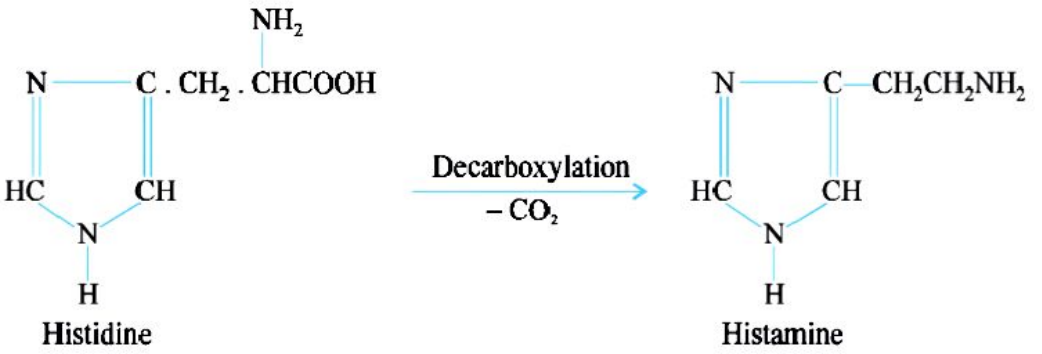
Chapter

15 Antihistaminics

1. INTRODUCTION

Histamine, 4-(2-aminoethyl) imidazole, as such could not for many years attract enough attention from physiologists, pharmacologists and biochemists alike because of the absence of any therapeutic utility. It occurs in many storage sites in the body in varying amounts. It is present in the mast cells of many body organs, in blood basophils, the mucosal cells of the gastrointestinal tract especially the acid-secreting parietal cells, in the hypothalamus and area postrema in the central nervous system.

In the living organism, **histamine** is synthesized from the naturally occurring α-amino acid, histidine, by the loss of a carboxyl group through bacterial or enzymatic decarboxylation as stated below :

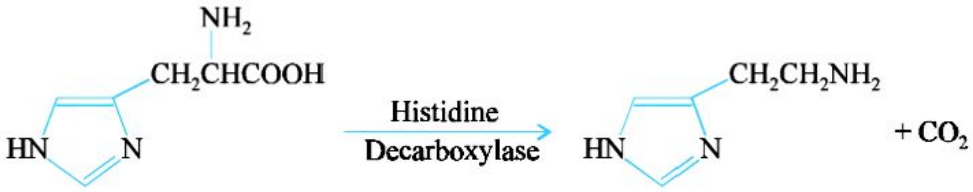


Histidine Histamine

A plethora of antigens (sensitizing substances) derived from food products, pollens, dust mite, house dust, human hair, sheep wool etc., may cause serious allergic and anaphylactic manifestations in human beings, due to the release of **histamine** with some other substances. The release of **histamine** gives rise to a number of physiological actions which are attributable to the activation by **histamine of histamine (H_1- & H_2-) receptors.** Some of the effects include dilation and enhanced permeability of the capillaries with oedema, vasodilation, reflex cardiac acceleration and bronchiole constriction. It also causes gastric acid secretion. A relatively mild release of **histamine** in the body leads to allergic reactions displayed by vivid skin rashes with itching, whereas in extreme instances it may result in an anaphylactic shock which may be fatal. The actions of **histamine** can be antagonized chemically using **histaminase** or formaldehyde but this is of no practical value. The actions are best modified by the use of substances that block competitively the **histamine sensitive receptors.** Such substances are known as **antihistamines (antihistaminics).** The term **antihistamine is** traditionally used to refer to drugs that block the **H_1-receptors.**

Best *et al.** (1927) made an epoch making observation that '**histamine**' was present in relatively high concentration in the lungs, which eventually gave rise to vasoconstriction, anaphylactic shock-like syndrome and acute respiratory distress in laboratory animals treated with IV administration. Subsequently, the histamine's specific role in the particular pathogenesis of the ensuing anaphylactic reaction was duly demonstrated and substantially established.

In the early 1930s, an amalgamation of sequential events and circumstancial evidences almost established the various deleterious and harmful effects caused by an excess of '**histamine**' ; and these findings were exclusively based on both *in vitro* and *in vivo* methods that were meticulously developed so as to screen the chemical effects upon the various physiological aspects, namely : bronchial, gastro-intestinal and other smooth muscle tissues. Thus, a broad platform was made available for the extensive as well as intensive screening of several synthesized drug molecules with respect to their possible viable '**histaminic activity**', in addition to their anticipated *anticholinergic* and *antiserotoninergic* pharmacological profile.



L-Histidine Histamine

Antihistaminics are widely used in the *palliative treatment in allergic conditions like hay fever, urticaria, some forms of pruritus, rhinitis, conjunctivitis, nasal discharge, mild asthma etc. A few antihistaminics possess potent antiemetic action and hence are frequently employed in the prevention and treatment of irradiation sickness, motion sickness (air, sea, road), nausea in pregnancy and post-operative vomiting.*

In general, the most common side-effect of **antihistaminics** is sedation which may be followed by drowsiness, impaired alertness and retarded ability to perform jobs which need high precision and concentration.

2. CLASSIFICATION

The commonly used **antihistaminics** may be classified on the basis of their chemical structures and these all are of the type **histamine H_1-receptor antagonists.** They are :

2.1. Histamine H_1-Receptor Antagonists

(*i*) **Aminoalkylethers :** *Examples*-Diphenhydramine Hydrochloride ; Bromodiphenhydramine Hydrochloride ; Dimenhydrinate ; Doxylamine Succinate ; Diphenylpyraline Hydrochloride.

(*ii*) **Ethylenediamines :** *Examples*-Mepyramine Maleate ; Tripelennamine Hydrochloride, Thonzylamine Hydrochloride ; Zolamine Hydrochloride.

(*iii*) **Thiophene Derivatives :** *Examples*-Methapyrilene Hydrochloride ; Methaphenilene Hydrochloride, Thenyldiamine Hydrochloride ; Chlorothen Citrate.

(*iv*) **Cyclic Basic Chain Analogues :** *Examples*

(*a*) **Imidazoline Derivatives,** *e.g.*, Antazoline Hydrochloride ; (*b*) Piperazine Derivatives, *e.g.*, Cyclizine Hydrochloride ; Chlorcyclizine Hydrochloride ; Meclizine Hydrochloride ; Buclizine Hydrochloride ; (*c*) Piperidine Derivativs, *e.g.*, Thenalidine Tartrate.

*Best CH *et al. J. Physiol,* **62** : 397, 1927.

(*v*) **Phenothiazine Derivatives :** *Examples*-Promethazine Hydrochoride ; Promethazine Teoclate ; Trimeprazine Tartrate ; Methdilazine Hydrochloride.

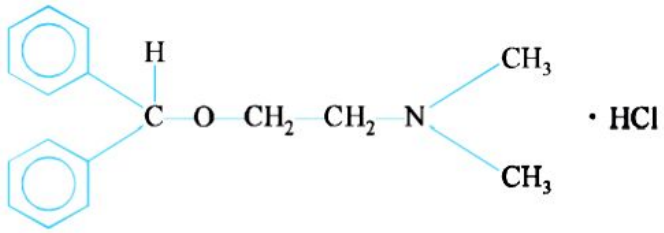
(*vi*) **Second-generation Non Sedating Antihistamines :** *Examples :* Terfenadine ; Astemizole ; Loratadine ; Acrivastine ;

(*vii*) **Miscellaneous Agents :** *Examples*-Phenindamine Tartrate ; Triprolidine Hydrochloride ; Chlorpheniramine Maleate ; Cyproheptadine Hydrochloride.

2.1.1. Aminoalkylethers

These are also referred to as basic ether group because of the presence of an alkyl amino function in the drug molecule.

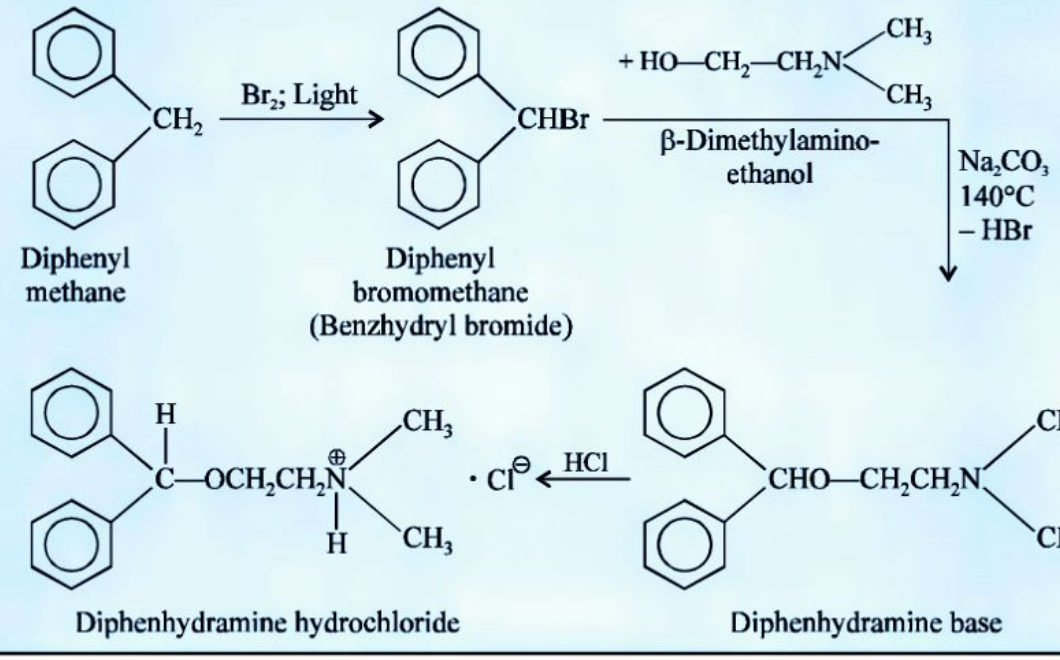
A. Diphenhydramine Hydrochloride BAN, USAN, Diphenhydramine INN,



2-(Diphenylmethoxy)-N, N-dimethylethylamine hydrochloride ; Ethanamine, 2-(diphenylmethoxy)-N, N-dimethyl-, hydrochloride ; BP ; BPC ; USP ;

Benadryl(R) (Parke-Davis) ; Bendylate(R) (Reid-Provident) ; SK-Diphenhydramine(R) (Smith Kline & French)

Synthesis

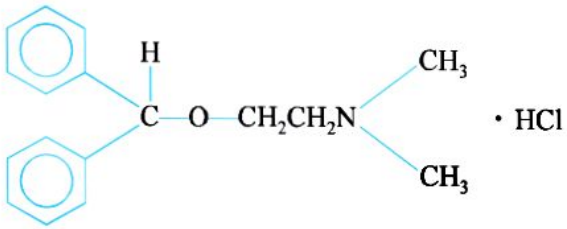


Diphenylbromomethane is first prepared by the bromination of diphenylmethane in the presence of light. Subsequently diphenhydramine base is obtained by heating diphenylbromomethane, β-dimethyl-amino-ethanol, and sodium carbonate is toluence. After distilling off toluene, the purified **diphenhydramine** is converted to the hydrochloride with hydrogen chloride.

It is *frequently used in mild, local allergic reactions due to insect bites. It possesses sedative, antiemetic and anti-tussive properties and can be used in seasonal allergic rhinitis, allergic manifestations due to urticaria and allergic conjunctivitis of inhalant allergens.*

Dose : *25–50 mg, usual, adult, oral dose 3 to 4 times a day, with maximum of 400 mg daily ; topical to skin 2% cream 3 or 4 times a day.*

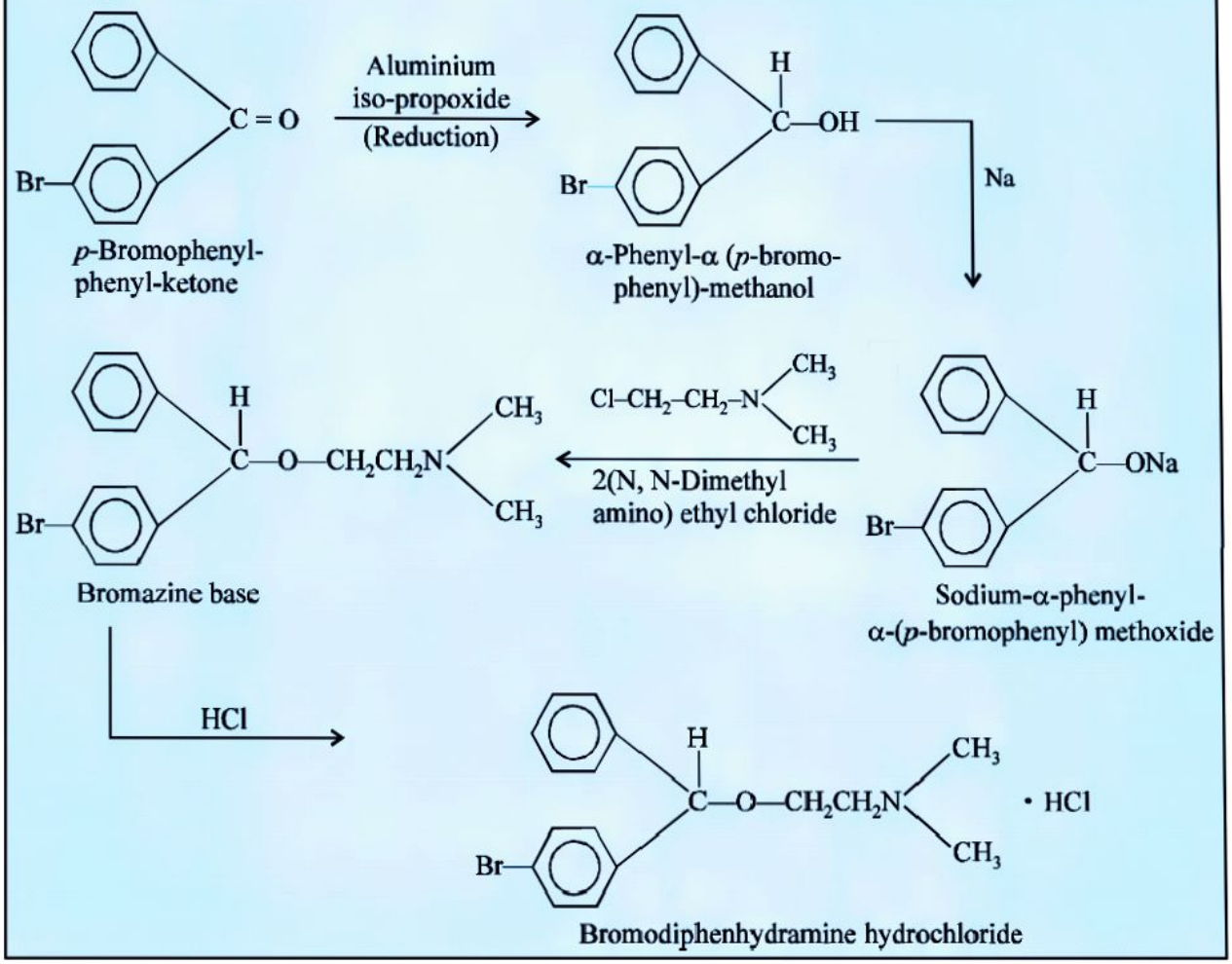
B. Bromodiphenhydramine Hydrochloride BAN, USAN, Bromazine INN,



2-[(*p*-Bromo-α-phenylbenzyl) oxy]-N, N-dimethylamine hydrochloride ; Ethanamine, 2-[(4-bromophenyl) phenylmethoxy]-N, N-dimethyl-, hydrochloride ; Bromazine hydrochloride ; BP ; USP ;

Ambodryl Hydrochloride(R) (Parke-Davis)

