Heroin is an opiate analgesic whose tragic addiction epidemic is well known. Heroin is produced from morphine, which is extracted from the poppy flower. Interestingly, heroin was sold over-the-counter as an analgesic in the decades around 1900.

1. (2) In the space below write the name of the one functional group present in heroin but absent in morphine.

2. (2) Write one letter in the blank. Combined with a mild base (B) reactant _____ is an efficient way to convert morphine into heroin.

   (a) \[\text{H}_3\text{C} \quad \text{O} \quad \text{O} \quad \text{CH}_3\]  
   (b) \[\text{H}_3\text{C} \quad \text{O} \quad \text{H}\]  
   (c) \[\text{H}_3\text{C} \quad \text{O} \quad \text{CH}_3\]  
   (d) \[\text{H}_3\text{C} \quad \text{O} \quad \text{OCH}_3\]

3. (6) Using the molecule you selected in question 2 plus mild base (B), write a mechanism for acetylation of the morphine phenolic OH group:

   \[\text{Ar} \quad \text{OH} \quad \text{Question 2 choice} \quad \text{B} \quad \text{Ar} \quad \text{O} \quad \text{CH}_3\]

4. (2) In each answer blank write 'T' (for true) or 'F' (for false). The mechanism I wrote in question 3 is an example of...

   ...the Fischer esterification reaction: ________  
   ...the Chichibabin reaction: ________

5. (2) Morphine can also be converted into heroin according to the following equilibrium:

   \[\text{Ar} \quad \text{OH} \quad + \quad \text{H}_3\text{C} \quad \text{SCH}_3 \quad \leftrightarrow \quad \text{ArO} \quad \text{CH}_3 \quad + \quad \text{CH}_3\text{SH} \quad \text{The equilibrium favors ________}.

   Morphine  
   Heroin

Complete the statement by writing 'M' (for morphine; \(K_{eq} < 1\)), 'H' (for heroin; \(K_{eq} > 1\)), or 'E' (if \(K_{eq} = 1\)) in the blank above.

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One reason for the strongly addictive nature of heroin (especially when injected) is rapid hydrolysis to morphine in the brain. The questions on this exam page concern this hydrolysis reaction.

6. (10) Write a mechanism for this hydrolysis reaction:

\[
\text{ArO} - \text{O} + \text{H}_{2}\text{O}^{+} \rightarrow \text{CH}_{3} \rightarrow \text{ArOH} + \text{H}_{3}\text{C} - \text{OH}
\]

7. (6) Refer to the heroin structure on page 1. Write a number (6, 2, or 0 if the rates are equal) in the blank. If you write 0 you are done with this question. If you write 2 or 6 in the blank complete the statement by adding *no more than ten words* of explanation. Hydrolysis of heroin group ______ is faster because this group...

8. (10) Various analogs of heroin have been made in order to study their drug properties. For each change in the heroin structure shown, write "F" if the change causes hydrolysis to be faster, or "S" if the hydrolysis is slower. Complete each explanation by adding *no more than fifteen words* in each case. Use a *very different explanation* in each case.

(a) \[\text{ArO} - \text{O} \text{CH}_{3} \text{ changed to } \text{ArO} - \text{O} \text{CF}_{3}\]
This change makes the hydrolysis ____ because this new structure...

(b) \[\text{ArO} - \text{O} \text{CH}_{3} \text{ changed to } \text{ArO} - \text{O} \text{H}\]
This change makes the hydrolysis ____ because this new structure...

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9. (9) Synthesis of other heroin analogs might be attempted using the reactions shown below. For each reaction, write two organic products. (*These are formed in equal amounts. Hint: think about the mechanisms.*) If no reaction occurs write NR in the boxes. Note that the portion of the structure abbreviated as 'Ar' does not change in these reactions.

