Heterocyclic Chemistry - Midterm

May 3rd, 2005

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Department of Chemistry
The Scripps Research Institute

Name: _____

Last 4 digits of your Social Security #: _____

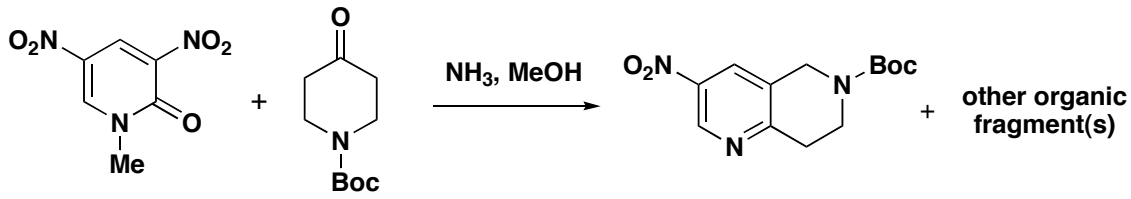
This is an "open-notes" exam designed to last 2 hours that you have 4 hours to complete
Definition of "open notes": Only handwritten notes (from lectures and any other source), no copies allowed. Lecture summaries are the only handouts permitted during test.

Please present ONLY your FINAL answers on these sheets

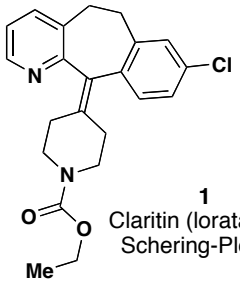
Question 1	**<**	**(15 points)**
Question 2	**<**	**(40 points)**
Question 3	**<**	**(15 points)**
Question 4	**<**	**(15 points)**
Question 5	**<**	**(15 points)**
Question 6	**<**	**(40 points)**
Question 7	**<**	**(15 points)**
Question 8	**<**	**(75 points)**
Question 9	**<**	**(20 points)**
Question 10	**<**	**(10 points)**
Question 11	**<**	**(25 points)**
Question 12	**<**	**(75 points)**
Bonus Question	**<**	**(25 points)**

Total _____ **out of 350 points**

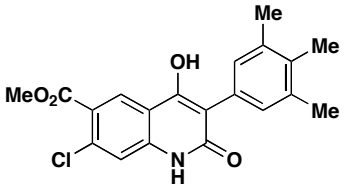
Question 1 (15 points). The following pyridine synthesis has been reported by Tohda (*Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820-2827). Provide a plausible mechanism for this complex transformation.



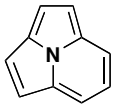
Question 2 (40 points). Provide practical synthetic routes to the following heterocycles (10 points each):



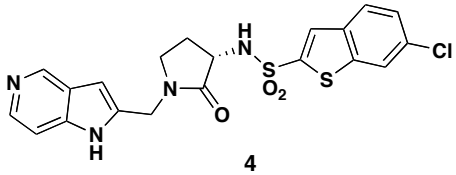
1
Claritin (loratadine)
Schering-Plough



2
(*J. Med. Chem.* **2001**, *44*, 917.)



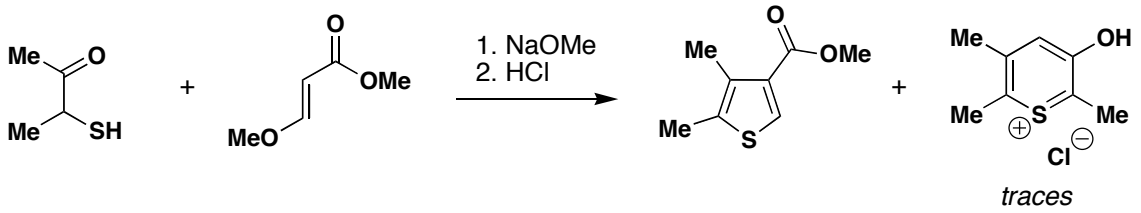
3
(3.2.2)cyclazine



4
(*J. Med Chem.* **2003**, *46*, 681.)

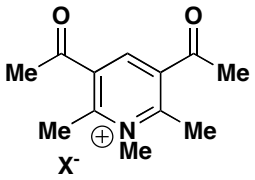
Question 3 (15 points). In 2004, the top 10 best selling drugs were Lipitor, Zocor, Zyprexa, Norvasc, Erypo, Prevacid, Nexium, Plavix, Advair, and Zoloft. Provide a synthetic route to any 3 of them.

Question 4 (15 points). During the process-scale synthesis of Latitude (silthiofam), researchers isolated a thiopyrylium byproduct in trace quantities. Propose a mechanism for its formation.

