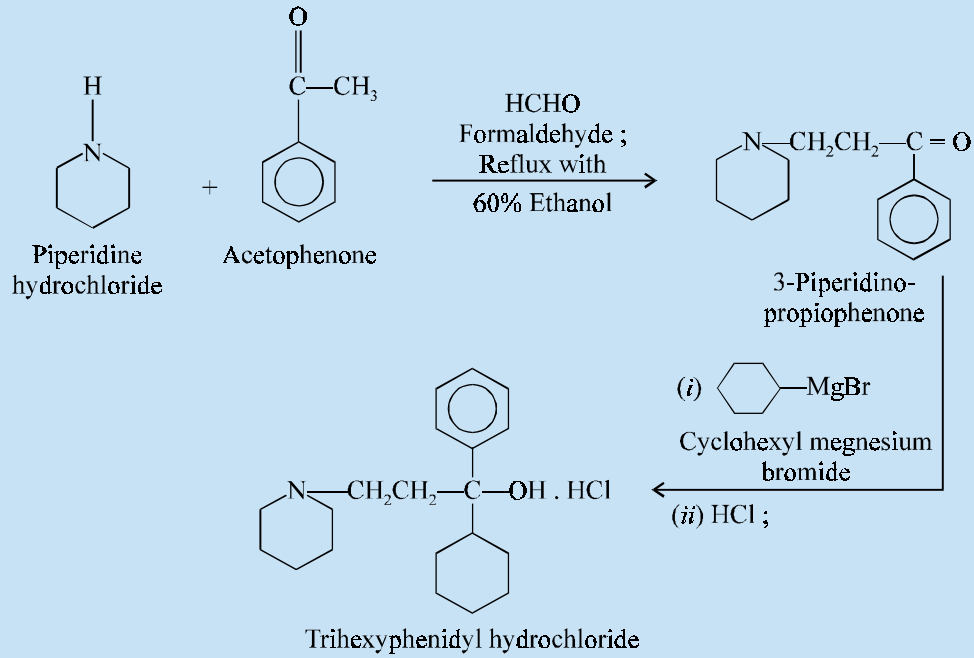
Dose : *Initial, oral, 12.5 mg 2 to 3 times daily ; maintenance dose, 3.75 to 15 mg per day.*

C. Trihexyphenidyl Hydrochloride USAN, Trihexyphenidyl INN, Benzhexol Hydrochloride BAN,



α-Cyclohexyl-α-phenyl-1-piperidinepropanol hydrochloride ; 1-Piperidine-propanol, α-cyclohexyl-α-phenyl-, hydrochloride ; USP ; Benzhexol Hydrochloride BP ; Artane(R) (Lederle) ; Pipanol(R) (Winthrop) ; Tremin(R) (Schering-Plough).

Synthesis



3-Piperidinopropiophenone is prepared by the **Mannich condensation** of acetophenone and piperidine with formaldehyde by refluxing the reactants in 60% ethanol. The resulting product is subjected to Grignard reaction with cyclohexyl-magnesium bromide to yield the corresponding base which is subsequently precipitated by passing a stream of hydrogen chloride through a solution of the base in a suitable solvent.

It is an **antiparkinsonism drug** possessing relatively weaker antispasmodic and antimuscarinic properties. In fact, *it is the drug of choice for the treatment of parkinsonism.* It is also employed *for the relief of akinesia, muscular rigidity, tremor and oculogyria.* It is also found to be useful in the *treatment of drug-induced extrapyramidal symptoms.*

Dose : *Initial, oral, 1mg on 1st day, followed by 2mg daily after 3 to 5 days ; maintenance dose, 6 to 10mg per day in 3 to 4 divided doses but not exceeding 20mg per day.*

2.1.1. Mechanism of Action

The mechanism of action of **'drugs'** discussed under Section 17.2.1 are dealt with in the pages that follows :

2.1.1.1. Biperiden Hydrochloride

The **'drug'** possesses a comparatively weak visceral anticholinergic, but a strong nicotinolytic, action with regard to its ability to *block nicotine-induced convulsions.* Perhaps it amply expatiates its neurotropic activity being distinctly low on the intestinal musculature together with the corresponding blood vessels. Besides, it has been demonstrated that the *'drug'* exhibits a comparatively stronger musculotropic action, that is almost equivalent to that of *papaverine,* in comparison to several synthetic

anticholinergic drugs, such as : **atropine**, **tropicamide**, **methixene hydrochloride**, **glycopyrrolate** etc. It is, however, pertinent to state here that the action of biperiden on the eye, although mydriatic, is found to be much lower relative to that of atropine. Interestingly, these prevailing inherent *weak anticholinergic actions* essentially add to its utility in the control, management and treatment of **Parkinson's syndrome** by decreasing the ensuing side effects appreciably.

Occasionally, the **'drug'** is of immense usefulness in specifically minimizing spasticity in certain disorders of the pyramidal tract, such as : **drug-induced extrapyramidal dyskinesia***, which is eventually managed adequately by its IV form (*i.e.*, the lactate).

2.1.1.2. Cycrimine Hydrochloride

The **'drug'** exerts its action very much similar to that of biperiden hydrochloride. However, it is found to be twice as potent as the biperiden salt perhaps due to the presence of a more compact **cyclopentyl ring** in place of the **biperiden ring**.

2.1.1.3. Trihexyphenidyl Hydrochloride

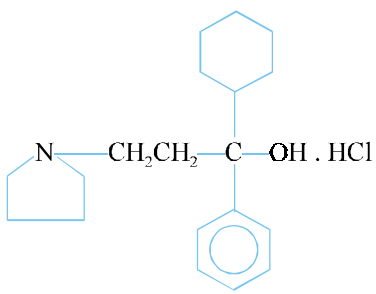
The **'drug'** has found a place in the control, management and treatment of parkinsonism ; besides, giving some sort of relief with respect to the prevailing mental depression invariably linked with this typical condition. It may undergo interaction with the **CNS-active antihypertensive drugs** (*e.g.*, **clonidine hydrochloride**, **guanfacine hydrochloride**, **methyl dopa** etc.,), ethanol and other **CNS-depressants**, **tricyclic antidepressants**, **MAOIs**, other **antimuscarinic drugs**, **dopamine agonists**, **dopamine antagonists**, **phenothiazine**, and **procainamide**. Importantly, whenever this **'drug'** is being employed in conjunction with **levodopa**, **amantadine**, or **bromocriptine**, the dosages of the individual drugs in *'combination'* may require reduction proportionately and substantially (than the individual doses).

2.2 Pyrrolidine Analogue

The introduction of a 5-membered heterocyclic ring, *i.e.*, **pyrrolidine** instead of the 6-membered **piperidine** ring also gave rise to important **antiparkinsonism agent**.

Example : Procyclidine Hydrochloride.

A. Procyclidine Hydrochloride BAN, USAN, Procyclidine INN,

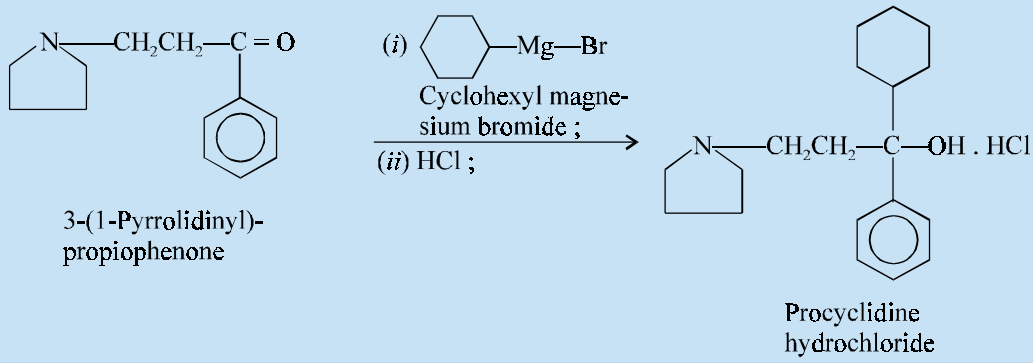


α-Cyclohexyl-α-phenyl-1-pyrrolidinepropanol hydrochloride ; 1-Pyrrolidine-propanol, α-cyclohexyl-α-phenyl-, hydrochloride ; 1-Cyclohexyl-1-phenyl-3-(pyrrolidin-1-yl) propan-1-ol hydrochloride ; BP ; USP ; Int. P., N.F. ;

Kemadrin(R) (Burroughs Wellcome).

*Outside the pyramidal tracts of the CNS-; a defect in the ability to perform voluntary movement.

Synthesis



It may be prepared by reacting 3-(1-pyrrolidinyl) propiophenone with a **Grignard reagent** cyclohexyl magnesium bromide to yield the **procyclidine (base)** which is subsequently treated with HCl to form the official compound.

Procyclidine being a structurally similar chemical congener of trihexyphenidyl possesses also similar properties. It is used for the *symptomatic treatment of postencephalitic parkinsonism. It has also been employed successfully to alleviate the extrapyramidal syndrome induced by such drugs as reserpine and phenothiazine analogues.*

Dose : *Initial, oral, 7.5mg per day in 3 or 4 divided doses after meals ; maintenance dose usually 20 to 30mg per day.*

2.2.1. Mechanism of Action

The mechanism of action of **procyclidine hydrochloride** is discussed as under :

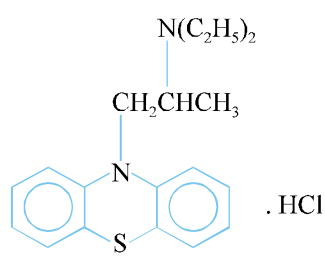
2.2.1.1. Procyclidine Hydrochloride

The **'drug'** exerts its potent peripheral anticholinergic effects that happen to be quite akin to its corresponding analogue methochloride (*i.e.*, tricyclamol chloride) ; however, its pivotal clinical usefulness solely lies in its ability to cause substantial relief to the *voluntary muscle spasticity* by virtue of its central activity precisely. Hence, it has been employed both successfully and efficaciously in the treatment of **Parkinson's syndrome**. Importantly, its ensuing activity on tremor is not quite anticipated ; and, therefore, must be supplemented by usual combination with other identical drug substances.

2.3 Phenothiazine Analogue

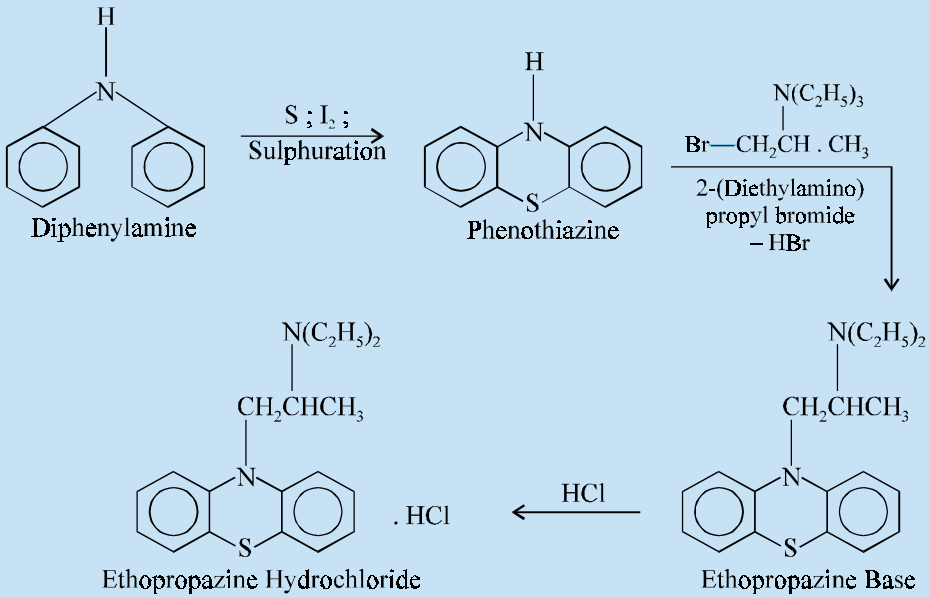
The only **phenothiazine analogue** official in USP and used in parkinsonism is **Ethopropazine hydrochloride**.

A. Ethopropazine Hydrochloride BAN, USAN, Profenamine INN,



10-[2-(Diethylamino) propyl] phenothiazine monohydrochloride ; 10H-Phenothiazine-10-ethanamine, N, N-diethyl-α-methyl-, monohydrochloride ; Isothazine Hydrochloride ; BP ; USP ; Int. P. ; Parsidol(R) (Parke-Davis).

Synthesis



Phenothiazine nucleus may be prepared by the sulphuration of diphenyl amine in the presence of sulphur and iodine which is then treated with the corresponding Grignard complex of 2-(diethylamino) propyl bromide to yield the ethopropazine (base). The resulting base is dissolved in an appropriate solvent and treated with an equimolar quantity of HCl to form the official compound.

It is employed in the *management of parkinsonism, particularly for the control of rigidity.* It has also been used to *reduce the spasm, tremor and oculogyration. It also possesses anticholinergic, adrenergic blocking, mild anti-histaminic, local anaesthetic and ganglionic blocking actions.*

Dose : *Usual, oral, initial, 50mg per day, slowly increased to 500mg per day in divided doses.*

2.3.1. Mechanism of Action

The mechanism of action of **ethopropazine hydrochloride** is described as under :

2.3.1.1. Ethopropazine Hydrochloride

The *'**drug**'* possesses antimuscarinic activity. It is particularly beneficial in the symptomatic treatment of parkinsonism. It finds its enormous therapeutic value in the control of rigidity ; besides, having a favourable response in oculogyric crises, tremor and sialorrhea.*

SAR of Ethopromazine. Another wonderful and dramatic appropriate example of appreciable pharmacologic differences existing between compound which are *'practically-look-alikes'* is the usage of *phenothiazine structural analogue* **'ethopropazine'** to control and treat the extrapyramidal Parkinson like syndrome caused by antipsychotics, for instance : **chlorpromazine** — the well-known neuroleptic chlorpromazine (Chapter : 18). A close examination of the prevailing chemical structures of the two types

*Excessive secretion of saliva.

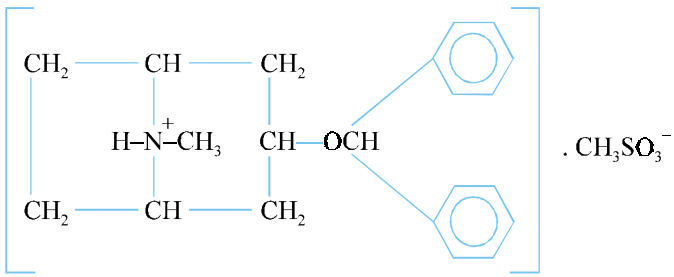
of drugs vividly shows that the *ring-N-atom* in the **antiparkinsonism drug** (*i.e.*, **ethopropazine**) is actually separated from the *chain-N-atom* by *2-C-atoms* ; whereas, the **antipsychotic** (*i.e.*, **chlorpromazine**) or tranquillizer essentially has a *3-C-atom* distance — indeed a *'small'* difference. Thus, the former *'drug'* exerts a antiparkinsonism action ; whereas, the latter is employed invariably as an antipsychotic having an overwhelming and appreciable ability to induct tremors.

2.4 Miscellaneous Drugs

There exist a good number of potent antiparkinsonism agents that do not fall into any of the classifications discussed above (A through C) ; and hence, they have been grouped together under this head.

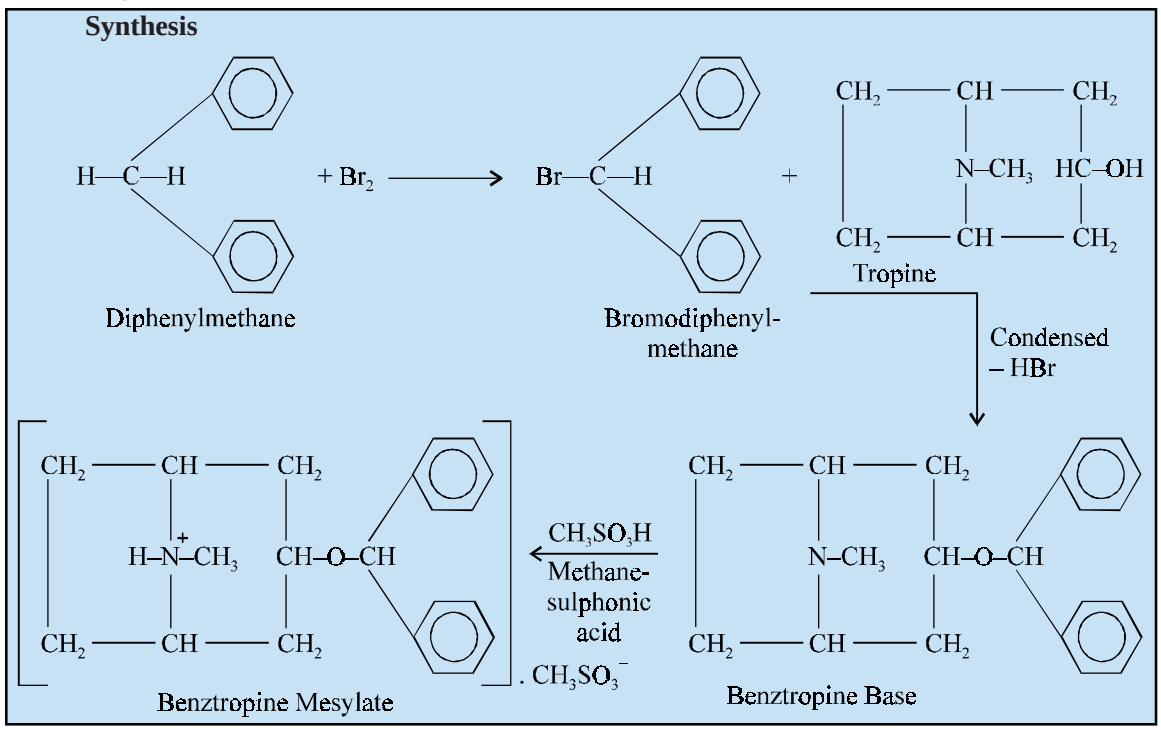
Examples : Benztropine mesylate ; **Orphenadrine citrate** ; **Chlorphenoxamine hydrochloride** ; **Levodopa and Amantadine hydrochloride**.

A. Benztropine Mesylate BAN, USAN, Benzatropine INN,



3α-(Diphenylmethoxy)-1αH-5αH-tropane methanesulphonate ; 8-Azabicyclo [3.2.1] octane, 3-(diphenylmethoxy)-, *endo*, methanesulphonate ; Benzotropine Methanesulphonate ; BP ; USP ; Cogentin(R) (MS & D).

Synthesis

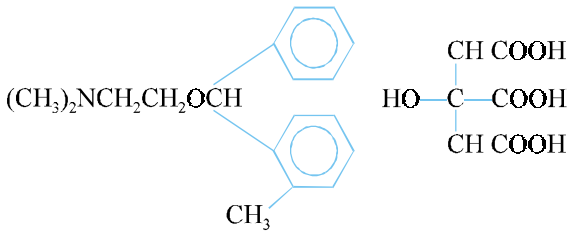


Bromodiphenylmethane may be prepared by the direct bromination of diphenylmethane which is then condensed with tropine, through the Williamson ether synthesis (making use of sodium alkoxide derivative of tropine), to yield the benztropine base. This is dissolved in an appropriate solvent and precipitated by treating it with an equimolar quantity of methanesulphonic acid.

It has a mixed chemical features of both diphenhydramine class of antihistaminics and atropine. It has been used successfully in the *treatment of parkinsonism, to arrest tremor and rigidity, oculogyric crises and pain secondary to muscular spasm.* It is also employed to *control extrapyramidal dyskinesia caused by tranquillizers, namely, chlorpromazine or reserpine.* Its actions and uses are similar to those of benzhexol and is preferred to that of the later due to its inherent sedative effective at its normal dose.

Dose : *Usual, initial, oral, 0.5 to 1mg, slowly increased to 500mcg after every 5 to 6 days till optimal dose is achieved ; i.m. or i.v. 1 to 2mg.*

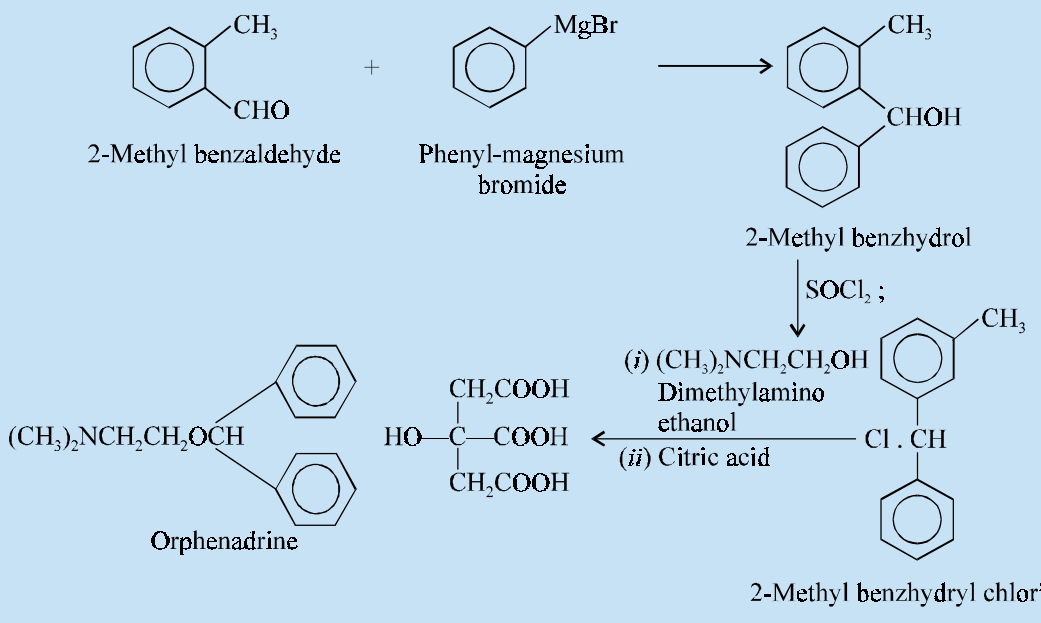
B. Orphenadrine Citrate BAN, USAN, Orphenadrine INN,



N, N-Dimethyl-2[*o*-methyl-α-phenylbenzyl) oxy] ethylamino citrate (1:1) ; Ethanamine, N, N-dimethyl-2-[(2-methylphenyl) phenylmethoxy]-, 2-hydroxy-1, 2, 3-propanetricarboxylate (1:1) Mephenamine Hydrochloride ; Orphenadin Hydrochloride ; BP ; USP ;

Norflex(R) (Riker).

Synthesis

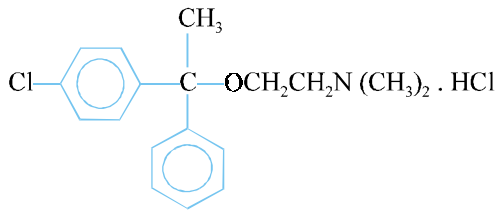


2-Methylbenzhydrol is prepared by the interaction of 2-methyl benzaldehyde and phenyl magnesium bromide, which on chlorination with thionyl chloride yields the 2-methyl benzhydryl chloride. The resulting product is then converted to the amino ether by reaction with dimethylamino ethanol. The orphenadrine (base) is caused to react, in an appropriate solvent, with an equimolar quantity of citric acid to form the official compound.

It is employed in the symptomatic control and management of Parkinson's disease. It has also been used in the *treatment of acute spastic disorders of the skeletal muscles caused by trauma, tension, and vertebral disk dislocation.* It is also used *alleviate the extrapyramidal syndrome induced by drugs, e.g.,* **reserpine** *and* **phenothiazine derivatives**.

Dose : *Initial, oral, 100mg 2 times per day ; i.m. or i.v. 60mg every 12 hours.*

C. Chlorphenoxamine Hydrochloride BAN, USAN, Chlorphenoxamine INN,

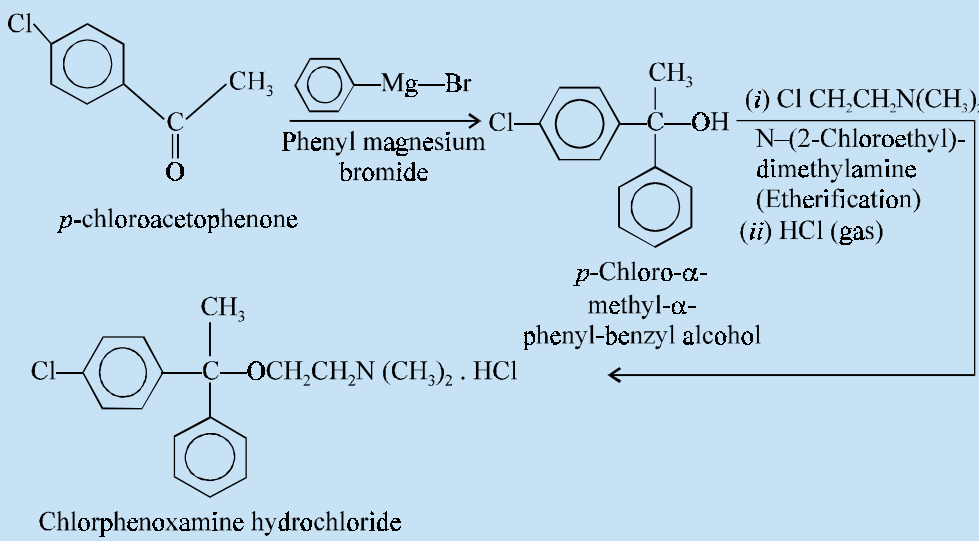


p-Chloro-α, α-dimethylphenethylamine hydrochloride ; Benzene-ethanamine, 4-chloro-α, α-dimethyl-, hydrochloride ; USP ; NF ;

Phenoxene(R) (Merrell Dow).

Synthesis

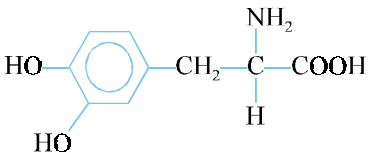
p-Chloro-α-methyl-α-phenyl benzyl alcohol is prepared by the grignardization of *p*-chloroacetophenone with phenyl magnesium bromide. This on etherification by treatment with N-(2-chloroethyl) dimethyl amine yields the chlorphenoxamine (base) which is then dissolved in an appropriate solvent and converted to the hydrochloride by a stream of hydrogen chloride to form the official compound.



It is mainly used for its central effects to *reduce muscular rigidity and also akinesia in subjects suffering from Parkinsons's disease.* Besides it *possesses antimuscarinic properties as well as antihistaminic activity.*

Dose : *Initial, oral, 50 to 100mg 3 or 4 times per day as per the response of the patient.*

D. Levodopa INN, BAN, USAN,

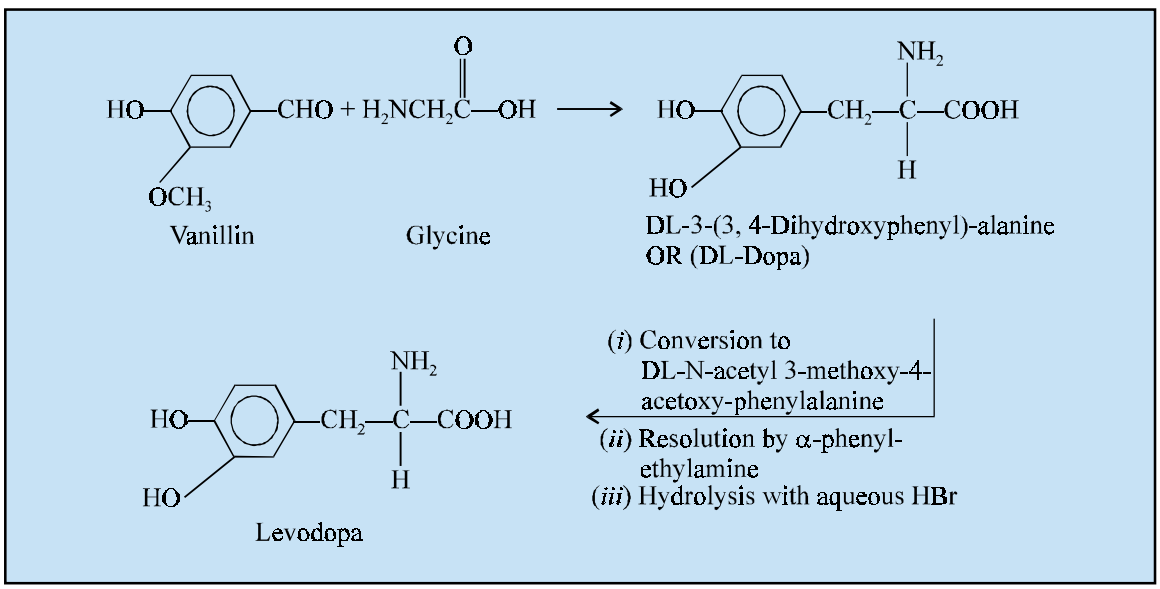


(–)-3-(3, 4-Dihydroxphenyl)-L-alanine ; L-Tyrosine, 3-hydroxy- ; L-Dopa ; BP ; USP

Larodopa(R) (Roche) ; Levopa(R) (SK & F) ; Bendopa(R) (ICN) ; Dopar(R) (Norwich Eaton).

Synthesis

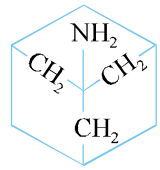
DL-Dopa may be first prepared from vanilline and glycine which is then converted to the DL-N-acetyl-3-methoxy-4-acetoxy phenylalanine. The resulting product is then resolved by means of α-phenyl-ethyl amine which upon hydrolysis with aqueous HBr forms levodopa.



It is considered to be one of the costliest and single most important drug for the treatment of incapacitating parkinsonism. *The maximum therapeutic effects could be seen vividly on rigidity and hypokinesia. It has also been used successfully to control the neurological symptoms arising from chronic manganese poisoning, which incidentally resemble those of parkinsonism.*

Dose : *Initial, oral, 100mg to 1g per day in divided doses with meals ; maintenance dose, 2.5 to 6g daily and must not exceed 8g.*

E. Amantadine Hydrochloride BAN, USAN, Amantadine INN,



. HCl

1-Adamantanamine hydrochloride ; Tricyclo [3, 3, 1, $1^{3,7}$] decan-1-amine, hydrochloride ; USP ; Symmetrel$^{(R)}$ (Endo).

Amantadine has been found to potentiate dopaminergic activity and hence it finds its use in the treatment of parkinsonism usually in conjunction with other therapy. It helps to improve hypokinesia and rigidity but usually displays relatively less effect on tremor.

Dose : *In parkinsonism, initial, 100 mg per day, increased to 100mg twice daily, after one week.*

2.4.1. Mechanism of Action

The mechanism of action of all the **'drugs'** described under Section 17.2.4 shall now be treated individually in the sections that follows :

2.4.1.1. Benztropine Mesylate

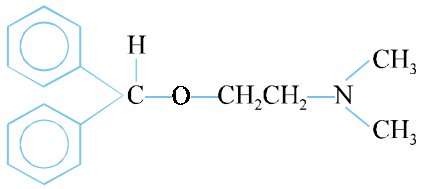
The **'drug'** exerts its distinct central actions to suppress tremor as well as rigidity that are gainfully employed therapeutically in Parkinsonism. It is also employed for the treatment of *extrapyramidal dyskinesia ;* but certainly not *tardive dyskinesia* which is caused due to the administration of various potent tranquillizers, namely : **reserpine**, **chlorpromazine (CPZ)** etc. It may be worthwhile to mention here that the **'drug'** fails to cause any sort of central stimulation (*i.e.*, a definite plus point), and instead produces the characteristic sedative effect normally seen amongst the antihistaminics.

SAR of Benztropine. Interestingly, this **'drug'** resembles as well as possesses the dual-characteristic features of **atropine**–an *antimuscarinic drug* (*i.e.*, having potency equivalent to almost 1/4th to that of atropine) ; and **pyrilamine maleate**-an *antihistaminic drug* (*i.e.*, having potency practically equal to that of **pyrilamine maleate**). One may look at this **'drug'** as an wonderful fusion of the two potential drug molecules namely : **atropine** and **pyrilamine**.

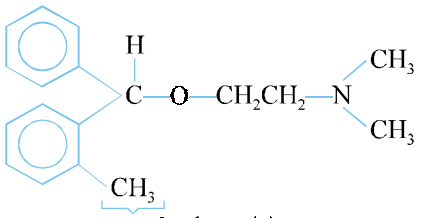
2.4.1.2. Orphenadrine Citrate

The **'drug'** is observed to minimise voluntary muscle spasm by a central effect. However, the indications for the citrate are considered usually as an adjunct for the relief of discomfort amalgamated with severe painful musculoskeletal conditions, which is not yet vividly understood, but that may be associated with the *'analgesic characteristics'* of the drug substance. It has been duly observed that it does not exert its action by relaxing directly the tense skeletal muscles in man. However, the observed peripheral atropine-like actions are relatively mild in nature. Importantly, it helps to minimise voluntary muscle spasm by virtue of its central inhibitory activity specifically on the *cerebral motor areas* ; of course, an apparent central effect very much identical to that of **atropine**.

SAR of Orphenadrine. The **'drug'** is very much closely related to **diphenhydramine**–an '**aminoalkylether**' antihistaminic structurally but possesses much **higher anticholinergic profile** and much **lower antihistaminic activity.**



Diphenhydramine



Orphenadrine

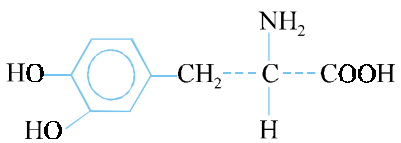
The strategical positioning of an additional *o*-methyl group at 2-α-phenylbenzyloxy moiety in orphenadrine makes the glaring difference between the two compounds as shown above.

2.4.1.3. Chlorphenoxamine Hydrochloride

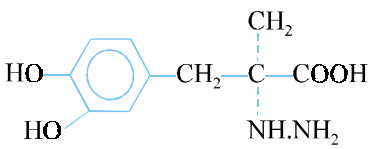
The '**drug**' exerts its action in causing an appreciable reduction in the *muscular rigidity* besides akinesia in patients having Parkinson's disease through the central effects exclusively. It also displays both **antimuscarinic** and antihistaminic activities that makes the **'drug'** a little sensitive and hence may be used with caution in patients.

2.4.1.4. Levodopa

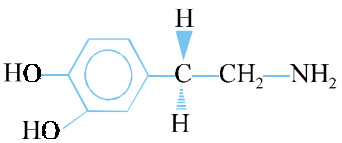
The **'drug'** is usually absorbed between 40-70% through the oral administration. It has been found that even less than 1% gets penetrated into the brain. Besides, it has been observed to undergo decarboxylation resulting to **'dopamine'** to the maximum extent of 99%. Interestingly, the concurrent administration of **carbidopa** normally checks peripheral decarboxylation and increases availability to the brain significantly. Peak concentrations of **dopamine** normally in the brain take place 1-2 hour after administration. The plasma half-life of levodopa above is 0.5 to 1 hour ; and in combination with carbidopa is 1.2 to 2.3 hour.



Levodopa



Carbidopa



Dopamine

Interestingly, **pyridoxine** is known to antagonize **'levodopa',** perhaps by promoting *possible premature decarboxylation* (as a coenzyme to dopa decarboxylase) before the **'drug'** has gained entry into the brain. It has been observed that **carbidopa** curtails antagonism by **pyridoxine** to a certain extent.

Note : Patients must not take multivitamin supplements containing pyridoxine during the course of levodopa therapy. L

Furthermore, both **methyldopa** and **reserpine**, that essentially interfere with the **catecholamine synthesis** as well as its storage, exacerbate the **Parkinson syndrome** and, therefore, antagonize the activity of levodopa. The pharmacological profile of levodopa actually synergized by antimuscarinics.

2.4.1.5. Amantadine Hydrochloride

The **'drug'** is found to inhibit the replication phenomenon of the *influenza type A viruses* specifically at low concentrations. The above admantanamine essentially possesses *two* vital mechanisms, namely :

(*a*) it particularly inhibits an initial *preliminary step* in the viral replication process—most probably **viral uncoating,*** and

*Hay AJ, : *Semin Virol,* **3** : 21, 1992.

(*b*) in certain strains they invariably affect a *later step* which most likely involves the **viral assembly,** perhaps by direct interference with *hemagglutinin processing.*

Salient Features. The various **salient features** that comprise of the *biochemical processes* are :

(*i*) the major biochemical locus of action is the typical **influenza type A virus M2 protein**, which happens to be an integral membrane protein component that virtually serves as an ion-channel,

(*ii*) the **M_2 channel** is recognized as a **'proton transport system',**

(*iii*) the actual interference with the **transmembrane proton pumping**, thereby sustaining a high intracellular proton concentration with respect to the extracellular concentration,

(*iv*) increasing the *p*H-induced conformational changes in the hemagglutinin content in the course of its intracellular transport at a later stage, and

(*v*) the prevailing comformational modifications taking place in the hemagglutinin content thereby check the transferance of the nascent virus particles specifically to the cell-membrane for causing exocytosis.

Special Note. The 'drug' shows the following three distinct characteristic noteworthy features :

(*a*) it exerts absolutely very little effect on influenza type B,

(*b*) it affords seasonal prophylaxis within a range of 70-90% protective against influenza type A,* and

(*c*) its primary side effects are very much associated with CNS, and are also dopaminergic.

Probable Questions for B. Pharm. Examinations

1. What are **Antiparkinsonism Agents** ? How would you classify them ? Give the structure, chemical name and uses of at least **one** compound from each category.

2. Give the structure and uses of the following drugs :

(*a*) Biperiden hydrochloride,

(*b*) Benzhexol hydrochloride.

3. Procyclidine—a structurally similar congener of trihexyphenidyl, exhibits similar properties. Discuss its synthesis from 3-(1-pyrrolidinyl)-propiophenone.

4. Describe how would you synthesize ethopropazine hydrochioride—a phenothiazine analogue from diphenylamine.

5. Explain the sequential steps adopted for the synthesis of :

(*a*) Benztropine mesylate from diphenylmethane,

(*b*) Levodopa from vanilline.

6. Name the two compounds that are used as **antiparkinsonism agents** and may be syntheized from :

(*a*) *p*-Chloroacetophenone,

(*b*) 2-methylbenzaldehyde,

Give the detailed synthesis of **one** drug.

---

*Douglas RG, *N Engl J Med.* **332,** 443, 1990.

7. Give a comprehensive account of the *mode of action* of various potent **antiparkinsonism agents** with the help of some typical examples.

8. Explain the following :

(*a*) Piperidine hydrochloride and acetophenone yields cycrimine hydrochloride,

(*b*) Piperidine and acetophenone yields trihexyl-phenidyl hydrochloride.

RECOMMENDED READINGS

1. RC Schwab and AC England, **'Newer Preparations in the Treatment of Parkinsonism'**, *Med. Clin. N. America*, March (1957).

2. AC England and RC Schwab, **'Parkinson Disease Management'**, *Arch. Int. Med.* 104, 111 and 439 (1959).

3. DLednicer and LA Mitsher, **'The Organic Chemistry of Drug Synthesis'**, John Wiley and Sons, New York (1995).

4. JEF Reynolds, Ed. **'Martindale : The Extra Pharmacopoeia'** (31st Edn.), The Royal Pharmaceutical Society, London (1996).

5. PJ Roberts, GN Woodruff and LL Iverson, eds., **'Dopamine**, **Adv. Biochem'**, **Psychopharmacol**., Raven Press, New York (1978).

6. DB Calne, '**Developments in the Pharmacology and Therapeutics of Parkinsonism**', *Ann Neurol.* **1**, 111, (1977).

7. JH Block and JM Beale, **'Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry'**, Lippincott Williams and Wilkins, New York, 11th edn., 2004.

