SPPU

MEDICINAL CHEMISTRY-I

(SCHEMES OF SYNTHESIS OF DRUGS GIVEN IN SYLLABUS)

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SEMESTER-IV

IMPORTANT NOTE

This document is only meant exclusively for the schemes of synthesis of drugs. Neglect the other content as it is not organized in order

ONLY STUDY THE HIGHLIGHTED CONTENT

d. Sulphones

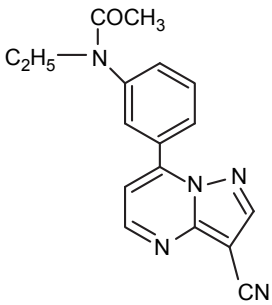
Toxic-not used

e. Plant extracts of

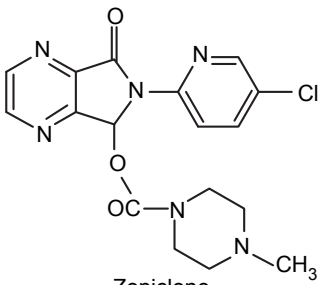
Radix valerianae
Rauwolfia serpentina
Avana sativa
Glandula lupuli

f. Endogenous substances: peptides

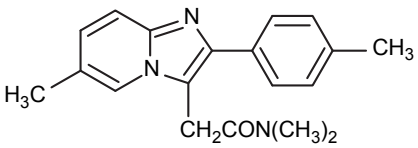
8. Newer agents



Zaleplon



Zopiclone



Zolpidem

SYNTHESIS AND DRUG PROFILE

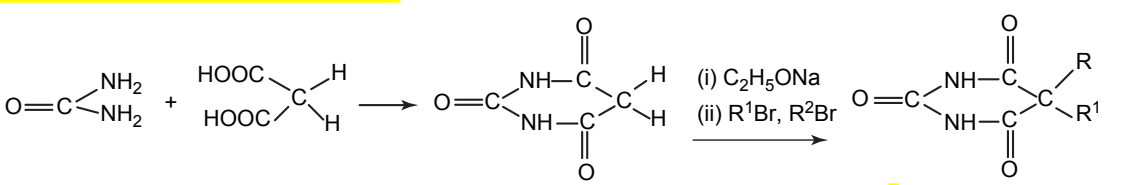
1. Barbiturates

Barbiturates are derivatives of barbituric acid. Their hypnotic activity is conferred by the replacement of H-atom attached to the C-5 position by aryl or alkyl radicals. They are generally synthesized by adopting the following route of synthesis.

Mode of action: Barbiturates primarily act on GABA: benzodiazepin receptor Cl^- channel complex and potentiate GABA ergic inhibitory action by increasing the lifetime of Cl^- channel opening induced by GABA. Barbiturates do not bind to benzodiazepine receptor promptly, but it binds to another site on the same macromolecular complex to exert the GABA ergic facilitator actions. The barbiturate site appears to be located on α and *ß* subunit. At high concentrations, barbiturates directly increases Cl^- conductance and inhibit Ca^{2+} dependent release of neurotransmitters and they also depress glutamate-induced neuronal depolarization.

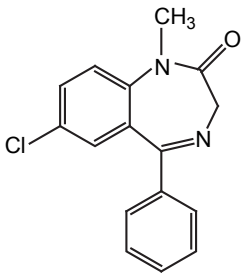
Synthesis

Route I: From urea and malonic acid



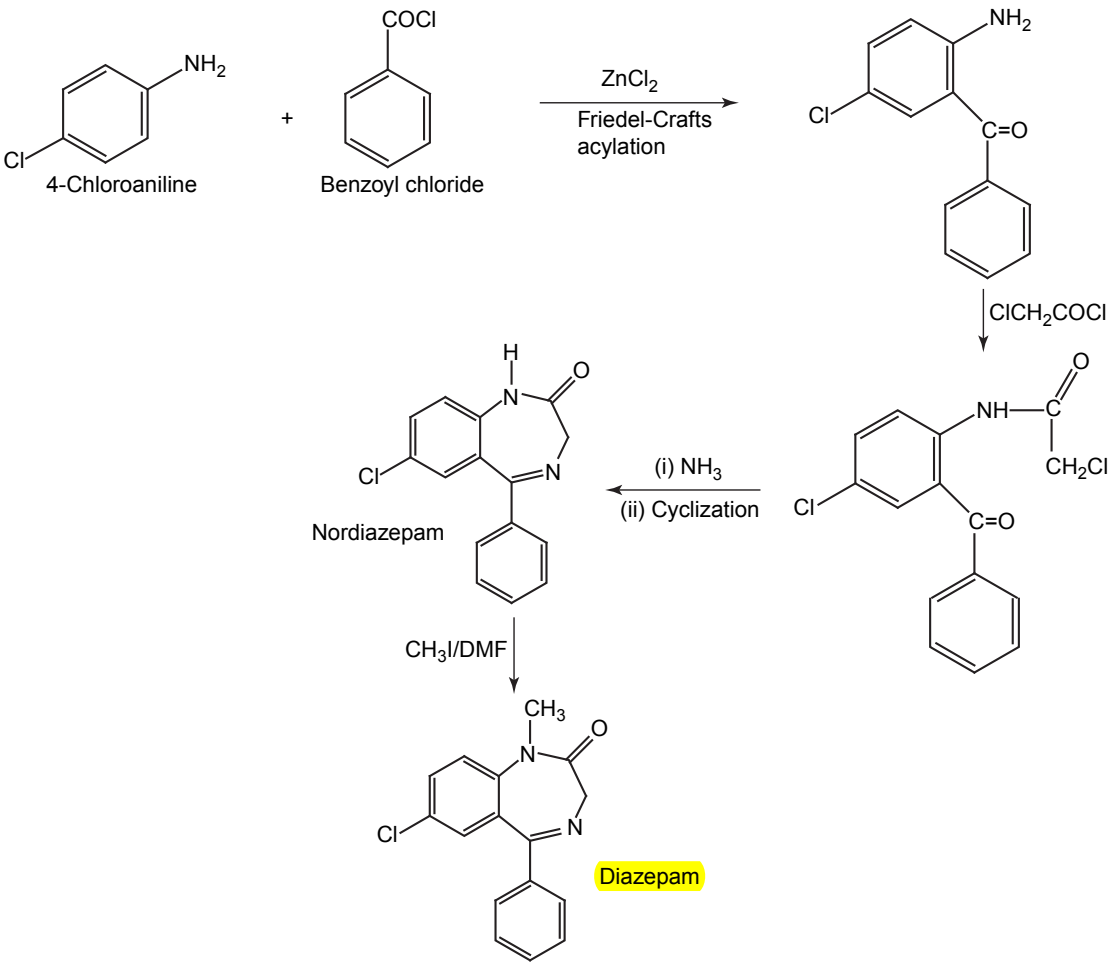
Urea Malonic acid Barbituric acid 5,5[1]-Substituted barbiturate

1. Diazepam (Calmpose, Valium, Diazep)



7-Chloro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one

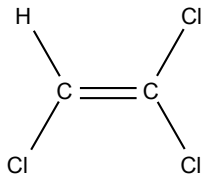
Synthesis



Ether is an absolute anaesthetic with pungent, irritant odour. It is flammable and explosive at concentrations necessary for anaesthesia.

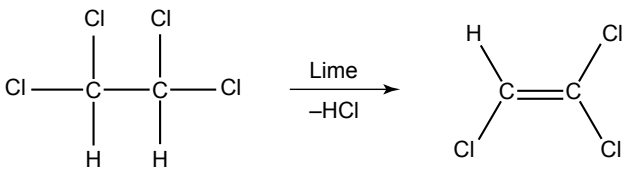
Storage: It should be stored in well-closed airtight containers and protected from light, stored at a temperature of 8°C–15°C.

