

Amines

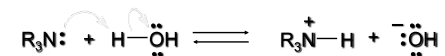
*Chemical / Biological / Neurological
Activity*

Measures of Basicity

- The basicity of amines may be measured and compared by using any of these values:
 - 1) K_b
 - 2) pK_b
 - 3) K_a of conjugate acid
 - 4) pK_a of conjugate acid

Basicity Constant (K_b) and pK_b

- K_b is the equilibrium constant for the reaction:

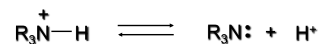


$$K_b = \frac{[R_3NH^+][HO^-]}{[R_3N]}$$

and $pK_b = -\log K_b$

K_a and pK_a of Conjugate Acid

- K_a is the equilibrium constant for the dissociation of the conjugate acid of the amine:



$$K_a = \frac{[R_3N][H^+]}{[R_3NH^+]}$$

and $pK_a = -\log K_a$

Relationships between acidity and basicity constants

$$K_a K_b = 10^{-14}$$

$$pK_a + pK_b = 14$$

Basicity of Amines in Aqueous Solution

Amine	Conj. Acid	pK_a
•NH ₃	NH ₄ ⁺	9.3
•CH ₃ CH ₂ NH ₂	CH ₃ CH ₂ NH ₃ ⁺	10.8

CH₃CH₂NH₃⁺ is a weaker acid than NH₄⁺; therefore, CH₃CH₂NH₂ is a stronger base than NH₃.

Effect of Structure on Basicity

- 1. Alkylamines are slightly stronger bases than ammonia.
- 2. Alkylamines differ very little in basicity.

Basicity of Amines in Aqueous Solution

•Amine	Conj. Acid	pK _a
•NH ₃	NH ₄ ⁺	9.3
•CH ₃ CH ₂ NH ₂	CH ₃ CH ₂ NH ₃ ⁺	10.8
•(CH ₃ CH ₂) ₂ NH	(CH ₃ CH ₂) ₂ NH ₂ ⁺	10.9
•(CH ₃ CH ₂) ₃ N	(CH ₃ CH ₂) ₃ NH ⁺	11.1

Notice that the difference separating a primary, secondary, and tertiary amine is only 0.3 pK units.

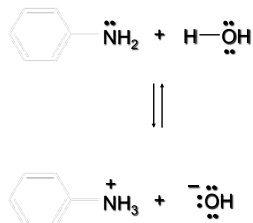
Effect of Structure on Basicity

- 1. Alkylamines are slightly stronger bases than ammonia.
- 2. Alkylamines differ very little in basicity.
- 3. Arylamines are much weaker bases than ammonia.

Basicity of Amines in Aqueous Solution

•Amine	Conj. Acid	pK _a
•NH ₃	NH ₄ ⁺	9.3
•CH ₃ CH ₂ NH ₂	CH ₃ CH ₂ NH ₃ ⁺	10.8
•(CH ₃ CH ₂) ₂ NH	(CH ₃ CH ₂) ₂ NH ₂ ⁺	10.9
•(CH ₃ CH ₂) ₃ N	(CH ₃ CH ₂) ₃ NH ⁺	11.1
•C ₆ H ₅ NH ₂	C ₆ H ₅ NH ₃ ⁺	4.6

Decreased basicity of arylamines



- Aniline (reactant) is stabilized by conjugation of nitrogen lone pair with ring π system.
- This stabilization is lost on protonation.

Decreased basicity of arylamines

- Increasing delocalization makes diphenylamine a weaker base than aniline, and triphenylamine a weaker base than diphenylamine.

	C ₆ H ₅ NH ₂	(C ₆ H ₅) ₂ NH	(C ₆ H ₅) ₃ N
K _b	3.8 x 10 ⁻¹⁰	6 x 10 ⁻¹⁴	~10 ⁻¹⁹

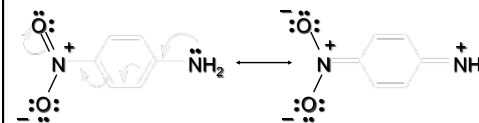
Effect of Substituents on Basicity of Arylamines

- 1. Alkyl groups on the ring increase basicity, but only slightly (less than 1 pK unit).
- 2. Electron withdrawing groups, especially ortho and/or para to amine group, decrease basicity and can have a large effect.