Synthesis

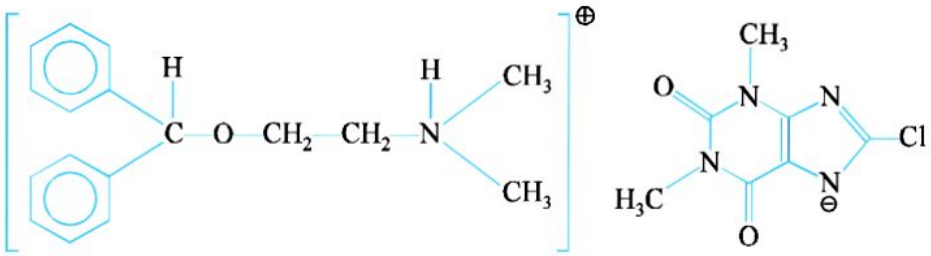


α-Phenyl-α-(*p*-bromophenyl) methanol is first prepared by the reduction of *p*-bromophenyl-phenyl ketone with aluminium isopropoxide, which on treatment with sodium metal results into the corresponding mono-sodium salt. This on reaction with 2(N, N-dimethyl amino) ethyl chloride loses a molecule of sodium chloride and provide the bromazine base which on neutralization with hydrogen chloride gives the **bromodiphenhydramine hydrochloride.**

It is probably effective for mild, local allergic reactions to insect bites, physical allergy, and *for minor drug reactions characterised by pruritis.*

Dose : *25 mg, usually 3 or 4 times daily.*

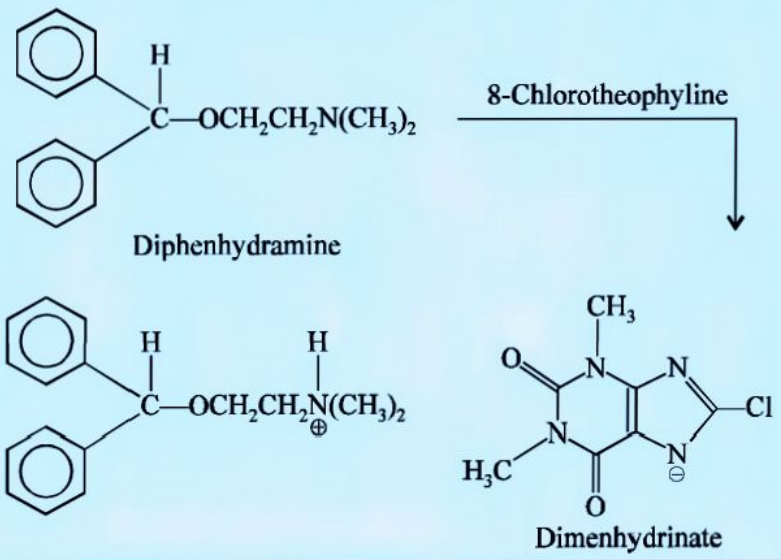
C. Dimenhydrinate INN, BAN, USAN,



8-Chlorotheophylline, compound with 2-(diphenylmethoxy)-N, N-dimethyl-ethylamine (1:1) ; 1H-Purine-2, 6-dioine, 8-chloro-3, 7-dihydro-1, 3-dimethyl-ethylamine (1:1) ; BP ; USP ; Int. P ; Ind. P ;

Dramamine(R) (Searle) ; Dommanate(R) (O'Neal, Jones and Feldman).

Synthesis

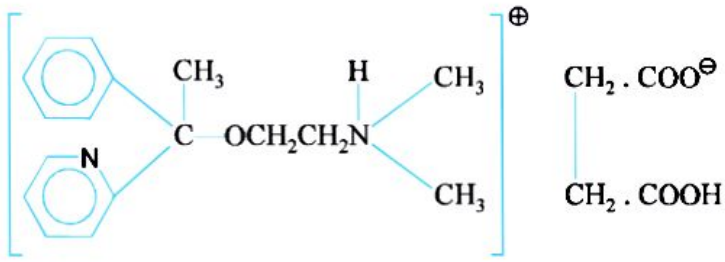


Dimenhydrinate is prepared from diphenhydramine and 8-chloro-theophylline in the stoichiometric proportion (1:1).

It is one and half time as potent as **diphenhydramine hydrochloride.** It is mostly used as an antinauseant, in motion sickness, radiation sickness and also in nausea of pregnancy.

Dose : *Usual, oral 50 mg thrice per day.*

D. Doxylamine Succinate BAN, USAN,



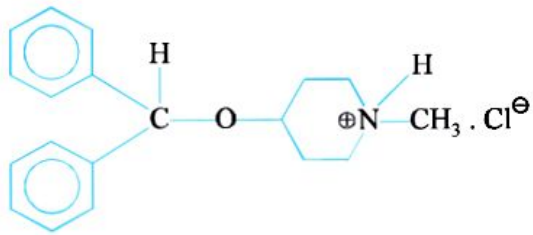
2-[α-[2-(Dimethylamino) ethoxy]-α-methylbenzyl] pyridine succinate (1:1) ; Ethanamine, N, N-dimethyl-2-[1-phenyl-1-(2-pyridinyl) ethoxy]-butanedioate (1:1) USP ;

Decapryn Succinate(R) (Merrell Dow) ; Unisom(R) (Pfizer)

It may be *used for allergic conjunctivitis due to inhalant allergens (like pollens and dust), seasonal and perennial allergic rhinitis, and uncomplicated allergic skin manifestations of urticaria.*

Dose : *12.5 to 25 mg ; Usual, adult, oral 4 to 6 times a day.*

E. Diphenylpyraline Hydrochloride BAN, USAN, Diphenylpyraline INN,



4-(Diphenylmethoxy)-1-methylpiperidine hydrochloride ; Piperidine, 4-(diphenylmethoxy)-1-methyl-, hydrochloride ; BP ; USP ;

Diafen(R) (Riker) ; Hispril(R) (Smith, Kline & French).

It may be employed for the *treatment of angioedema, dermographism and amelioration of reactions to blood or plasma. It is also effective for use in seasonal and perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods.*

Dose : *Usual, adult, oral 5 mg, 2 times a day.*

2.1.1.1. Mechanism of Action

The mechanism of action of aminoalkylethers dealt with in the previous section shall be discussed as under :

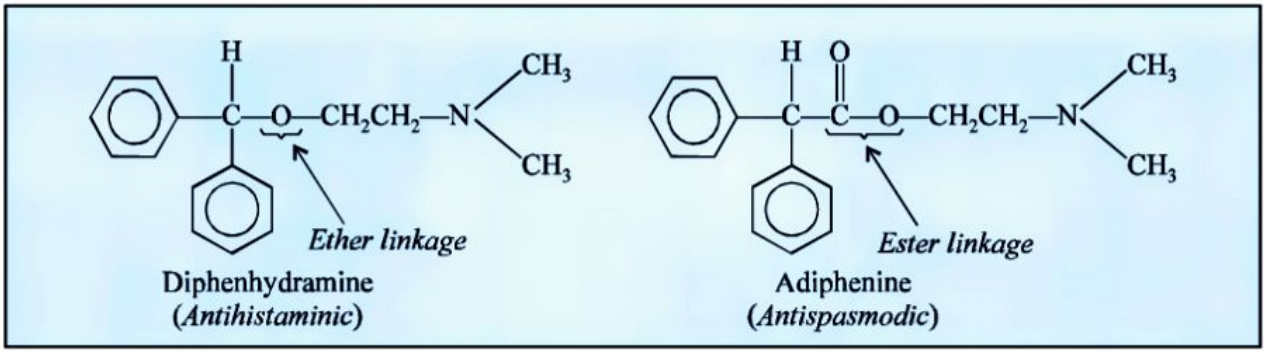
2.1.1.1.1. Diphenhydramine Hydrochloride

The **'drug'** is found to be well-absorbed after the oral administration ; and the first-pass metabolism is notedly so predominant that only 40-60% virtually reaches systemic circulation almost unchanged. It has been observed that the peak-plasma concentrations are invariably accomplished within a span of 1 to 4 hr, 80 to 85% gets bound to plasma protein and the elimination half-life varies between 2.4 to 9.3 hour.

As the **'drug'** has an atropine-like specific action, it needs to be administered with great caution and supervision in subjects having a history with asthma.

In reality, quite a few of the so called **'first-generation' H_1-antihistaminics** are believed to antagonize ACh. Nevertheless, the parasympatholytic activity could be regarded as the major undesirable side effects because it essentially gives rise to dry mouth and voiding difficulties. Interestingly, the ability to minimise nasal discharges (secretions) may be loohed upon as a positive clinical attribute, when included in *'hay fever'* and several *'cold'* medicaments.

SAR of Diphenhydramine. The **antihistaminic 'drug'** may be viewed as possessing an isosteric relationship with adiphenine an antispasmodic *i.e.*, the latter has an additional carbonyl moiety to give it the status of the *'ester'* compound as given below :



Diphenhydramine (*Antihistaminic*) Adiphenine (*Antispasmodic*)

The **'etiology'** of this drugs anticholinergic activity may be explained explicity if one takes into consideration the two functional moieties *viz.*, ether and ester as isosterically related to one another.

2.1.1.1.2. Bromodiphenhydramine Hydrochloride

The **'drug'** is found to be more lipid soluble in comparison to **diphenhydramine.** It is observed to exert almost twice its effective activity particularly in the guinea pigs against the lethal effects of histamine aerosols.

2.1.1.1.3. Dimenhydrinate

It is an **ethanolamine antihistaminic agent** belonging to the **first-generation H_1-antagonist** drug classes causing appreciable sedation. Besides, it also exhibits significiant anticholinergic activity.

2.1.1.1.4. Doxylamine Succinate

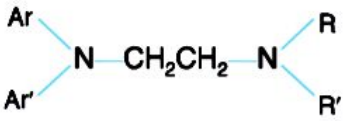
The **'drug'** is an ethanolamine antihistamine agent having appreciable sedative pharmacologic activity ; and, generally, listed in OTC* *sleep aids.* It also possesses significant anticholinergic activity.

2.1.1.1.5. Diphenylpyraline Hydrochloride

It exerts its antihistaminic properties along with antimuscarinic and central sedative pharmacologic activities. Though it may be applied topically but it has a risk of sensitization. Therefore, it finds its enormous application for the relief of hypersensitivity reactions, such as : *urticaria, angiodema, rhinitis, conjunctivitis,* and in pruritic skin disorders.

2.1.2. Ethylenediamines

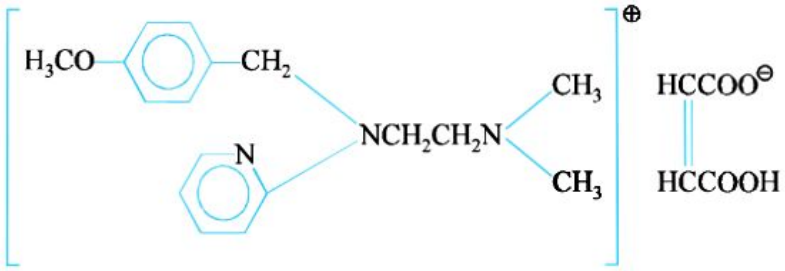
This class of compounds essentially have the following **general structure :**



*OTC = Over the Counter.

where Ar and Ar′ are aromatic or heteroaromatic moieties, and *R* and *R′* are small alkyl entities. A few classical members of this category shall be discussed here.

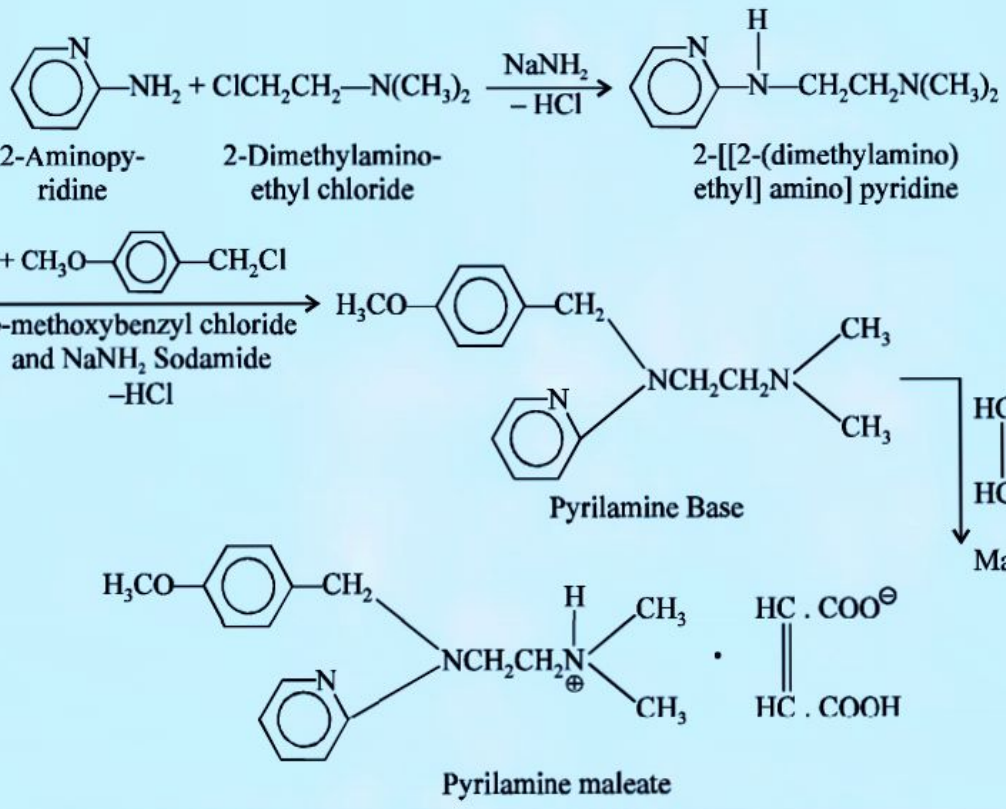
A. Mepyramine Maleate BAN, Pyrilamine Maleate USAN, Mepyramine INN,



2-[[(2-Dimethylamino) ethyl] (*p*-methoxybenzyl) amino] pyridine maleate (1:1) ; 1, 2-Ethanediamine, N-[(4-methoxy-phenyl) methyl]-N′, N′-dimethyl-N-2-pyridinyl-, (Z)-2-butanedioate ; Pyranisamine maleate ; Mepyramine Maleate BP ; Int. P., Ind. P. ; Purilamine Maleate U.S.P.,

Anthisan(R) (May & Baker) ; Dorantamin(R) (Dorsey Lab.) ; Minihist(R) (Ives) ; Pymafed(R) (Hoechst-Roussel)

Synthesis :



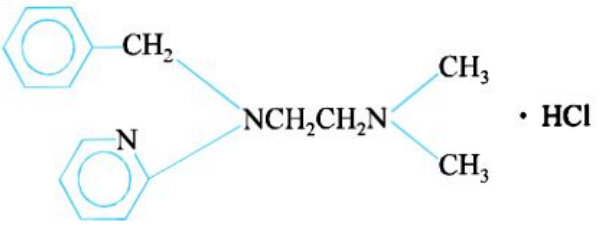
In the first step, 2-[[2-(dimethylamino) ethyl] amino] pyridine is prepared by the condensation of 2-aminopyridine with 2-dimethylamino ethyl chloride with the elimination of a molecule of hydrogen chloride in the presence of sodamide. The resulting product on further condensation with *p*-methoxy

benzyl chloride in the presence of sodamide yields the pyrilamine base which on neutralization with maleic acid gives rise to the desired product **pyrilamine maleate.**

It is a **potent antihistaminic agent with a low incidence of sedative effects.** It has acclaimed a legitimate entrance as component in a number of proprietary antitussive formulations.