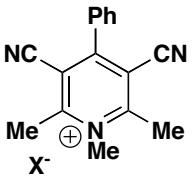


traces

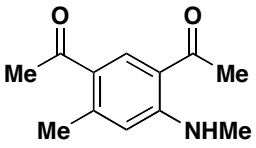
Question 5 (15 points). When **1** and **2** are treated with ethanolic NaOH for 1 hour, **3** and **4** are formed respectively. Provide mechanisms for these conversions. Note: There are no typos in the structures.



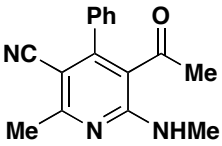
1



2

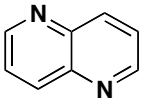


3

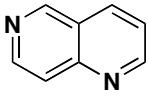


4

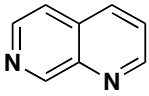
Question 6 (40 points). Derive syntheses of the four isomers of naphthyridine and benzo[4,5]furopyridine from pyridine (5 points each).



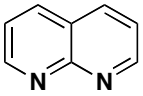
1,5-naphthyridine



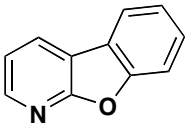
1,6-naphthyridine



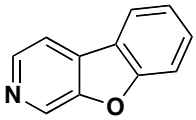
1,7-naphthyridine



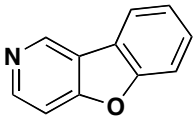
1,8-naphthyridine



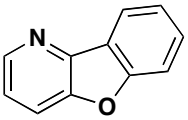
benzo[4,5]furo
[2,3-*b*]pyridine



benzo[4,5]furo
[2,3-*c*]pyridine

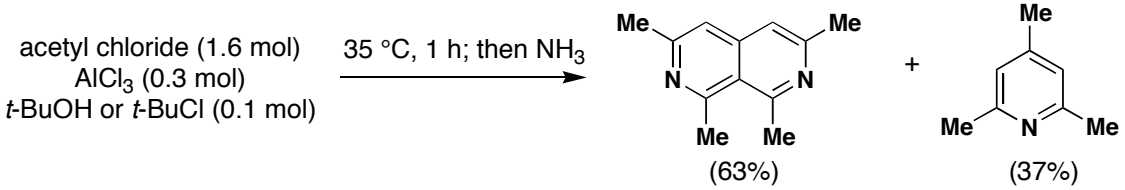


benzo[4,5]furo
[3,2-*c*]pyridine

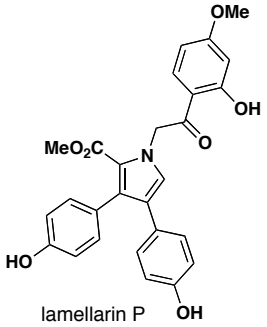


benzo[4,5]furo
[3,2-*b*]pyridine

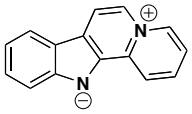
Question 7 (15 points). Propose a detailed mechanism for the following one-pot synthesis of 1,3,6,8-tetramethyl-2,7-naphthyridine and 2,4,6-trimethylpyridine.



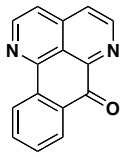
Question 8 (75 points). Propose total syntheses of the following natural products via aromatic heterocycles (15 points each).



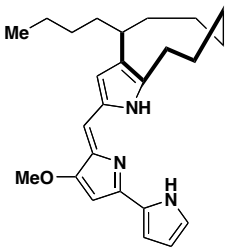
lamellarin P



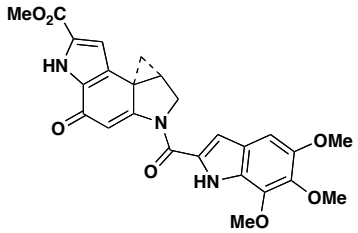
sempervirine



sampangine

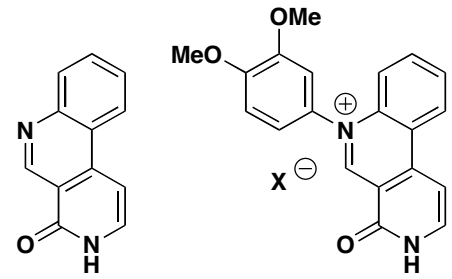


butylcycloheptylprodigiosin



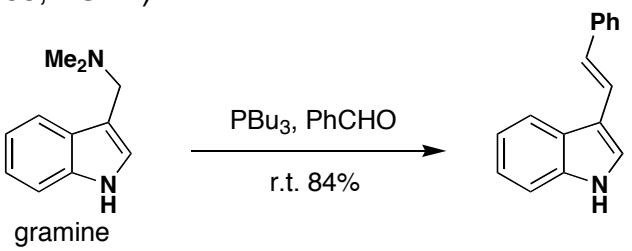
duocarmycin SA

Question 9 (20 points): Perlolidine (**1**) and perloline (**2**) have been discovered in various species of grass. 1. Propose a synthesis of perolidine (**1**) from simple starting materials, 2. Propose a plausible biomimetic synthesis of **1** from tryptamine, 3. Suggest a strategy for the conversion of **1** to **2**.