Basicity of Arylamines

X	pK_b	pK_a
H	9.4	4.6
CH ₃	8.7	5.3
CF ₃	11.5	2.5
O ₂ N	13.0	1.0

p-Nitroaniline

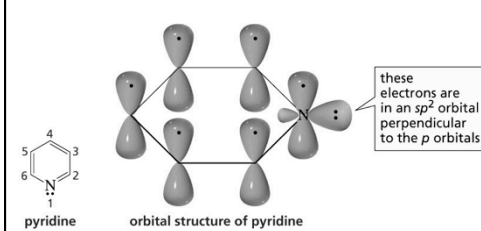
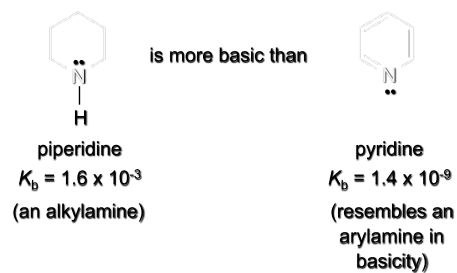


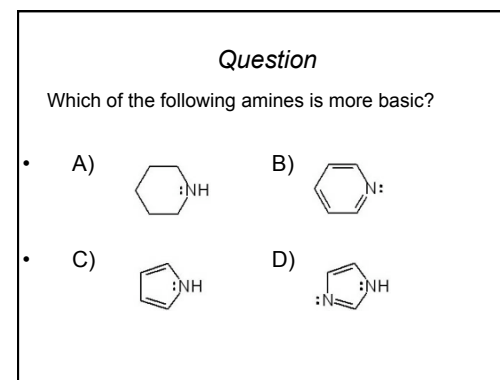
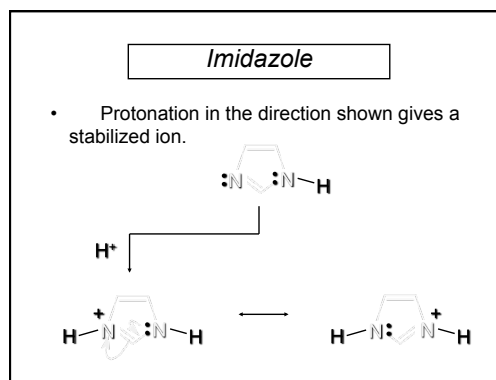
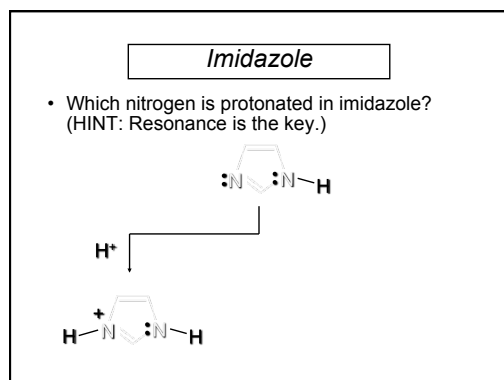
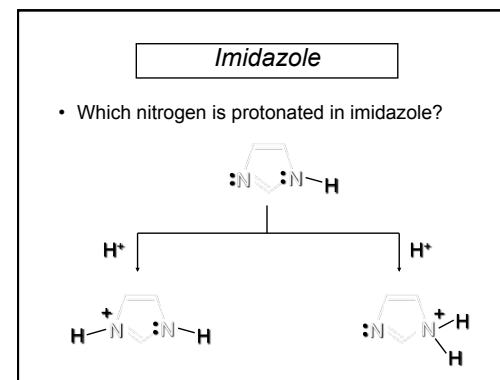
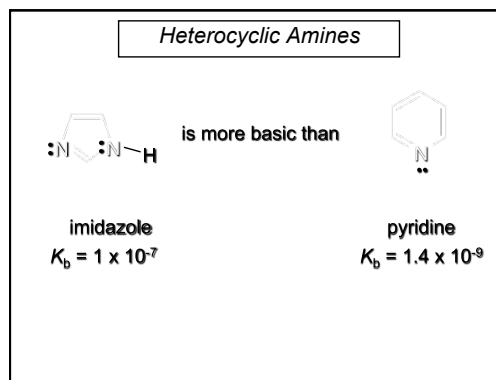
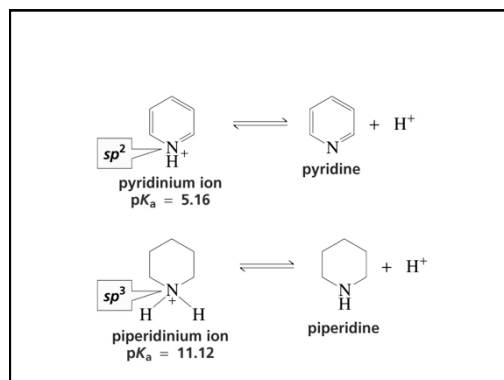
• Lone pair on amine nitrogen is conjugated with *p*-nitro group—more delocalized than in aniline itself. Delocalization lost on protonation.

