

### Final Exam Answer Key

Final Exam Mean: 159  
Final Exam Median: 161  
Final Exam St. Dev.: 23

I miscalculated the total number of points on the printed exam; the values of the 12 problems add up to 190, not 200. As a result, we gave everyone 10 points right off the bat.

1. DMSO- $d_6$  is always contaminated with a small amount of monoprotonated DMSO- $d_5$  ( $C_2D_5HSO$ ), and the H in this molecule is what is observed at  $\delta = 2.5$  ppm.

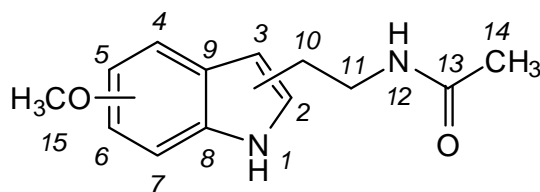
Rubric: 5 points for mentioning protonated DMSO.

*3 points partial if it's totally clear the written answer actually refers to completely protonated DMSO ( $C_2H_6SO$ ). There is no  $C_2H_6SO$  in DMSO- $d_6$ .*

2. N-H and O-H protons are usually broadened by a combination of exchange and intermolecular hydrogen bonding. DMSO- $d_6$  is a hydrogen-bond acceptor, but a pretty poor one, so it alone probably won't cause broadening. But protic impurities, like water, will certainly contribute to broadening. (And acidic impurities, like the trace DCI that's common in  $CDCl_3$ , are even worse. But DMSO- $d_6$  probably doesn't have those.) This wouldn't happen if the sample was extremely dry and free of other impurities.

Rubric: 5 points for "dry", "free of protic impurities", or anything like that.

- 3-5. Looking at the molecule and the 1-D NMR spectrum, there are a few  $^1H$  assignments we can make right off the bat. There are two, 3H-intensity resonances that must be the two methyl groups; the  $-OCH_3$  methyl group (H15) must be the one at  $\delta = 3.76$ ,

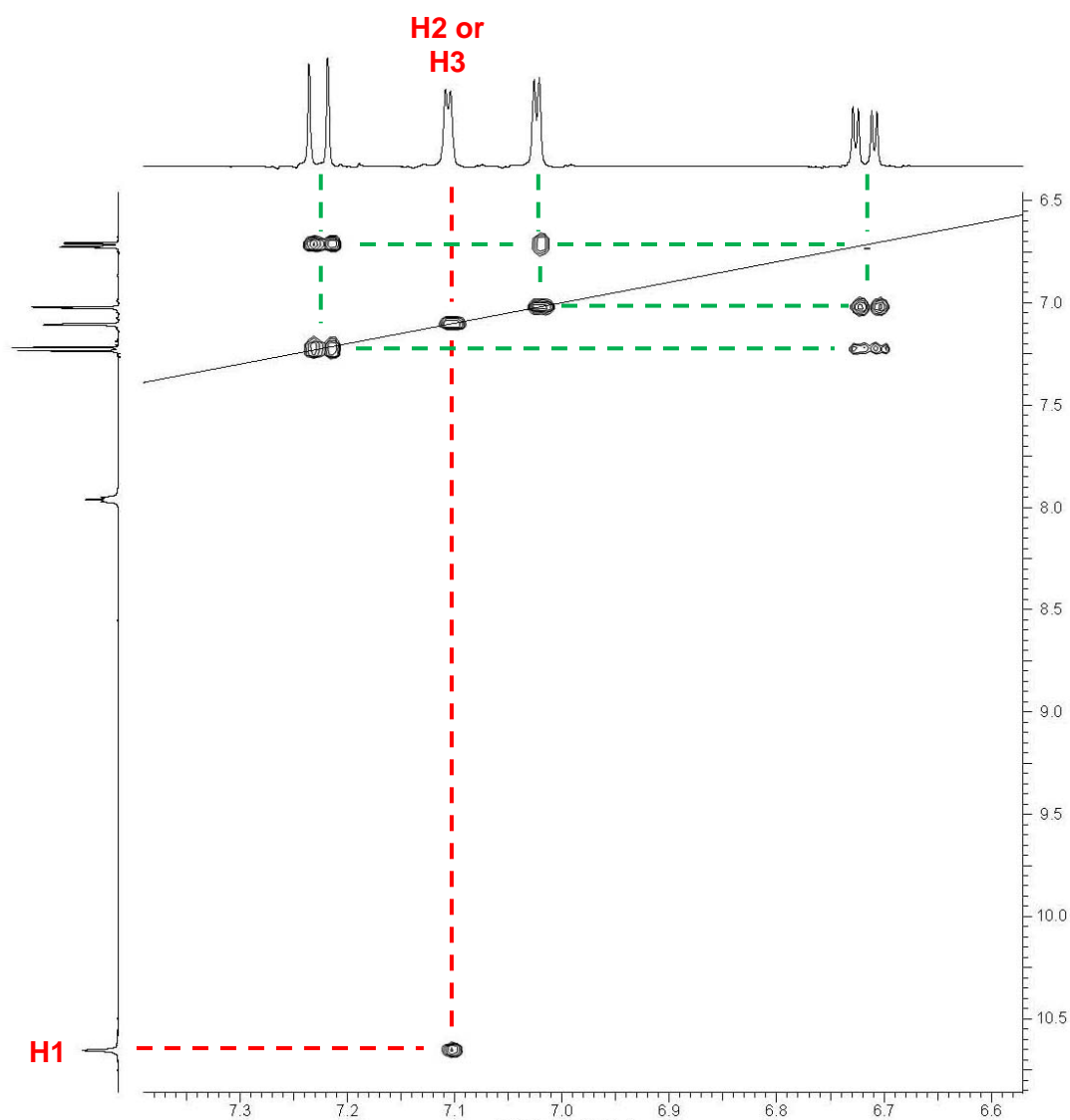


and the acetyl  $-CH_3$  must be the one at  $\delta = 1.81$ . There are also two resonances at extremely high  $\delta$  values, which should be the two  $-NH$  protons. Pretsch says that the amide  $-NH$  should be around  $\delta = 7$ , and gives a variety of chemical shifts (as low as 7, as high as 15) for N-H atoms that are part of heteroaromatic systems. Ordinarily, you don't get coupling information from  $-OH$  or  $-NH$  protons, but here, both are split. The resonance at  $\delta = 7.96$  ppm is a triplet, which could only be H12 (adjacent to two

H11 neighbors). And the resonance at  $\delta = 10.66$  ppm is a doublet, which means that it is probably H1, coupled to either H2 or H3.