8. Gringauz A, **'Introduction to Medicinal Chemistry'**, Wiley-VCH, New York, (1997).

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18

Expectorants and Antitussives

Chapter

18 Expectorants and Antitussives

1. INTRODUCTION

Expectorants are drugs employed to aid in the relief of congestion in the lower respiratory tract below the epiglottis, in the trachea, bronchi, or lungs ; and, therefore, they are helpful in the treatment of cough. **Expectoration** may be caused by (*i*) **enhancing bronchial secretion,** (*ii*) **making secretion less viscous,** or (*iii*) **suppressing cough.** Besides, **expectorants** may also possess antiseptic, anaesthetic, or other pharmacological activity.

Release and clearance of sputum may be helped by humidifying the respiratory tract with **luke-warm beverages** (*e.g.,* **tea, coffee**) or by inhalation of **sodium chloride aerosols.** Sometimes the inhalation of a surface-active agent like **tyloxapol** may find its useful application. Mucolytic agents like (-) **bromhexine hydrochloride [Bisolvon$^{(R)}$ (Boehringer Ingelheim)], acetylcystein, trypsin** and **chymotrypsin** have also been found to help the excretion of sputum by changing its structure.

Another school of thought designates the **expectorants** as — **'drugs that are proved to be beneficial in loosening and liquefying mucous, in soothening irritated bronchial mucosa, and in making coughs more productive'.** In reality, these agents are believed to afford an appreciable affect upon the respiratory tract in *two* different manners, namely :

- by minimising the viscosity of the bronchial secretions, which in turn remarkably stimulates their elimination thereby helping in the removal of the local irritants ; and thus, the ineffective coughing is either alleviated significantly or rendered more productive.
- by enhancing the quantum of respiratory tract fluid thereby producing a demulscent action on the dry mucosal lining ; and thus, relieving the unproductive cough considerably.

Antitussives are agents that are employed invariably in the symptomatic control of cough by way of depressing the cough-centre strategically situated in the medulla. Interestingly, these are also commonly known as : **anodynes, cough suppressants,** and **centrally acting antitussives.**

Importantly, the **'narcotic analgesic agents'** (see Chapter 11) retained an almost comfortable status in this are upto the recent times, such as : **morphine, hydromorphone, codeine, hydrocodone, methadone** and **levorphanol.**

It is, however, pertinent to mention here that in the recent years, a good number of newer drug substances have been synthesized meticulously which remarkably exhibited significant antitussive characteristic feature absolutely devoid of the absurd and most discouraging **'addiction liabilities'** of the aforesaid **narcotic drugs.** Surprisingly, quite a few of these agents usually exert their activity very much identical fashion *via* a central effect.

1.1. Hypotheses suggested for relief of cough

In early 1960s, *two* befitting hypotheses were put forward to expatiate most logically and convincingly the probable mechanism for the ultimate relief of cough, namely :

(*a*) Salem and Aviado's hypothesis, and

(*b*) Chappel and Seemann's hypothesis.

These hypothesis shall now be discussed briefly as under :

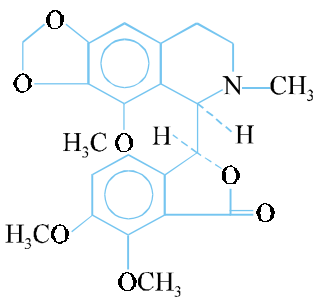
1.1.1. Salem and Aviado's Hypothesis

According to their considered proposal and suggested explanation — **'bronchodilation is a critically essential and important mechanism exclusively responsible for the relief of cough'.** It further gives a plausible account that irritation of the mucosa first and foremost gives rise to bronchoconstriction which subsequently excites the **'cough receptors'.**

1.1.2. Chappel and Seemann's Hypothesis

As per the hypothesis put forward by these researchers — a large variety of the antitussives belonging to this category normally fall into *two* structural variants, namely :

(*a*) **Large structural moieties.** They have a close resemblance to that of **methadone** (see Chapter : 11). **Noscapine** is a suitable example of this type, as shown below :

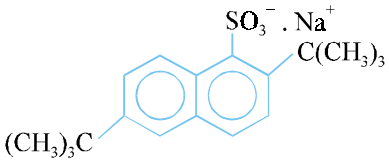


Noscapine (*l*-Narcotine)

(*b*) **Large bulky substituents.** They essentially possess large bulky substituents particularly on the acid residue of an ester, normally linked with the help of a long, ether containing chain to a *tertiary* amino functional moiety, such as : **carbetapentane citrate.**

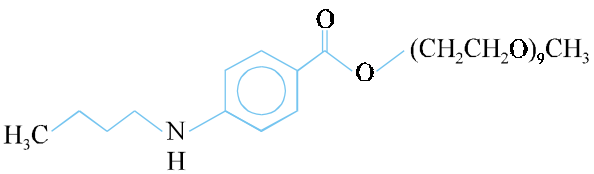
Exceptions. The following *two* drugs used as **'antitussives'** are exceptions as given below :

(*i*) **Sodium Dibunate :**



(Antitussive)

(*ii*) **Benzonatate :**



(Antitussive)

2. CLASSIFICATION

Expectorants and **antitussive agents** may be broadly classified into the following *three* categories :

(*i*) Sedative Expectorants

(*ii*) Stimulant (Irritant) Expectorants

(*iii*) Centrally Acting Antitussive Agents.

2.1. Sedative Expectorants

These group of drugs specifically help in the secretion of a protective mucous film that covers up inflamed membranes and increases the efficiency of the removal of slimy exudates by coughing.

Sedative expectorants may be further sub-divided into *three* different classes :

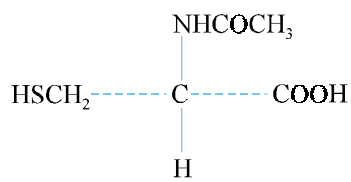
(*a*) **Saline Expectorants :** These usually enhance bronchial secretion and help to ‘‘loosen’’ the cough, *e.g.,* **ammonium carbonate,** ammonium chloride, ammonium acetate, alkali citrates (Na or K) and inorganic iodides (KI or NaI).

(*b*) **Nauseant Expectorants :** These act as expectorants in small doses and nauseant and emetic in large doses, *e.g.,* **tartar emetic, ipecac,** etc. These are usually mixed with sweet-tasting cough syrups that help to cure *croupous bronchitis* in children.

(*c*) **Demulcent Expectorants :** These agents are normally mucilaginous in nature and serve to coat and protect the mucous membrane of the upper respiratory tract, *e.g.*, **syrup of acacia, ginger, glycyrrhiza (liquorice), tolubalsam** and the like.

A few examples belonging to the class of sedative expectorants will now be discussed here. **Examples : Acetylcysteine ; Bromhexine hydrochloride ; Ammonium chloride ; Prepared Ipecacuanha ; Liquorice ; Cocillana ; Potassium iodide.**

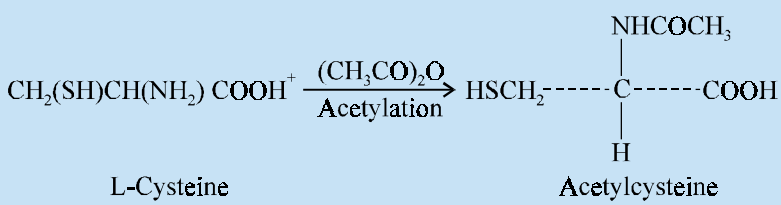
A. Acetylcyteine INN, BAN, USAN,



N-Acetyl-L-cysteine ; L-Cysteine, N-acetyl-; USP ;

Mucomyst(R) (Mead Johnson) ; Aribron(R) (Duncan, Flockhard, U.K.) ;

Synthesis



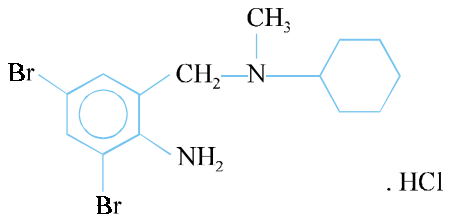
It may be prepared by carrying out the direct acetylation of naturally occurring L-cysteine.

Acetylcysteine is used to *reduce the viscosity of pulmonary secretions and thereby help their removal. Therefore, it is usually incorporated as an adjuvant in preparations meant for bronchopulmonary*

disorders when mucolysis is sought for. Lowering of viscosity of the mucous may be due to the opening of the disulphide bond present in the sulphydryl moiety in the mucous medium.

Dose : *Direct instillation, 1 to 2 ml of a 10 or 20% solution every 1 to 4 hours ; inhalation of nebulized solution, 3 to 5 ml of a 20% solution daily.*

B. Bromhexine Hydrochloride BAN, USAN, Bromhexine INN,



3, 5-Dibromo-Nα-cyclohexyl-Nα-methyltoluene-α, 2-diamine monohydrochloride ; Benzenemethanamine, 2-amino-3, 5-dibromo-N-cyclohexyl-N-methyl-, monohydrochloride ; BP ; Bisolvon(R) (Boehringer Ingelheim, U.K.).

Bromhexine hydrochloride has been reported to alter the structure of bronchial secretion, besides playing the dual role of enhancing the volume and reducing the viscosity of sputum.

Dose : Usual, adult, 8 to 16mg 3 or 4 times per day ; For children below 5 years, 4mg 2 times per day ; and for 5 to 10 years, 4mg 4 times per day ; i.m. or i.v. 8 to 24mg per day.

C. Ammonium Chloride BAN, USAN,

NH_4Cl

BP ; USP ; Eur. P., Int. P.;

Expigen(R) (Pharmacia, Denm).

It is used as an ingredient of expectorant cough mixtures.

Dose : *300 mg to 1g.*

D. Prepared Ipecacuanha BAN,

BP ; Eur. P., Int. P., Ind. P., Powdered Ipecac USP ;

It is the finely powdered ipecacuanha, the dried root or rhizome and roots of *Cephaelis ipecacuanha* [(*i.e., Uragoga ipecacuaha* (*Rubiaceae*)] adjusted with powdered ipecacuanha of lower alkaloidal content or powdered lactose to contain 1.9 to 2.1% of total alkaloids, calculated as emetine.

Prepared ipecacuanha is employed in smaller doses as an expectorant.

Dose : *25 to 100 mg (approximately 0.5 to 2 mg of total alkaloid).*

E. *Liquorice* BAN,

Glycyrrhiza ; Glycyrrhizae Radix ; BP ; Ind. P., Liquorice root (Eur. P.).

Liquorice essentially consists of the dried unpeeled root and stolons of *Glycyrrhiza glabra (Leguminosae)* containing not less than 25% of watersoluble extractive, having approximately 7% of glycyrrhizin consisting of the potassium and calcium salts of glycyrrhizinic acid (a glucoside of glycyrrhetinic acid). It possesses a characteristic odour and a slightly aromatic sweet taste.

Liquorice is used as a **demulcent** *and* **expectorant.** It is mostly used as a *flavouring agent in cough mixtures specifically containing nauseous components like alkali iodides, ammonium chloride,*

creosote, and cascara liquid extract. In grandmother's prescription a decoction of liquorice and linseed has long been used reputably as a cure for cough and bronchitis. **Deglycyrrhizinised liquorice** has been used in the treatment of peptic ulcer owing to its **reduced mineral corticoid activity.**

Dose : *Liquorice Extract (BPC 1973), 0.6 to 2 g.*

F. Cocillana BAN,

Grape Bark ; Guapi bark ; BP ; Cocillana Liquid Extract (BPC ; 1973).

Cocillana is the dried bark of *Guarea rusbyi (Meliaceae)* containing not less than 3.5% of alcohol soluble extract.

It has been employed as a *substitute for ipecacuanha in the treatment of coughs.* It usually forms an ingredient as the liquid extract along with other expectorants in cough mixtures.

Dose : *0.5 to 1ml.*

G. Potassium Iodide BAN, USAN,

KI

BP ; USP ; Eur. P ; Ind. P., Ind. P. ;

SSKI$^{(R)}$ (Upsher-Smith, U.S.A.).

Potassium iodide is used as an expectorant and also in the treatment of cutaneous lymphatic sporotrichosis.

Dose : *250 to 500 mg.*

2.1.1. Mechanism of Action

The **mechanism of action** of a few compounds discussed under Section 18.2.1 shall be treated with in the sections that follows :

2.1.1.1. Acetylcysteine

The **'drug'** is usually employed as adjuvant therapy specifically in *bronchopulmonary disorders* when mucolysis is to be accomplished. It is, however, believed that the **sulphhydryl functional moiety** present in the molecule helps to **open** the disulphide bondages in the mucous whereby the viscosity is lowered. Importantly, the mucolytic activity of the **'drug'** is directly associated with the *p*H ; and an appreciable mucolysis takes place within a *p*H range of 6 and 9.

Note. The *'drug'* when administered either orally or parenterally serves as a potential 'antidote' to check or lower the hepatotoxicity caused due to acetaminophen (paracetamol) overdosage.

2.1.1.2. Bromhexine Hydrochloride

It has been duly observed that the **'drug'** virtually brings about a change in the structure of the ensuing bronchial secretion. In addition to this, it also plays the dual role of increasing not only the actual volume but also minimising the viscosity of the sputum to a considerable extent.

2.1.1.3. Ammonium chloride

The **'drug'** exerts its action as a **'saline expectorant'.** The basic mechanism by which it brings forth a net loss of the *extracellular fluid* is due to the fact that the NH_4^+ ion gets changed to urea, and the liberated H^+ ion reacts with HCO_3 and similar body buffers. The ultimate outcome being that Cl^- ion displaces HCO_3^- ion ; and the latter eventually gets converted to CO_2. In this way, a significant quantum of Cl^- — load practically excapes reabsorption along with an equivalent amount of cation (mostly Na^+) together with an isoosmotic quantum of water. In short, NH_4Cl releases the secretion of relatively viscous cough and promotes relief to the patient.

2.1.1.4. Prepared Ipecacuanha

The **total alkaloids** (as **'emetine'**) varying between 1.9 to 2.1% (*w/w*) serve as an **expectorant.**

2.1.1.5. Liquorice

The **'drug'** contains 7% of **glycyrrhizin** that exerts its action as a demulcent and expectorant.

2.1.1.6. Potassium Iodide

The **'drug'** is found to exert its action by liquefying the thick and tenacious sputum in chronic bronchitis, bronchietasis, bronchial asthma, and pulmonary emphysema. In reality, the precise therapeutic value of KI as an expectorant has not yet been proved substantially and convincingly.

2.2 Stimulant (Irritant) Expectorants

Drugs in this category usually induce healing in chronic inflammatory processes of the mucous membranes of the respiratory tract. These mostly comprise of mildly irritating volatile terpenoid oils and phenolic compounds based on creosote that may be inhaled and augment repair in the inflammed areas of the bronchis.

Some official preparations belonging to this classification are : **Creosote** ; **Guaifensin** ; **Eucalyptol** ; **Terpin hydrate** ; **Sulfogaiacol**.

A. Creosote BAN,

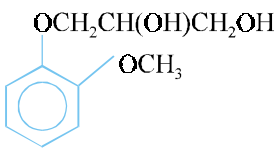
Wood Creosote ; BPC ; (1959) ; N.F. XII ; Ind. P.

A mixture of phenols obtained from fractional distillation of wood tar consisting mainly of cresol, guaicol, phlorol ($C_8H_{10}O$) and methylcresol.

Creosote has **expectorant** actions and been used in bronchitis and bronchiectasis.

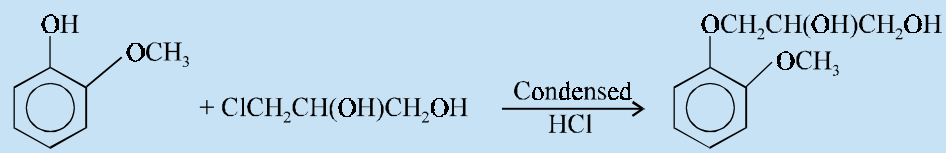
Dose : *0.12 to 0.6 ml.*

B. Guaifensin INN, USAN, Guaiphensin BAN,



3-(*o*-Methoxyphenoxy)-1, 2-propanediol ; 1, 2-Propanediol, 3-(2-methoxyphenoxy)-; Glyceryl guaicolate ; Guaiphensin BP ; Guaifensin, USP ; Glyceryl Guaicolate N.F.

Synthesis

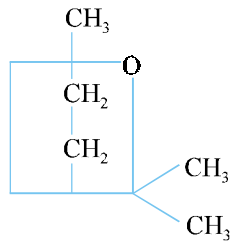


It may be prepared by the condensation of guaiacol and 3-chloro-1, 2-propanediol through the elimination of a molecule of hydrogen chloride. The reaction proceeds by warming the reactants with a base.

Guaifensin finds its extensive use as an expectorant. It is reported to *lower the viscosity of the tenacious secretions by enhancing the volume of the respiratory tract fluid.*

Dose : *Usual, 100 mg every 3 or 4 hours.*

C. Eucalyptol USAN, Cineole BAN,

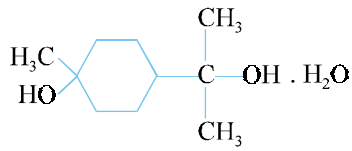


1, 8-Epoxy-*p*-menthane ; 1, 3, 3-Trimethyl-2-oxabicyclo [2, 2, 2] octane ; NF XII ; Cineole BPC (1973).

Preparation : It may be conveniently separated from the purified volatile oils by making use of its salient feature of forming crystals on being subjected to a low temperature.

It is used locally for its antiseptic action in inflammations of nose and throat. It is also used by inhalation in bronchitis.

D. Terpin Hydrate BAN, USAN,



p-Menthane-1, 8-diol monohydrate ; Cyclohexanemethanol, 4-hydroxy-α, α-4-trimethyl-, monohydrate ; Terpine, Terpinol ; BPC ; 1968, USP ; Ind. P.; Terpin Hydrate and Dextromethorphan Hydrobromide Elixir (USP); Terpin Hydrate, Codeine Phosphate,

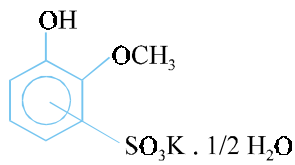
Cineole and Menthol as Tercoda(R) (Sinclair U.K.).

Terpin hydrate may be separated from a good quality terpentine oil (or pine oil) by stirring it with 2 to 3 times its volume of 30% sulphuric acid at a temperature ranging between 20-30°C. The stirring is usually prolonged continuously for 4 to 6 days with intermittent passage of air blowing through the mixture so as to assure thorough contact. The crude crystals of **terpin hydrate** separate which may be recrystallized from alcohol.

It is frequently employed as an *expectorant in bronchitis, in combination with other components like dextromethorphan hydrobromide and codeine phosphate for cough mixtures.*

Dose : *Usual, 125 to 300 mg every 6 hours.*

E. Sulfogaiacol INN, Potassium Guaiacosulphonate BAN, Potassium Guiacosulfonate USAN,

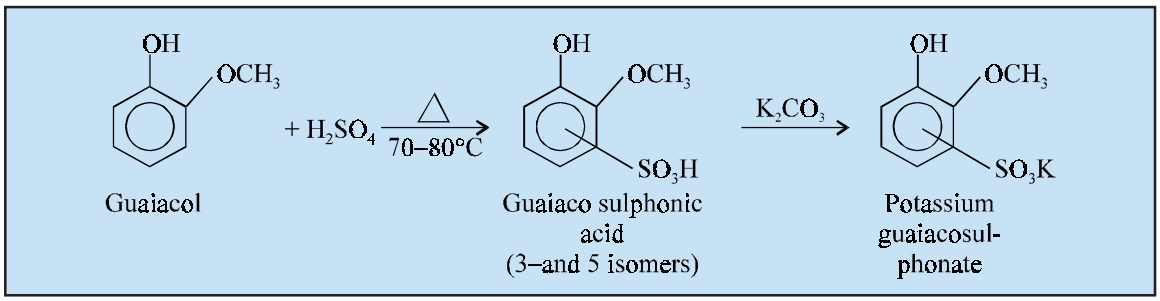


Potassium hydroxymethoxybenzenesulphonate hemihydrate ; Benzenesulphonic acid, hydroxymethoxy-, monopotassium salt, hemihydrate ;

Broncovanil(R) (Scharper, Italy).

Synthesis

It is reported to be a mixture of 3- and 5-sulphonate isomers. It may be prepared by the interaction of guaiacol with sulphuric acid at 70 to 80°C to form guaiaco sulphonic acid. After adequate dilution the reaction mixture is *first* neutralized with barium carbonate to remove excess of H_2SO_4 as a precipitate of barium sulphate ; and *secondly*, the filtrate is treated with potassium carbonate to neutralize the guaicosulphonic acid itself and also to precipitate any excess barium. The reaction mixture is filtered and the filtrate concentrated to crystallization.



Potassium guaiacosulphonate is employed both as an *expectorant in bronchitis and also as an intestinal antiseptic.*

Dose : *0.5 to 1 g.*

2.2.1. Mechanism of Action

The mechanism of action of certain compounds described under Section 18.2.2. are dealt with in the sections that follows :

2.2.1.1. Guaifensin

It has been established adequately through various subjective clinical studies that the action of guaifensin essentially makes better the *'dry unproductive cough'* by (*a*) distinctly lowering the sputum viscosity ; (*b*) difficulty encountered in expectoration ; and (*c*) enhancing the sputum volume considerably. However, experimentally, it simply augments the respiratory tract secretions significantly ; and that too when given in doses much higher than those usually employed therapeutically.

2.2.1.2. Eucalyptol (Cineol ; Cajeputol)

The **'drug'** exerts its *'antiseptic effect'* in the inflammations of the throat and nose. It is quite often employed by inhalation in bronchitis.

2.2.1.3. Terpin Hydrate

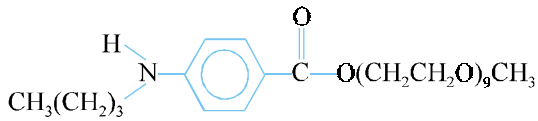
The **'drug'** exhibits its therapeutic action in *bronchitis* as an expectorant. It has been duly observed that the **'terpin hydrate elixir'** as such normally contains too little of the active compound to make it effective single ; and, therefore it is invariably used mainly as a vehicle for the cough mixtures, namely : (*a*) **Terpin Hydrate and Dextromethorphan Elixir ;** and (*b*) **Terpin Hydrate and Codeine Elixir.**

2.3 Centrally Acting Antitussive Agents

These drugs specifically act by depressing the meduallary cough centre in the central nervous system (CNS) to suppress cough reflex. They are mostly narcotics. The centrally acting antitussives consist primarily of the phenanthrene alkaloids of opium. In this classification are other synthetic agents that are not derived from the opium derivatives but essentially exhibit antitussive action. These drugs, like the opium alkaloids, are thought to act selectively on the medullary centres to suppress the cough reflex.

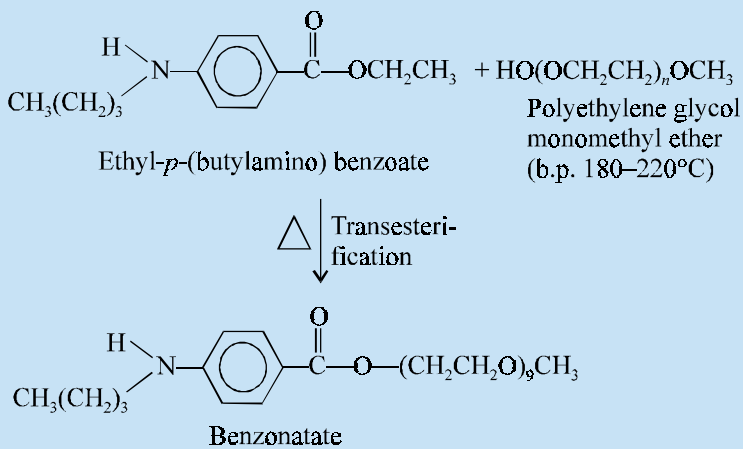
Examples : Benzonatate ; Carbetapentane citrate ; Noscapine ; Levopropoxyphene napsylate ; Dextromethorphan hydrobromide ; Pholcodine.

A. Benzonatate INN, BAN, USAN,



2, 5, 8, 11, 14, 17, 20, 23, 26-Nonaoxaoctacosan-28-yl *p*(butyl-amino) benzoate ; Benzoic acid, 4-(butylamino)-, 2,5,8,11,14,17,20,23,26-nonaoxaoctacos-28-yl-ester ; Benzonatine ; USP ; Tessalon(R) (Endo).

Synthesis

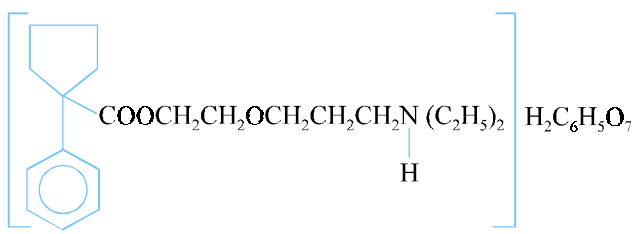


Benzonatate may be prepared by the transesterification of ethyl-*p*-(butylamino) benzoate with a polyethyleneglycol monomethyl ester (b.p. 180-220°C) at 1 mm Hg. The reaction is carried out *in vacuo* whereby a thin stream of xylene is made to pass through it. After complete removal of the traces of moisture and volatile components, a solution of sodium methoxide in methanol is added to the reaction mixture. The contents are heated *under vacuo,* after addition of xylene, for 2 to 3 hours at 100°C. The crude benzonatate thus obtained may be purified by suitable means.

It is a potent antitussive agent. *It usually acts by inhibiting transmission of impulses of the cough reflex in the vagal nuclei of the medulla and predominantly depresses polysynaptic spinal reflexes. It is regarded as a cough suppressant acting both centrally and peripherally.*

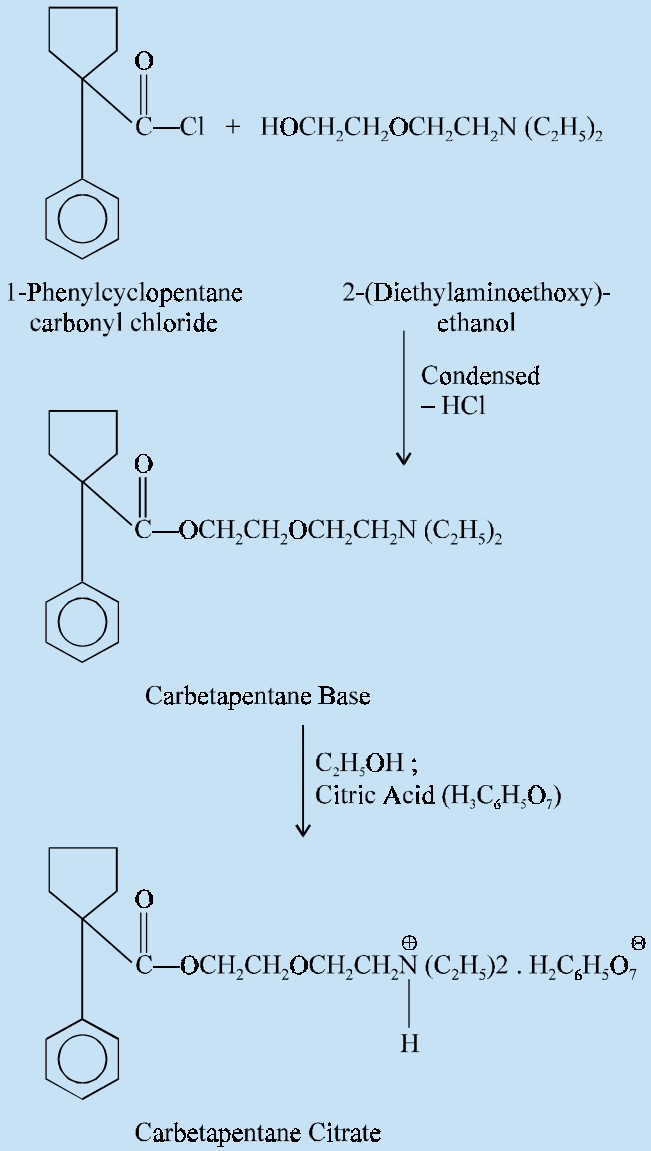
Dose : *100 to 200 mg ; usual, 100mg 3 times daily*.

B. Carbetapentane Citrate BAN, USAN, Pentoxyverine INN,



2-[2-(Diethylamino) ethoxy] ethyl 1-phenylcyclopentane-carboxy citrate (1:1) ; NF XIII ; Toclase(R) (Pfizer).

Synthesis

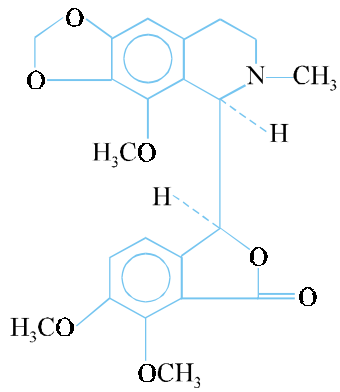


It may be prepared by the condensation of 1-phenyl-cyclopentane carbonyl chloride with 2-(diethylaminoethoxy) ethanol to yield carbetapentane base by the elimination of a mole of hydrogen chloride. The base is dissolved in ethanol and treated with a equimolar portion of citric acid to give the official compound.

Carbetapentane citrate is a cough suppressant and is reported to reduce bronchial secretions. It is found to be *effective in acute coughs associated with common upper respiratory infections.*

Dose : *25 to 150 mg per day in divided doses.*

C. Noscapine INN, BAN, USAN,



(3S)-6, 7-Dimethoxy-3-[(5R)-5, 6, 7, 8-tetrahydro-4-methoxy-6-methyl-1, 3-dioxolo [4, 5-g] isoquinolin-5-yl] phthalide ; Narcotine ; L-α-Narcotine ; BP ; USP ; Eur. P ; Int. P ;

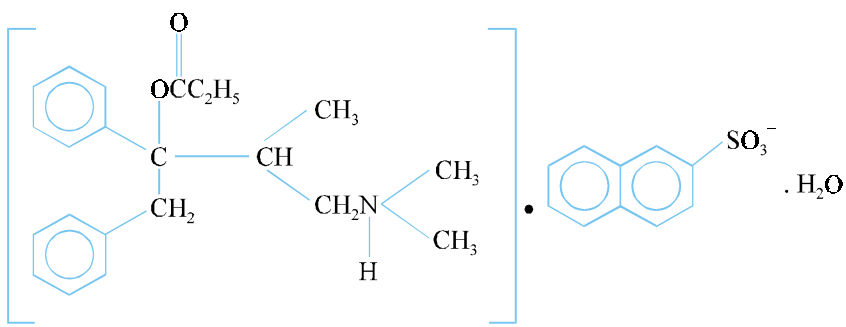
Tusscapine(R) (Fisons).

It is isolated from opium in which noscapine concentration ranges from 3 to 10%.

Noscapine is invariably employed in the control and management of cough due to bronchial asthma and pulmonary emphysema. It remakably reduces both the frequency and intensity of coughing paroxyms. Besides, it possesses weak bronchodilator actions and stimulates the respiration. It has no analgesic activity.

Dose : *Usual, 15 to 30 mg 3 or 4 times per day.*

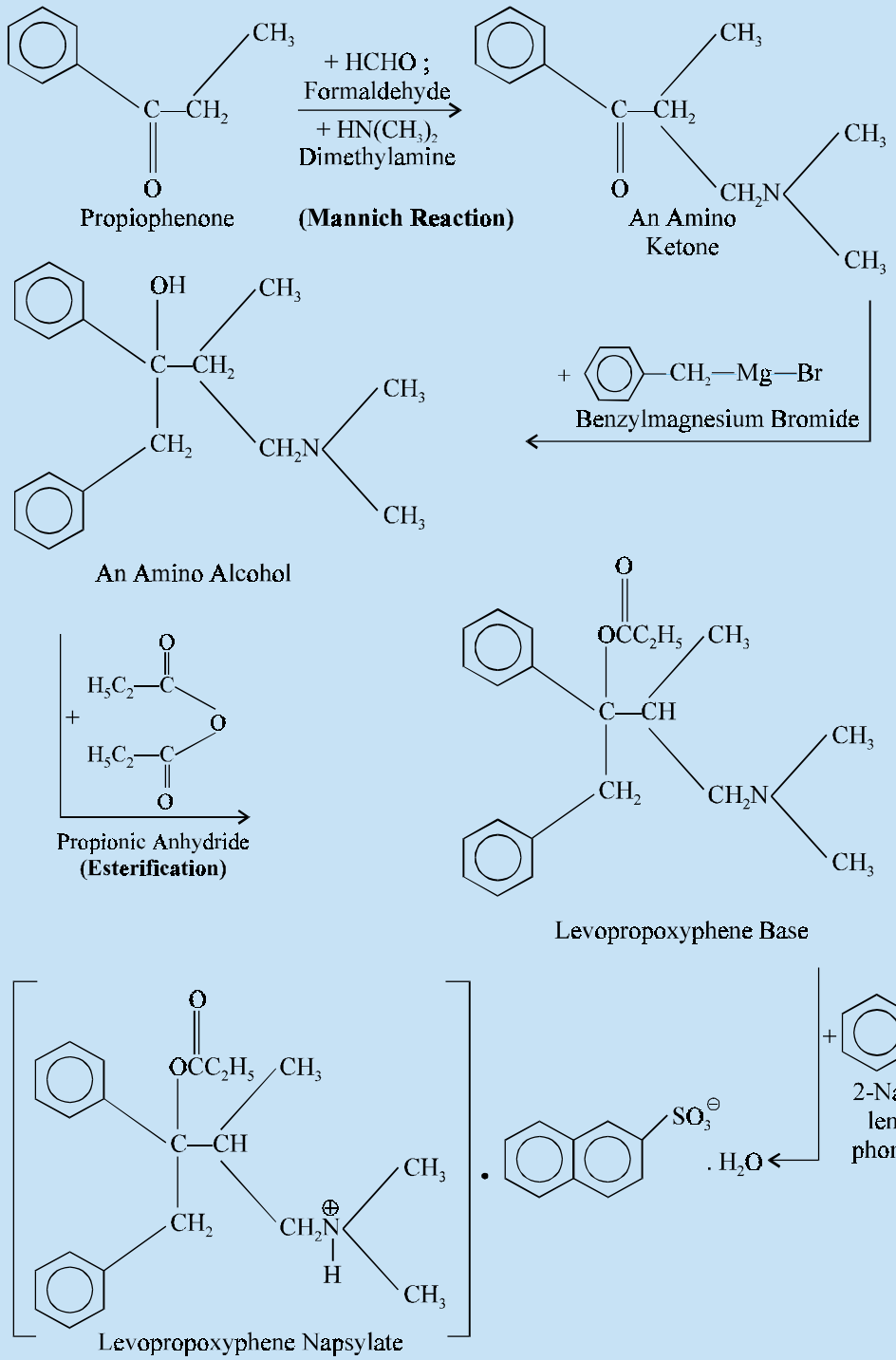
D. Levopropoxyphene Napsylate BAN, USAN, Levopropoxyphene INN,



2-Naphthalenesulphonic acid compound with (—)-α-[2-(dimethylamino)-1-methylethyl]-α-phenylphenethyl propionate (1:1) monohydrate ; Benzeneethanol, α-[2-dimethyl-amino)-1-methylethyl]-α-phenyl-, propanoate (ester), [R-(R•, S•)]-, compound with 2-naphthalenesulphonic acid (1:1); USP ;

Novrad(R) (Lilly).

Synthesis


CH3
C—CH2
O
Propiophenone
+ HCHO ;
Formaldehyde
+ HN(CH3)2
Dimethylamine
(Mannich Reaction)
CH3
C—CH2
O
CH2N
CH3
CH3
An Amino
Ketone
OH
CH3
C—CH2
CH2
CH2N
CH3
CH3
An Amino Alcohol
+
CH2—Mg—Br
Benzylmagnesium Bromide
H5C2—C
O
O
H5C2—C
O
Propionic Anhydride
(Esterification)
O
OCC2H5
CH3
C—CH
CH2
CH2N
CH3
CH3
Levopropoxyphene Base
O
OCC2H5
CH3
C—CH
CH2
CH2N
H
CH3
CH3
Levopropoxyphene Napsylate
SO3⊖
. H2O
+
SO3H
2-Naphtha-
lene sul-
phonic acid

Mannich reaction of propiophenone with formaldehyde and dimehtylamine yields the corresponding amino ketone, which on treatment with benzylmagnesium bromide gives rise to the corresponding amino alcohol. Esterification of this alcohol with propionic anhydride forms the levopropoxyphene base, which on reaction with an equimolar quantity of 2-naphthalene sulphonic acid gives the official compound.

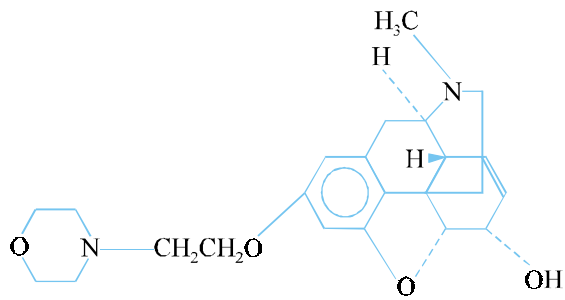
Levopropoxyphene napsylate is an antitussive and a cough suppressant. It has been found to be relatively less potent than codeine in the treatment of cough reflexes.

Dose : *Usual, 50 to 100 mg (base equivalent) after every 4 hours.*

E. Dextromethorphan Hydrobromide

This compound has already been discussed in details under **'narcotic analgesics'.**

F. Pholcodine INN, BAN, USAN,



Morpholinylethylmorphine ; O^3-(2-Morpholinoethyl) morphine monohydrate ; Pholcod ; BP ; Eur. P., Int. P.;

Ethnine Simplex$^{(R)}$ (Purdue Frederick).

It is a cough suppressant with mild sedative but practically negligible analgesic action. It is employed for the relief of unproductive cough.

Dose : *Adult, 5 to 15 mg ; Children over 2 years 5 mg ; children below 2 years 2.5 mg.*

2.3.1. Mechanism of Action

The mechanism of action of the compounds discussed under section 18.2.3. shall now be treated individually in the sections that follows :

2.3.1.1. Benzonatate

The **'drug'** exerts its action by reducing the cough reflex at its source by anaesthetizing the **stretch receptors** strategically located in the respiratory passages, lungs and pleura. Though its antitussive potency and profile is fairly comparable to that of **codeine** when evaluated against artificially (experimentally) induced cough in man as well as in animals, yet it is slightly inferior with regard to its effect in comparison to **codeine** against cough associated with clinical illness.

2.3.1.2. Carbetapentane Citrate

The **'drug'** is found to act by causing an appreciable reduction in the bronchial secretion. Morren*(1957) and Levis *et al.*** (1955) synthesized and evaluated a number of closely related compounds, of which **carbapentane** was found to be the most active. Its activity was one and a half times more potent than *codeine.*

*Morren HG, *Chem. Abstr.* **51,** 7443, 1957.

Levis S *et al. Arch. Int. Pharmacodyn.* **103, 200, 1995.

SAR of Carbetapentane. It has been duly established that either by increasing or decreasing the size of the hydrocarbon ring of **carbetapentane** remarkably lowers its therapeutic activity.

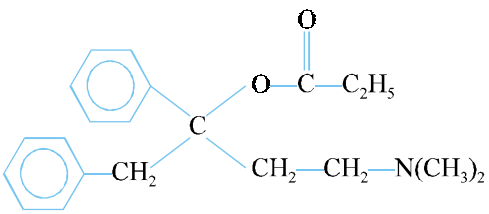
2.3.1.3. Noscapine [(–)-Narcotine]

Noscapine* usually makes up 0.75—9% of opium alkaloids. It is found to exert a marked and pronounced action both on the frequency as well as the intensity of the coughing paroxyms.

2.3.1.4. Levopropoxyphene Napsylate

The (–)-isomer of the **'drug'** (*i.e.*, levopropoxyphene) showed greater antitussive activity in comparison to either the (+)-isomer or the racemic mixture.