Effect is Cumulative

- Aniline is 3800 times more basic than *p*-nitroaniline.
- Aniline is ~1,000,000,000 times more basic than 2,4-dinitroaniline.

Heterocyclic Amines





Preparation of Amines by Reduction

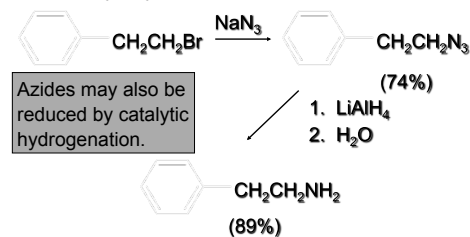
Preparation of Amines by Reduction

• Almost any nitrogen-containing compound can be reduced to an amine, including:

- azides
- nitriles
- nitro-substituted benzene derivatives
- amides

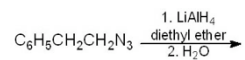
Synthesis of Amines via Azides

• S_N2 reaction, followed by reduction, gives a primary alkylamine.



Question

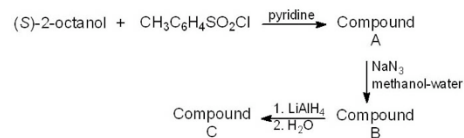
- What is the product of the reaction shown?



- A) $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2$
- B) $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NO}_2$
- C) $\text{C}_6\text{H}_5\text{CH}_2\text{CNH}_2$
- D) $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$

Question

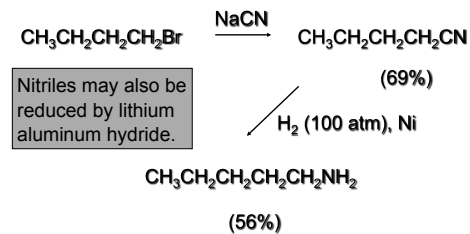
- Identify **compound C** formed in the synthetic sequence below.



- A) (R)-2-octanamine
- B) (S)-2-octanamine
- C) (R)-2-octanol
- D) octane

Synthesis of Amines via Nitriles

• S_N2 reaction, followed by reduction, gives a primary alkylamine.



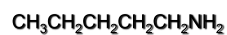
Synthesis of Amines via Nitriles

• S_N2 reaction, followed by reduction, gives a primary alkylamine.



The reduction also works with cyanohydrins.

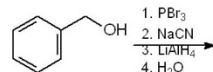
(69%)



(56%)

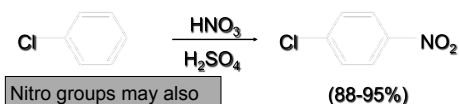
Question

• What is the major organic product of the synthesis shown?



- A) C₆H₅CH₂CN
- B) C₆H₅CH₂CHO
- C) C₆H₅CH₂CH₂NH₂
- D) C₆H₅CH₂NH₂

Synthesis of Amines via Nitroarenes



Nitro groups may also be reduced with tin (Sn) + HCl or by catalytic hydrogenation.

1. Fe, HCl
2. NaOH



(95%)

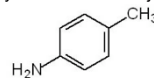
Question

• Which one of the following is produced when *m*-nitroacetophenone is treated with Sn and HCl followed by NaOH?

- A)
- B)
- C)
- D)

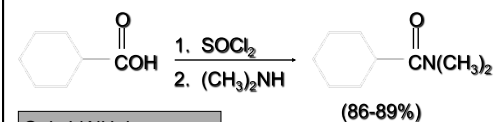
Question

• Starting with benzene, which of the sequences below will produce *p*-methylaniline as the major product of the reaction?



