Model Answer

(AR-7483)

Subject: Pharmaceutical Chemistry-VI

B.Pharm VI Semester

Section A

1.

a) Prodrug: Refer a pharmacologically inactive compound that is metabolically activated in the mammalian system.

Example:

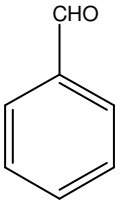
Levodopa (prodrug) Dopamine (active form)

Sulfasalazine (prodrug) -------5 amino salicylic acid (active form)

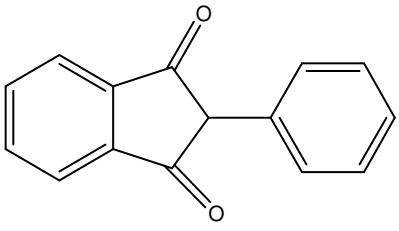
b) MAO: Monoamine oxidase

COMT: Catechol –o- methyl transferase

c) A:



Benzaldehyde, B:



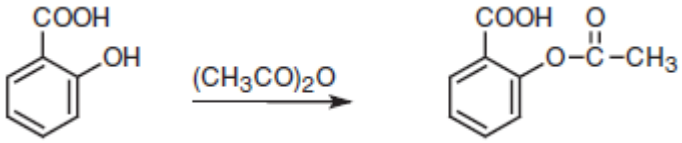
Phenindione

d) Major coagulation Factors:

Thromboplastin,
Prothrombm.
Fibrinogen
and ionized calciumum

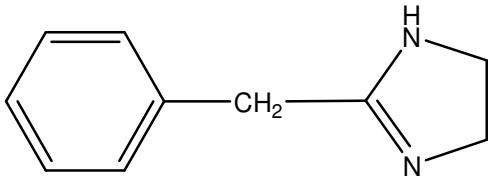
e) Aspirin synthesis:

Aspirin, acetylsalicylic acid , is synthesized by the acetylation of salicylic acid using acetic anhydride or acetyl chloride.



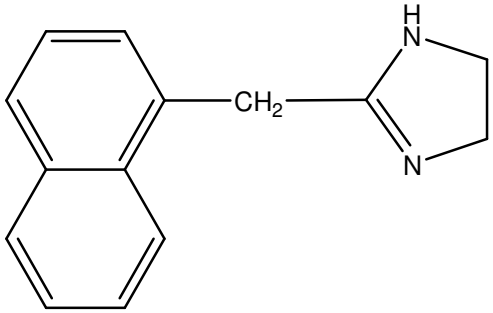
f) Imidazoline ring containing nasal decongestant