SAR of Levopropoxyphene. In a series of congeners of the esters of 1, 2-diphenyl-4-dialkylamino-2-butanol which were duly synthesized and tested for their corresponding **antitussive** and **analgesic** activity the following compound exhibited an active **antitussive property** without any **analgesic activities.**



(Antitussive Activity)

2.3.1.5. Dextromethorphan Hydrobromide

The **'drug'** acts by controlling cough spasms by depressing the cough centre in the medulla. It has been amply demonstrated in man that it exhibits a cough depression potency almost one-half that of *codeine*. Interestingly, the **'drug'** does not afford any **addiction,** whatsoever, even after the usage of large doses for prolonged durations. Besides, it possesses the antitussive characteristics of codeine, without having any analgesic, central depressant, and constipating features. However, it legitimately provides an enormous opportunity to register the ensuing specificity of action displayed by quite intimately related molecules.

In this particular instance, the (+) and (–) isomers both should get attached to the definitive receptors actually responsible for the suppression of the cough reflex. In fact, the prevailing (+) form (isomer) bears a steric relationship which essentially precludes being attached to the definitive receptors particularly associated in the various therapeutic activities, such as : analgesic, constipative, addictive, and other properties displayed by the corresponding (–) form (isomer).

2.3.1.6. Pholcodine

The *'drug'* exerts its action as an effective cough suppressant, having almost minimal side effects and practically very little physical-dependence liability.**

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*An opium alkaloid first isolated in 1817 by Robiquet, rather easily from the drug by ether extraction.

May AJ *et al. Brit J Pharmacol*, **9, 335, 1954.

Probable Questions for B. Pharm. Examinations

1. Give the structure and chemical name of the **five** important drugs that are used abundantly in :

(*a*) Enhancing bronchial secretion,

(*b*) Making secretion less viscous, and

(*c*) Suppressing cough.

2. How would you classify the **expectorants** and **antitussive agents ?** Support your answer with the help of least one example from each category.

3. What are **sedative expectorants ?** Classify them and give the structure chemical name and uses of one compound from each group.

4. Give a brief account of the **'stimulant expectorants'.** Discuss the synthesis of guaiphensin and potassium guaiacosulphonate from guaiacol with 3-chloro-1, 2-propanediol and sulphuric acid respectively under different experimental parameters.

5. Give the structure, chemical name and uses of **two** important drugs obtained from the natural products *viz* ; eucalyptus oil and pine oil (turpentine oil).

6. 'Centrally acting antitussive agents act by depressing the medullary cough centre in the CNS to suppress cough reflexes'. Justify the statement by citing at least **three** potent drugs.

7. Discuss the synthesis of :

(*a*) Benzonatate

(*b*) Carbetapentane citrate.

8. Name **two** drugs that act as centrally acting antitussive agents and are analogues of morphine. Discuss the synthesis of **one** such compound.

9. Mannich reaction of propiophenone yields levopropoxyphene napsylate. Describe its course of reaction to the final product.

RECOMMENDED READINGS

1. Block JH and Beale JM, **'Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry',** Lippincott Williams and Wilkins, New York, 5th edn., (2004).

2. EM Boyd, **'Expectorants and Respiratory Tract Fluids',** *Pharmacological Reviews*, Dec. (1954).

3. MC Griffiths, **'USAN and the USP Dictionary of Drug Names',** United States Parmacopeial Convention, Inc. Rockville (1985).

4. ME Wolff (ed.) : **Burger's Medicinal Chemistry and Drug Discovery,** (5th edn.), John Wiley and Sons. Inc., New York, (1995).

5. *Remington :* **The Science and Practice of Pharmacy,** Vol. I and II (20th, edn.), Lippincot Williams and Wilkins , New York (2000).

19

Sulphonamides

Chapter

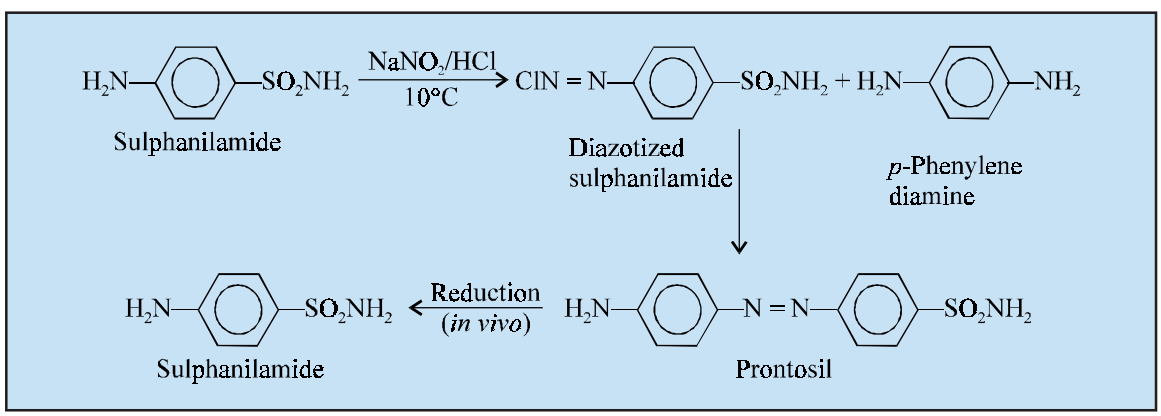
19 Sulphonamides

1. INTRODUCTION

A considerable progress had been made before 1930 towards the development of externally applicable bactericides, but most bactericides that could be administered internally having reasonably safety margin unfortunately lost their activity in the presence of blood serum. There are limited agents available for the treatment of most diseases of bacterial origin. Diseases like pneumonia, meningitis, dysentry etc., could not be treated effectively until the epoch-making discovery of **sulpha drugs**.

The compound ***p*-aminobenzenesulphonamide**, now known as **sulphanilamide,** was first synthesized by Gelmo in 1908 as an intermediate in the study of azo dyes. Surprisingly it was many years before its therapeutic value was actually ascertained. Gerhard Domagk* in 1935 screened a number of these azo-dyes for their antibacterial effects and observed that they were active against *streptococci.* In 1935, a German firm prepared a red dye 4-sulphonamide-2′, 4′-diamino-benzene or *p*′-sulphonyl chrysoidine, and after three years Domagk suggested significant curative properties of this compound and named it *Prontosil.*

Trefouel *et al.*** (1935) at Pasteur Institute discovered that **Prontosil** breaks down in the tissues to ***p*-aminobenzenesulphonamide,** now known as **sulphanilamide,** and suggested that the antibacterial characteristics of the drug resided in this part of the molecule.



*Domagk, G : *Dtsch. Med. Wochenschr.* **61**, 250, 1935.

Trefouel J *et al.* : *CR Senaces Soc. Biol.* **120, 756, 1935

Prontosil may be prepared by the diazotization of sulphanilamide and subsequent reaction with *m*-phenylene-diamine.

Interestingly, it has been observed that **Prontosil** is absolutely **inactive** *in vitro* but possesses superb and excellent antimicrobial activity *in vivo*. In fact, this specific characteristic property of the drug eventually gained overwhelming recognition and stimulated an astronomical extensive and intensive research activity focussed onto the **sulphonamides.**

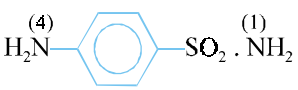
Fuller* (1937) further substantiated and confirmed by isolating **'free sulphonamide'** from the blood and urine of subjects being treated with **Prontosil**. Nevertheless, copius clinical findings were adequately reported with **Prontosil** and its **active metabolite**, sulphanilamide, in the control, management and treatment of *puerperal sepsis*** and meningococcal infections. In reality, these critical findings and observations legitimately and judiciously opened the prevailing **'modern era of chemotherapy'** ; besides, afforded a tremendous push towards the very concept and ideology of the **'prodrug'.**

In 1937, two British researchers prepared **'sulphapyridine'** that was indeed the first and foremost structural analogue of **'sulphanilamide'.** This particular compound proved to be a grand and tremendous success in curing pneumonia. This magnificent discovery, in fact, paved the flood gates for the synthesis and screening of hundreds of derivatives of **sulphanilamide,** but only a few have retained the glory of being potent medicinal compounds.

As on date, there exist a few *typical* **sulphonamides** and particularly the **sulphonamide-trimethoprim combinations** which find their applications exclusively and most extensively for the management and treatment of the **opportunistic infections** in humans having AIDS.*** A few typical examples are as illustrated below :

S.No.	Sulphonamide Commonly Used	Disease/Infection
1	**Trimethoprim + Sulphamethoxazole**	• Treatment/prophylaxis of *Pneumocystis carinii* pheumonia. • First attack of Urinary Tract Infections (UTIs).
2	**Pyrimethamine + Sulphadiazine**	• Treatment and prophylaxis of cerebral taxoplasmosis.
3	**Silver sulphadiazine + Mafenide**	• Burn therapy : prevention and treatment of bacterial infection.

The two N-atoms present in the **sulphanilamide molecule** have been designated N_1 and N_4 as shown below :



Many structural modifications of **sulphanilamide** were made by the substitution of heterocyclic aromatic nuclei at N_1 which yielded highly potent compounds. The substitution at N_4 is comparatively rare. It must be noted that the *ortho*- and *meta*-isomers are valueless therapeutically, and any substitution on the aromatic ring either destroys or reduces the activity of the drug.

Since the past four decades **sulphonamides** have been extensively used against many common **Gram-positive bacterial infections.**

*Fuller AT : *Lancet*, **1** : 194, 1937.

**Septicemia following child birth.

***McDonald L *et al. Formulary*, **31** : 470, 1996.

It is, however, pertinent to state here that one may take cognizance of the various cardinal factors while selecting **'systemic antimicrobial agents'** for therapy in subjects must include :

- identification of probable or specific microorganisms
- antimicrobial susceptibility
- bactericidal *Vs* bacteriostatic activity
- status of host
- allergy history, age, pharmacokinetic factors, renal and hepatic function, pregnancy status, genetic or metabolic abnormalities
- anatomical site of infection and host defenses, particularly neutrophil function.

2. CLASSIFICATION

Sulphonamides *i.e.*, the **systemic antibacterial drugs** may be classified broadly on the basis of their **site of action** as described in the sections that follows :

2.1. Sulphonamides for General Infections

These **sulphonamides** are invariably employed against the streptococcal, meningococcal, gonococcal, staphylococcal and pneumococcal infections.

Examples : sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfamerazine, sulfadimidine, sufalene, sulfamethizole etc.

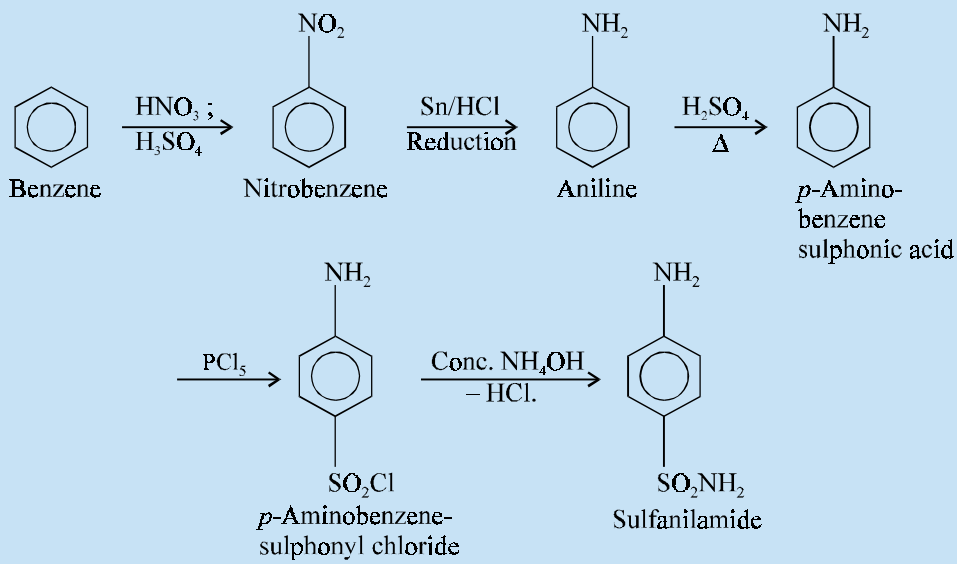
A. Sulfanilamide INN,

p-Aminobenzenesulfonamide ; Sulphanilam ; Solfammide ; BPC ; 1968 ; Int. P., Rhinamid(R) (Bengué U.K.).

Synthesis

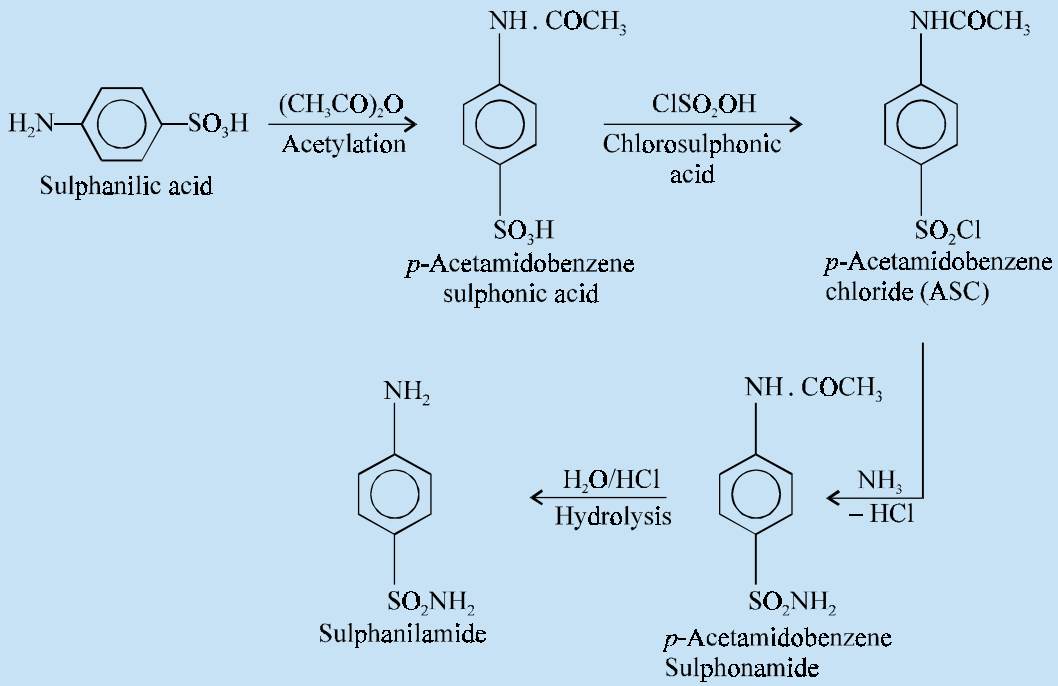
Sulfanilamide may be prepared by any one of the *three* following methods, namely :

Method-I (From Benzene)



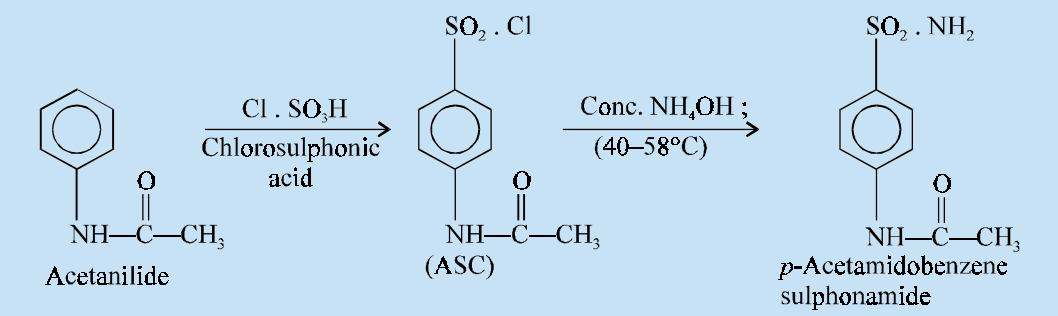
Benzene on nitration yields nitrobenzene which on reduction gives aniline. *p*-Amino benzene sulphonic acid is obtained by treating aniline with hot concentrated sulphuric acid which on chlorination with phosphorus pentachloride gives *p*-aminobenzene sulphonyl chloride ; and this on amination with concentrated ammonia solution yields **sufanilamide.**

Method-II (From Sulphanilic Acid)

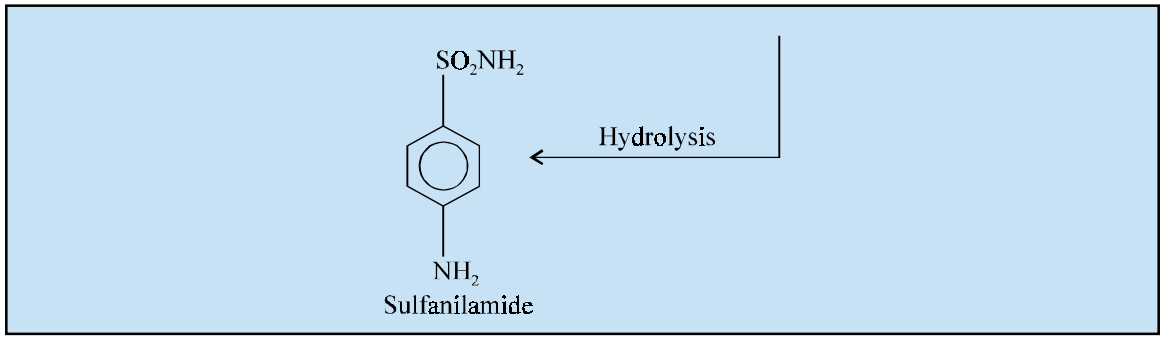


The free and active amino function in sulphanilic acid is first protected by acetylation and the resulting *p*-acetamido-benzene sulphonic acid is chlorinated with chlorosulphonic acid to obtain *para*-acetamido benzene sulphonyl chloride. This on amination with concentrated ammonia solution changes into its corresponding sulphonamide analog, which on hydrolysis results into the formation of sulfanilamide.

Method-III (From Acetanilide)



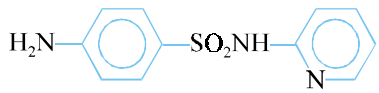
(*Contd...*)



Acetanilide on treatment with chlorosulphonic acid gives *p*-acetamidobenzene sulphonyl chloride which on amination and further hydrolysis yields **sufanilamide.**

It is now used very rarely because of its high toxicity and hence now being replaced by comparatively less toxic sulpha drugs and antibiotics. It is still used in veterinary medicine.

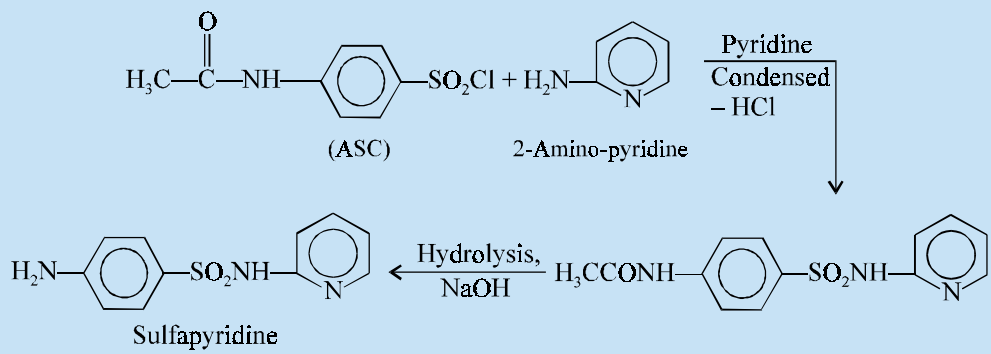
B. Sulfapyridine INN, USAN, Sulphapyridine BAN,



N^1-2-Pyridylsulfanilamide ; Benzene sulfonamide, 4-amino-N-2-pyridinyl-; Sulphapyrid ; Sulphapyridine BP ; BPC ;

Sulfapyridine USP ; M & B 693(R) (May & Baker).

Synthesis

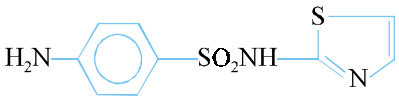


***p*-Acetamidobenzene sulphonyl chloride (ASC)** is condensed with 2-aminopyridine using pyridine as a solvent, followed by alkaline hydrolysis of the resulting product to yield sulfapyridine.

It is mainly used in the treatment of *dermatitis herpetiformis for such patients who do not give positive response to dapsone*. It is effective in pneumonia. Though more potent than **sulfanilamide,** it is more toxic and has been replaced by **sulfadiazine**.

Dose : *0.5 to 3 g daily ; USP dose range 0.5 to 6 g daily.*

C. Sulfathiazole INN, USAN, Sulphathiazole BAN,



N^1-2-Thiazolylsulfanilamide ; Benzenesulfonamide, 4-amino-N-2-thiazolyl ; Norsulfazolum ; M & B 760 ; USP ; BP ; Int. P.,

Cerazole(R) (Beecham) ; Sulfex(R) (Smith Kline & French) ; Thiazamide(R) (May & Baker) ; Cibazol(R) (Ciba),

Synthesis

It may be prepared by :

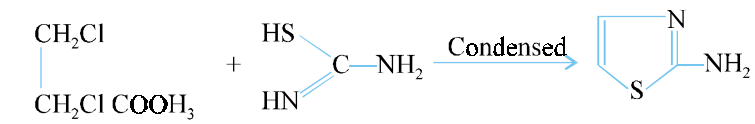
(*i*) Preparation of *p*-acetamidobenzene sulphonyl chloride (ASC)

(*ii*) Preparation of 2-aminothiazole

(*iii*) Condensation of (*i*) and (*ii*) above

(*a*) **Preparation of ASC :** It can be prepared by a method described under sulfanilamide.

(*b*) **Preparation of 2-aminothiazole :**



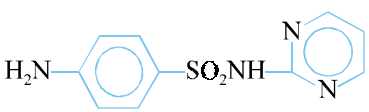
1, 2-Dichloro-ethyl acetate — Thiourea — 2-Aminothiazole

It may be prepared by the condensation of ASC and 2-aminothiazole in pyridine and subsequently hydrolysing the product in the presence of sodium hydroxide.

It is occasionally used, as an adjunct to antibiotics, in severe staphylococcal infections. It is of general use, but *specifically useful against staphylococcal infections and also in bubonic plague.*

Dose : *3 g initially ; subsequent doses, 1 g every 4 hours.*

D. Sulfadiazine INN, USAN, Sulphadiazine, BAN,



N^1-2-Pyrimidinylsulfanilamide ; Benzenesulfonamide, 4-amino-N-2-pyrimidinyl ; Sulfapyrimidine ; USP ; BP ; Eur. P ; Int. P ; Ind. P ;

Codiazine(R) (Beecham) ; Coco-Diazine(R) (Lillly) ; Eskadiazine(R) (SK & F) ; Diazyl(R) (Abbott).

Synthesis

It may be prepared by the condensation of :

(*i*) *p*-Aminobenzene sulphonyl chloride (ASC) and

(*ii*) 2-Aminopyrimidine

(*a*) ***Preparation of ASC*** : It can be prepared as described under sulfanilamide.

(*b*) ***Preparation of 2-amino-pyrimidine***

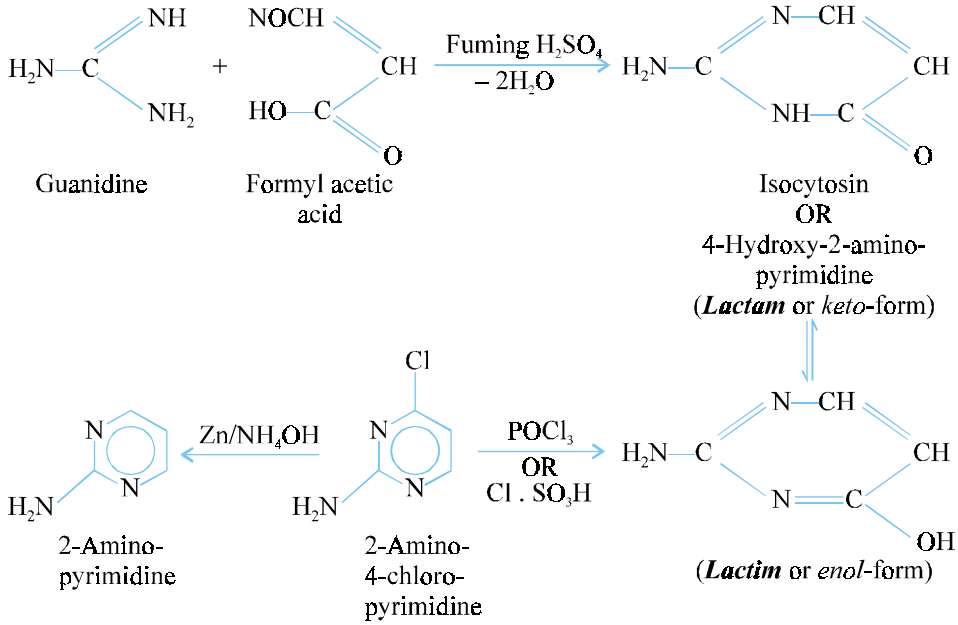
(*i*) **Formyl Acetic Acid**

It is prepared by the interaction of fuming sulphuric acid on malic acid followed by its dehydration and decarboxylation :

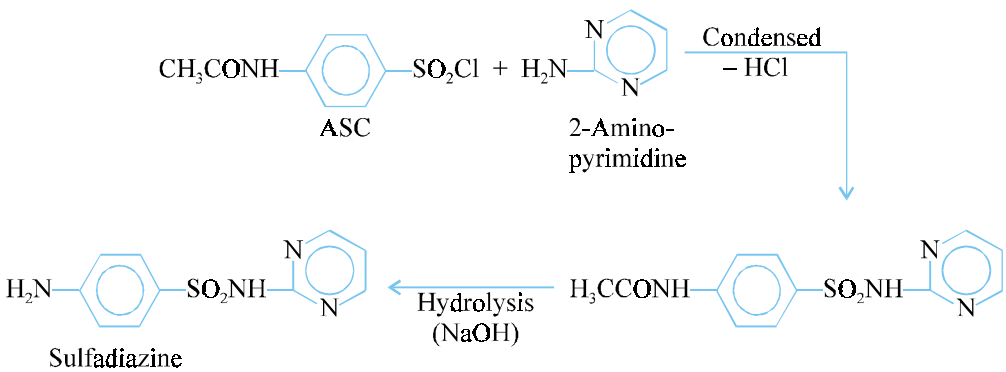
$$\underset{\text{Malic acid}}{HOOC.CH(OH)CH_2COOH} \xrightarrow[(ii)\ \text{Dehydration and decarboxylation}]{(i)\ \text{Fuming } H_2SO_4} \underset{\text{Formyl acetic acid}}{HOC = C.COOH} + H_2O + CO$$

(*ii*) **Condensation of Formyl Acetic Acid with Guanidine**

Formyl acetic acid and guanidine undergo cyclization after condensation in the presence of fuming sulphuric acid with the loss of two moles of water. The cyclized product undergo **keto-enol tautomerism,** when the *enol*-form, *i.e.*, 4-hydroxy-2-amino pyrimidine is subsequently chlorinated with either phosphorus oxychloride ($POCl_3$) or chlorosulfonic acid ($ClSO_2OH$) and finally reduced with zinc metal and ammonium hydroxide to obtain 2-amino-pyrimidine.



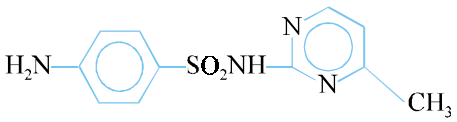
(*iii*) **Condensation of ASC with 2-Aminopyrimidine**



It is effective against most coccus infections. It is *better tolerated than sulfanilamide or sulfathiazole*. In fact, it is as potent as sulfathiazole and possesses fewer side reactions. It has also been used in the *treatment of chancroid due to Haemophilus ducreyi.* It may also be used for the prophylaxis of recurrences of rheumatic fever.

Dose : *3 g initially ; USP dose range 2 to 8 g daily.*

E. Sulfamerazine INN, USAN, BAN,



N^1-(4-Methyl-2-pyrimidinyl) sulfanilamide ; Benzenesulfonamide, 4-amino-N-(4-methyl-2-pyrimidinyl)-; Sulfamethyl-pyrimidine ; Sulfamethyldiazine ; BP ; USP ; Int. P ;

Solumedine(R) (Specia).

Synthesis

It is obtained by the condensation of :

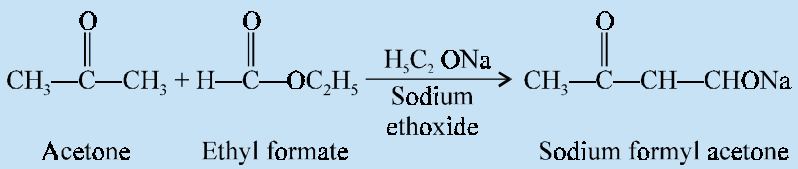
(*a*) *p*-aminobenzene sulphonyl chloride (ASC) and

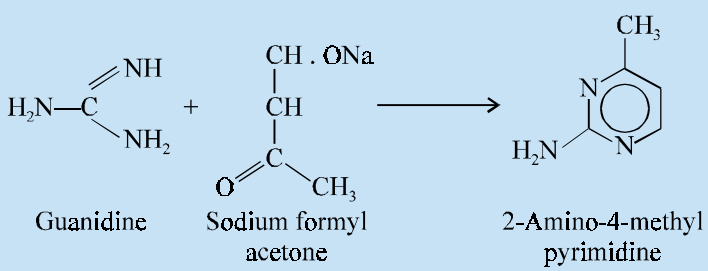
(*b*) 2-amino-4-methyl pyrimidine

(*c*) alkaline hydrolysis

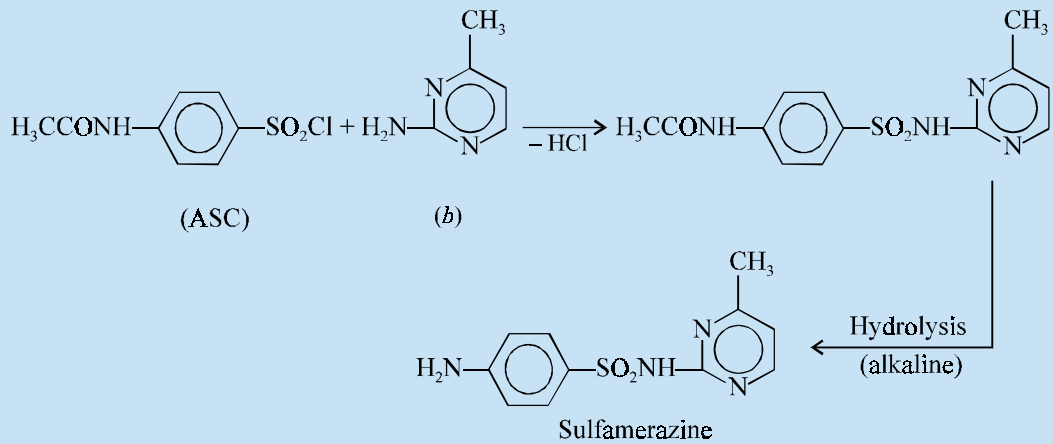
(*a*) **Preparation of ASC :** It has been discussed under sulfanilamide.

(*b*) **2-Amino-4-methyl pyrimidine :** It is achieved by the interaction of sodium derivative of formyl acetone with guanidine as follows : Guanidine





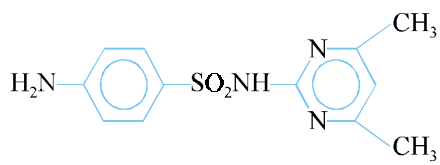
(*c*) **Condensation of (a) and (b) followed by alkaline hydrolysis :**



It has the general properties of the sulphonamides. It is mostly used in conjunction with other sulphonamides.

Dose : *4 g initially ; subsequent doses 1 g every 6 hours.*

F. Sulfadimidine INN, Sulphadimidine BAN, Sulfamethazine USAN,



N^1-(4, 6-Dimethyl-2-pyrimidinyl) sulfanilamide ; Benzenesulfonamide, 4-amino-N-(4, 6-dimethyl-2-pyrimidinyl)-; Sulphadimethylpyrimidine ; USP ; BP ; Eur. P ; Int. P ; Ind. P ;

Synthesis

It may be prepared from

(*i*) *p*-Acetamido benzene sulphonyl chloride (ASC)

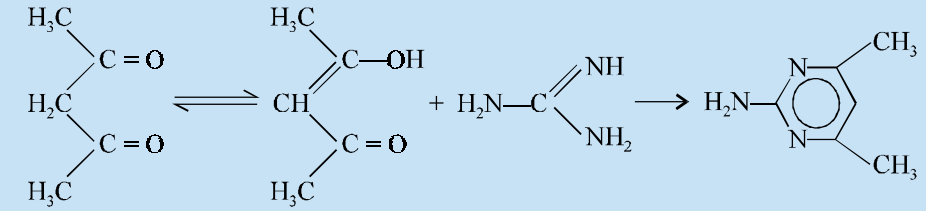
(*ii*) 2-Amino-4, 6-dimethylpyrimidine

(*iii*) Condensation of (*i*) and (*ii*) and

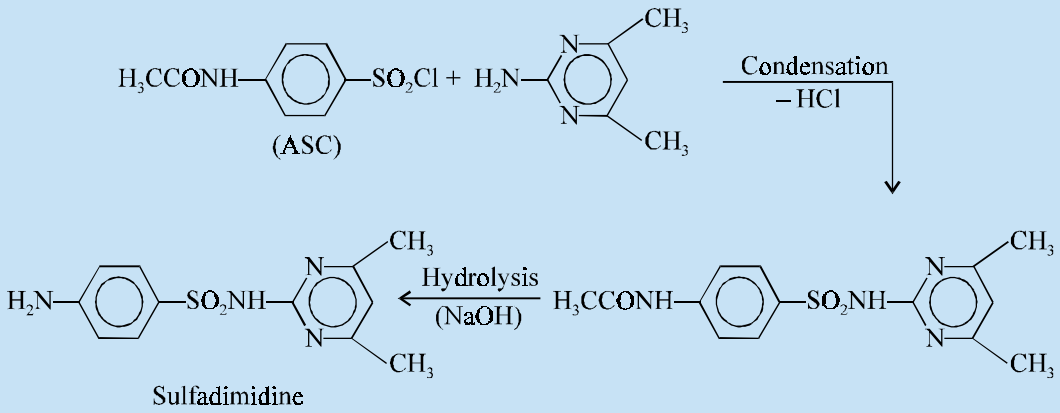
(*iv*) Hydrolysis in alkaline medium

(*a*) **Preparation of ASC :** It has been described under sulfanilamide.

(*b*) **Preparation of 2-amino-4, 6-dimethyl pyrimidine :** It is prepared by reacting together the *Lactim*-form of acetyl acetone and guanidine as follows :



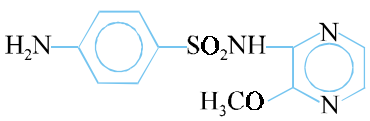
(*c*) *Condensation of (i) and (ii) :*



It is comparatively less effective than sulfadiazine in meningal infections because of its poor penetration into the cerebrospinal fluid. However, for other infections *it is often regarded as the choicest sulphonamide. It is readily absorbed from the gastro-intestinal tract, hence desired concentration in blood may be achieved with regular oral doses.*

Dose : *3 g initially ; subsequent doses up to 6 g per day in divided doses.*

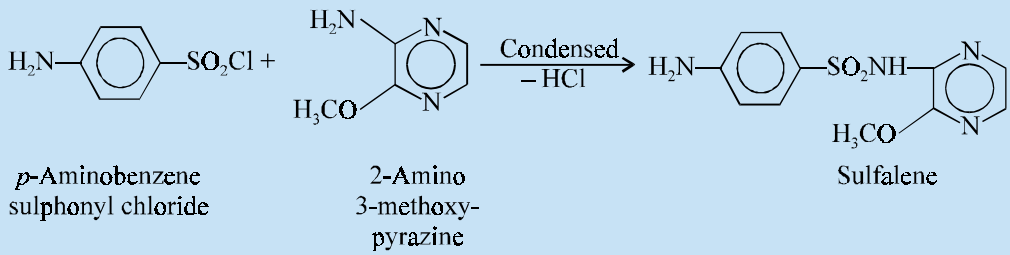
G. Sulfalene INN, USAN, Sulfametopyrazine BAN,



N^1-(3-Methoxypyrazinyl) sulfanilamide ; Benzenesulfonamide, 4-amino-N-(3-methoxypyrazinyl)-; Sulfametopyrazine ; Sulfamethoxypyrazine ; Int. P ;

Kelfizina$^{(R)}$ (Abbott).

Synthesis



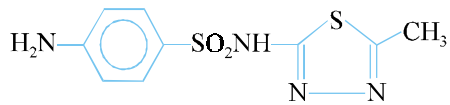
p-Aminobenzene sulphonyl chloride — 2-Amino 3-methoxy-pyrazine — Sulfalene

It is prepared by the condensation of *p*-aminobenzene sulphonyl chloride with 2-amino-3-methoxy-pyrazine when a molecule of hydrogen chloride is eliminated.

It is recommended for the *treatment of chronic bronchitis, urethritis, malaria and respiratory tract infections.*

Dose : *800 mg ; initial dose, followed by 200 mg daily.*

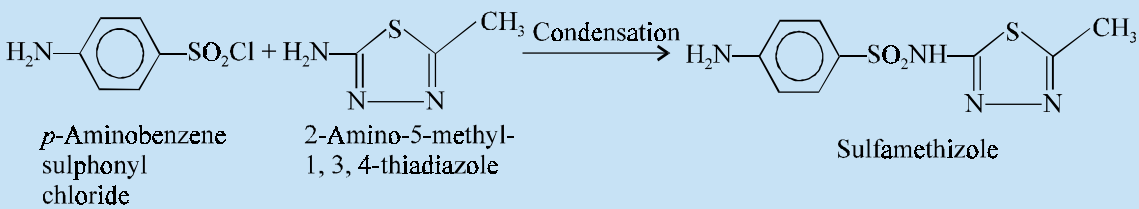
H. Sulfamethizole INN, USAN, Sulfamethizole BAN,



N^1-(5-Methyl-1, 3, 4-thiadiazol-2-yl) sulfanilamide ; Benzenesulfonamide, 4-amino-N-(5-methyl-1, 3, 4-thiadiazol-2-yl) ; USP ; BP ; BPC ;

Thiosulfil(R) (Ayerst) ; Ultrasul(R) (Alcon) ;

Syntehsis



p-Aminobenzene sulphonyl chloride — 2-Amino-5-methyl-1, 3, 4-thiadiazole — Sulfamethizole

It may be prepared by the condensation of *p*-aminobenzene sulphonyl chloride with 2-amino-5-methyl-1, 3, 4-thiadiazole.

It has the general properties of sulphonamides. It is also employed in the *treatment of coliform infections of the urinary tract.*

Dose : *2 to 4 g initially, followed by 2 to 4 g per day in 3 to 6 divided doses.*

2.1.1. Mechanism of Action

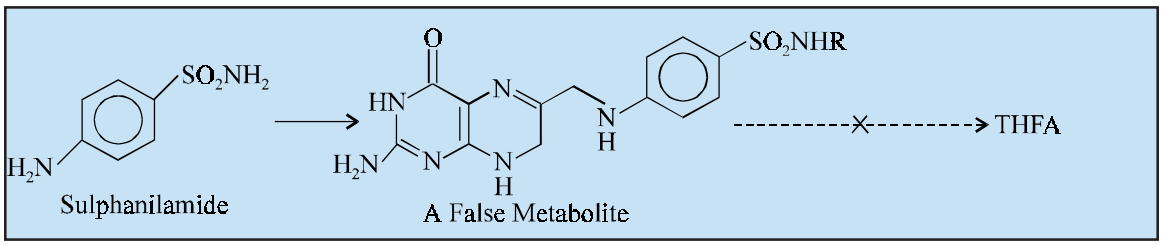
The mechanism of action of various drugs discussed under Section 19.2.1 shall now be treated individually in the sections that follows :

2.1.1.1. Sulfanilamide

The **'drug'** has been largely superseded in medicine by other qualified structural analogues that are either less toxic or are for individual purposes preferable. It has been duly observed that the overall net result remains the same, but the prevailing molecular basis of the effect is rather different in these

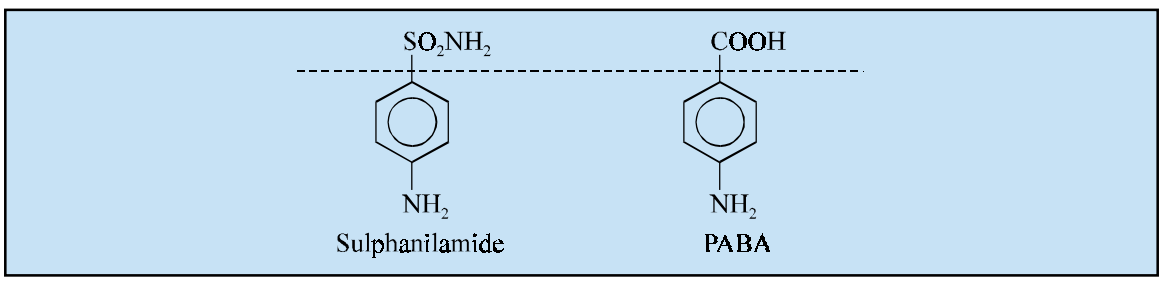
strains *e.g.*, streptococcal, pneumococcal, meningococcal, gonococcal and *E. coli.* However, the bacteria that are capable of taking up the preformed **folic acid** into their cells are found to be intrinsically resistant to the sulphonamides.

