ANSWERS TO QUESTIONS
Chapter 2: Drug Design and Relationship of Functional Groups to Pharmacologic Activity

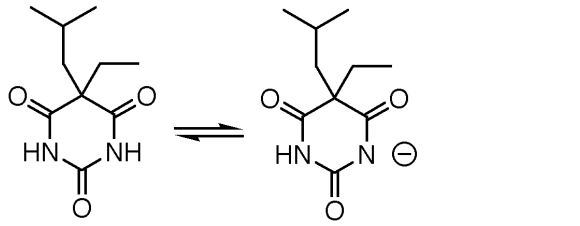
Question #1 Answer:

At pH 2.0 amobarbital is in the acid or unionized form (100%) since the pH is 6 log units below the pKa of the compound.

At a pH of 5.5 the acid form still predominates (99.7%).

At a pH of 8.0 there are equal amounts of acid form and conjugate base (or ionized) form:

$8 = 8 + \log [HA]/[A^-]$
$0 = \log [HA]/[A^-]$
$10^0 = 1 = [HA]/[A^-]$
(% HA = 1/2 x 100 = 50%)



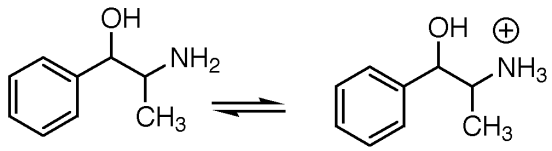
Acid form
pK_a 8.0

Conjugate base

The trend seen is, that as pH increases, the amount of conjugate base (or ionized form of the drug) increases. The opposite trend would be seen with a basic molecule.

Question #2 Answer

The acid/base properties of phenylpropanolamine are shown below. At a pH of 2.0 the compound exist in the conjugate acid (ionized) form (>99%) as shown. At a pH of 5.5 phenylpropanolamine is 99.7% ionized, and at pH 8.0 the conjugate acid form still predominates but it has decreased to 96%.

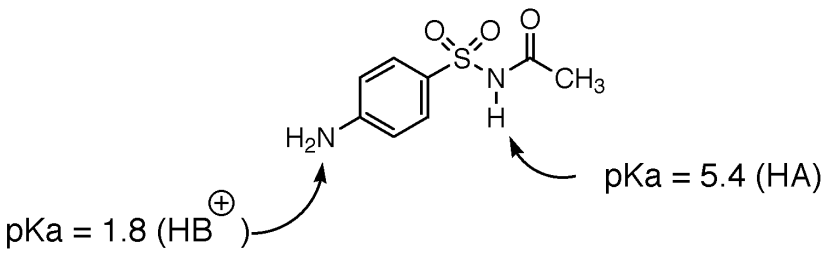


Base form

Conjugate acid form
pK_a 9.4

Question #3 Answer

Sulfacetamide has the following structure and pKa values:



Calculation of percent ionization in the stomach (pH ~ 2):

Sulfonamide:

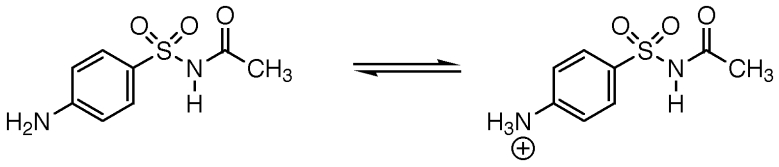
$5.4 = 2 + \log [HA]/[A^-]$
$3.4 = [HA]/[A^-]$
$10^{3.4} = [HA]/[A^-]$
$2512 = [HA]/[A^-]$

% HA = 2512/2513 x 100 = 99.96%
% A^- = 0.04% ionized

Aromatic amine:

$1.8 = 2 + \log [BH^+]/[B]$
$-0.2 = [BH^+]/[B]$
$10^{-0.2} = [BH^+]/[B]$
$0.63 = [BH^+]/[B]$

% BH^+ = 0.63/1.63 x 100 = 38.6%



61.4% 38.6%

Calculation of percent ionization in the duodenum (pH ~5.5):

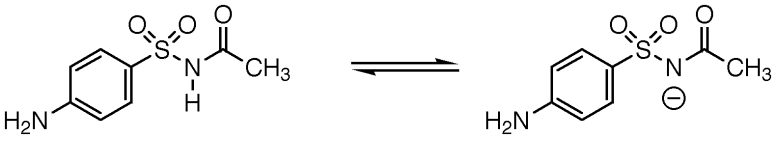
Sulfonamide:

