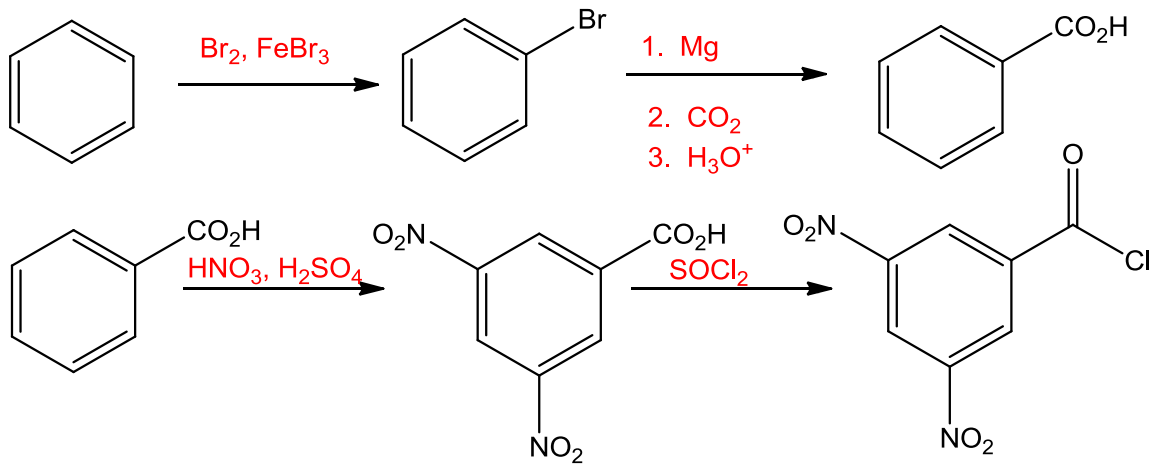
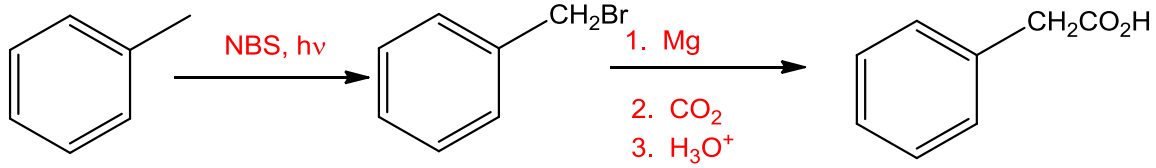
Problem Set 9 – Reactions of carboxylic acid and their derivatives

1. Propose a sequence of reactions to effect the following conversions:

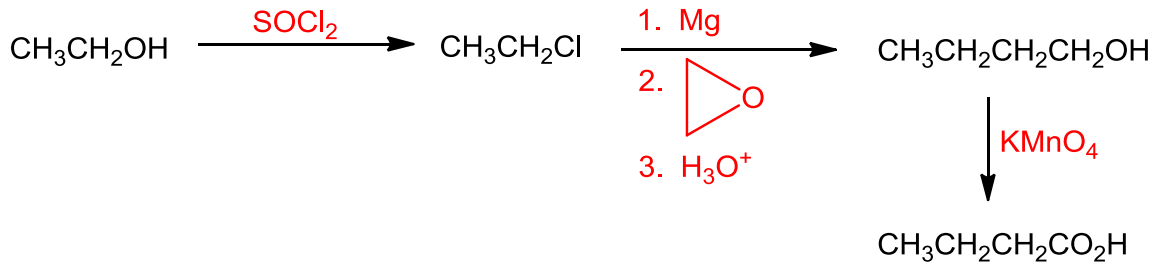
   a. 3,5-dinitrobenzoyl chloride from benzene