2. Trichloro ethylene



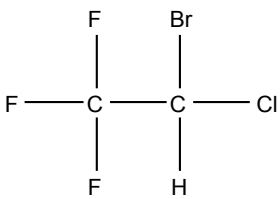
1,1,2-Trichloroethene

Synthesis



Tetrachloro ethane — Trichloro ethylene

Properties and uses: It may be used sporadically as a weak volatile anaesthetic, administered through inhalation. It possess an excellent analgesic property. It is frequently employed in short surgical operations, where a mild anaesthesia having potent analgesia is desired.

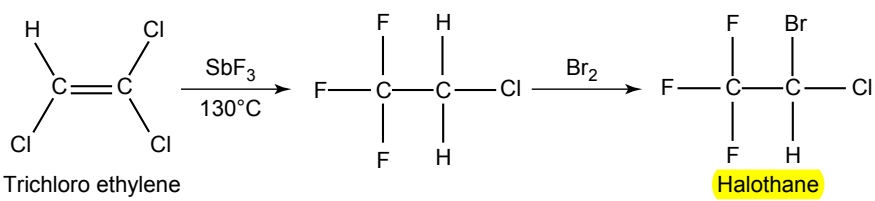


2-Bromo-2-chloro-1,1,1-trifluoro ethane

3. Halothane

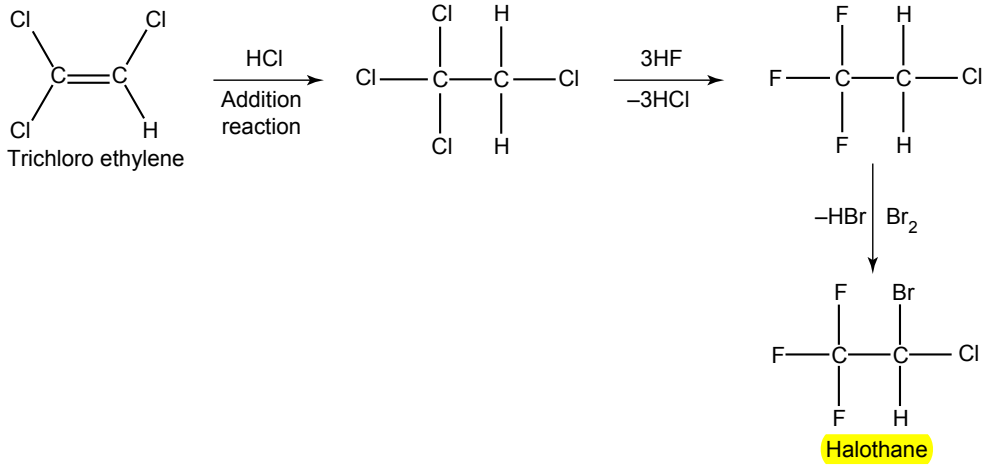
Synthesis

Route I. From: Trichloro ethylene

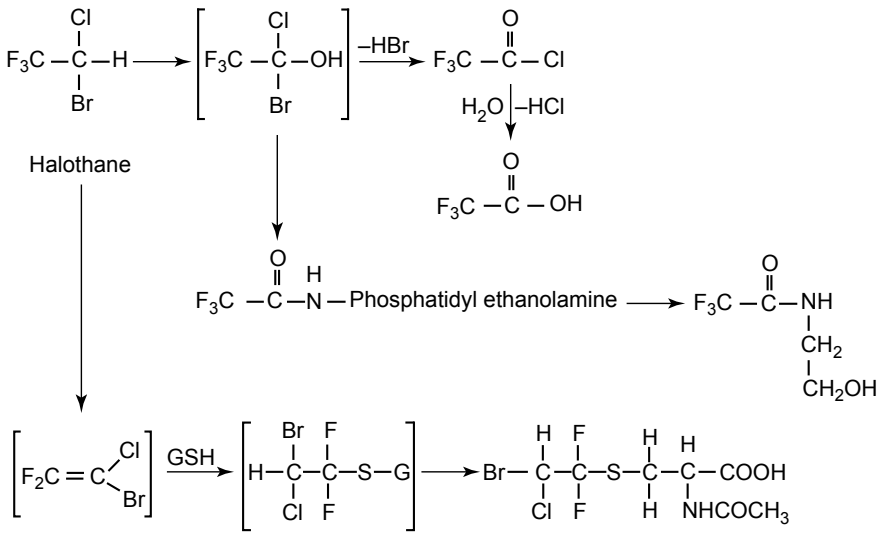


Trichloro ethylene — Halothane

Route II. From: Trichloro ethylene



Metabolism: It is metabolized to three major metabolic products, trifluroacetic acid, *N*-trifluro acetyl ethanolamine, and *N*-acetyl-*s*-(2-bromo,2 chloro-1,1-difluro ethyl)-1-cysteine

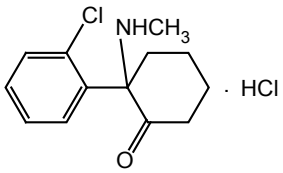


Properties and uses: It is a clear, colourless, heavy, nonflammable liquid, slightly soluble in water, miscible with ethanol, and with trichloroethylene. Halothane lacks flammability. It may produce any depth of anaesthesia without causing hypoxia. Being a nonirritant, its inherent hypotensive effect retards capillary bleeding and renders a comparatively bloodless field. It is a potent, relatively safe general inhalation anaesthetic used in conjunction with N_2O. For skeletal muscle relaxation, it is used with succinyl choline or tubocurarine.

Storage: It should be stored in well-closed airtight containers, protected from light, at a temperature not exceeding 25°C in a nonreactive metal container.

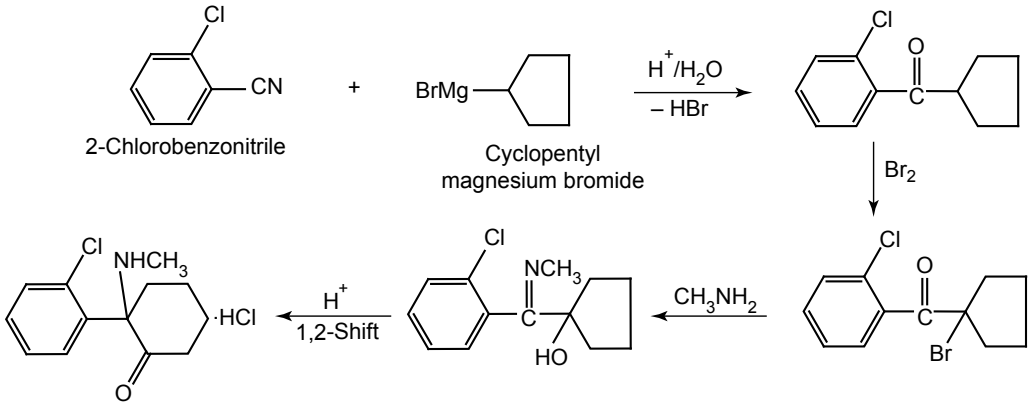
b. Arylcyclohexylamines

1. Ketamine HCl



2-(2-Chloro phenyl)-2-(methylamino) cyclohexanone

Synthesis



Properties and uses: It is a white or almost white crystalline powder, freely soluble in water, methanol, and ethanol. Its another name is 'dissociative anaesthetic' because it produces unpleasant hallucinations and strong feelings of dissociation from the environment. It is a rapidly acting nonbarbiturate general anaesthetic that produces anaesthesia and is characterized by profound analgesia.

Assay: Dissolve the substance in methanol and add 1.0 ml of 0.1 M hydrochloric acid, and perform potentiometric titration, using 0.1 M sodium hydroxide.

