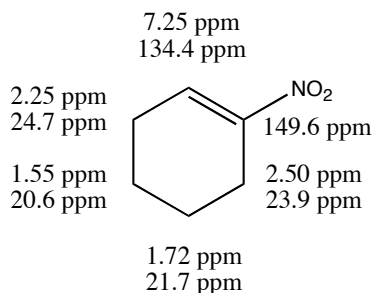


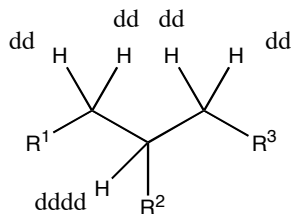
Answers/Suggested Solutions to Saturday May 7 Problem-Solving Session Problems

1. (Discussed on Saturday) – The MeO group is at the 5-position of the indole ring.

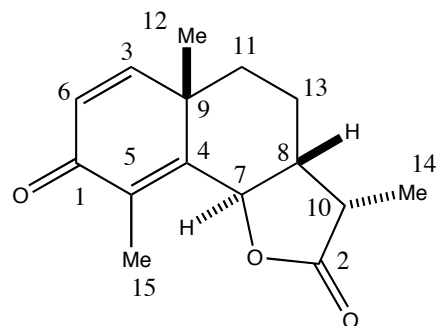
2. (Discussed on Saturday):



3. (Discussed on Saturday) – The spin system is

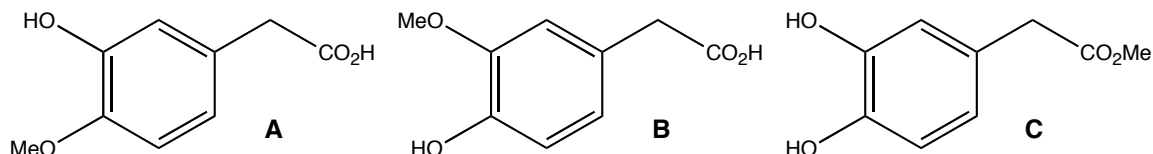


4. a. C=O and O–C=O (given) + 3 C + 5 CH + 2 CH<sub>2</sub> + 3 CH<sub>3</sub> gives C<sub>15</sub>H<sub>18</sub>O<sub>3</sub>. IHD = 7.  
 b. 7 – 2 (C=O's) = 5. From <sup>13</sup>C spectrum, 4 C=C (between 125 and 155 ppm). Therefore, there are 3 rings in the unknown.  
 c. The compound is **santonin**. The natural stereochemistry is shown, which cannot be deduced from the INADEQUATE spectrum.



5. (Discussed on Saturday) – The structure is definitely a trisubstituted aromatic ring (C<sub>6</sub>H<sub>3</sub>, with substituents in a 1,2,4 relationship (splitting pattern in <sup>1</sup>H NMR), and has an MeO group (CH<sub>3</sub>O) an isolated CH<sub>2</sub>, and an O–C=O group (<sup>13</sup>C spectrum), giving a partial MF of C<sub>9</sub>H<sub>8</sub>O<sub>3</sub> and partial MW of 164, leaving 18 amu unaccounted for. H<sub>2</sub>O most easily accounts for this, which means that 2 of the H in the molecule are exchangeable, since only 8 are observed in the <sup>1</sup>H NMR.

Since all of the chemical shifts are upfield of 7.0 ppm (unusual), it is likely that two RO groups (MeO or OH) are directly attached to the aromatic ring and that the electron-withdrawing O–C=O group is not for reasons we discussed. Since that leaves one remaining substituent for the aromatic ring, and since only the isolated CH<sub>2</sub> group is left, it can satisfy the above by being attached to both the ring and the O–C=O. In other words, our unknown is one of the following:



Personally, I'm not convinced one can conclusively differentiate among these three with the available data. The best way I can think of to do so quickly is a 1-D nOe DIFF experiment, by irradiating on the Me singlet. Compound **A** would show an nOe to the aromatic doublet at 6.75 ppm and no other non-exchangeable protons. Compound **B** would show an nOe to only the doublet at 6.85 ppm, and finally Compound **C** would likely show an nOe to the isolated CH<sub>2</sub> and possibly weak ones to the aromatic d and the aromatic dd (but I doubt it).

(Incidentally, the reason I am not certain of the structure is because it was taken from another class, and the answer given in the solution that I could track down is that the unknown is 1-hydroxy-2-methoxyphenylacetic acid, OH ortho to the CH<sub>2</sub>CO<sub>2</sub>H and MeO meta. This is impossible because of the splitting pattern in the <sup>1</sup>H NMR.)

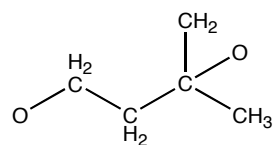
6. Many possible ways to solve this one. The <sup>13</sup>C shows 6 signals (C<sub>6</sub>), an O=C=O (probably), 2 C-O (probably), and three others. The HMQC tells us that one of the C-O is a CH<sub>2</sub>O. The <sup>1</sup>H NMR tells us that one of the C is an isolated CH<sub>3</sub>. Combining information from these two spectra tells us that the 36 ppm C is a CH<sub>2</sub> (integration = 2), as is the 45 ppm C.

