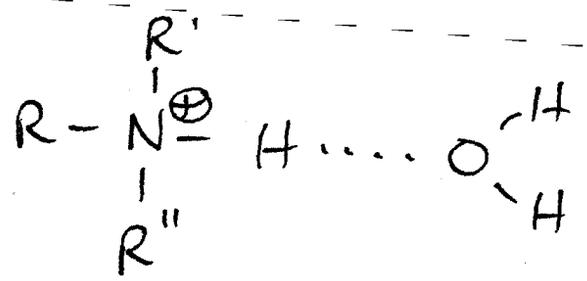
Basicity of Amines – gas phase vs. sol'n

Gas phase: $NH_3 < RNH_2 < R_2NH < R_3N$

In sol'n: $NH_3 < NR_3 \sim NH_2R < NHR_2$

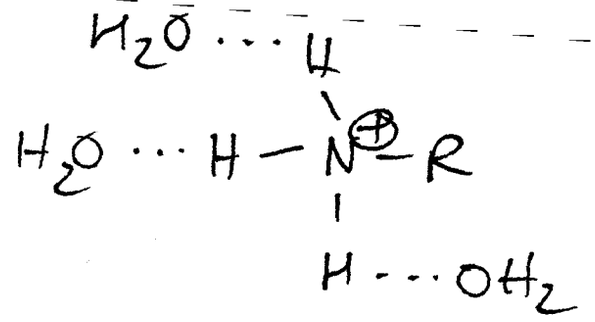
What's going on? Basicity is a function of the availability of the lone pair

1. Alkyl groups increase basicity by e⁻ donation via induction
2. Solvation – stabilization of the ammonium ion by H-bonding.



3° amine

<u>one</u> H-bond



1° amine

<u>three</u> H-bonds

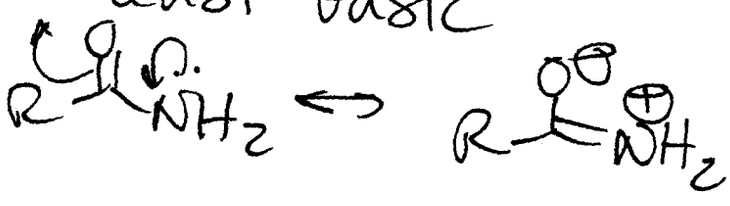
tradeoff - the more R groups you have, the fewer H-bonds can be formed.

2° amines have the best combination - 2 R groups donating e's 2 H's for H-bonding.

---

amides < aryl amines < alkylamines

least basic

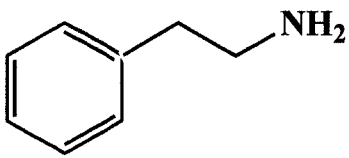


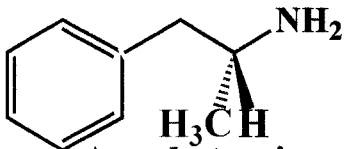
(as above)

Some Biologically Important Amines

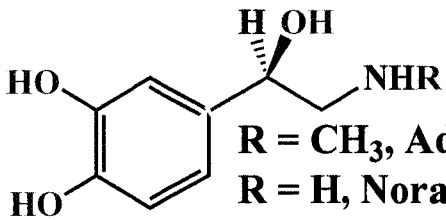
Amines are widely encountered in biological and pharmacological studies. Some important examples are the 2-phenylethylamines, some vitamins, antihistamines, tranquilizers, and neurotransmitters.

2-Phenylethylamines

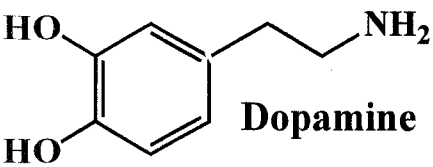




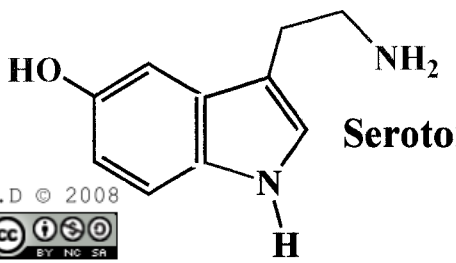
Amphetamine (Benzidrine)