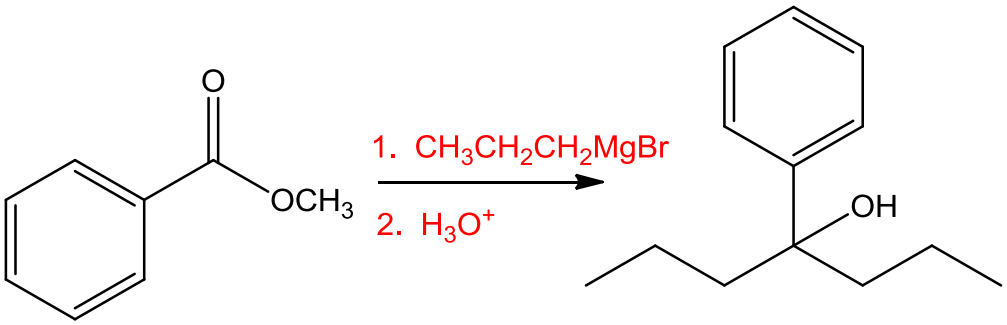
   b. phenylethanoic acid from toluene



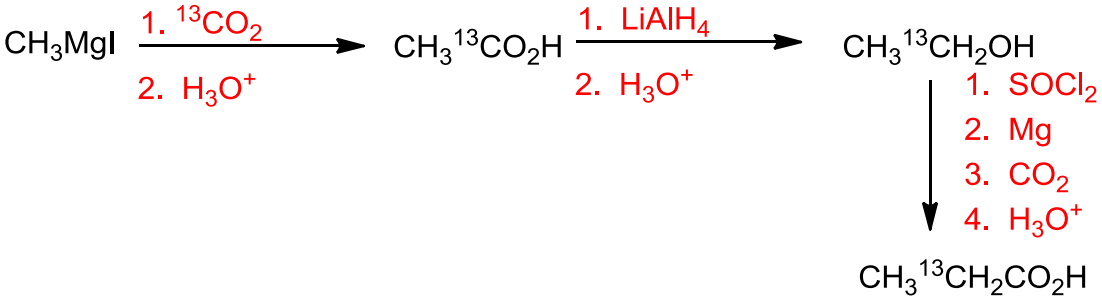
   c. butanoic acid from ethanol



   d. 4-phenyl-4-heptanol from methyl benzoate

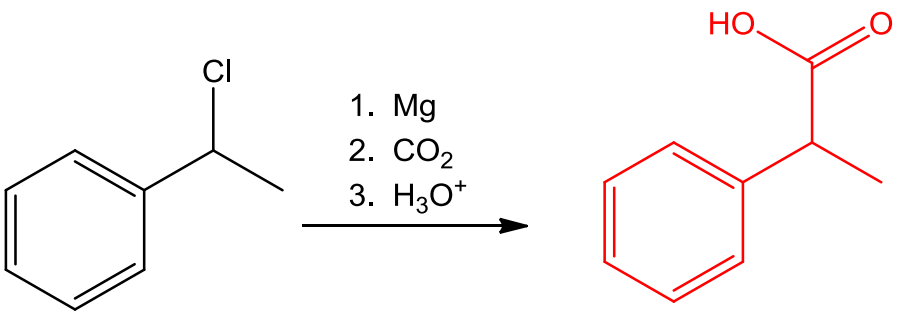


2. Propose a synthesis of $CH_3{}^{13}CH_2CO_2H$ using $^{13}CO_2$ as source of ^{13}C.

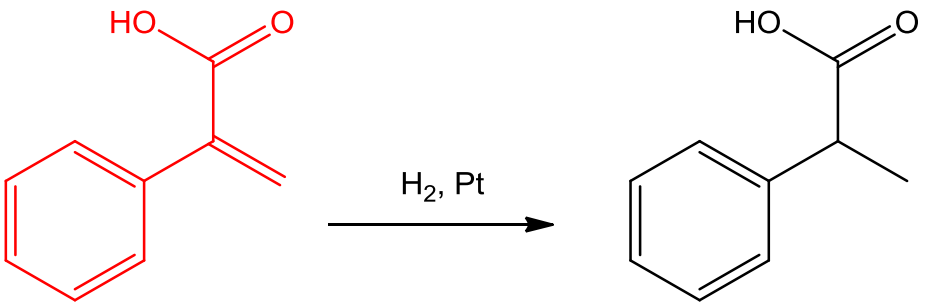


3. Tropic acid is isolated from atropine, an alkaloid found in Atropa belladona (deadly nightshade). Its molecular formula is $C_9H_{10}O_3$. Tropic acid forms benzoic acid on oxidation with hot $KMnO_4$. Tropic acid also reacts with HBr to form compound "A", $C_9H_9O_2Br$. Compound "A" reacts with alcoholic KOH to give atropic acid, $C_9H_8O_2$. On catalytic hydrogenation, atropic acid forms hydratropic acid, $C_9H_{10}O_2$. Hydratropic acid may be synthesized by treating the Grignard reagent formed from 1-chloro-1-phenylethane with dry ice followed by acid workup. Oxidation of tropic acid gives a dicarboxylic acid, $C_9H_8O_4$.

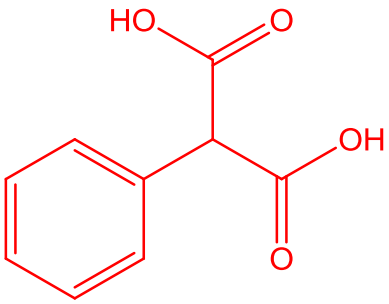
   a. What is the structure of hydratropic acid?



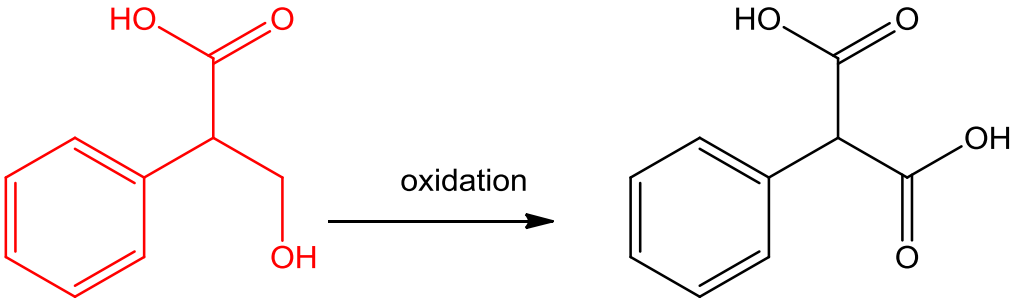
   b. What is the structure of atropic acid?



c. What is the structure of the dicarboxylic acid?

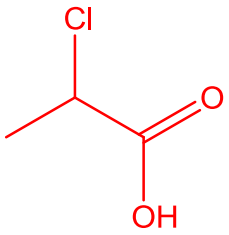


d. What is the structure of tropic acid?

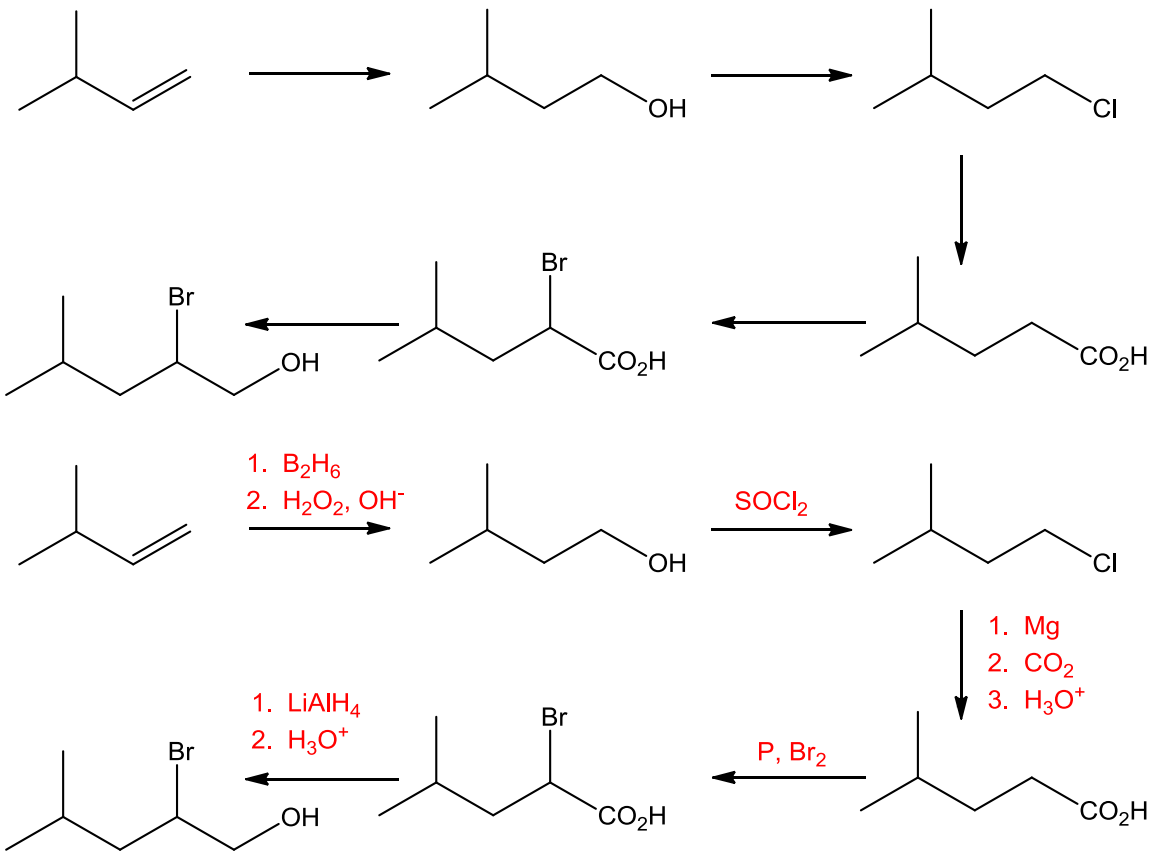


4. Give a structure of compound "X", $C_3H_5ClO_2$, consistent with the following ^1H NMR data:

   δ = 1.73 (3H, doublet), δ = 4.47 (1H, quartet), δ = 11.22 (1H, singlet).