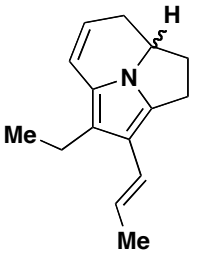


1: perlolidine **2**: perloline

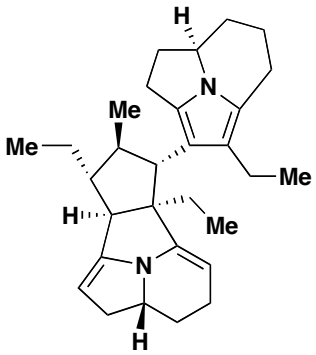
Question 10 (10 points): Provide a mechanism for the following conversion reported recently by Magdomenov (*Org. Lett.* **2005**, ASAP).



Question 11 (25 points). Propose a total synthesis of myrmicarin 213. Suggest conditions or a strategy for accessing myrmicarin 430 from myrmicarin 213 and support your proposal with a mechanism.



myrmicarin 213



myrmicarin 430

Question 12 (75 points). Deduce the structures of the following heterocycles (5 points each).

A. ($C_9H_6OS_2$) Obtained upon treatment of thiophene with *n*BuLi, then CO_2 then with P_2O_5 and thiophene.

B. ($C_6H_4N_4S$) Obtained by reacting $(NC)_2C=C(CN)_2$ with H_2S.

C. ($C_{15}H_{13}NO$) Obtained by reacting DMFDMA with 2-benzyloxy-6-nitrotoluene then treating the resulting product with H_2/Pt.

D. ($C_9H_8N_2O_2$) Formed when 2-methyl-5-nitropyridine is reacted with bromoacetone and subsequent treatment with $NaHCO_3$.

E. ($C_{16}H_{11}NO_2$) From isatin/NaOH, then acetophenone.

F. ($C_9H_7NO_3$) From 4-fluoronitrobenzene with $Me_2C{=}NONa$ then HCl/heat.

G. ($C_{18}H_{19}NO$) From 3-methylindole and 2-hydroxy-3,5-dimethylbenzyl chloride.

H. ($C_{11}H_{15}NO_3$) By reaction of $MeCOCH_2CO_2Et$ with HNO_2, then a combination of Zn/AcOH and pentane-2,4-dione.

I. ($C_5H_6N_2O_2$) Major product obtained upon treatment of 2-methylpyrrole with Ac_2O/HNO_3

J. ($C_{10}H_{10}N_2O$) Obtained by mixing phenyl hydrazine and methyl acetoacetate and heating.

K. ($C_9H_{12}N_2$) Two isomers (show both) obtained upon treating 4-bromopyridine with sodium *tert*-butoxide and pyrrolidine.

L. ($C_{10}H_6NOCl$) By reaction of acetanilide and $POCl_3$ in DMF.

M. (C_6H_7NO) Obtained upon treatment of 2-acetyfuran with ammonia.

Bonus Question (25 points):

The following is the authentic transcript of a conversation that took place at the Welch Foundation Conference in 1974 between Professor Heck and Professor Brown. For 10 points, can you deduce what amine Professor Brown is talking about? For another 10 points, propose a synthesis of this amine.

Dr. Herbert C. Brown (Speaker), *Purdue University:* I was going to discuss on a comment of yours a moment ago. You said that you would like very much to know an amine which reacts with acid, but doesn't react with methyl iodide. I was amazed that you could make such a request here, with a thousand organic chemists present, and no one came forth to suggest one for you.

We described such a base, ? back in 1953.

Dr. Heck: I don't think it will work because it's too weak a base.

Dr. Brown: But you said you want an amine that would react with protons but would not react with methyl iodide, and ? is such an amine.

Dr. Heck: We have used a tetramethylpiperidine and that's not as hindered. It reacts with methyl iodide, apparently.

Dr. Brown: But, ? is a very nice base to know. At one time, when I taught advanced inorganic chemistry, one of the topics was G. N. Lewis' approach to acids and bases. I used to point out that if one had cylinders of HCl and BF_3 which were not labeled, it would be difficult to distinguish between them by a test for an acid which HCl would give, but which BF_3 would not. At that time there was no such test. However, the discovery of ? provides such a test — this base neutralizes HCl, but not BF_3. It differentiates between the two acids in terms of their relative steric requirements.

Dr. Heck: And it won't react at 100 degrees with methyl iodide?

Dr. Brown: That is correct.

Dr. Heck: Thank you.

See *JACS* **1953**, *75*, 3865 for the answer.