R = CH_3, Adrenaline
R = H, Noradrenaline

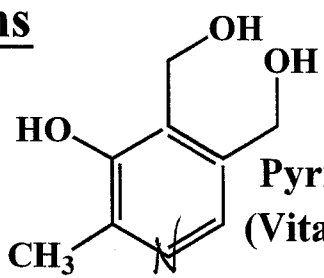


Dopamine

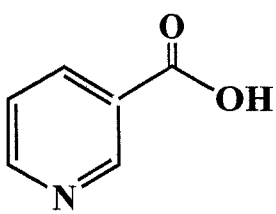


Serotonin

Vitamins

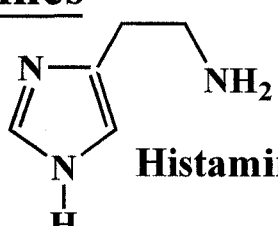


Pyridoxine (Vitamin B_6)



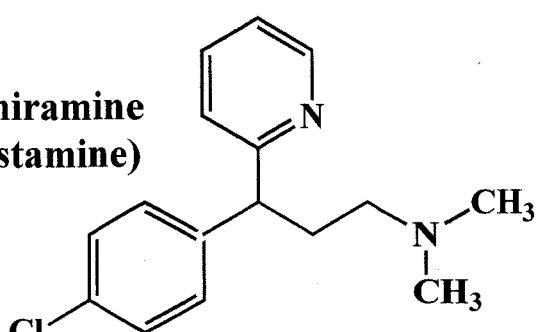
Nicotinic acid (Niacin)

Antihistamines



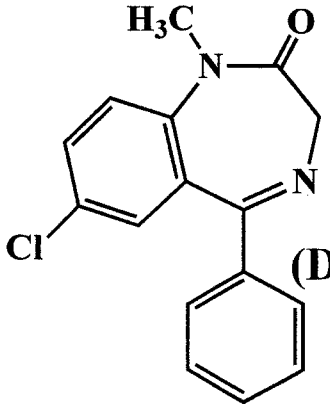
Histamine

Chlorpheniramine (an antihistamine)

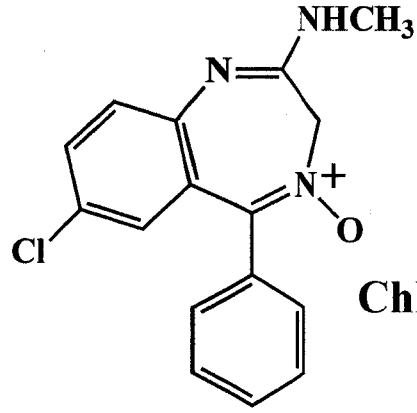


Tranquilizers

These examples are both 1,4-benzodiazepine anxiolytics.



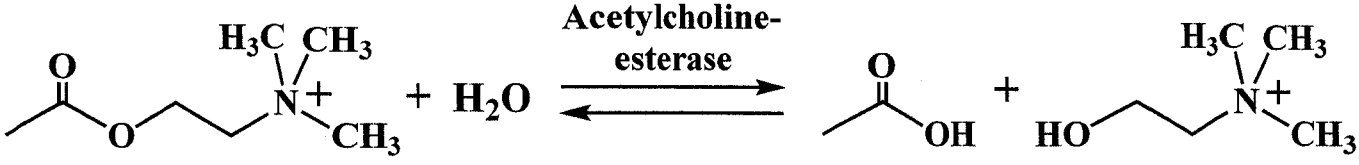
Valium (Diazepam)



Chlordiazepoxide

Neurotransmitters

Besides 2-phenylethylamines like noradrenaline, dopamine, and serotonin, the simpler amine-family compound acetylcholine is a neurotransmitter, one of great importance that acts at neuromuscular synapses.



Acetylcholine **Choline**

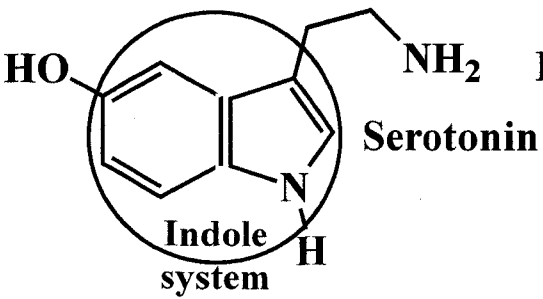
An essential feature of this system is that the esterase can almost immediately hydrolyze the neurotransmitter that has been received at the receptor site, freeing it to receive a later nerve impulse.