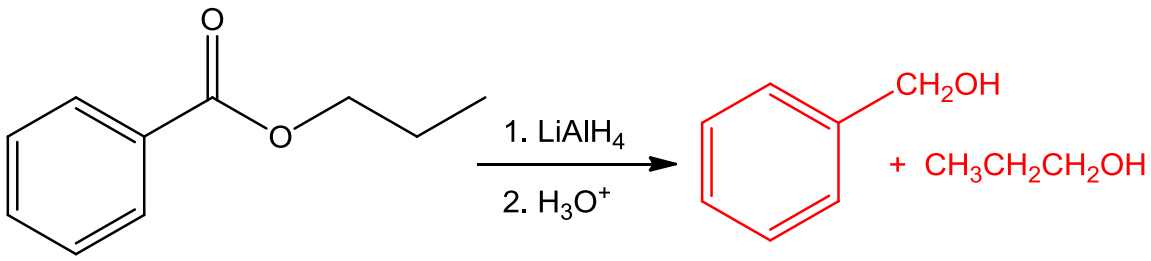


5. Identify the reagents in the following scheme:

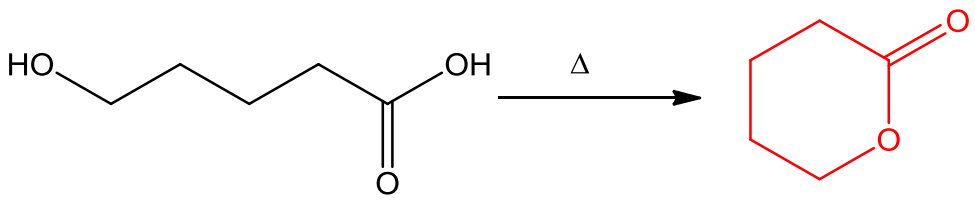


6. Write the structure(s) of the organic product(s) of the following reactions:

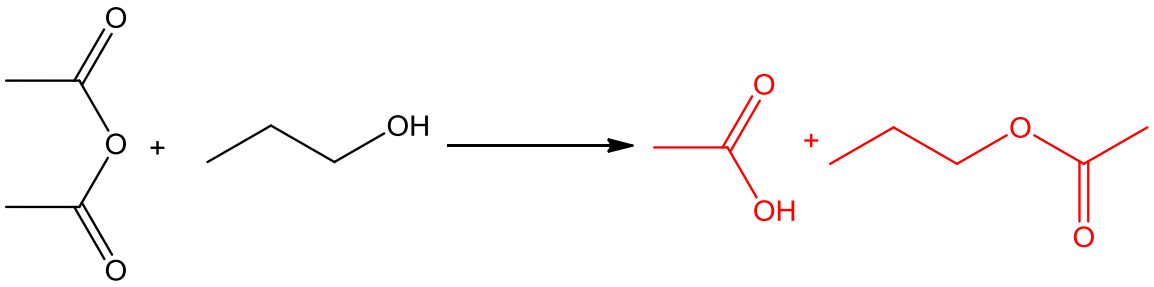
   a. propyl benzoate + i) $LiAlH_4$ ii) H_3O^+