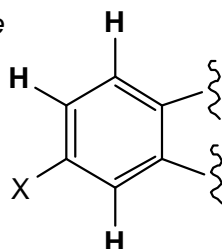
I think H10 and H11 are also pretty easy to assign. The downfield ( $\delta = 3.31$ ) 2H-intensity quartet—or maybe a little more complicated than a quartet—should be H11, neighboring the two H10 and the one NH neighbors. And the nearby triplet ( $\delta = 2.78$ ) must be H10 (with just the two H11 neighbors).

In the  $^1\text{H}$  NMR, that leaves us with just the four aromatic resonances to assign. The  $^1\text{H}$ - $^1\text{H}$  COSY says that three of the four are coupled to one another (marked below in green), and the fourth one is coupled only to H1 (the NH, marked in red).

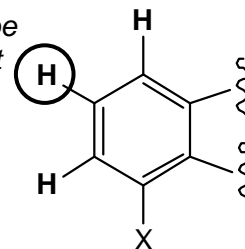


The three resonances marked in green have a very specific pattern of coupling constants: one has a single, large coupling constant; another has a large one and a small one; and the last has just a small coupling constant. I think that pattern is consistent with a pair of adjacent protons on the left-side benzene ring separated from the third proton, and is not consistent with all three left-side protons being adjacent. (If all three were adjacent, I'd expect the center H to have two large, vicinal coupling constants.)

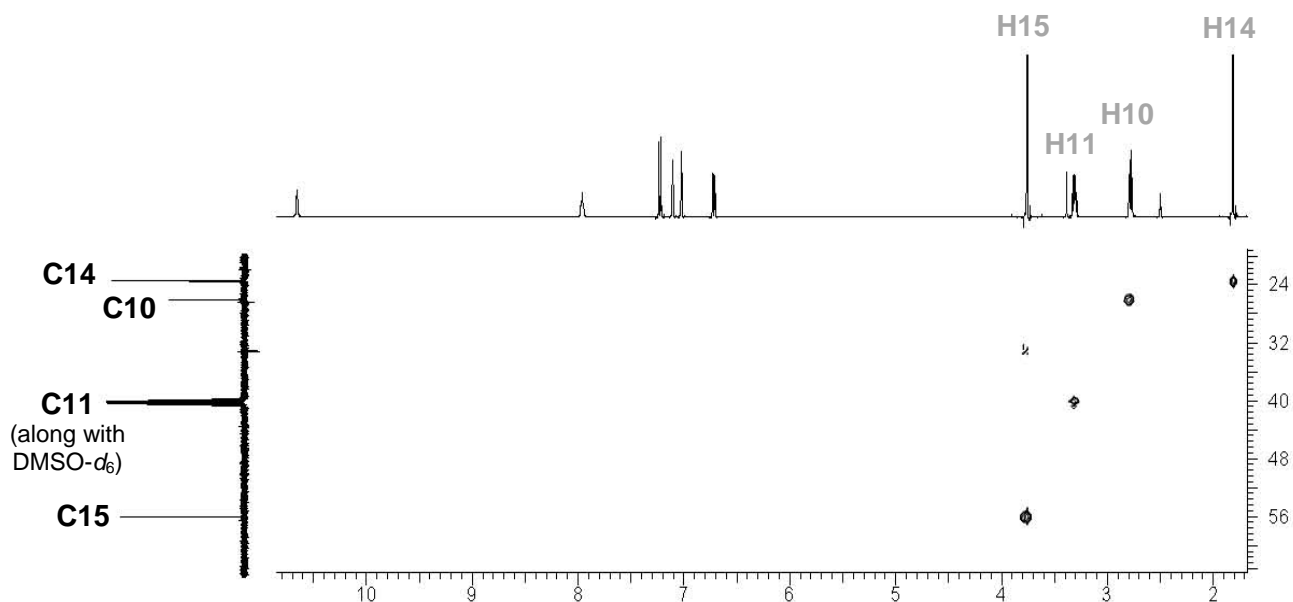
*makes sense--but is the small J a  $^4J$  or a  $^5J$ ?*