Structure-Reactivity Relationships

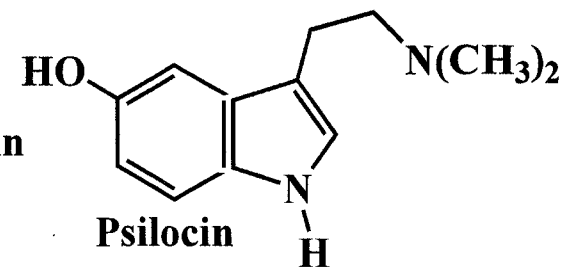
Medicinal chemists have long used structural features as a key to drug design. The structural similarity between the amphetamines and the natural brain hormones (like adrenaline, noradrenaline, and dopamine) is an example.

Serotonin Mimics

Another example of structure-reactivity relationships appears to be the hallucinogenic effect of a number of compounds of the indole type.

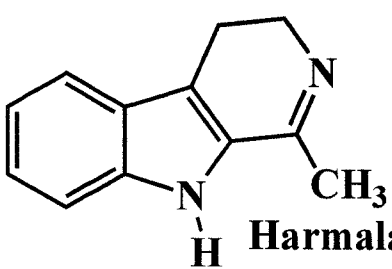


Serotonin



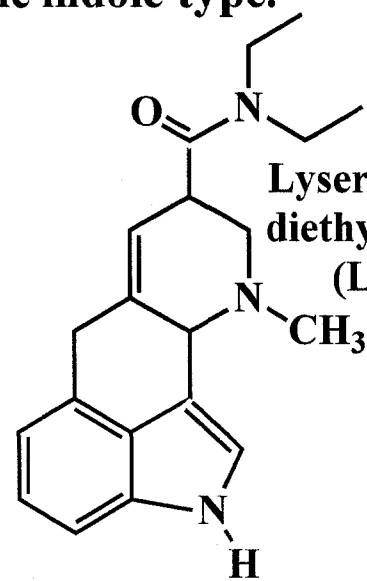
Psilocin

A hallucinogenic alkaloid obtained from the "sacred" mushrooms of Central America, *Psilocybe mexicana.*



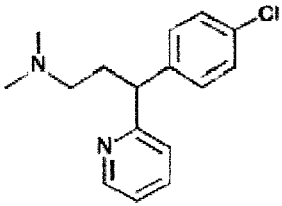
Harmala alkaloids

Found in plants in Peru, Ecuador, Columbia and Brazil. Used as a hallucinogen by native indians.

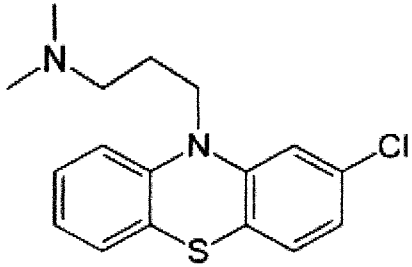


Lysergic acid diethyl amide (LSD)

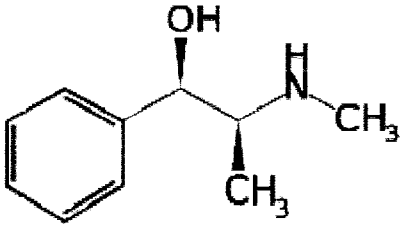
First synthesized by Albert Hofmann in 1938 at Sandoz Pharmaceutical Co. while working on derivatives of the hallucinogenic ergot alkaloids .