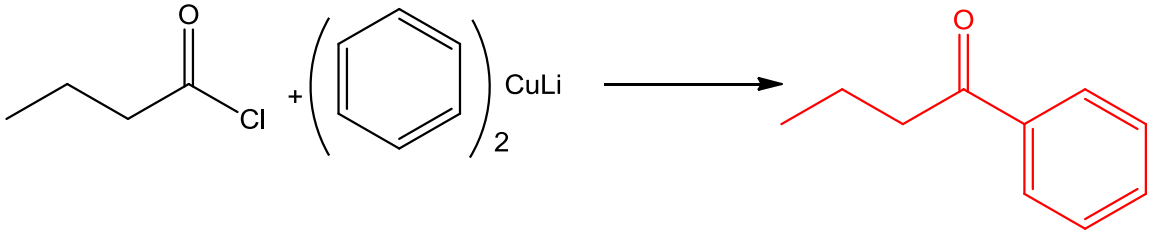
   b. 5-hydroxypentanoic acid + Δ



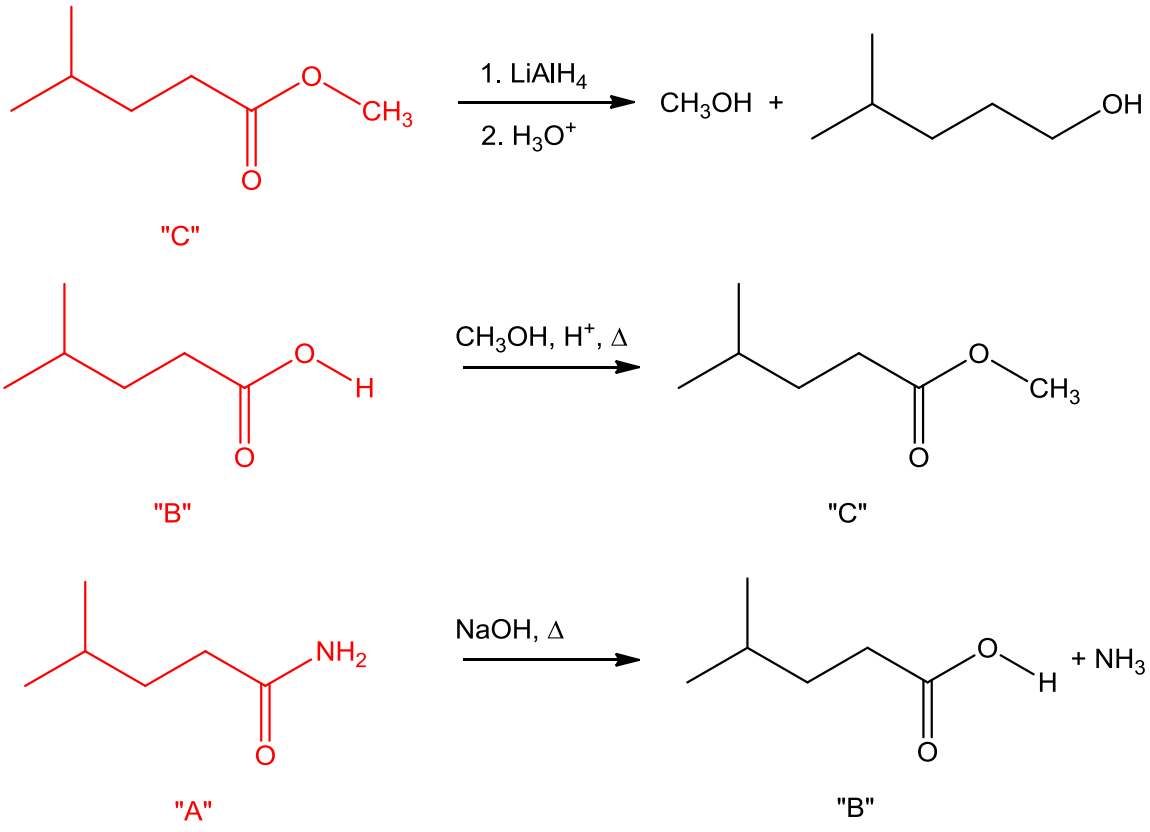
   c. acetic anhydride + 1-propanol



d. butanoyl chloride + lithium diphenylcuprate

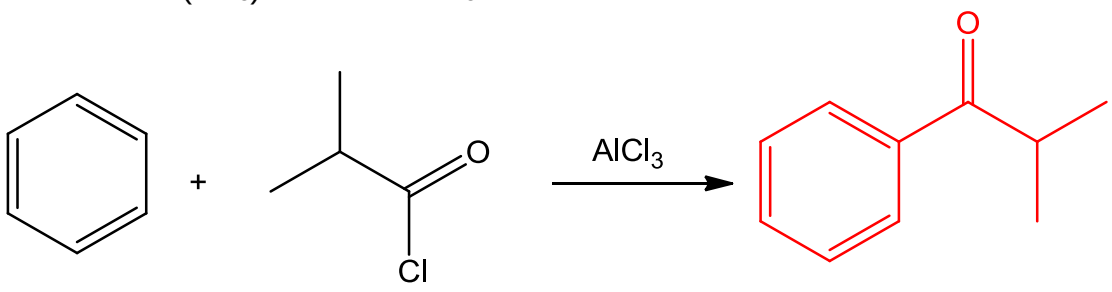


7. Compound “A”, $C_6H_{13}NO$, produces a gas on heating with aqueous NaOH. When the resulting solution is acidified and extracted with ether, compound “B” is isolated. “C” is formed when “B” is heated with acidic methanol. Reduction of “C” with $LiAlH_4$ yields methanol and 4-methyl-1-pentanol. What are the structures of “A”, “B” and “C”?

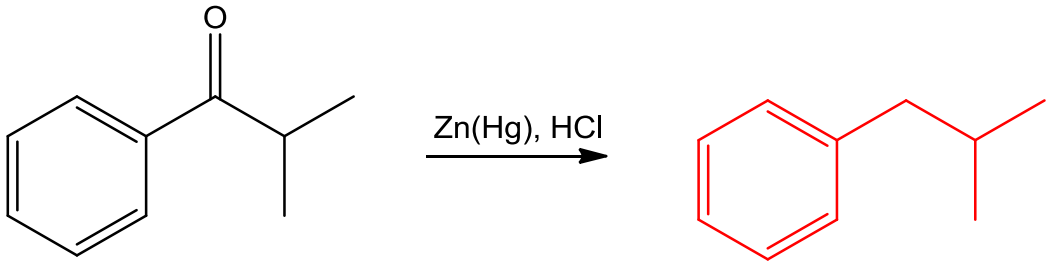


8. (S)-Ibuprofen is an antiinflammatory drug. Racemic ibuprofen can be synthesized from benzene:

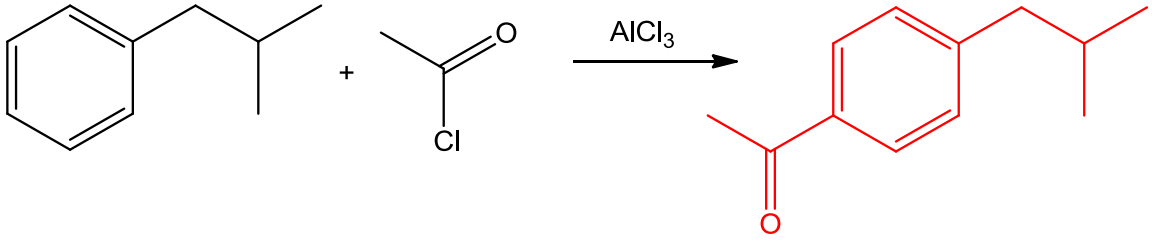
Benzene + $(CH_3)_2CHCOCl/AlCl_3$ → "A"



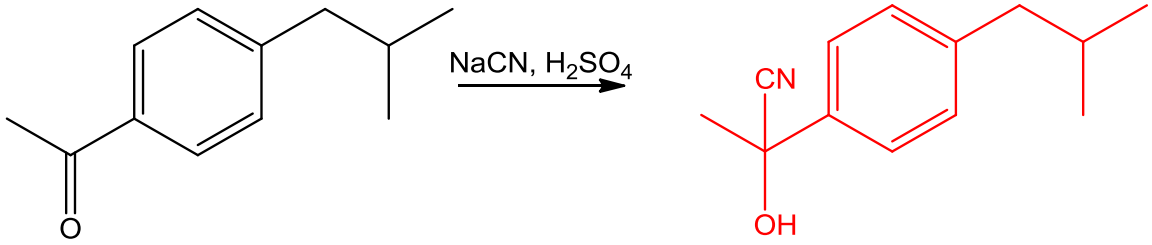
"A" + Zn(Hg)/HCl → "B"



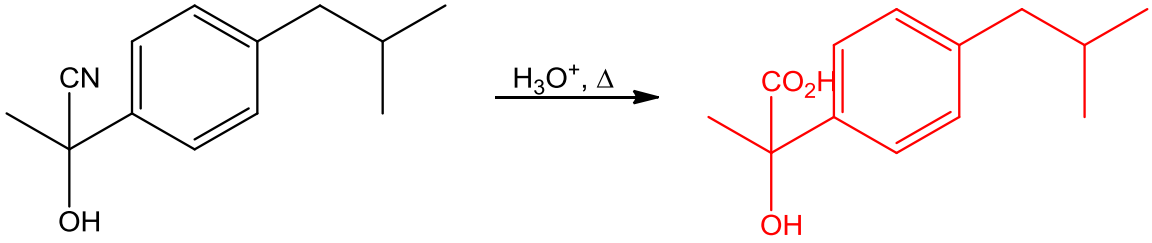
"B" + $CH_3COCl/AlCl_3$ → "C" (para substitution occurs)