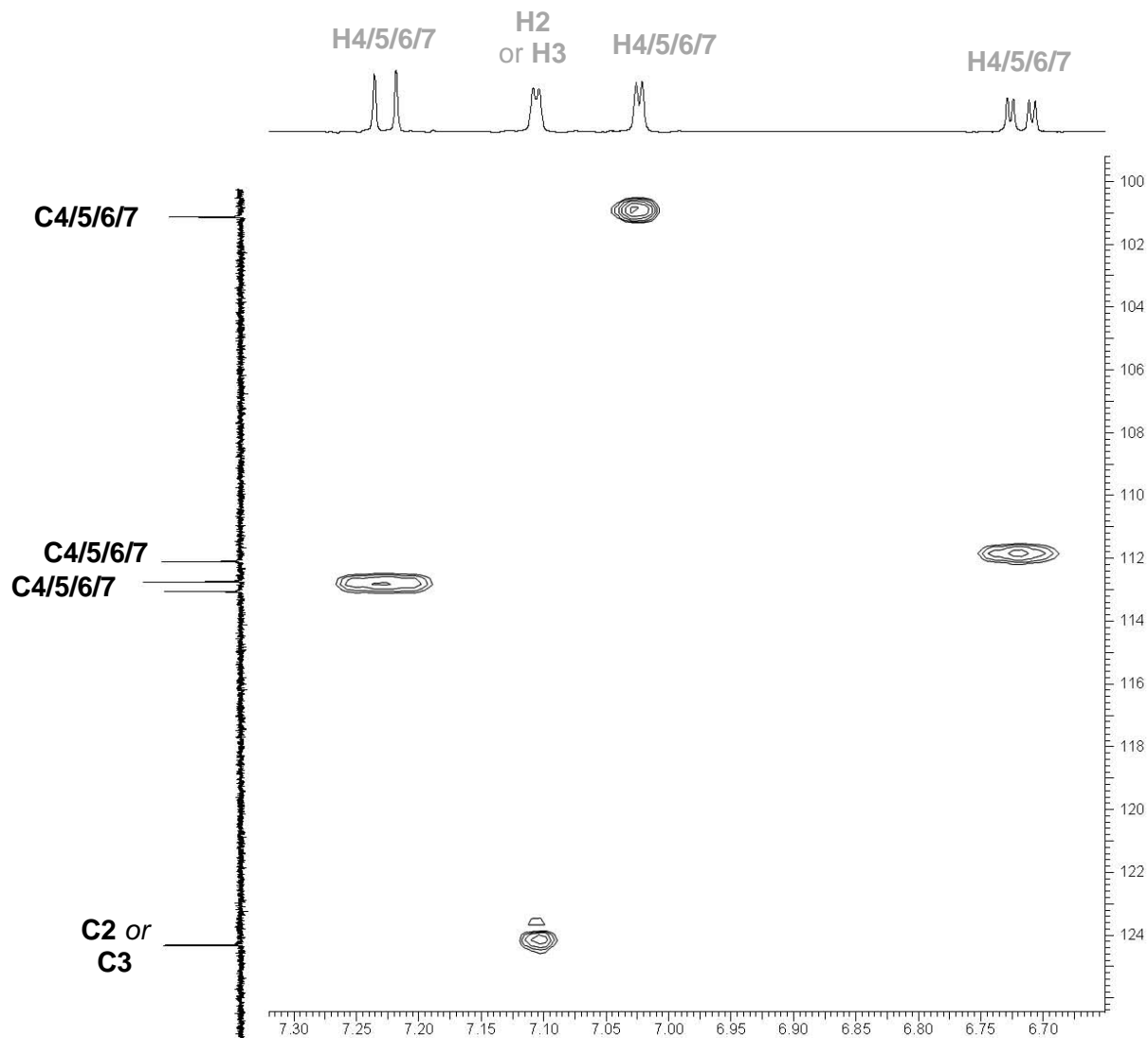


*should be a triplet*



This tells us that the  $-\text{OCH}_3$  group must be at position 5 or 6, but it doesn't tell us which. I think in order to tell where the substitutions are, we need to assign some  $^{13}\text{C}$  shifts, and to use the HMBC spectrum to connect C's and H's. The HSQC spectrum lets us make definite and group assignments to carbons in the molecule. Here's what we can know:

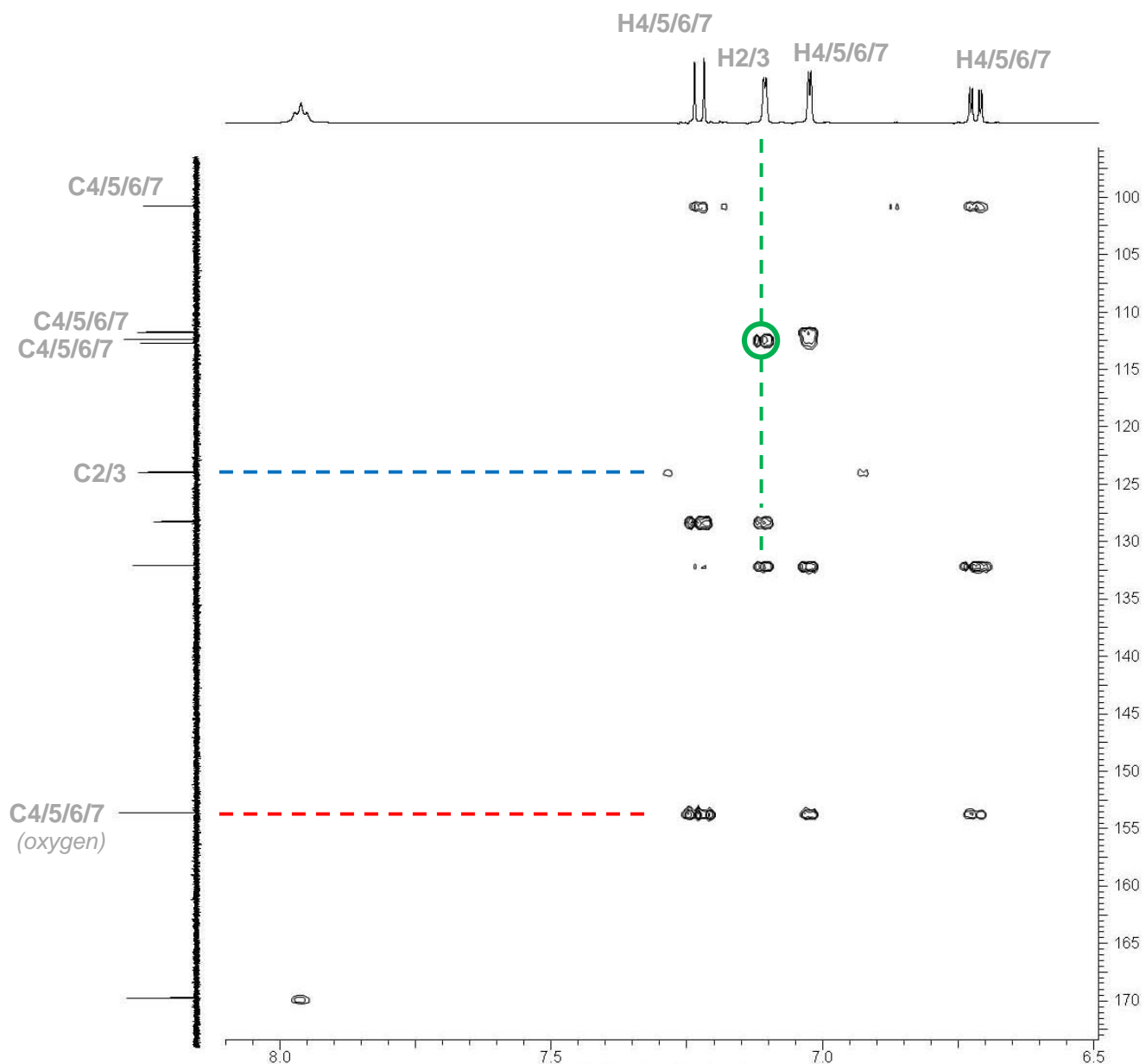




I think there are also a couple of <sup>13</sup>C assignments we can make from chemical shifts alone. The carbon that is farthest downfield ( $\delta = 169.1$ ) is probably the amide carbonyl carbon, and the next farthest ( $\delta = 153.0$ ) is probably the aromatic carbon substituted with oxygen. (Whichever numbered carbon that is.)

Let's see if we can use this information in the HMBC, to either connect the 2/3 side to the 5/6/7/8 side, or to connect 2/3 to the alkylamide (next page). Some features of the HMBC to note:

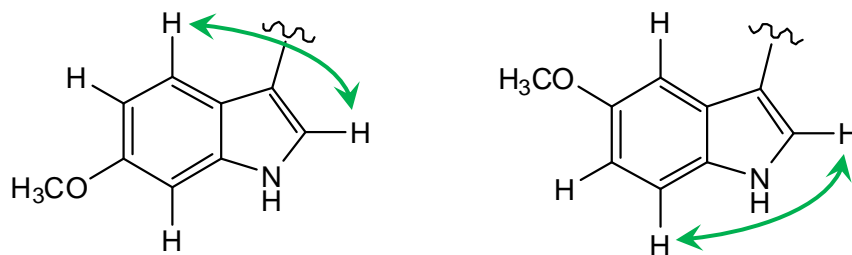
Red dashed line: The aromatic carbon attached to the methoxy group (could be C6 or C7) is nearby all three aromatic H's, but not any others. That makes good sense.



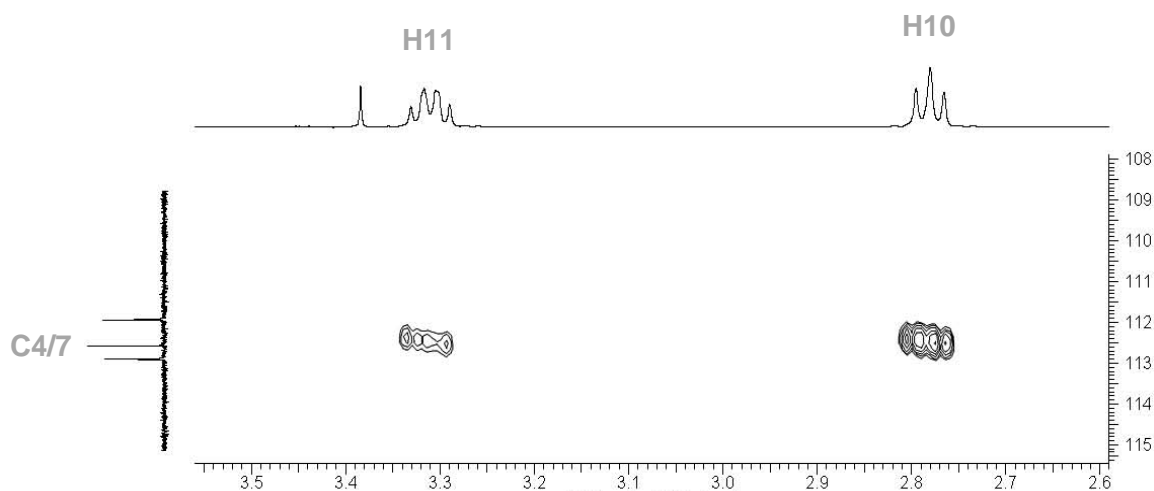
Blue dashed line: The pyrrole carbon that has a proton attached (marked "C2/3") doesn't appear to have any HMBC correlations with any other aromatic protons. That's a little unusual, and says to me that the pyrrole proton is probably H2. (I would assume that, if it were H3, that C3 would show correlation with H4.) But it's not conclusive; I'll hope to find some other evidence that points that same way.

Green dashed line: H2/3 (as I mention above, I think it's H2) shows correlations with a couple of carbons that have no carbons attached, as well as just one that does, the carbon at  $\delta = 111.7$  ppm (marked with the green circle). According to the HSQC, the proton attached to this carbon has just one coupling constant, a big one,

consistent with a vicinal coupling. I think this is consistent with this proton being either H4, vicinally coupled to H5, or H7, vicinally coupled to H6.



To be honest, I'm not sure this issue can be resolved with the spectra you're given. I think another closeup region of the HMBC spectrum addresses this issue, but maybe doesn't resolve it:



That carbon that we've narrowed to either C4 or C7 is also coupled to the H's on the alkyl chain. If the carbon were C8, these would represent  $^5J$  and  $^6J$  values, which is awfully far for coupling. On the other hand, if the carbon is C4, these crosspeaks would represent  $^4J$  and  $^5J$  values—still pretty long-distance, but a bit more reasonable. We accepted answers with either of these arrangements of protons, with the methoxy group attached at C5 or C6.