From these spectra we have a partial MF of C=O + C-O (quaternary) + CH<sub>2</sub>O + CH<sub>2</sub> + CH<sub>2</sub> + CH<sub>3</sub> = C<sub>6</sub>H<sub>9</sub>O<sub>3</sub>, which has a partial MW of 129, 1 amu short of the value provided, i.e. one additional H that could be the broad signal at about 2.5 ppm in the <sup>1</sup>H NMR. The IHD for C<sub>6</sub>H<sub>10</sub>O<sub>3</sub> is 2. One is accounted for by the C=O. Since there is no evidence of π bonds in the <sup>13</sup>C, we have a cyclic compound, possibly a lactone or possibly a cyclic carboxylic acid.

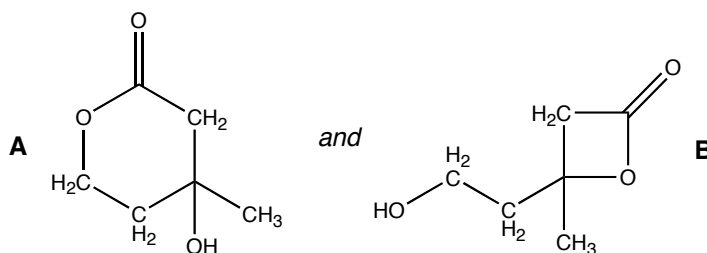
The TOCSY tells us that two of the CH<sub>2</sub> are connected because the cross peaks are very strong. It also suggests that the other 2 H visible are isolated, coupled only to each other – an AB quartet that is distorted by a broad peak at about 2.5 ppm (could be OH in molecule if not fully exchanged (see above); could also be H<sub>2</sub>O in the sample).

So our pieces are CH<sub>2</sub>-CH<sub>2</sub> (with one (and only one) of the CH<sub>2</sub> attached to oxygen), isolated CH<sub>2</sub> (definitely not connected to oxygen since chemical shift is less than 3.0 ppm), isolated CH<sub>3</sub> (definitely not attached to O, i.e not a Me ester or MeO in general), and an a remaining H, an isolated C-O and a O=C=O.

The only way to isolate the CH<sub>3</sub> without attaching it to an O is to connect the isolated C-O and the CH<sub>3</sub>. Same reasoning for the non-O-connected CH<sub>2</sub>, the isolated one and the one that is part of the O-CH<sub>2</sub>CH<sub>2</sub> fragment. Taken together, we are left with only the C=O and the following partial structure:



We also know that this must be a cyclic compound and that the “hanging” CH<sub>2</sub> group must be attached to the C=O in order to isolate it without attaching it to an O. Since we know that this C=O is part of an O=C=O, it must be connected to one of the O atoms. There are now only two possible structures that can be constructed, both lactones:



Reasons that the unknown is most likely **A**: The chemical shift of the most downfield CH<sub>2</sub> is typical of ester CH<sub>2</sub> groups (e.g. EtOAc has a 2H quartet at about 4.2 ppm) and not of CH<sub>2</sub> in

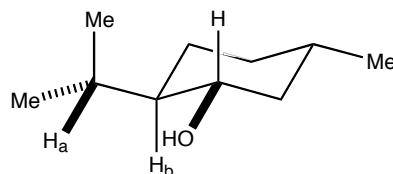
primary alcohols. Also, one would not expect the coupling pattern of this CH<sub>2</sub> in structure **B** – the *J* values would be closer to 7 Hz, and since this group is separated by a CH<sub>2</sub> from the stereogenic center and can freely rotate, it's possible that it would appear as a 2H t (if not coupled to the O–H), i.e. that the two H of this CH<sub>2</sub> would appear to be chemically equivalent. In contrast, since it is in a ring in **A**, there is likely to be greater variation in the *J* values for this reason alone.

The easiest way I can think of to differentiate conclusively between these two is IR. They should be very different in their C=O stretch values: About 1735 vs. about 1840 cm<sup>-1</sup>.

7. (Discussed on Saturday) – The unknown is 2-chloronaphthalene.

“8.” The unknown that we discussed in class that we postponed until the Saturday session was **menthol**.

This is a very challenging case with the data provided because so many of the resonances in the <sup>1</sup>H are close in chemical shift and coupled to one another and because a critical coupling is not visible in the COSY and is not particularly intense in either TOCSY, that between H<sub>a</sub> and H<sub>b</sub>, probably because the dihedral angle between the C–H<sub>a</sub> and C–H<sub>b</sub> bonds is between 60 and 90°, closer to the latter. Such a conformation avoids 1,3-strain between either of the *i*-Pr Me groups and the C–O bond.



What we were going to discuss on Saturday, but didn't because of time limitations (and because I thought the other problems were more instructive), was how arrive at one of two structures, make a guess based on the TOCSY, and then use a NOESY to differentiate between these two possibilities.

I hope Saturday was effective and helpful. Good luck on the exam!