Tolazoline



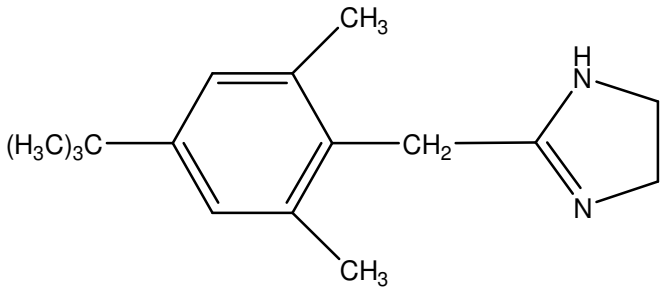
or

Naphazoline



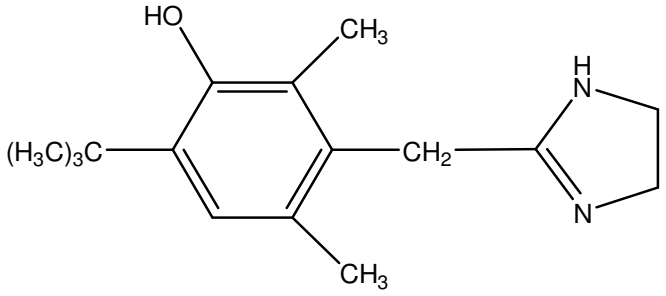
or

Xylometazoline

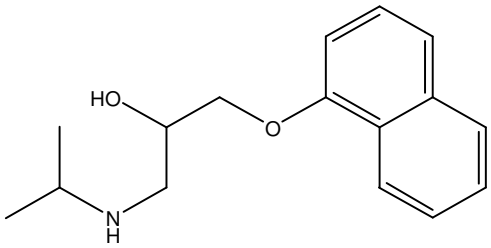


or

Oxymetazoline

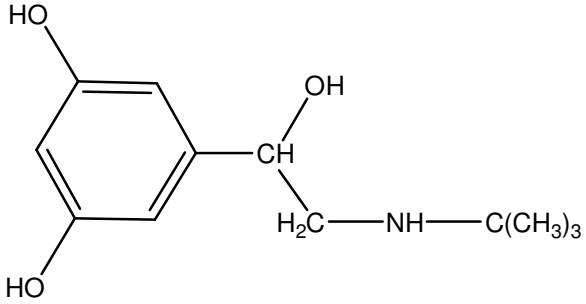


g) Propanolol



1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol

Terbutaline

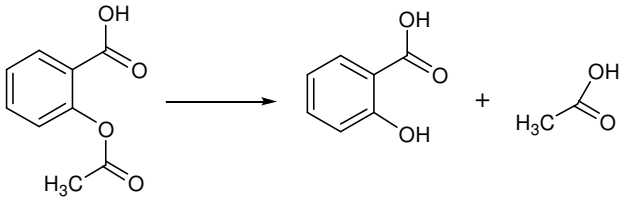


5-(2-(*tert*-butylamino)-1-hydroxyethyl)benzene-1,3-diol

h) Hydrolysis in Phase I metabolism: Cleavage of Drug Molecule by taking up a molecule of water.

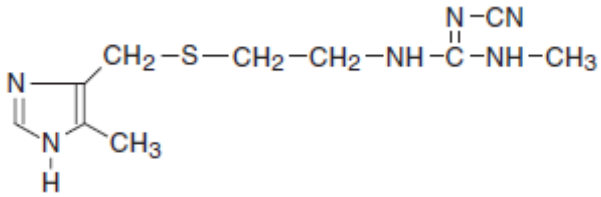
Ester + H_2O ⟶ Acid+ Alcohol

Hydrolyzes (adds water to) esters and amides and their isosteres; the OH from water ends up on the carboxylic acid (or its isostere) and the H in the hydroxy or amine



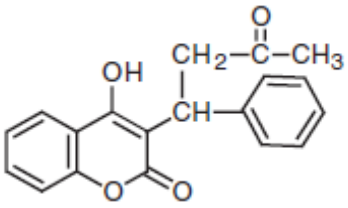
Aspirin Salicylic Acid

i) **Cimetidine**



1-cyano-2-methyl-3-[2-[[5-[[methylimidazol-4-yl)methyl]thio]ethyl] guanidine

Warfarin

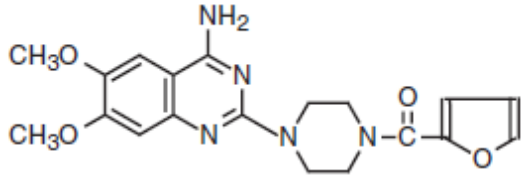


3-(α-acetonylbenzyl)-4-hydroxycoumarin

j) Anticholinergics having antiparkisonian activity: Trihexyphenidyl, procyclidine, biperiden, Benztropine etc.

k) Anticholine esterases are the agents which inhibit choline esterase and protect hydrolysis of acetylcholine hydrolysis by binding either anionic or esteric site of acetyl choline esterase.

l) **Prazosin**



1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine

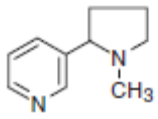
Section B

2. The parasympathomimetic alkaloids are as follows

Muscarininc alkaloid: Muscarine, Pilocarpine

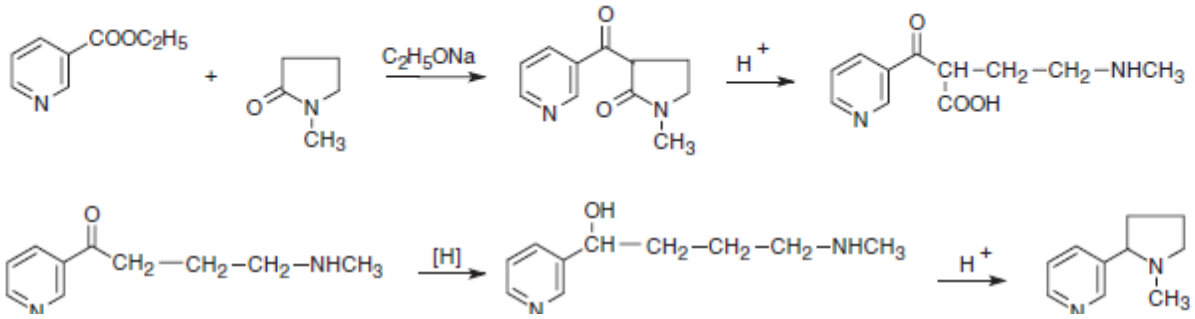
Nicotinic alkaloid: Nicotine, Lobeline

Nicotine:



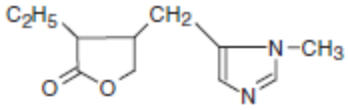
Nicotine, 1-methyl-2-(3-piridyl)pirrolidine

Synthetic Route



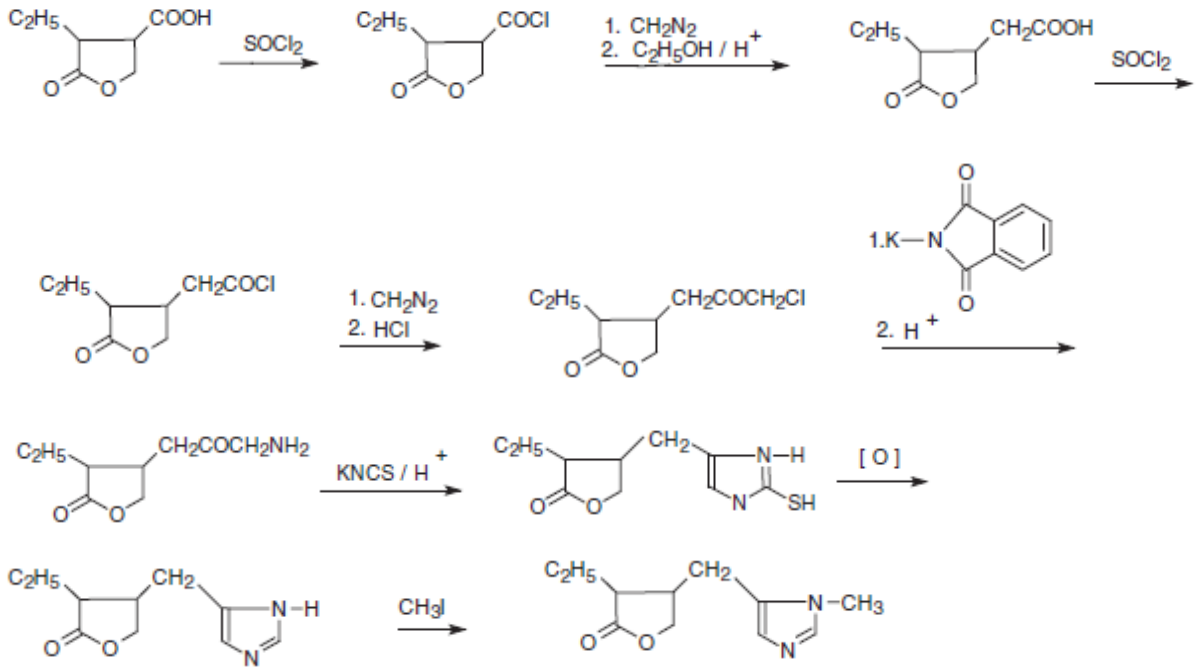
In particular, it is proposed to proceed from nicotinic acid ethyl ester, which is condensed with *N*-methylpyrrolidone, giving 1-methyl-2- nicotinoyl pyrrolidone-2. Acidic hydrolysis of this compound leads to an opening of the pyrrolidine ring giving the intermediate , which under the reaction conditions is decarboxylated to the γ -aminoketone . The carbonyl group is reduced to an alcohol and the resulting product undergoes dehydration to nicotine

Pilocarpine:



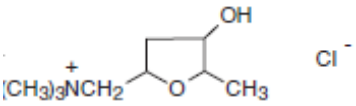
3-ethyl-4-(1-methyl-5-imidazolymethyl)tetrahydrofuran-2-one