This actually completes the assignments of nearly everything. So far we've got:

proton	$\delta$ (ppm)
H1	10.66
H2	7.11
H3	<i>blank</i>
H4	7.23 or 7.02

proton	$\delta$ (ppm)
H5	6.72 or <i>blank</i>
H6	6.72 or <i>blank</i>
H7	7.23 or 7.02
H10	2.78

proton	$\delta$ (ppm)
H11	3.31
H12	7.96
H14	1.81
H15	3.76

proton	$\delta$ (ppm)
C2	123.3
C3	?
C4	100.1 or 111.7
C5	153.0 or 111.1
C6	153.0 or 111.1

proton	$\delta$ (ppm)
C7	100.1 or 111.7
C8	?
C9	?
C10	25.3

proton	$\delta$ (ppm)
C11	39.5
C13	169.1
C14	22.7
C15	55.3

This assigns everything but three aromatic carbon atoms that have no protons attached. The only  $^{13}\text{C}$  resonances we have left to assign are at  $\delta = 112.0$ ,  $127.6$ , and  $131.4$  ppm. I think the most problematic part of making these assignments is that the  $\delta = 112.0$  ppm resonance shows no crosspeaks in the HMBC spectrum, so we can't directly assign it. And, the three carbons in question are so close to one another, I don't think we can assign it by elimination either (because all three should be coupled to many of the same things). So we just gave credit for any assignment.

So, summarizing the scoring for problems 3-5:

3.

proton	$\delta$ (ppm)
H1	10.66
H2	7.11
H3	<i>blank</i>
H4	7.23 or 7.02

proton	$\delta$ (ppm)
H5	6.72 or <i>blank</i>
H6	6.72 or <i>blank</i>
H7	7.23 or 7.02
H10	2.78

proton	$\delta$ (ppm)
H11	3.31
H12	7.96
H14	1.81
H15	3.76

Rubric: 4 points per box.

2 points partial per box for switching H2 and H3.

If the same  $\delta$  value is listed more than once, you get credit for it only once.

4.

coupling constant name “ $J(H\#,H\#)$ ”	$J$ (Hz)
$J(H10,H11)$	7-8
$J(H4,H5)$ or $J(H6,H7)$	8-9
$J(H5,H7)$ or $J(H4,H6)$	2-3
$J(H1,H2)$	2-3
$J(H10,H11)$	6-7

Rubric: 4 points per box. (16 points total, any four of these five will do.)



5.

proton	$\delta$ (ppm)
C2	123.3
C3	112.0 or 127.6 or 131.4
C4	100.1 or 111.7
C5	153.0 or 111.1
C6	153.0 or 111.1

proton	$\delta$ (ppm)
C7	100.1 or 111.7
C8	112.0 or 127.6 or 131.4
C9	112.0 or 127.6 or 131.4
C10	25.3

proton	$\delta$ (ppm)
C11	39.5
C13	169.1
C14	22.7
C15	55.3

Rubric: 3 points per box. (39 points total.)

*2 points partial per box for switching C2 and C3.*

*If the same  $\delta$  value is listed more than once, you get credit for it only once.*

6.  $^{13}\text{C}$ - $^{13}\text{C}$  INADEQUATE detects correlations between neighboring  $^{13}\text{C}$  atoms. However, the probability of any carbon atom being a  $^{13}\text{C}$  is very low (~1%) and that means the probability of any pair of carbons being both  $^{13}\text{C}$ 's is extraordinarily low (~0.01%). As a result of this,  $^{13}\text{C}$ - $^{13}\text{C}$  INADEQUATE suffers from very low sensitivity, and typically requires way too much instrument time to be practical.

Rubric: 5 points for mentioning low probability of  $^{13}\text{C}$  pairs.

*3 points partial for low sensitivity or "takes too long". Those answers are true, but not as informative.*

*0 points partial for "it's no good". Also true, but even less informative.*

7. The major contributor to the UV absorption of melatonin is the

**indole**  
3

amide

or

**both contribute  
equally**

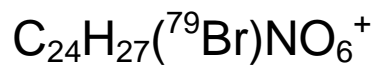
? (Circle one.)



The printed exam had a couple of errors in Bo Zhou's data, and in problem #10, that I gave fixes for on the whiteboard at the beginning of the exam. I also spent some of the exam time explaining the corrections out loud. As a result, we won't be giving credit for answers that don't match the corrected question.

10. The molecular formula for starting material **1** given in the problem is  $C_{24}H_{26}BrNO_6$ . In general, electrospray MS generates even-electron,  $[M+H]^+$  ions, so I'd expect that the molecular formula for the parent ion would have an additional proton, would be  $C_{24}H_{27}BrNO_6^+$ . The Br in this formula is an "A+2" atom, with  $^{79}Br$  and  $^{81}Br$  isotopes that are found at roughly equal abundance in nature. This is why the peaks in the spectrum of **1** appear in pairs; the pair corresponds to ions that contain either  $^{79}Br$  or  $^{81}Br$ . So the  $m/z = 504$  peak should be

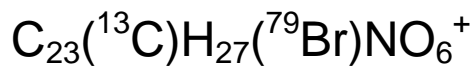
$m/z = 504:$



The problem asks you to give isotope information on any isotope that is less than 90% abundant in nature;  $^{79}Br$  fits this bill.

The smaller  $(M+H)+1$  peak at  $m/z = 505$  can't be due to a bromine isotope difference; it must be due to an  $(A+1)$  isotope. All of the other atoms in molecule **1** have an  $A+1$  isotope, but the one that has the greatest abundance (relative to the normal isotope) is  $^{13}C$ . So the *most likely* molecular formula in the  $m/z = 505$  peak would be one in which a single  $^{12}C$  is replaced by a  $^{13}C$ :

$m/z = 505:$



**Rubric:** 5 points each box. (10 points total.)

*The format of your answer wasn't important, but isotope elements and formula was.*

$m/z = 504:$

*-2 points for not labeling " $^{79}Br$ ", and just writing "Br". It's less than 90% abundance, so instructions say it needs to be labeled.*

*-1 point for omitting charge.*

*No partial if formula doesn't add to 504 amu.*

*No partial if you didn't fix the problem like I announced in class and wrote on the board. Work with me, please.*

$m/z = 505:$

*-2 points for not labeling " $^{79}Br$ ", and just writing "Br". It's less than 90% abundance, so instructions say it needs to be labeled.*

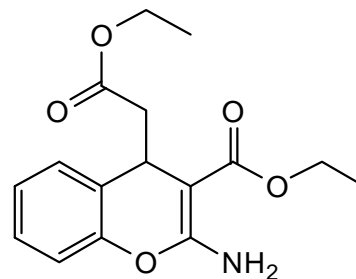
-2 points for choosing an A+1 isotope other than carbon.