In fact, **sulphanilamdie** gives rise to a **'false metabolite'** that eventually prevents its ultimate conversion to **tetrahydrofolic acid (THFA)** as shown below :



SAR of Sulphanilamide

The fundamental basis of the prevailing structural resemblance of **sulphanilamide**-in particular and **sulphonamides**-in general to ***para*-aminobenzoic acid (PABA)** which is so destructive to these microorganisms is found to be quite evident.



The most glaring difference between the functional group which essentially differs in the two above cited molecules is the **carboxyl of PABA** and the **sulphonamide** moiety of **sulphanilamide.** Interestingly, the latter contains an evidently strong electron withdrawing feature by virtue of the *aromatic SO_2 moiety* that renders the N-atom to which it is directly linked partially elecropositive in character. This, in turn, eventually enhances the acidity of the two H-atoms linked to the N-atom thereby making this functional moiety (*i.e.*, **sulphonamide moiety**) slightly acidic in nature (*p*K*a* 10.4). In contrast, the *p*K*a* value of the former, due to the presence of the carboxyl moiety of **PABA,** stands at 6.5. Based on this wonderful theory, immediately persued by a vigorous synthetic drive programme, that specifically involved the critical replacement of one of the H-atoms attached to the sulphonamido N-atoms by an **electron-withdrawing heteroaromatic nucleus** (ring) remarkably gave rise to the following *two* advantageous and useful features, namely :

(*a*) consistently improved antimicrobial activity, and

(*b*) appreciably acidified the remaining H-atom and substantially increased potency.

The wisdom and the skill of the **'medicinal chemist'** in designing newer drug entities brought about the following apparent changes :

- *p*K*a* value came down to almost very close to that of PABA (*i.e.*, 6.5) ; *e.g.*, sulfisoxazole *p*K*a* : 5.0,
- Significant enhancement of the *'antibacterial potency'* of the newer product, and
- dramatically potentiated the water solubility under the prevailing physiologic conditions.

2.1.1.2. Sulfapyridine

The **'drug'** enjoys the reputation of being the first agent to exhibit a remarkable significant curable action on pneumonia by Whitby.

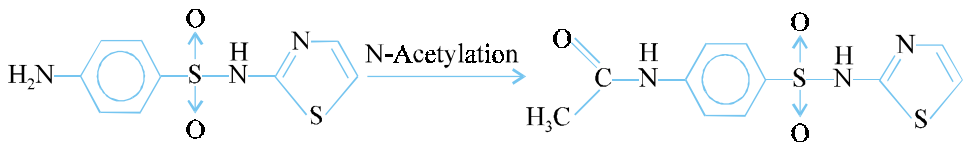
SAR of Sulfapyridine. The **'drug'** afforded a tremendous impetus to the study of the whole class of N^1-heterocyclically modified and substituted structural analogues of **sulphanilamide**.

2.1.1.3. Sulfathiazole

The primary amino moiety of this **'drug'** gets acetylated *in vivo*, and the resulting amides usually exhibit retarded solubility that may ultimately lead to toxic effects. Perhaps the poor solubility of the insoluble acetylated metabolite of **sulfathiazole** may even prove fatal in case it blocks the kidney tubules.

Note : It is always recommended to use a combination of the sulpha-drugs, rather than using a single one with higher dose level, so as to avoid 'crystal-urea' formation thereby reducing the chances of kidney blockade.

The possible **metabolism of sulphathiazole** is depicted as under :



Sulfathiazole Metabolite (Insoluble)

2.1.1.4. Sulfadiazine

It has been duly observed that derivatives of **'pyrimidine'** have enjoyed the most effort and accomplished the highest clinical success. Importantly, the effect of this **'drug'** is almost equal to 2-sulfapyrazine (*i.e.*, the 1, 4-diazine derivative) both *in vitro* and *in vivo* studies against a host of organisms.*

Comparison of Sulphadiazine *Vs* Sulphanilamide

It has been proved adequately that **sulphanilamide** essentially needs **142 times** the actual concentration of **sulfadiazine** so as to prevent the growth of *Escherichia coli*. In reality, the lipid solubility of the latter **(sulphadiazine)** is first **2.5 times** greater than that of the former **(sulphanilamide)** that would not be a strong enough evidence to explain explicitely the vast difference in their therapeutic potency. In case, one takes into consideration the prevailing *p*K*a* values of the two drug susbtances calculated at pH 7.4 it may be observed that only 0.03% of sulphanilamide shall undergo ionization ; whereas, **sulfadiazine** would get ionized upto 80% under such experimental conditions.

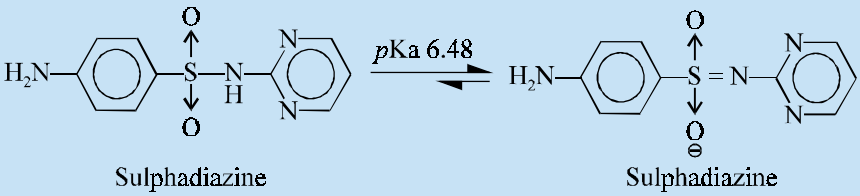
It is, however, pertinent to state here that even though sulphanilamide has sufficient lipid solubility (10.5%) to cross the bacterial membrane, 99.7% of the total available molecules would usually remain in the molecular **(inactive)** state once inside. Based on the above statement of facts the existing difference in the **'lipoidal solubility'** between the two aforesaid drugs would certainly permit the scope of prediction that **'sulfadiazine'** should possess a distinct **longer biological half-life.**

SAR of Sulfadiazine. The 5-sulphanilamido isomer together with various methoxy and methyl structural analogues are found to be comparatively less active *in vitro* than **sulfadiazine.** However, the *para*-isomer is nearly equivalent to **sulfadiazine** *in vitro* but very poorly active *in vivo.* It has been observed that the corresponding 4- and 5-isomers are relatively less active orally against streptococci in mice.**

*Bell PH *et al. J Am Chem Soc*, **64**, 2905, 1942

Redin GS *et al. Chemotherapia*, **11, 309, 1966.

The replacement of the **thiazole ring** with a more **electron withdrawing pyrimidine nucleus** enhanaces the acidity of the NH proton by stabilizing the anion ultimately. Consequently, sulphadiazine and its metabolite are appreciably ionized at pH of blood thereby rendering them **more soluble** and **less toxic** as illustrated below :



Sulphadiazine
(Unionized)

Sulphadiazine
(Ionized 86%)

2.1.1.5. Sulfamerazine

The **'drug'** gets easily absorbed from the GI-tract after oral administration ; and, therefore, the desired concentration in blood is accomplished with usual dosage regimen employed. As it exhibits relatively poor penetration right into the **cerebrospinal fluid** ; hence, it is much less effective in the treatment of meningal infections in comparison to the congener **sulfadiazine.**

2.1.1.6. Sulfamethazine

Because the **'drug'** is more soluble in acidic urine in comparison to sulfamerazine, therefore, its chances and scope of *'kidney damage'* by its usage is lowered to a great extent. Its *p*K*a* value stands at 7.2. Its plasma half-life is 7 hours.

SAR of Sulfamethazine. The **'drug'** possesses almost similar chemical properties to those of *sulfadiazine* and *sulfamerazine,* but does show greater water-solubility than either.

2.1.1.7. Sulfalene

A combination of the **'drug'** with trimethoprim has exhibited an almost spectacular effect in clinical trials against the resistant falciparum malaria contracted in Vietnam, when the American soldiers were fighting there in the late sixties.*

2.1.1.8. Sulfamethiazole

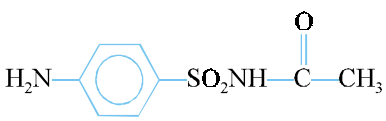
A **'drug'** almost acts in the same manner as the sulphanilamide. However, its action is specifically useful in the treatment of UTIS. It has a plasma half-life of 2.5 hours.

2.2. Sulphonamides for Urinary Infections

A number of **sulphonamides** have been used extensively for the prevention and cure of urinary-tract infections over the past few decades. They are used sometiems as a prophylactic before and after manipulations on the urinary tract. A few such sulphanilamide analogues belonging to this category shall be dealt with here.

Examples : sulfacetamide, sulfafurazole, sulfisoxazole acetyl, sulfacitine, etc.

A. Sulfacetamide INN, USAN, Sulphacetamide BAN,



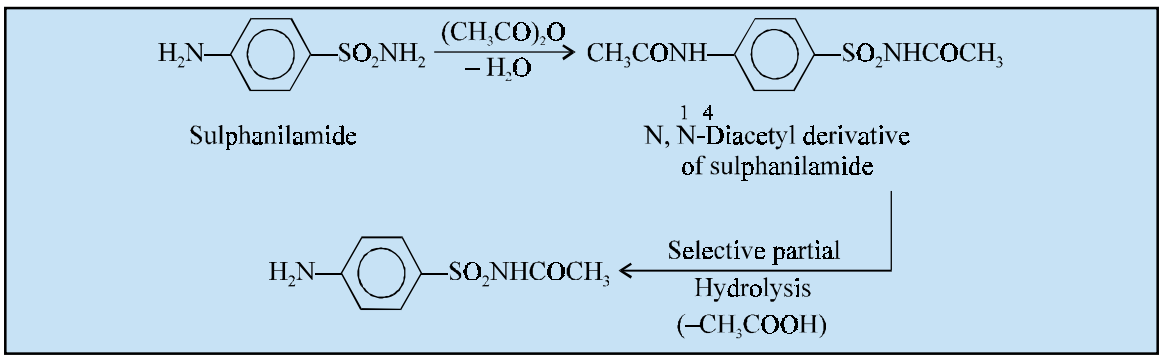
N-Sulfanilylacetamide ; Acetamide, N-[(4-aminophenyl) sulfonyl]-; BPC ; 1959 ; Ind. P ;

*Modell W, *Science,* **162**, 1346 (1968).

Synthesis

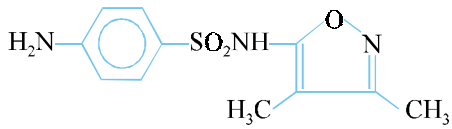
It is prepared by the selective and partial hydrolysis of the N^1, N^4-diacetyl derivative of sulphanilamide which is obtained by the acetylation of **sulfanilamide.**

It possesses general characteristics of a **sulphonamide** and was formerly used in the treatment of bacterial infections of the urinary tract.



Dose : *4 g initially ; 1 g every 4 hours.*

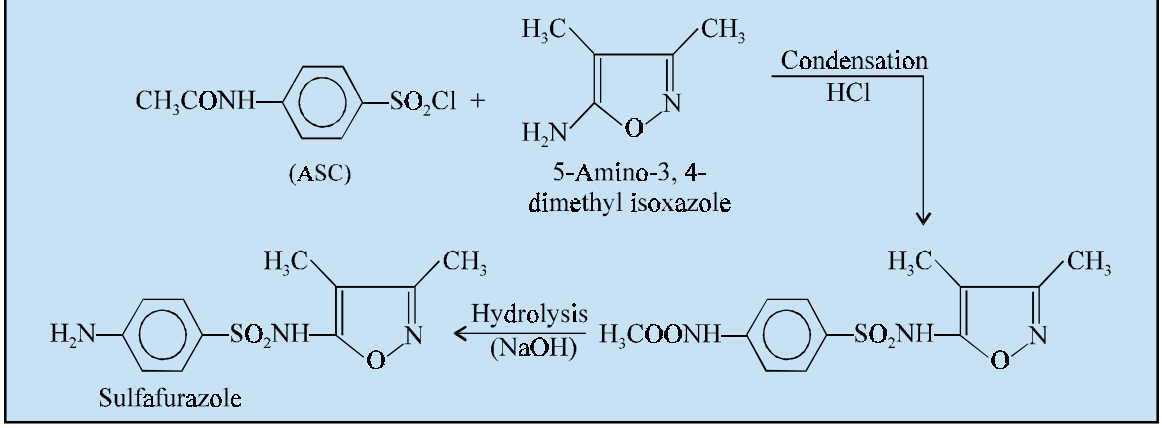
B. Sulfafurazole INN, Sulfisoxazole USAN, Sulphafurazole BAN,



N^1-(3, 4-Dimethyl-5-isoxazolyl) sulfanilamide ; Benzenesulfonamide, 4-amino-N-(3, 4-dimethyl-5-isoxazolyl)-; BP ; USP ; Ind. P ; Int. P ;

Gantrisin(R) (Roche) ; SK-Soxazole(R) (SK & F) ; Soxomide(R) (Upjohn) ; Sulfalar(R) (Parke-Davis).

Synthesis

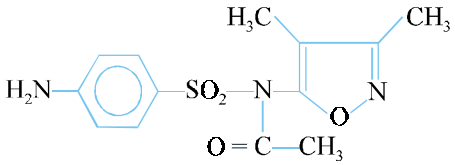


It is prepared by condensing together *p*-acetamidobenzene sulphonyl chloride (ASC) with 5-amino-3, 4-dimethyl isoxazole and hydrolysing the resulting product in an alkaline medium.

Its characteristics and therapeutic utilities are almost similar to those of sulfadiazine. It finds favour in the treatment of various urinary-tract infections. It may be used in the form of topical preparations for the *treatment of some infections, such as vaginitis caused by Hemophilus vaginalis.*

Dose : *2 to 4 g initially ; oral, followed by 4 to 8 g a day in 4 to 6 divided doses.*

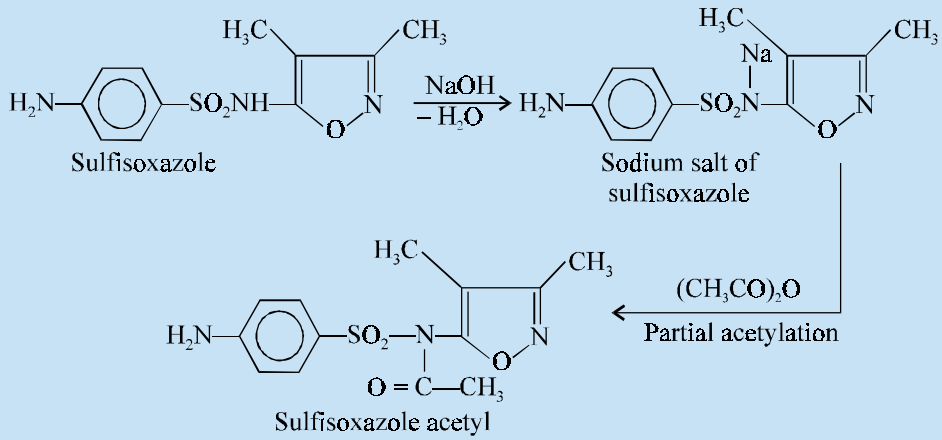
C. Sulfisoxazole Acetyl INN, USAN, Acetyl Sulphafurazole BAN,



N-(3, 4-Dimethyl-5-isoxazolyl)-N-sulfanilyl-acetamide ; Acetamide, N-[(4-aminophenyl) sulfonyl]-N-(3, 4-dimethyl-5-isoxazolyl)-; USP ;

Lipo Gantrisin(R) (Roche).

Synthesis

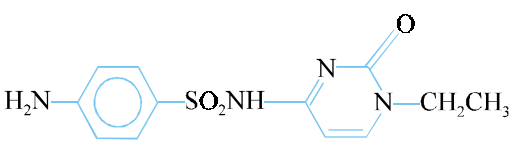


It is prepared by first converting **sulfisoxazole** into its sodium salt by treatment with sodium hydroxide and then carrying out the selective acetylation at N^1 with an equimolar quantity of either acetic anhydride or acetyl chloride.

It is tasteless, unlike its parent compound, hence it is more suitable for liquid oral preparations. Its *renal toxicity is lower than that of* ***sulfadiazine***.

Dose : *2 to 4 g oral, adult and initial dose ; maintenance dose 4 to 8 g per day in divided doses.*

D. Sulfacitine INN, Sulfacytine USAN, BAN,



N^1-(1-Ethyl-1, 2-dihydro-2-oxo-4-pyrimidinyl)-sulfanilamide ; Benzenesulfonamide, 4-amino-N-(1-ethyl-1, 2-dihydro-2-oxo-4-pyrimidinyl)-; 1-Ethyl-N-sulfanilylcytosine ;

Renoquid(R) (Parke-Davis).

Sulfacitine is a **short-acting sulphonamide** which is employed likewise to **sulfafurazole** in the *treatment of acute urinary-tract infections.*

Dose : *Initial loading dose 500 mg ; maintenace dose 250mg 4 times per day up to 10 days.*

2.2.1. Mechansim of Action

The mechanism of action of the *four* compounds described under section 18.2.2 are dealt with in the Sections that follows :

2.2.1.1. Sulfacetamide

The **'drug'** exerts its action topically in conjunction with **sulphabenzamide** and **sulfathiazole** for the control and treatment of vaginitis caused due to the microorganism *Gardnerella (Hemophilus) vaginalis.* It has half-life of 7 hours.

2.2.1.2. Sulfisoxazole

The **'drug'** does not penetrate cells and happen to pass through barriers as well as most sulphonamides. Therefore, it is found to be not always effective against the systemic infections which are particularly sensitive to other **sulphonamides.** Importantly, in the specific genitourinary tract infections wherein penetration right into the involved tissues is required essentially, it may not prove to be as useful as **sulphadiazine.** It is known that the *'drug'* gets secreted into the *prostatic fluid ;* however, it has not yet been ascertained whether it gets secreted likewise into other genitourinary fluids.

It has been duly observed that the **'drug'** gets metabolized primarily by *acetylation* and *oxidation* in the liver. Interestingly, the **'drug'** as well as its conjugate are excreted rapidly by the kidney and thereby attains high concentration in the urine. The half-life stands at 6 hours. It is, however, pertinent to state here that the **free** as well as the **acetylated** forms of the drug substance are *highly soluble, even in an acidic urine ;* and, therefore, the adjuvant follow-up **'alkali therapy'** is not absolutely necessary and also fluids need not be forced.

2.2.1.3. Sulfisoxazole Acetyl

The **'drug'** more or less shares the activities and applications of the parent compound *i.e.*, **sulfisoxazole.** However, the **'drug'** is practically tasteless as compared to the parent drug ; hence, most suitable for liquid oral formulations for paediatric usage.

The acetyl compound is usually split in the *intestinal tract* and subsequently gets absorbed as **'sulfisoxazole'**, *i.e.*, it is a befitting **'prodrug'** for **sulfisoxazole.**

2.2.1.4. Sufacytine

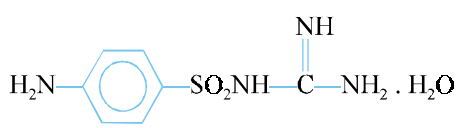
The **'drug'** exerts its action for a relatively shorter duration ; and is employed invariably for the management and treatment of severe UTIs very much akin to **sulphafurazole.**

2.3. Sulphonamides for Intestinal Infections

A plethora of insoluble **sulphonamide** analogues, for instance **phthalylsulfathiazole** and **succinylsulfathiazole,** are not readily absorbed from the gastrointestinal tract. However, the release of active sulphonamide in high concentration, obtained due to hydrolysis in large intestine, enables their application for intestinal infections and also for pre-operative preparation of the bowel for surgery. A few examples of sulphonamides belonging to this specific use will be discussed here.

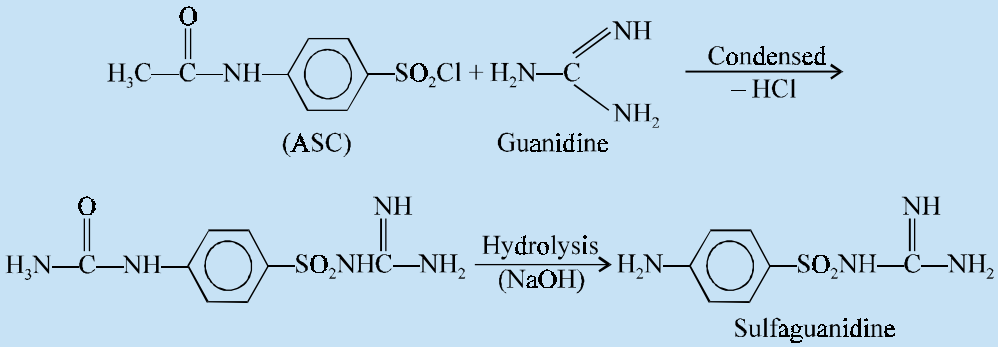
Examples : sulfaguanidine, phthalylsulfathiazole, succinylsulfathiazole, phthalylsulfacetamide, salazosulfapyridine, etc.

A. Sulfaguanidine, INN, Sulphaguanidine BAN,



N^1-(Diaminomethylene) sulfanilamide ; Benzenesulfonamide, 4-amino-N-(diaminomethylene)-; N-*p*-Aminobenzenesulfonyl guanidine monohydrate ; Sulphaguanid ; BPC ; 1973 ; NF ; XI ; Int. P.; Ind. P ;

Synthesis

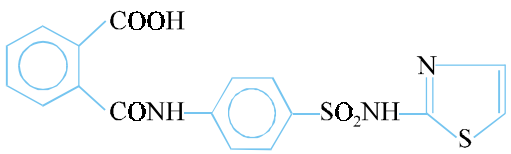


It may be prepared by condensing *p*-amino benzene sulfonyl chloride with guanidine and hydrolysing the resultant in the presence of sodium hydroxide.

It has been used for the *treatment of local intestinal infections, specifically bacillary dysentry, but it has mostly been replaced by comparatively less toxic analogues, namely ; phthalylsulphatiazole and succinylsulphathiazole.*

Dose : *3g, 3 to 4 times per day for 3 days.*

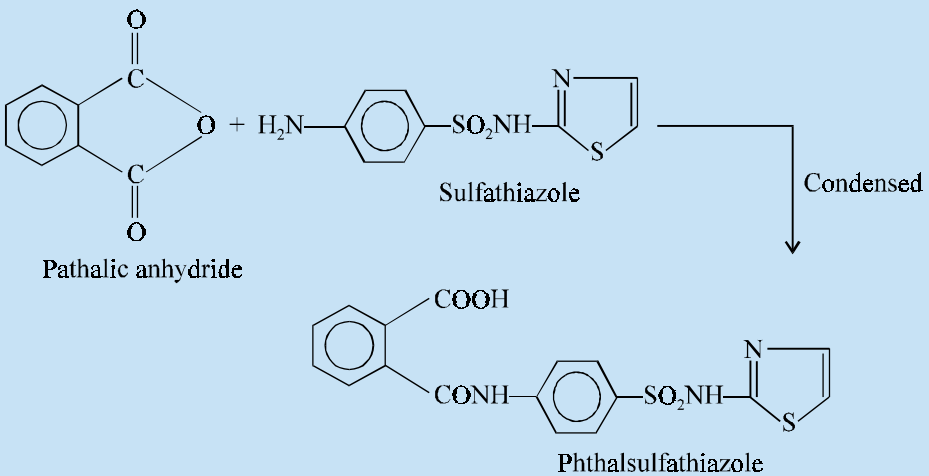
B. Phthalylsulfathiazole, INN, USAN, Phthalylsulphathiozole BAN,



4′-(2-Thiazolylsulfamoyl) phthalanilic acid ; 2*p*-(*o*-Carboxy-benzamido) benzene sulfonamido thiazole ; Sulfaphtalyl-thiazole ; USP ; BP ; Ind. P ; Int. P ;

Thalazole(R) (May and Baker, U.K.).

Synthesis



It may be prepared by the interaction of sulfathiazole and phthalic anhydride in equimolar proportions.

It exerts its bacteriostatic effect in the gastro-intestinal tract. It has been found to be twice as active as **sulfaguanidine** in the treatment of bowel irregularities. It is often effective in watery diarrhoeas and ulcerative colitis. It is also used in the pre-operative treatment of patients undergoing surgery of the intestinal tract. It may also be recommended in the *treatment of acute bascillary dysentry of the Sonne, Flexner and Shiga species.*

Dose : *5 to 10 g per day in divided doses.*

C. Succinylsulphathiazole BAN, Succinylsulfathiazole USAN,

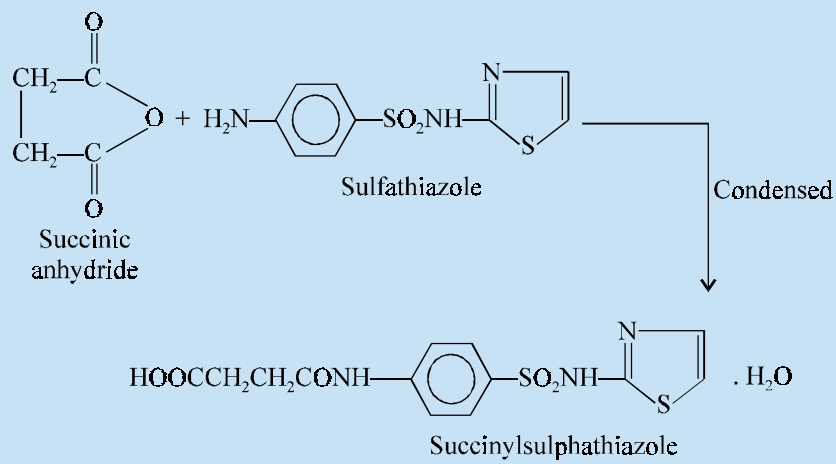
4′-(2-Thiazolylsulfamoyl-succinanilic acid monohydrate ; 2-*p*-(3-Carboxy-propionamide) benzene sulfonamido thiazole monohydrate ; USP ; XVIII, BP ; Eur. P ; Ind. P ; Int. P ;

Sulfauxidine(R) (Merck Sharp and Dohme).

Synthesis

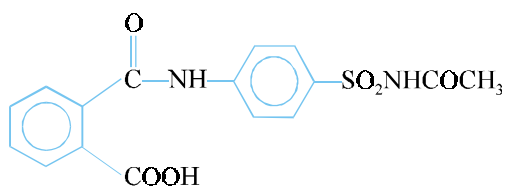
It can be prepared by heating together succinic anhydride and sulfathiazole.

It is used in bacillary dysentry and cholera. Its other uses are more or less the same as that of **phthalylsulfathiazole.**



Dose : *10 to 20 g per day in divided doses.*

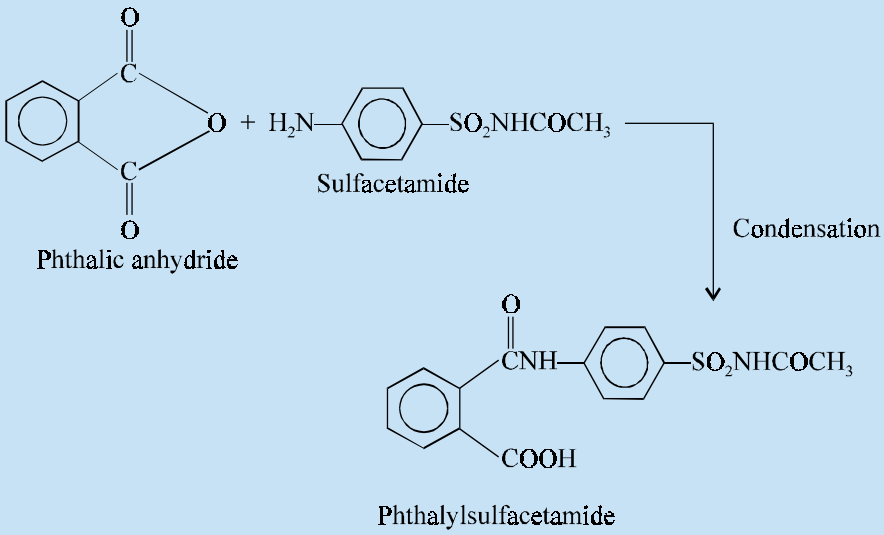
D. Phthalylsulfacetamide USAN, Phthalylsulphacetamide BAN,



4′-(N-Acetylsulfamoyl) phthalanilic acid ; N-[*p*(*o*-Carboxybenzamido) benzene sulfonyl] acetamide ; NF ; XIII, Ind. P.,

Talsigel(R) (Squibb) ; Thalisul(R) (Beecham) ; Thalamyd(R) (Schering-Plough).

Synthesis

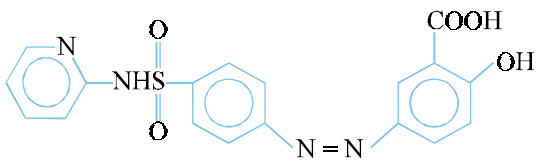


It may be prepared by the interaction of phthalic anhydride and sulfacetamide.

The therapeutic uses of this compound is very much similar to phthalylsulfathiazole.

Dose : *6 g per day in divided doses.*

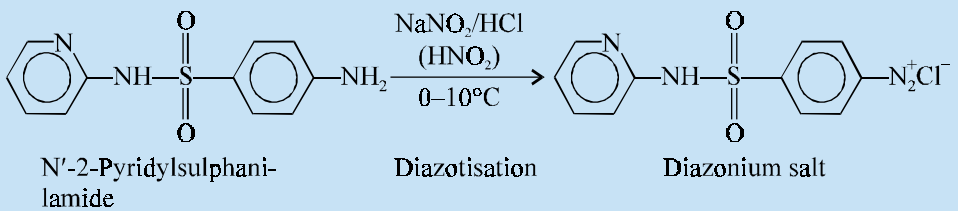
E. Salazosulfapyridine INN, Sulfasalazine USAN, Sulphasalazine BAN,



5-[[*p*-(2-Pyridylsulfamoyl) phenyl]azo] salicylic acid ; Benzoic acid, 2-hydroxy-5-[[4-(2-pyridinylamino) sulfonyl]-phenyl] azo-; USP ; NF ;

Azulfudine(R) (Lederle) ; Salazopyrin(R) (Pharmacia U.K.) ; SAS–500(R) (Rowell).

Synthesis



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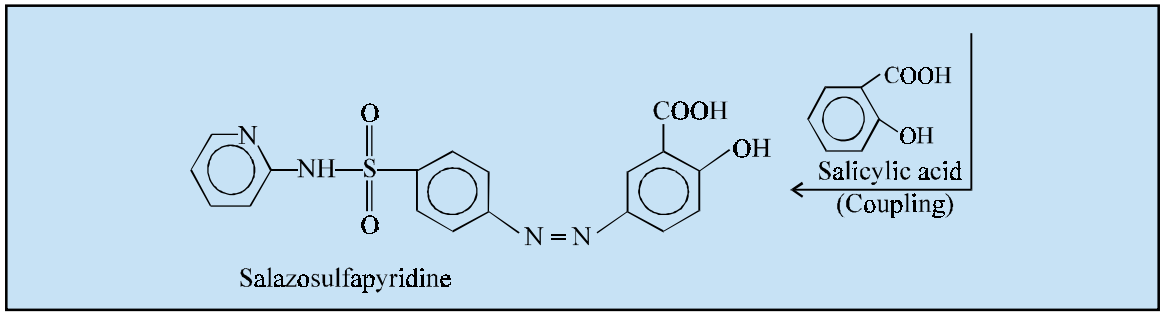


It may be prepared *first* by diazotising N^1-2-pyridyl-sulfanilamide at 0-10°C and *secondly* by coupling the resulting diazonium salt with salicylic acid.

It has a suppressive effect on ulcerative colitis. This therapeutic action may perhaps be attributed to a local immunosuppressive effect. **Salazosulfapyridine** ultimately releases **sulfapyridine** and 5-aminosalicyclic acid in the colon with the aid of bacterial enzymes. It often imparts a yellow colour to alkaline urine.

Dose : *2 to 8 g per day preferably in 4 to 8 divided doses.*

2.3.1. Mechanism of Action

The mechanism of action of the compounds discussed in section 18.2.3. are now treated individually in the sections that follows :

2.3.1.1. Sulphaguanidine

The percentage unbound *i.e.,* the protein-unbound portion which is predominantly significant for the ensuing activity, toxicity, metabolism and glomerular filtration of the **'drug',** ranges from 95% for **sulfaguanidine** to 0.2—0.5% for *4-sulfa-2, 6-dimethoxyprimidine.* From the above observations one may infer that the criterion of *'protein-binding'* would lead ultimately one to believe that an extensively bound **'drug entity'** is quite undesirable not only from the antibacterial but also from the pharmacological stand point crtically. It also gets very slightly absorbed from the intestinal mucosa.

2.3.1.2. Phthalylsulfathiazole

The **'drug'** is of low inherent toxicity. Besides, it also enjoys an additional plus point for being only slightly absorbed by the intestinal mucosa ; and, therefore, may be safely administered in comparatively large doses in the management and treatment of bacillary infections of the intestine. The drug is not absorbed orally and is mostly employed for ulcerative colitis.

2.3.1.3. Succinylsulfathiazole

The **'drug'** almost exerts its action very much identical to that of phthalylsulfathiazole discussed earlier.

2.3.1.4. Phthalylsulfacetamide

The mechamism of action of this **'drug'** is very much akin to phthalylsulfathiazole.

2.3.1.5. Sulfasalazine

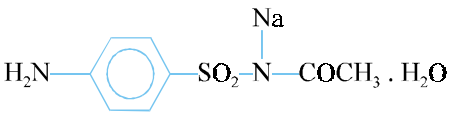
The **'drug'** gets poorly absorbed from the small intestine, so as to enable a major portion of the drug to penetrate into the **colon** (*i.e.,* **large intestine**) where the **bacterial enzymes** strategically release both *5-aminosalicylic acid* and **sulfapyridine** from the drug. However, the local antibacterial effect of **sulfapyridine** (*i.e.,* the **ensuing metabolite**) in lowering the anaerobic bacteria may not be of a significant magnitude on account of adequate systemic absorption. Interestingly, the first metabolite *i.e.,* 5-aminosalicylic acid specifically inhibits the **arachidonic acid casade** *i.e.,* both *cyclooxygenase* and *lipooxygenase* pathways, effectively. Perhaps the most prominent and important would be the legitimate inhibition of leukotriene B_4 production by PMNs.

2.4. Sulphonamides for Local Infection

There are some **sulphonamides** which are used exclusively for certain local applications. A few such typical **sulphonamides** shall be discussed below :

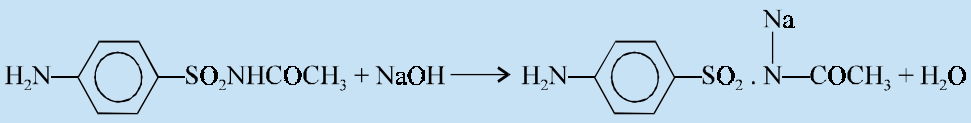
Examples : Sulfacetamide sodium, Mafenide, etc.

A. Sulfacetamide Sodium USAN, Sulphacetamide Sodium BAN,



N-Sulfanilylacetamide monosodium salt monohydrate ; Acetamide ; N-[(4-Aminophenyl) sulfonyl]-, monodium salt, monohydrate ; Soluble sulphacetamide ; USP ; BP ; Int. P ; Ind. P ;
Albucid(R) (Nicholas U.K.) ; Cetamide(R) (Alcon) ; Sulf-10(R) (Cooper Vision).

Synthesis



Sulfacetamide — Sulfacetamide sodium

It may be prepared by heating together **sulfacetamide** and sodium hydroxide in *equimolar concentrations.*

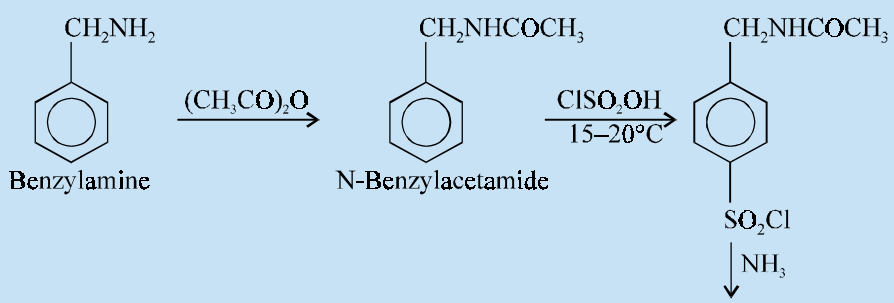
It is chiefly employed by local application in injuries or infections of the eyes at various strengths ranging from 10 to 30%. It is also used in the *treatment of acute conjunctivitis and in the prophylaxis of ocular infections after injuries or burns.*

Dose : *In eye, drops 10%, 15%, 20% and 30% ; In ointments 2.5% and 6%.*

B. Mafenide INN, BAN, USAN,

α-Amino-*p*-toluenesulfonamide ; Benzenesulfonamide, 4-(amino-methyl)-; Marfanil ; Mafenide Acetate, USP ; Mafenide Hydrochloride, Jap. P ; BPC ; 1949 ;
Mafenide Propionate, Sulfonyl(R) (Winthrop).

Synthesis



Benzylamine — N-Benzylacetamide

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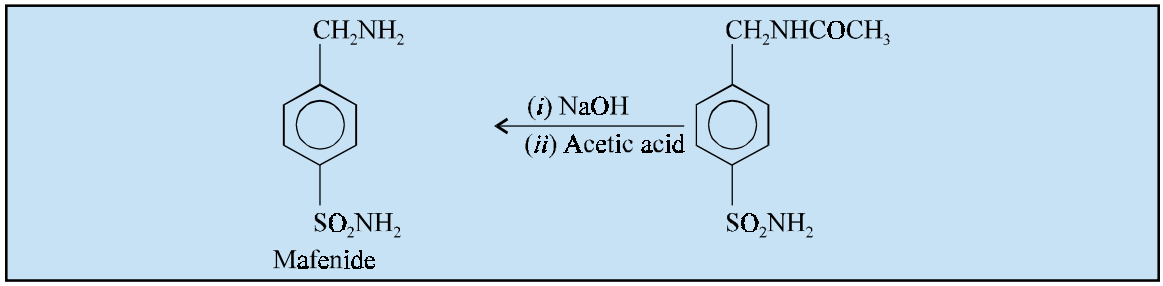


N-Benzylacetamide is prepared by the acetylation of benzylamine, which on treatment with chlorosulfonic acid at 15-20°C yields *p*-benzylacetamido sulphonyl chloride. This on amination gives the corresponding sulfonamide derivative, which upon hydrolysis with sodium hydroxide and subsequent neutralization with acetic acid yields **mafenide.**

It is used in the treatment and cure of gas gangrene. It is also used for the *treatment of infection especially that caused by Pseudomonas alruginosa, in second-and third-degree burns.*

Dose : *5% solution of mafenide hydrochloride or mafenide propionate for topical use.*

2.4.1. Mechanism of Action

The mechanism of action of the *two* compounds described under Section 19.2.4 are treated separately as under :

2.4.1.1. Sulfacetamide Sodium

The **'drug'** is relatively less potent in comparison to **'other sulphonamides'**. This retardation of therapeutic value is perhaps due to the poor penetration into both *tissues* and *bacteria.* However, if used in high concentration by means of local application, it is found to be of great utiliry in different types of *ophthalmologic infections*, especially those produced by pyogenic cocci, gonococcus, *E. coli* and Koch-Week's bacillus.

