Heterocyclic Chemistry – Final Exam

June 7th, 2005

Professor Baran
Department of Chemistry
The Scripps Research Institute

Name: _____

Any 4-digit number you will remember: _____

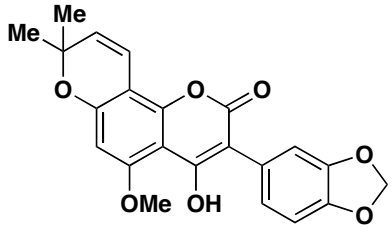
This is an "open-notes" exam designed to last 2 hours that you have 4 hours to complete
Definition of "open notes": Only handwritten notes (from lectures and any other source), no copies allowed. Lecture summaries are the only handouts permitted during test.

Please present ONLY your FINAL answers on these sheets

Question 1	**<**	**(100 points)**
Question 2	**<**	**(40 points)**
Question 3	**<**	**(20 points)**
Question 4	**<**	**(20 points)**
Question 5	**<**	**(30 points)**
Question 6	**<**	**(20 points)**
Question 7	**<**	**(40 points)**
Question 8	**<**	**(80 points)**
Bonus Question	**<**	**(25 points)**
Total		**out of 350 points**

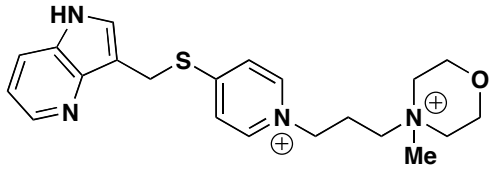
Question 1 (100 points). Provide syntheses of the following heterocycles from simple starting materials:

A.

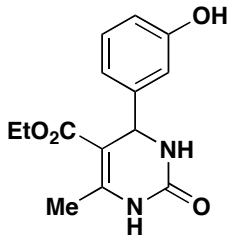


isorobustin

B.

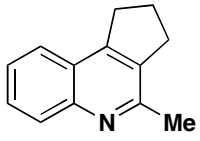


C.

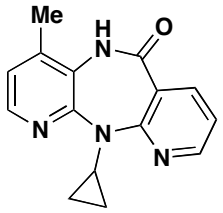


monastrol

D.



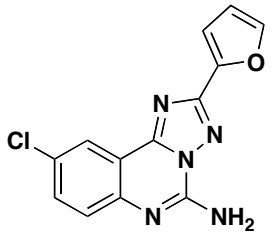
E.



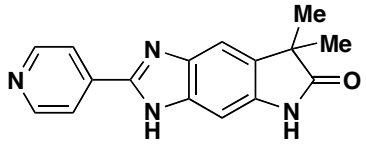
roxane

F. Indoxacarb

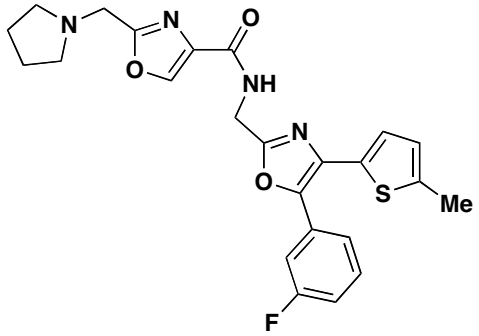
G.



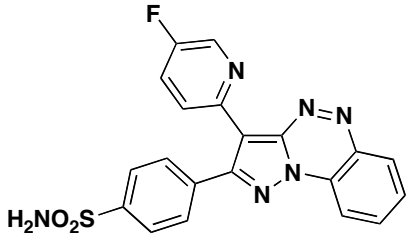
H.



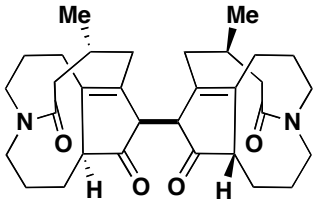
I.



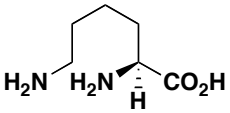
J.



Question 2 (40 points). Propose a biogenetic hypothesis for the formation of phlegmariurine C from L-lysine.

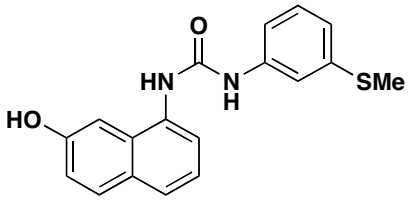


phlegmariurine C

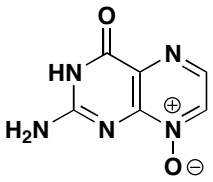


L-lysine

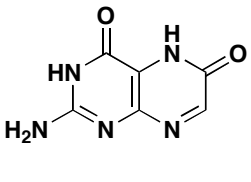
Question 3 (20 points). Based on the following HTS hit, provide a synthesis of five different analog scaffolds (each must differ in the ring systems used in the naphthalene core).



