What is the order of increasing acidity for the following compounds? (least to most)

1. a. IV, I, III, II
   b. III, II, I, IV
   c. II, III, I, IV
   d. III, II, IV, I

2. a. IV, I, III, II
   b. IV, II, III, I
   c. II, III, I, IV
   d. I, III, II, IV

3. a. IV, II, I, III
   b. I, II, IV, III
   c. III, I, II, IV
   d. III, IV, II, I
Give the major organic product(s) for each of the following reactions or sequences of reactions. Show all relevant stereochemistry.

4. 

5. 

6. 

7. 

8. 

9. 

10. 

11. 

12.
Choose the best reagent(s) for carrying out the following conversions from the list below. Place the letter corresponding to the best choice in the blank to the left of the conversion.

1. Mg, ether
2. CO₂
3. H₃O⁺
4. NaCN
5. H₂SO₄, H₂, heat
6. O₃, then Zn and HOAc
7. CH₃I

14. ___CH₃CH=CHCH₂COOH → CH₃COOH + HOOCCH₂COOH

15. ___

16. ___

17. ___

18. Propose a synthesis of the anti-inflammatory drug Ibuprofen from benzene. Show all reagents and all intermediate structures. Assume that ortho and para isomers can be separated.
Show how you would accomplish the following transformations. More than one step may be required. Show all reagents and all intermediate structures.

19.

20.

What is the order of *decreasing* reactivity towards nucleophilic acyl substitution for the carboxylic acid derivatives? (most reactive first)

21.

a. I, II, III, IV
b. I, III, IV, II
c. II, IV, III, I
d. II, I, III, IV

22.

23. Write the complete stepwise mechanism for the basic hydrolysis of acetamide, shown below. Show all electron flow with arrows and draw all intermediate structures.
Consider the reaction below to answer the following question(s):

\[
\begin{align*}
&\text{C-left side structure} & \text{NaH} & \rightarrow & \text{C-right side structure} & + & \text{H}_2 & + & \text{EtNO}_\text{Na}^+ \\
&\text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow
\end{align*}
\]

24. Write the complete stepwise mechanism for this reaction. Show intermediate structures and all electron flow with arrows.

25. Methyl butanoate has been isolated from pineapple oil and can be prepared by the Fischer esterification reaction shown below. Write the complete stepwise mechanism for this reaction. Show all electron flow with arrows and include all intermediate structures.

\[
\begin{align*}
&\text{C-left side structure} & + & \text{CH}_3\text{OH} & \rightarrow & \text{C-right side structure} & + & \text{H}_2\text{O} \\
&\text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow
\end{align*}
\]

26. Write the complete stepwise mechanism for the acid-catalyzed hydrolysis of the following amide to yield mandelic acid. Show all electron flow with arrows and draw the structures of all intermediate species.

\[
\begin{align*}
&\text{C-left side structure} & \rightarrow & \text{C-right side structure} & + & \text{NH}_4^+ \\
&\text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow
\end{align*}
\]

Consider the information below to answer the following question(s).

The reaction of a carboxylic acid with an alcohol in the presence of acid is termed Fischer esterification.

\[
\begin{align*}
&\text{A} & \rightarrow & \text{B} & \rightleftharpoons & \text{C} \\
&\text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow & \text{OH} & \rightarrow
\end{align*}
\]

27. Write the stepwise mechanism for the Fischer esterification reaction of benzoic acid and methanol given above. Show all electron flow by using curved arrows, and include all intermediate structures.
Provide structure(s) for the starting material(s), reagent(s) or the major organic product(s) of each of the following reactions or sequences of reactions. Show all relevant stereochemistry.

28. 

29. 

30. 

31. 

32. 

33.
34. Phenylacetate $\xrightarrow{\text{HCl, H}_2\text{O}}$ +

35. 

$\xrightarrow{\text{(CH}_3\text{CH}_2)_2\text{CuLi, ether, }-78^\circ}$

36. 

1. LiAlH$_4$, ether
2. H$_3$O$^+$

37. $\text{CH}_3\text{COCl} \xrightarrow{\text{NaOH, H}_2\text{O}} \text{CH}_3\text{CON(CH}_3)_2$

38. 