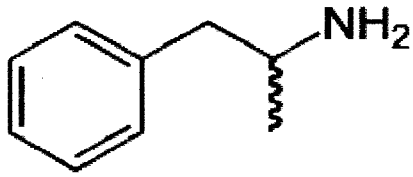
Chlorphenamine – an antihistamine



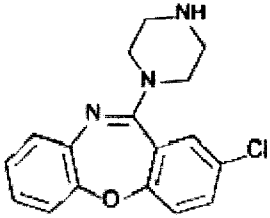
Chlorpromazine (Thorazine™) – an antipsychotic, used to treat schizophrenia



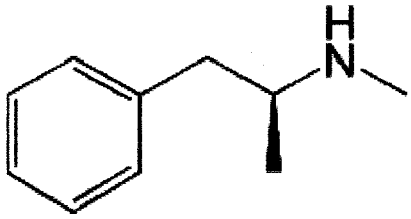
Ephedrine – a decongestant



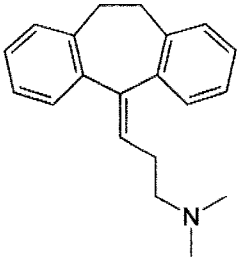
Amphetamine



Amoxapine – an antidepressant

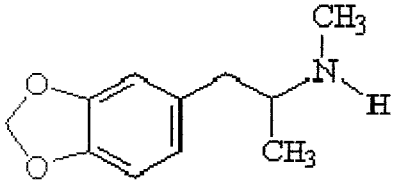


Methamphetamine

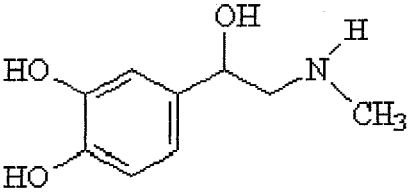


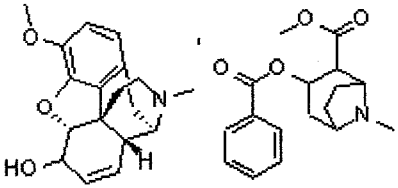
Amitryptiline - an antidepressant

MDMA (Ecstasy)



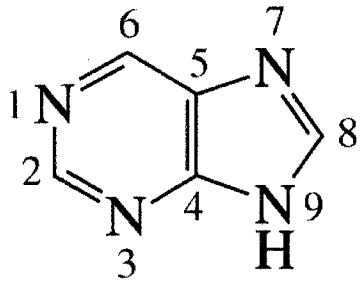
Adrenaline (epinephrine)