-1 point for omitting charge.

No partial if formula doesn't add to 505 amu.

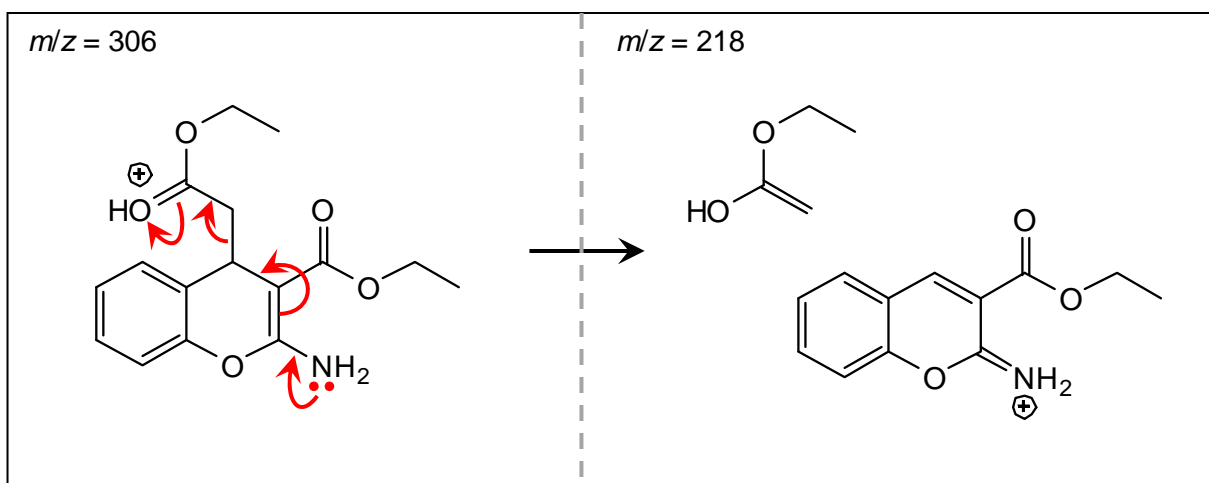
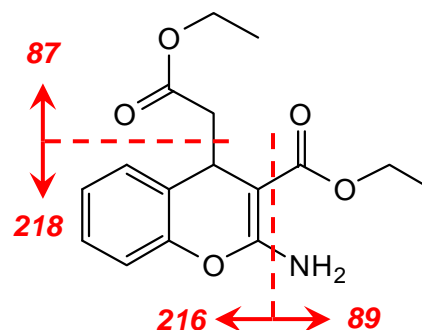
No partial if you didn't fix the problem like I announced in class and wrote on the board.

11. Okay, two challenging problems in one here. First, what molecule does the  $m/z = 306$  ion correspond to? Remember that our ESI-MS spectrum gives protonated ions that are 1 amu heavier than the neutral parent molecule, so our unknown neutral product has  $m = 305$ . Our expected product **2** had molecular formula  $C_{16}H_{18}BrNO_5$ , which has a neutral mass of 383 (if it contains  $^{79}Br$ ) or 385 (if it contains  $^{81}Br$ ). Our observed product is lighter than this, and it doesn't have that characteristic A+2 pattern of peaks, which suggests that it doesn't have a bromine atom in it. In fact, if we replace the bromine atom from **2** with an H, we get exactly the  $m = 305$  we are looking for.

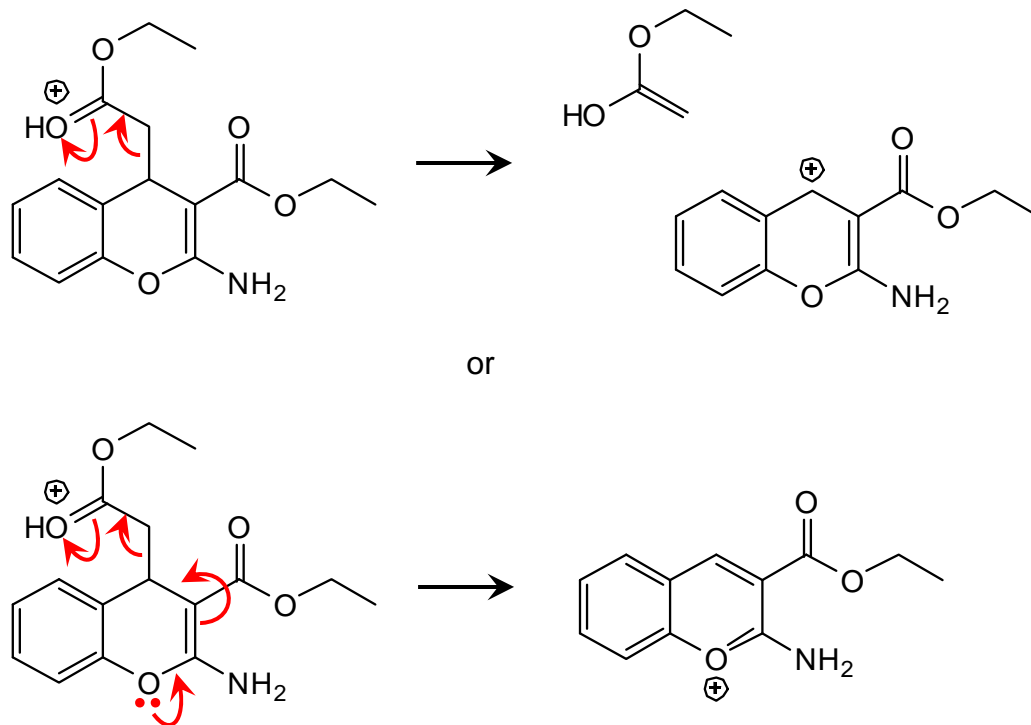


unknown product  
( $C_{16}H_{19}NO_5$ ,  
 $m = 305$ )