$\xrightarrow{\text{CH}_3\text{OH, HCl}}$

39. 

$\text{C}_6\text{H}_5\text{Cl} + \text{C}_5\text{H}_5\text{N} \xrightarrow{\text{pyridine}}$

40. 

$\xrightarrow{\text{1. DIBAH, ether, 2. H}_3\text{O}^+}$
41. 

42. Ethyl phenylacetate is a pleasant smelling compound used in perfumery. Draw structures for each of the intermediates in the synthesis of ethyl phenylacetate below.

43. Consider the reaction below to answer the following question(s):

44. Write the complete stepwise mechanism for the reaction above. Show all intermediate structures and all electron flow with arrows.
Each of the following compounds can be prepared by a mixed aldol condensation reaction. Give the structures of the aldehyde and/or ketone precursors for each aldol product and formulate the reaction.

45. 
\[
\begin{array}{c}
\text{O} \\
\text{CH} &=& \text{CH} \text{CH}_3
\end{array}
\]

46. 
\[
\text{CH}_3 \text{CCH}=\text{CH}_2
\]

47. 
\[
\begin{array}{c}
\text{O} \\
\text{Ph}
\end{array}
\]

Consider the reaction below to answer the following question(s).

\[
\begin{array}{c}
\text{A} \\
\text{H} & \text{H} \\
\text{B} \\
5\% \text{ NaOCH}_3, \text{CH}_3\text{OH} \\
\text{C} \\
\text{CH}_2\text{OH}
\end{array}
\]

48. Which carbonyl compound functions as the electrophile in this reaction?

49. Draw the structure of the enolate ion that is generated during the course of this reaction.

50. This reaction is an example of:
   a. a mixed Claisen condensation.
   b. a Dieckman condensation.
   c. a Michael reaction.
   d. a mixed aldol reaction.
Consider the reaction below to answer the following question(s):

Acetoacetic ester can be prepared by the Claisen self-condensation reaction of ethyl acetate.

\[
\text{\begin{align*}
\text{CH}_3\text{C} & \text{OCH}_2\text{CH}_3\quad 1. \text{NaOEt, EtOH} \\
\text{CH}_2\text{C} & \text{OCH}_2\text{CH}_3
\end{align*}}
\]

51. Write the complete stepwise mechanism for this reaction. Show all electron flow with arrows and draw all intermediate structures.

Consider the compound 2-methyl-2-carboethoxycyclopentanone, whose structure is shown below, to answer the following question(s).

52. When 2-methyl-2-carboethoxycyclopentanone is treated with sodium ethoxide in ethanol solution followed by a mild aqueous acid work-up, 5-methyl-2-carboethoxycyclopentanone is isolated as the major product. This reaction proceeds by a reverse Claisen condensation mechanism followed by a recyclization. On the structures provided below, show electron flow with arrows in this interesting reaction.
Consider the reaction below to answer the following question(s).

The Stork enamine reaction is a variation on the Michael reaction which utilizes an enamine nucleophile.

\[
\begin{array}{c}
\text{Pyridine} \\ + \text{H}_2\text{C=CH-C≡N} \\
\longrightarrow \\
\text{Ketone} + \text{Amine}
\end{array}
\]

53. On the structures above, draw arrows indicating electron flow in each step of this reaction.

54. Draw the structures of the Ketone + Amine products of this reaction.

55. Show how you might use a Stork enamine reaction to prepare the following compound.
Provide the indicated starting material and intermediate in the synthetic sequence below involving a Dieckmann cyclization, followed by a Robinson annulation.

Give the major organic product(s) for each of the following reactions or reaction sequences.
Consider the data in the Table below to answer the following question(s):

<table>
<thead>
<tr>
<th>Y</th>
<th>Y−CH₂COOH</th>
<th>pKₐs at 25°C</th>
<th>Y−C₆H₄COOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>4.75</td>
<td>4.19</td>
<td>4.19</td>
</tr>
<tr>
<td>CN</td>
<td>2.47</td>
<td>3.64</td>
<td>3.55</td>
</tr>
<tr>
<td>OCH₃</td>
<td>3.57</td>
<td>4.09</td>
<td>4.46</td>
</tr>
</tbody>
</table>

58. Explain why cyanoacetic acid and methoxyacetic acid are more acidic than their correspondingly substituted benzoic acid counterparts.