As the **'drug'** is obviously nonirritating in nature even at a high dosage regimen, it may be employed safely in sufficient concentration to accomplish adequate penetration of the ocular tissues with much ease and fervour.

2.4.1.2. Mafenide

It is **not a true sulfanilamide-type** drug substance, because it is *not* inhibited by **PABA**. Evidently, its antibacterial activity predominantly involves a mechanism which essentially differs from that of the true **sulphanilamide-type compounds.**

Interestingly, the **'drug'** is specifically effective against *Clostridium welchii* as a prophylaxis of wounds in the form of topical medicaments *viz.*, lotions, ointments, or dusting powder.

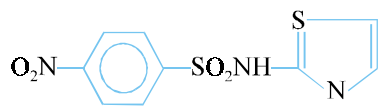
Note. The corresponding acetate salt *i.e.*, mefenide acetate used in an ointment base proved to be the most efficacious agent devoid of any untoward metabolic acidosis.

2.5. Sulphonamide Related Compounds

There are some **sulphonamides** which essentially differ from the **basic sulphonamide nucleus,** but do possess anti-bacterial properties. A few such typical examples belonging to this type of compounds are dealt with below :

Examples : **Nitrosulfathiazole, dapsone, silver sulfadiazine,** etc.

A. Nitrosulfathiazole INN, *Para*-Nitrosulfathiazole USAN, Paranitrosulphathiazole BAN,



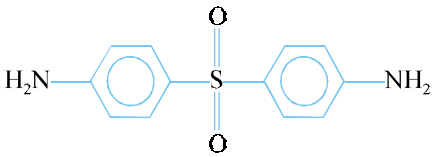
p-Nitro-N-2-thiazolylbenzenesulfonamide ; 4-Nitro-N-(thiazol-2-yl) benzenesulphonamide ; NFXI ;

Nisulfazole(R) (Breon) ;

It is only administered as a rectal injection as an adjunct in the local treatment of non-specific ulcerative colitis.

Dose : *10ml of a 10% suspension after each stool and at bed time.*

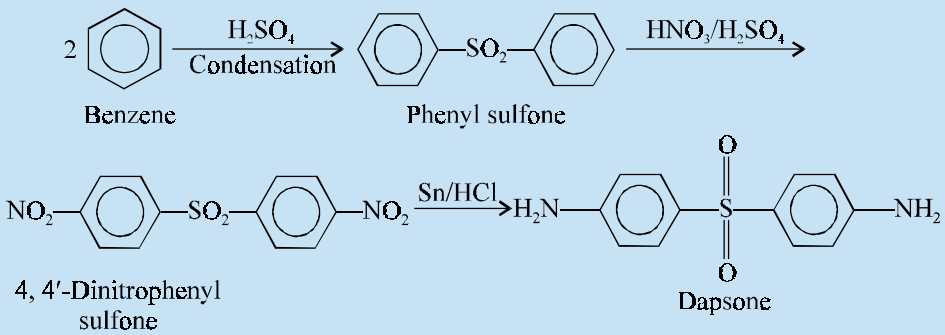
B. Dapsone BAN, USAN,



4, 4′-Sulfonyldianiline ; Benzenamine, 4, 4′-Sulfonyl *bis*- ; Diaphenylsulfone ; Disulone ; BP ; USP ; Int. P ; Ind. P ;

Avlosulfon(R) (Ayerst).

Synthesis

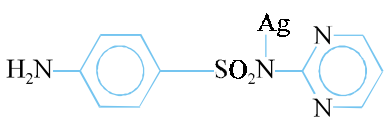


Benzene is made to condense with sulphuric acid to give phenyl sulfone, which is then nitrated and subsequently reduced to obtain **dapsone.**

It exhibits an antibacterial spectrum and mechanism of action similar to that of sulphanilamide. *It is the drug of choice in the chemotherapy of leprosy and also for the treatment of nocardiosis.* It has also been used successfully as a suppressant in the treatment of *dermatitis herpetiformis.*

Dose : *As leprostatic, 25 mg twice a week initially for one month followed by 25 mg per day each month ; As suppressant for dermatitis herpetiformis-100 to 200 mg per day.*

C. Silver Sulfadiazine USAN, Silver Sulphadiazine BAN,



N^1-2-Pyrimidinylsulfanilamide monosilver (1+) salt ; Benzene-sulfonamide, 4-amino-N-2-pyrimidinyl-, mono-silver (1+) salt ;

Flint SSD(R) (Flint) ; Silvadene(R) (Marion).

It is an effective topical antimicrobial agent, especially against *Pseudomonas species.* It finds its extensive use in burn-therapy because it attacks the *pseudomonas* radically which is perhaps considered to be the ultimate cause of failures in the treatment of burn cases.

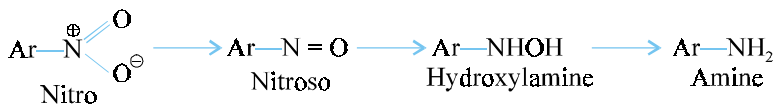
2.5.1. Mechanism of Action

The mechanism of action of compounds discussed under Section 19.2.5. shall be dealt with individually in the sections that follows :

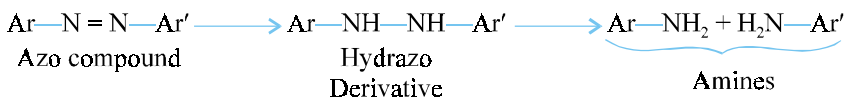
2.5.1.1. Paranitrosulfathiazole

In general, the reduction of both aromatic into and azo xenobiotics ultimately gives rise to the corresponding **primary amine metabolites.*** These reactions may be summarized explicitely in the following *two* steps :

(*a*) **Conversion of nitro-to an amine group.** An aromatic nitro compound usually get reduced initially to the nitroso and hydroxylamine intermediates, as illustrated in the following metabolic sequence :



(*b*) **Conversion of azo-to amines.** It is, however, believed that an azo reduction normally proceeds *via* a hydrazo intermediate (—NH—NH—) which subsequently gets cleaved by undergoing reduction to give rise to the corresponding aromatic amines, as depicted under :



In reality, **paranitrosulfathiazole** undergoes bioreduction by the aid of **NADPH-dependent microsomal** and **soluble nitro reductases** usually located in the liver. It has been duly observed that a multicomponent hepatic microsomal reductase system requiring **NADPH** appears to be solely responsible for the ensuing azo reduction.** Besides, the bacterial reductases normally available in the intestine may also reduce both **nitro- and azo-compounds,** particularly those that are either absorbed very poorly or excreted abundantly in the bile.***

2.5.1.2. Dapsone

The **'drug'** exerts its antibacterial spectum and mechanism of action almost identical to those of **sulfanilamide**. It is duly absorbed by the oral route. It has been observed that the absorption is more efficient with comparatively low than with high doses. It gets eliminated in the liver by acetylation. The half-life is 10 to 50 hours ; and at least 8 days are normally needed to accomplish *plateau concentrations.*

Combinations with other drugs	Therapeutic Usages
Dapsone + Rifampin Dapsone + Clofazimine	Prevention of **multibacillary leprosy**
Dapsone + Pyrimethamine	Prevention/treatment of **Malaria**
Dapsone + Trimethoprim	Treatment of *Pneumocystis carinii pneumonia* (PCP)

*Gillette JR : In Brodie BB and Gillette JR (eds.) *Concepts in Biochemical Pharmacology,* Part 2, Springer-Verlag, Berlin, 349, 1971.

Hernandez PH *et al. Biochem. Pharmacol* **16 : 1877, 1967 ; Gillette JR *et al. Mol. Pharmacol,* **4 :** 541, 1968.

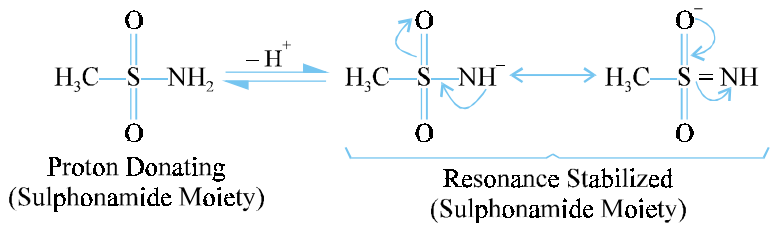
***Scheline RR : *Pharmacol Rev.* **25** : 451, 1973.

2.5.1.3. Sodium Sulfadiazine

The **'drug'** is a combination in *'one single compound'* the **antibacterial** properties of Ag^+ ion and **sulfadiazine.** It is found to be specifically effective against *Pseudomonas aeruginosa.* Although sulfadiazine gets absorbed systematically to a certain extent ; however, it is not sufficient to afford **'crystalluria formation'.** Importantly, Ag^+ ion usually inactivates proteolytic enzymes employed for **debridement** (*i.e.*, removal of foreign material and dead or damaged tissue, especially in a wound).

3. IONIZATION OF SULPHONAMIDES

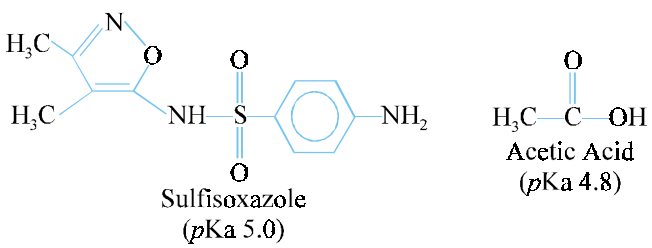
It is squarely demonstrated and established that the sulfonamide functional moiety (SO_2NH_2), has an apparent tendency to gain stability provided it happens to lose a proton, which fact is adequately substantiated as the resulting negative charge gets **resonance stabilized** ultimately as shown under :



Furthermore, it can be expatiated by considering the fact that because the proton-donating form of the functional moiety (*i.e.*, sulphonamide) bears absolutely no charge, one may even characterize the same as an HA acid, just in the same vein as *phenols, thiols* and *carboxyl* groups.

Consequently, the loss of a *'proton'* may be directly linked to a *p*K*a* value of the *'drug'* under investigation ; and, therefore, it also applies to all the structural analogoues (*i.e.*, congeners or series).

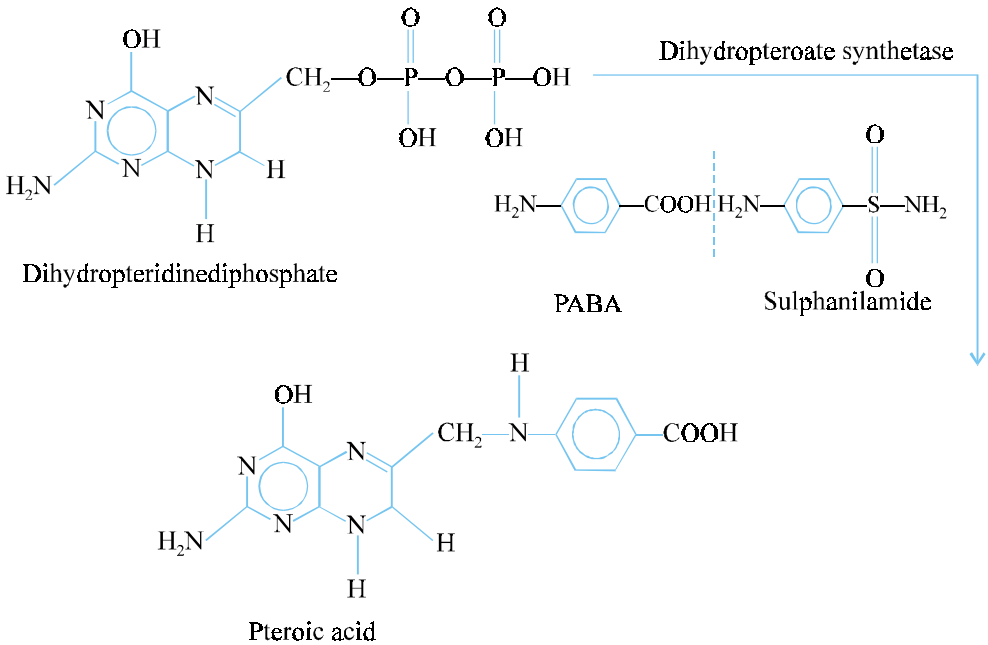
Example : Sulfisoxazole (see under Section 19.2.2.B) has a *p*K*a* value 5.0 which evidently shows that this specific sulphonamide is a slightly weaker acid in comparison to the acetic acid (p*Ka* 4.8) as shown below :



4. SULPHONAMIDE INHIBITION AND PROBABLE MECHANISMS OF BACTERIAL RESISTANCE TO SULPHONAMIDES

The coupling of **dihydropteridinediphosphate** and **PABA** to yield **pteroic acid** is catalyzed by an enzyme known as dihydropteroate synthetase, which is, in fact, inhibited by **sulphanilamide.**

The varying degree of response of organisms to **sulphanilamide-type antibacterial action** may be attributed to various factors, namely : *first*, being the different biological nature of organisms which essentially involves a quantitative difference in the capacity of the enzyme, dihydropteroate synthetase, to result **folic acid from PABA** in the presence of **sulphanilamide**. *Secondly*, it is the biological difference towards preferential permeability of the cell for some specific **sulphonamides**. Thirdly, it is due to electronic configuration and steric factors of the drugs causing the individual folic acid synthesizing together with the relative permeability of bacterial cell walls to these drugs.



5. CHEMOTHERAPEUTIC CONSIDERATION

In general, the **sulphonamides** are converted *in vitro* to N^4-acetyl analogues, a portion of which is excreted as such. It is, however, pertinent to observe here that these acetylated products have a lower *pKa* value and lower solubility than the corresponding unacetylated sulphonamides. These N^4-acetylated products have a tendency to crystalize in the renal tubules, thereby causing obstruction in the kidney and ultimately may lead to kidney damage. The degree of crystalluria formation is solely dependent on certain cardinal factors, namely : solubility of the **free sulphonamide** in the urine, degree of acetylation, solubility of the acetylated product, rate of excretion of sulphonamide and its metabolites and lastly the pH and volume of the urine excreted.

The **crystalluria formation** can be minimised by several ways : *first*, by increasing the intake of water specifically during sulphonamide therapy ; *secondly*, alkalinization of the urine by administering

sodium bicarbonate or other alkaline formulations ; and *thirdly*, by administering a mixture of two or more sulphonamides, belonging to the same category, in such quantities that none of the drugs may reach a concentration which would otherwise cause crystalluria.

Probable Questions for B. Pharm. Examinations

1. (*a*) Explain how an 'azo-dye' breaks down *in vivo* to yield sulphanilamide ?

(*b*) N1-substitution in sulphanilamide is more effective and useful than N4-substitution. Explain.

2. Classify sulphonamide on the basis of their site of action. Give the structure, chemical name and uses of **one** potent drug each class.

3. How would you synthesize sulphanilamide from :

(*a*) Acetanilide (*b*) Benzene (*c*) Sulphanilic acid.

4. Give the structure, brand name, official status and uses of :

(*a*) Sulphapyridine (*b*) Sulphathiazole (*c*) Sulphadiazine (*d*) Sulfamerazine.

Discuss the synthesis of any **two** drugs.

5. How would you synthesize the following drugs employed for urinary-tract infections :

(*a*) Sulphacetamide from sulphanilamide

(*b*) Sulfafurazole from *p*-acetamidobenzene sulphonyl chloride

(*c*) Sulfisoxazole acetyl sulfisoxazole

6. Give the structure, chemical name the uses of the following branded drugs :

(*a*) Thalazole® (*b*) Sulfauxidine® (*c*) Thalisul®.

7. Describe the synthesis of a potent sulphonamide used mostly in :

(*a*) Gas-gangrene

(*b*) Second-and third degree burns.

8. Name any **two** important members of sulphonamide related compounds that are used in chemotherapy of leprosy and burn-therapy. Discuss the synthesis of **one** medical compound.

9. Give a comprehensive account of the **'mode of action of sulphonamides'.** Support your answer with suitable examples.

10. (*a*) Enumerate briefly sulphonamide inhibition and probable mechanisms of bacterial resistance to sulphonamides.

(*b*) Write a short note on **'chemotherapeutic consideration of sulphonamides'.**

RECOMMENDED READINGS

1. AGoldstein : Antibacterial Chemotherapy, *New England J Med.* (240) (1949).

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3. EN Northey : **Sulphonamides and Allied Compounds,** *Am. Chem. Soc. Monograph.*, (1948).

4. F Hawking and JS Lawrence : **The Sulfonamides,** Grune and Stratton New York (1961).

5. FW Schuler : **Molecular Modification in Drug Design,** *Am. Chem. Soc.* Advanced in Chemistry Series No. 45, Washington. D.C. (1964).
6. H Busch and M Lane, **Chemotherapy,** Yearbook Medical Publishers Chicago (1967).
7. JK Seydel : **Molecular Basis for the Action of Chemotherapeutic Drugs, Structure-activity Studies of Sulfonamides,** Proc. III International Pharmacology Congress, Sao Paulo, Pergamon Press, New York (1966).
8. JN Delgado and WA Remers : **Wilson and Gisvold's Textbook of Organic and Medicinal Chemistry,** (11th edn.), Philadelphia, J B Lipincott Company (2004).
9. ME Wolff (ed.) : **Burger's Medicinal Chemistry and Drug Discovery,** (5th edn.), John Wiley and Sons. Inc., New York, (1995).
10. WO Foye : **Principles of Medicinal Chemistry,** (5th Edn.) Lippincott Williams and Wilkins, New York, 2002.

20

Antimalarials

Chapter

20 Antimalarials

1. INTRODUCTION

Antimalarials are chemotherapeutic agents which are used for the prevention and treatment of malaria.

Malaria is still one of the most dreadful protozoal diseases affecting man. Until recently it was of a world-wide spread. However, the disease occurs now mainly in tropical countries of the world. It is quite painful and distressing to know that more than one million people die of malaria each year and most of these people belong to the third world countries. Malaria has been eradicated from the developed countries as a result of the **Malaria Eradication Programme** of the **World Health Organization (WHO).** This was achieved through improved living conditions, use of insecticides, destruction of breeding places for mosquitoes and use of antimalarials as prophylactic agents. Similar efforts in developing countries have not yielded good results.

The causal organisms responsible for malaria belong to the genus *plasmodium* which is of the class of protozoa known as **sporozoa.** There are four different species which are accepted as being responsible for human malaria. These are *Plasmodium malariae,* the parasite of *quartan malaria ; Plasmodium vivax,* the parasite of benign *tertian malaria, Plasmodium falciparum,* the parasite of *malignant* or *subtertian malaria,* and *Plasmodium ovale,* the parasite that causes a mild type of *tertian malaria.*

These protozoa have complex life cycles embodying both the female anopheles mosquito and the liver and the erythrocyte of the human host. Hence, an ideal antimalarial must be able to exert an effect on two fronts simultaneously, namely : to eradicate the microzoan from the blood and also from the tissues, in order to produce an effectife **'radical cure'.** It has been established beyond reasonable doubt that the various **antimalarials** differ essentially in their point of interruption of the cycle of the parasite and, therefore, the stages of the infection that is effected.

In actual practice, there are *three* well recognized and predominant manners to control malaria effectively, namely ;

(*a*) Elimination of the vector*,

(*b*) Drug therapy, and

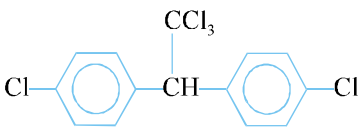
(*c*) Vaccination.

*A carrier, usually an insect or other arthropod, that transmits the causative organisms of disease from infected to non infected individuals, especially one in which the organism goes through one or more stages in its life-cycle.

Elimination of the Vector. Currently, the elimination of the vector is considered to be one of the easiest and most cost-effective measure adopted across the globe.

In fact, there are *two* different ways to control the **'mosquito carrier'.** *First,* being check and prevent the usual contact usually taking place between the insect and the human beings. It is, however, pertinent to observe here that the **Anopheles mosquito** happens to be a **nocturnal feeder** ; and, therefore, it is relatively much easier to control than the corresponding **Aedes aegypti mosquito** which is a *day feeder* and is responsible solely for carrying **dengue** as well as **yellow fever** (prevalent in the African continent). Simply by installing nylon or iron screens on widows and using mosquito netting (at night while sleeping) in bed-rooms may provide an effective measure of prevention. *Secondly,* the elimination of the **Anopheles mosquito**, normally by total erradication by the application of *insecticide* and drastically destroying the breeding hide-outs, is believed to be one of the most practical ways to eliminate (as opposed to control) malaria.

Examples : Dichloro diphenyl trichloroethane (DDT) an insecticide discovered by the Nobel laureate Dr. Muller (1948), almost kills the malaria-carrying **Anopheles mosquito** completely. Though its *long lasting* effect is eventually very much beneficial from the standpoint of Anopheles mosquito control, but it gets accumulated in the environment unfortunately that may ultimately gain entry into the **food chain** and can affect both **humans** and **animals** equally. Hence, the use of **DDT** has been banned completely by **FDA, WHO** and other law enforcing authorities ; and duly replaced by other **'safer insecticides'.**



DDT

Drug Therapy. A host of **'drug substances'** either isolated from the **plant sources,** such as : **quinine ; quinidine, cinchonine, cinchonidine, artimisinine ;** or **synthetic compounds** for instance : **chloroquine, paludrine, pamaquine** etc., are being used profusely in topical countries to fight the menace of malaria as the *'life-saving drugs'*. It is worth noting at this juncture that the currently employed **'antimalarials',** while being effective against certain species, also exhibit certain adverse reactions, and noticeable resistance is enhancing also progressively.

Vaccination. Inspite of the tremendous impetus and thrust instituted legitimately by **WHO,** the dream of developing an effective, safer, economically viable **'antimalarial vaccine'** is yet to be discovered to combat the human sufferings, more specifically the rate of infant mortality in economically less privileged and developed countries of the world.

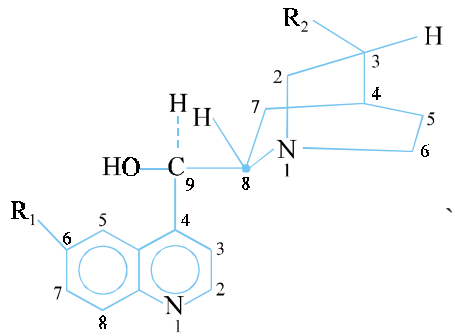
It has been duly observed that the **malaria parasite** does elicit obviously an immune-response, demonstrated by virtue of the fact that usually the children, in particular, having an initial exposure are more prone to die than the adults who have since experienced/exposed to several recurring attacks.

Besides, a **T-cell response** which essentially comprise of both **$CD4^+$ and $CD8^+$ T-cells,** production of **interferon gamma,** and **nitric oxide synthase** induction serves as an additional proof of evidence that the **human-immune system** is *able to detect the parasite and hence responds accordingly.**

A plethora of chemotherapeutic agents having divergent chemical structures have been introduced clinically since the mid-twenties, *e.g.*, **pamaquine (1926), quinacrine (1930).** Although historical evidence of **cinchona** dates back to 1638 when it was used to treat **Countess of Cinchona,** wife of the

*Pombo DJ *et al. Lancet,* **360** : 610, 2002.

then governor of Peru, and hence the name. Later on, in 1820, Polletier and Caventou succeeded in the isolation of quinine from the circhona bark. Now, more than twenty-five alkaloids from the circhona bark have been characterized, out of which only a few are useful clinically, *viz.*, **quinine, quinidine, cinchonine, cinchonidine.**



Quinine : $R_1 = OCH_3$; $R_2 = -CH = CH_2$; (–) 8S : 9R isomer

Quinidine : $R_1 = OCH_3$: $R_2 = -CH = CH_2$; (+) 8R : 9S isomer

Cinchonine : $R_1 = H$; $R_2 = -CH = CH_2$; (+) 8R : 9S isomer

Cinchonidine : $R_1 = H$; $R_2 = -CH = CH_2$; (–) 8S : 9R isomer

All these alkaloids bearing the same substitution at R_1 and R_2 are essentially **diastereoisomers,** only having different configuration at the *third and fourth chiral centres (C-8 and C-9).*

Soon after the Second World War (1943), a large number of compounds were synthesized and tested for **antimalarial** actions, and these eventually gave birth to a host of potent drugs like, **chloroquine, proguanil, comoquine and amodiaquine,** etc.

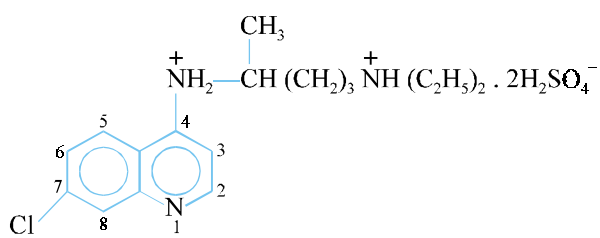
2. CLASSIFICATION

The **antimalarials** may be classified on the basis of their basic chemical nucleus as stated below and some representative examples belonging to each class are given.

2.1. 4-Aminoquinoline Analogues

In 1942, a group of German researchers first reported that 4-, 6- and 8-aminoquinolines when duly substituted produced **antimalarial agents**. An extensive research in East and West was augmented due to the acute shortage of cinchona bark during the Second World War. These drugs are found to be active against the erythrocytic form of most malarial parasites ultimately affecting a clinical cure. They do not cause prevention of the disease, and they are inactive against the liver-infecting forms.

A. Chloroquine Phosphate BAN, USAN, Chloroquine INN,



7-Chloro-4-[[4-(diethylamino)-1-methyl] butyl] amino]-quinoline phosphate (1:2) ; 1, 4-Pentanediamine, N^4-(7-chloro-4-quinolinyl)-N^1, N^1-diethyl-, phosphate (1:2) ; Resochin ; BP ; USP ; Int. P., Ind. P. ;

Aralen(R) (Winthrop).

Synthesis

It is prepared by adopting the following *four* steps *viz.*,

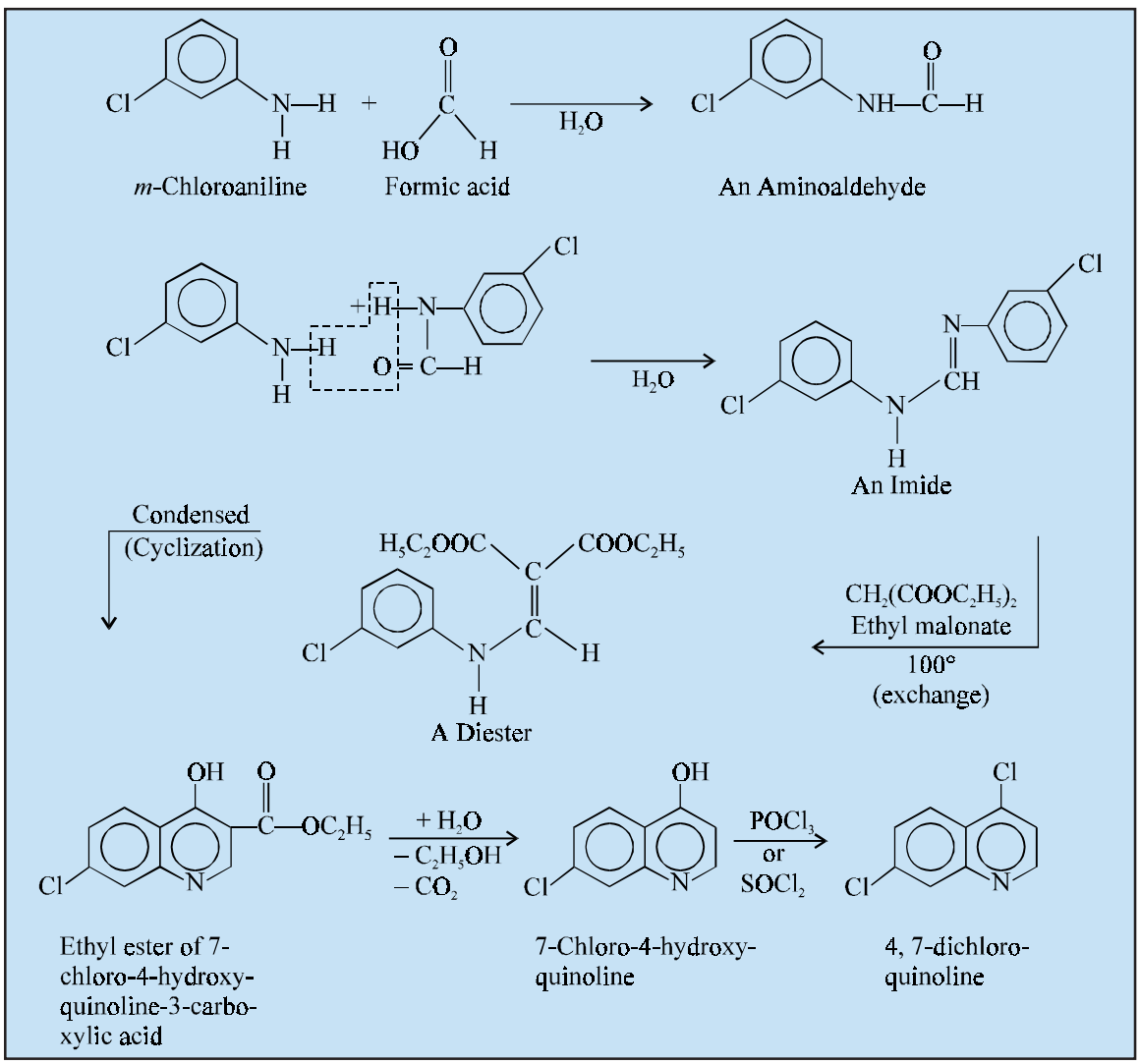
(*a*) Preparation of 4, 7-Dichloroquinoline (*i.e.*, the nucleus)

(*b*) Preparation of 2-amino-5-diethyl amino pentane, or 1-diethylamino-4-amino pentane (*i.e.*, the side chain).

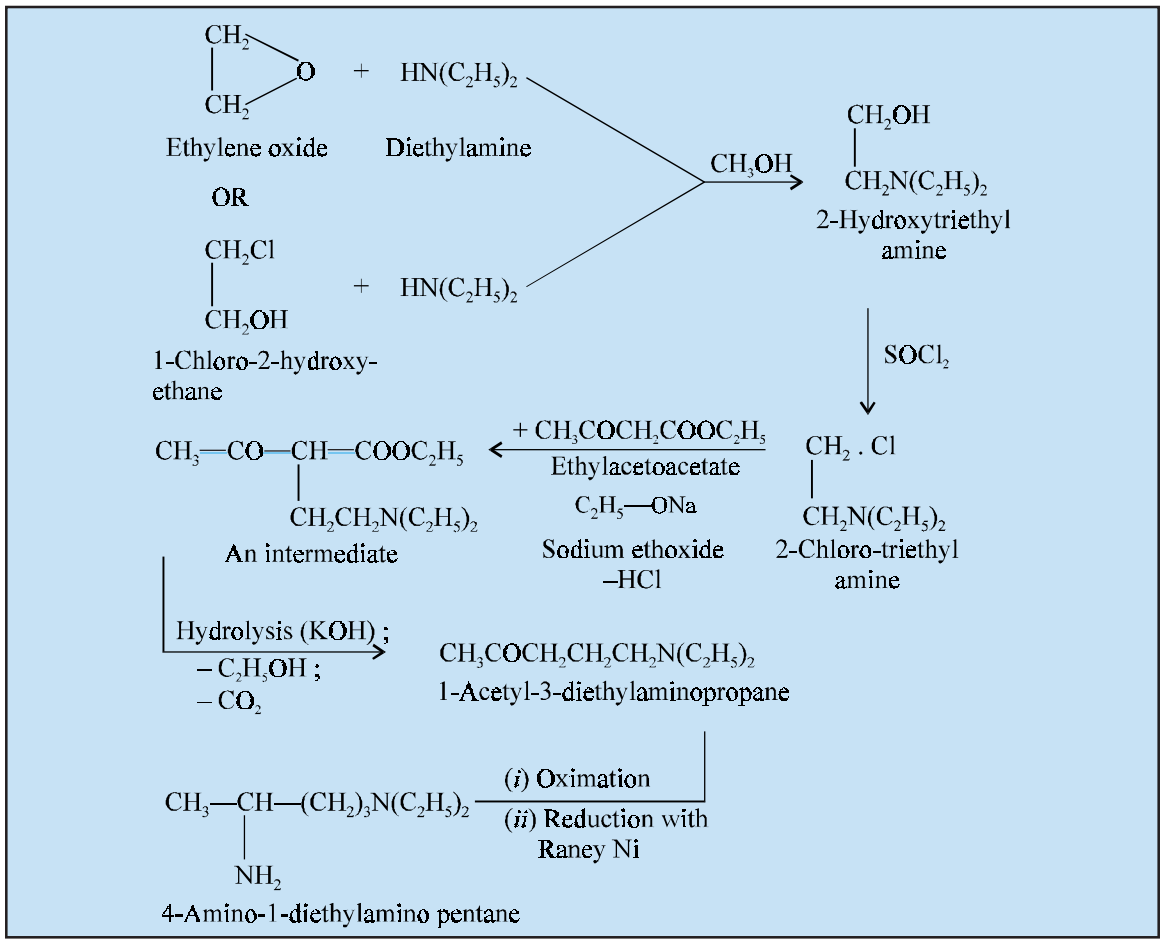
(*c*) Condensation of '*a*' and '*b*'.

(*d*) Addition of concentrated phosphoric acid to a hot ethanolic solution of the condensed product.

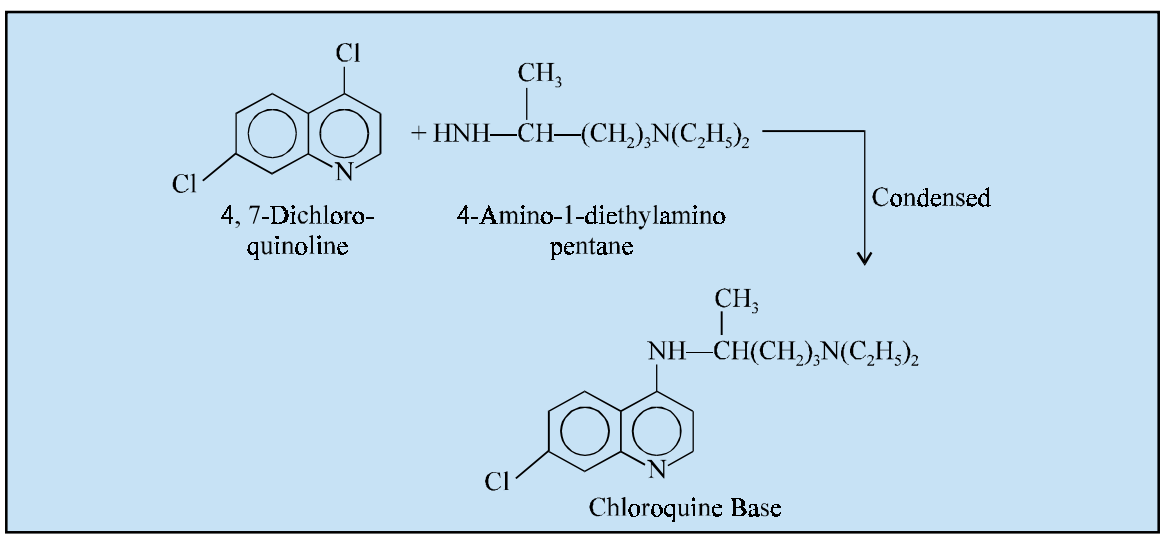
(*a*) **Preparation of Nucleus**



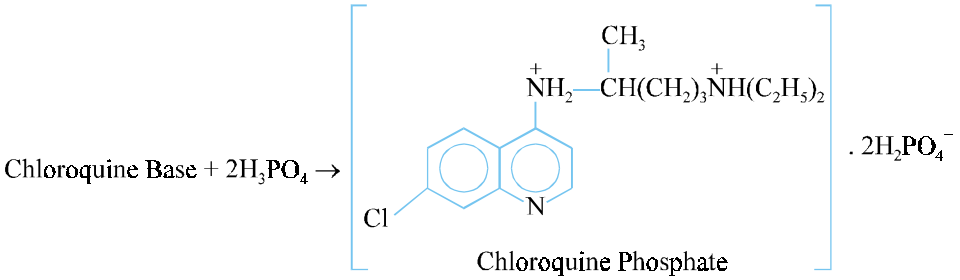
(*b*) **Preparation of Side Chain**



(*c*) **Condensation of (*a*) and (*b*)**



(*d*) **Preparation of Phosphate Salt**



Reaction between two moles of *m*-chloroaniline and a mole of formic acid yields an imidine which on treatment with ethyl malonate at 100° undergoes exchange and results into a diester. This further undergoes cyclization through condensation to yield the corresponding ethyl ester of 7-chloro-4-hydroxy-quinoline-3-carboxylic acid which on hydrolysis gives 7-chloro-4-hydroxy quinoline. Finally, on chlorination with either phosphorus oxychloride or thionyl chloride yields the nucleus 4, 7-dichloro quinoline.

The side chain is prepared by the interaction between either ethylene oxide or 1-chloro-2-hydroxy ethane with diethyl amine in methanol yields 2-hydroxy-triethyl hydrochloride. This on chlorination with thionyl chloride yields 2-chloro-triethyl amine which on treatment with ethyl aceto-acetate in the presence of sodium ethoxide gives an intermediate compound. Alkaline hydrolysis produces 1-acetyl-3-diethylamino propane which on reduction with **Raney Nickel** followed by oximation yields 4-amino-1-diethylamino pentane.

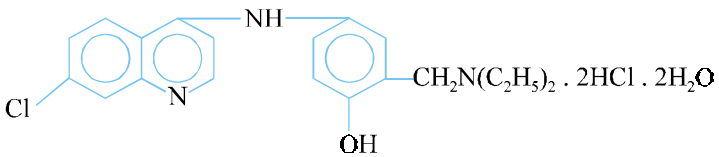
Condensation of the nucleus and the side chain gives rise to the **chloroquine base** which on treatment with hot phosphoric acid in an ethanolic solution yields the official compound.

Chloroquine is extensively employed for the suppression and treatment of malaria. *It has been found to exert a quick schizonticidal effect and seems to affect cell growth by interfering with DNA.*The overall activity of chloroquine appears to be partially dependent on the preferential accumulation in the infected erythrocyte. It has been observed that *it specifically kills the erythrocytic forms of all malaria parasites at all states of development, but has no effect on the malaria parasite in the human liver cells. Hence, chloroquine produces complete cure of malaria caused by P. falciparum.* It fails to check the relapse caused by the secondary exoerythrocytic phase of *P. malariae, P. ovale and P. vivax.*

Dose : *As prophylactic, suppressive, 500 mg once per week ; therapeutic, initially, 1 g, followed by 500 mg in 6 hours, and 500 mg on the 2nd and 3rd days.*

Chloroquine sulphate is another salt of **chloroquine [Nivaquin(R), May & Baker]** which possesses almost similar actions to those of **resochin.**

B. Amodiaquine Hydrochloride BAN, USAN, Amodiaquine INN,



4-[(7-Chloro-4-quinolyl) amino]-α-(diethylamino)-*o*-cresol dihydrochloride dihydrate ; Phenol, 4-[(7-Chloro-4-quinolyl)-amino]-2-[(diethylamino) methyl]-dihydrochloride, dihydrate, Amodiachin Hydrochloride ; BP ; USP ; Int. P ; Ind. P ;

Camoquin(R) (Parke-Davis).