$5.4 = 5.5 + \log [HA]/[A^-]$
$-0.1 = [HA]/[A^-]$
$10^{-0.1} = [HA]/[A^-]$
$0.79 = [HA]/[A^-]$
% HA = 0.79/1.79 x 100 = 44%

Aromatic amine:

$1.8 = 5.5 + \log [BH^+]/[B]$
$-3.7 = [BH^+]/[B]$
$10^{-3.7} = [BH^+]/[B]$
$\sim 0.0002 = [BH^+]/[B]$
% BH^+ = 0.0002 /1.0002 x 100 = ~0.02%

% A^- = 56% ionized



44% 56%

Calculation of percent ionization in the ileum (pH ~8):

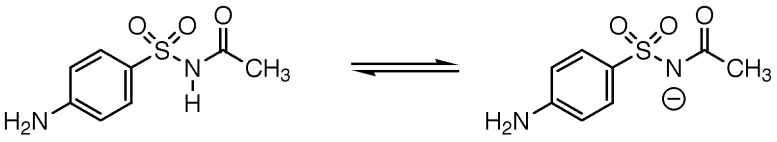
Sulfonamide:

$5.4 = 8 + \log [HA]/[A^-]$
$-2.6 = [HA]/[A^-]$
$10^{-2.6} = [HA]/[A^-]$
$0.0025 = [HA]/[A^-]$
% HA = 0.0025/1.0025 x 100 = 0.25%

Aromatic amine:

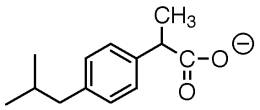
$1.8 = 8 + \log [BH^+]/[B]$
$-6.2 = [BH^+]/[B]$
$10^{-6.2} = [BH^+]/[B]$
$6.3 \times 10^{-7} = [BH^+]/[B]$
% BH^+ = 6.3×10^{-7} /1+ 6.3×10^{-7} x 100 =~0%

% A^- = 99.75% ionized

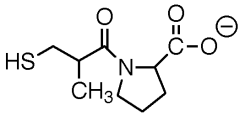


.25% 99.75%

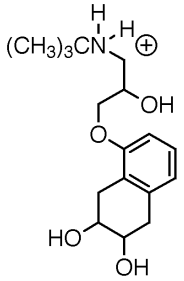
Question #4 Answer:



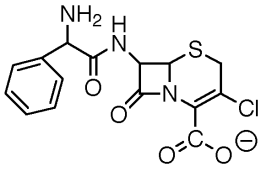
Ibuprofen



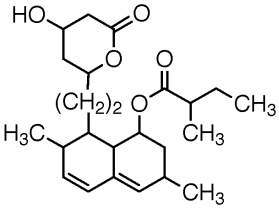
Captopril



Nadolol



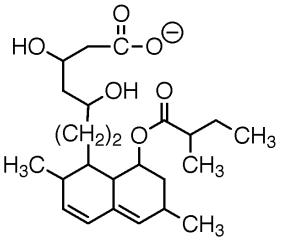
Cefaclor



Lovastatin

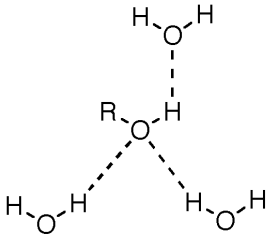
Hydrolysis

H_2O

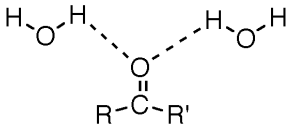


No ionization until after hydrolysis

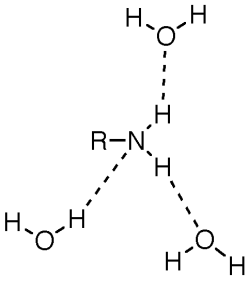
Question #5 Answer:



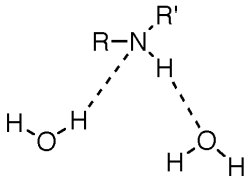
Alcohol



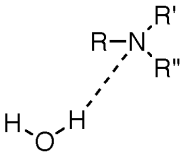
Ketone



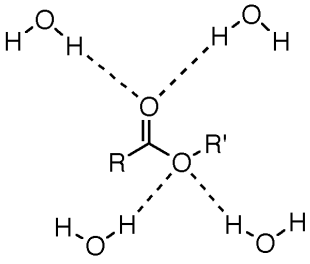
Primary amine



Secondary amine



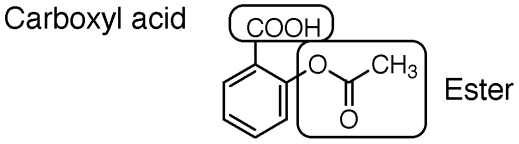
Tertiary amine



Ester

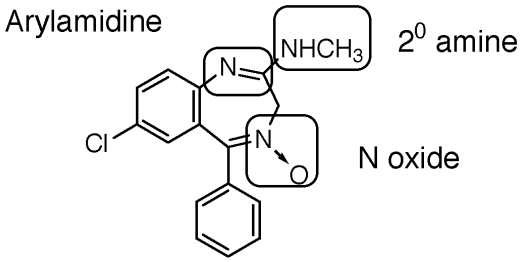
Question #6 Answer:

Aspirin:



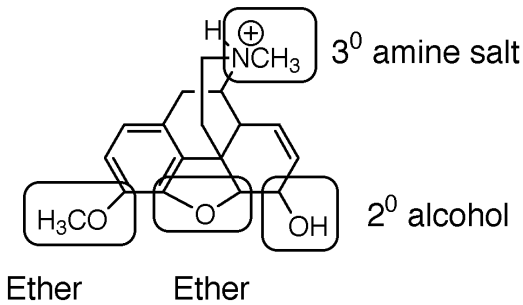
1 Carboxylic acid	3 carbons	
1 Ester	3 carbons	
Total	6 carbons	Insoluble (solubilizing potential less than carbon content, $C_9H_8O_4$)

Chlordiazepoxide:



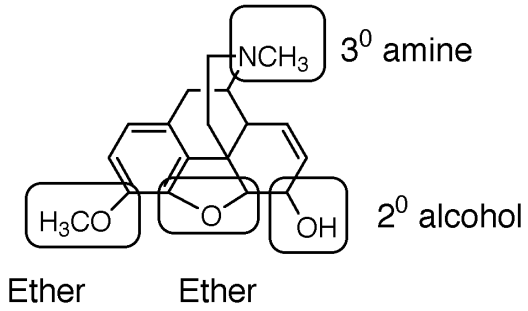
1 Arylamidine	~3 carbons*	
1 2^0 amine	3 carbons	
1 N oxide	~2 carbons	
Total	~8 carbons	Insoluble (solubilizing potential less than carbon content ($C_{16}H_{14}ClN_3O$). *Estimate by counting number of potential hydrogen bonds with water for each group.

Codeine phosphate:



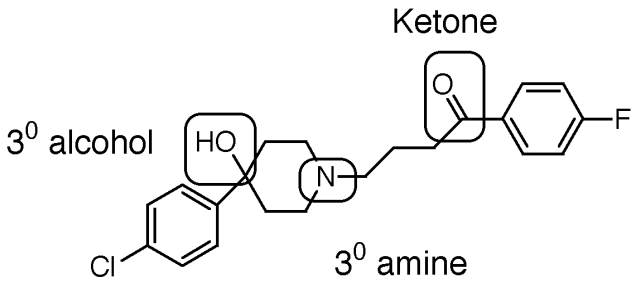
1 3^0 amine salt	20-30 carbons	
1 2^0 alcohol	3-4 carbons	
2 Ethers	4 carbons	
Total	27-38 carbons	Soluble (solubilizing potential is more than carbon content ($C_{18}H_{21}NO_3.\ H_3PO_4$).