Synthetic Route



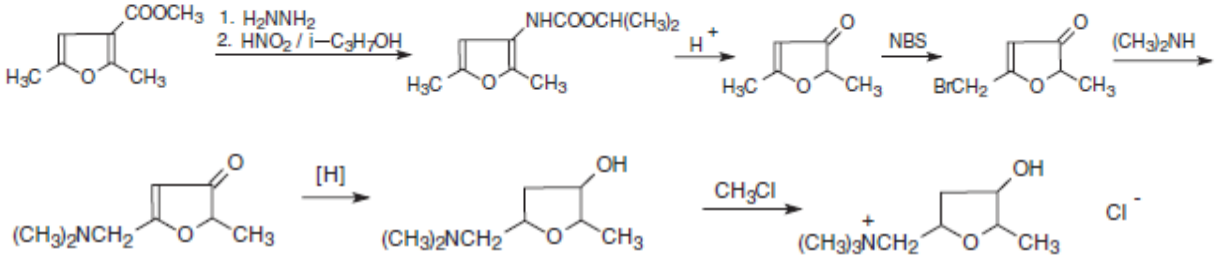
It is synthesized from 2-ethyl-3-carboxy-2-butyrolactone , which with the help of thionyl chloride is turned into the acid chloride and further reacted with diazomethane and ethanol, to give the corresponding ethyl ester (Arndt–Eistert reaction), which is hydrolyzed into the acid. The resulting acid is again changed into the acid chloride by thionyl chloride. The obtained acid chloride is treated with diazomethane. But in this case the intermediate forming ketene is treated with hydrogen chloride to give the chloroketone . Reacting this with potassium phthalimide and subsequent removal of the phthalimide protecting group by acid hydrolysis gives the aminoketone ,which is reacted with an acidic solution of potassium thiocyanate, forming 3-ethyl-4-(2-mercapto-5-imidazolylmethyl)tetrahydrofuran-2-one. Mild oxidation of this product allows to remove the mercapto- group from the product (13.1.20), giving 3-ethyl-4-(5-imidazolylmethyl)tetrahydrofuran-2-one. Alkylation of the resulting product with methyl iodide leads to the formation of pilocarpine.

Muscarine:



2-methyl-3-hydroxy-5-(*N*,*N*,*N*-trimethylammonium) methylentetrahydrofuran chloride

Synthetic Route:



It can be synthesized in various ways from completely different substances, particularly from 2,5-dimethyl-3-carboxymethylflurane, which undergoes a Curtius reaction, i.e. successive reactions with hydrazine and further with nitrous acid in isopropyl alcohol, which forms the urethane, the acidic hydrolysis of which gives 2,5-dimethyl-2*H*-furane-3 . Allylic bromination of this gives 2-methyl-5-bromomethyl-2*H*-furanone-3 (13.1.11), which is reacted with dimethylamine, forming 2-methyl-5-dimethylaminomethyl-2*H*-fluranone-3. Reducing this compound leads to formation of 2-methyl-3-hydroxy-5-dimethylaminomethyltetrahydroflurane, the reaction of which with methyl chloride gives muscarine as a mixture of stereoisomers.

3. a) Antihistaminic Drugs

Key points to be covered

Definition

Significance

Chemical classification of first, 2nd and third generation antihistamics drugs

Mechanism of action and

Synthesis of some important drugs.

Useful application

b) Antiplatelet agents

Key points to be covered by the students by their own languages

Definition

Significance

Mechanism of action and

Classification and Clinically used drugs

Synthesis of some important drugs.

Useful application

C) Factors affecting drug metabolism:

Key points to be covered by the students by their own languages

Age Differences

Species and strain differences

Hereditary or Genetic factors

Sex differences

Enzyme Induction

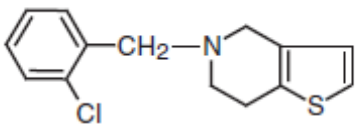
Enzyme Inhibition

Miscellaneous

Stereo chemical factors

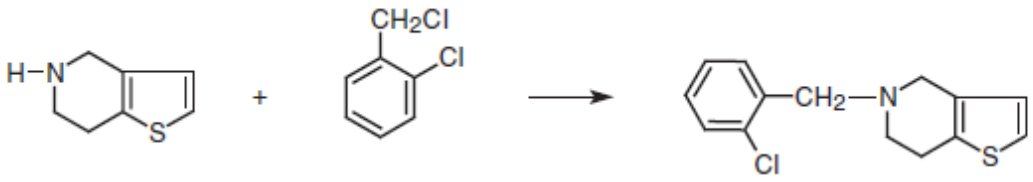
4.

a) Ticlopidine



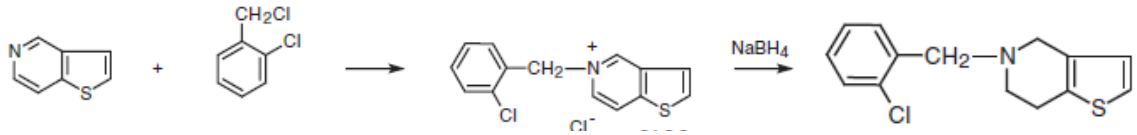
5-(*o*-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