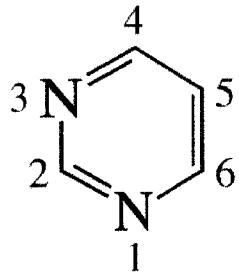


Codeine

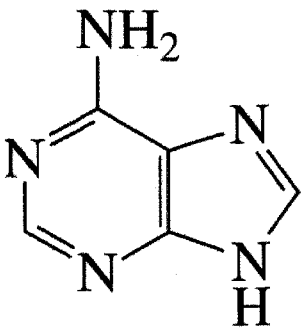
Purine and Pyrimidine



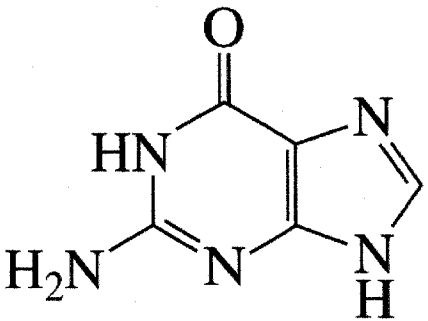
purine



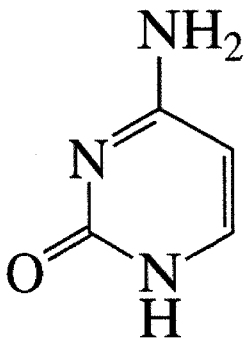
pyrimidine



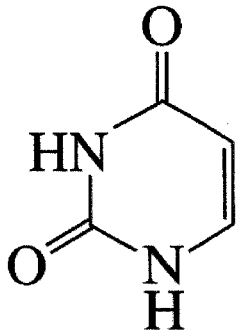
adenine



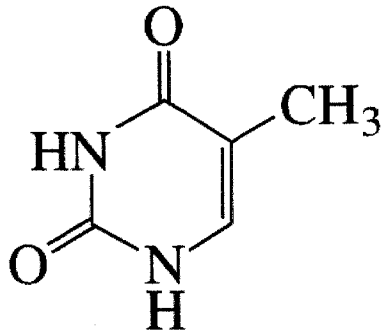
guanine



cytosine

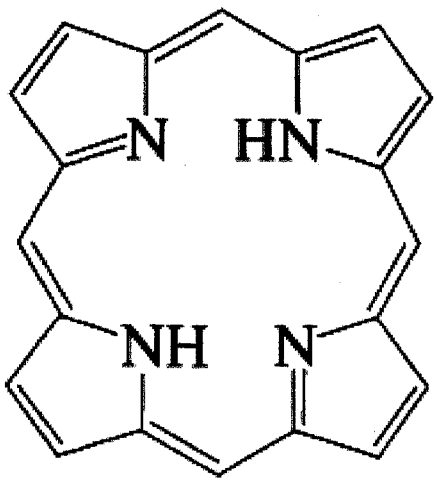