Dose : *25 to 50 mg ; adult, oral, 3 to 4 times daily.*

B. Tripelennamine Hydrochloride BAN, USAN, Tripelennamine INN,



2-[Benzyl [2-(dimethylamino) ethyl] amino] pyridine monohydrochloride ; 1, 2-Ethanediamine, N, N-dimethyl-N′-(phenylmethyl)-N′-2-pyridinyl-, monohydrochloride ; BP 1963 ; USP ; Int. P., Ind. P. ;

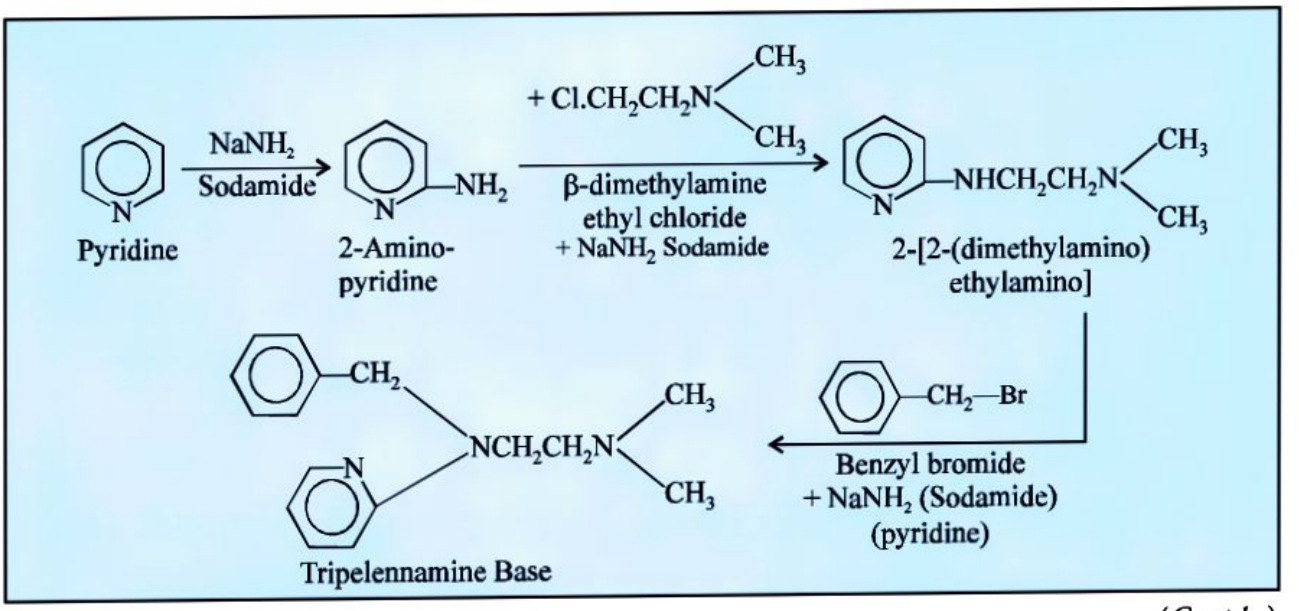
Pyribenzamine Hydrochloride(R) (Ciba-Geigy).

Synthesis

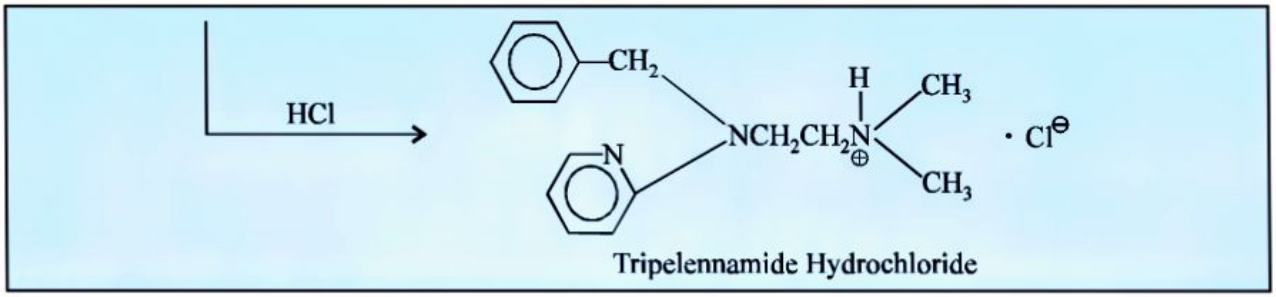
Tripelennamine can be prepared as follows : 2-aminopyridine, prepared by the action of sodamide on pyridine, is reacted with β-dimethylaminoethyl chloride in the presence of sodamide, and the resulting 2-[2-(dimethylamino) ethylamino] pyridine is subsequently condensed with benzyl bromide in the presence of sodamide. The corresponding hydrochloride salt is obtained from the base by treatment with hydrogen chloride in an organic solvent.

It is frequently employed in the *treatment of perennial and seasonal allergic rhinitis, allergic conjunctivitis due to inhalant allergens and foods, simple allergic skim manifestations of urticaria and angioedema, dermographism and anaphylactic reactions as an adjunct to adrenaline.*

Dose : *25 to 50 mg ; Usual, adult, oral 4 to 6 times a day.*

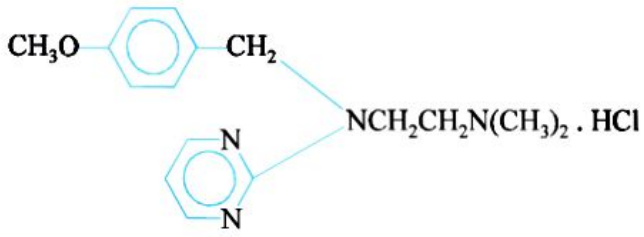


(*Contd...*)



Tripelennamide Hydrochloride

C. Thonzylamine Hydrochloride INN, BAN, USAN,

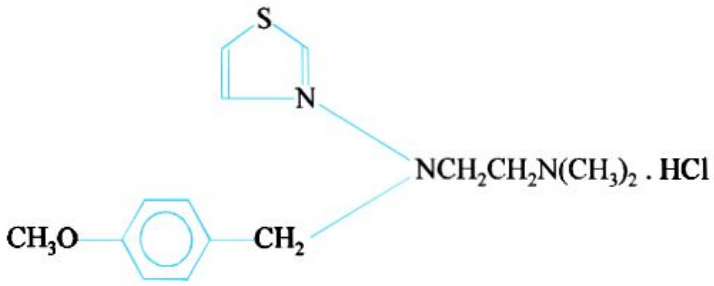


2-{[2-(Dimethylamino) ethyl]-(*p*-methoxybenzyl) amino} pyrimidine hydrochloride ; NF XII ; Resistab(R) (Bristol-Myers) ; Neohetramine Hydrochloride(R) (Nepera)

It is recommended for use with streptomycin in exudative human tuberculosis. It is used in treating the symptoms of hay fever, urticaria, drug reactions and other mild allergic conditions.

Dose : *50 mg ; Usual, adult, oral up to 4 times a day.*

D. Zolamine Hydrochloride USAN, Zolamine, INN,



2-[[2-(Dimethylamino) ethyl]-(*p*-methoxybenzyl) amino] thiazole monohydrochloride ; 1, 2-Ethanediamine, N-[(4-methoxyphenyl) methyl]-N′, N′-dimethyl-N-2-thiazolyl-, monohydrochloride.

It is used both as an antihistaminic and anaesthetic (topical) agent.

2.1.2.1. Mechanism of Action

The mechanism of action of some of the **ethylenediamines** are described as under :

2.1.2.1.1. Mepyramine Maleate (Pyrilamine Maleate)

The **'drug'** and **tripelennamine** are both pronounced clinically to belong to the category of less potent antihistaminics. It has been reported to be highly potent particularly in antagonizing the histamine-

*Casy AF : **Chemistry of H_1-Histamine Antagonists** : In : Rochae Silva M (ed.). **Handbook of Experimental Pharmacology,** Vol. 18.2, p-175, Springer-Verlag, New York. 1978.

induced contractions produced in guinea-pig ileum*. By virtue of this marked and pronounced local anaesthetic action, the **'drug'** is recommended to be taken along with food and **not be chewed prohibitively.**

SAR of Pyrilamine. It essentially differs structurally from **tripelennamine** by having a methoxy (OCH_3) functional moiety strategically positioned at the *para*-position of the benzyl radical.

2.1.2.1.2. Tripelennamine Hydrochloride

The **'drug'** (and its citrate) seem to be get metabolized almost completely to either quaternary ammonium N-glucuronide or *O*-glucuronides of the corresponding hydroxylated metabolites. The drug also undergoes several chemical modifications *in vivo*, namely : (*a*) ring hydroxylation ; (*b*) N-oxidation ; and (*c*) N-demethylation. In view of these glaring evidences the *'drug'* gets excreted principally in the urine as its conglomerate of metabolites.

Incidentally, **tripelennamine** enjoys the reputation of being the first and foremost **ethylenediamine** ever developed in the American Laboratories.

2.1.2.1.3. Thonzylamine Hydrochloride

The overall activity of this *'drug'* seems to be very much identical to **tripelennamine** but it is pronounced to have much less toxicity.

SAR to Thonzylamine. The only difference between this **'drug'** and tripelennamine is the presence of a **'pyrimidine nucleus'** instead of the **'pyridine nucleus'** in the latter, which perhaps retards its toxicity profile to an appreciable extent because of its comparatively faster metabolism *in vivo.*

2.1.2.1.4. Zolamine Hydrochloride

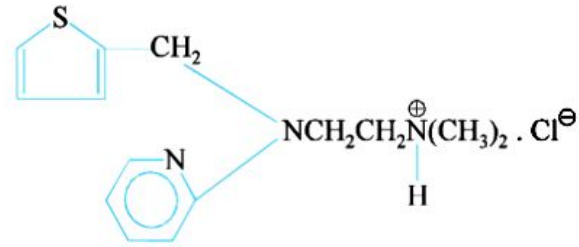
The **'drug'** possesses less toxicity in comparison to tripelennamine and thonzylamine. It exhibits both antihistaminic and anaesthetic pharmacological profile.

SAR of Zolamine. It essentially contains the **'thiazole moiety'** instead of the **pyridine** and **pyrimidine** groups present in tripelennamine and a 5-thonzylamine respectively. Being, a 5 membered ring (thiazole) which is certainly much more compact than the 6-membered heterocyclic ring present in the other two compounds.

2.1.3. Thiophene Derivatives

The **thiophene** moiety is an essential component of this group of compounds which exhibit significant antihistaminic properties. Though these compounds also possess an ethylene-diamine nucleus yet the presence of a **thiophene** group makes them belong to a separate category altogether.

A. Methapyrilene Hydrochloride BAN, USAN, Methapyrilene INN,



2-[[2(Dimethylamino) ethyl]-2-thenylamino] pyridine monohydrochloride ; 1, 2-Ethanediamine, N, N-dimethyl N′-2-pyridinyl-N′-(2-thenylmethyl)-, monohydrochloride ; USP ;

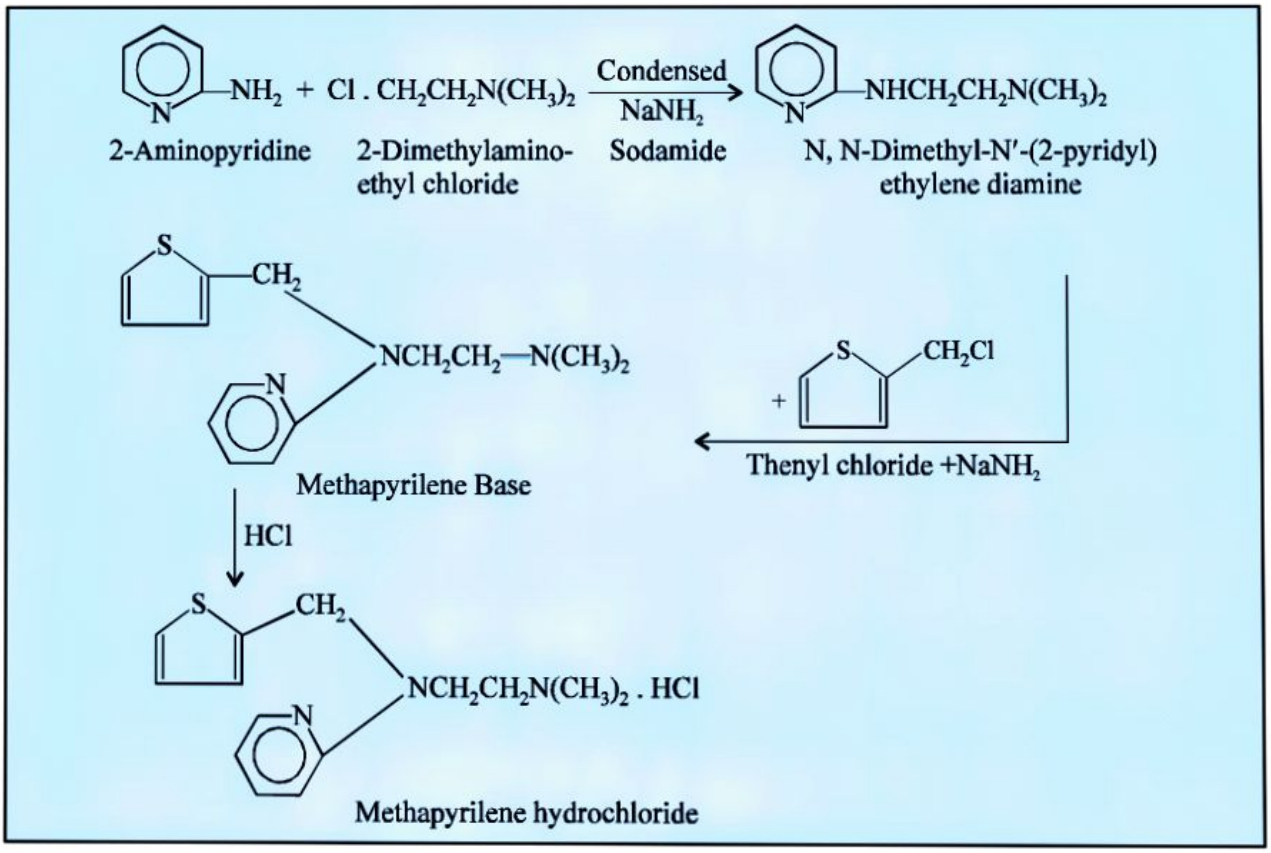
Histadyl$^{(R)}$ (Lilly) ; Semikon Hydrochloride$^{(R)}$ (Beecham) ; Thenylene Hydrochloride$^{(R)}$ (Abbott).

Synthesis

N, N-Dimethyl-N′-(2-pyridyl)-ethylene diamine is prepared by the condensation of 2-amino pyridine and 2-dimethylamino ethyl chloride in the presence of sodamide. The resulting product is

further condensed with 2-thenyl chloride, using sodamide as a catalyst, to obtain the methapyrilene base, which on neutralization with hydrogen chloride yields the methapyrilene hydrochloride.

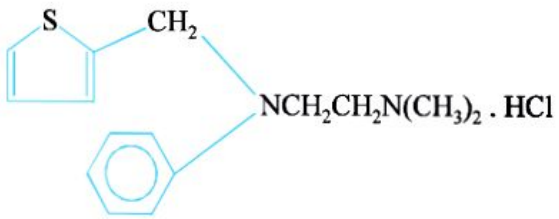
It essentially differs from tripelennamine in having a 2-thenyl (*i.e.*, thiophene-2-methylene) moiety instead of the benzyl group.



It possesses a low incidence of side-effects and may be employed in the treatment of all types of suspected allergies, namely—hay fever, chronic urticarias, allergic rhinitis and allergic dermatitis.

Dose : *50 to 100 mg, 3 to 4 times a day.*

B. Methaphenilene Hydrochloride USAN, Methaphenilene INN,



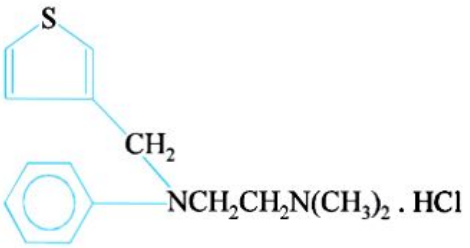
N, N-Dimethyl-N'-(α-thenyl)-N'-phenethylenediamine hydrochloride ; NF X ;

Diatrine Hydrochloride(R) (Warner Chilcott).

It is an effective antihistaminic agent. It induces slow incidence of side reactions but possesses a moderate tendency to cause gastro-intestinal irritation. It is a drug of choice for the symptomatic relief of upper respiratory infections.