1st way



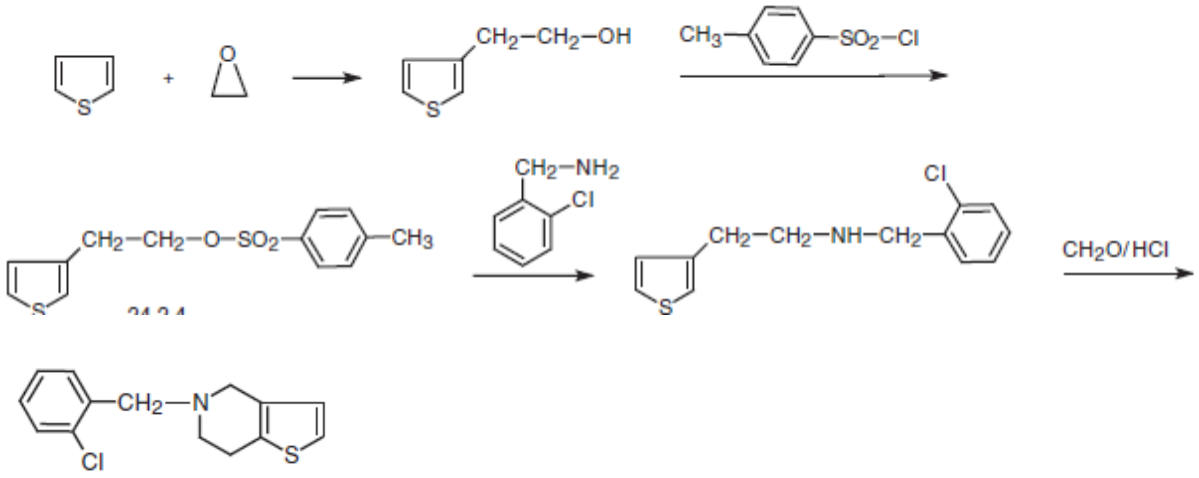
The first way consists of N-alkylation of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine with 2-chlorobenzylchloride

2nd way



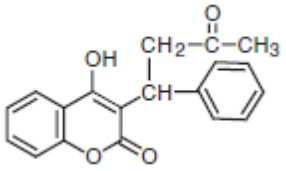
second way, thieno[3,2-c]pyridine undergoes N-alkylation using 2-chlorobenzylchloride, and the resulting pyridinium salt (24.2.2) is further reduced by sodium borohydride to the desired ticlopidine.

3rd way

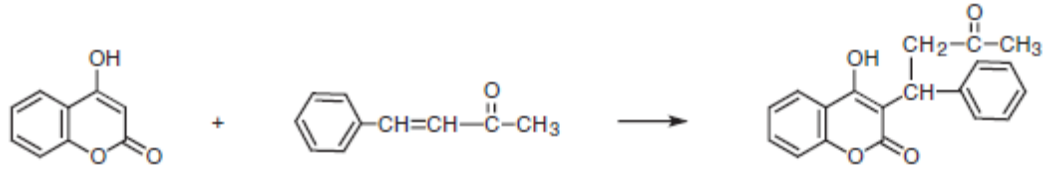


The third way of making this drug consists of alkylating thiophene with ethylene oxide, forming 2-(2′-hydroxy)ethylthiophene, which reacts with *p*-toluenesulfonic acid chloride to give the corresponding tosylate. Substitution of the tosyl group using 2-chlorobenzylamine gives an amine , which under reaction conditions for chloromethylation cyclizes to the desired ticlopidine.