uracil

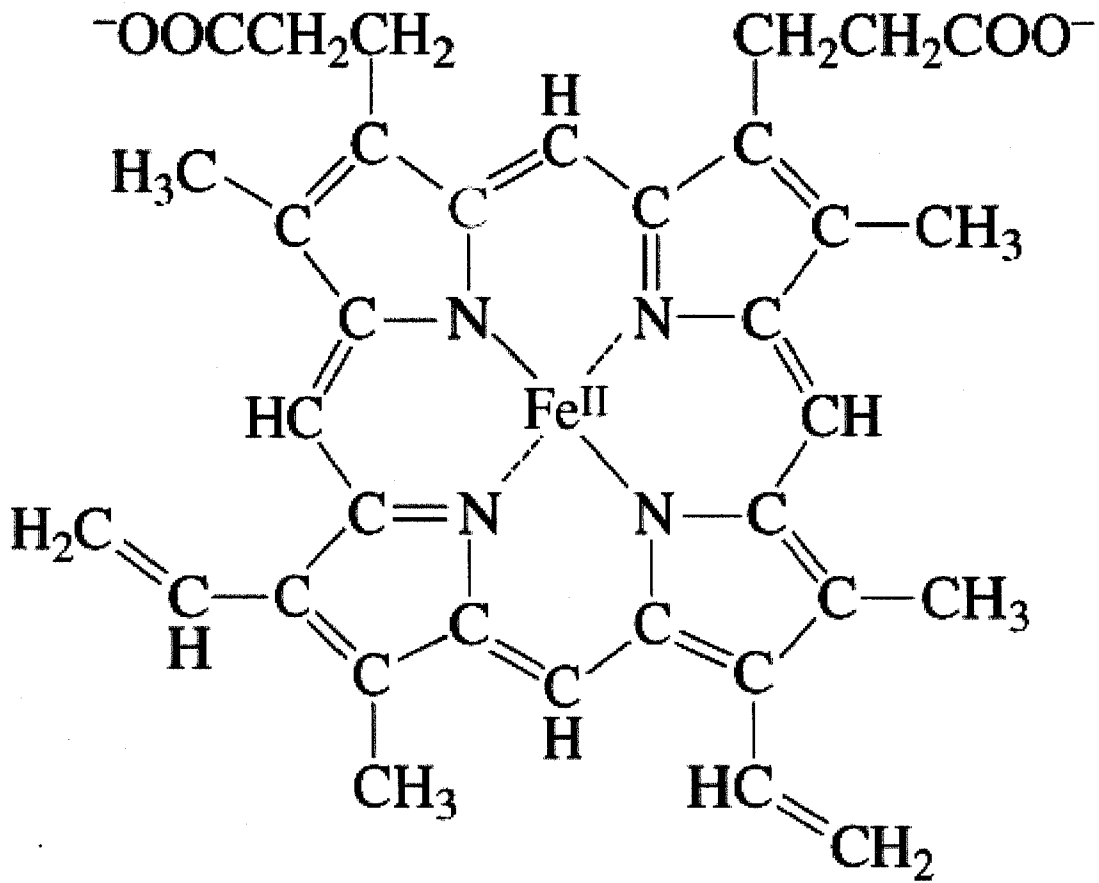


thymine

Porphyrin



a porphyrin ring system



iron protoporphyrin IX
heme

SKIP 20.5 – Phase Transfer

Synthesis of Amines

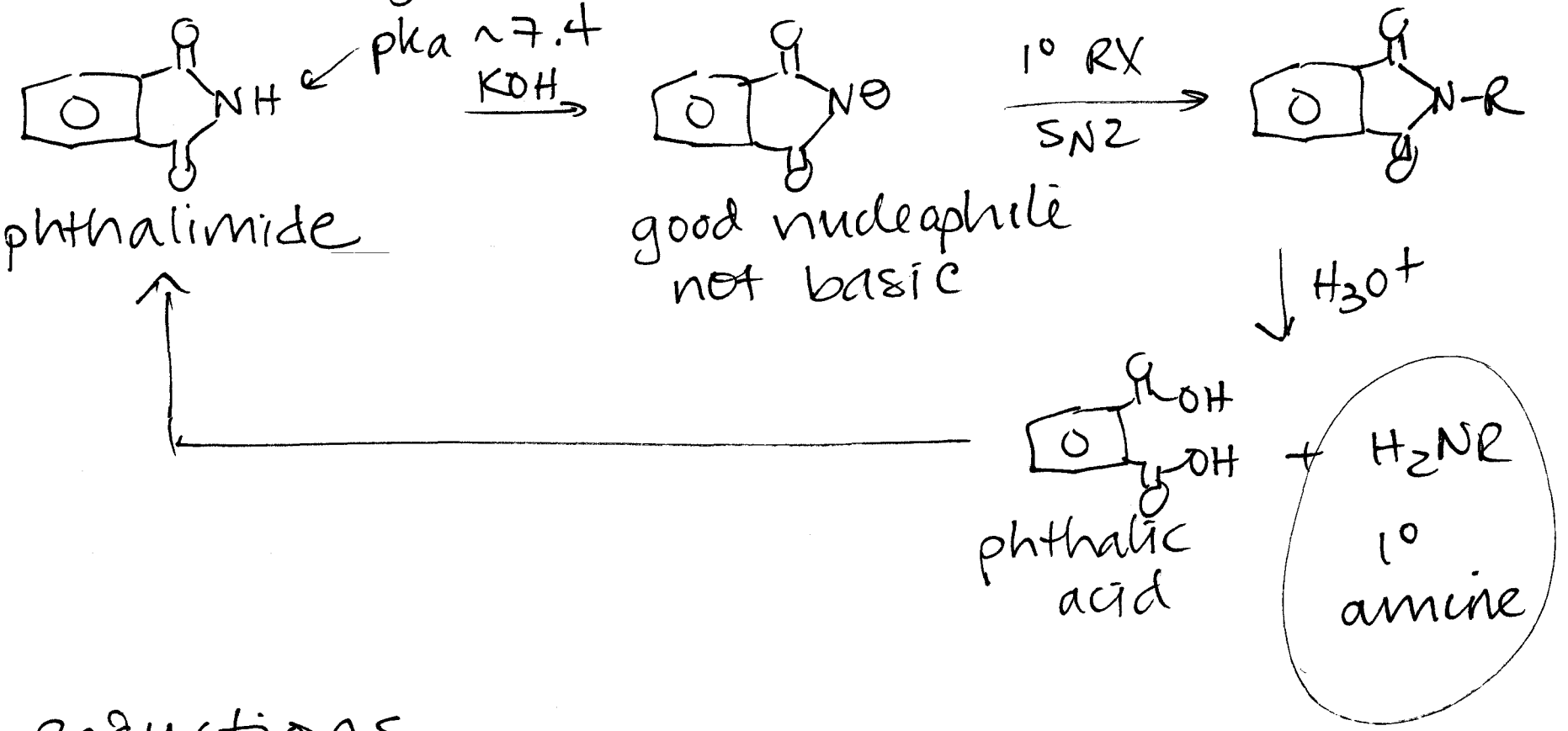
1. S_N2 – alkylation of ammonia

$$NH_3 + CH_3I \longrightarrow CH_3NH_2 + (CH_3)_2NH + (CH_3)_3N + (CH_3)_4N^{\oplus}I^{\ominus}$$