- A) 1. HNO₃, H₂SO₄; 2. CH₃Cl, AlCl₃; 3. Fe, HCl; 4. NaOH
- B) 1. HNO₃, H₂SO₄; 2. Fe, HCl; 3. NaOH; 4. CH₃Cl, AlCl₃
- C) 1. CH₃Cl, AlCl₃; 2. HNO₃, H₂SO₄; 3. Fe, HCl; 4. NaOH
- D) 1. CH₃Cl, AlCl₃; 2. HNO₃, H₂SO₄; 3. H₂

Synthesis of Amines via Amides



Only LiAlH₄ is an appropriate reducing agent for this reaction.

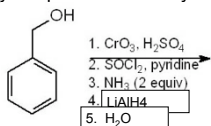
1. LiAlH₄
2. H₂O



(88%)

Question

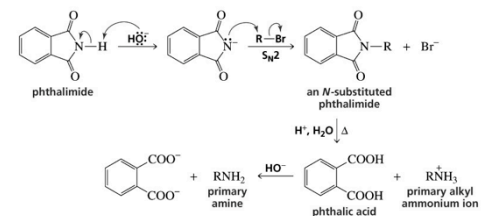
- Identify the product of the synthesis shown.



- A) $\text{C}_6\text{H}_5\text{NH}_2$
- B) $\text{C}_6\text{H}_5\text{CH}=\text{NH}$
- C) $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$
- D) $\text{C}_6\text{H}_5\text{C}(=\text{O})\text{NH}_2$

Preparation and Reactions of Amines

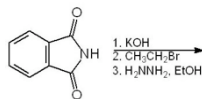
The Gabriel Synthesis of Primary Amines



Question

- What is the product of the Gabriel synthesis shown?

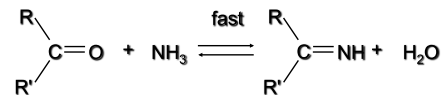
- A) diethyl ether
- B) ethanol
- C) ethyl amine
- D) $\text{CH}_3\text{CH}_2\text{NHNH}_2$



Reductive Amination

Synthesis of Amines via Reductive Amination

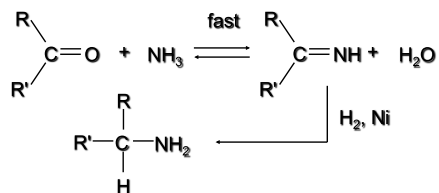
In reductive amination, an aldehyde or ketone is subjected to catalytic hydrogenation in the presence of ammonia or an amine.



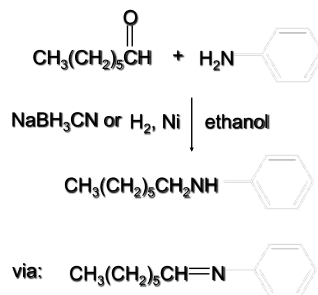
•The aldehyde or ketone equilibrates with the imine faster than hydrogenation occurs.

Synthesis of Amines via Reductive Amination

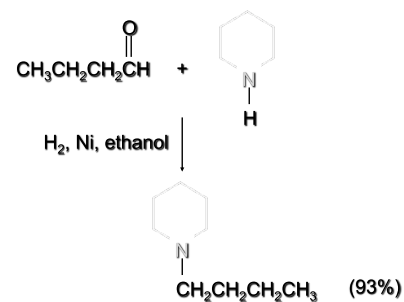
The imine undergoes hydrogenation faster than the aldehyde or ketone. An amine is the product.



Example: Primary amines give secondary amines

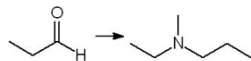


Example: Secondary amines give tertiary amines



Question

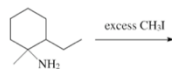
- How would you accomplish the conversion of propanal into *N*-ethyl-*N*-methylpropanamine?