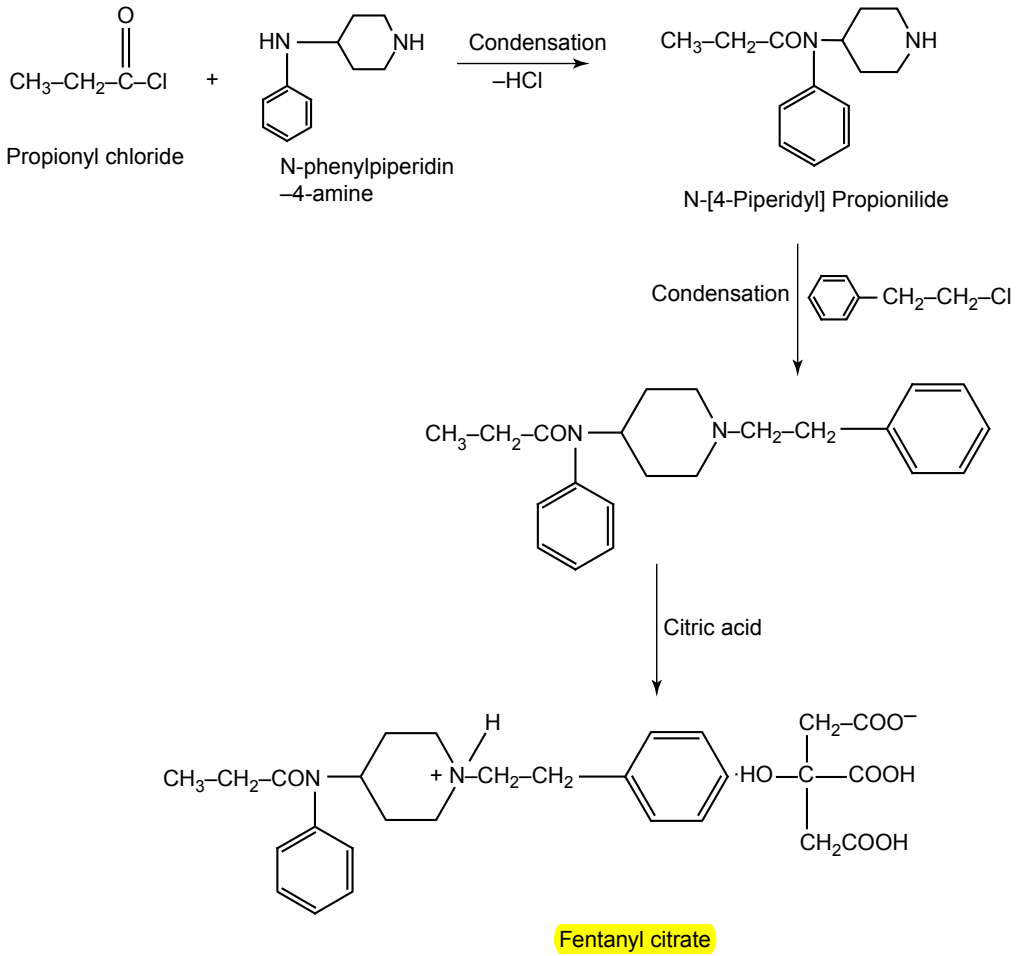
Storage: It should be stored in well-closed airtight containers, protected from light.

Dosage forms: Ketamine HCl injection I.P., B.P.

c. Benzodiazepines

Metabolism: This is discussed in Sec III, Chapter 'Sedatives and Hypnotics'.

Synthesis



Fentanyl citrate

analgesic employed for the arrest of pain and it may also be employed as an adjuvant for all such drugs mostly used for regional and general anaesthesia.

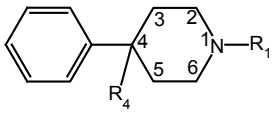
Assay: Dissolve the substance in a mixture of 1 volume of anhydrous acetic acid and 7 volumes of methyl ethyl ketone. Titrate with 0.1 M perchloric acid using naphtholbenzein solution as indicator.

Storage: It should be stored in well-closed airtight container and protected from light.

Dose: By I.M. in preoperative medication 0.05 to 0.1 mg, 30 to 60 min before surgical treatment, for rapid analgesic action, 0.05 to 0.1 mg by IV.

Dosage forms: Fentanyl injection B.P.

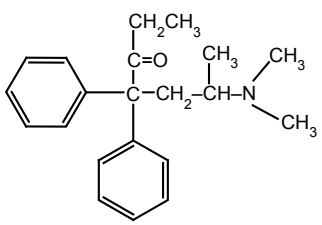
SAR of Meperidine Analogues



- Placement of *m*-hydroxyl group on the phenyl ring increases activity. The effect is more significant on the keto compound than on the pyridine.
- Substitution of carbethoxy group in meperidine by acyloxy group provides better analgesic as well as spasmolytic activity (alpha prodine).
- The presence of phenyl and ester group at 4th position of 1-methylpiperdine results in optimum activity.
- The replacement of C-4 phenyl group of meperidine by hydrogen, alkyl, other aryl, aralkyl, and hetero cyclic groups reduces analgesic activity.
- Replacement of phenyl group by phenyl ethyl derivatives is seen to be about three times as active as the meperidine. The amino analogue, anileridine is about four, times more active.
- Contraction of piperidiene ring to the pyrrolidine gives a more active compound, but causes abuse liability. For example, alphaprodine and procilidine.
- Enlargement of piperidine ring to a 7-membered hexa hydroazepine yield active compounds with low incidence of side effects. For example, Proheptazine.
- The C-3 methyl analogue with an ester group at the C-4 position like lofentanil 8,400 times more potent than meperidine as an analgesic.
- In fentanyl, the phenyl and acyl groups are separated by nitrogen. It is 50 times stronger than morphine with minimal side effects. Its short duration of action makes it well suited for use in anaesthesia.
- The *p*-chloro analogue (loperamide) has been shown to bind to opiate receptors in the brain, but it cannot penetrate the blood-brain barrier sufficiently to produce analgesia.
- Diphenoxylate, a structural hybrid of meperidine and methadone type, devoid of analgesic activites. It is effective as an intestinal spasmolytic and is used in the treatment of diarrhoea.

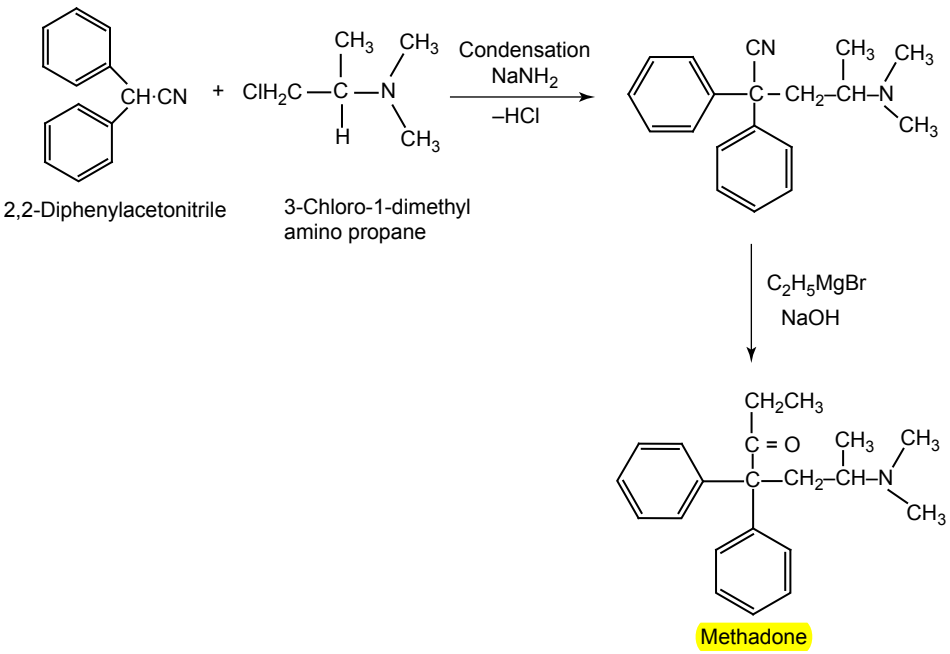
III. Methadone analogues

a. Methadone



6-Dimethylamino-4, 4-diphenylheptan-3-one

Synthesis



Metabolism: Methadone metabolizes to form an active α-dinormethadol and dinor-L-α-acetylmethadol (LAAM), then it undergoes *N*-demethylation to form inactive pyrrolidines an pyrrolines which are excreted in urine.