"C" + $NaCN/H_2SO_4$ → "D"

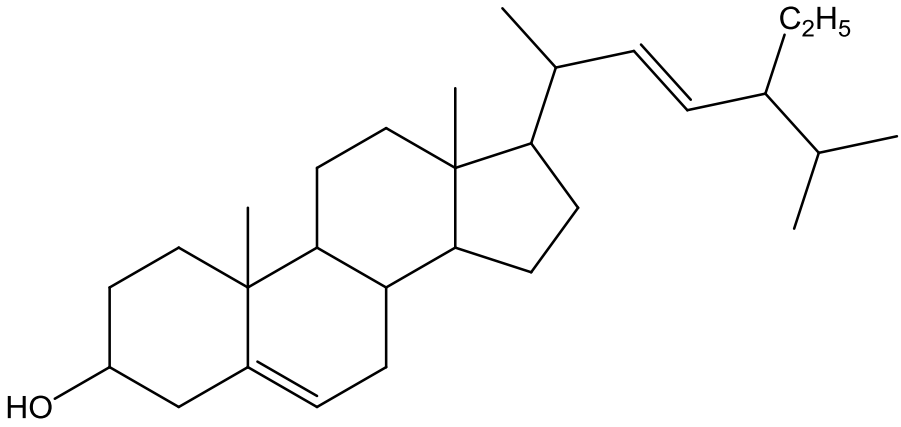


"D" + H_3O^+ → ibuprofen



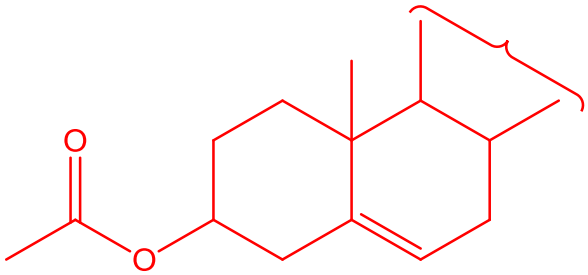
Give the structures of "A", "B", "C", "D" and ibuprofin.

9. Progesterone is a hormone, secreted by the corpus luteum. It is involved in the control of pregnancy. It can be synthesized from stigmasterol, obtained from soybean.

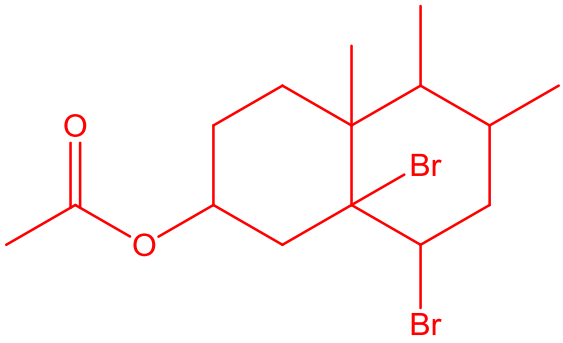


stigmasterol

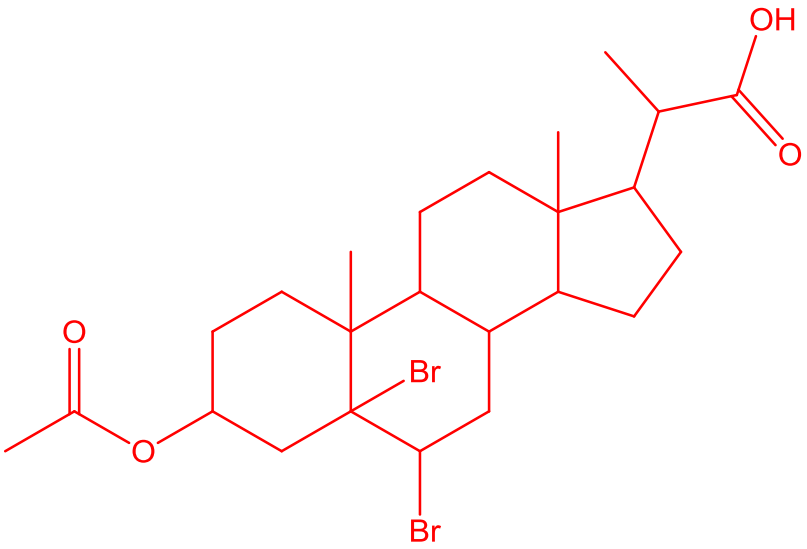
stigmasterol ($C_{29}H_{48}O$) + acetic anhydride $\rightarrow$ “A” ($C_{31}H_{50}O_2$)



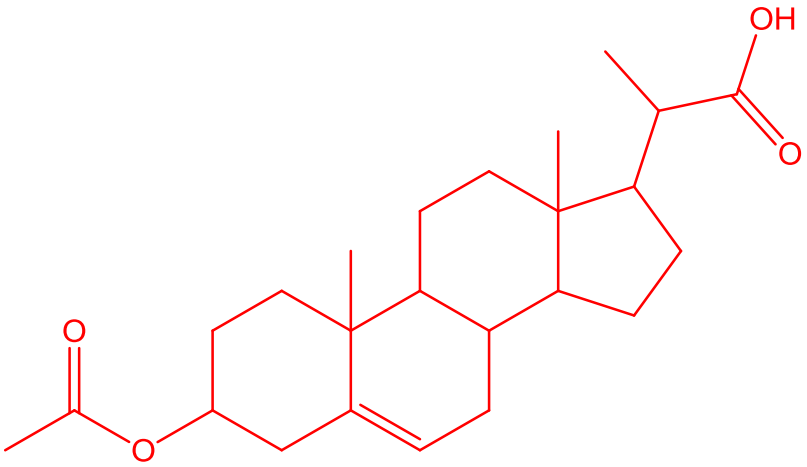
“A” + Br_2 $\rightarrow$ “B” ($C_{31}H_{50}O_2Br_2$)



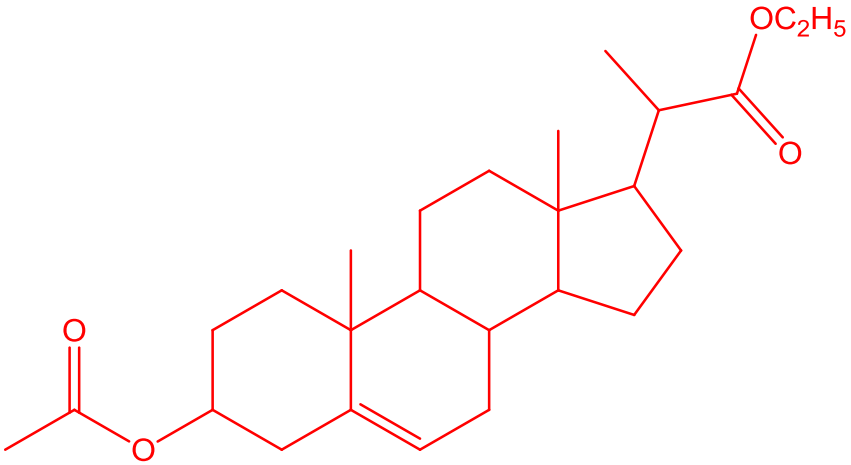
“B” + O_3, then Ag_2O $\rightarrow$ “C” ($C_{24}H_{36}O_4Br_2$)