Question 4 (20 points). Paying attention to issues of regioselectivity, propose a synthesis of pterin 8-oxide (**1**). Treatment of **1** with a 1:1 mixture of TFA-TFAA (1 hour, 50 °C) followed by evaporation of solvent and exposure to NaOH followed by acidification gave xanthopterin (**2**) in quantitative yield. Provide a mechanism for the transformation of **1** to **2**.

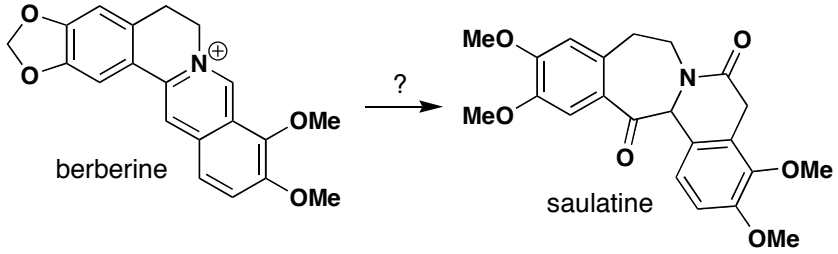


1

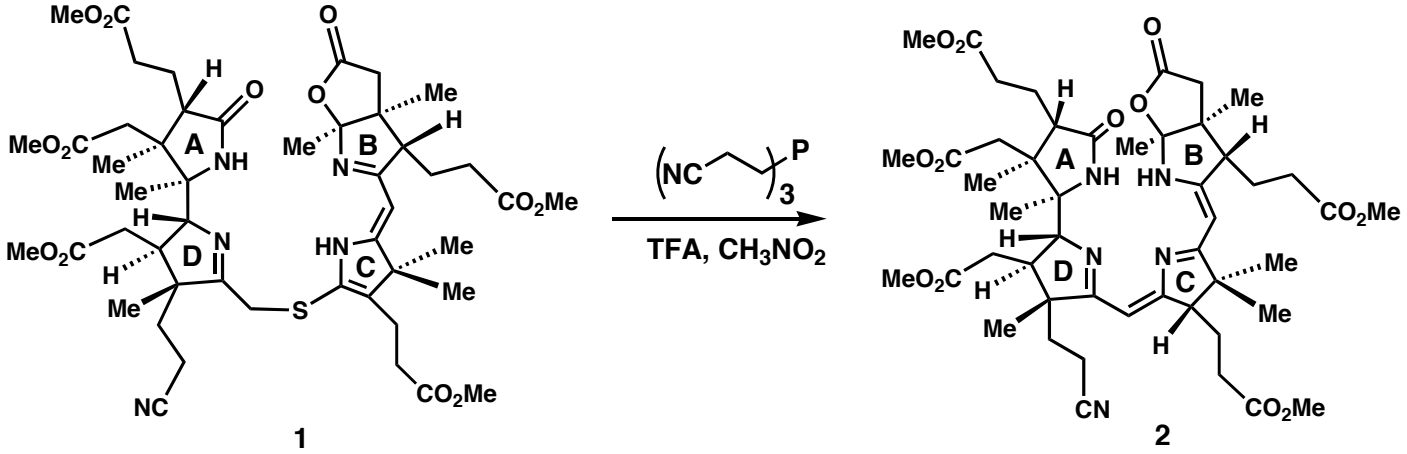


2

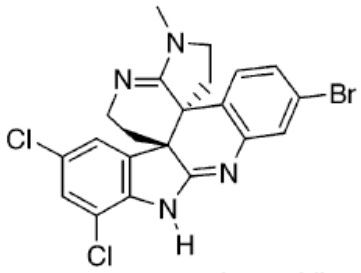
Question 5 (30 points). The Shamma group at Penn State has shown (*J. Nat. Prod.* **1986**, *49*, 398 – 405) that saulatine is not "natural" and is simply an artifact of isolation (silica gel chromatography using $CHCl_3$/MeOH). Provide a mechanism for its formation from the common alkaloid berberine (20 points). Also, describe the biosynthetic origin of berberine (10 points).



Question 6 (20 points). Provide a mechanism for the Eschenmoser sulfide contraction (**1** to **2**), which proceeds *via* a heterocycle we did not discuss in class.



Question 7 (40 points). Propose a biogenetic hypothesis and total synthesis for perophoramidine.



perophoramidine

Question 8 (80 points). Deduce the structures of the following heterocycles based on the clues provided.

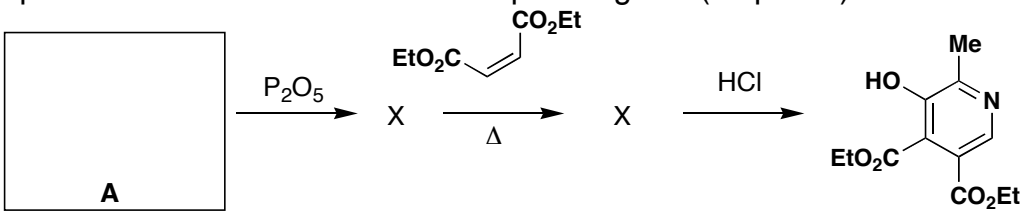
A. ($C_5H_8N_4S$) Derived from the condensation of thiourea and malonodinitrile (MeOH, MeONa), then treatment with MeI. (5 points)