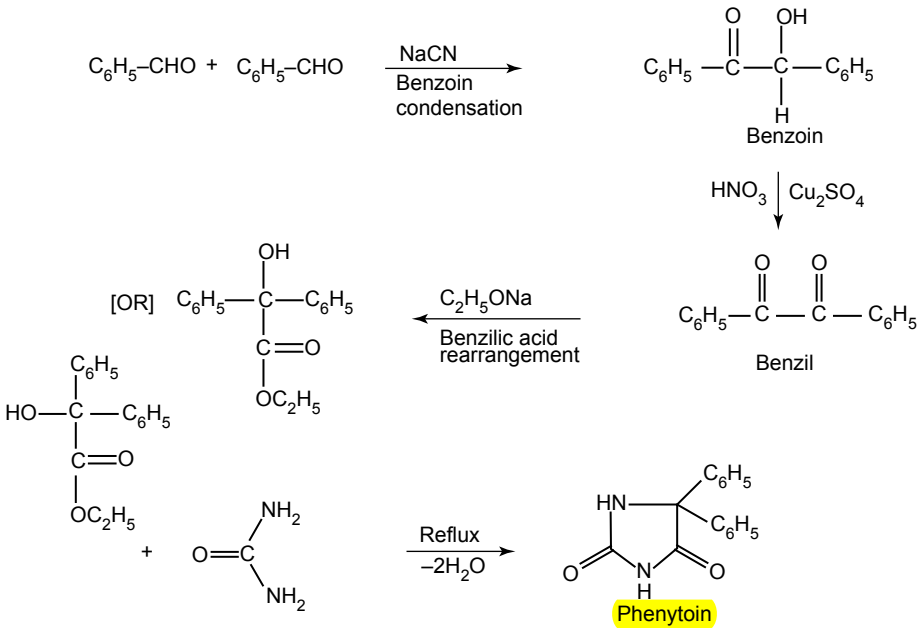
Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and soluble in water. Even methadone, which looks structurally different from other opioid agonists, has steric forces that produce a configuration that closely resembles the opioid agonists. Methadone is more active and more toxic than morphine. It can be used for the relief of many types of pain. In addition, it is used as narcotic substitute treatment because it prevents morphine abstinence syndrome. The toxicity of methadone is three to ten times that of morphine, but its analgesic effect is twice that of morphine and ten times that of meperidine.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and anhydrous ethanol by using 0.1 M sodium hydroxide to perform potentiometric titration.

Storage: It should be stored in well-closed airtight containers and protected from light.

Dosage forms: Methadone HCl injection I.P., Methadone HCl tablets I.P., Methadone injection B.P., Methadone Linctus B.P., Methadone oral solution (1 mg/ml), B.P., Methadone tablets B.P.

Synthesis



Metabolism: Phenytoin is metabolized by CYPC9 into a primary metabolite 5-(hydroxyl phenyl)-5-phenyl hydantoin (HPPH).

Properties and uses: It is a white crystalline powder, slightly hygroscopic, insoluble in methylene chloride, soluble in water and alcohol. Phenytoin is the first anticonvulsant in which it was clearly demonstrated that anticonvulsant activity could definitely be separated from sedative-hypnotic activity. A common side effect is gingival hyperplasia, a reaction that seldom occurs with mephenytoin, and apparently, never with cardiac arrhythmias. It is one of the most widely used antieplietic agents and it is effective in most forms of epilepsy, except absence of seizures. Some cases of trigeminal and neuralgias respond well to phenytoin. It is also used in the treatment of cardiac arrhythrmias.

Assay: Suspend the sample in water, add 0.05 M sulphuric acid and heat gently for 1 min, to this add methanol and cool. Perform the potentiometric titration, using 0.1 M sodium hydroxide. After reaching the first point of inflexion, interrupt the addition of 0.1 M sodium hydroxide, add 5 ml of silver nitrate solution in pyridine, mix, and continue the titration. Read the volume of 0.1 M sodium hydroxide added between the two points of inflexion.

Storage: It should be stored in well-closed airtight containers.

Dose: The usual dose is 50 to 100 mg.

Dosage forms: Phenytoin capsules B.P., Phenytoin injection B.P., Phenytoin tablets B.P.

Mode of action: It is a lipid soluble GABA analogue. It does not bind with $GABA_A$ receptor, causes no inhibition on GABA reuptake and is not a $GABA^-_T$ (GABA amino transferase enzyme that metabolizes GABA to succinic semialdehyde) inhibitor, thus, the mechanism of action is unknown.

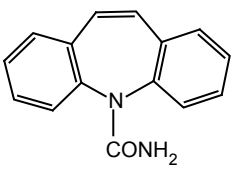
Properties and uses: It is a colourless, crystalline substance, soluble in water. It has been endorsed as an effective drug for the management of neuropathic pain.

Dose: For epilesy (partial seizures with or without secondary generalization): Adult: Initially, 300 mg on the first day; 300 mg twice/day on the second day; and 300 mg thrice/day on the third day. Thereafter, the dose may increase until effective antiepileptic control is achieved. Usual maintenance range: 0.9–3.6 g daily, daily dose to be taken in three equally divided doses and maximum dosing interval of 12 h. Maximum: 4.8 g daily.

IX. Iminostilbenes

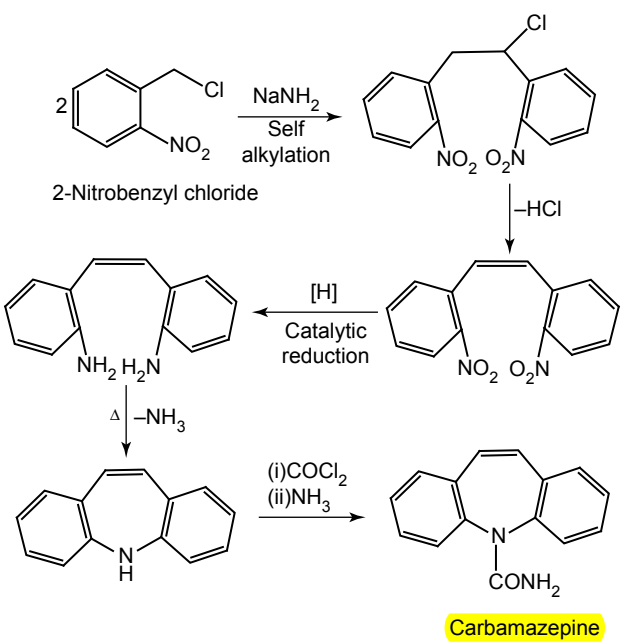
Mode of action: Similar to phenytoin, iminostilbenes limits the repetitive firing of action potential and appears to reduce the rate of recovery of voltage-gated sodium channel from inactivation.

a. Carbamazepine (Tegretol, Zen, Zeptol)



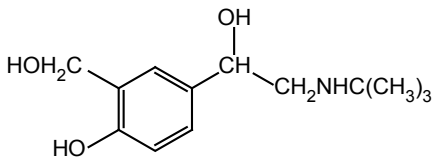
Dibenzazepine-5-carboxamide

Synthesis



Properties and uses: The racemic mixture has a higher proportion of cardiovascular effects than the dextro isomer. For most medical uses, the dextrorotatory isomer is preferred. It is one of the most important sympathomimetic agents. CNS stimulant effect is due to stimulation of the cortex. The D-isomer is three to four times more potent than the L-isomer. It also has an anorexic action and can be used in the treatment of obesity.