Synthesis

It consists of the preparation of :

(*i*) 4, 7-Dichloroquinoline (*i.e.*, nucleus),

(*ii*) 4-Amino-2-diethylaminomethyl phenol,

(*iii*) Condensation of (*i*) and (*ii*),

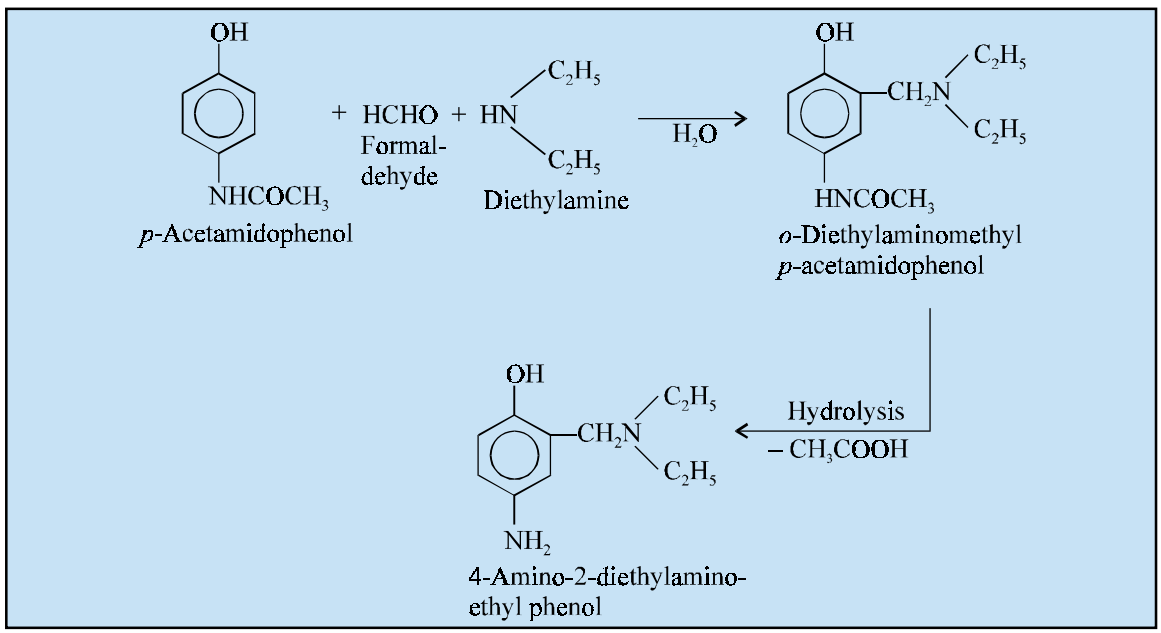
(*iv*) Formation of hydrochloride salt.

(*a*) *Preparation of 4, 7-dichloroquinoline nucleus.* It is prepared as described under chloroquine phosphate earlier.

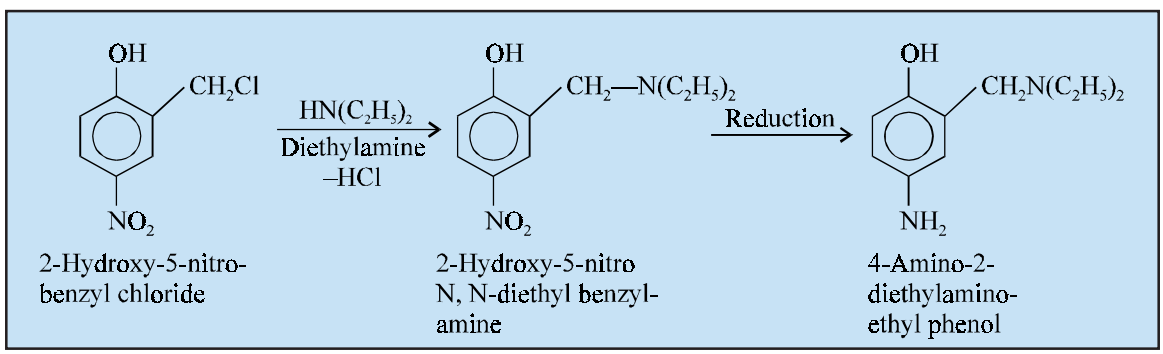
(*b*) *Preparation of the side chain 4-amino-2-diethylamino-ethyl phenol* : It may be prepared by two methods as described below :

Method-I : From p-Acetamido phenol

o-Diethylaminomethyl-*p*-acetamidophenol is prepared by the interaction of *p*-acetamidophenol, formaldehyde and diethyl amine with the elimination of a molecule of water. Hydrolysis of this product yields 4-amino-2-diethylamino ethyl phenol with the elimination of a mole of acetic acid.

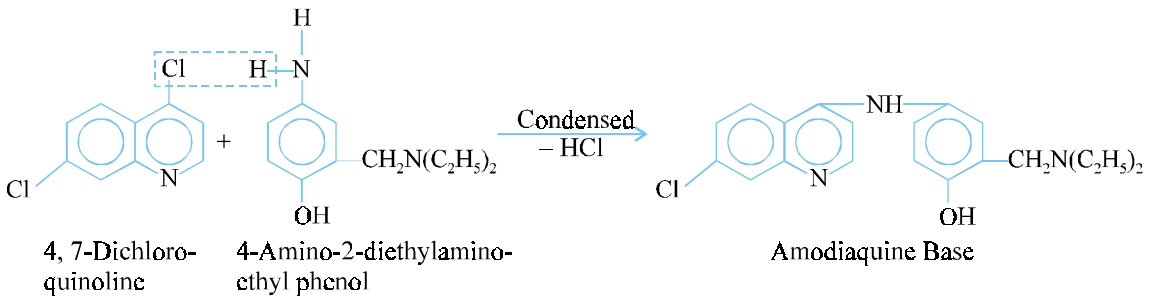


Method-II : From 2-Hydroxy-5-nitrobenzyl chloride



The reaction between 2-hydroxy-5-nitro-benzyl chloride with diethylamine yields 2-hydroxy-5-nitro-N, N, diethyl benzyl amine, which on reduction gives 5-amino-2-diethylamino ethyl phenol.

(*c*) **Condensation of (*a*) and (*b*), we have :**



4, 7-Dichloro-quinoline — 4-Amino-2-diethylamino-ethyl phenol — Amodiaquine Base

(*d*) **Preparation of Hydrochloride Salt :**

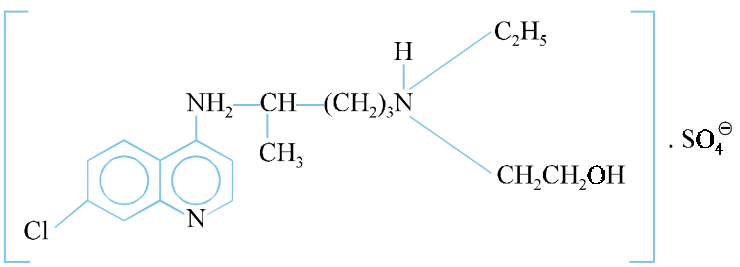
$$\text{Amodiaquine Base} \xrightarrow{\text{HCl}} \text{Amodiaquine Hydrochloride}$$

The condensation of the nucleus and the side chain prepared above in (*a*) and (*b*) gives the amodiaquine base which on neutralization with hydrochloric acid yields the official compound.

Its antimalarial action is very much similar to that of chloroquine and hence may be used alternatively for the same purpose.

Dose : *Initially, 600 mg of base followed by 300 mg doses 6, 24, 48 hours later.*

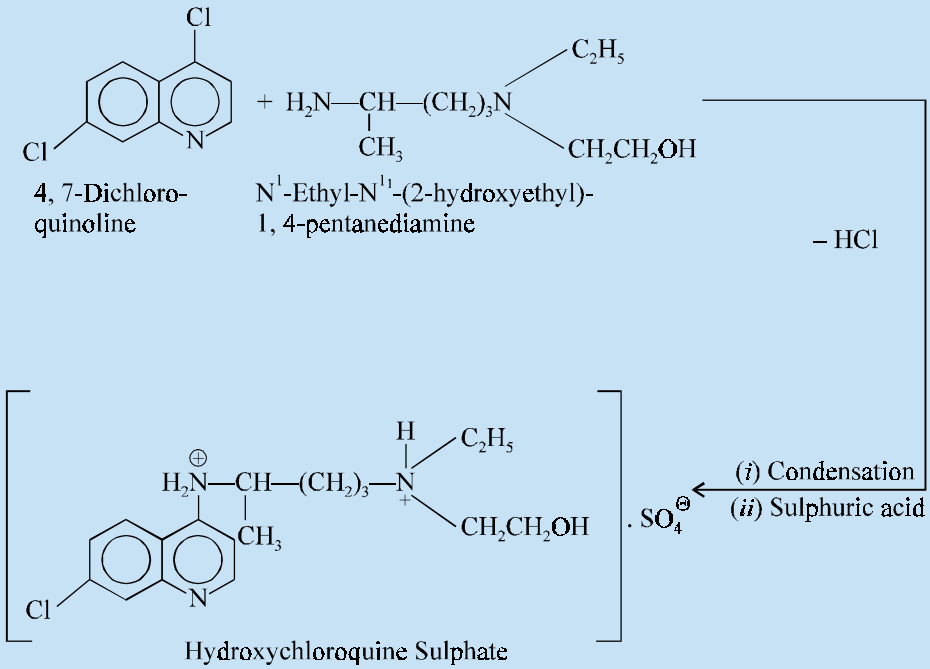
C. Hydroxychloroquine Sulphate BAN, Hydroxychloroquine Sulfate USAN,



2-[[4-(7-Chloro-4-quinolyl] amino] pentyl] ethylamino] ethanol sulphate (1:1) (salt) ; Ethanol, 2-[[4-(7-chloro-4-quinolyl) amino]-pentyl] ethylamino]-, sulphate (1:1) salt ; Oxichlorochin Sulphate ; Hydrochloroquine Sulphate BP ; Hydroxychloroquine Sulfate USP ;

Plaquenil Sulfate$^{(R)}$ (Winthrop).

Synthesis

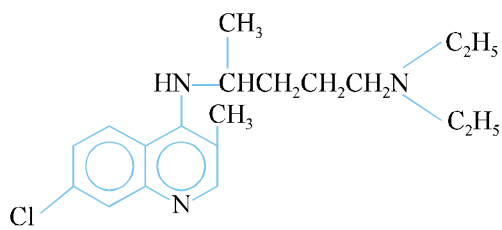


It may be prepared by the condensation of 4, 7-dichloro quinoline and N^1-ethyl-N^1-(2-hydroxyethyl)-1, 4-pentanediamine and dissolving the resulting **hydroxychloroquine base** in absolute ethanol. The coversion to the corresponding sulphate is achieved by treating with an equimolar portion of sulphuric acid.

Its actions and uses are similar to those of **chloroquine**. Owing to its specific action on the erythrocytic phase of the malaria parasite it fails to serve as a 'radical cure' for *P. vivax* infections. *It also finds its clinical usefulness in the treatment of rheumatoid arthritis and lupus erythematosus.*

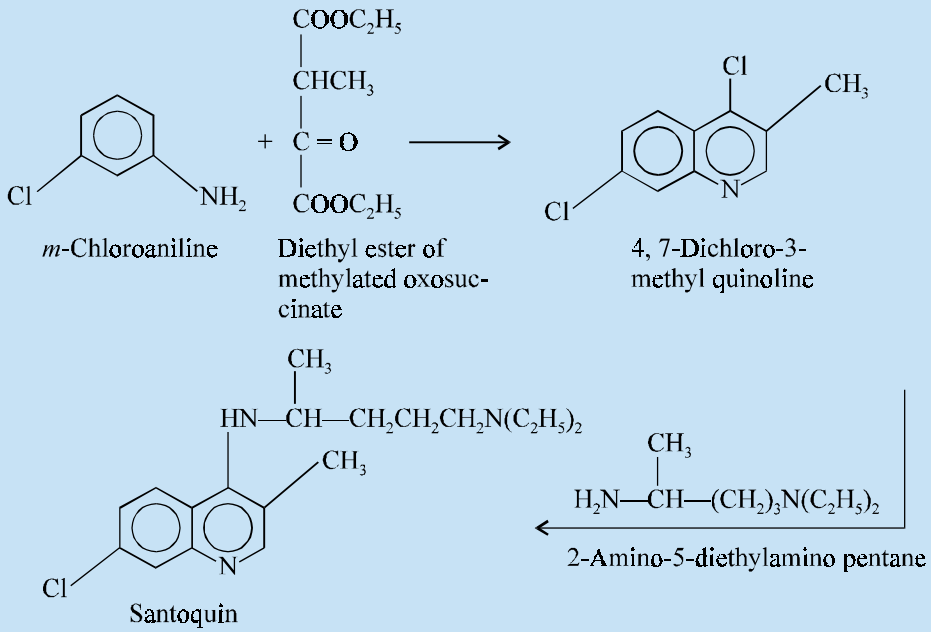
Dose : *In P. falciparum infections, 1.25 g in a single dose or in 2 divided doses at 6-hour intervals ; in rheumatoid arthritis, 400 mg daily ; in lupus erythematosus, 200 to 400 mg 1 or 2 times daily.*

D. Santoquin



7-Chloro-4-{[4-(diethylamino)-1-methylbutyl]-amino}-3-methylquinoline.

Synthesis



4, 7-Dichloro-3-methylquinoline is prepared by the interaction of *m*-chloroaniline and diethyl ester of methylated oxosuccinate which on treatment with 2-amino-5-diethyl-amino pentane affords santoquin.

It has an additional methyl group at C-3 in the quinoline nucleus of **chloroquine**. It is found to be less reactive than **chloroquine**.

2.1.1. Mechanism of Action

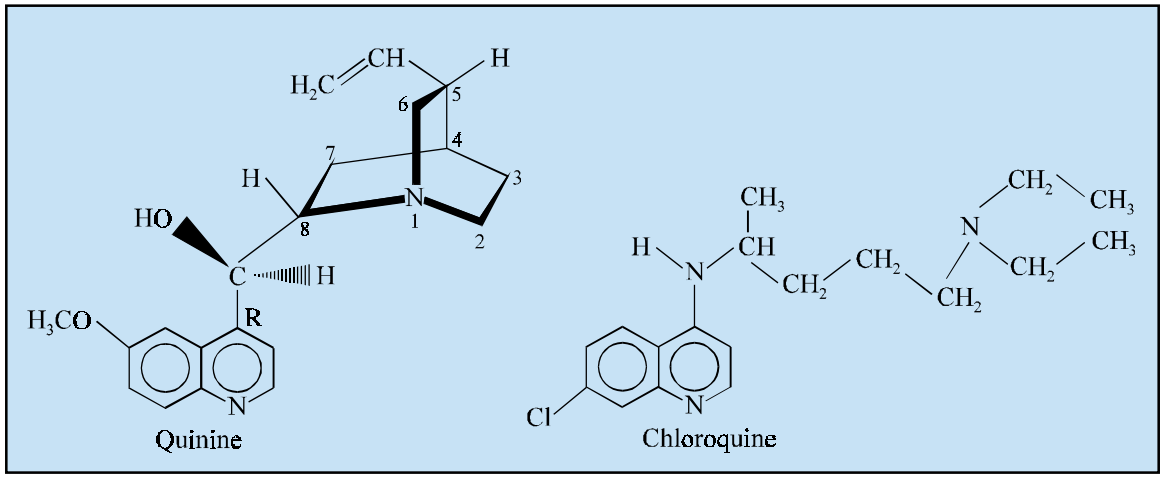
The mechanism of action of the four compounds described under Section 20.2.1 shall be dealt with individually in the sections that follows :

2.1.1.1. Chloroquine Phosphate

The **'drug'** particularly causes significant dysfunction of the *acid phagosomes in plasmodia* and also in human leukocytes and macrophages. It is neither a prophylactic nor a radical curative agent in vivax malaria. Interestingly, in regions wherein *Plasmodium falciparum* is invariably sensitive to chloroquine, it is specifically and predominantly effective in terminating acute attacks of **non-resistant falciparum malaria ;** and, therefore, normally affords total cure in this type of malaria. As **chloroquine** is well tolerated, it has been recommended to be used rountinely in **amebiasis** *without any demonstrable hepatic involvement.*

The **'drug'** usually gets absorbed almost completely from the GI tract when administered orally. The parenteral IM administraction is usually given with its HCl-salt. It has also been observed that the tissues bind the drug, but not to the same extent as that of **quinacrine**. It gets degraded in tissues to unknown products.

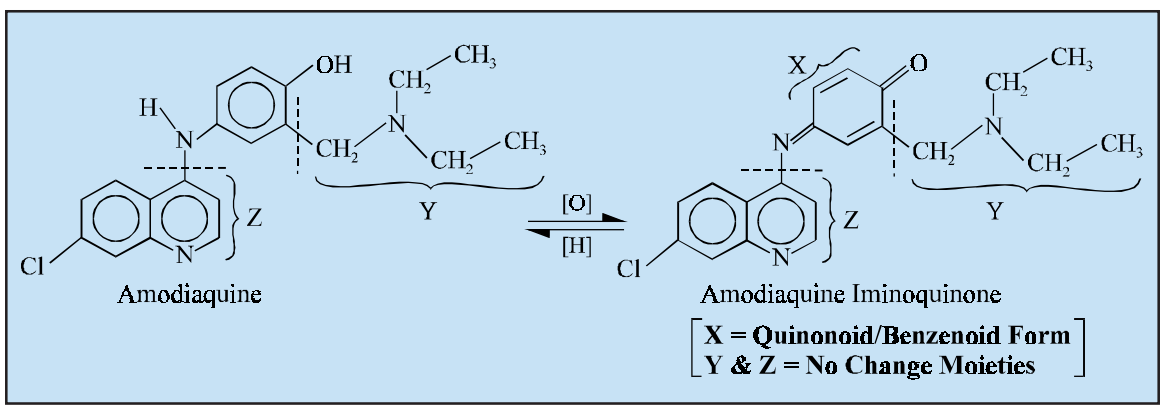
SAR of chloroquine. It may be regarded as the **prototypical** structure which overwhelmingly succeeded **'quinine'** and recognized as a potential **'synthetic antimalarial drug'** since the mid-1940s, as shown below :



2.1.1.2. Amodiaquine Hydrochloride

The **'drug'** resembles very similar to **chloroquine** mechanistically ; and it does not possess any added advantages over the other **4-aminoquinoline drugs**. It has been demonstrated amply that the **hydroquinone (phenol) amine system** rapidly gets oxidized to a corresponding **quinone-imine system,** either accomplished *via* **antioxidatively** and/or **metabolically ;** and the resulting product may be solely responsible for the ensuing **amodiaquine toxicity.**

Note : The quinine-imine system is almost identical to the acetaminophen (paracetamol) toxic metabolite.



In other words, **amodiaquine** upon oxidation gets converted to its *ketone-form* termed as **amodiaquine iminoquinone** which essentially embodies in it a quinonoid/benzenoid moiety.

2.1.1.3. Hydroxychloroquine Sulfate

The **'drug'** exerts its action exclusively in the *suppressive treatment* of **autoimmune inflammatory** diseases, for instance : *rheumatoid arthritis* (RA) and *systemic lupus erythromatosus* (SLS). Just like **chloroquine (CQ),** this **'drug' (HCQ)** is found to remain in the body for over a month and the prophylactic dosage is once-*a*-week only. It is somewhat less toxic than **CQ**.

SAR of HCQ. Structurally, it essentially differs exclusively in having an additional hydroxy (OH) moiety strategically attached to one of the terminal N-ethyl functions which eventually renders it less toxic than **CQ** perhaps due to H-bonding *in vivo.*

2.1.1.4. Sontoquine

The **'drug'** is found to be effective against **amaebic hepatitis** in *man* as well as *hamsters*. Unfortunately, the drug fails to show any specifically promising activity against the intestinal infections, most probably by virtue of the fact that it gets rapidly absorbed and do not reach the *lower intesine zone* in an effective therapeutic concentrations.

2.2. 8-Aminoquinoline Analogues

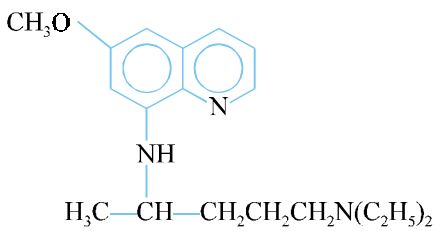
These structural analogues, unlike **4-aminoquinolines** offer a rather more significant derivative from the basic quinine moiety. From the structural aspect these drugs seem to be optimally substituted as evidenced by the presence of a side-chain consisting of 4 to 6-carbon atoms as well as the location of methoxy group at C-6. In general, the **8-aminoquinoline analogues** are relatively more toxic than the **4-aminoquinoline counterparts**.

They are active against the pre- or exoerythrocytic form of the malarial parasite, but lack activity against the erythrocytic forms. The 8-amino-quinolines possess gametocidal activity. They are used mainly for the radical cure of relapsing malaria like vivax malaria.

A few classical examples belonging to this category are discussed below :

Pamaquine ; Primaquine phosphate ; Pentaquine phosphate ; Isopentaquine and Quinocide hydrochloride.

A. Pamaquine INN, Pamaquin BAN, Pamaquine Naphthoate USAN,



8-(4-Diethylamino-1-methylbutylamino)-6-methoxyquinoline ; Pamachin ; Pamaquine Embonate ; Plasmoquinum ; BP ; 1953, NF IX.

Synthesis

It consists of the preparation of :

(*a*) 4-amino-diethylamino pentane, *i.e.*, side-chain,

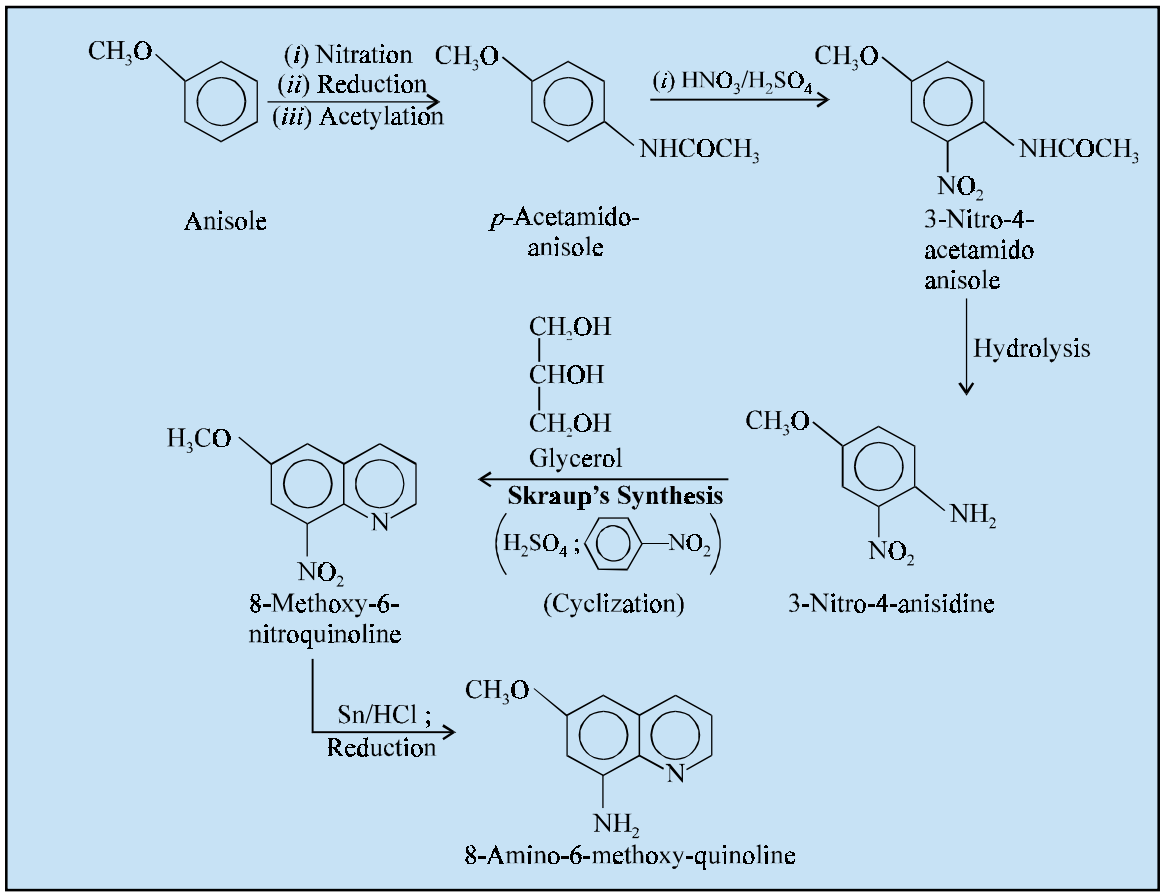
(*b*) 8-amino-6-methoxy quinoline, *i.e.*, quinoline nucleus,

(*c*) Condensation of (*a*) and (*b*).

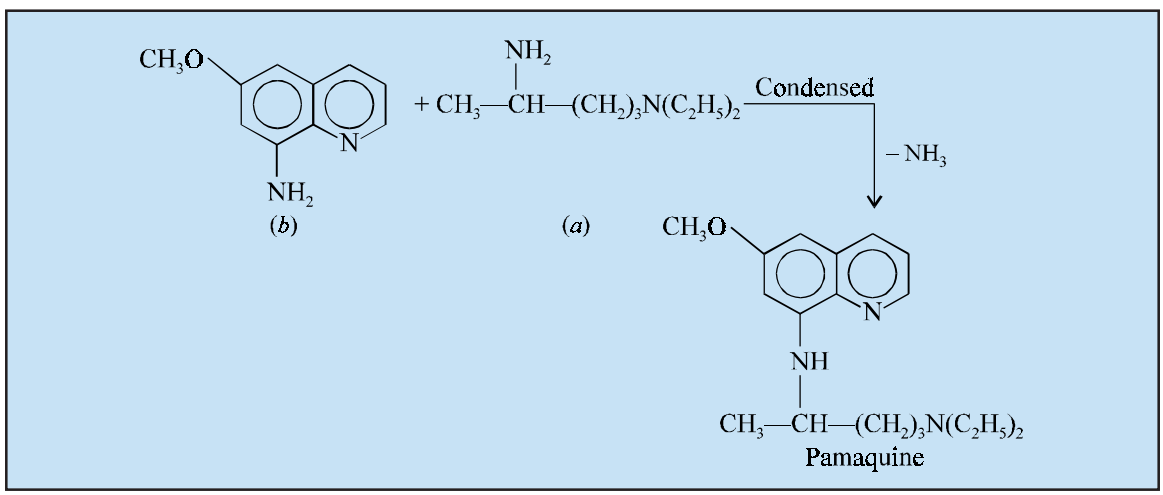
(*a*) *Preparation of Side-Chain*

It has been described earlier under chloroquine phosphate.

(*b*) **Preparation of Quinoline Nucleus**

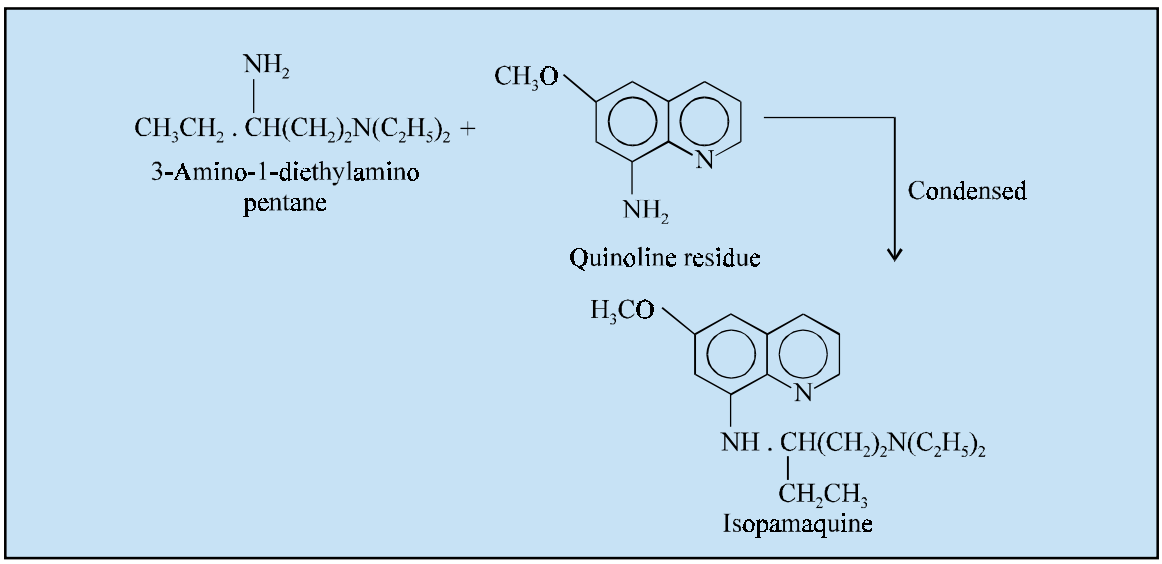


(*c*) **Condensation of (*a*) and (*b*)**



p-Acetamido anisole may be prepared by the sequential nitration, reduction and acetylation of anisole which on further nitration yields 3-nitro-4-acetamido anisole. This on hydrolysis gives 3-nitro-4-anisidine which on treatment with glycerol in the presence of concentrated sulphuric acid and nitrobenzene undergoes cyclization through **Skraup's synthesis** to yield 8-methoxy-6-nitro quinoline. Reduction of the resulting product gives rise to 8-amino-6-methoxy quinoline. Condensation of this quinoline residue with 4-amino-1-diethylamino pentane forms **pamaquine**.

Craig (1944) first discovered the presence of an isomeric form of pamaquine known as **isopamaquine,** in the commercial sample of pamaquine. The evolution of isopamaquine may be logically explained on the basis of the fact that the oximation of the amino alcohol obtained from the reduction of 1-acetyl-3-diethylamino propane actually gives rise to 4-amino-1-diethylamino pentane as major product together with 3-amino-1-diethylamino pentane as minor product. The latter product then condenses with 8-amino-6-methoxy quinoline to yield **isopamaquine** as given below :



The antimalarial activity of **isopamaquine** and **pamaquine** are fairly identical.

Toptchiev and Braude, in 1947, put forward a modified synthesis for **pamaquine** which consists of the following steps, namely :

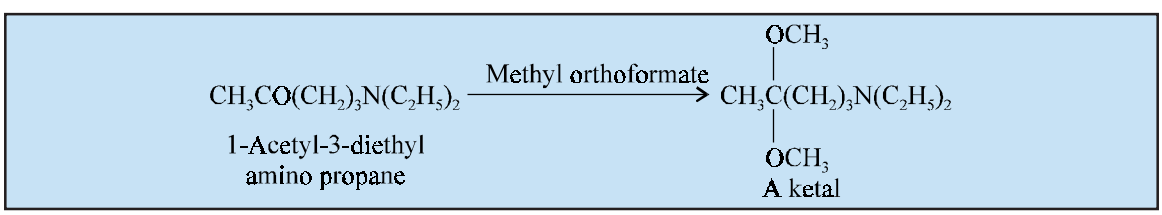
(*a*) Preparation of a ketal from 1-acetyl-3-diethyl amino propane

(*b*) Preparation of 8-amino-6-methoxy quinoline

(*c*) Condensation of (*a*) and (*b*)

(*d*) Reduction of the condensed product.

(*a*) **Preparation of a Ketal**

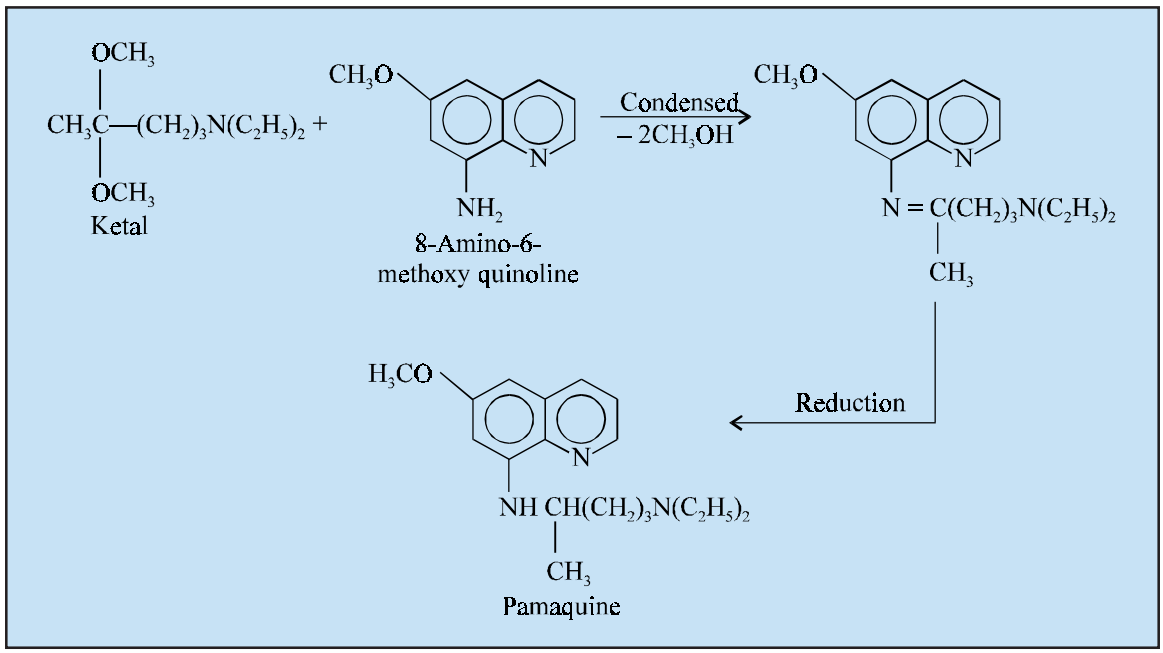


The starting compound is prepared by the method described earlier for the preparation of the side chain, which on treatment with methyl orthoformate yields a ketal.

(*b*) **Preparation of quinoline residue**

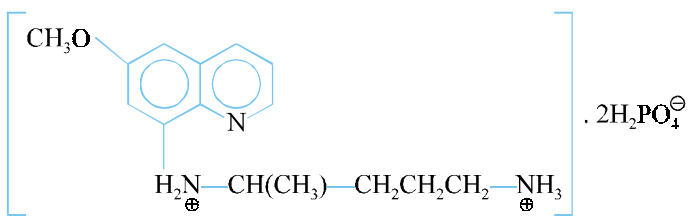
It is same as described under pamaquine.

(*c*) **Condensation of (*a*) and (*b*) ; and (*d*) Reduction.**



Pamaquine was initially employed for the treatment of malaria but has since been superseded by primaquine phosphate.

B. Primaquine Phosphate, BAN, USAN, Primaquine INN,

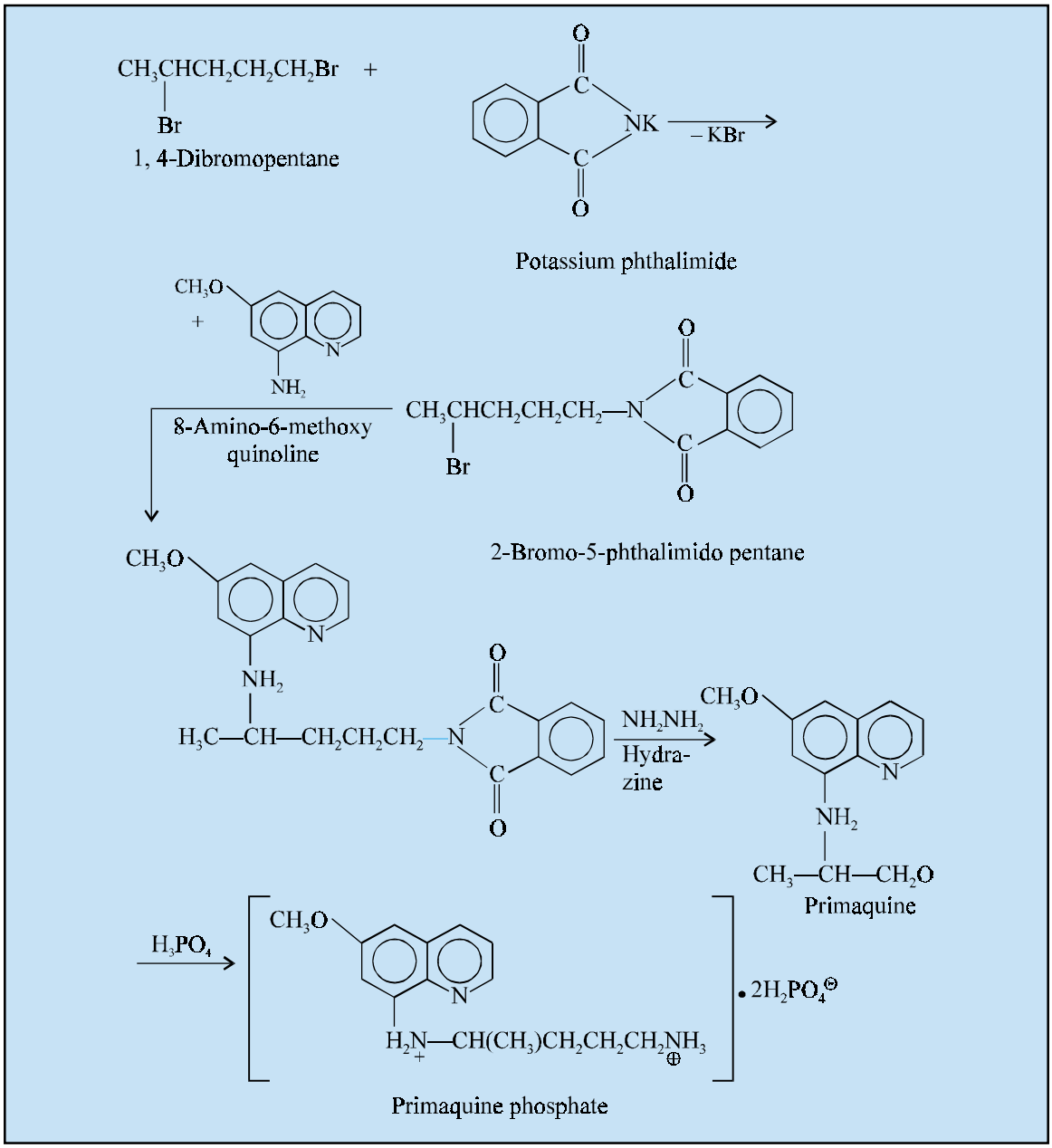


8-[(4-Amino-1-methylbutyl) amino]-6-methoxy quinoline phosphate (1:2) ; 1, 4-Pentanediamine, N^4-(6-methoxy-8-quinolyl)-, phosphate (1:2) ; Primachin phosphate ; BP ; USP ; Int. P. ; Primaquine Phosphate(R) (ICI Pharmaceuticals, U.K.)

Synthesis

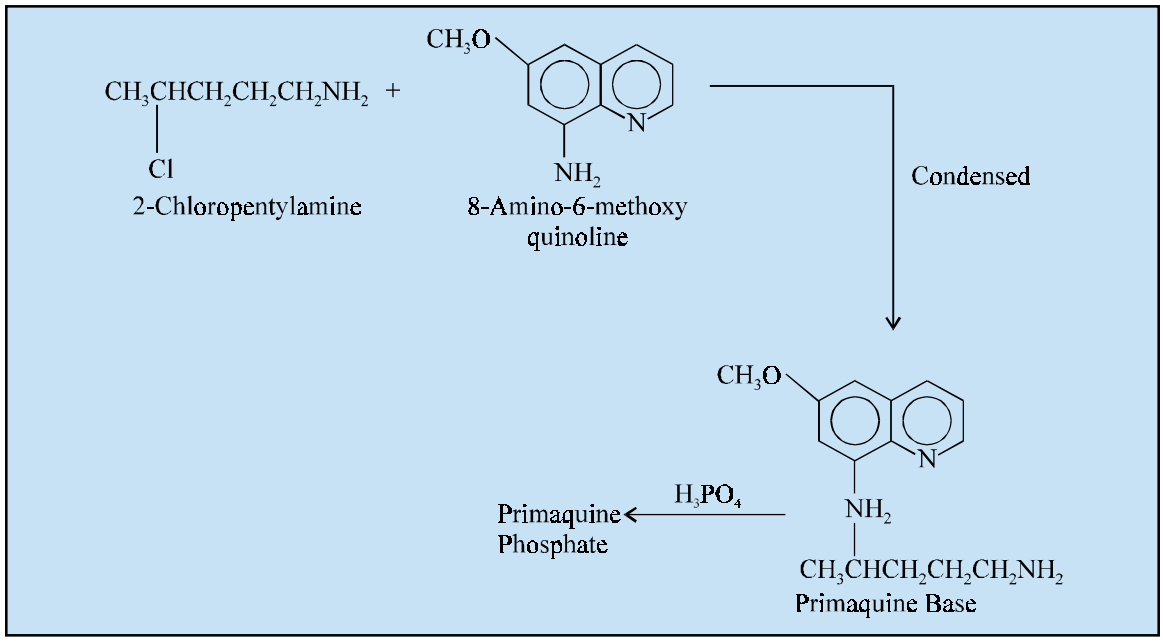
The synthesis of **primaquine phosphate** may be accomplished by either of the *two* following methods :

Method-I ; Elderfield's Method from 1, 4-Dibromopentane



2-Bromo-5-phthalimido pentane is prepared by the interaction of 1, 4-dibromopentane with potassium phthalimide, which on reaction with 8-amino-6-methoxy quinoline yields the condensed product. Further treatment with hydrazine eliminates the phthalimido residue and yields the **primaquine base** which on reaction with a double molar quantity of phosphoric acid forms the official compound.