- A) $\text{NH}_3, \text{NaBH}_3\text{CN}; \text{CH}_3\text{I}; \text{CH}_3\text{CH}_2\text{I}$
- B) $\text{CH}_3\text{NH}_2, \text{NaBH}_3\text{CN}; \text{CH}_3\text{COCl}, \text{pyridine}; \text{LiAlH}_4; \text{H}_2\text{O}$
- C) $\text{CrO}_3, \text{H}_2\text{SO}_4; \text{SOCl}_2, \text{pyridine}; 2 \text{ equiv } \text{CH}_3\text{NH}_2; \text{CH}_3\text{I}$
- D) $\text{CH}_3\text{CH}_2\text{NH}_2, \text{H}_2, \text{Ni}; (\text{CH}_3\text{CO})_2\text{O}, \text{pyridine}; \text{NaBH}_4$

Quarternary Amines Can Undergo an E_2 Elimination Reaction

Ⓢ The Hofmann elimination proceeds by E_2 elimination of a quarternary ammonium hydroxide. It begins with exhaustive methylation of an amine. To begin the reaction, click on the NUCLEOPHILE in the reaction below.



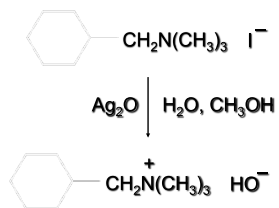
The Hofmann Elimination

The Hofmann Elimination

- a quaternary ammonium hydroxide is the reactant and an alkene is the product
- is an anti elimination
- the leaving group is a trialkylamine
- the regioselectivity is opposite to the Zaitsev rule.

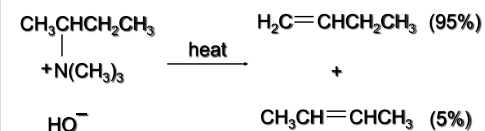
Quaternary Ammonium Hydroxides

are prepared by treating quaternary ammonium halides with moist silver oxide

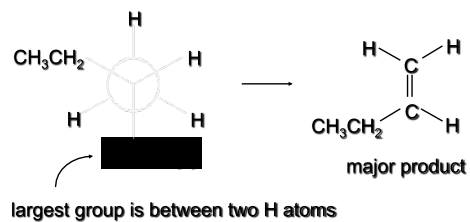


Regioselectivity

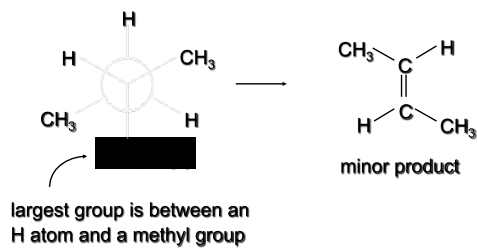
Elimination occurs in the direction that gives the less-substituted double bond. This is called the Hofmann rule.



Regioselectivity



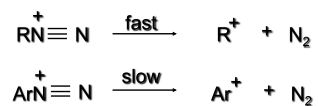
Regioselectivity



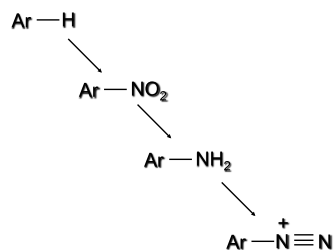
Nitrosation of Arylamines

Nitrosation of Primary Arylamines

- Gives aryl diazonium ions.
- Aryl diazonium ions are much more stable than alkyl diazonium ions.
- Most aryl diazonium ions are stable under the conditions of their formation (0-10°C).

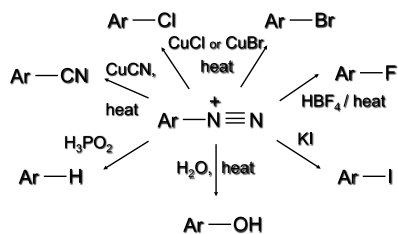


Synthetic Origin of Aryl Diazonium Salts



Synthetic Transformations of Aryl Diazonium Salts

Transformations of Aryl Diazonium Salts

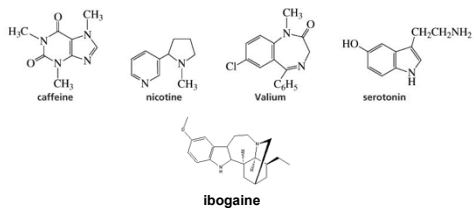


Question

- Identify the product isolated from the reaction of *p*-nitroaniline with NaNO₂ in H₂SO₄ followed by the addition of potassium iodide (KI).
- A) nitrobenzene
- B) *p*-iodoaniline
- C) *p*-iodonitrobenzene
- D) *p*-diiodonitrobenzene