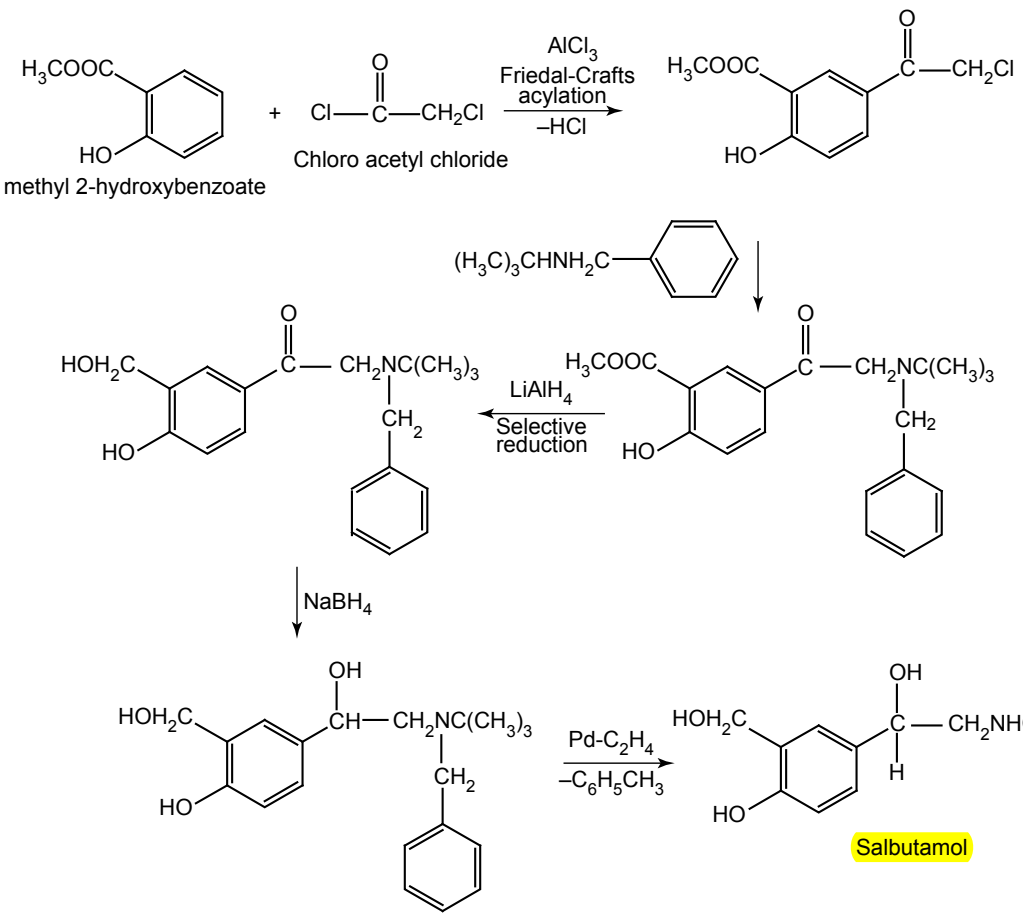
c. Salbutamol (Synonym: Albuterol, Asthalin, Salbid)



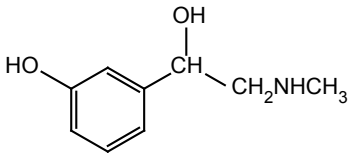
4-Hydroxy-3-hydroxy methyl-alpha-[(tert butylamino)methyl]benzyl alcohol

Synthesis

Route I. From: Methyl-2-hydroxbenzoate



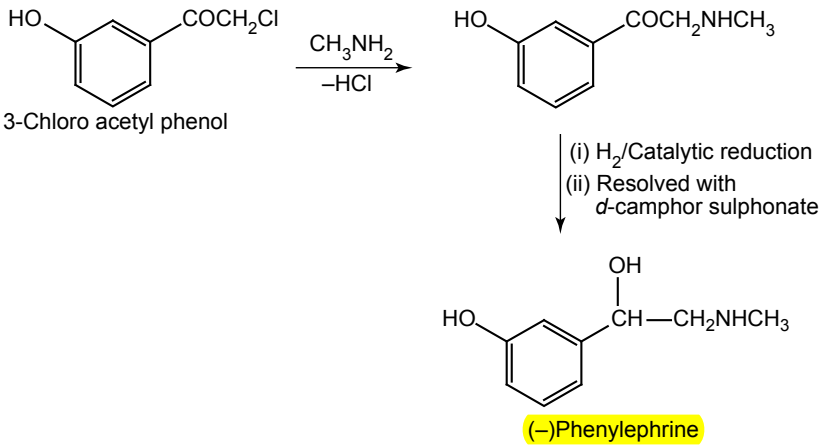
f. Phenylephrine



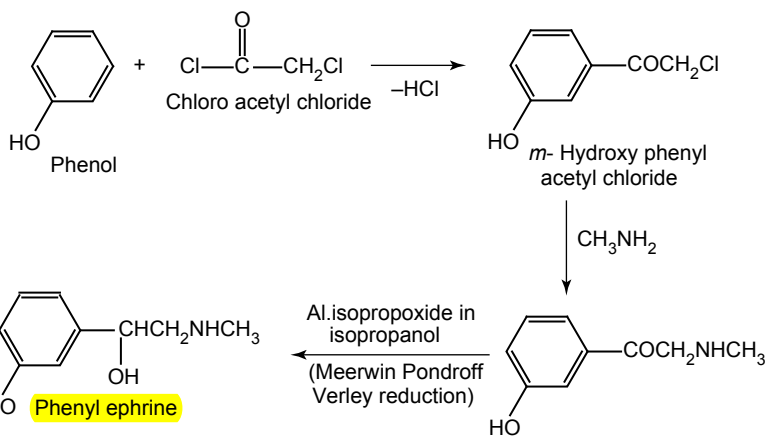
1-(3-Hydroxy phenyl)-2-methylamino ethanol

Synthesis

Route I. From: 3-Chloro acetyl phenol

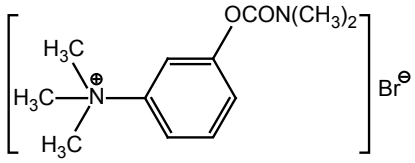


Route II. From: Phenol



Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and water. Phenylephrine differs from adrenaline only by lacking the 4th OH group on the benzene ring, and