So then how does this molecule protonate (to give the  $m/z = 306$  peak in the ESI-MS) and then fragment to yield a  $m/z = 218$  ion? This represents a loss of 88 amu, which is around 6 heavy atoms. Looking at our unknown product structure above, there aren't many places we could imagine "cutting" the molecule to yield that sort of fragment, but two places would be the bonds connecting the esters to the rest of the molecule. Of those two, I think only the top one could come off (somehow) to yield the desired  $m/z = 218$  ion, so we can concentrate there. Protonating the top ester, and then kicking it out with oxygen/nitrogen electrons, would work:



(In my answer, I've cascaded electrons to draw what I think would be the most representative resonance structure of the product, but technically, you could draw any valid resonance structure as your ion product. So you could draw:



All of these answers were fine.)

Rubric: 18 points total this problem.

6 points for drawing any protonated version of the product I've illustrated above.

*(I think the proton needs to be on top ester to fragment correctly, but any protonated ion will do for first 6 points.)*

*-2 points for structural errors, including omitting charge or proton.*

6 points for drawing correct fragmentation product (in any resonance form).

*-2 points for structural errors, including omitting charge or proton.*

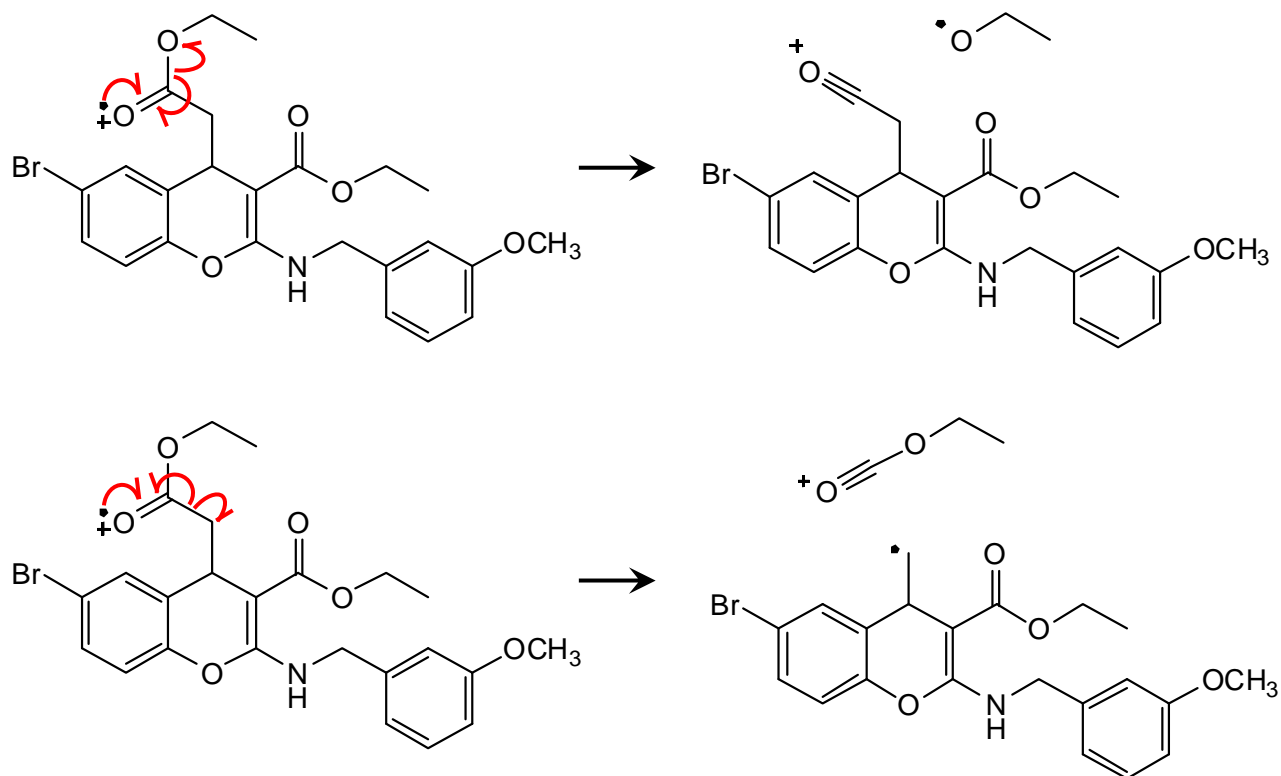
*Full credit for any  $m/z = 218$  product that could come from your  $m/z = 306$  ion.*

*In other words, you don't need to get the first 6 points to get the second six.*

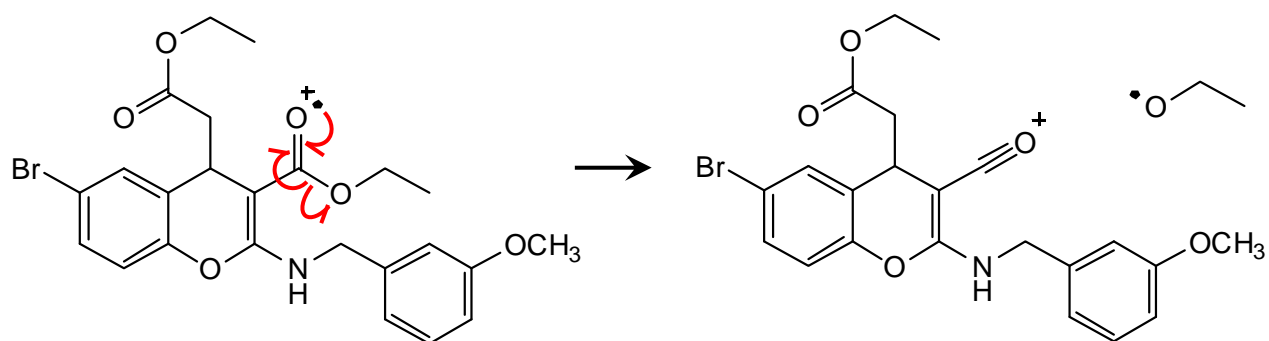
6 points for paired-electron mechanism (using double-barbed arrows) that connects the two.