Dose : *Usual, 25–50 mg 4 times per day.*

C. *Thenyldiamine Hydrochloride* BAN, *Thenyldiamine* INN, USAN,



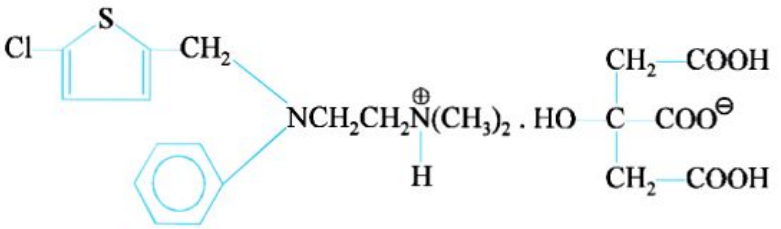
2-[[2-(Dimethylamino) ethyl]-3-thenylamino] pyridine-hydrochloride ; N, N-Dimethyl-N′-(2-pyridyl)-(3-thenyl)-ethylene-diamine hydrochloride ;

Thenfodil hydrochloride(R) (Winthrop) ;

It is an antihistaminic agent which is recommended in comparatively milder type of allergic conditions.

Dose : *Usual, oral, 15 mg up to 6 times per day.*

D. Chlorothen Citrate USAN, Chloropyrilene INN, Chloropyrilene Citrate BAN,



2-[(5-Chloro-2-thenyl [2-(dimethylamino) ethyl] amino] pyridine dihydrogen citrate ; Chloromethapyrilene citrate ; N.F. XIII ;

Panta(R) (Valeas, Italy).

Chlorothen is similar in structure to tripelennamine, the only difference being that the benzyl group in the latter is substituted by the 5-halothenyl moiety. It has been observed that the halogen-substitution enhances the antihistaminic activity and renders the compound less toxic than its corresponding non-halogenated version.

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

2.1.3.1. Mechanism of Action

The mechanism of action of the **thiophene structural analogoues** of histamine shall be discussed briefly as under :

2.1.3.1.1. Methapyrilene Hydrochloride

The FDA has declared it a potential carcinogen in 1979, and hence, it is no longer in use.

SAR of Methapyrilene. It essentially differs from **tripelennamine** in possessing a 2-thenyl (thiophene-2-methylene) moiety in place of the benzyl moiety. Besides, the thiophene ring is regarded to be isosteric with the benzene ring ; and, therefore, the isosteres found to display almost identical activity. An exhaustive study with respect to the **'solid-state conformation'** of this **'drug'** evidently showed that the geometrical *trans*-conformation is obviously the most preferred one for the two ethylene N-atoms.

2.1.3.1.2. Methaphenilene Hydrochloride

It is a potent antihistaminic agent that may give rise to rather mild type of gastro-intestinal irritation.

2.1.3.1.3. Thenyldiamine Hydrochloride

The *'drug'* is regarded as a traditional antihistaminic which action is usually associated with both troublesome sedative and antimuscarinic effects.

2.1.3.1.4. Chlorothen Citrate (Chloropyrilene Citrate)

It is invariably associated with an antibacterial formulation that is indicated mostly for the treatment of vasomotor rhinitis and other hypersensitivity reaction of the upper respiratory tract (URT) complicated by bacterial infections.

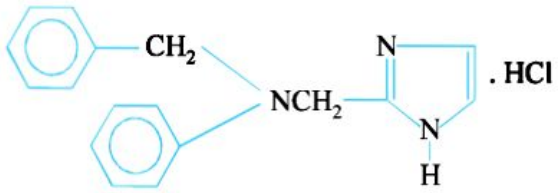
2.1.4. Cyclic Basic Chain Analogues

A variety of more potent and less toxic **antihistaminic agents** have been tailored by effecting molecular modifications of the general ethylenediamine structure whereby the dimethylamino function is essentially replaced by a small compact heterocyclic ring.

Thus, the cyclic basic chain analogs may be further sub-divided into **three** categories, namely :

(*a*) **Imidazoline Derivatives**

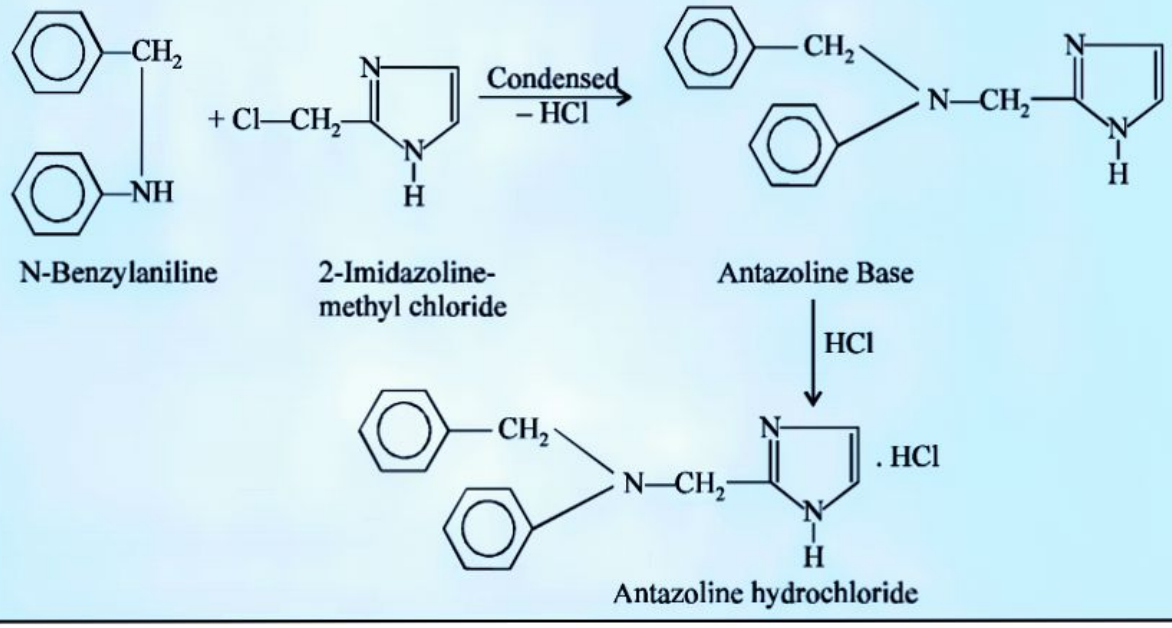
A. Antazoline Hydrochloride BAN, USAN, Antazoline INN,



2-(N-Benzylanilino) methyl-2-imidazoline hydrochloride ; N-Benzyl-N-(2-imdazoline-2-yl-methyl) aniline hydrochloride ; BP ; 1973, USP ; XV, Int. P., Ind. P.,

Antistine(R) (Ciba) ; Histostab(R) (Boots).

Synthesis



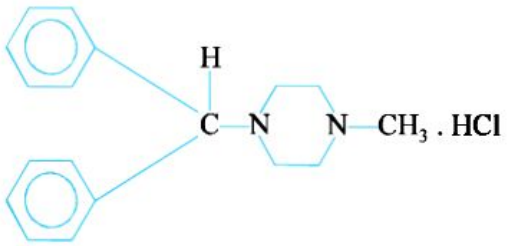
Antazoline base is prepared by the interaction of N-benzyl aniline with 2-imidazoline methyl chloride with the elimination of hydrogen chloride. The base is neutralized with hydrogen chloride to yield the desired **antazoline hydrochloride.**

It is less active than most of the other antihistaminic drugs, but has the advantage of being devoid of local irritant characteristics.

Dose : *50 to 100 mg.*

(*b*) **Piperazine Derivatives**

A. Cyclizine Hydrochloride BAN, USAN, Cyclizine INN,



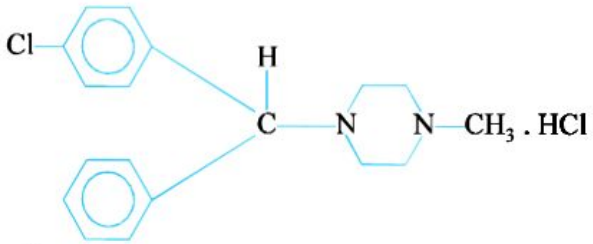
1-(Diphenylmethyl)-4-methylpiperazine monohydrochloride ; Piperazine, 1(diphenylmethyl)-4-methyl-, monohydrochloride ; BP ; USP ; Int. P., Ind. P.,

Marezine(R) (Burroughs Wellcome)

It is mostly employed as a prophylaxis and for treatment of motion sickness.

Dose : *25 to 50 mg.*

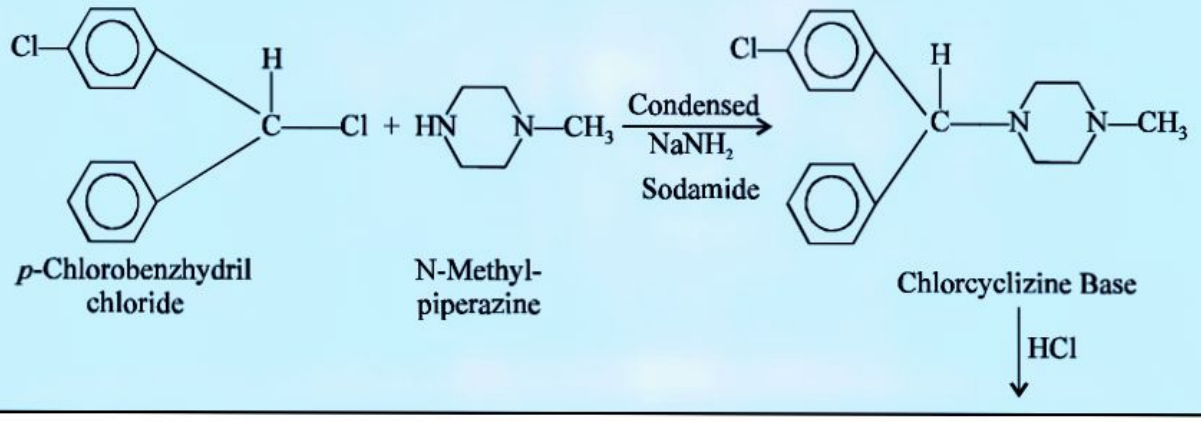
B. Chlorcyclizine Hydrochloride BAN, USAN, Chlorcyclizine INN,



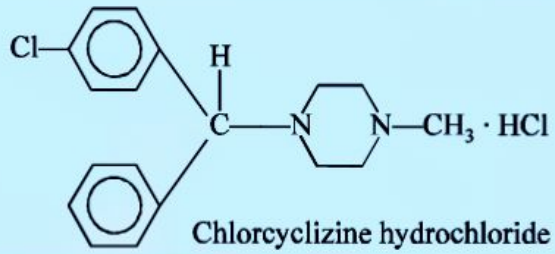
1-(*p*-Chloro-α-phenylbenzyl)-4-methylpiperazine monohydrochloride ; Piperazine, 1-[(4-chlorophenyl) phenylmethyl]-4-methyl-, monohydrochloride ; BP ; USP ; Int. P., Ind. P.,

Di-Paralene(R) (Abbott) ; Perazil(R) (Burroughs Wellcome)

Synthesis



(*Contd...*)



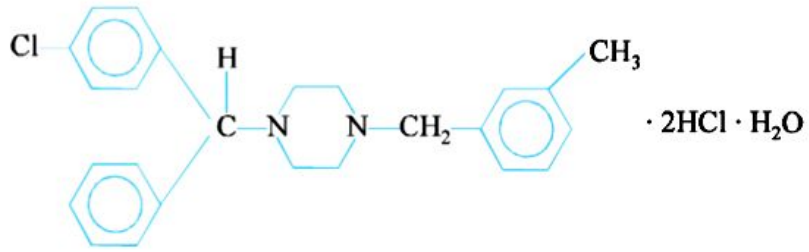
Chlorcyclizine hydrochloride

Chlorocyclizine base is first prepared by condensing together *p*-chlorobenzhydril chloride with N-methylpiperazine in the presence of sodamide. The resulting base is neutralized with hydrogen chloride to obtain the required chlorcyclizine hydrochloride.

Though it is less potent, it possesses a prolonged **antihistaminic action** of similar duration to that of **promethazine hydrochloride.** It has local anaesthetic, antiemetic and anticholinergic characteristics.

Dose : *50 to 200 mg.*

C. Meclizine Hydrochloride USAN, Meclozine INN, BAN,



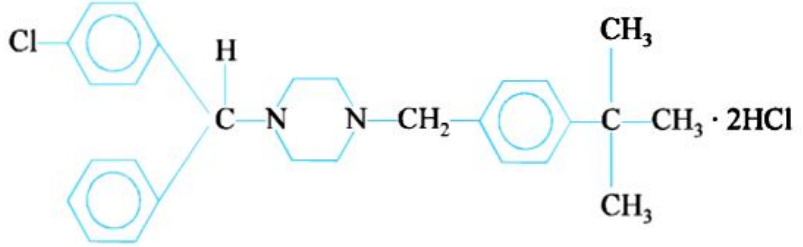
1-(*p*-Chloro-α-phenylbenzyl)-4-(*m*-methylbenzyl) piperazine dihydrochloride monohydrate ; Piperazine, 1-[(4-chlorophenyl) phenylmethyl]-4-[(3-methylphenyl)-methyl]-, dihydrochloride, monohydrate ; BP ; USP ; Int. P., Ind. P.,

Antivert(R) (Roerig) ; Bonine(R) (Pfizer).

It is mostly employed for its inherent antiemetic action which is quite marked and pronounced and lasts for up to 24 hours. It has also been used for the prevention and treatment of motion sickness and also for the relief of allergic conditions.

Dose : *25 to 50 mg.*

D. Buclizine Hydrochloride BAN, USAN, Buclizine INN,



1-(*p-tert*-Butylbenzyl)-4-(*p*-chloro-α-phenylbenzyl) piperazine dihydrochloride ; Piperazine, 1-[(4-chlorophenyl) phenylmethyl]-4-[(1, 1-dimethylethyl) phenyl] methyl]-, dihydrochloride ;

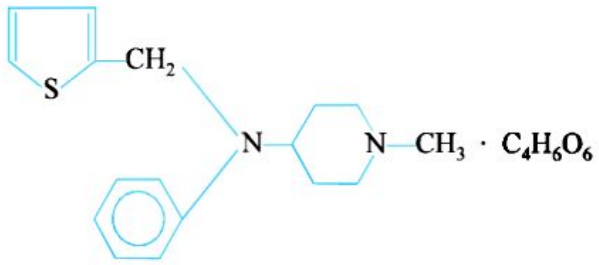
Bucladin-S(R) (Stuart) ; Vibazine(R) (Pfizer).

It is chiefly used for its antiemetic properties. It possesses less pronounced sedative effects than promethazine. *It is also recommended for the symptomatic treatment of allergic conditions and vertigo.*

Dose : *25 to 50 mg, 2 to 3 times a day.*

(*c*) **Piperidine Derivatives**

A. Thenalidine Tartrate BAN, Thenalidine INN,



1-Methyl-4-(N-then-2-ylanilino) piperidine tartrate ; Thenophenopiperidine Tartrate ; Thenopiperidine Tartrate ;

Sandosten(R) (Sandoz)

It is used for the prevention and treatment of allergic conditions.

Dose : *100 to 150 mg per day.*

2.1.4.1. Mechanism of Action

The mechanism of action of all compounds enumerated under sections (*a*) through (*c*) shall be treated individually in the sections that follows :

2.1.4.1.1. Antazoline Hydrochloride

The **'drug'** is less soluble than the corresponding phosphate salt and is mostly administered orally. It is found to be less active than a host of other antihistaminics ; however, it has been duly characterized by its predominant absence of local irritation.

Besides, it exhibits more than double than local anaesthetic potency of **'procaine'** and also exhibits the anticholinergic properties.

SAR of Antazoline. Just like the **ethylenediamines,** it also essentially comprises of an N-benzylamino function directly attached to a basic N-atom through a 2-carbon chain.

2.1.4.1.2. Cyclizine Hydrochloride

The **'drug'** is basically employed as a potent prophylaxis and also for the control, management and treatment of motion sickness.

2.1.4.1.3. Chlorcyclizine Hydrochloride

The **'drug'** is used invariably in the symptomatic relief of urticaria, hay fever, and a few other allergic manifestations.

SAR of Chlorcyclizine. It has been adquately demonstrated that the distribution or substitution of halogen either at the *ortho*-or at the *meta*-position of any of the two **'benzhydryl functional rings'** mostly gives rise to such compounds that do possess appreciably less potent acitivity.

2.1.4.1.4. Meclizine Hydrochloride

The **'drug'** is effective in vertigo intimately associated with such ailments that essentially affect the vestibular system. As the **'drug'** also exhibits anticholinergic activity, it may be employed in patients having a history of asthma, glaucoma, or prostatic enlargement.