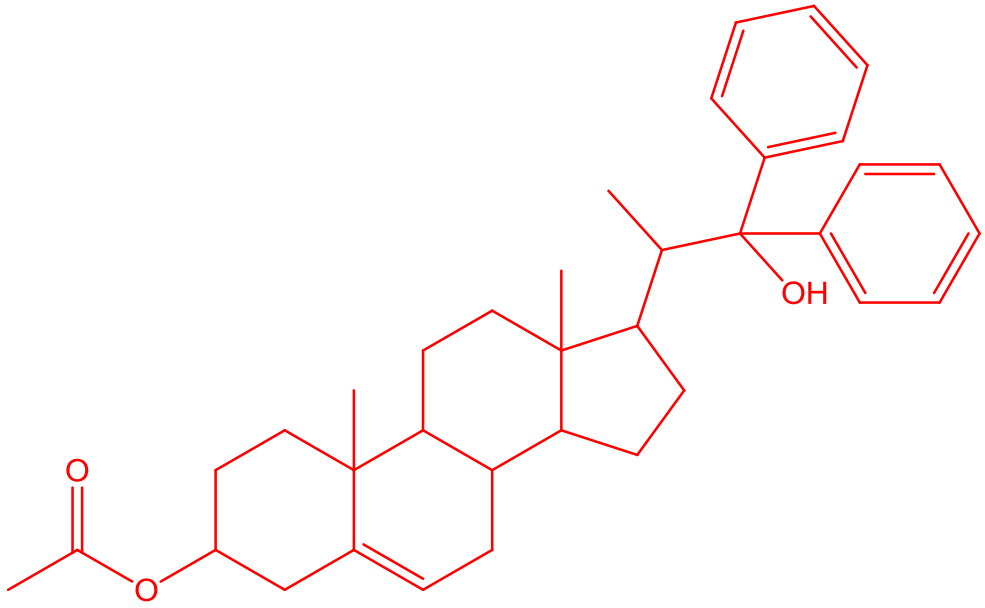
“C” + Zn/CH_3CO_2H → “D” ($C_{24}H_{36}O_4$)



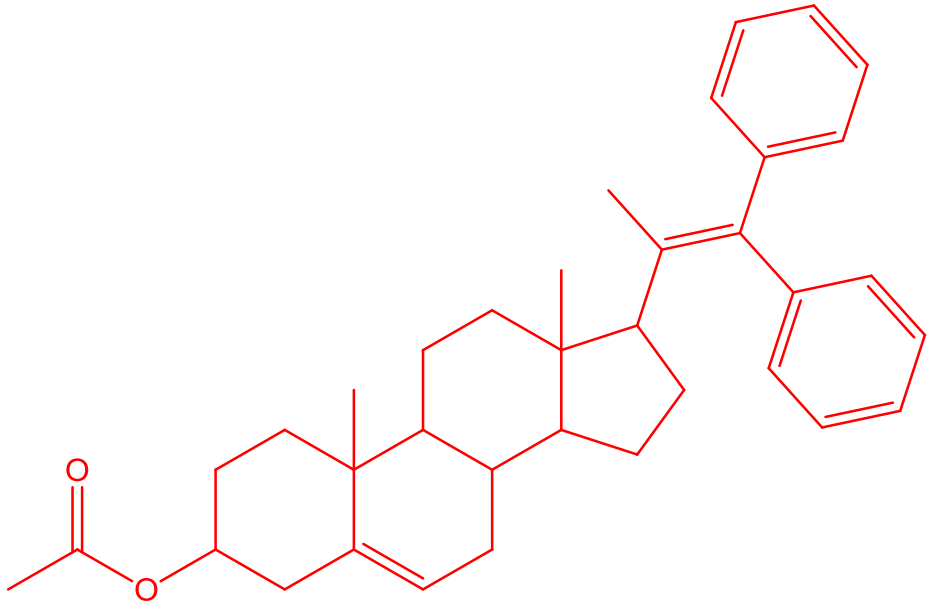
“D” + C_2H_5OH/H^+ → “E” ($C_{26}H_{40}O_4$)



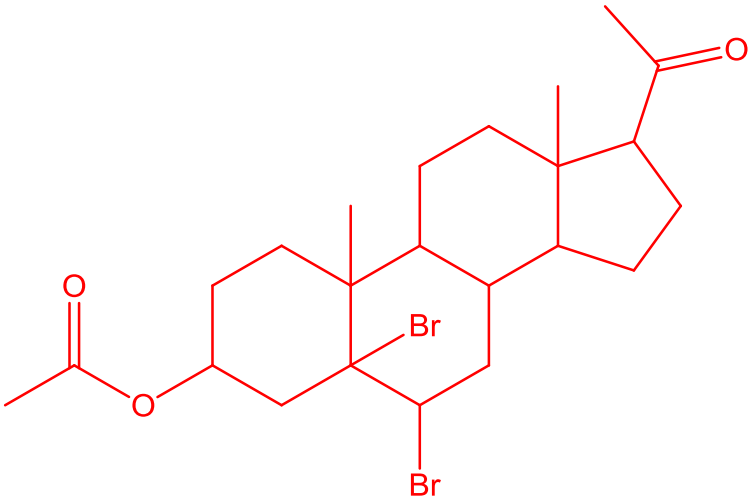
“E” + C_6H_5MgBr, then H_2O → “F” ($C_{36}H_{46}O_3$)



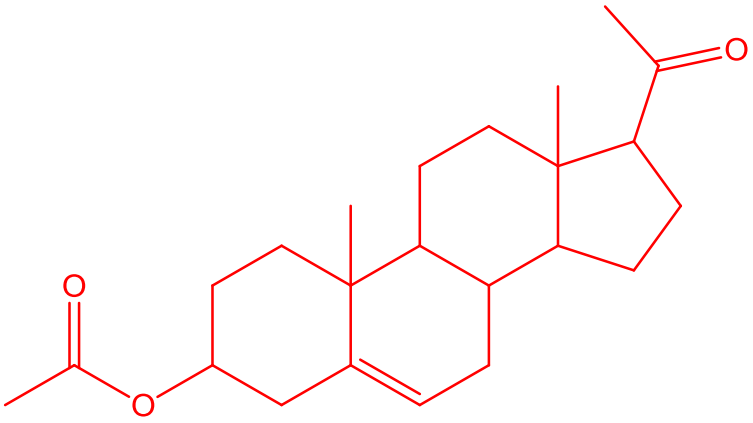
“F” + H_3PO_4 → “G” ($C_{36}H_{44}O_2$)