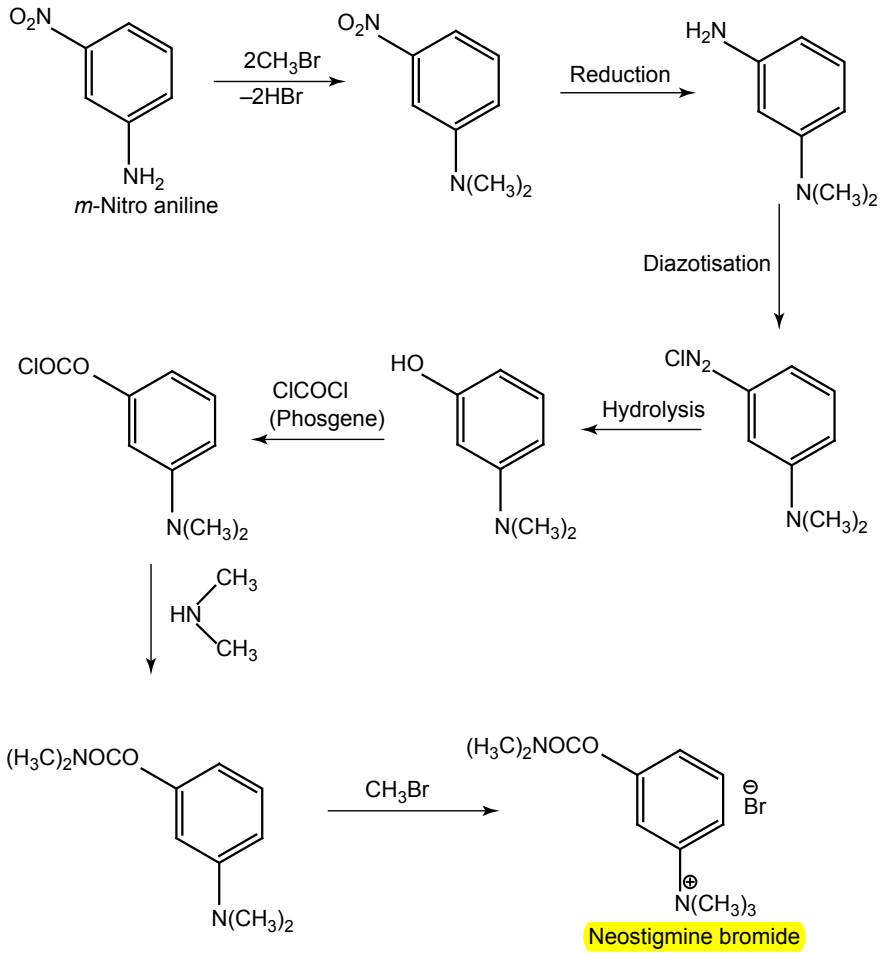
ii. Neostigmine Bromide (Synonym: Prostigmine, Myostigmin, Tilstigmin)



3-{[(Dimethyl amino) carbonyl] oxy}-*N*, *N*, *N*-trimethyl benzene ammonium bromide.

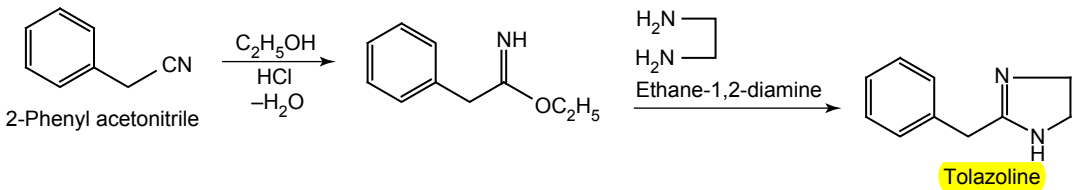
Synthesis

Route I. From: Meta nitro aniline



Synthesis

Route I. From: Phenyl acetonitrile



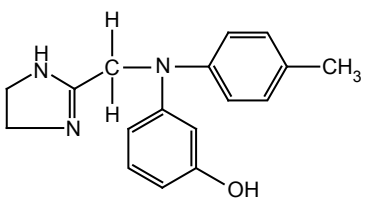
2-Phenyl acetonitrile

Tolazoline

Properties and uses: It is a white, bitter taste, crystalline compound with a slight aromatic odour, soluble in water, alcohol, and chloroform, but sparingly soluble in ether. It is an imidazolidine derivative. It is a competitive alpha adrenergic antagonist and possesses similar affinity for α_1 and α_2 receptors. It is a vasodilator and has a sympathomimetic effect to stimulate the heart and causes mydriasis. It is of some use in the treatment of Raynaud's disease, cerebral vascular accidents. It has been used in the treatment of persistent pulmonary hypertension of the newborn.

Dose: By I.M., I.V., S.C., for adults: 25 mg slowly, then increased upto 50 to 75 mg twice/day to 2 or 3 times/week.

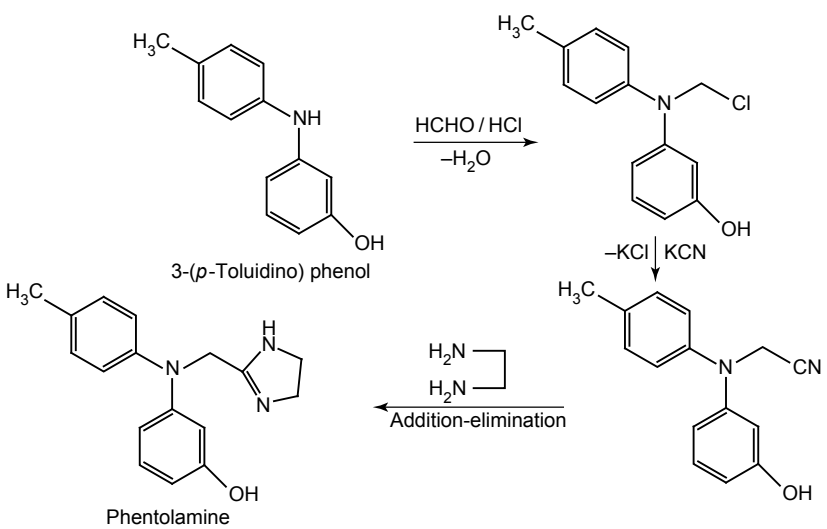
iv. Phentolamine mesylate



3[(4,5-Dihydro-1-imidazole-2yl)methyl](4-methyl-phenyl)amino phenol

Synthesis

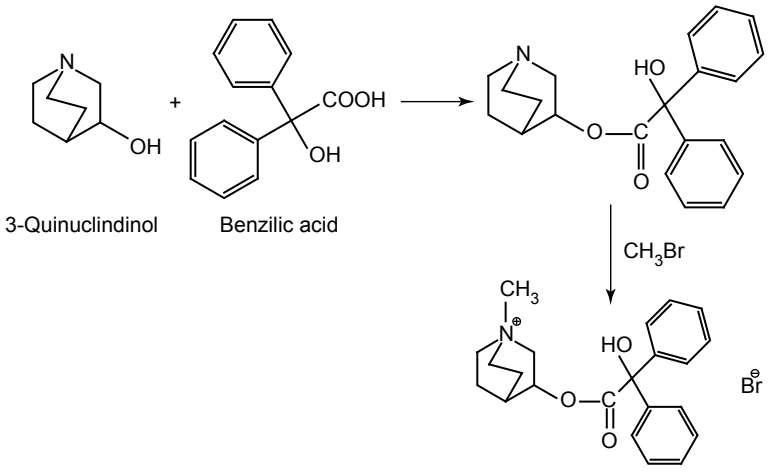
Route I: From 3-(*p*-Toluidino) phenol



3-(*p*-Toluidino) phenol

Phentolamine

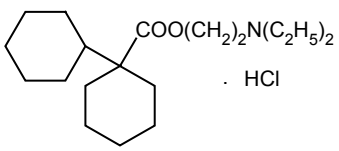
Synthesis



Clindinium bromide

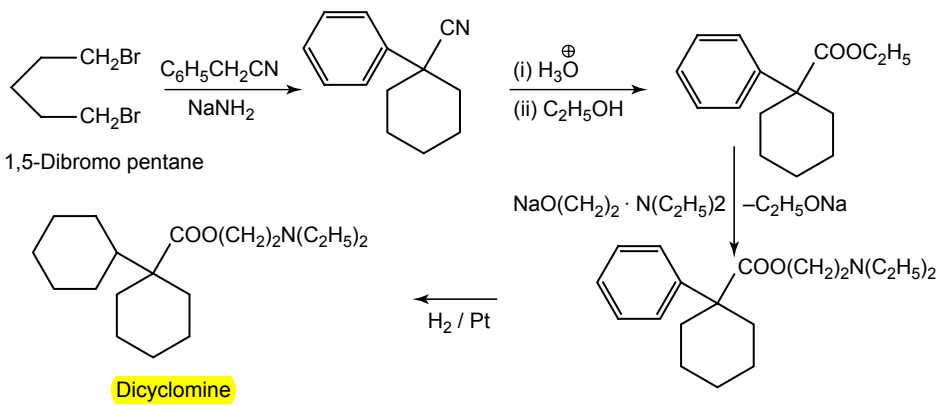
Uses: Used as a bronchodilator in asthmatic conditions. It has a longer lasting effect as compared to β-agonists.