The only way to make this work is to use excess NH_3 → 1° amine

Also use xs CH_3I (exhaustive methylation) → 4° ammonium iodide

2. Gabriel Synthesis (section 16.18)

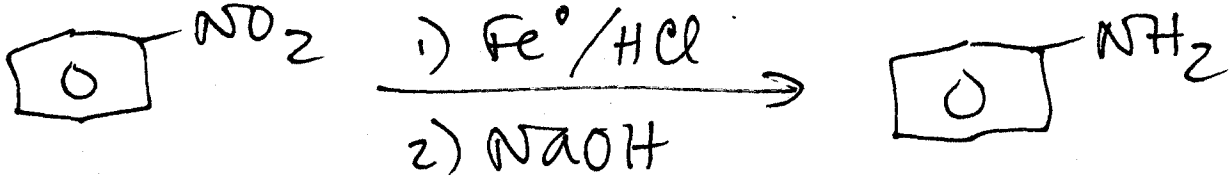


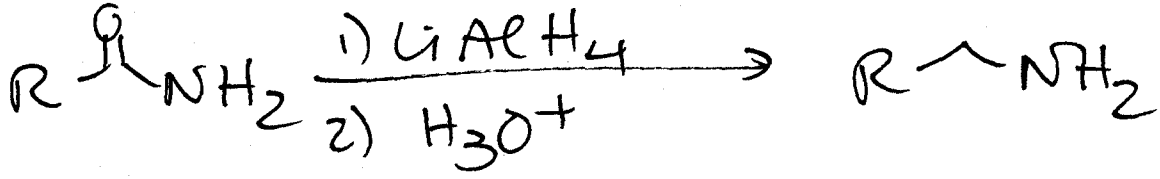
3. Reductions

a. $RX + NaN_3 \xrightarrow{SN2} RN_3 \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4} RNH_2 + N_2$

alkyl azide

b. $RX + NaCN \xrightarrow{SN2} RCN \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4} RCH_2NH_2$

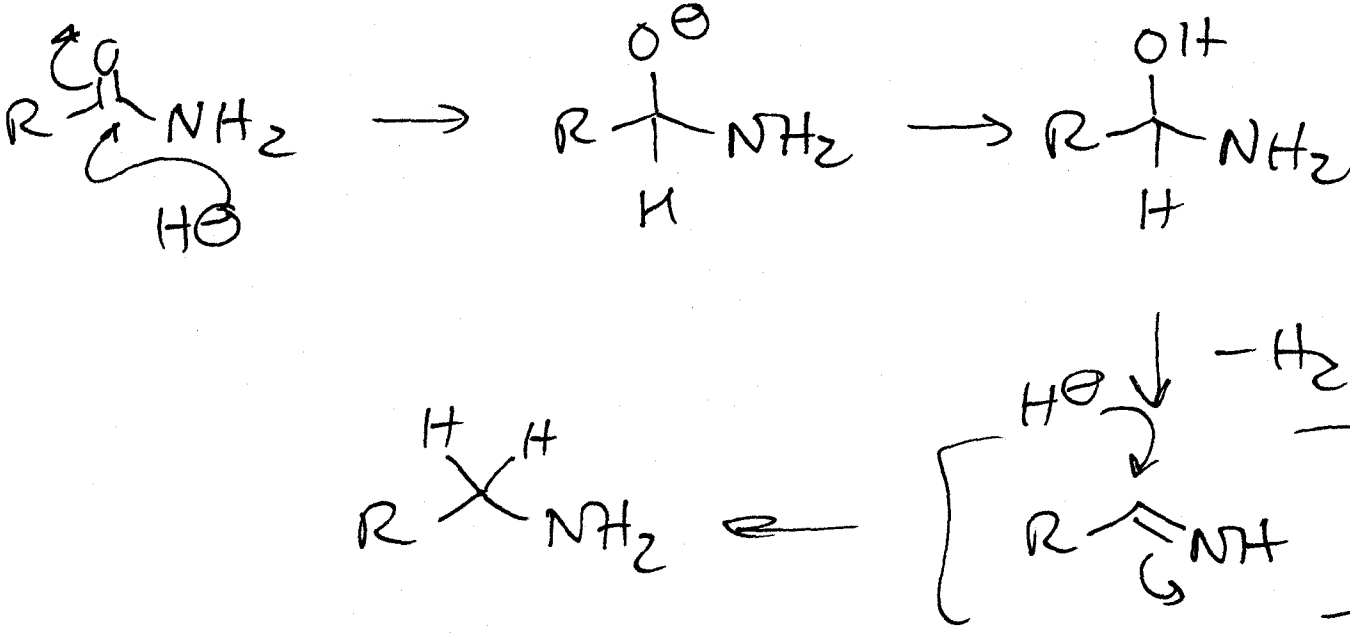
c. 

d. 