b) ***Warfarin:***

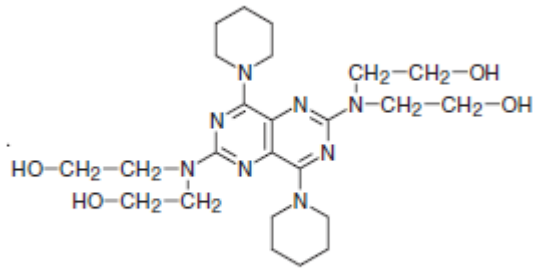


3-(α-acetonylbenzyl)-4-hydroxycoumarin

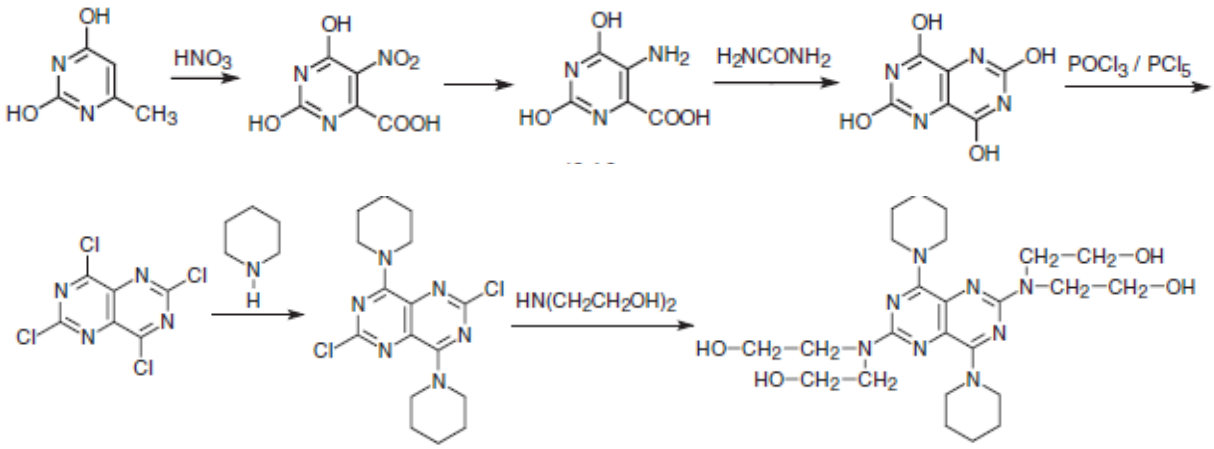


Synthesized via Michael reaction by attaching 4-hydroxycoumarin to benzalacetone in the presence of pyridine

c)Dipyridamole:

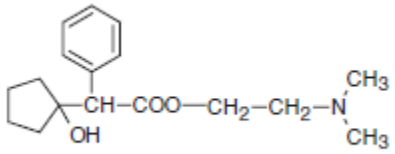


2,2′,2″,2‴-[(4,8-dipiperidinopirimido[5,4-d]pirimidin-2,6-diyl)-diimino]-tetraethanol.

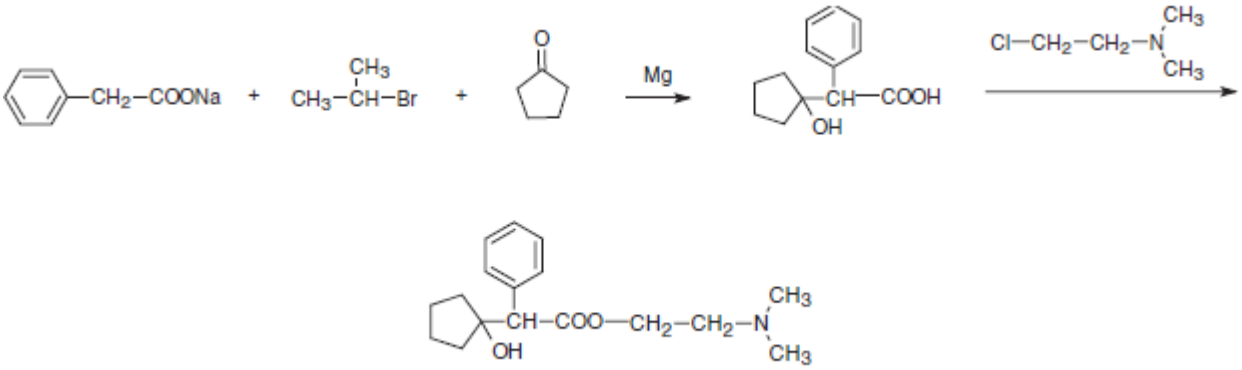


It is easily synthesized from 5-nitroorotic acid , easily obtained, in turn, by nitrating of 2,4-dihydroxy-6-methylpyrimidine, which is usually synthesized by the condensation of urea with acetoacetic ether. Reduction of the nitro group in 5-nitroorotic acid by various reducing agents gives 5-aminoorotic acid, which is reacted with urea or with potassium cyanide to give 2,4,6,8-tetrahydroxypyrimido[5,4-d]pyrimidine. This undergoes a reaction with a mixture of phosphorous oxychloride and phosphorous pentachloride, which forms 2,4,6,8-tetrachloropyrimido[5,4-d]pyrimidine. Reacting the resulting tetrachloride with piperidine replaces the chlorine atoms at C4 and C8 of the heterocyclic system with piperidine,giving 2,6-dichloropyrimido-4,8-dipiperidino[5,4-d]pyrimidine. Reacting the resulting product with diethanolamine gives dipyridamole.

d) Cyclopentolate:

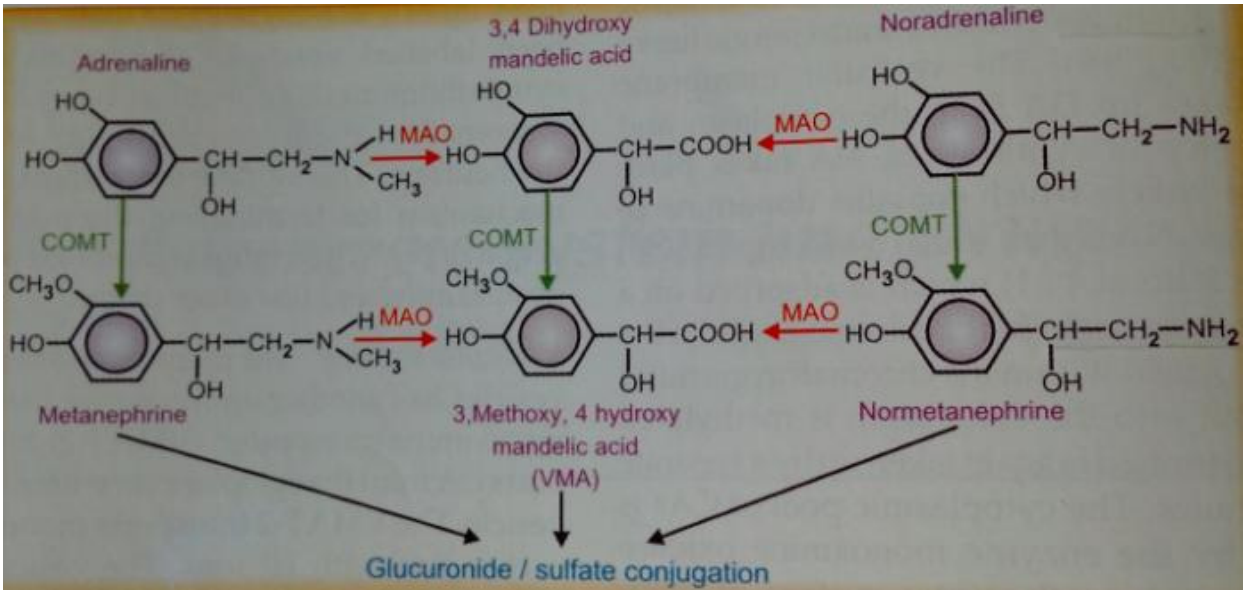


2-(dimethylamino)ethylic ester of 1-hydroxycyclopentane- α-phenylacetic acid



is synthesized by the esterification of α-(1- droxycylopentyl) phenylacetic acid using 2-dimethylaminoethylchloride, α-(1- Hydroxycyclopentyl) phenylacetic acid is synthesized by reacting the sodium salt of phenylacetic acid with cyclopentanone in the presence of isopropylmagnesium bromide.

5. a) Metabolism of catecholamines



Explanation of the above by students by their own language

Therapeutic Classification of Adrenergic drugs

Key points

1. Pressor agents: Examples of drugs

2. Cardiac Stimulant: Examples of drugs

3. Bronchodilators: Examples of drugs

4. Nasal Decongestant: Examples of drugs

5. CNS stimulants: Examples of drugs

6. Anorectics: Examples of drugs

7 Uterine relaxant and vasodilators: Examples of drugs

b) Cardio selective β-blockers

key points

β-blockers

Significance

Name and structures of cardioselctive β-blockers

Synthetic route of some important β-blockers

Useful applications

6. Definition of local anesthetic

Chemical classification

1. The ester: examples

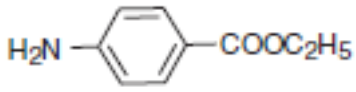
2. Piperidine or tropane derivatives: examples

3. The Amides: examples

4. The quinoline and Iso quinoline Analogues: examples

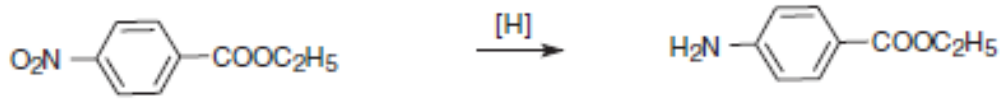
5. Miscellaneous: examples

Benzocaine:



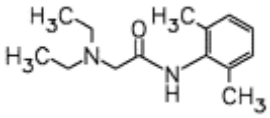
Ethyl ester of 4-aminobenzoic acid

Synthetic route

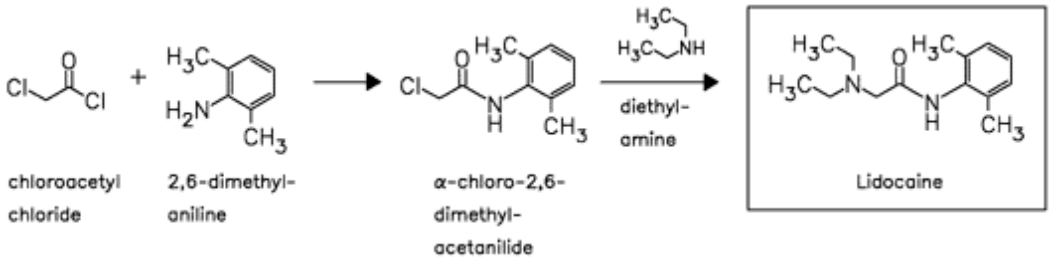


The classic, optimal way of benzocaine synthesis is the reduction of the nitro group of the ethyl ester of 4-nitrobenzoic acid to benzocaine by hydrogen, which generates directly in the reaction medium by the reaction of iron filings with dilute acids.

Lignocaine

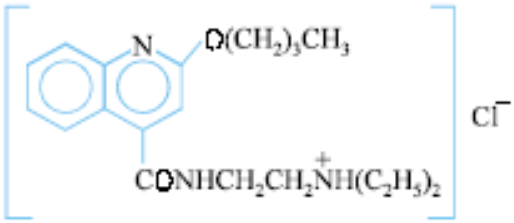


2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide

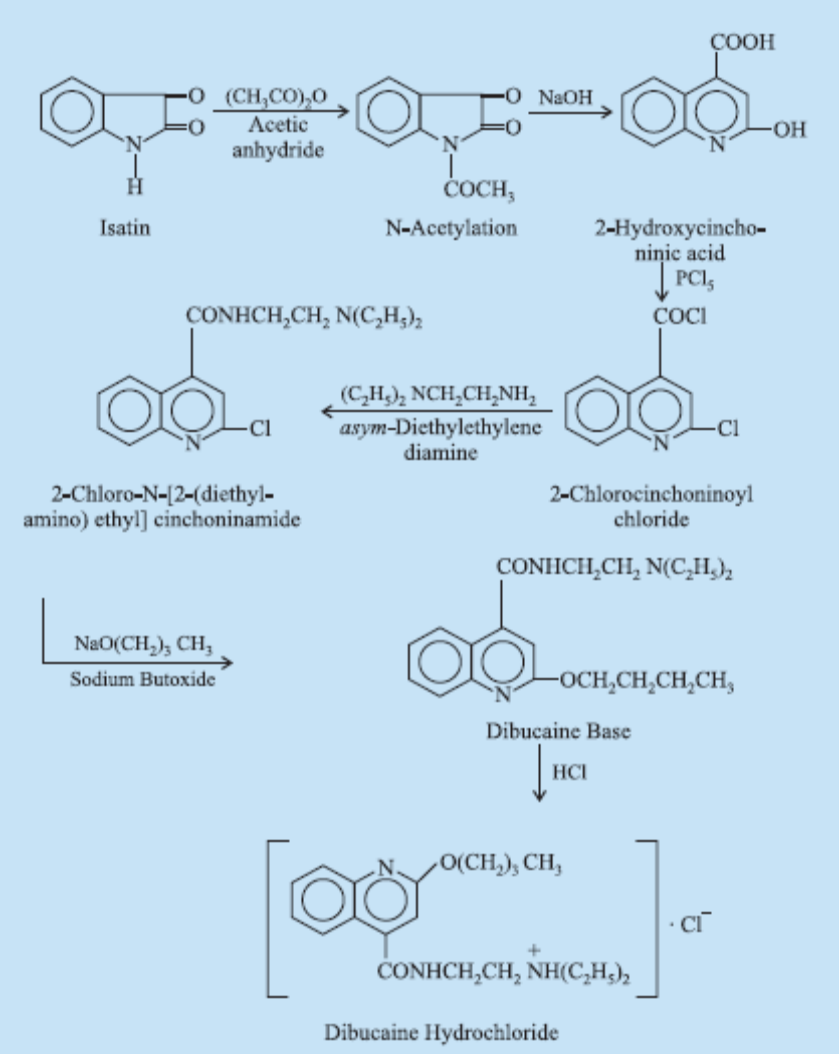


Explanation by student by their own language

Dibucaine Hydrochloride



2-Butoxy-N-[2-(diethylamino)-ethyl]-, monohydrochloride



Explanation by student by their own language

7. a) Acetyl Choline:

Key points

Significance

Structure and synthesis

Functions

Analogues

Clinical use

b) Anticoagulant

Key points

Definition

Chemical classification of anticoagulant

Mechanism of action

Useful applications

c) Drugs acting on uterus

Significance

Drugs used (Ergot alkaloids, Prostaglandins, oxytocin) and their short descriptions

(* Explanation language will be the students own/book language)