iii. Dicyclomine HCl (Bentyl, Mesbentyl)



2-(Dimethylamino) ethyl bicyclohexyl-1-carboxylate HCl

Synthesis



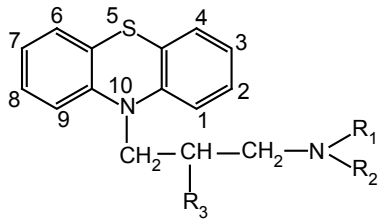
Dicyclomine

Properties and uses: It exists as a white, crystalline powder with a bitter taste, soluble in water and chloroform. Dicyclomine HCl behaves both as an antimuscarinic and a nonspecific antispasmodic agent. It

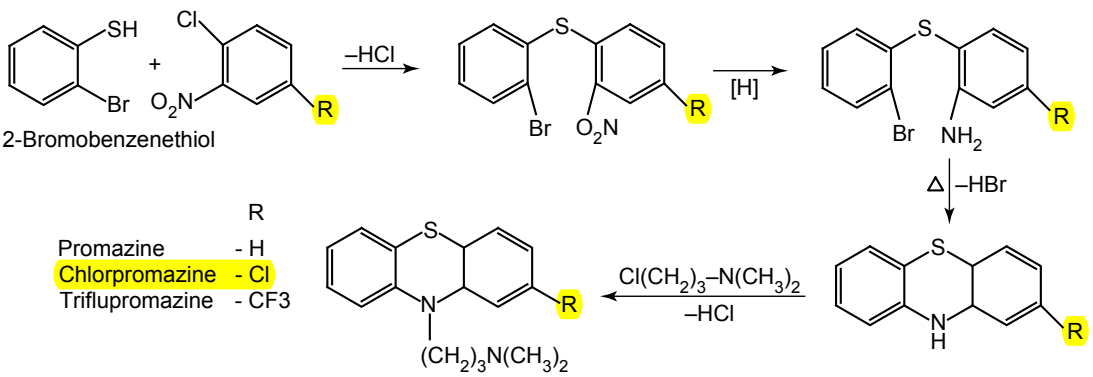
SYNTHESIS AND DRUG PROFILE

I. Phenothiazines

a. General synthesis of propyl dialkylamino side chain derivatives



Synthesis



a. Promazine

Properties and uses: It is a white or almost white crystalline powder, slightly hygroscopic in nature. It is well soluble in water, alcohol, and methylene chloride. It has low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action. It is used as dopamine receptor antagonist and neuroleptic.

Assay: Dissolve the sample in a mixture of 0.01 M hydrochloric acid and 50 ml of alcohol. Perform the potentiometric titration using 0.1 M sodium hydroxide.

Storage: It should be stored in well-closed airtight container and protected from light.

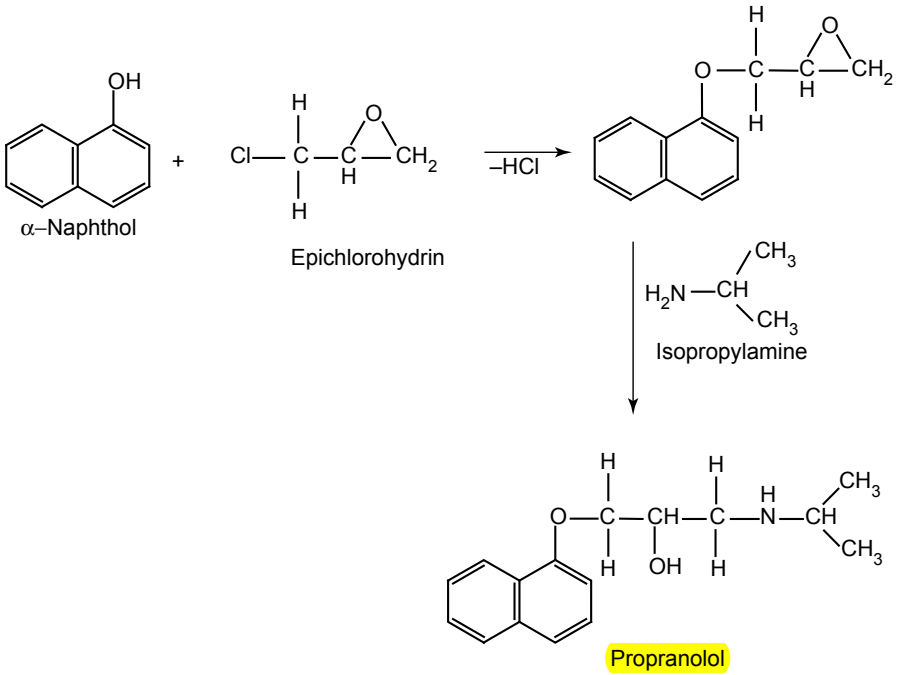
Dosage forms: Promazine injection B.P., Promazine oral suspension B.P., Promazine tablets B.P.

Chlorpromazine (Cain, Chlorpromazine, Megatil)

Metabolism: It is demethylated, sulphoxidized, hydroxylated, and glucuronidated to yield 7-*o*-glu-nor chlorpromazine.

Properties and uses: It is a white or almost white crystalline powder, freely soluble in ethanol and well soluble in water. The drug has significant sedative and hypotensive properties, possibly reflecting central

Synthesis



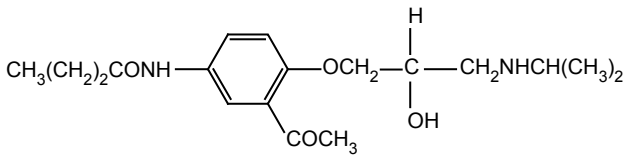
Properties and uses: It is a white or almost white powder, soluble in water and in ethanol. Currently, it is approved for hypertension associated cardiac arrhythmia, angina pectoris, due to coronary atherosclerosis and prophylaxis of migraine headache. It is a nonselective β-adrenergic antagonist and it has equal affinity for β_1 and β_2 receptors.

Assay: Dissolve the sample in ethanol and titrate with 0.1 M sodium hydroxide. Determine the end point potentiometrically.

Dose: The oral adult dose for arrhythmias is 10 to 30 mg 3 to 4 times/day.

Dosage forms: Prolonged-release propranolol capsules B.P., Propranolol injection B.P., Propranolol tablets B.P.

ii. Acebutalol (Sectral)

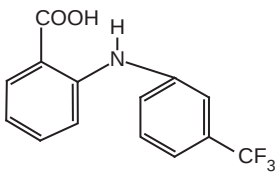


N-3 Acetyl-4-[2-hydroxy-3-(isopropyl)-amino propoxy]phenyl butyramide

SAR of Anthranilic Acid Derivatives (Fenamates)

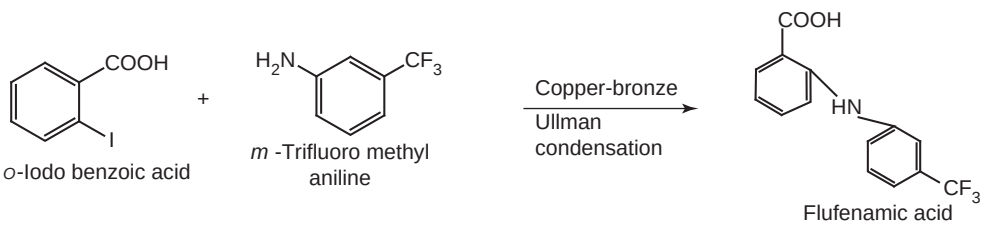
- The position of the carboxyl function is important for the activity of anthranilic acid derivatives that are active, whereas the 3 and 4 amino benzoic acid analogues are not active.
- Replacement of carboxylic acid function with the isosteric tetrazole results in the retention of anti-inflammatory activity.
- Placement of substitution on the anthranilic acid ring generally reduces the activity.
- Substitution on the *N*-aryl ring can lead to conflicting results. In the ultraviolet erythema assay for anti-inflammatory activity, the order of activity was generally 3′ > 2′ > 4′ for mono substitution with CF_3 group (flufenamic acid) being particularly potent. The opposite order of activity was observed in rat paw oedema assay, the 2′–Cl derivatives being more potent than 3′–Cl analogues.
- In disubstituted derivatives, where the nature of the two substitutes is the same 2′, 3′-disubstitution appears to be the most effective (mefenemic acid).
- The NH moiety of anthranilic acid is essential for the activity as the replacement of NH function with O, CH_2, S, SO_2, N-CH_3, or $NCOCH_3$ functionalities significantly reduced the activity.