59. Even through the para position is one carbon farther from the carboxy group than the meta position, p-cyanobenzoic acid is more acidic than m-cyanobenzoic acid. Explain the differences in acidity between p-cyanobenzoic acid and m-cyanobenzoic acid.

60. Explain the differences in acidity between p-methoxybenzoic acid and m-methoxybenzoic acid.
SHORT ANSWER

1. ANS: 
b
   PTS: 1
2. ANS: 
a
   PTS: 1
3. ANS: 
c
   PTS: 1
4. ANS: 
   \[
   \begin{array}{c}
   \text{H} \\
   \text{Br} \\
   \text{H} \\
   \text{Br} \\
   \end{array}
   \xrightarrow{\text{KMnO}_4, \text{H}_2\text{O}^+}
   \begin{array}{c}
   \text{H} \\
   \text{COOH} \\
   \text{COOH} \\
   \end{array}
   \]
   PTS: 1
5. ANS: 
   \[
   \begin{array}{c}
   \text{H} \\
   \text{Br} \\
   \text{H} \\
   \text{Br} \\
   \text{NaCN} \\
   \text{NaOH, H}_2\text{O, heat} \\
   \text{H}_2\text{O}^+
   \end{array}
   \xrightarrow{1. \text{LiAlH}_4, \text{THF, heat}}
   \begin{array}{c}
   \text{H} \\
   \text{HOOC} \\
   \text{H}
   \end{array}
   \]
   PTS: 1
6. ANS: 
   \[
   \begin{array}{c}
   \text{CH}_2\text{COOH} \\
   \text{H}_2\text{O}^+
   \end{array}
   \xrightarrow{1. \text{LiAlH}_4, \text{THF, heat}}
   \begin{array}{c}
   \text{CH}_2\text{OH}
   \end{array}
   \]
   PTS: 1
7. ANS: 
   \[
   \begin{array}{c}
   \text{CH}_2\text{Br} \\
   \text{H}_2\text{O}^+, \text{heat}
   \end{array}
   \xrightarrow{1. \text{NaCN, acetone}}
   \begin{array}{c}
   \text{CH}_2\text{COOH}
   \end{array}
   \]
   PTS: 1
8. **ANS:**

\[
\text{[Chemical structure]} \xrightarrow{\text{CrO}_2\cdot\text{H}_2\text{O}^+} \text{[Chemical structure]}
\]

**PTS:** 1

9. **ANS:**

\[
\text{[Chemical structure]} \xrightarrow{1.\text{Mg, ether, } 2.\text{CO}_2} \xrightarrow{3.\text{H}_3\text{O}^+} \text{[Chemical structure]}
\]

**PTS:** 1

10. **ANS:**

\[
\text{[Chemical structure]} + \text{CH}_3\text{Mgl} \xrightarrow{\text{ether}} \text{[Chemical structure]}^+_{\text{Mgl}} + \text{CH}_4
\]

**PTS:** 1

11. **ANS:**

\[
\text{[Chemical structure]} \xrightarrow{1.\text{LiAlH}_4, \text{THF, } 2.\text{H}_3\text{O}^+} \text{[Chemical structure]}
\]

**PTS:** 1

12. **ANS:**

\[
\text{[Chemical structure]} \xrightarrow{1.\text{(CH}_3)_2\text{CHMgBr, ether, } 2.\text{H}_3\text{O}^+} \text{[Chemical structure]}
\]

**PTS:** 1

13. **ANS:**

\[
\text{[Chemical structure]} \xrightarrow{\text{SOCl}_2, \text{benzene}} \xrightarrow{\text{heat}} \text{[Chemical structure]}
\]

**PTS:** 1

14. **ANS:**

\[a\]

**PTS:** 1

15. **ANS:**

\[g\]

**PTS:** 1
16. ANS:
   b

   PTS: 1

17. ANS:
   c

   PTS: 1

18. ANS:

19. ANS:

   PTS: 1
20. ANS:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3\text{CH}_2\text{C} - \text{Br} & \quad \text{CH}_3\text{CH}_2\text{C} - \text{CN} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