*No partial credit for a radical mechanism here. Even-electron ions do not fragment via radical reactions.*

12. There are a number of ways that molecule 1 might fragment via  $\alpha$ -cleavage. I think the most prominent will be via ionization at oxygen lone pairs:



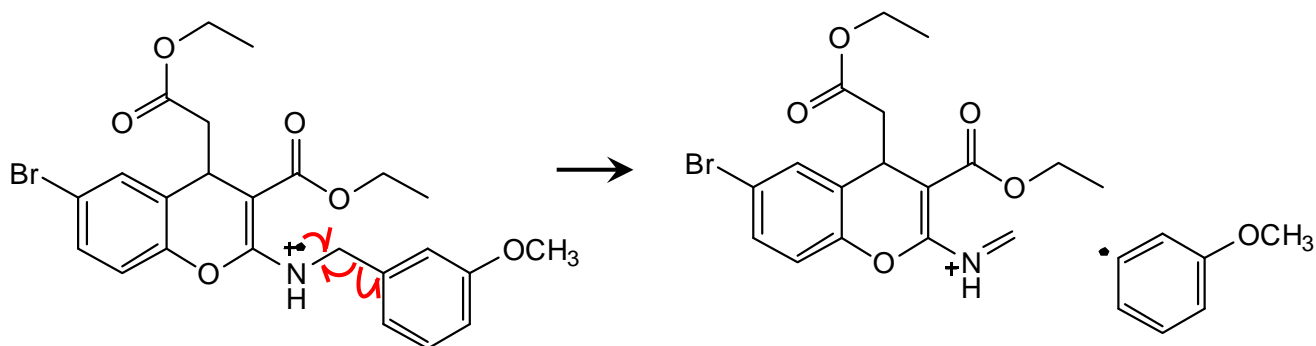
(You could also draw the above mechanism from a radical cation on the single-bonded oxygen. That would be fine.)



(And others.)

A couple of you drew ionization at nitrogen (as shown on the next page). I don't think this is as likely—partly because the nitrogen lone pair is conjugated (so it's

really a “ $\pi$ ” pair of electrons rather than an “ $n$ ” pair), and partly because  $\alpha$ -cleavage doesn't generate a terribly stable radical product—but we gave partial credit for it.



Rubric for  $\alpha$ -cleavage part: 9 points total this part.

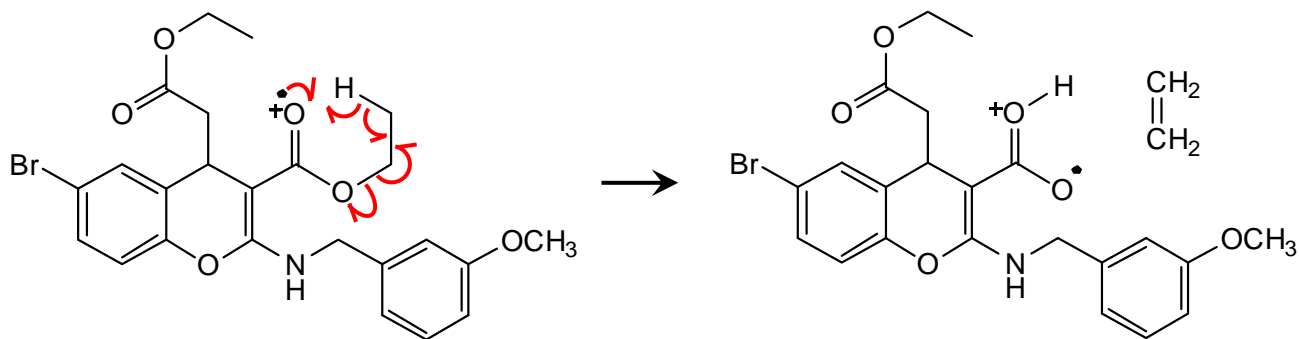
3 points for drawing an oxygen-centered radical cation of molecule 1.

1 point partial for any other radical cation.

6 points for drawing a radical mechanism—with single-barbed arrows—that illustrates an  $\alpha$ -cleavage from your radical cation.

-2 points for each structural error, including omitting a charge, radical, or arrow.

The McLafferty rearrangement is a 6-centered electrocyclic rearrangement that is common for carbonyl compounds with  $\gamma$ -protons. Here, McLafferty rearrangement could occur at either ester:



In my opinion, there are a number of ways to push the electrons in the McLafferty rearrangement; you can push single electrons as I have above, you can push pairs of electrons such that the mechanism looks like a 6- $e^-$  electrocyclic rearrangement, as long as you (i) break two bonds, (ii) eliminate an alkene, and (iii) end up with a new radical cation (and don't end with the radical and cation going separate ways).

Rubric for McLafferty part: 9 points total this part.

3 points for drawing an oxygen-centered radical cation of molecule 1.

*1 point partial for any other radical cation.*

6 points for drawing a mechanism—with single- or double-barbed arrows, either one works here—that illustrates a McLafferty rearrangement from your radical cation.

*-2 points for each structural error, including omitting a charge, radical, or arrow.*