i. Flufenamic Acid (Arlef, Tarlef)



N (α,α,α-Trifluoro-*m*-tolyl) Anthranilic acid

Synthesis



o-Iodo benzoic acid

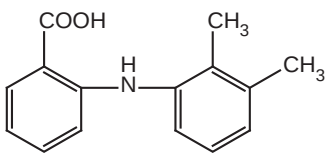
m -Trifluoro methyl aniline

Flufenamic acid

Properties and uses: Flufenamic acid is a pale yellow crystalline powder or needles. It has analgesic, anti-inflammatory, and antipyretic actions; it is employed in the treatment of rheumatic disorder and dysmenorrhoea.

Dose: 400–600 mg per day in divided doses.

ii. Mefenamic acid



2-(2,3-Dimethylphenylamino)benzoic acid

Synthesis

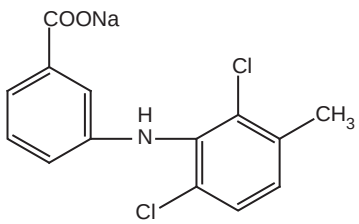
2-Chlorobenzoic acid 2,3-Dimethylbenzenamine Mefenamic acid

An analogues approach by reaction of *o*-chloro benzoic acid with 2,3-dimethyl aniline.

Metabolism: Its metabolism occurs through regioselective oxidation of 3-methyl group and glucuronidation of mephanamic acid. Majority of the 3-hydroxy methyl metabolite and dicarboxylic acid products are excreted.

Uses: Used as an analgesic and anti-inflammatory agent.

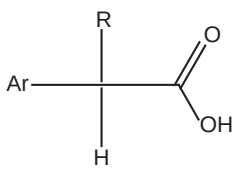
iii. Meclofenamate Sodium



Sodium 3-(2,6-dichloro-3-methylphenylamino)benzoate

Synthesis: It is obtained by Ullman condensation employing 2, 6 dichloro 3-methyl aniline.

V. Arylalkanoic acids



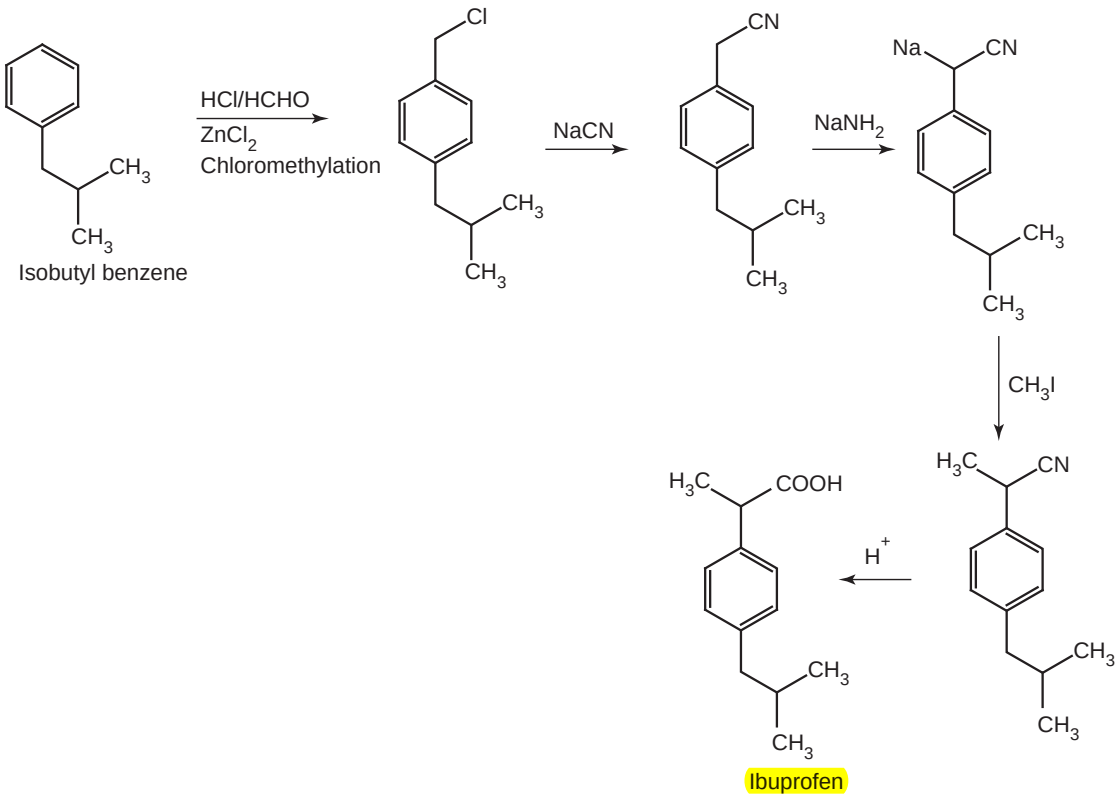
General structure

SAR of Arylalkanoic Acids

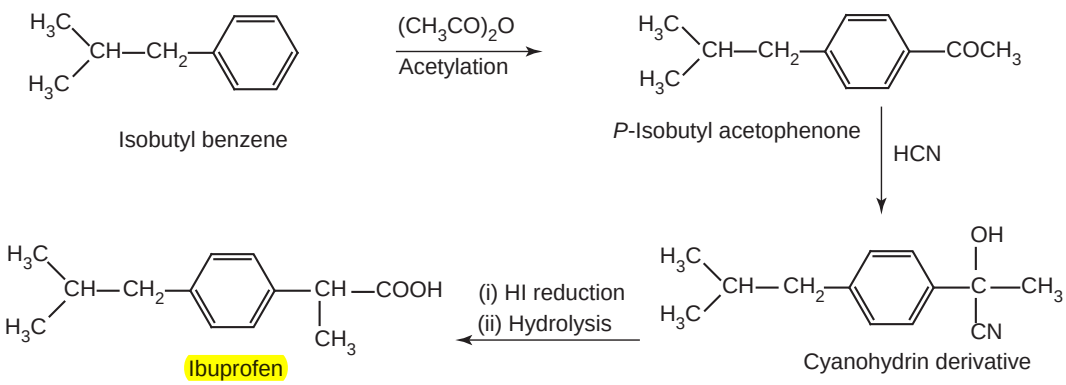
1. The centre of acidity is usually located one carbon atom adjacent to a flat surface represented by an aromatic or hetero aromatic ring.
2. The distance between these centres is critical because increasing this distance to two or three carbons generally decreases activity.
3. All agents possess a centre of acidity, which can be represented by a carboxylic acid and hydroxamic acid, a sulphonamide or a terazole.
4. Substitution of a methyl group on the carbon atom separating the aromatic ring leads to enhancement of anti-inflammatory activity.

Synthesis

Route I. From Isobutyl benzene



Route II. From: Isobutyl benzene



Metabolism: Oxidative metabolite of ibuprofen and unchanged drugs are excreted in urine. Oxidation involves ω, ω_1, and ω_2 oxidation of the para isobutyl side chain, followed by alcohol oxidation, resulting from ω oxidation to corresponding carboxylic acid.