(a) \[
\text{ArO} \quad \text{CH}_3 \quad \text{MgBr} \quad \rightarrow \quad \text{1. CH}_2\text{CH}_2\text{H}_2\text{O}^+ \\
\text{ArO} \quad \text{CH}_3 \quad \text{H}_3\text{O}^+ 
\]

(b) \[
\text{ArO} \quad \text{CH}_3 \quad \text{NaBH}_4 \quad \rightarrow \quad \text{2. CH}_2\text{CH}_2\text{OH} 
\]

(c) \[
\text{ArO} \quad \text{CH}_3 \quad \text{NH}_3 \quad \rightarrow \quad \text{2. CH}_2\text{NH}_2\text{H}_2\text{O} 
\]

To increase its water solubility and aid in excretion, morphine (abbreviated here as M–OH) is metabolically converted into its glucuronide by coupling with glucuronic acid. Glucuronic acid is derived from glucose. Questions 10 and 11 refer to this reaction scheme:

Glucose \[\rightarrow\] Glucuronic acid \[\rightarrow\] Morphine glucuronide

10. (4) For each carbon in the scheme above, write "O" if this carbon is oxidized in this conversion, "R" if it is reduced, "N" if neither oxidation nor reduction occurs, or "B" if oxidation and reduction both occur simultaneously.

Glucose \[\rightarrow\] glucuronic acid: ________
Glucuronic acid \[\rightarrow\] morphine glucuronide: ________

11. (8) Write a mechanism for the simplified coupling of morphine (M–OH) with glucuronic acid to produce morphine glucuronide (shown at the right). The enzyme (Enz) is both an acid and a base.
12. (3) Another problem with the current heroin epidemic is that heroin is being mixed with fentanyl, a very powerful and short-acting opioid analgesic. A dose of as little as 2 milligrams of fentanyl can be fatal. Complete the following reaction for synthesis of a fentanyl precursor molecule by writing a reasonable reactant in the reactant box. OK to use 'Ph' where appropriate for this question.

\[
\text{Reactant} \quad \xrightarrow{\text{LiAlH}_4} \quad \text{Fentanyl precursor}
\]

The remaining exam questions are not directly related to heroin, morphine, or fentanyl.

13. (3) For equilibrium A, \( K_{eq} \approx 1 \). For equilibrium B, \( K_{eq} \ll 1 \).

\[
\begin{align*}
\text{Equilibrium A (} K_{eq} \approx 1 \text{)} & : \\
\text{Equilibrium B (} K_{eq} \ll 1 \text{)} & :
\end{align*}
\]

Complete this explanation by adding no more than fifteen words in each answer space: Equilibrium A has \( K_{eq} \approx 1 \) but equilibrium B has \( K_{eq} \ll 1 \) because equilibrium A...

...whereas equilibrium B...

14. (4) In protein synthesis, the carboxylic acid end of one amino acid cannot be coupled with the amine end of another amino acid to produce a new peptide bond:

\[
\text{Instead, the carboxylic acid must be converted into the corresponding phosphate to make the protein:}
\]

Complete this statement by adding no more than fifteen words: The OH to phosphate conversion is necessary because...
15. (3) Write the names of three carbonyl-containing functional groups that have resonance delocalization over no less than three atoms.

Questions 16 and 17 concern molecule C:

16. (2) Write the name of all carbonyl-containing functional group in molecule C.

17. (9) Write the names of the three common carbonyl group fates, as discussed in lecture. Illustrate each using molecule C and water as the only reactants. Include all curved arrows, but do not go beyond one mechanism step. Do not use HB/B for this problem. If the fate can occur in more than one way show only the most likely pathway. If the fate named is not likely to occur, write “not likely” instead of illustrating the fate.

Name of carbonyl group fate # 1: _______________________________

Illustration: 

Name of carbonyl group fate # 2: _______________________________

Illustration: 

Name of carbonyl group fate # 3: _______________________________

Illustration: 

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18. (3) Assign $pK_a$ values to the indicated protons by writing numbers below the arrows. $pK_a$ choices: 9, 19, and 21. Each $pK_a$ value will be used exactly once. SCoA is an abbreviation for sulfur bonded to a large biological group whose exact structure is irrelevant to the question.

19. (6) Write a reasonable mechanism for the following reaction. The enzyme (Enz) is both a moderate acid and a moderate base. *If any molecules involved have resonance show only the most significant resonance contributor for that molecule.*

20. (2) Write exactly two or three words in the blank. Be specific! The reaction of the previous question is an example of a(n) _________________ reaction.

21. (2) Write a clear example of an aldol reaction using the given starting material. *Include all reactants and products, but do not include a mechanism.*

22. (2) In the blank after each term or concept below write the number of one question from this exam, such as 36(x), which contains an example of that term. If no exam question includes this term or concept, write '0'.

- Organometallic compound: ______
- Nucleophilic carbonyl substitution without a tetrahedral intermediate: ______