Method-II. From 2-Chloropentylamine

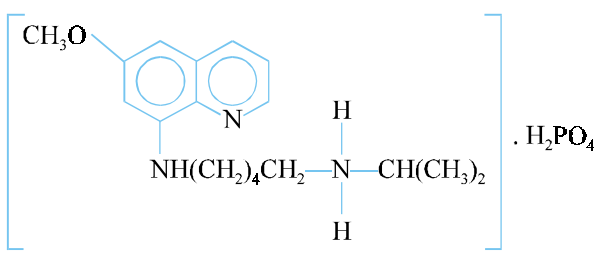


It may also be prepared by the condensation of 2-chloro-pentylamine with 8-amino-6-methoxy quinoline to obtain primaquine base which on treatment with bimolar quantity of phosphoric acid yields **primaquine phosphate**.

It is an **antimalarial drug** which *specifically kills the primary exoerythrocytic stages of P. vivax, P. falciparum, P. malariae and P. ovale, and the secondary exoerythrocytic form of all except P. falciparum,* which has no secondary forms. It is extensively used for the radical cure of relapsing vivax malaria, but is not normally employed either for arresting the severe attacks of the disease or for suppressive therapy. It invariably kills gametocytes of all species, or inhibits their growth and development in the mosquito. *It fails to produce any significant effect on other erythrocytic stages and hence it must not be employed alone for the treatment of malaria.*

Dose : *17.5 to 26.3 mg (10 to 15 mg of base) once daily for 14 days.*

C. Pentaquine Phosphate BAN, USAN, Pentaquine INN,



8-(5-Isopropylaminoamylamino)-6-methoxy quinoline phosphate ; 8-(5-Isopropylaminopentyl-amino)-6-methoxyquinoline phosphate. USP ; XIV.

Synthesis :

It consists of the preparation of :

(*a*) 8-Amino-6-methoxy quinoline

(*b*) 1-Chloro-5-isopropylamino pentane

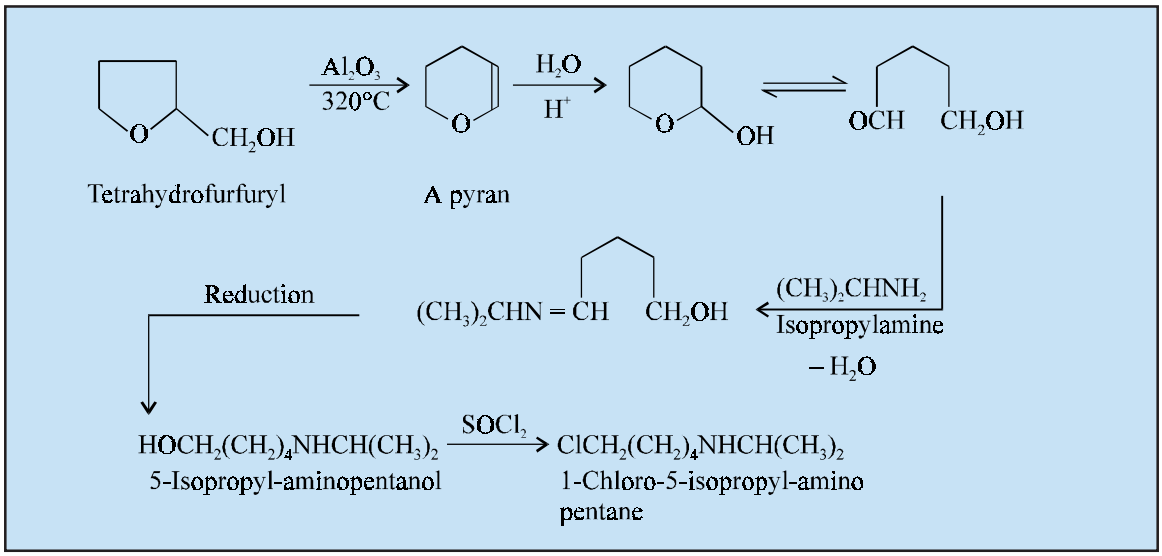
(*c*) Condensation of (*a*) and (*b*) and

(*d*) Phosphate salt.

(*a*) **Preparation of 8-amino-6-methoxy quinoline**

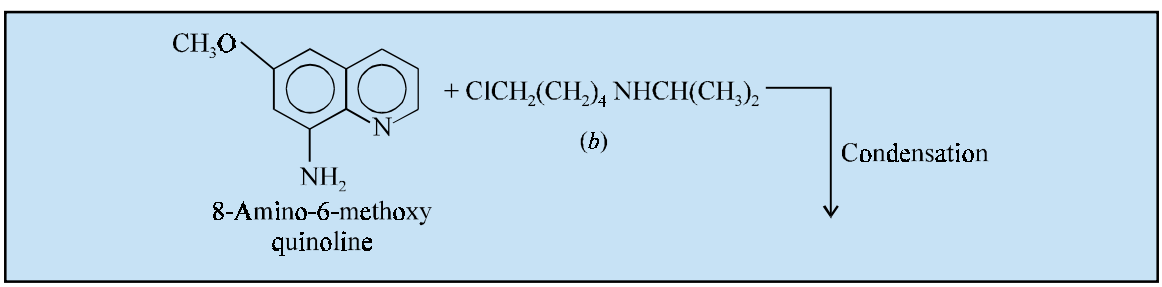
It is prepared as described under pamaquine.

(*b*) **Preparation of 1-chloro-5-isopropylamino pentane**

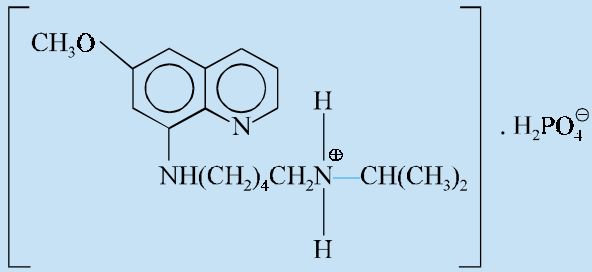


Tetrahydrofurfuryl alcohol on heating with aluminium oxide at 320° forms a partially saturated pyran which upon hydrolysis in an acidic medium yields a hydroxy analogue of pyran. This undergoes cleavage and the cleaved product on treatment with isopropyl amine forms an intermediate which on reduction gives rise to 5-isopropyl amino pentanol. Chlorination with thionyl chloride yields-1-chloro-5-isopropyl amino pentane.

(*c*) **Condensation of (*a*) and (*b*), (*d*) Treatment with H_3PO_4**



(*Contd...*)



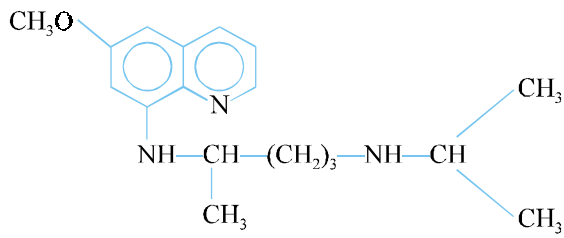
Pentaquine Phosphate

Condensation of the quinoline residue (*a*) and the side chain (*b*) yields the pentaquine base which on treatment with one mole of phosphoric acid forms the official compound.

Its actions and uses are similar to those of primaquine.

Dose : *100 mg per day.*

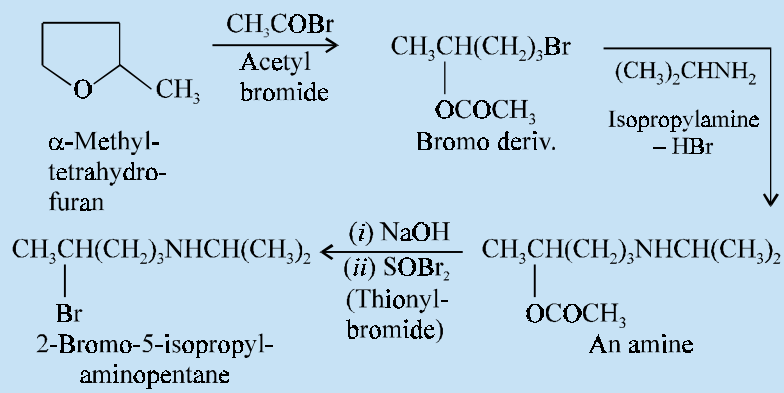
D. Isopentaquine



8-[[4-(Isopropylamino)-4-methylbutyl] amino]-6-methoxy-quinoline.

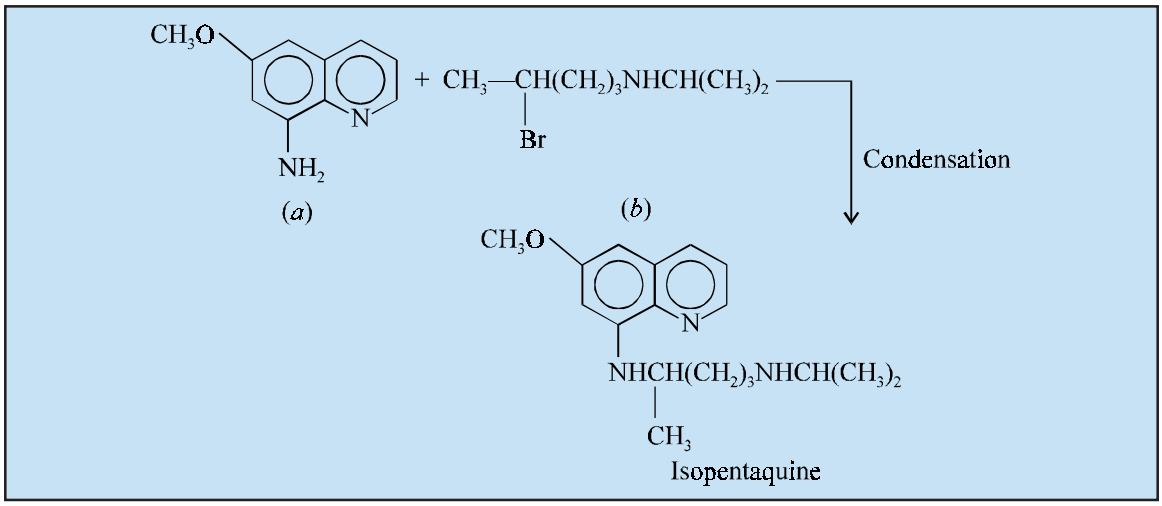
Synthesis

It consists of the preparation of the side chain 2-bromo-5-isopropylaminopentane as given below :



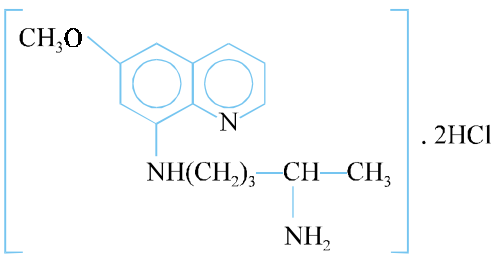
Interaction between α-methyl-tetrahydrofuran and acetyl bromide yields bromo derivative which on treatment with isopropyl amine forms a corresponding amine derivative. This on treatment with aqueous NaOH and thionyl bromide gives the side chain.

Treatment of the 8-amino-6-methoxy quinoline residue (*a*) with the side chain (*b*) yields the isopentaquine as shown below :



Isopentaquine is an isomer of **pentaquine,** and reported to be more active than the later as an antimalarial agent. It is also less toxic than pentaquine.

E. Quinocide Hydrochloride BAN, Quinocide INN, USAN,



8-(4-Aminopentylamino)-6-methoxyquinoline dihydrochloride.

It is a structural isomer of **primaquine,** has actions and uses resembling to those of **primaquine phosphate.**

Dose : *30 mg per day.*

2.2.1. Mechanism of Action

The mechanism of action of the various compounds discussed under Section 20.2.2. are dealt with separately in the pages that follows :

2.2.1.1. Pamaquine

The **'drug'** exerts its action against the exoerythrocytic stages of *P. ovale* and primary exoerythrocytic stages of *P. falciparum.* It has also been observed that it particularly inhibits the **gametocyte stage,** that essentially helps to eliminate the form required to infect the *'mosquito carrier'.* It also appears to disrupt and destabilize the parasite's mitochondria *via* several processes that include maturation into the subsequent resulting forms. The glaring advantage being the destruction of the exoerythrocytic forms before the parasite may actually infect the erythrocytes *i.e.,* the specific stage in the *'infectious process'* which ultimately renders malaria so weakening.

SAR of Pamaquine. It is indeed structurally related to the cinchona alkaloids essentially having a 6-methoxy group like quinine, but the various substituents on the **'quinoline nucleus'** are strategically positioned at C-8 rather than C-4 as found on the cinchona alkaloids. It has a *four-carbon alkyl linkage* or *bridge between the two N-atoms.* It has only one **chiral centre.** Though it has been critically observed that there exists certain differences in the metabolism of each stereoisomer and type of adverse response, there is hardly any difference in the antimalarial action based on the **pamaquin's stereochemistry.**

2.2.1.2. Primaquine

Its mechanism of action is very much similar to that of **'pamaquin'.** However, its spectrum of activity is regarded to be one of the narrowest of all the currently employed antimalarials ; and is recommended exclusively for exoerythrocytic *P. vivax* malaria.

SAR of Primaquine. Structural modifications of **pamaquine** produced the *unsubstituted primary aminoalkyl derivative i.e.,* **primaquine,** whose relatively more predominant therepeutic activity and significantly much lower toxicity (specifically the tendency for causing hemolysis) essentially replaced pamaquine virtually as the most well recognized **tissue schizonticide** of choice.

2.2.1.3. Pentaquine

The degree of toxicity in the **8-amino quinoline structural analogues** appears to be directly associated with the degree of substitution at the terminal amino function.* Using the said criterion **pamaquine**, having a *tertiary amino moiety,* happens to be **more toxic** than **primaquine,** having a *primary terminal nitrogen ;* whereas, **pentaquine** and **isopentaquine,** having *secondary terminal amino moieties,* are found to be **intermediate in toxicity.**

SAR of Pentaquine. It may be observed that with the exception of **pentaquine**, the other *three* **8-aminoquinolines** *viz.*, **pamaquin, primaquine** and **isopentaquine** have only one **chiral centre** (*i.e.*, asymmetric carbon). In fact, certain differences do take place in the actual metabolism of individual stereoisomer, but there exists practically little difference in the antimalarial profile based on the compound's stereochemistry.

2.2.1.4. Isopentaquine

The **'drug'** possesses an intermediate degree in toxicity because it has an essential secondary terminal amino moiety. Besides, the two N-atoms are duly separated by a chain of four C-atoms.

2.2.1.5. Quinocide (Chinocide)

The *'drug'* is an isomer of **primaquine,** has been studied extensively by Russian researchers.** It has been used widely in the Eastern Europe, but despite claims to the contrary its chemotherapeutic index is appreciably lower in comparison to **primaquine**.***

2.3. 9-Aminoacridines

The earlier hypothesis put forward by Ehrlich that methylene blue exerts antimalarial activity paved the way for the discovery of a number of acridine analogues. The 9-aminoacridine analogues, however, are found to be extremely toxic in nature and, therefore, they have been successfully replaced by the **4-aminoquinoline analogues** to a great extent. A few typical examples of this category are discussed below :

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*Edgeombe JH *et al. J Natl Malaria Soc*, **9**, 285 (1950).

Lysenko AJ *et al. Med Parasitol Parasit Dis* (USSR) **24, 132, 137, (1955).

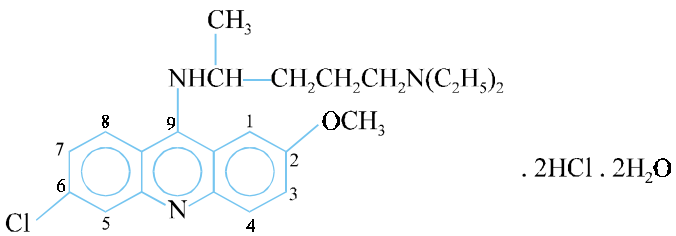
***Powell RD : *Clin Pharmacol Therap.* **7,** 48, (1966).

A. Mepacrine Hydrochloride BAN, Quinacrine Hydrochloride USAN, Mepacrine INN,

6-Chloro-9-[[4-(diethylamino)-1-methylbutyl] amino]-2-methoxy-acridine dihydrochloride dihydrate ; 1, 4-Pentane-diamine, N^4-(6-chloro-2-methoxy-9-acridinyl)-N^1, N^1-diethyl-, dihydrochloride, dihydrate ; Acrinamine ; Mepacrine Hydrochloride BP ; Eur. P ; Int. P ; Ind. P ;

Quinacrine Hydrochloride USP ;

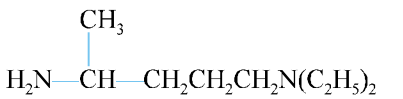
Atabrine Hydrochloride(R) (Winthrop).



Synthesis :

It essentially consists of the following steps :

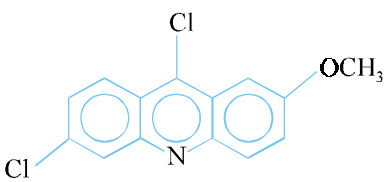
(*i*) **Preparation of the side chain :**



4-Diethylamine-1-methylbutylamine ;

4-Diethylamine-1-methylbutylamine ;

(*ii*) **Preparation of the acridine nucleus :**



2, 5-Dichloro-7-methoxy-acridine ;

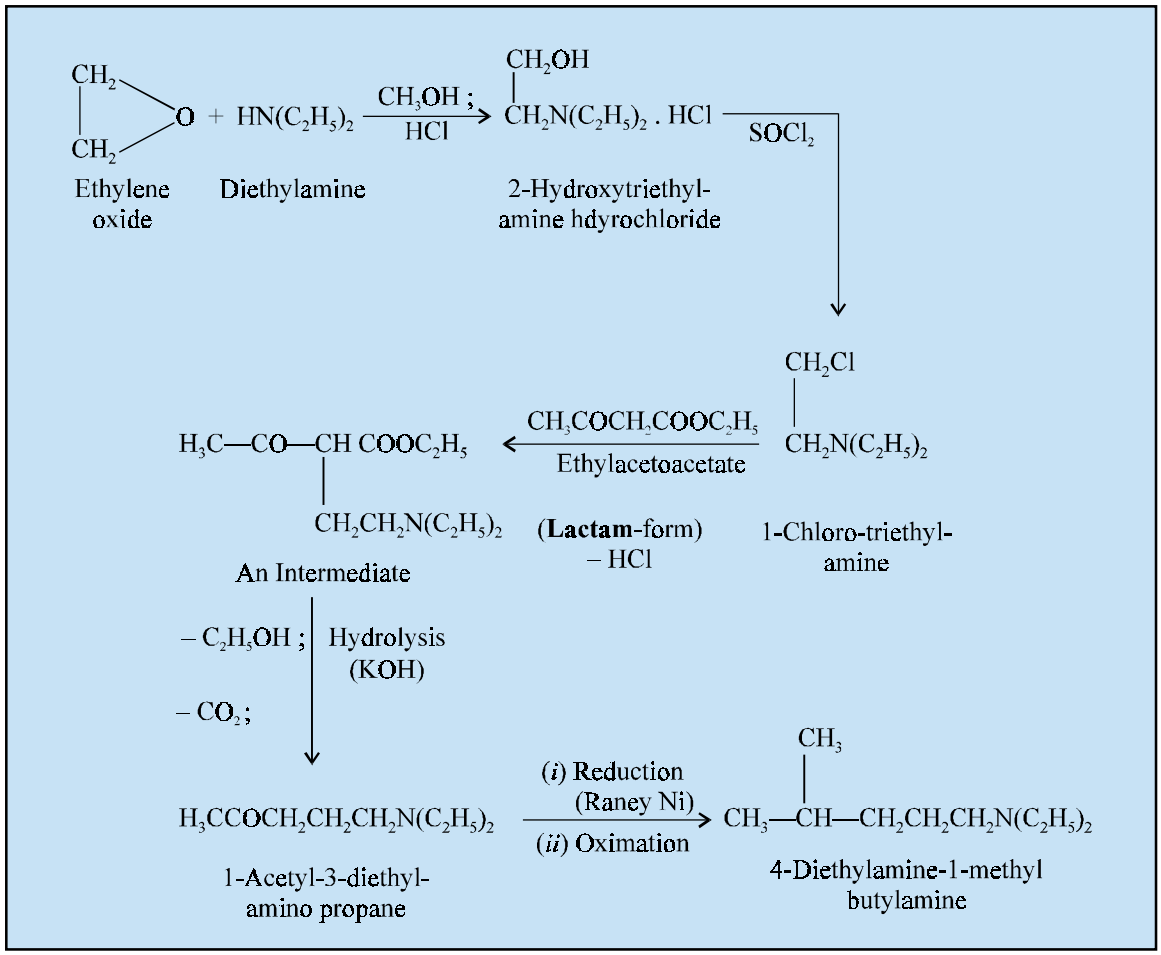
2, 5-Dichloro-7-methoxy-acridine ;

(*iii*) **Condensation of (*i*) and (*ii*)**

(*iv*) Preparation of the hydrochloride salt.

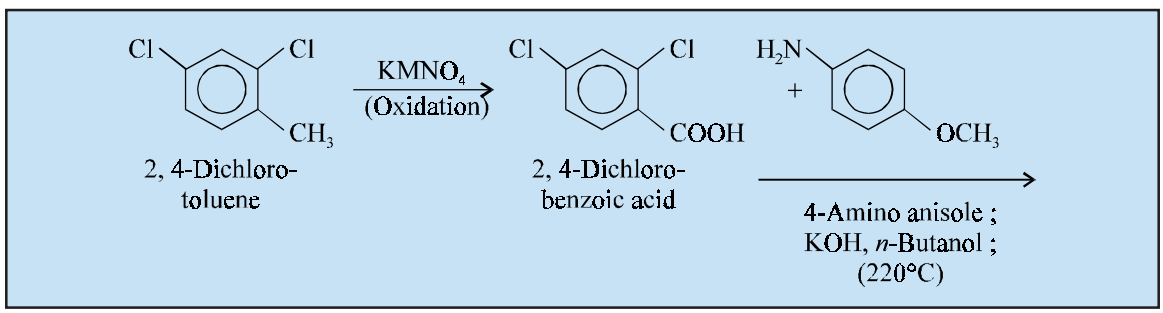
(*a*) **Preparation of the side chain**

2-Hydroxy triethylamine hydrochloride is obtained by the interaction of ethylene oxide and diethylamine in the presence of methanol and hydrochloric acid which on chlorination with thionylchloride yields 1-chloro-triethylamine.



The resulting compound on treatment with the *lactam*-form of ethylacetoacetate forms an intermediate which when subjected to reduction and oximation gives 4-diethylamine-1-mthyl butylamine.

(*b*) **Preparation of the acridine nucleus**



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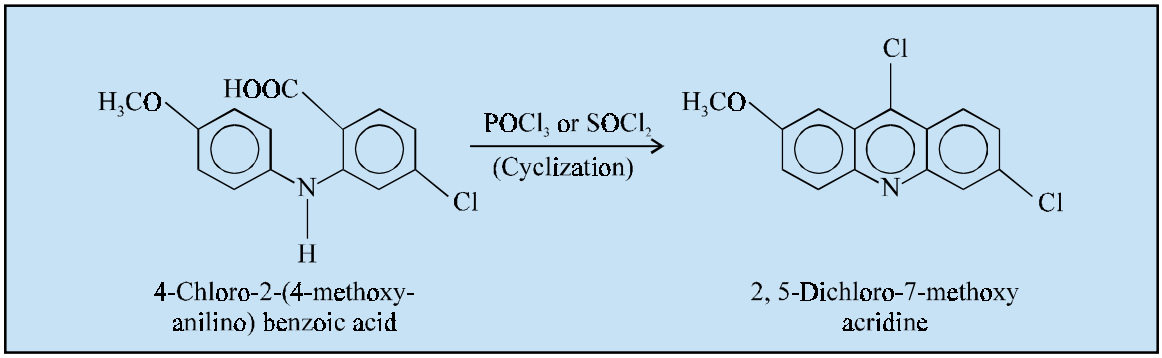
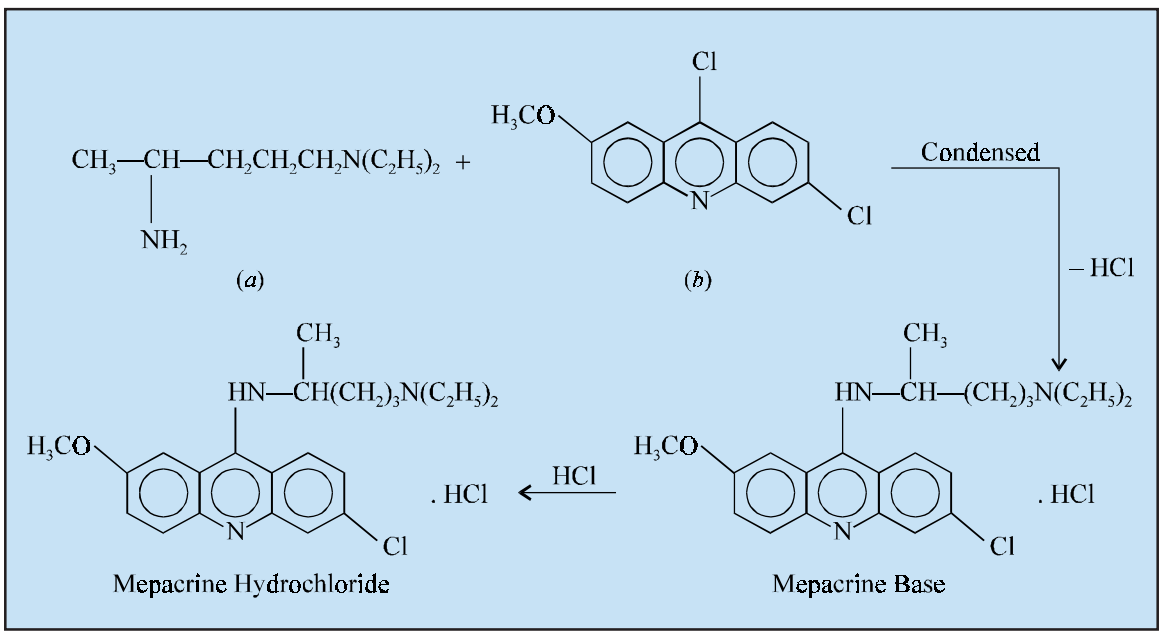


4-Chloro-2-(4-methoxy-anilino) benzoic acid

2, 5-Dichloro-7-methoxy acridine

(*c*) **Condensation of (*a*) and (*b*) above ; and (*d*) Treatment with Hydrochloric Acid**



Mepacrine Hydrochloride

Mepacrine Base

2, 5-Dichloro-7-methoxy acridine may be prepared by the oxidation of 2, 4-dichloro toluene and treating the resulting acid with 4-amino anisole at 220°C in the presence of KOH and *n*-butanol ; the additional compound when reacted with either $POCl_3$ or $SOCl_2$ undergoes cyclization. One mole each of the side chain and the acridine residue get condensed to yield the **mepacrine base** which on treatment with hydrochloric acid gives the official compound.

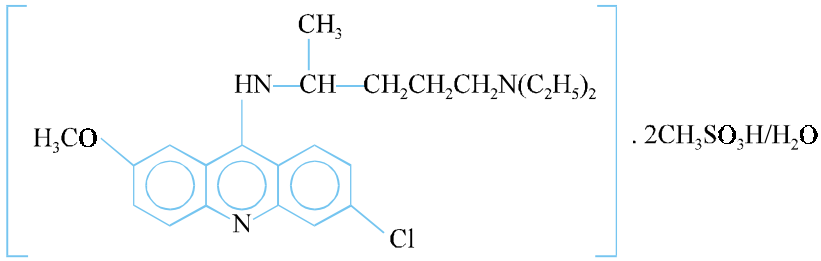
Mepacrine hydrochloride inhibits the erythrocytic state of development of the malarial parasite. It is considered neither as a causal prophylactic nor as a radical curative agent. It is found to be more toxic and less effective than chloroquine. *Besides, it has also been used in giardiasis, amebiasis, tapeworm and pinworm infestations.*

Dose : *As therapeutic, 200 mg with 300 mg of sodium bicarbonate each 6 hours up to 5 doses, followed by 100 mg 3 times per day for 6 days ; as suppressive, 100 mg once daily.*

B. Mepacrine Mesylate BAN,

Mepacrine Methanesulphonate ; Quinacrine methanesulphonate ; BPC ; (1963) ;

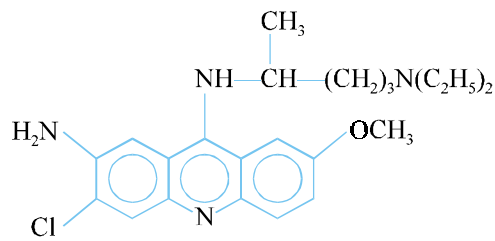
Quinacrine Soluble(R) (May and Baker).



It is much more soluble than mepacrine hydrochloride. It has been used more conveniently for parenteral administration in acute cases of *falciparum* malaria.

Dose : *360 mg intramuscularly in 2 to 4 ml 'Water for Injection'.*

C. Aminoacrichin



7-Amino-6-chloro-9-[[4-(diethylamine)-1-methylbutyl] amino] 2-methoxy-acridine ;

Its use as an **antimalarial drug** has been discontinued and replaced by more effective and less toxic agents.

2.3.1. Mechanism of Action

The mechanism of action of the antimalarial agents described under Section 20.2.3. shall now be treated individually as under :

2.3.1.1. Quinacrine Hydrochloride

The *'drug'* almost exhibits the same effects as those caused by the **4-aminoquinolines**. The GI irritancy is registered to be much higher than the **4-aminoquinolines** ; and, therefore, it is a common practice to administer sodium bicarbonate concomitantly.

It is absorbed quite rapidly from the GI-tract and also from IM and intracavitary sites of injection. The *'drug'* gets excreted very gradually in the urine and gets accumulated in tissues on chronic administration.

Interestingly, the **'drug'** is believed to act at several sites within the cell, including **intercalation of DNA strands, succinic dehydrogenase, mitochondrial electron transport system,** and **cholinesterase.** It may serve as *tumorigenic* and *mutagenic*, and hence, has been employed profusely as a **sclerosing agent**.*

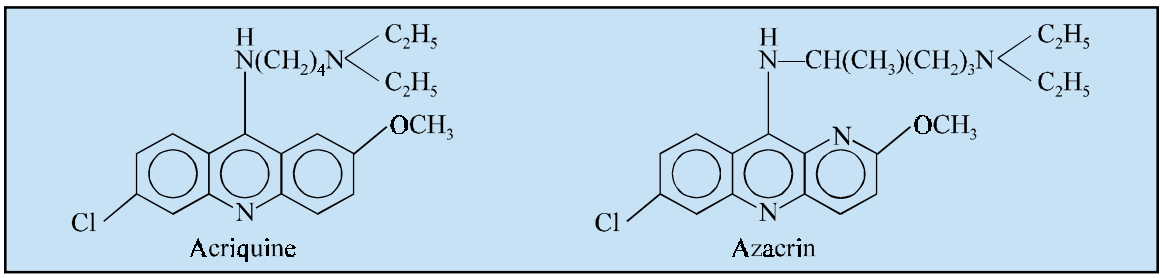
*An agent that causes or developes *sclerosis* (*i.e.*, hardening or induration of an organ or tissue, especially that due to excessive growth of fibrous tissue.

2.3.1.2. Mepacrine Mesylate

The '**drug**' is a methanesulphonate salt of **mepacrine** (or **quinacrine**) whose therapeutic potency is relatively higher than its corresponding HCl-salt.

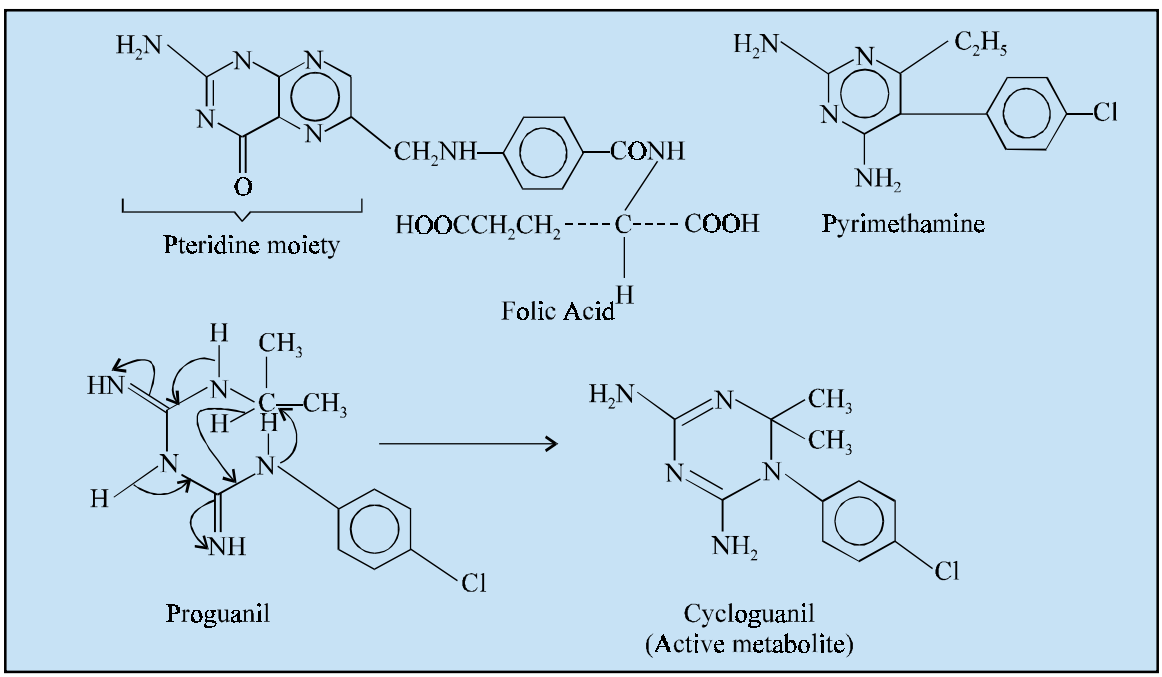
2.3.1.3. Aminoacrichin

The '**drug**' along with its two other acridine structural analogues, namely : **acriquine** and **azacrin** were introduced based on a combined structural features of **8-aminoquinoline** and **4-aminoquinoline**, but were not so successful due to their high toxicity.



2.4. Guanidine Analogues (Biguanides)

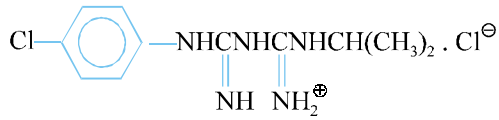
The **guanidine analogues**, in general, are not found to be active unless and until they get cyclized metabolically to a **dihydro-s-triazine analogue** having a close resemblance either to the **pteridine moiety** of folic acid or **pyrimethamine** as shown below :



The other structural analogues of **guanidine** are also metabolised in a similar fashion.

A few members of this class of compounds are described below, *viz.*, **Proguanil hydrochloride ; Cycloguanil embonate ; Chlorproguanil ; Bromoguanil.**

A. Proguanil Hydrochloride BAN, Proguanil INN, Chlorguanide Hydrochloride USAN,



1-(*p*-Chlorophenyl)-5-isopropylbiguanide hydrochloride ; Imidodicarbonimidic diamide, N-(4-chlorophenyl)-N′-(1-methyl-phenyl)-, monohydrochloride ; Proguanide Hydrochloride ; Proguanil Hydrochloride BP ; Int. P ; Ind. P ; Chlorguanide Hydrochloride USPXIV ;

Paludrine(R) (ICI Pharmaceuticals, U.K.).

Synthesis

It consists of the preparation of :

(*a*) *p*-Chlorophenyl guanidine

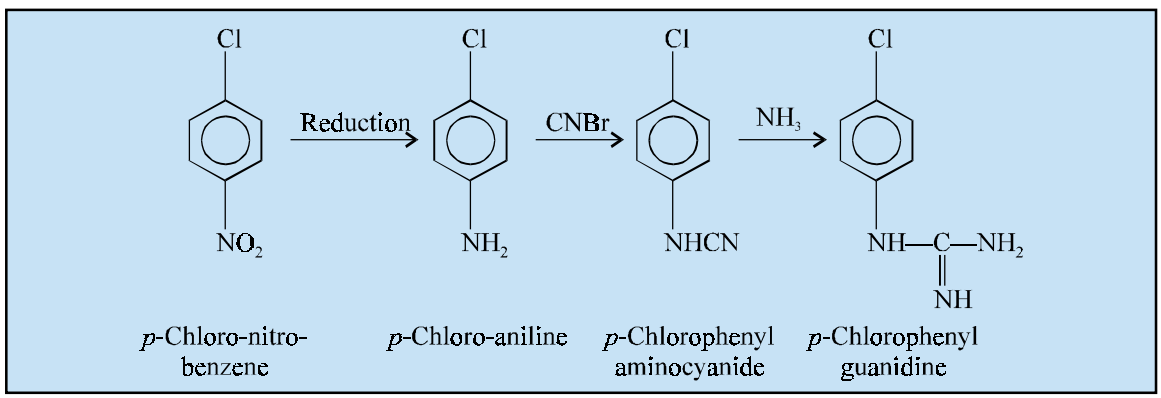
(*b*) Iso-propyl cyanamide

(*c*) Condensation (*a*) and (*b*)

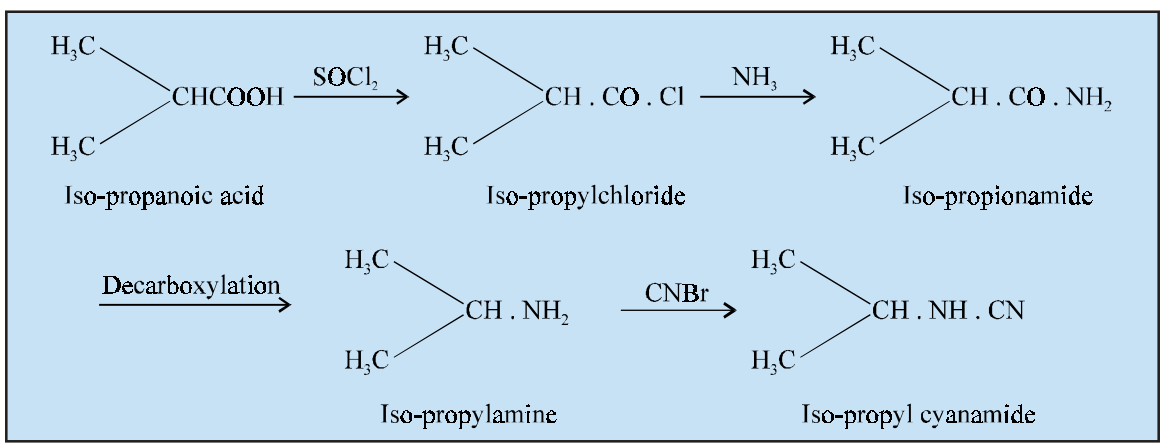
(*d*) Hydrochloride salt.