SAR of Meclizine. It apparantly differs from chlorcyclizine by possessing an N-*m*-methylbenzyl functional moiety instead of the prevailing N-methyl moiety. Thus, it exhibits moderately potent antihistaminic profile.

2.1.4.1.5. Buclizine Hydrochloride

The **'drug'** acts by exerting appreciable anticholinergic and antihistaminic activities. Besides, it possesses CNS-depressant profile. Hence, indicated for the control and management of nausea, vomitting and dizziness closely related to motion sickness.

SAR of Buclizine. Importantly, buclizine-a member of the **piperazine class of antihistaminics** are very much structurally related to both the **ethylenediamines** as well as the **benzyhydryl ethers of ethanolamines.** Its structure essentially include the 2 carbon separation existing between the N-atoms, that forms a part of the piperazine ring.

2.1.4.1.5. Thenalidine Tartrate

The **'drug'** possesses the actions and uses of antihistaminics ; and has been employed parenterally for the symptomatic relief of hypersensitivity reactions.

2.1.5. Phenothiazine Derivatives

Since 1945, plethora of **antihistaminics** have come into existence as a consequence of bridging the aryl functional moieties of agents that were intimately related to the ethylene-diamines. **Phenothiazines** essentially possess S-atom as the bridging entity.

It is, however, pertinent to state here that the **phenothiazines** which predominantly exhibit therapeutically potential and useful antihistaminic activities should essentially contain the following characteristic features, namely :

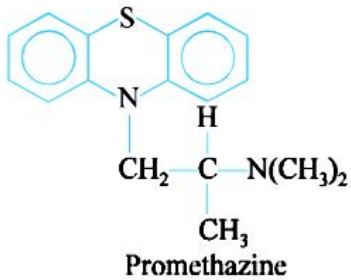
- at least 2 to 3 C-atom
- branched alkyl chain between the prevailing ring system
- terminal N-atom

Thus, the significant point of difference between the **phenothiazine antihistaminics** and the **phenothiazine antipsychotics** is that the latter should have an **unbranched propyl chain.** However, there are *two* most important aspects that are most essential for the phenothiazine antihistaminics, namely :

(*a*) 3 C-bridge between N-atoms are more potent *in vitro,* and

(*b*) heterocyclic ring of the antihistamines should be unsubstituted (*i.e.,* unlike the phenothaizine antipsychotics*.)

Toldy *et al.** (1959) resolved the two enantiomers of promethazine and observed identical antihistaminic and a number of other pharmacologic activities, such as : antiemetic, anticholinergic, and sedating agent. Importantly, this specific feature in **promethazines** is found to be in absolute contrast with regard to investigative studies carried out with **pheneramines** and **carbinoxamines,** wherein the strategically located chiral centre is located quite closer to the aromatic feature of the drug molecule.

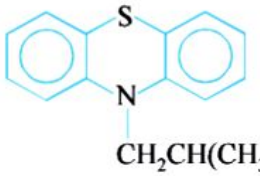


Promethazine

A number of **phenothiazine** derivatives have evolved into potent antihistaminic agents ; a few important ones are described below :

*Toldy L *et al. Acta. Chim. Acad. Sci. Hung.,* **19** : 273, 1959.

A. Promethazine Hydrochloride BAN, USAN, Promethazine INN,



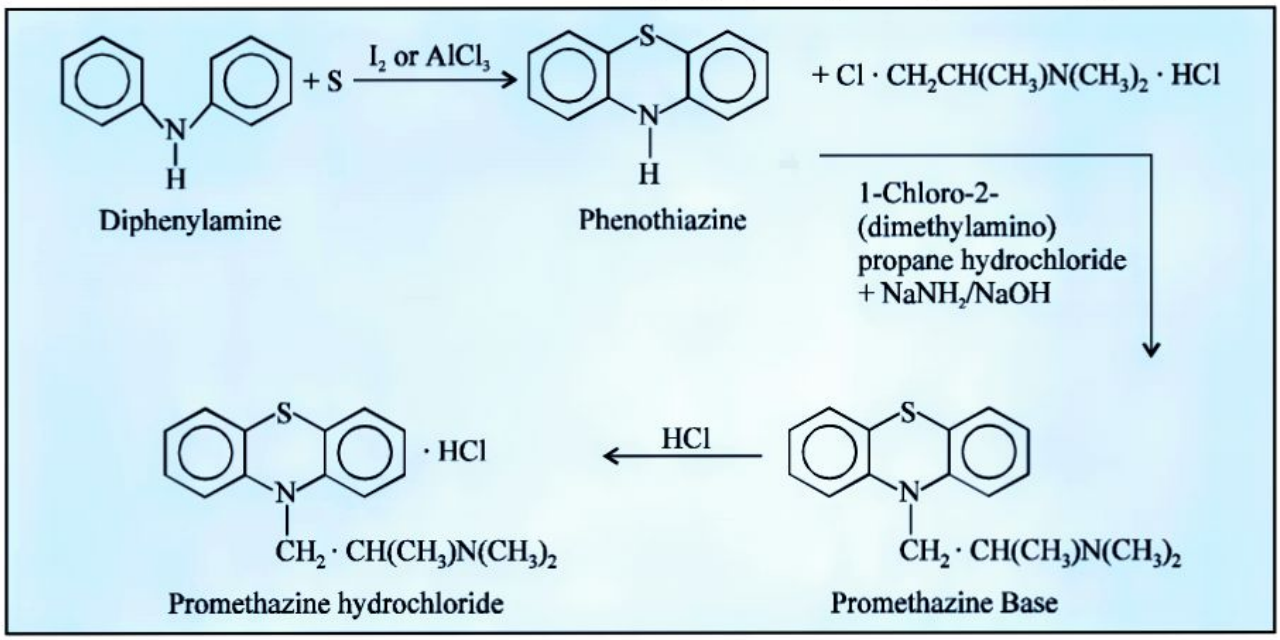
$CH_2CH(CH_3)N(CH_3)_2 \cdot HCl$

10-[2-(Dimethylamino) propyl] phenothiazine monohydrochloride ; 10H-Phenothiazine-10-ethanamine, N, N, α-trimethyl-, monohydrochloride ; BP ; USP ; Eur. P., Int. P., Ind. P ;

Phenergan(R) (Wyeth) ; Remsed(R) (Endo) ; Zipan(R) (Savage) ; Ganphen(R) (Reid-Provident) ; Fellozine(R) (O'Neal, Jones & Feldman) ; Tixylix(R) (May & Baker, U.K.)

Synthesis

Phenothiazine is first prepared by fusing together diphenylamine and sulphur in the presence of iodine or aluminium trichloride. Promethazine base may be prepared by reacting the resulting phenothiazine

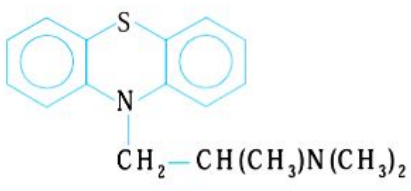


with 1-chloro-2-(dimethylamino) propane hydrochloride in the presence of sodamide and sodium hydroxide in xylene. The corresponding base is extracted, purified and converted to the hydrochloride.

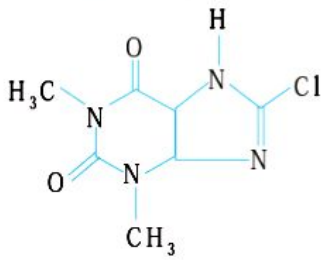
It has a prolonged duration of action. It may be used effectively in perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods ; and certain milder type of skin manifestations of urticaria. It also possesses some anticholinergic, antiserotoninergic, and marked local anaesthetic properties.

Dose : *20 to 50 mg per day (B.P.) ; 12.5 to 150 mg per day (USP).*

B. Promethazine Teoclate INN, USAN, Promethazine Theoclate BAN,



$CH_2-CH(CH_3)N(CH_3)_2$



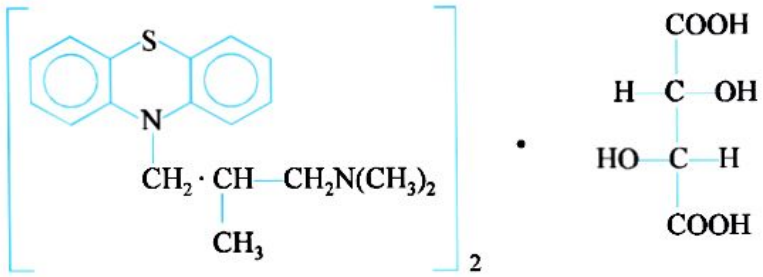
10-(2-Dimethylaminopropyl) phenothiazine compound of 8-chlorotheophylline ; Promethazine chlorotheophyllinate ; BP ; BPC ; USP ;

Avomine(R) (May & Baker)

It is mainly used as an antiemetic in the prevention and treatment of motion sickness. It may also be used in post-operative vomiting, the nausea and vomiting of pregnancy, drug-induced nausea and vomiting and in irradiation sickness.

Dose : *25 to 50 mg per day.*

C. Trimeprazine Tartrate BAN, USAN, Alimemazine INN,



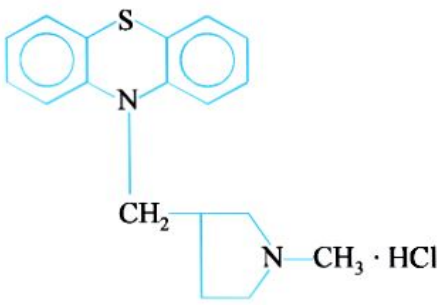
10-[3-(Dimethylamino)-2-methylpropyl] phenothiazine tartrate (2:1) BP ; USP ;

Temaril(R) (Smith, Kline & French)

It is used mainly for its marked and pronounced effect in the *relief of pruritus.* Its overall pharmacological characteristic lie between that of promethazine and chlorpromazine.

Dose : *10 to 40 mg ; adult, oral per day.*

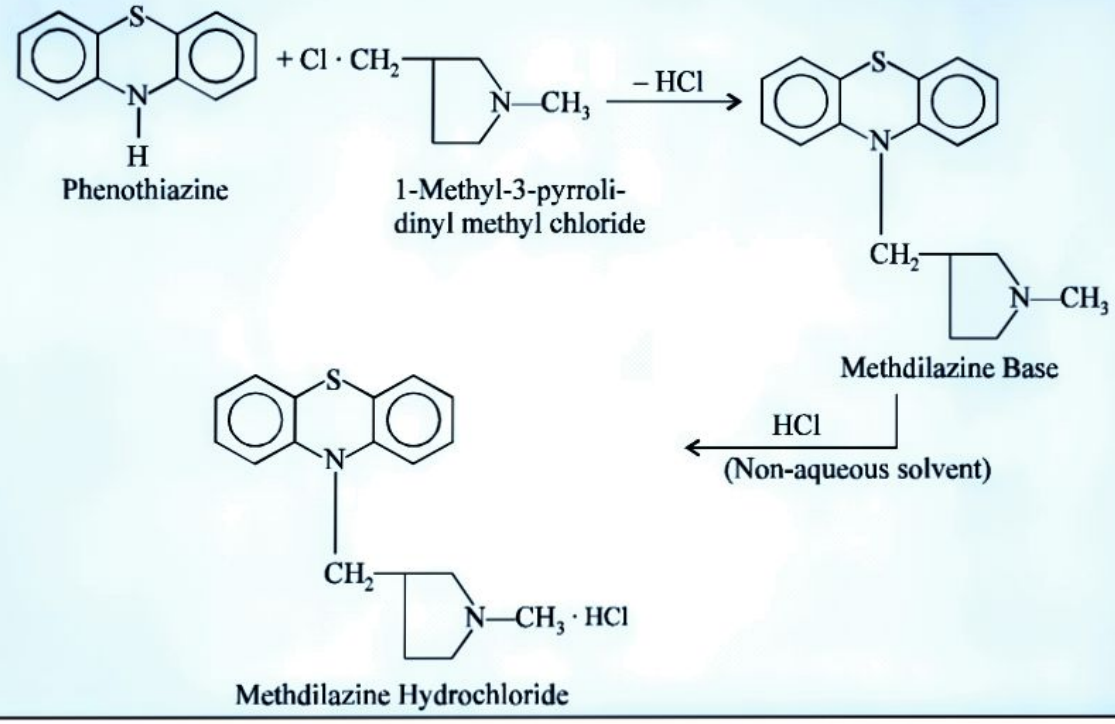
D. Methdilazine Hydrochloride BAN, USAN, Methdilazine INN,



10-[(1-Methyl-3-pyrrolidinyl)-methyl phenothiazine monohydrochloride ; 10H-Phenothiazine, 10-[(1-methyl-3-pyrrolidinyl) methyl]-, monohydrochloride ; USP ;

Tacaryl Hydrochloride(R) (Westwod)

Synthesis



Methdilazine is prepared by reacting together phenothiazine and 1-methyl-3-pyrrolidinyl methyl chloride ; the resulting base is treated with equimolar quantity of hydrogen chloride in a non-aqueous solvent.

It may be used for the symptomatic relief of urticaria. It has also been used successfully for the treatment of migraine headache.

Dose : *8 mg usual, adult, oral 2 to 4 times a day.*

2.1.5.1. Mechanism of Action

The mechanism of action of certain members of this particular category of **antihistaminics** shall be discussed below :

2.1.5.1.1. Promethazine Hydrochloride

The **'drug'** is found to be well absorbed, and the peak optimum effects invariably take place very much within a span of 20 minutes after adequate oral, rectal, or IM administration. It is also observed to get bound to the plasma proteins to an extent of 76-80%. However, the **'drug'** gets excreted gradualy both in the urine and faeces, primarily in the form of its corresponding **inactive metabolites** *viz.*, **sulphoxides,** and **glucuronides.**

2.1.5.1.2. Trimeprazine Tartrate

The **'drug'** has an additional methylene ($-CH_2-$) unit in the side-chain of **promethazine,** which renders it more active than the latter, and interestingly less active than **CPZ** in histamine-induced bronchospasm in the guinea pigs. Hence, it is mainly used as an antipuritic drug.

2.1.5.1.3. Methdilazine Hydrochloride

The replacement of the moderately longer side chain of **promethazine (PMZ)** at position 10 has been meticulously substituted by a methylene-linked N-methyl pyrrolidine nucleus, which being rather

compact and small in its dimensions, enables the '**drug**' to exert its effect solely for the symptomatic relief of *urticaria*. It is also indicated invariably in very seriously ill or dehydrated children on account of the significantly greater susceptibility of *dystonias** with the **phenothiazines.**

2.1.6. Second-generation Nonsedating Antihistamines

Since 1980s an enormous impetus has been geared towards the development of improved H_1 selectivity so that the new breed of antihistaminics should bear practically no sedative properties, and may also possess adequate antiallergic activities. In fact, the outcome of such an overwhelming rigorous concerted research activities towards producing an altogether new class of antihistaminics have been baptised as the **second generation antihistamines.**

It has been critically observed that most of these newer compounds belonging to this category do possess a wide variation in their structural profile ; however, their pharmacologic characteristic features are not so variant in nature, as they invariably exert their action principally in the periphery. It is pertinent to mention here that the structural resemblance to the **first generation H_1-antogonists** (see Section 2.1) is not strictly adhered to by virtue of the fact that most of these drug substances came into existence first in the normal process of investigation pertaining to several other diversified pharmacologic targets.

In general, the **second-generation non-sedating antihistamines** essentially possess selective peripheral H_1-antagonism activities, and the specifically exhibit much less anticholinergic activity. Besides, they are associated with lowered affinity for adrenergic and serotonergic receptors, and usually possess very limited CNS-effects.