Alkaloids

**Alkaloids: Naturally Occurring Bases
Nitrogen Heterocycles**



Amines & Neurotransmitters

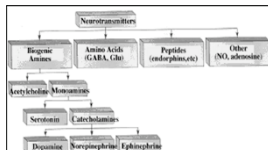
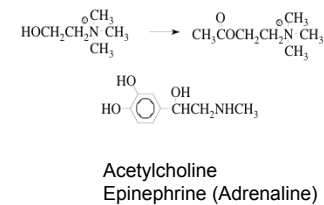
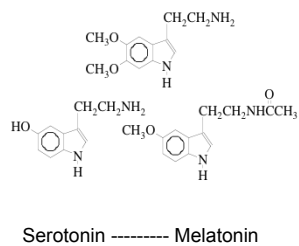
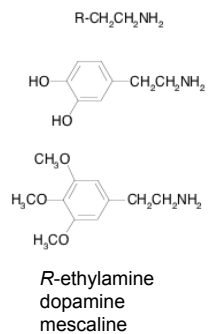
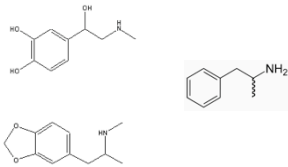


Table 2.1: Major Neurotransmitters in the Body ^{1, 2, 3}	
Neurotransmitter	Role in the body
Acetylcholine	A neurotransmitter used by spinal cord neurons to control muscles and by many neurons in the brain to regulate memory. In most instances, acetylcholine is excitatory.
Dopamine	The neurotransmitter that produces feelings of pleasure when released by the brain reward system. Dopamine has multiple functions depending on where in the brain it acts. It is usually inhibitory.
GABA (gamma-aminobutyric acid)	The major inhibitory neurotransmitter in the brain.
Glutamate	The most common excitatory neurotransmitter in the brain.
Glycine	A neurotransmitter used mainly by neurons in the spinal cord. It probably always acts as an inhibitory neurotransmitter.
Norepinephrine	Norepinephrine acts as a neurotransmitter and a hormone in the peripheral nervous system. It is part of the fight-or-flight response. In the brain, it acts as a neurotransmitter regulating normal brain processes. Norepinephrine is usually excitatory, but is inhibitory in a few brain areas.
Serotonin	A neurotransmitter involved in many functions including mood, appetite, and sensory perception. In the spinal cord, serotonin is inhibitory in pain pathways.





Catechols: epinephrine, mdma
Principal sympathomimetic adrenal hormone
& 2 controlled substances: *X* and *Adderall*

Drug Uptake:

Rank from slowest to fastest.

a) injection; b) ingestion; c) inhalation; d) snorting

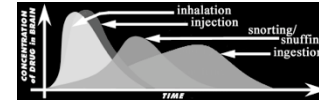


- A) $a < b < c < d$ B) $c < a < d < b$
C) $b < d < a < c$ D) $d < b < c < a$

Drug Uptake:

Rank from slowest to fastest.

a) injection; b) ingestion; c) inhalation; d) snorting



- A) $a < b < c < d$ B) $c < a < d < b$
C) $b < d < a < c$ D) $d < b < c < a$

Drug Uptake:

Rank from slowest to fastest.

a) injection; b) ingestion; c) inhalation; d) snorting

Adderall's effects are similar to other CNS stimulants of the same class and preparation. (See amphetamine for details.)

Urinary and stomach pH levels can have a strong effect on DL-amphetamine excretion and absorption.[9] An acidic stomach and GI pH will decrease the absorption of Adderall [10] and acidic urine levels will decrease the reabsorption of the drug through the renal system.[11] Co-administration of acidic substances (e.g. citric acid) causes decreased renal reabsorption of DL-amphetamine, while alkaline agents (e.g. antacids) may cause a marked increase in renal tubular reabsorption. The increased reabsorption can increase the retention of amphetamines, potentially resulting in dangerously high serum levels.[11]

- A) $a < b < c < d$ B) $c < a < d < b$
C) $b < d < a < c$ D) $d < b < c < a$

<http://www.2Drcti.rutgers.edu/%7Elwh/drugs/>
<http://web.indstate.edu/thcma/mwking/nerves.html#table>
<http://www.sfn.org/briefings/addiction.html>
<http://faculty.washington.edu/chudler/amp.html>