Codeine



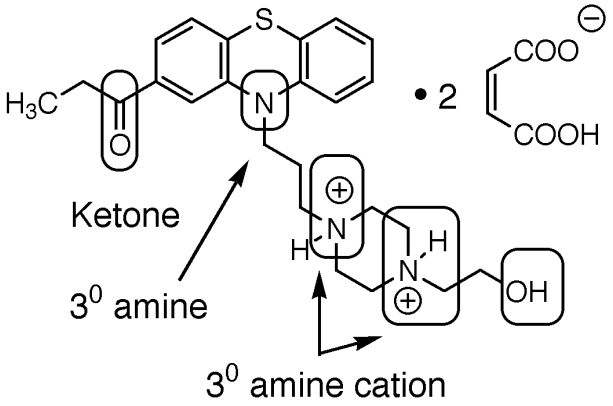
1 3^0 amine	3 carbons	
1 2^0 alcohol	3-4 carbons	
2 Ethers	4 carbons	
Total	10-11 carbons	Insoluble (solubilizing potential is less than carbon content ($C_{18}H_{21}NO_3$).

Haloperidol:



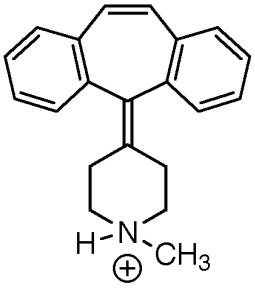
1 3^0 alcohol	3-4 carbons	
1 3^0 amine	3 carbons	
1 Ketone	2 carbons	
Total	8-9 carbons	Insoluble (solubilizing potential is less than carbon content ($C_{21}H_{23}ClFNO_2$).

Carphenazine maleate:



2 3^0 amine salts 40-60 carbons
1 3^0 amine 3 carbons
1 Ketone 2 carbons
1 1^0 alcohol 3-4 carbons
Total 48-69 carbons Soluble (solubilizing potential is more than carbon content ($C_{24}H_{31}N_3O_2$. $2C_4H_4O_4$).

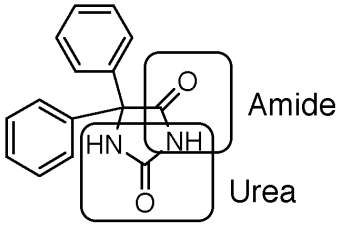
Cyproheptadine hydrochloride:



3^0 amine cation

1 3^0 amine salt 20-30 carbons Soluble (solubilizing potential is more than carbon content ($C_{21}H_{21}N$. HCl).

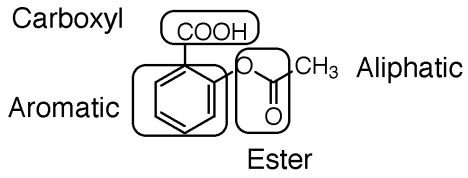
Phenytoin



2 Amides 4-6 carbons or 1 Amide 2-3 carbons
1 Urea 2 carbons
Total 4-5 carbons Insoluble (solubilizing potential is less than carbon content ($C_{15}H_{12}N_2O_2$).

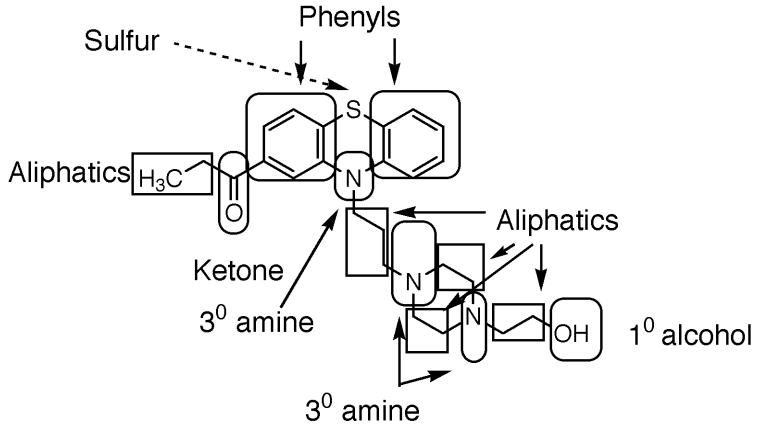
Question #7 Answer:

Aspirin:



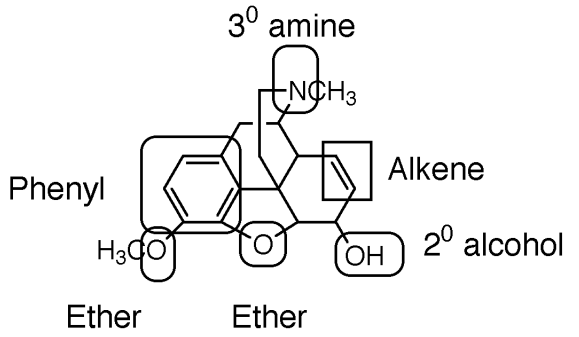
1 Phenyl +2.0
1 Carboxyl -0.7
1 Ester -0.7
1 Aliphatic C +0.5
logP +1.1 (Found 1.19± 0.226)