The mechanism of action of these agents show that they do not penetrate the blood brain barrier (BBB) appreciably most probably on account of the following cardinal factors, such as :

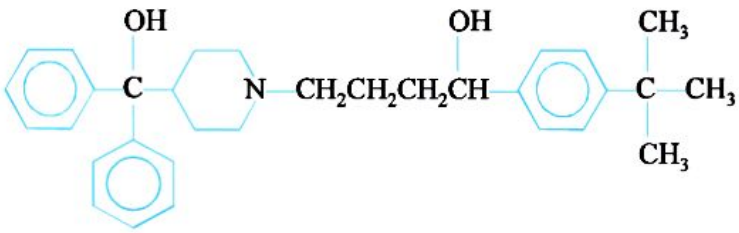
(*a*) Amphoteric nature (*i.e.*, majority of them are usually zwitter ionic at the prevailing physiologic pH) ;

(*b*) Partitioning properties ; and

(*c*) Behave as substrates for the drug efflux of either **P-glycoprotein transporter** or organic anion transporter protein.**

A few typical members of this category of **antihistaminics** shall now be discussed as under :

A. Terfenadine USAN, BAN,



Alpha-[4-(1, 1-Dimethylethyl) phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol ;

Seldane(R) ;

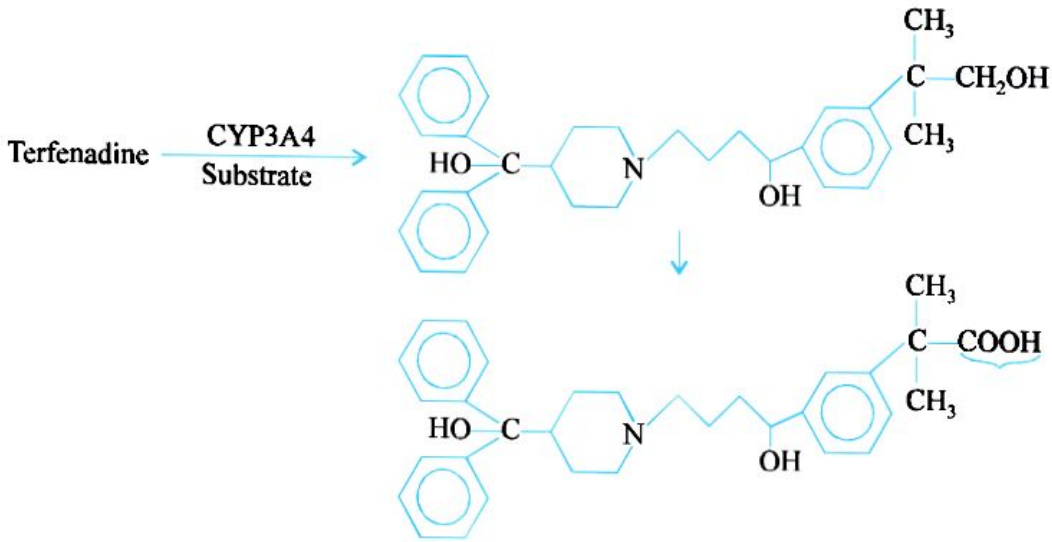
SAR : Terfenadine was discovered in the course of an extensive and intensive search for new **butyrophenone antipsychotic drugs** as could be seen by the presence of the N-phenylbutanol substituent. It is also studded with a **diphenylmethyl piperidine group structural analogous** as is normally observed in the **piperazine antihistaminics.**

*Prolonged muscle contractions that may cause twisting and repititive movements or abnormal posture.

Cvetkovic M *et al. Drug Metab. Dispos.* **27, 866–871, 1999.

Although **terfenadine** once enjoyed the very popular nonsedating antihistamines, but the extensive clinical experience pronounced it to be an altogether dangerous drug causing serious cardiac arrythmias, taking place very often in the event when certain other drugs were administered concomitantly. Such effects are caused due to the blockade of delayed rectifier K^+ channels in cardiac tissue, and hence are intimately related to the parent molecule.

Mechanism of Action. The '**drug**' undergoes rapid oxidation *in vivo* that finally gives rise to the formation of the corresponding carboxylic acid metabolite,* which is presently marketed as **fexofenadine** as given below :

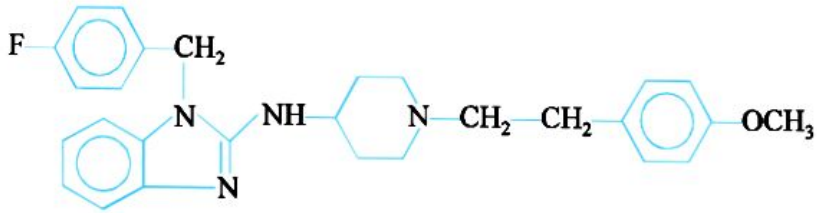


Fexofenadine

In fact, the acid metabolite is ultimately responsible for the antihistaminic properties of *terfenadine* in humans because the parent compound is readily metabolized *via* CYP3A4 substrate catalyzed processes in due course.

Nevertheless, the **histamine receptor** affinity of terfenadine are supposed to be associated primarily to the presence of the respective diphenylmethyl piperidine functional group. The actual cause of its prolonged action is solely on account of its slow dissociation from these receptors**.

B. Astemizole BAN, USAN,



1H-Benzimidazol-2-amine, 1-[4-fluorophenyl] methyl]-N-[1-[2, 4-methoxyphenyl) ethyl]-4-piperidinyl- ;

Hismanal(R) ;

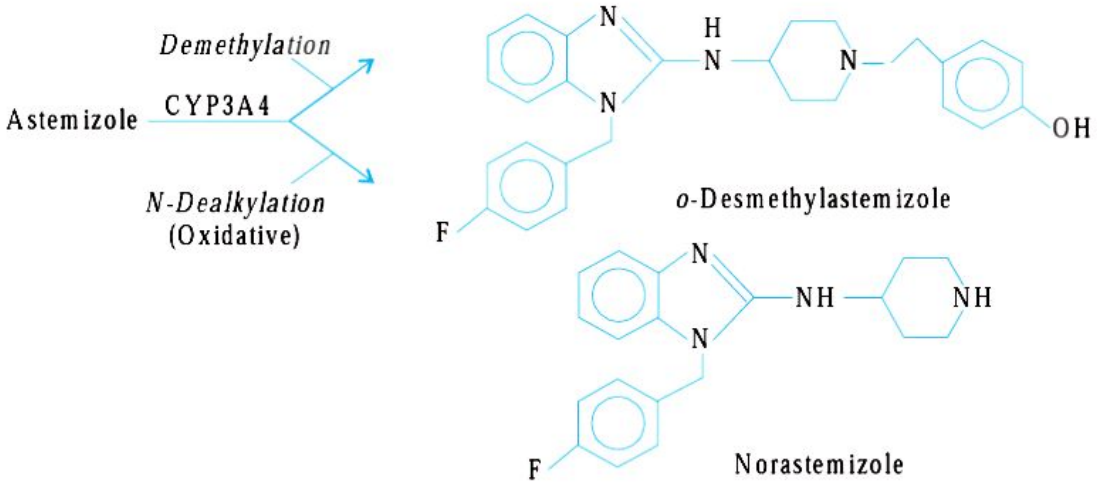
*Lalonde RL *et al. Pharm. Res.* **13**, 832–8, 1996.

**Facts and Comparison pp. 188-194C, 1993.

Astemizole is the creative product by the medicinal chemists of an extensive as well as intensive search of a series of **benzimidazoles.*** These new breed of the synthesized products may be regarded as the 4-aminopiperidines wherein the *para*-amino functional moiety essentially holds the *two aromatic rings viz., first,* present in the benzimidazol structure itself ; and *secondly,* as the *para*-fluorophenyl moiety linked at one of the N-atoms.

The **drug** is found to be more potent and possesses longer duration of action than the terfenadine. It is a slow-onset, long acting and nonsedating **piperidine antihistaminic** having practically little anticholinergic activity. It is indicated for seasonal allergic rhinhitis and chornic urticaria.

Mechanism of Action. At least two **active metabolites,** namely : (*a*) **o-desmethylastemizole ;** and (*b*) **norestemizole,** as shown below are obtained :



Kamei *et al.* ** (1991) confirmed the presence of a **'third metabolite'** that may also contribute to the effects of **astemizole** to a certain extent.

Astemizole gets largely distributed in the peripheral tissues having the highest concentration found in the *liver, pancreas,* and *adrenal glands.* The **'drug'** is observed to undergo substantial first-pass metabolism involving such processes as : oxidative dealkylation, aromatic hydroxylation, and glucuronidation. Interestingly, one of the active metabolites *i.e, o*-desmethylastemizole essentially possesses antihistaminic activity comparable to the parent drug, and hence helps to enhance the therapeutic activity.

Besides, **astemizole** is highly protien bound (96%) and has a plasma half-life of 1–6 days. However, the metabolite **desmethylastemizole** shows a half-life ranging between 10 to 20 days, that solely depends on the dosage regimen and its frequency.

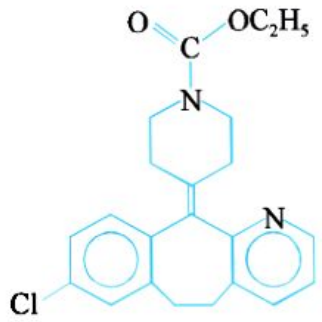
SAR of Astemizole. The piperidino-amino-benzimidazol group seems to be absolutely an essential requisite for the H_1-receptor affinity ; besides, helping appreciably to the persistent receptor binding which ultimately gives rise to the prolonged action.

---

*Janssens F *et. al. J. Med. Chem.*, **28**, 1943–7, 1985.

Kamei C *et. al Arzneim Forsch,* **41, 932–6, 1991.

C. Loratadine BAN, USAN,

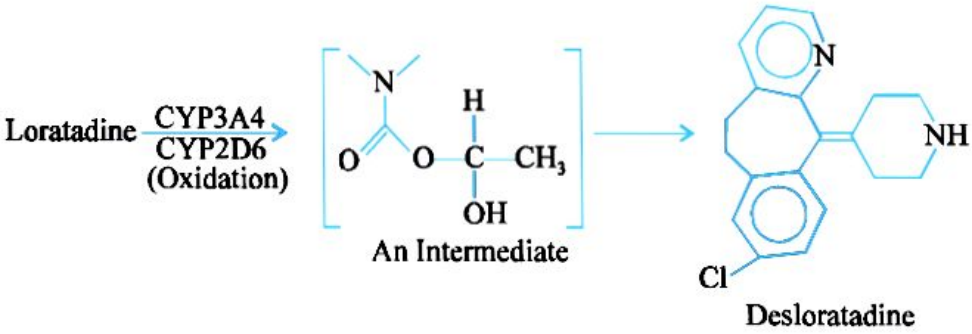


1-Piperidinecarboxylic acid, 4-(8-chloro-5, 6-dihydro-11H-benzo [5, 6]-cycloheptal [1, 2-*b*] pyridin-11-ylidene]- ;

Claritin$^{(R)}$;

It is a long-acting, nonsedating tricyclic antihistaminic drug. It possesses practically little anticholinergic activity. It shows potency that is fairly comparable to **astemizole** and significantly greater than **terfenadine.***

Mechanism of Action. Loratadine undergoes metabolic conversion to the corresponding major metabolite **decarboethoxyloratadine (desloratadine)** that specifically occurs *via* an **oxidative process** rather than *via* a direct means of **hydrolysis** as depicted below :



It has been observed that both CYP2D6 and CYP3A4 seem to be the perspective CYP450 isoenzymes that particularly help in the process of catalysis of this oxidative metabolic phenonomenon**. Interestingly, the ensuing metabolite **(desloratadine)** fails to gain its entry into the CNS in appreciable concentrations. It is, however, pertinent to state here that apparently among the **nonsedating second-generation antihistaminics,** this specific metabolite is found to be the only **nonzwitterizonic species.** Simons *et al.**** (1999) made a critical observation that while on one hand the failure of zwitterionic concentrations to have an easy access to the respective CNS sites in reasonably appreciable concentrations may be rationalized promptly, while on the other an identical explanation is not probably apparant for either the parent drug *loratadine* or its corresponding metabolite **desloratadine.*****

*Ahn HS *et. al. Eur. J. Pharmacol,* **127,** 153, 1986.

Yumibe N *et. al. Biochem Pharmacol,* **51 : 165–72, 1996.

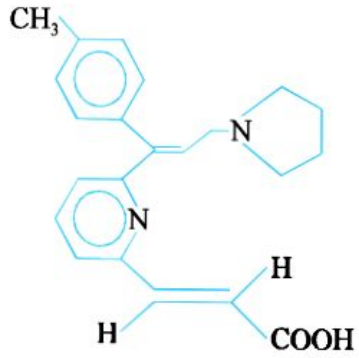
***Simons FE and Simons KJ, *Clinical Pharmacokinetics,* **36,** 329–52, 1999.

****Smith SJ, *Cardiorascular toxicity of antihistamines : Otolaryngol Head Neck Surg.* **III,** 348–54, 1994.

Besides, the competitive substrates for **CYP3A4** do not significantly give rise to drug-drug interaction, as could be seen with **astemizole** and **terfenadine,** by virtue of the fact that the parent molecule **(loratadine)** overwhelmingly lacks effect on K^+ rectifying channels located in the cardiac tissue.

SAR of Loratadine. The *'drug'* is intimately related to the **first generation tricyclic antihistaminics** and also to the **antidepressants.**

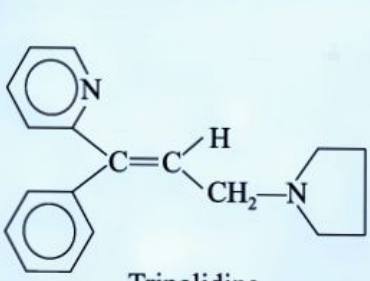
D. **Acrivastine** BAN, USAN,



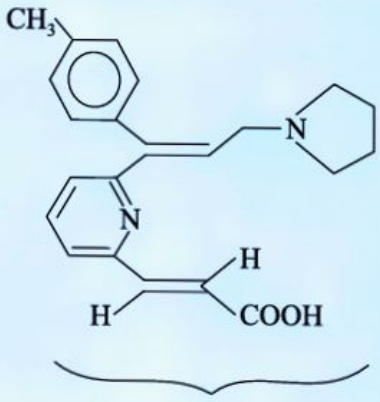
(E, E)-3-[6-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl-2-puridinyl]-2-propenoic acid ; (Semprex)$^{(R)}$;

Acrivastine displays antihistaminic potency as well as the duration of action fairly comparable to *tripolidine* ; however, unlike latter the former fails to exhibit appreciable anticholinergic activity at the therapeutic concentrations. Besides, the obvious increase in the polarity of **acrivastine** on account of the strategically positioned carboxyethyl actually limits the BBB penetration significantly which ultimately allows this *'drug'* to cause less sedation in comparison to **tripolidines.**

SAR of Acrivastine. The **'drug'** is of specific interest solely from a **'drug design'** standpoint. In fact, making an intensive search for new molecular entities, it does not bring forth any **'new chemistry'.** Interestingly, the already known old compound, **tripolidine,** has been restructured by enhancing the hydrophilicity *via* strategically introducing an acrylic acid functional moiety that ultimately yielded acrivastine as shown below :



Tripolidine
[Actidil$^{(R)}$]
(An 'Alkenylamine')



Acrylic acid
Acrivastine
[Semprex$^{(R)}$]

The lowering of the lipoidal solubility characteristic feature in the drug molecule still retained an effective H_1-antagonism peripherally. It also drastically squeezed in the $t_{1/2}$ to 1.7 hours only when compared to 4.6 hours for the parent molecule tripolidine.

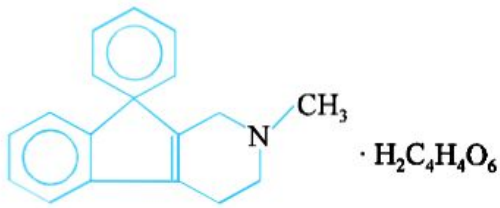
Mechanism of Action. The **'drug'** has a mean peak plasma concentration varying too widely ; and it seems to penetrate the CNS quite sluggishly. However, the metabolic fate of the **'drug'** is yet to be established.

Usual adult dose : Oral, 8 mg/60 mg/3–4 times per day.