1. Mg, ether
2. CO_2
3. H_3O^+

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3\text{CH}_2\text{C} - \text{COOH} & \quad \text{CH}_3\text{CH}_2\text{C} - \text{COCl} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

SOCl_2, benzene heat

PTS: 1

21. ANS:

b

PTS: 1

22. ANS:

d

PTS: 1

23. ANS:

\[
\begin{align*}
\text{H}_3\text{C} - \text{C} - \text{NH}_2 & \quad \text{H}_3\text{C} - \text{C} - \text{OH} \\
\text{H}_2\text{O} & \quad \text{H}_3\text{C} - \text{C} - \text{O} - \text{H} \\
\text{H}_3\text{C} - \text{C} - \text{CONH}_2 & \quad \text{H}_3\text{C} - \text{C} - \text{CO}_2^- + \text{NH}_3
\end{align*}
\]

PTS: 1
24. ANS:

25. ANS:

PTS: 1

PTS: 1
26. ANS:

\[
\begin{array}{c}
\text{OH} \quad \text{C} \quad \text{NH}_2 \quad \text{H}_2\text{O} \quad \text{OH} \\
\text{C} \quad \text{NH}_2 \quad \text{H} \quad \text{OH} \\
\text{NH}_4^+ \\
\text{H}^+ \text{ transfer}
\end{array}
\]

PTS: 1

27. ANS:

\[
\begin{array}{c}
\text{O} \\
\text{C} \quad \text{OH} \\
\text{H} - \text{Cl} \\
\text{H} \quad \text{OCH}_3 \\
\text{H}^+ \text{ transfer}
\end{array}
\]

PTS: 1

28. ANS:

\[
\begin{array}{c}
\text{OH} \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{O} \quad \text{OEt} \\
1. \text{LiAlH}_4, \text{ ether} \\
2. \text{H}_2\text{O}^+
\end{array}
\]

PTS: 1
29. ANS:

\[(\text{CH}_3\text{CH})\text{C-Cl} + \text{CH}_3\text{CO-CH}_3 \xrightarrow{\text{ether}} \text{(CH}_3\text{CH})\text{C-O-C-CH}_3\]

PTS: 1

30. ANS:

\[
\begin{align*}
\text{CH}_3\text{C-} & \xrightarrow{\text{SOCl}_2} \text{CH}_3\text{C-Cl} \\
\text{C-CH}_3 & \xrightarrow{1. \text{(CH}_3\text{CH)MgBr, ether}} \text{C-CH}_3
\end{align*}
\]

PTS: 1

31. ANS:

\[
\text{CN} \xrightarrow{1. \text{(CH}_3\text{CH)MgBr, ether}} \xrightarrow{2. \text{H}_2\text{O}^+} \text{C-CH}_3
\]

PTS: 1

32. ANS:

\[
\begin{align*}
\text{COOH} & \xrightarrow{\text{(CH}_3\text{CO})_2\text{O, NaOH, H}_2\text{O}} \text{COOH} \\
\text{OH} & \xrightarrow{\text{ether}} \text{OH}
\end{align*}
\]

PTS: 1

33. ANS:

\[
\begin{align*}
\text{O} & \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \xrightarrow{2. \text{H}_2\text{O}^+} \text{H}_3\text{C} \\
\text{O} & \xrightarrow{} \text{OH}
\end{align*}
\]

PTS: 1
34. ANS:

\[
\text{HCl} \xrightarrow{\text{H}_2\text{O}} \text{O} \quad \xrightarrow{+ \text{CH}_3\text{OH}} \]

35. ANS:

\[
\text{(CH}_3\text{CH}_2\text{)}_2\text{CuLi} \quad \xrightarrow{\text{ether, -78°}} \quad \text{ether, -78°}
\]

36. ANS:

\[
\text{H} \quad \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \quad \xrightarrow{2. \text{H}_3\text{O}^+} \quad \text{ether}
\]

37. ANS:

\[
\text{HN(CH}_3\text{)}_2 \quad \xrightarrow{\text{NaOH, H}_2\text{O}} \quad \text{ether}
\]