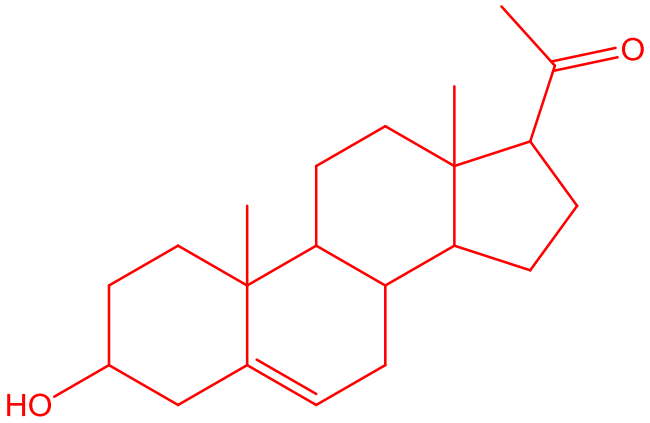
“G” + Br_2 then CrO_3/H^+ → “H” ($C_{23}H_{34}O_3Br_2$)



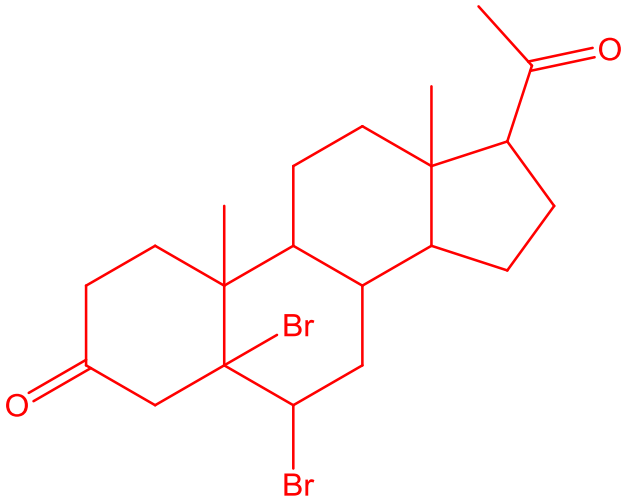
“H” + Zn/CH_3CO_2H → “I” ($C_{23}H_{34}O_3$)



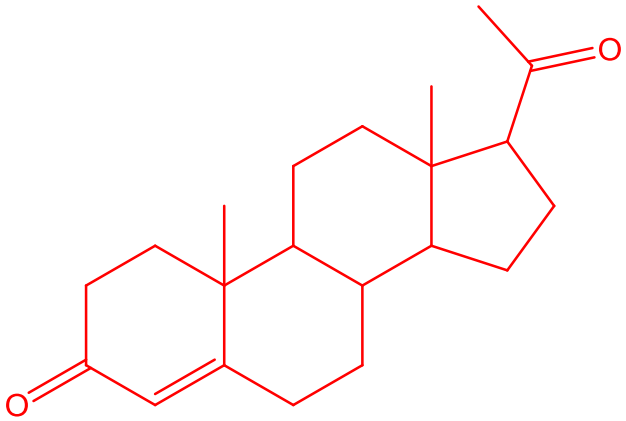
“I” + H_3O^+/Δ → “J” ($C_{21}H_{32}O_2$) pregnenolone



pregnenolone + Br_2 then CrO_3/H^+ → “K” ($C_{21}H_{30}O_2Br_2$)

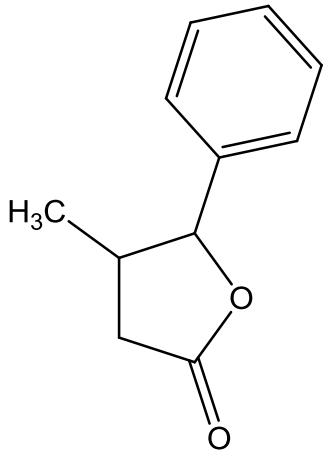


"K" + Zn/CH_3CO_2H $\rightarrow$ progesterone ($C_{21}H_{30}O_2$)

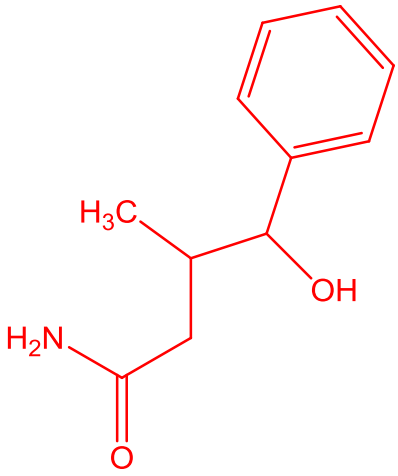


What are the structures of pregnenoline and of progesterone?