B. ($C_3H_2N_4S$) By treatment of 2-hydrazinothiazole with nitrous acid. (5 points)

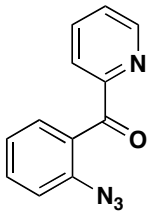
C. ($C_9H_{10}N_6O_2$) By the following sequence of transformations on 1,2-dimethyl-5-nitroimidazole: 1. DMFDMA, heat, 2. Ac_2O, heat, 3. guanidine. (10 points)

D. ($C_{12}H_{11}NO_3$) Formed upon reaction of benzoyl chloride and EtO_2CCH_2NC in the presence of KO-*t*-Bu. (5 points)

E. Identify compound **A** based on the reaction sequence given (10 points):

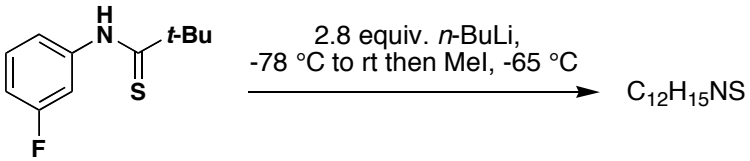


F. ($C_{12}H_8N_2O$) Formed by simply heating the following compound (5 points):

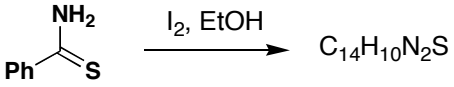


G. ($C_{13}H_9NO$) Derived from 2-chlorobenzophenone by treatment with hydroxylamine followed by 50% KOH in $MeO(CH_2)_2OH$ at reflux. (10 points)

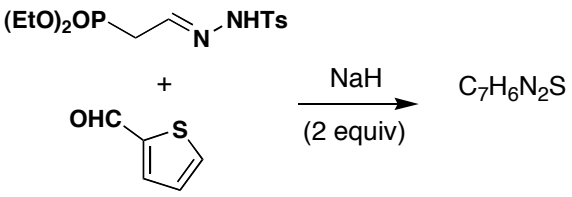
H. (10 points)



I. (10 points)

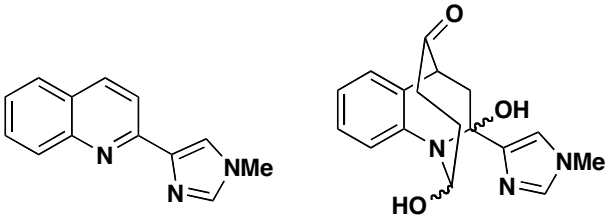


J. (10 points)



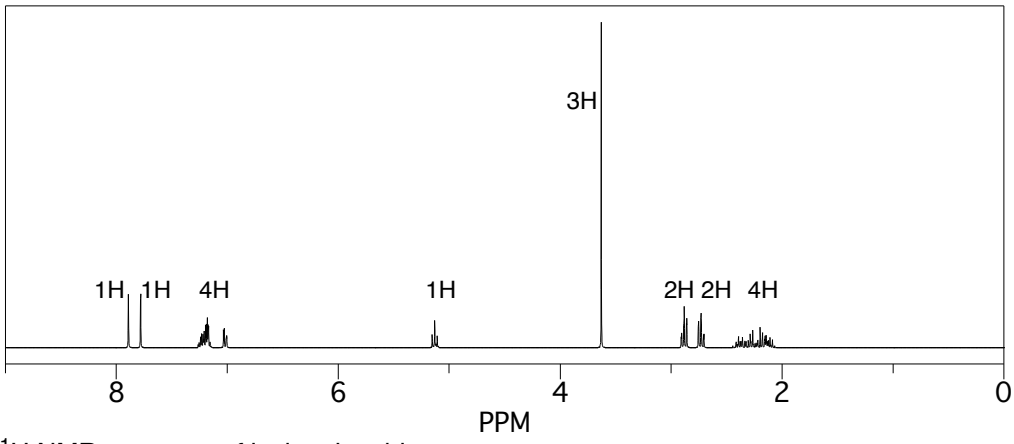
Bonus Question (25 points):

In 1976 Woodward revised the structure of isolongistrobine (*Tetrahedron* **1976**, *32*, 1085). This natural product could be converted into isomacrorine by treatment with 2:1 AcOH/HCl (concentrated) followed by oxidation. This was the biggest clue that the proposed structure was flawed since a reasonable mechanism could not be drawn for this conversion. Isolongistrobine could be further oxidized to dehydrolongistrobine (which now lacked the triplet at *ca* 5.1 ppm in the ^{1}H NMR). For 10 points, what is the real structure of isolongistrobine and dehydrolongistrobine? For 10 points, propose a total synthesis of these structures. Given that the natural products longistrobine and macrorine have the same molecular weight, what are their likely structures (5 points)?



isomacrorine

isolongistrobine
(proposed structure)



^{1}H NMR spectrum of isolongistrobine

It was a joy to have you all in class! Have a great summer!