2.1.7. Miscellaneous Agents

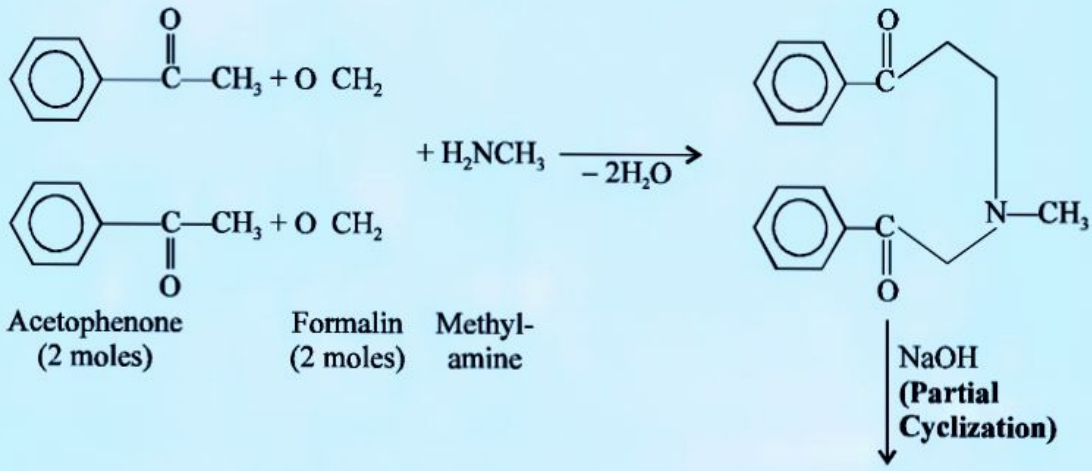
A few medicinally potent **antihistaminics** that cannot be conveniently accommodated under the above-mentioned categories (*viz* : *A* to *E*), but possess one or two nitrogen atoms in a heterocyclic system are discussed below :

A. Phenindamine Tartrate BAN, USAN, Phenindamine INN,

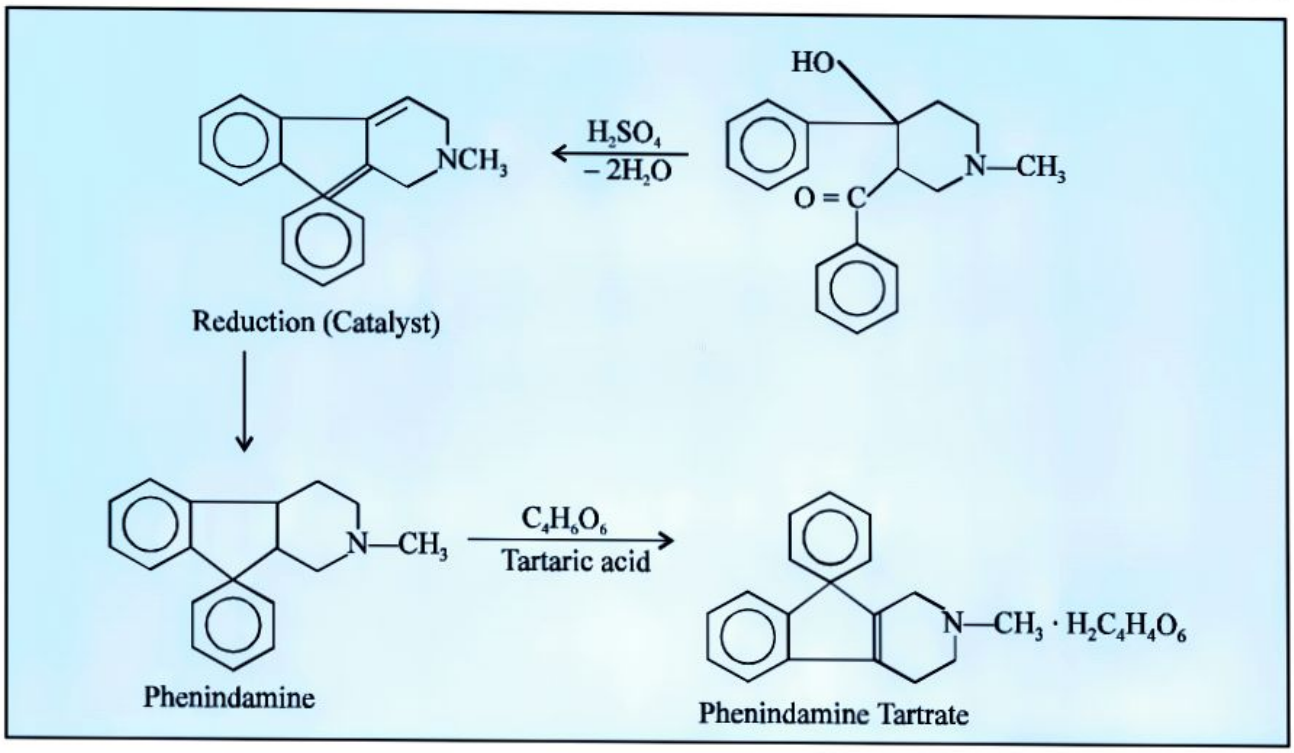


1, 2, 3, 4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate ; 2, 3, 4, 9-Tetrahydro-2-methyl-9-phenyl-1H-indenol [2, 1-C] pyridine hydrogen tartrate ; BP ; NF XIV, Int. P., Ind. P., Theophorin(R) (Hoffmann-La Roche)

Synthesis



(*Contd...*)

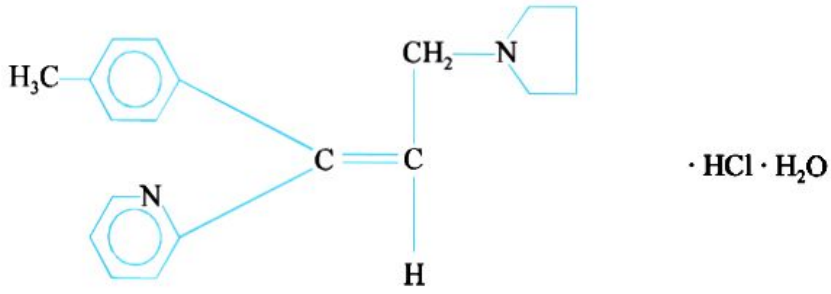


Two moles each of acetophenone, formaldehyde and one mole of methylamine are condensed to form an intermediate compound with the loss of two moles of water. This intermediate product on treatment with sodium hydroxide undergoes partial cyclization. On further treatment of the resulting product with concentrated sulphuric acid the complete cyclization takes place thereby losing two moles of water. This compound on catalytic reduction yields phenindamine which on treatment with an equimolar proportion of tartaric acid yields **phenindamine tartrate.**

It is less effective than promethazine but it does not generally produce drowsiness and may even cause a mild stimulation.

Dose : *75 to 150 mg per day.*

B. Triprolidine Hydrochloride BAN, USAN, Triprolidine INN,

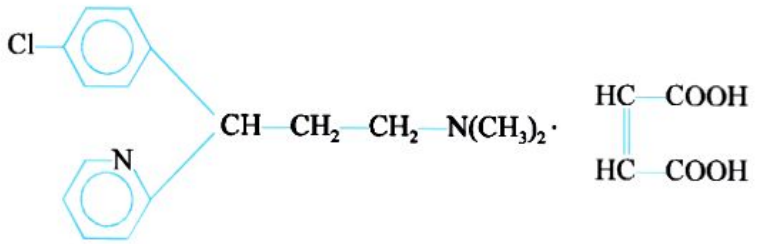


(E)-2 [3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl] pyridine monohydrochloride monohydrate ; BP ; USP ; Actidil$^{(R)}$ (Burroughs Wellcome)

It is one of the more potent of the antihistaminics and its action last for up to 12 hours.

Dose : *5 to 7.5 mg per day.*

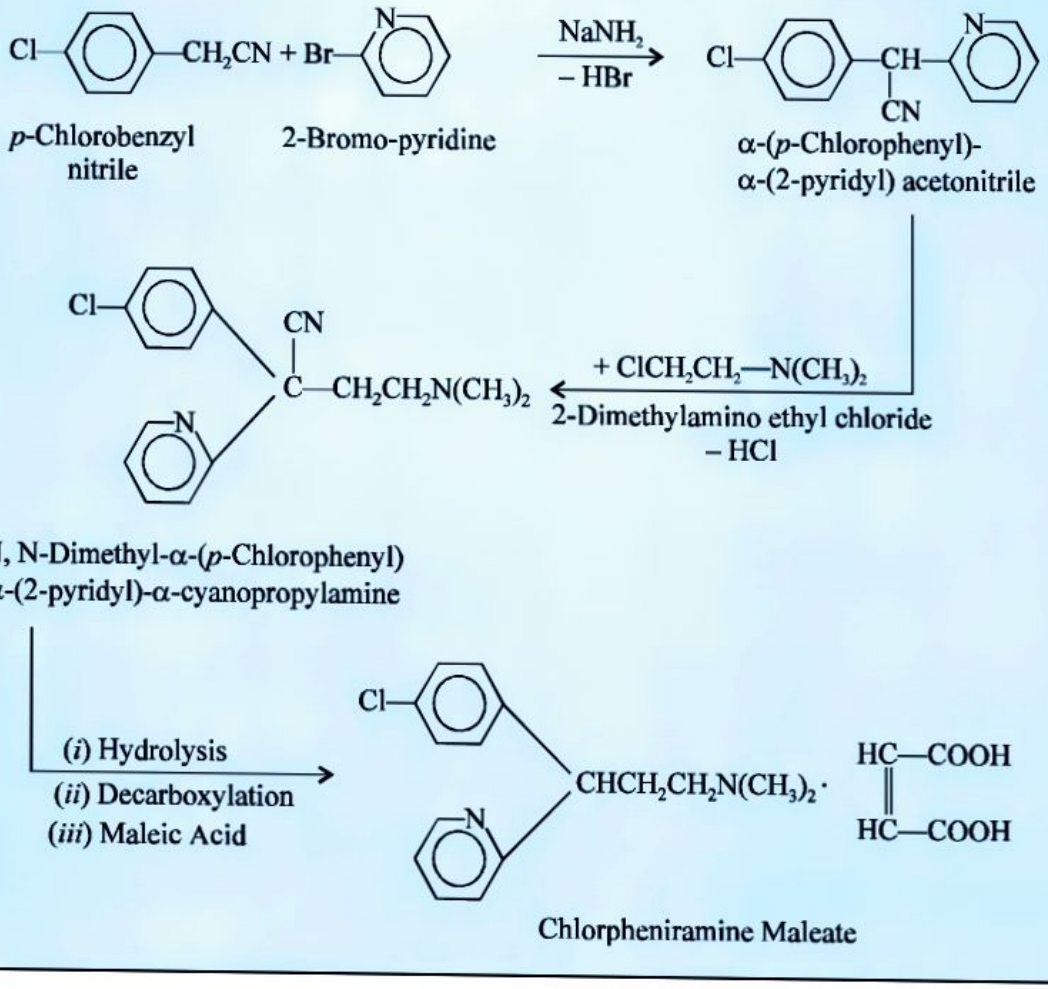
C. Chlorpheniramine Maleate BAN, USAN, Chlorphenamine INN,



2-[*p*-Chloro-α-[2-(dimethylamino) ethyl] benzyl] pyridine maleate (1:1) ; 2-Pyridinepropanamine, γ-(4-chlorophenyl)-N, N-dimethyl-, (Z)-2-butenedioate (1:1) ; Chlorphenamine Maleate ; Chlorprophenpyridamine Maleate ; BP ; USP ;

Piriton(R) (Allen & Hanburys U.K.) ; Chlor-Trimeton(R) (Schering-Plough) ; Alermine(R) (Reid-Provident).

Synthesis

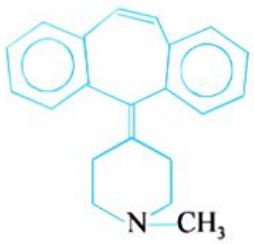


α-(*p*-Chlorophenyl)-α-(2-pyridyl) acetonitrile is prepared by the interaction of *p*-chlorobenzyl nitrile and 2-bromopyridine in the presence of sodamide with the elimination of a molecule of hydrogen bromide. This on treatment with 2-dimethylamino ethyl chloride abstracts the lonely active hydrogen atom present in the acetonitrile function as hydrogen chloride and yields N, N-dimethyl-α-(*p*-chlorophenyl)-α-(2-pyridyl)-α-cyano-propyl amine. The resulting product when subjected to hydrolysis, followed by decarboxylation and finally heated with maleic acid gives rise to the official compound.

It is one of the most potent of the antihistaminics which generally causes less sedation than promethazine.

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

D. Cyproheptadine Hydrochloride BAN, USAN, Cyproheptadine INN,



4-(5H-Dibenzo [*a, d*] cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride sequihydrate ; Piperidine, 4-(5H-dibenzo [*a, d*]-cyclohepten-5-ylidene)-1-methyl-, hydrochloride, sesquihydrate ; BP ; USP ;

Periactin(R) (Merck Sharp & Dohme)

It possesses antiserotonin, anticholinergic and antialdosterone characteristics. It is *highly potent and is effective in smaller doses than* **promethazine hydrochloride** *though the effect lasts for a short duration. It helps to stimulate the appetite in under-weight patients and those suffering from anorexia nervosa.*

Dose : *Usual, adult, oral, 4 mg 3 to 4 times a day.*

2.1.7.1. Mechanism of Action

The mechanism of action of certain important members of this particular class of compounds shall now be discussed as under :

2.1.7.1.1. Phenindamine Tartrate

The **'drug'** exerts its action by temporarily relieving running nose and also sneezing related to the common cold. However, it may cause drowsiness sleepiness, just similar to most of the antihistaminics ; but at the same time it may also give rise to a mild stimulating action in patients and may cause insomnia when taken prior to going to bed.

SAR of Phenindamine. Phenindamine may be structurally related to an unsaturated propylamine analogue wherein the rigid ring system essentially embedded with a distorted *trans*-alkene system. The presence of either oxidizing substances or an exposure to heat may render this compound to undergo *isomerization* which ultimately leads to an **inactive** form.

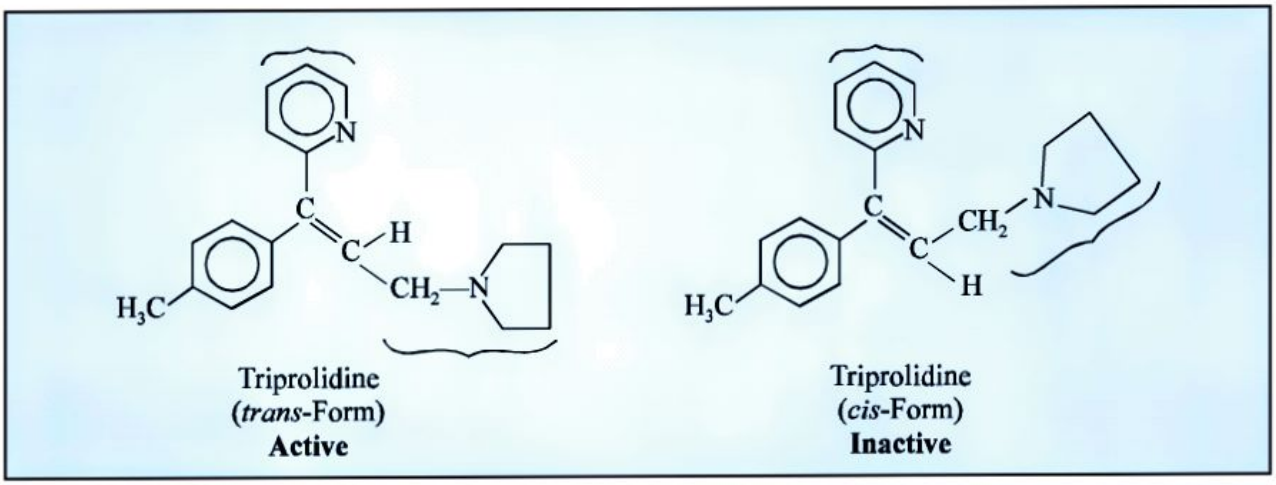
*Ison RR *et. al. J. Pharm. Pharmacol,* **25,** 887, 1973.