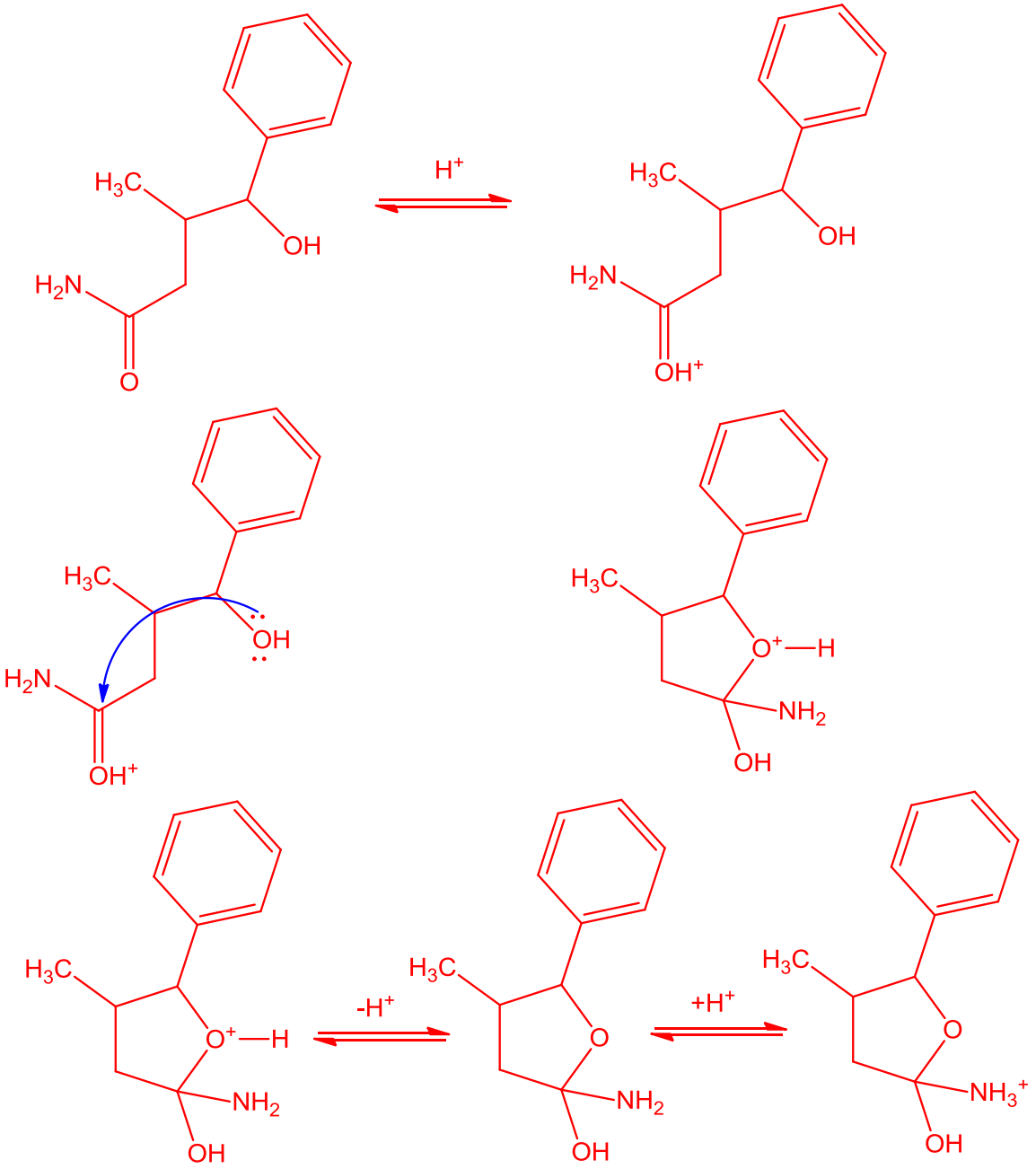
10. In clinical studies with atherosclerotic patients it was found that one of the metabolites of the hyperlipidemia drug (*Z*)-3-methyl-4-phenyl-3-butenamide is compound "A" which has the formula $C_{11}H_{15}NO_2$. When heated with aqueous acid, the following lactone is formed along with NH_4^+:

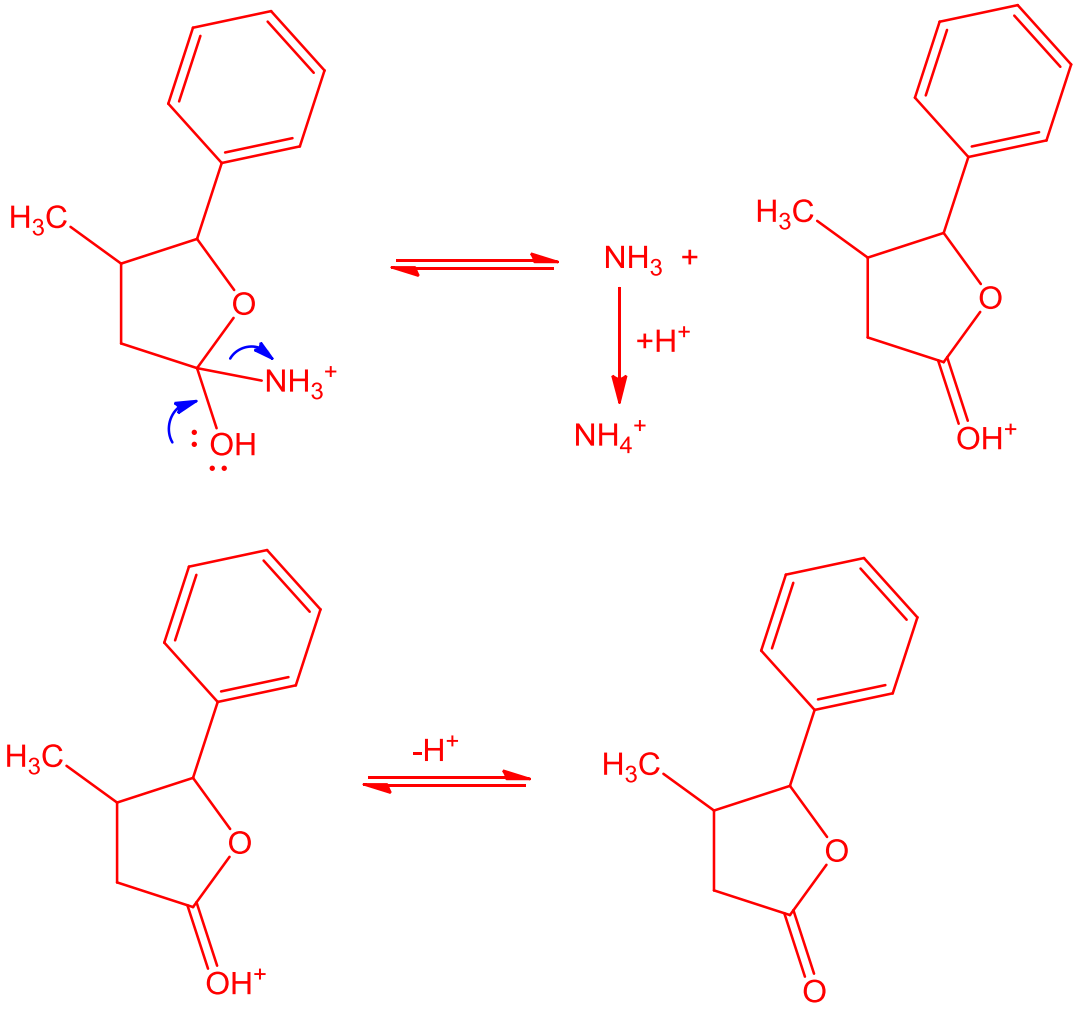


a. What is the structure of metabolite “A”?



b. Write a mechanism for its transformation into the lactone.


H3C
OH
H2N
O
H+
H3C
OH
H2N
OH+
H3C
OH
H2N
OH+
H3C
O+—H
NH2
OH
H3C
O+—H
NH2
OH
-H+
H3C
O
NH2
OH
+H+
H3C
O
NH3+
OH


H3C
O
NH3+
: OH
NH3 +
+H+
NH4+
H3C
O
OH+
H3C
O
OH+
-H+
H3C
O
O