38. ANS:

\[
\text{O} \quad \xrightarrow{\text{CH}_3\text{OH}} \quad \xrightarrow{+ \text{HCl}} \quad \text{ether}
\]

PTS: 1
39. ANS:

\[ \text{phenylacetyl chloride} + \text{pyridine} \rightarrow \text{product} \]

PTS: 1

40. ANS:

\[ \text{cyclohexanone} \xrightarrow{\text{1. DIBAL, ether}} \xrightarrow{\text{2. H_2O^+}} \text{product} \]

PTS: 1

41. ANS:

\[ \text{compound} \xrightarrow{\text{CH_3OH}} \text{product} \]

PTS: 1

42. ANS:

\[ \text{cyclohexanone chloride} \xrightarrow{\text{benzene, AlCl_3}} \text{product} \]

PTS: 1
43. ANS:

44. ANS:

45. ANS:

46. ANS:

PTS: 1
47. ANS:

\[
\begin{align*}
\text{pentane} & + \text{acetophenone} \xrightarrow{5\% \text{ NaOH, EtOH \ heat}} \text{pentene} + \text{H}_2\text{O} \\
\end{align*}
\]

PTS: 1

48. ANS:

A

PTS: 1

49. ANS:

\[
\begin{align*}
\text{alkyl anion} \\
\text{cyclohexene}
\end{align*}
\]

PTS: 1

50. ANS:

\[
\begin{align*}
\text{diagram of chemical reactions}
\end{align*}
\]

PTS: 1

51. ANS:

\[
\begin{align*}
\text{diagram of chemical reactions}
\end{align*}
\]

PTS: 1
52. ANS:

53. ANS:

54. ANS:

PTS: 1
55. ANS:

\[
\text{\begin{align*}
\text{\includegraphics[width=0.5\textwidth]{chemistryDiagram1.png}}
\end{align*}}
\]

PTS: 1

56. ANS:

\[
\text{\begin{align*}
\text{\includegraphics[width=0.7\textwidth]{chemistryDiagram2.png}}
\end{align*}}
\]

PTS: 1
57. ANS:

\[
\begin{align*}
\text{CH}_3 + \text{H}_2\text{C} = \text{CH} - \text{C} = \text{CH}_3 & \quad \xrightarrow{\text{NaOEt, EtOH}} \quad \text{CH}_3 \\
& \quad \xrightarrow{\text{NaOEt, EtOH, heat}} \quad \text{CH}_2\text{CH}_2\text{CCH}_3
\end{align*}
\]

\text{Michael addition}

\text{Robinson annelation product}

PTS: 1

58. ANS:

Electron-withdrawing groups, like \(-\text{CN}\) and \(-\text{OCH}_3\), inductively withdraw electron density, which stabilizes the resulting carboxylate anion and, thus, increases the acidity of the carboxylic acid. These inductive effects are strongly dependent on distance. The \(-\text{CN}\) and \(-\text{OCH}_3\) substituents are closer to the carboxylate in the substituted acetic acids than in the substituted benzoic acids, so their effect is greater.

PTS: 1

59. ANS:

In \(p\)-cyanobenzoic acid, the negative charge of the carboxylate can be better stabilized than in the \textit{meta} isomer because the electron-withdrawing cyano group polarizes the benzene ring and places a positive charge next to the negatively charged carboxyl group. The same polarization occurs in \(m\)-cyanobenzoic acid, but the effect is not as great because the charge is one carbon farther away from the carboxy group.

\[
\begin{align*}
\text{\(p\)-cyanobenzoic acid} & \quad \xrightarrow{\text{WTFIS}} \quad \text{\(m\)-cyanobenzoic acid}
\end{align*}
\]

PTS: 1
60. **ANS:**

$p$-Methoxybenzoic acid is less acidic than $m$-methoxybenzoic acid because the carboxyl group is directly conjugated, through the benzene ring, with the electron-donating oxygen lone pairs of the methoxy group. This destabilizes the $p$-methoxybenzoate anion relative to the $m$-methoxybenzoate anion by placing two negative charges on the carboxylate group.

![Diagrams of carboxylate groups](image)

**PTS:** 1