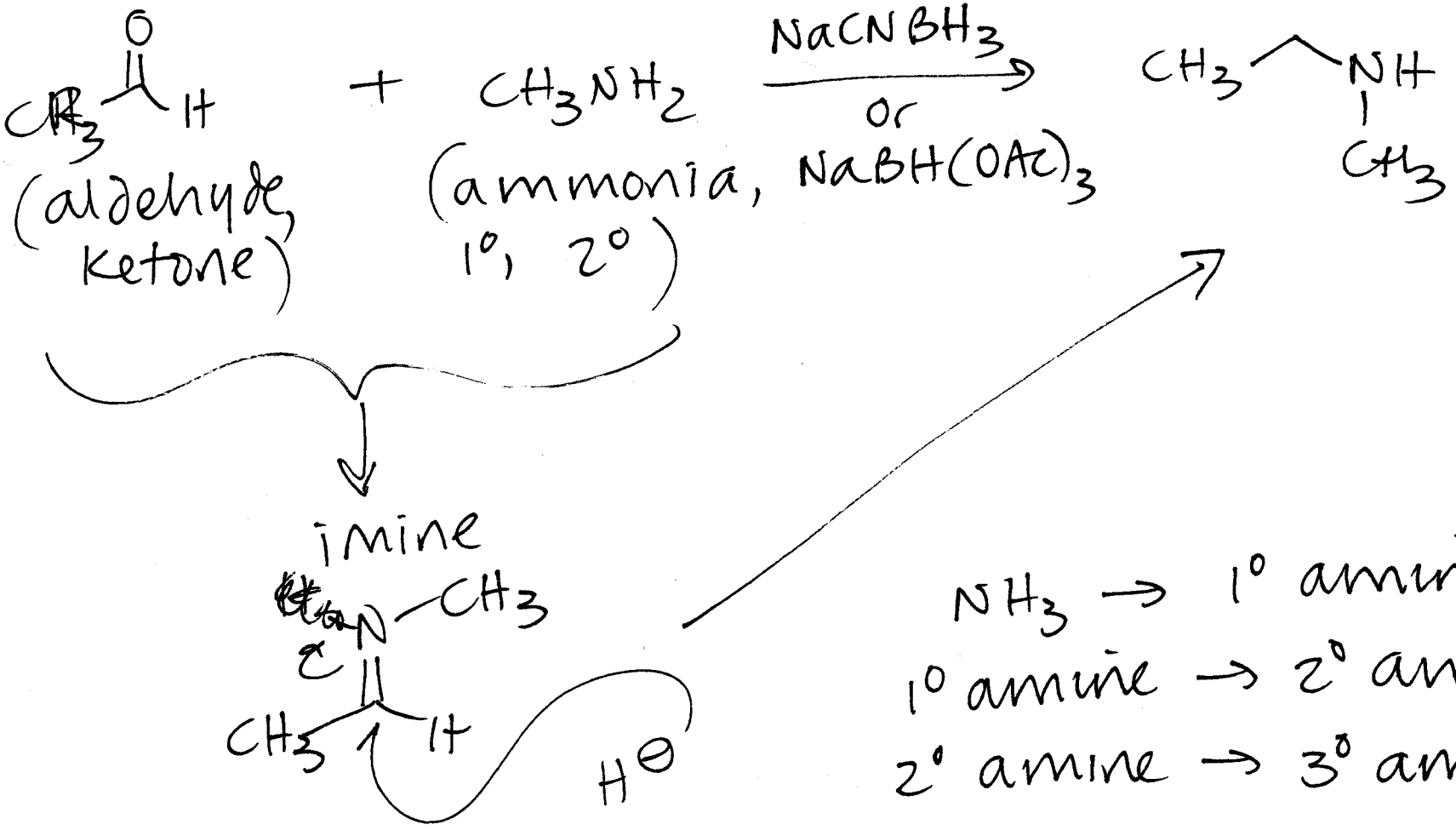
1° amide → 1° amine

2° amide → 2° amine

3° amide → 3° amine



4. Reductive Amination (Ch. 17)



$NH_3 \rightarrow$ 1° amine

1° amine $\rightarrow$ 2° amine

2° amine $\rightarrow$ 3° amine

always get C(H)–N

↑

hydride