2.1.7.1.2. Triprolidine Hydrochloride

The **'drug'** is shown to exhibit both high *activity* and *superiority* of its **(E)-isomer** with respect to its corresponding **(Z)-isomer** as the **H_1-antagonists.*** It has been adequately demonstrated using the guinea pig ileum sites that the actual prevailing affinity of **triprolidine** for the **H_1-receptors** was found to be higher more than 1,000 times the affinity exhibited

by its (Z)-isomer. However, the overall relative potency of this *'drug'* is very much comparable to that of **dexchlorpheniramine.**

SAR of Triprolidine. It has been established that the pharmacoligic activity solely resides in the geometric isomer wherein the pyrrolidinomethyl moiety is present as *trans*-to the corresponding 2-pyridyl functional moiety as given below :



2.1.7.1.3. Chlorpheniramine Maleate

The **'drug'** is widely used as an essential component of a plethora of **antitussive formulations.** It is found to attain appreciable first-pass metabolism ranging between 40–55%. The peak plasma levels of 5.9 and 11 ng. mL^{-1} are accomplished within a span of 2–6 hours.

SAR of Chlorpheniramine. The presence of the strategically positioned chloro moiety at the *para*-position of the benzene ring affords a 10-times enhancement in its potency without making an significant alteration in its toxicity. Besides, it has been observed that the maximum activity of the **'drug'** resides in the *dextro*-enantiomorph exclusively.

2.1.7.1.4. Cyproheptadine Hydrochloride

The **'drug'** is an antihistamine having serotonin-antagonist, and calcium channel blocking activities. Besides, it also exhibits antimuscarinic and central sedative actions.

2.1.7.2. Structure Activity Relationships (SARs) Amongst H_1-Receptor Blockers

The large number of potent **antihistaminic agents** used in the therapeutic armamentarium belong to various defined chemical categories, namely : **aminoalkylethers, ethylenediamines, thiophene analogs, cyclic basic chain analogs and phenothiazine derivatives**. However, it is now possible to derive some important conclusions with respect to their structural requirements for optimal activity and pharmacological actions, namely :

1. In all derivatives the terminal N atom must be tertiary amine so as to exhibit maximum activity.

2. The terminal N atom may constitute part of a heterocyclic structure, *e.g.*, **pyribenzamine hydrochloride, thenylene hydrochloride,** etc.
3. For maximum activity the carbon-chain between the O and N atoms or the N and N atoms must be the ethylene moiety, *i.e.*, —CH_2CH_2—. However, a long or branched chain combination gives rise to a less potent analog.
4. It is interesting to observe that in the promethazine hydrochloride molecule the two carbon chain is linked with an iso-propyl moiety, but the presence of the phenothiazine group might exert better therapeutic effect on the molecules as such.
5. Introduction of a halogen atom *viz*, Cl, Br at the *para*-position of the phenyl function improves the antihistaminic activity of the parent molecule, *e.g.*, **pheniramine** compared with, **chloropheniramine** and **brompheniramine**.
6. Amongst the ethylenediamine analogs many potent compounds have evolved due to the inclusion of various groups on the second N of the chain. Such groups may be either heterocyclic aromatic rings or isocyclic group. Hydrogenation of such ring(s) leads to loss in activity.
7. The nucleus of an antihistaminic must bear a minimum of two aralkyl or aryl functions or an equivalent embeded in a polycyclic ring.
8. Antihistaminics exhibiting optical isomerism revealed that the *dextro*-isomer supersedes the *levo*-in their potency, *e.g.*, **dexchlorpherniramine**, **dexbrompheniramine**, **triprolidine** etc.
9. For enhanced effectiveness is antihistaminics it is essential that one of the aromatic moieties is α-pyridyl while the second substituent on the N atom could be either a benzyl function of a substituted benzyl group or one of the isosteres of the benzyl moiety, *e.g.*, **thenyldiamine**, **pyrilamine**, etc.
10. Introduction of basic-cyclic ring system by altering the position of dimethyl amino group also enhances the antihistaminic activity, *e.g.*, **cyclizine**, **chlorcyclizine**, **meclizine** etc.

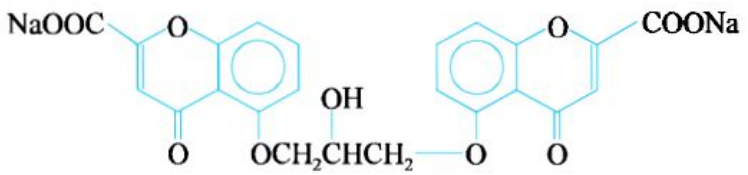
2.2. Prevention of Histamine Release

The release of **histamine** *in vitro* may be prevented by the aid of certain medicinally acive compounds. Such substances are not usually absorbed by the gastro-intestinal tract. An attempt has been made to find a similar substance which might be absorbed when administered orally and which possesses anti-allergic properties. Two such compounds are disucssed below namely : **Sodium cromoglycate** and **Ketotifen fumarate.**

A. Sodium Cromoglycate BAN, Cromolyn Sodium USAN, Cromoglicic Acid INN

Sodium 5, 5′-(2-hydroxytrimethylenedioxy) *bis* (4-oxo-4H-chromene-2-carboxylate ; Disodium 4, 4′-dioxo-5, 5′-(2-hydroxytrimethylenedioxy) di (4H-chromene-2-carboxylate) ; Sodium Cromoglycate BP ; BPC ; Cromolyn Sodium USP ;

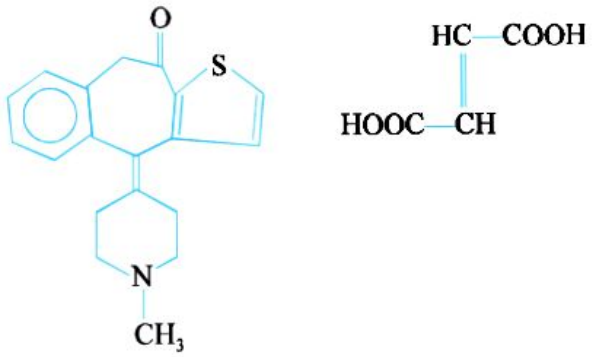
Intal$^{(R)}$ (Fisons ; U.K.) ; Aarane$^{(R)}$ (Syntex)



Sodium cromoglycate is a chromono derivative which inhibits the release of histamine and SRS-A in allergic reactions. It is mostly employed in the prophylactic treatment of asthma. It is administered only by inhalation, either alone or in conjunction with a small quantity of **isoprenaline** to prevent bronchospasm caused by the inhalation of the fine powder.

Dose : *20 mg, by inhalation 2 to 6 times a day.*

B. Ketotifen Fumarate USAN, Ketotifen INN, BAN,



4, 9-Dihydro-4-(1-methyl-4-piperidylidene)-10H-benzo [4, 5] cyclohepta [1, 2-*b*] thiophen-10-one fumarate (1:1) ; 10H-Benzo [4, 5]-cyclohepta [1, 2-*b*] thiophen-10-one, 4, 9-dihydro-4-(1-methyl-4-piperidinylidene)-, (E)-2-butenedioate (1:1) ; USP ;

Zaditen$^{(R)}$ (Sandoz).

It possesses anti-allergic properties similar to those of sodium cromoglycate and is used in the prophylactic treatment of asthma.

Dose : *Usual, oral, equivalent to 1 mg of ketotifen 2 times per day.*

2.2.1. Mechanism of Action

The mechanism of action of these compounds shall be described as under :

2.2.1.1. Sodium Cromoglycate

Though the precise mechanism of action of this **'drug'** remains uncertain, it is believed to exert its action primarily by preventing the release of mediators of inflammation from the sensitised mast cells through the stabilization of mast-cell membranes.

2.2.1.2. Ketotifen Fumarate

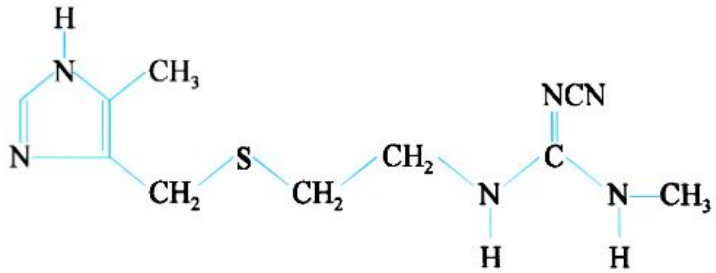
The **'drug'** is an antihistamine which also inhibits release of inflammatory mediators. It also exerts stabilizing action on the mast cells analogous to that of sodium cromoglycate.

2.3. Histamine (H_2) Receptor Blockers

As stated earlier, histamine activates two types of receptors *viz.*, **H_1 and H_2 receptors.** The activation of **H_2 receptors** leads to increased gastric acid secretion, increased contraction of the isolated atria and inhibition of isolated uterus. These effects are blocked by **H_2-receptor antagonists** which are now being used for the treatment of peptic ulcer.

Examples : Cimetidine ; Ranitidine ; Oxmetidine Hydrochloride

A. Cimetidine INN, BAN, USAN,



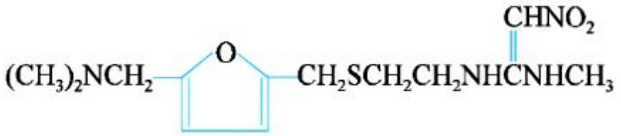
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl) methyl]-thio] ethyl] guanidine ; Guanidine, N''-cyano-N-methyl-N'-[2-[[(5-methyl-1H-imidazol-4-yl) methyl] thio] ethyl]- ; SKF 92334 ; BPC ; USP ;

Tagamet(R) (Smith Kline & French)

Cimetidine being a **histamine H_2-receptor antagonist** not only inhibits gastric acid secretion but also prevents other actions of **histamine mediated by H_2-receptors.** *It is employed in gastric and duodenal ulcer, and in all other situations where an inhibition of the secretion of gastric juice is considered to be useful.*

Dose : *Usual, oral, 200 mg 3 times per day with meals and 400 mg at night.*

B. Ranitidine INN, BAN, USAN,



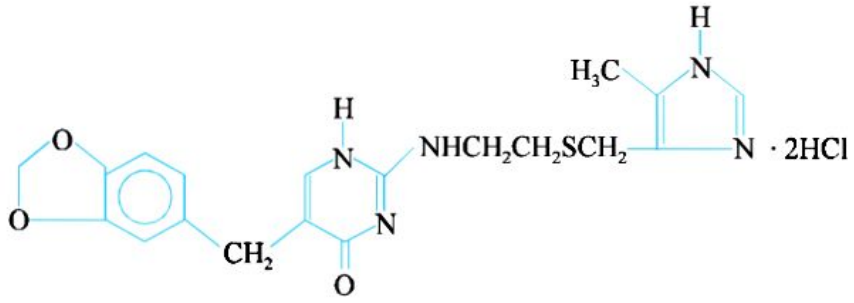
N-[2-[[5-[(Dimethylamino) methyl] furfuryl] thio] ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine ; 1, 1-Ethenediamine, N-[2-[[[5-[(dimethylamino) methyl]-2-furanyl] methyl] thio] ethyl]-N'-methyl-2-nitro ;

Zantac(R) (Glaxo, U.K.)

The actions and uses of ranitidine are similar to **cimetidine.**

Dose : *Usual, 150 mg (as the hydrochloride) 2 times a day.*

C. Oxmetidine Hydrochloride BAN, USAN, Oxmetidine INN,



2-[[2-[[(5-Methylimidazol-4-yl) methyl] thio] ethyl] amino]-5-piperonyl-4-(1H)-pyrimidinone dihydrochloride ;

SK & F 92994-A_2(R) (Smith Kline & French)

It is reported to have **histamine H_2 receptor blocking activity.**

2.3.1. Mechanism of Action

The mechanism of action of the compounds enumerated under Section 15.2.3. are described as under :

2.3.1.1. Cimetidine*

The **'drug'** is observed to minimise the hepatic metabolism of such drugs that are eventually biotransformed by the **cytochrome P-450** mixed oxidase system by way of either delaying the elimination or enhancing the serum levels of these pharmacologic agents.

*Introduced in 1977 and enjoyed the reputation of being one of the most profusely prescribed drugs in history for several years.

Importantly, it exhibits relatively higher oral bioavailability (60–70%), and a plasma half-life of – 2 hour that gets enhanced particularly either in agedsubjects or those having a renal and hepatic impairment. However, it has been observed that nearly 30 to 40% of a cimetidine dose gets metabolized either as **S-oxidation** or a **5-CH_3 hydroxylation.** Finally, the parent drug and the metabolites are virtually eliminated primarily by the renal excretion.

2.3.1.2. Ranitidine

Zantac gives rise to *three* known metabolites, namely : (*a*) **ranitidine N-oxide ;** (*b*) **ranitidine S-oxide ;** and (*c*) **desmethyl ranitidine.** It is observed to be only a weak inhibitor of the **hepatic cytochrome P-450** mixed function oxidation system. The plasma half-life ranges between 2 to 3 hours ; and it usually gets excreted together with its metabolites in the urine.

Note : It is established that some 'antacids' may afford a reduction in the ranitidine absorption ; and, therefore, must not be taken at least within a span of one hour of the administration of this H_2-blocker particularly. In fact ranitidine is a stronger base (pKa 8.44).

2.3.1.3. Oximetidine Hydrochloride

The **'drug',** which being a 3-pyridyl structural derivative soon gained recognition by virtue of the fact that it predominantly exhibited certain **H_1-antagonism.**

SAR of Oximetidine. It essentially possesses a 5-substituted isocytosine functional moiety and also shows the latitude and complexitiy of digression from the urea permitted that renders the **'drug'** to become a potent **selective H_2-antagonist.**

Probable Questions for B. Pharm. Examinations

1. What are allergens ? What is the importance of **'antihistaminics'** in combating various types of allergic conditions ? Give suitable examples to support your answer.
2. Classify the Histamine **H_1-Receptor Antagonists.** Give the structure, chemical name and uses of **one** compound from each cateogry.
3. Name any **three 'aminoalkylethers'** being used as antihistaminics. Discuss the synthesis of **one** of them.
4. Give the structure, chemical name and uses of :

   (*a*) Mepyramine maleate and

   (*b*) Tripelenamine hydrochloride

   Describe the synthesis of any **one** drug.
5. **'Thiophene** derivatives have low side-effects and may be employed in the treatment of all types of suspected allergies'. Justify the statement with the help of at least **two** typical examples.
6. Cyclic basic-chain analogues essentially having

   (*a*) Imidazoline,

   (*b*) Piperazine and

   (*c*) Piperidine

   the above **three** types of heterocyclic nucleus give rise to potent 'antihistaminics'. Explain.
7. Discuss the synthesis of :

   (*a*) Promethazine hydrochloride

(*b*) Methdilazine hydrochloride

Elaborate their applications separately.

8. Phenindamine tartrate and chlorpheniramine mealeate are two important antihistaminics. Describe the synthesis of **one** drug in detail.

9. Give a brief account of :

(*a*) Drugs used in the 'Prevention of Histamine Release'

(*b*) Histamine (H_2) Receptor Blockers

10. Give a comprehensive account of :

(*a*) SAR-amongst H_1-receptor blockers

(*b*) Mode of action of antihistaminics.

RECOMMENDED READINGS

1. B Idson **Antihistamine Drugs** *Chem Rev* 47 (1950).
2. D Lednicer and LA Mitscher **The Organic Chemistry of Drug Synthesis** John Wiley and Sons New York (1995).
3. DT Witiak **Antiallergic Agents in Medicinal Chemistry and Drug Discovery,** M E Wolff (ed.) 5th Edn. Wiley & Sons Inc., New York (1995).
4. DT Witiak **Antiallergic Agents,** In : **Principles of Medicinal Chemistry** (ed.) W O Foye Lea & Febiger Philadelphia (1974).
5. JH Burn Antihistamine B M J ii (1955).
6. JW Black and KEV Spencer In : **Cimetidine, International Symposium on Histamine H_2 Receptor Antagonists** (eds. Cl Wood and MA Simkins) Smith Kline and French Laboratories Ltd. Welwyn Garden City, Dasprint Limited, London (1973).
7. KLandsteiner, In : **The Specificity of Serological Reactions,** Dover Publications, Inc. New York (1962).
8. RB Hunter and DM Dunlop, **A Review of Antihistamine** *Drugs Q J Med 25* (1948).
9. RP Orange, MA Kaliner and KF Austen In : **Biochemistry of the Acute Allergic Reaction** (eds.) KF Austen and EL Becker, Blackwell Oxford (1971).
10. **USAN and the USP Dictionary of Drug Names** (ed.) MC Griffiths United States Pharmacopeial Convention Inc., Rockville (1985).