Carphenazine:



2 Phenyls +4.0
11 Aliphatic C +5.5
3 Amines -3.0
1 Alcohol -1.0
1 Ketone -0.7
1 Sulfur 0.0
logP +4.8 (Found 3.847 ± 0.426)

Codeine:

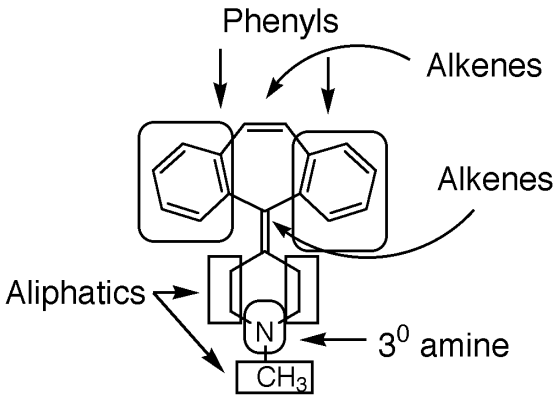


(Uncircled carbons = aliphatic C)

1 Phenyl	+2.0
10 Aliphatic C	+5.0
2 Alkene C	+1.0 - +0.66*
2 Ethers	-2.0
1 Alcohol	-1.0
1 Amines	-1.0
logP	+4.0 - +3.66 (Found 2.04 ± 0.661)

*Estimation based upon -CH= being equivalent to +0.33

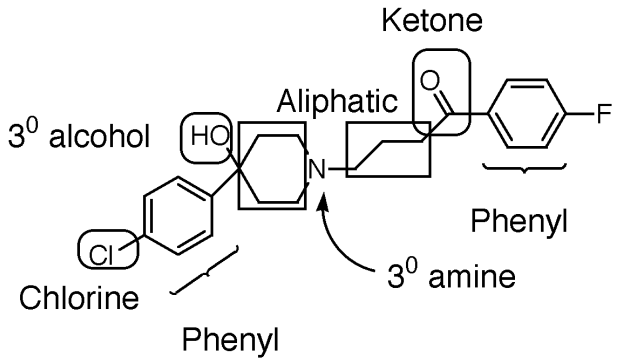
Cyproheptadine



2 Phenyls	+4.0
5 Aliphatic C	+2.5
4 Alkene C	+1.32*
1 Amine	-1.0
logP	+6.82 (Found 6.62 ± 0.359)

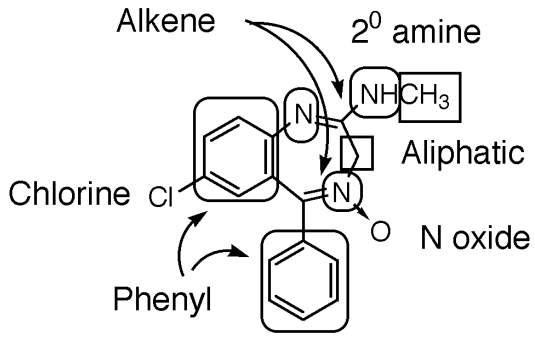
*Estimation based upon -CH= being equivalent to +0.33

Haloperidol:



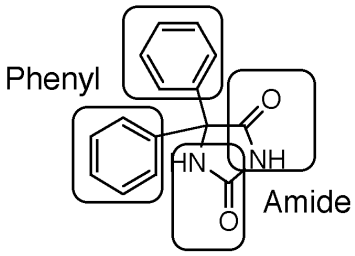
2 Phenyls	+4.0
1 Chlorine	+0.5
8 Aliphatic C	+4.0
1 Ketone	-0.7
1 Alcohol	-1.0
1 Amines	-1.0
logP	+5.8 (Found 4.063 ± 4.446)

Chlordiazepoxide:



2 Phenyls	+4.0
1 Chlorine	+0.5
2 Aliphatic C	+1.0
2 Alkene C	+1.0 - +0.66
3 Amines	-3.0*
1 N oxide	-1.0*
logP	+2.5 - +2.16 (Found 2.49± 0.895)