(*a*) **Preparation of p-Chlorophenyl guanidine**

p-Chloro-nitrobenzene is subjected to reduction, treatment with cyanobromide and amination to yield *p*-chlorophenyl guanidine.



(*b*) **Preparation of iso-propyl cyanamide**



Iso-propyl cyanamide may be prepared by the chlorination of iso-propionic acid followed by amination, decarboxylation and finally treating with cyanogen bromide.

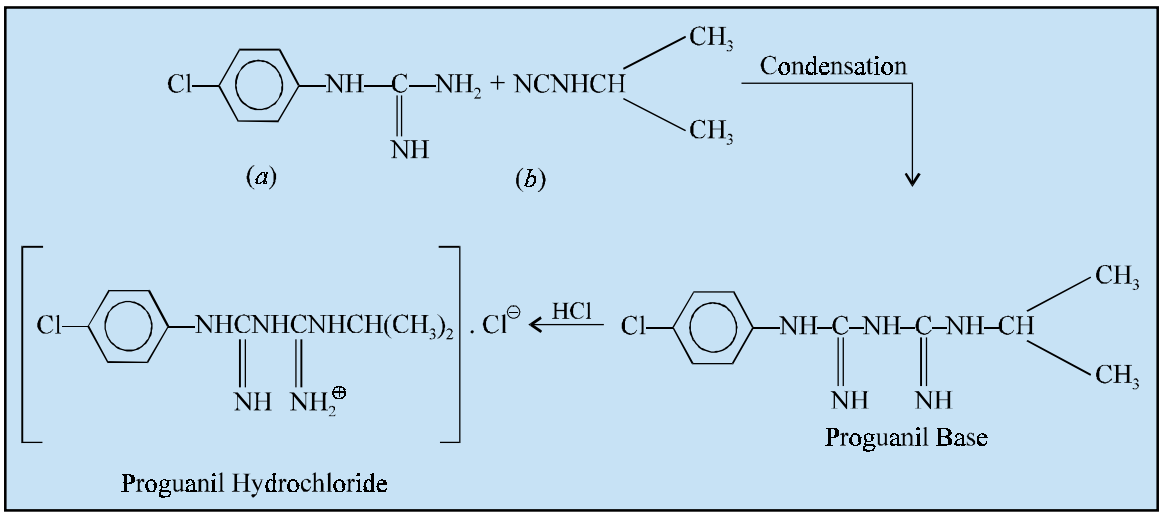
(*c*) **Condensation of (*a*) and (*b*) ; (*d*) Formation of Hydrochloride Salt**

Condensation of *p*-chlorophenyl guanidine with iso-propyl cyanamide gives the **proguanil base** which on treatment with one mole of hydrochloric acid yields **proguanil hydrochloride**.

It is an antimalarial drug whose metabolite is a potent dihydrofolate reductase inhibitors. It is active against the pre-erythrocytic (liver) forms of malaria. It is also active against the erythrocytic forms but their activity is slow.

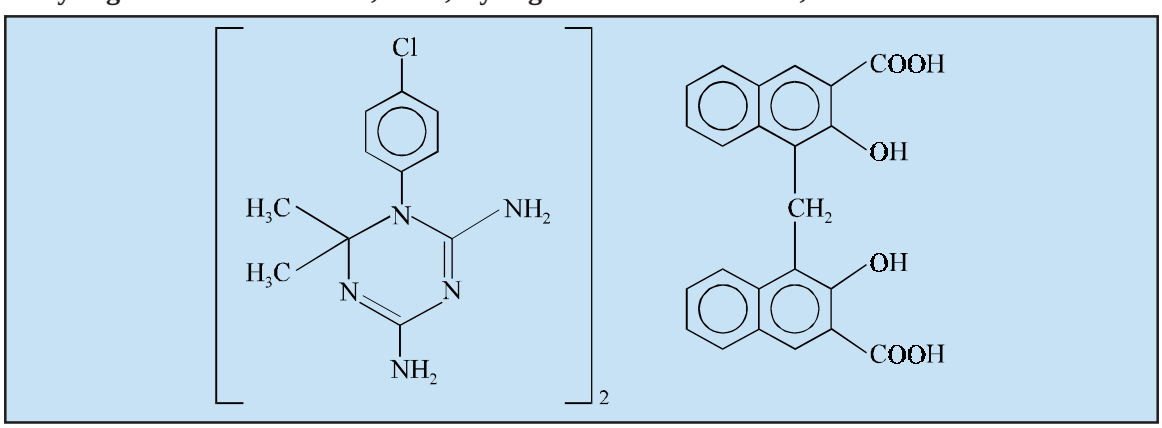
Hence, proguanil is used mainly for prophylactic treatment of malaria.

Dose : As prophylactic and suppressant, 100 to 200mg per day in non-imune subjects ; 300mg per week or 200mg 2 times per week in semi-imune subjects ; in acute vivax malaria, initial loading dose



300 to 600mg followed by 300mg per day for 5 to 10 days ; in falciparum malaria, 300mg 2 times daily for 5 days.

B. Cycloguanil Embonate INN, BAN, Cycloguanil Pamoate USAN,



4, 6-Diamino-1-(*p*-chlorophenyl)-1, 2-dihydro-2, 2-dimethyl-s-triazine compound (2:1) with 4, 4′ methylene-bis [3-hydroxy-2-naphthoic acid] ;

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

Cycloguanil is the active metabolite of **proguanil** as shown earlier. Its actions and uses are similar to paludrine. It has been recognized as a dihydrofolate reductase inhibitor and employed for the suppression of malaria, but failed to achieve a wide acceptance. It exerts little therapeutic value in such cases where resistance to either **proguanil** or **pyrimethamine** is prevalent. *To attain prolonged immunization in areas infested with hyperendemic malaria, administration of cycloguanil and amodiaquine every 4 months is recommended.*

Dose : *Usual, adult, intramuscular, 350mg of cycloguanil base every 4 months.*

2.4.1. Mechanism of Action

The mechanism of action of two drug substances discussed under section 20.2.4. shall be dealt with separately as under :

2.4.1.1. Chlorguanide Hydrochloride (Proguanil HCl)

British scientists during World War II had adopted an altogether different line of action in breaking away from the normal quinoline and acridine types of structure, and eventually paved the way in the epoch making discovery of the biguanide, **chlorguanide.**

The **'drug'** gets metabolised into a product which has proved to be a potent **dihydrofolate reductase inhibitor.**

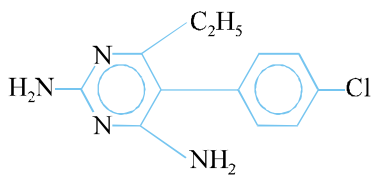
2.4.1.2. Cycloguanil Pamoate

The **'drug'** is proved to afford a high percentage of cures in *L. brasiliensis** and *L. mexicana*** pathogenic infections even with a single IM dosage.

2.5 Pyrimidine Analogues (Diaminopyrimidines)

The **pyrimidine analogues** have a close similarity to the pteridine moiety of dihydrofolic acid, and are directly responsible for its subsequent reduction to tetrahydrofolic acid by means of the enzyme dihydrofolate reductase. The site of action of **pyrimidine analogues** are exoerythrocytic and erythrocytic forms of *P. falciparum*, together with the exoerythrocytic forms of *P. vivax*. A few examples of this category of antimalarials are described below :

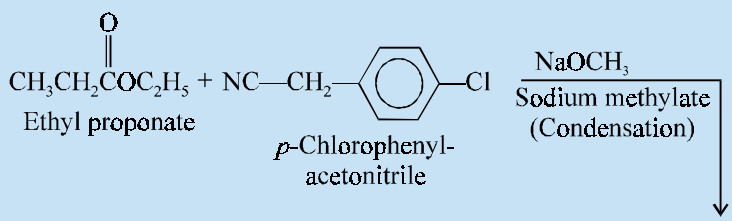
A. Pyrimethamine INN, BAN, USAN,



2, 4-Diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine ; 2, 4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl-; BP ; USP ; Int. P. ;

Daraprim(R) (Burroughs Wellcome).

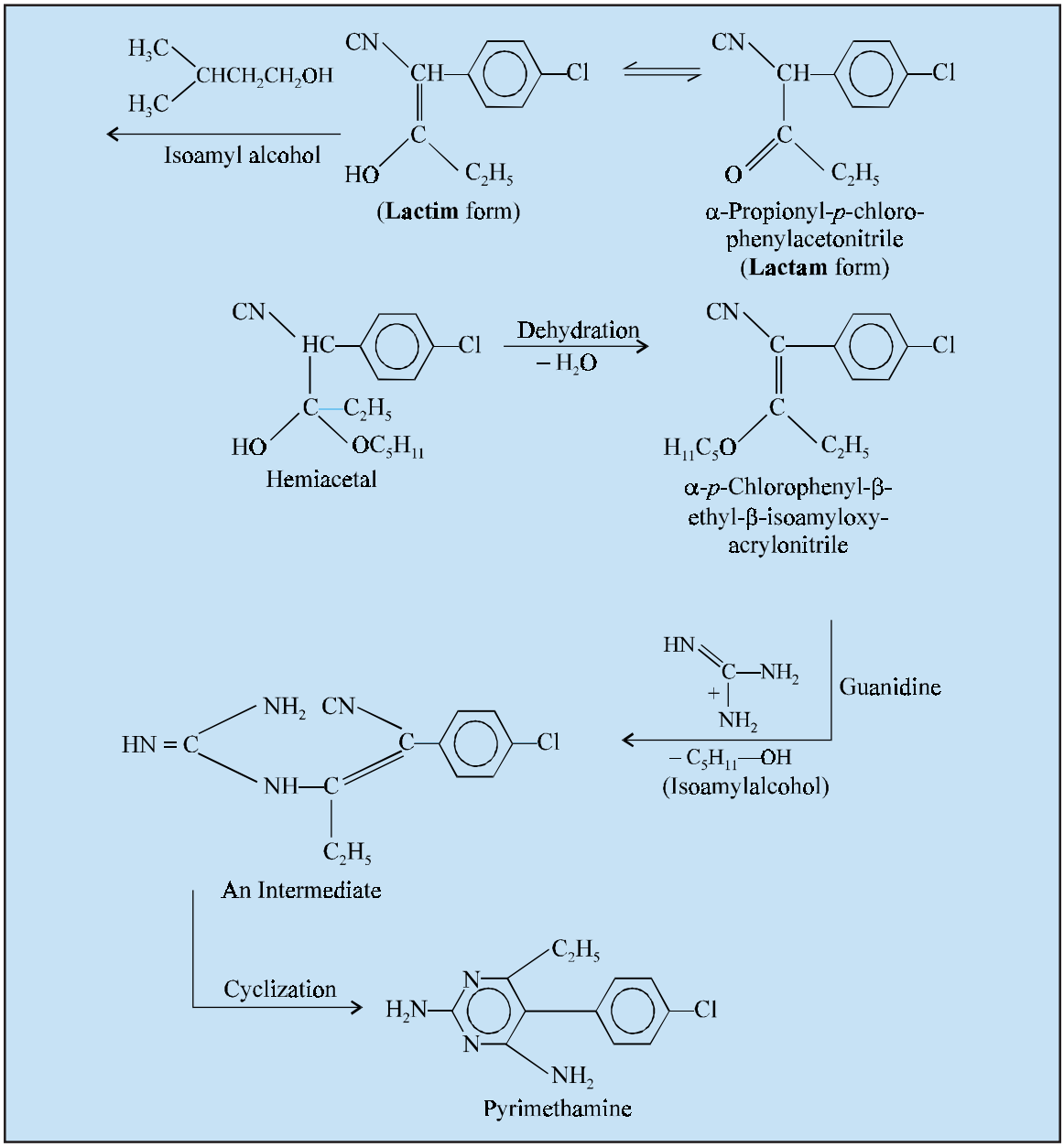
Synthesis



(*Contd...*)

*Pena-Chavarria *et al. J Am Med Assoc,* **194**, 1142 (1965).

Beltran F *et al. Prensa Med Mex,* **31, 365 (1966).



α-Propionyl-*p*-chlorophenylacetonitrile (*lactum*-form) is prepared by the condensation of ethyl propionate and *p*-chlorophenylacetonitrile which undergoes **tautomerism** to form the corresponding *lactim*-form. This on reaction with isoamyl alcohol forms the hemiacetal which upon dehydration yields α-(*p*-chlorophenyl)-β-ethyl-β-isoamyloxyacrylo-nitrile. The resulting product on treatment with guanidine affords cyclization *via* two different steps : *first*, elimination of a mole of isoamyl alcohol by condensation involving the imino hydrogen of guanidine, and *secondly*, an addition reaction between an amino group of guanidine and the nitrile group of the intermediate compound.

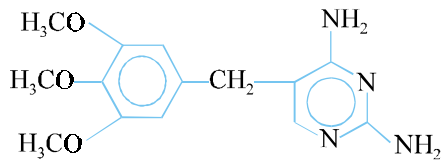
Like the **biguanides** it is a potent **inhibitor of dihydrofolate reductase** of the plasmodium (mammalian enzyme is about 200 times less sensitive). Thus it blocks the synthesis of tetrahydrofolic from dihydrofolic acid and this is essential for the synthesis of purines and pyrimidines and hence DNA.

It finds its extensive use as a suppressive prophylactic for the preventation of severe attacks due to P. falciparum and P. vivax. It is also used in the treatment of toxoplasmosis and as an immunosuppressive agent.

Pyrimethamine in conjunction with **sulfadoxine** (25mg : 500mg), under the brand name **Fansidar(R) (Roche),** has been used successfully as an **antimalarial drug** for those subjects who display sensitization towards **chloroquine** therapy in malaria.

Dose : *As suppressive, 25 mg once a week ; as therapeutic, 50 to 75 mg once a day for 2 days when used alone, otherwise 25 mg.*

B. Trimethoprim INN, BAN, USAN,



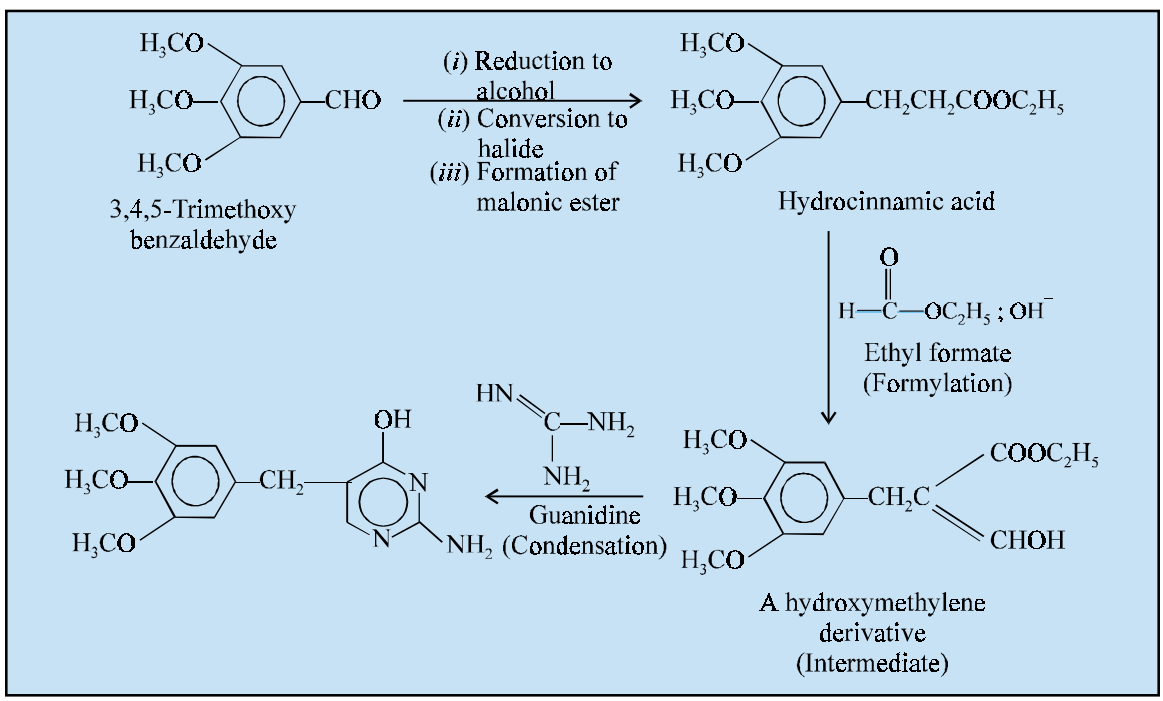
2, 4-Diamino-5-(3,4,5-Trimethoxybenzyl) pyrimidine ; 2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl) methyl]-; Trimethoxyprim ; BP ; USP ;

Proloprim(R) (Burroughs Wellcome) ; Trimpex(R) (Roche).

Synthesis

It may be prepared by *two* different methods described below :

Method-1. From 3, 4, 5-trimethoxy benzaldehyde via hydrocinnamic acid



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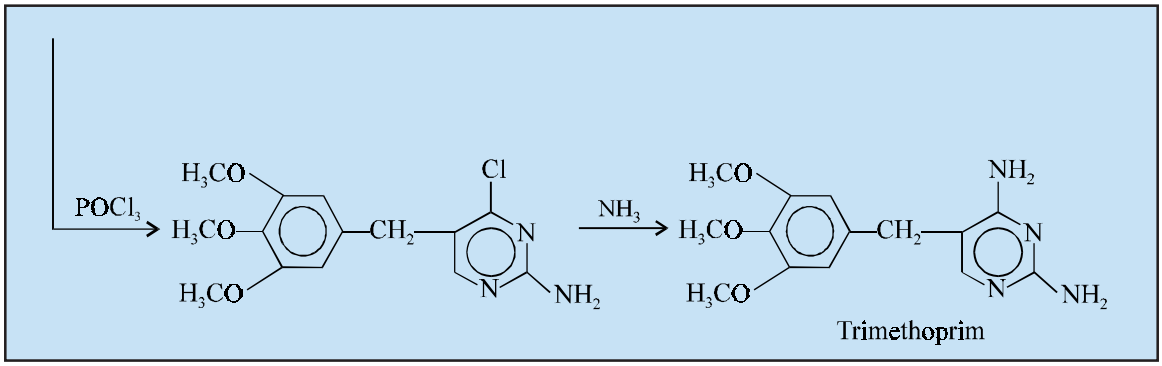
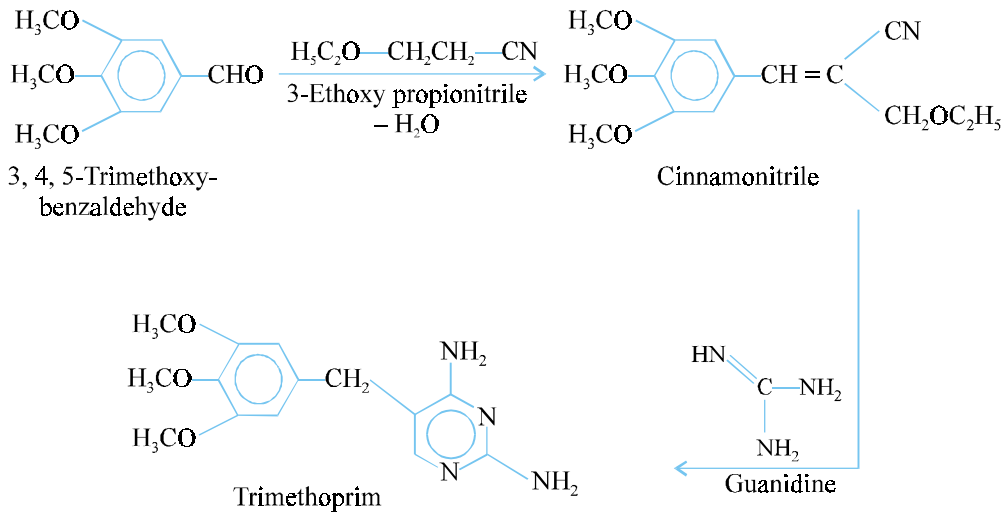


Hydrocinnamic acid is prepared by the bishomologation of 3, 4, 5-trimethoxy benzaldehyde, *i.e.*, subjecting the later to reduction forming an alcohol, coversion to halide and finally formation of the malonic ester. This is then subjected to formylation with ethyl formate and base to yield the corresponding hydroxymethylene derivative. Condensation of this intermediate with guanidine gives the pyrimidine residue, by a scheme very similar to the one discussed under pyrimethamine. The hydroxyl moiety present in the pyrimidine nucleus is converted to the chloro group by treatment with phosphorus oxychloride and finally amination leads to the formation of the official compound.

Method-II. From 3, 4, 5-trimethoxybenzaldehyde via cinnamonitrile



It is comparatively a shorter course of reaction whereby cinnamonitrile is prepared by the interaction of 3, 4, 5-trimethoxy-benzaldehyde with 3-ethoxy propionitrile with the elimination of a mole of water. The resulting product on treatment with guanidine affords the formation of **trimethoprim** directly.

Like **pyrimethamine, trimethoprim is a potent inhibitor of dihydrofolate reductase.** It has been employed in conjunction with **sulfametopyrazine** in the treatment of **chloroquine-resistant malaria** but unfortunately could not attain wide acceptance. *It has also been used in conjunction with* **sulphonamides** *in the treatment of bacterial infections viz.,* **trimethoprim with sulphamethoxazole.**

Dose : *1.5 g with 1 g of sulfametopyrazine per day for 3 days.*

2.5.1. Mechanism of Action

The mechanism of action of the compounds described under Section 20.2.5. are dealt with individually in the sections that follows :

2.5.1.1. Pyremethamine

The **'drug'** inhibits dehydrofolate reductase in plasmodia* ; and thereby the developing parasite cannot synthesize and use nucleic acid precursors needed for their normal growth. Furthermore, its prevailing action in checking the development of the erythrocytic phase of the parasite is slow and sluggish ; therefore, it is of rather little value in the suppression of acute attacks, except as an adjunct to quinine. Importantly, it is invariably employed as a *suppressive prophylactic* for the prevention of clinical attacks by *Plasmodium falciparum* in regions particularly where the **organism is resistant to chloroquine,** in which instance it is administered in conjunction with **sulfadoxine.**

Besides, it also helps in rendering the *'parasite'* incapable of sporulating in the mosquito whereby the **'life-cycle of the parasite'** is disrupted squarely.

It has been duly reported that success rate of the **'drug'** is almost 90% in certain regions, which may be increased to even 95% by the addition of **quinine.** However, in the control, management and treatment of *toxoplasmosis*** it is usually combined with **trisulfapyrimidines.**

2.5.1.2. Trimethoprim

The **'drug'** also shows its action by the inhibition of dihydrofolate reductase, though its potency is appreciably lower. However, it is found to be most important as an **'antibacterial agent'.** It is worthwhile to mention here that the **bacterial dihydrofolate reductases** are invariably more susceptible in comparison to the plasmodial ones. Hence, the **'drug'** is observed to be extremely effective against all bacteria which should exclusively synthesize their own **folinic acid (leucovorin)**. This specific characteristic profile renders the **'drug'** to acclaim a broad spectrum against a host of pathogenic (causative) microorganisms, such as :

Streptopyrogenes, viridans, and *pneumoniae* ; *Staphylococcus aureus* and *epidermidis ; H. influenzae ; Klebsiella-Enterobacter Serratia, E. coli,* different *Shigella* and *Salmonella, Bordetella pertussis ; Vibrio cholerae ; Pneumocystis carinii, Toxoplasma gondii ;* and *Plasmodia.*

It is, however, pertinent to mention here that the **mammalian dihydrofolate reductase** is approximately 1 : 10,000 to 1 : 50,000 as sensitive to it as the bacterial enzymes, so that there prevails almost **little interference with folate metabolism in humans.**

The volume of distribution is nearly 1.8 mL g^{-1}. The concentration in the cerebrosphinal fluid (CSF) attains a level ranging between 30-50% of the drug in plasma. It gets excreted mostly into the urine. The plasma half-life ranges between 9 to 12 hr. in normal adults having normal kidney-function ; however, it may be enhanced even upto 2 to 3 times in a situation whereby the **creatinine clearance** falls below 10 mL . min^{-1}.

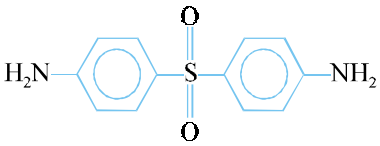
2.6. Sulfones

A large number of **diphenylsulfone analogues** have been developed for the treatment of leprosy. Incidentlly one such member chemically known as **4, 4′-diaminodiphenyl sulfone (dapsone)** exhibited prophylactic activity against resistant *P. falciparum.* Dapsone in conjunction with **pyrimethamine** has been effectively used in the treatment of malaria due to chloroquine resistant *P. falciparum.*

Med. Lett.* **29, 53, 1987.

**A disease caused by infection with the protozoan *Toxoplasma gondii.*

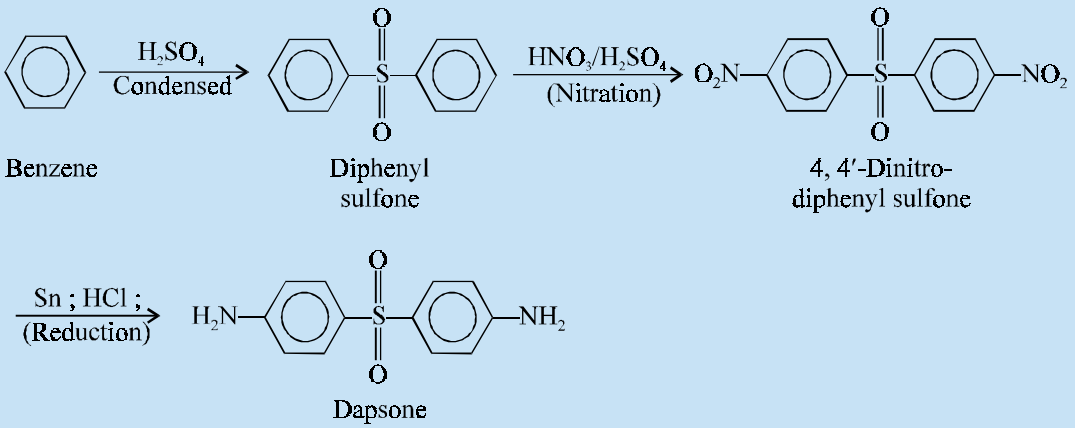
A. Dapsone INN, BAN, USAN,



4, 4′-Sulfonyldianiline ; Benzeneamine, 4, 4′-sulfonylbis-; 4, 4′-Diaminodiphenyl sulfone ; Diaphenylsulfone ; Disulone ; BP ; USP ; Int. P ; Ind. P. ;

Avlosulfon$^{(R)}$ (Ayerst).

Synthesis



Diphenyl sulfone is prepared by the condensation of benzene with sulphuric acid. Nitration is afforded by treatment with a mixture of nitric acid and sulphuric acid to yield **4, 4′-dinitrodiphenyl sulfone** which on reduction with tin and hydrochloric acid gives the official compound.

Dapsone possesses limited therapeutic value in the treatment of malaria, except when combined with other agents for the treatment of chloroquine-resistant cases.

2.6.1. Mechanism of Action

The mechanism of action of **'dapsone'** shall be discussed as under :

2.6.1.1. Dapsone

Its mechanism of action is very much similar to that of **sulphanilamide.** It is employed profusely in the treatment of both *lepromatous* and *tuberculoid* types of leprosy. However, in combination with **rifampin,** it is regarded as the **'drug of choice'** in the chemotherapy of leprosy. Besides, the combination with **clofazimine** affords a similar therapeutic effect. The *'drug'* is the most preferred **'sulfone'** because of the two cardinal facts, such as : (*a*) cost-effective ; and (*b*) equally efficacious to other sulfones.

Interestingly, when combined with **trimethoprim,** it is found to exert almost identical activity as **trimethoprim-sulfamethoxazole** in the plausible treatment of *Pneumocystis carinii pneumonia*. Also used with **pyrimethamine** for treatment of malaria.

It is most absorbed by the oral administration. Absorption is more efficient at low than high dosage regimen. Finally, it gets eliminated in the liver by acetylation. Patients may respond to this *'drug'* as 'slow' and 'fast' acetylators. The plasma half-life ranges between 10 to 50 hours ; and at least 8 hours are needed to accomplish plateau concentrations.

2.7. Quinine Analogues

Quinine is an alkaloid obtained from the bark of *Cinchona officinalis* Linne (*C. ledgeriana* Moens) belonging to the family *Rubiaceae* or other species of *Cinchona.*

A. Quinine Sulphate BAN, Quinine Bisulfate USAN,

Quinine sulphate (2:1) salt dihydrate ; Quinine Sulphate BP ; Quinine sulfate USP ; Quinine Bisulate NFXI ;

Kinine(R) (ICN, Canada) ;

Preparation

The **quinine** is isolated from the bark of *Cinchona* sp., after recrystallization several times from mildly acidified (H_2SO_4) hot water. **Quinine sulphate** obtained after recrystallization retains up to seven moles of water, but undergoes efflorescence in dry environment to lose up to five moles of water.

However, the dihydrate salt is fairly stable and hence is the official compound.

Quinine only affects the erythrocytic form of the plasmodia. *It is employed extensively for the suppression and control of malaria caused due to P. vivax, P. malariae and P. ovale.* It has been found to be less effective in *P. falciparum.* It is rarely used now except for chloroquine-resistance cases when its administration is followed by combination of purimethamine and sulfadoxine [*i.e.*, Fansidar(R) (Roche)].

2.7.1. Mechanism of Action

The mechanism of action of **quinine sulphate** is discussed as under :

2.7.1.1. Quinine Sulfate

The **'drug'** only affects the erythrocytic form of the plasmodia ; and, therefore, is employed particularly as a suppressive in the management and treatment of severe attacks of *P. vivax. P. malariae* and *P. ovale* malaria. It may cure upto 50% of infections caused by *P. falciparum.* The *'drug'* may be employed in combination with **pyrimethamine** and a **sulphonamide,** but it seems to be antagonized by **chloroquine.**

Choice of combinations with other drugs : A few typical examples are as follows :

(*i*) **Quinine-pyrimethamine-sulfadiazine (or sulfadoxine).** In the treatment of choice for infections caused by chloroquine-resistant *Plasmodium falciparum ;*

(*ii*) **Quinine-tetracycline.** In infections produced by chloroquinine-resistant *P. falciparum.*

(*iii*) **Quinine-Clindamycin.** In the treatment of choice for *babesiosis.*

The **'drug'** has a tendency to suppress neuromuscular transmission, and hence used in **myotonia congentia** or **Thomsen's disease.**

Note. The 'drug' is mostly given orally after meals to minimize gastric irritation.

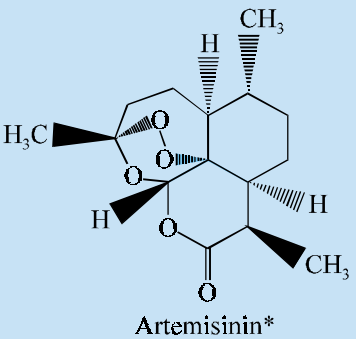
2.8. New Antimalarial Drugs

A few important **newer antimalarial drugs** are discussed as under :

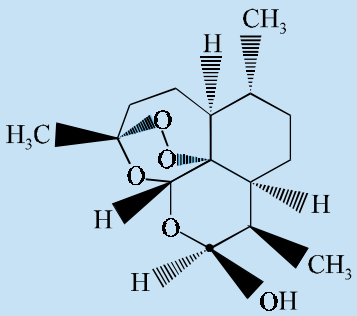
2.8.1. Artemisinin

The marked and pronounced antimalarial activity of **'Quinghausu'** as the constituent of a traditional Chinese medicinal herb *Artemisia annuna* L., **(sweet wormwood)** has been known in China for over 200 years. However, the active principle was first isolated in 1972 and found to be a sesquiterpene lactone with a peroxy moiety.

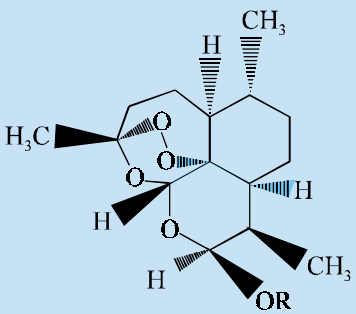
The following *four* chemical structures, namely : (*i*) **artemisinin ;** (*ii*) **dihydroartemisinin ;** (*iii*) **artemether (oil-soluble) ;** (*iv*) **artemotil (oil soluble)** ; and (*v*) **artesunate (water soluble)** are found to be active against the entire *Plasmodium* genera that cause malaria predominantly across the tropical regions of the globe, such as : Africa, Indian sub-continent, South East Asia and the like.



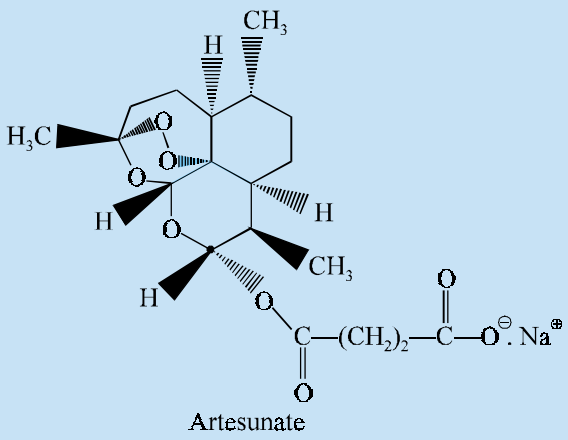
Artemisinin*



Dihydroartemisinin



Artemether [R = CH_3]
Artemotil [R = C_2H_5]



Artesunate

SAR of Artemisinin. The most important, critical and key structure of the **'drug',** artemisinin, is the presence of a **'trioxane'** moiety which essentially consists of the **endoepoxide** and **doxepin oxygens** that is evidently displayed by a rather simplified versions of *3-aryltrioxanes* as shown in the following section, which are responsible for exerting the antimalarial activity against the parasite.

It is, however, pertinent to state here that the prevailing stereochemistry at C-12 is not so critical and vital.**

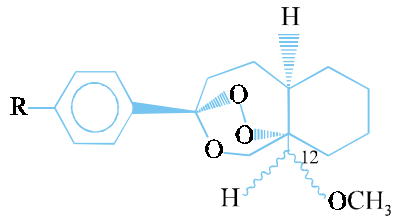
Mechanism of Action. In humans (*i.e.*, the host) erythrocyte, it has been observed that the *malaria parasite* actually consumes the haeomoglobin comprising mainly of Fe^{2+} iron, thereby changing it to the corresponding *toxic hematin* consisting of Fe^{3+} iron, subsequently get reduced to heme with its Fe^{2+} iron. Later on, the resulting **'heme iron'** eventually interacts with the prevailing *trioxane moiety,* thereby releasing the **'reactive oxygen' carbon radicals** and the extremely reactive $\mathbf{Fe^{IV} = O}$ species. It has been established that the latter is proved to be lethal to the parasite.***

***Chemical name of Artemisinin :**

(3α, 5αβ, 6β, 8αβ, 9α, 12β, 12aR*)- (+)-Octahydro-3, 6, 9-trimethyl-3, 12-epoxy-12H-pyrano [4, 3-j]-1, 2-benzodioxepin-10 (3H)-one ; ($C_{15}H_{22}O_5$).

Posner GH *et al. J Med Chem* **44, 3054, 2001.

***Posner GH *et al. J Am Chem Soc,* **118,** 3537, 1996.



Aryltrioxanes [R = – F or —COOH]
(Simplified Versions)

Interestingly, the reduction of **artemisinin** to **dihydroartemisinin** gives rise to a **chiral centre,** as shown by a bold black spot in the structure of dihydro artemisinin that may ultimately lead to the formation of **'prodrugs'** which could be either oil soluble or water soluble.

A few characteristic vital features of the above cited **'prodrugs'** are enumerated as under :

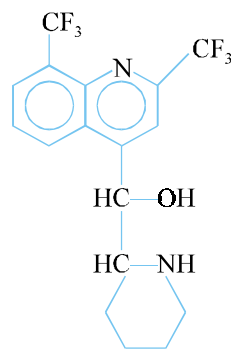
(*i*) The two prevailing stereoisomers are found to be **active,** just as with the simpler aryltrioxanes.

(*ii*) Only one isomer of the ensuing **artemisinin prodrug** exhibits predominance exclusively.

(*iii*) The α-isomer predominates in forming the subsequent hemisuccinate ester which is water-soluble.

(*iv*) The β-isomer predominates in producing the subsequent nonpolar methyl and ethyl ethers.

2.8.2. Mefloquine INN, USAN, Mefloquine Hydrochloride BAN,



DL-*erythro*-α-2-Piperidyl-2-, 8-*bis* (trifuoromethyl)-4-quinolinemethanol ; 4-Quinolinemethanol, α-2-piperidinyl-2, 8-*bis* (trifuoromethyl)-, (R•, S•)-(±)-;

This is the outcome of many years of research by the United States department of the Army. It belongs to the 4-quinoline methanol series, several of which were found to have potent schizonticidal activity but could not be used clinically, because they possessed photosensitizing activity in man. Mefloquine is devoid of this effect.

It is very effective against the erythrocytic forms of malaria. However, its use is restricted to cases of chloloquine-resistant falciparum malaria in order to prevent the emergence of parasites that are resistant to it.

Dose : *Oral single dose, 0.4 to 1.5 g.*

Probable Questions for B. Pharm. Examinations

1. (*a*) What are the causal organisms responsible for malaria ? How do the antimalarials affect the life cycle of mosquito ? Explain.

(*b*) With the help of a 'General Structure' give the status of four important alkaloids isolated from cinchona bark.

2. Classify the synthetic antimalarials based on their basic chemical nucleus. Give examples of at least **one** compound from each class.

3. Modifications of the side-chain at C-4 on the 4-amino-7-chloro quinoline nucleus give rise to the following drugs :

(*a*) Chloroquine phosphate

(*b*) Amodiaquine hydrochloride

(*c*) Santoquin

Give their structures and the synthesis of any **one** drug.

4. Name **three** important antimalarials derived from **8-amino-6-methoxy quinoline nucleus.** Give their structure, chemical name, uses and the synthesis of any **one** drug.

5. Elaborate the synthesis of **mepacrine hydrochloride** by adopting the following steps sequentially :

(*i*) **Side chain :** 4-Diethylamine-1-methylbutyl amine.

(*ii*) **Nucleus :** 2, 5-Dichloro-7-methoxy acridine

(*iii*) Condensation of (*i*) and (*ii*) and

(*iv*) HCl.

6. Discuss the synthesis of **'Primaquine Phosphate'** :

(*a*) Elderfield's method—from 1, 4-dibromopentane

(*b*) From 2-chloropentylamine.

7. Interaction of **8-amino-6-methoxy quinoline** with the following side chains :

(*a*) 1-chloro-5-isopropylamine pentane

(*b*) 2-bromo-5-isopropylamino pentane

yield **two** potent antimalarials. Discuss their synthesis in details.

8. Ehrlich's hypothesis that methylene blue exerts antimalarial activity led to the discovery of **Mepacrine Mesylate.** Describe its synthesis sequentially.

9. Paludrine (proguanil hydrochloride) the wonder drug for malaria gets metabolizsed to its active form cycloguanil *in vivo.*

(*a*) Explain its biotransformation

(*b*) Give its synthesis from *p*-chlorophenyl guanidine and *iso*-propyl cyanamide.

10. (*a*) Discuss the synthesis of **one** important antimalarial drug belonging to the class :

(*i*) Diaminopyrimidines (*ii*) Sulfones.

(*b*) Give a brief account of the **'Mode of Action'** of antimalarials.

Or

Give a comprehensive account of 'ARTEMISININ'

RECOMMENDED READINGS

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4. GM Findlay, **'Recent Advances in Chemotherapy',** (2nd edn), Vol. 2, Philadelphia, Blakiston, (1951).
5. Honingsbaum M : **The Fever Trail : In Search for the Cure for Malaria,** Farrar, Straus and Girous, New York, 2001.
6. JEF Reynolds (ed.), **'Martindale : The Extra Pharmacopoeia'** : 31st Edn., The Pharmaceutical Press London (1997).
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