Phenytoin:

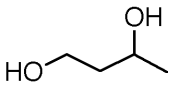


2 Phenyls	+4.0	
1 Aliphatic C	+0.5	
2 Amides	-1.5	
logP	+3.0	(Found 2.53 ± 0.383)

Question #8 Answer:

Example of answers: $C_4H_{10}O_2$

1,3-Butylene Glycol:

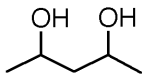


MW 90.12

bp = 207.5^0

Viscous liquid
Soluble in water and ethanol
Insoluble in aliphatic hydrocarbons
Dielectric constant 28.8 @ 25^0

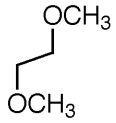
2,3-Butylene Glycol:



MW 90.12

3 isomer forms: *meso* -form(*erythro*-form)
mp = 34.4
DL-*threo*-form
mp = 7.6^0
D(-)*threo*-form
mp = 19.7^0
L(+)-*threo*-form
bp = $179\text{-}182^0$

1,2-Dimethoxyethane

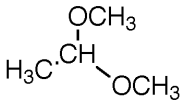


MW 90.12

bp = $82 - 83^0$

Liquid
Miscible with water, alcohol
Soluble in hydrocarbon solvents

Dimethylacetal

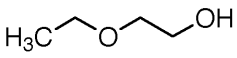


MW 90.12

bp = 64.5

Liquid
Miscible with water, alcohol, chloroform, ether

2-Ethoxyethanol

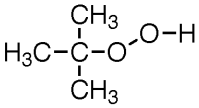


MW 90.12

bp = 135^0

Liquid
Miscible with water, alcohol, ether

tert-Butyl Hydroperoxide

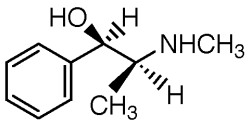


MW 90.12

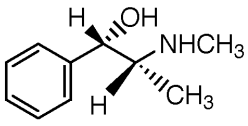
mp = -8^0

Liquid
Soluble in organic solvents

Question #9 Answer:

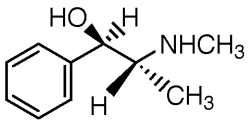


R,S

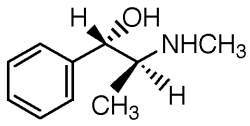


S,R

Ephedrine



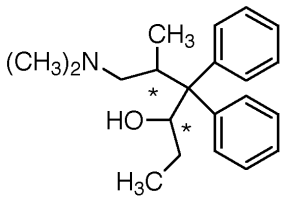
R,R



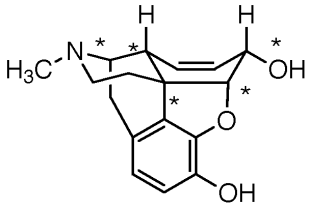
S,S

Pseudoephedrine

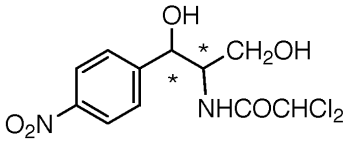
Question #10 Answer:



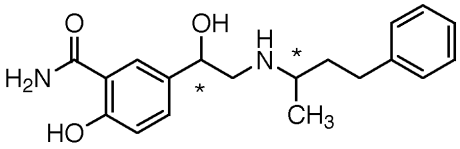
Isomethadol



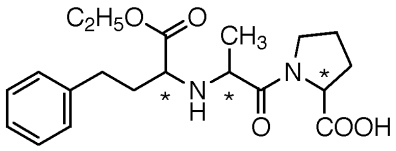
Morphine



Chloramphenicol



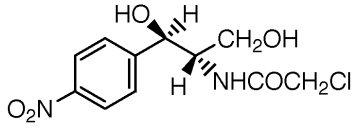
Labetalol



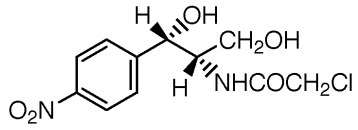
Enalapril

Question #11 Answer:

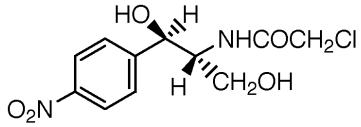
Chloramphenicol



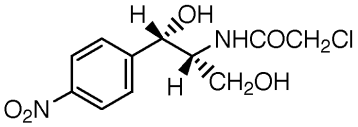
R,S



S,S

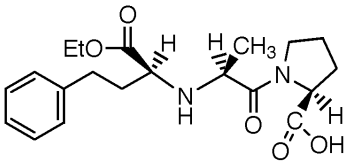


R,R

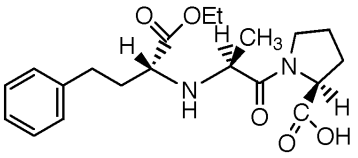


S,R

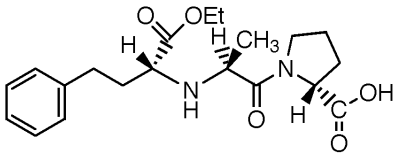
Enalapril



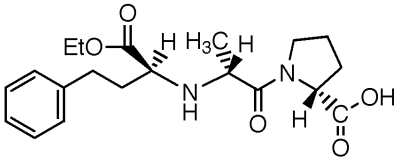
S,S,S



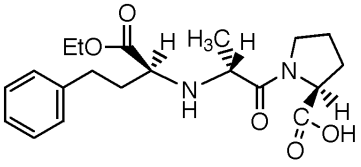
R,S,S



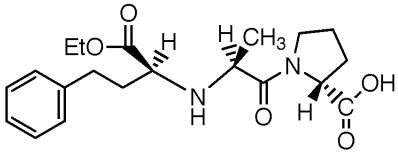
R,S,R



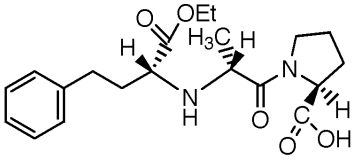
S,R,R



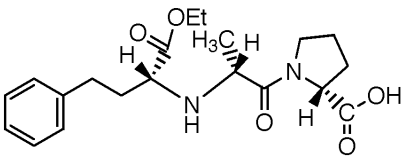
S,R,S



S,S,R

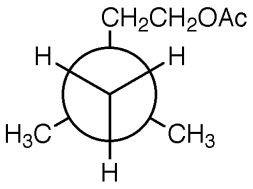


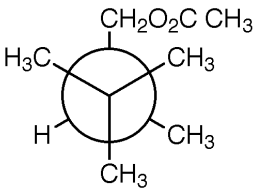
R,R,S

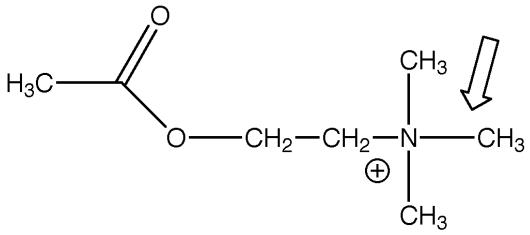


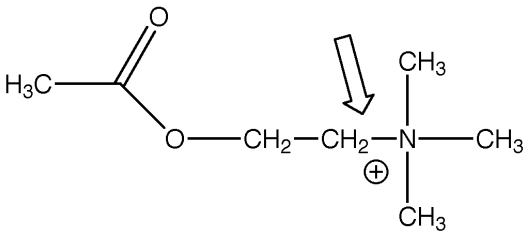
R,R,R

Question #12 Answer:



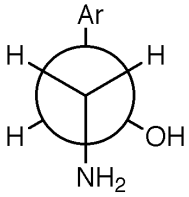


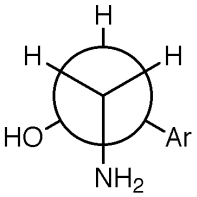


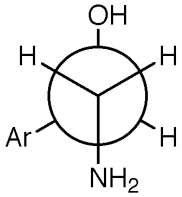


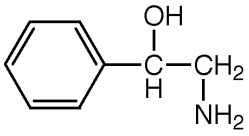
Due to the symmetry of the methyl group, rotation around the N-CH_3 bond does not alter the 3D relationship of the atoms (left figure). The same hold true when viewing along the N-CH_2 bond (right figure). Conformational isomers therefore do not exist along these bonds.

Question #13 Answer:









Norepinephrine

Both the far left and middle rotamers (trans and gauche rotamers) could be stabilized by an H-bond between the amine and hydroxyl groups.