

Heterocyclic Chemistry – Final Exam

June 6th, 2006

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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 _____ < (20 points)

Question 2 _____ < (50 points)

Question 3 _____ < (40 points)

Question 4 _____ < (20 points)

Question 5 _____ < (50 points)

Question 6 _____ < (60 points)

Question 7 _____ < (20 points)

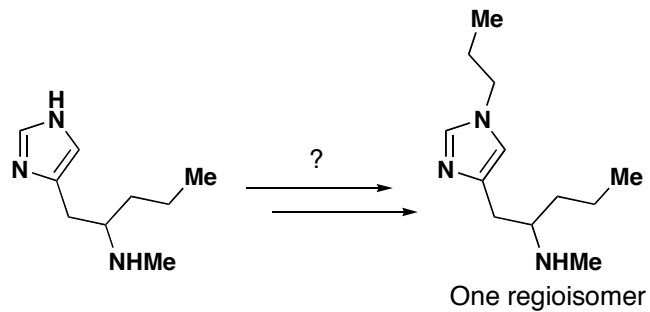
Question 8 _____ < (40 points)

Question 9 _____ < (50 points)

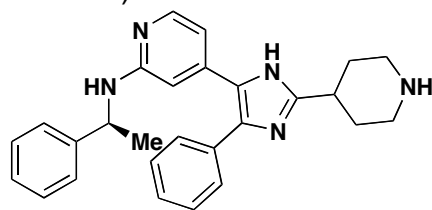
Bonus Question _____ < (25 points)

Total _____ out of 350 points

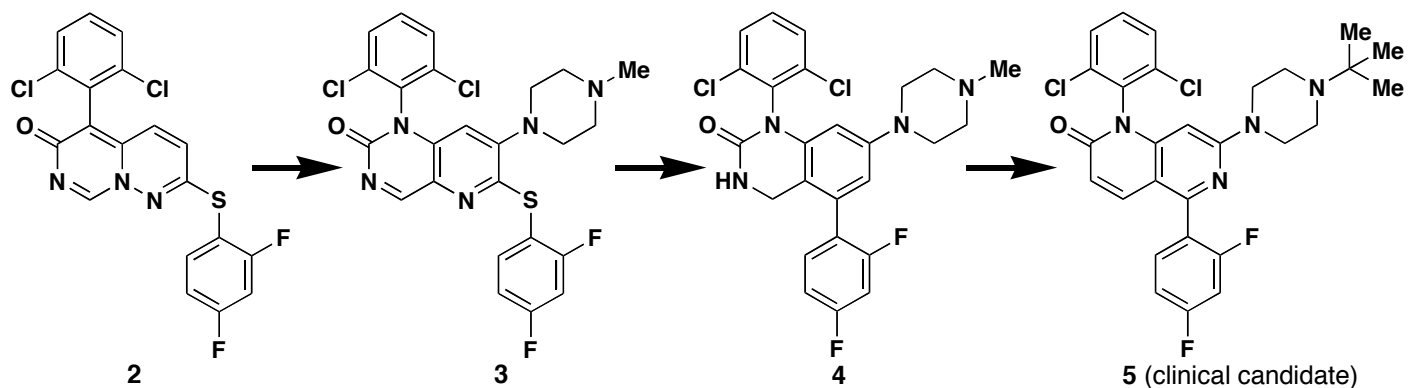
Question 1 (20 points). During a Pfizer study on potential treatments for thrombosis, a clever scheme was devised in order to selectively obtain one regioisomer of the following alkylated imidazole. Suggest a route which would give complete selectivity.



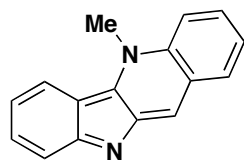
Question 2 (50 points). Please provide viable synthetic routes to the following evolution of p38 inhibitors from Merck (**1-5**, 10 points each):



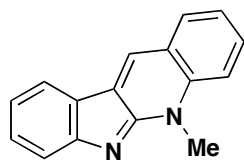
lead molecule (1)



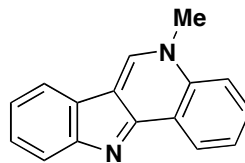
Question 3 (40 points). Provide viable routes to the following antimalarial agents (10 points each).



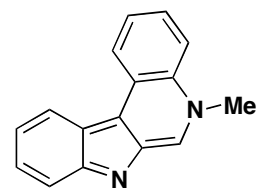
cryptolepine



neocryptolepine

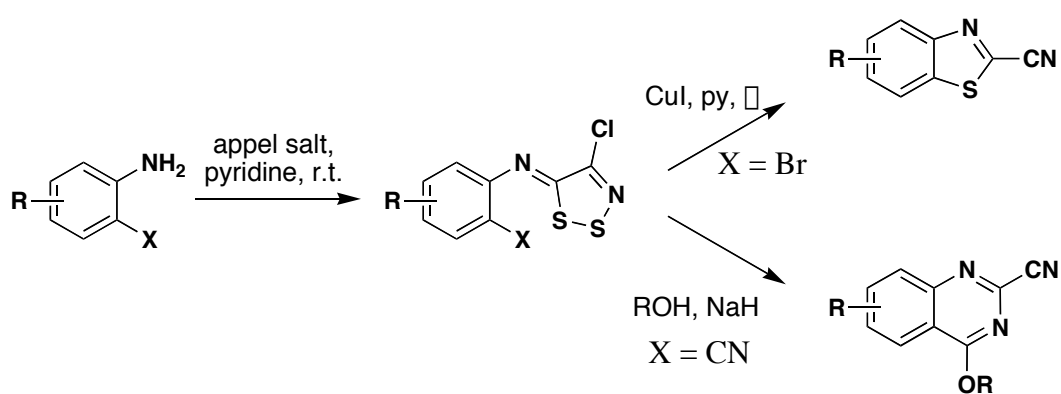
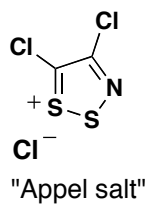


isocryptolepine

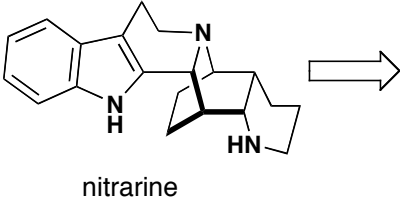
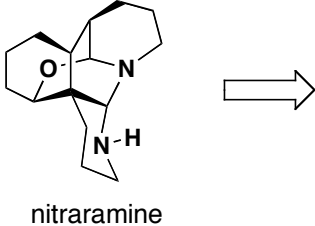


isoneocryptolepine

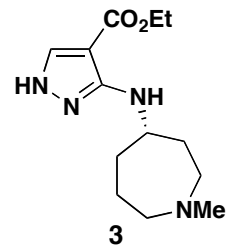
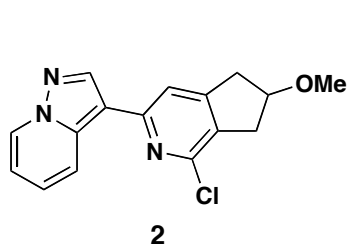
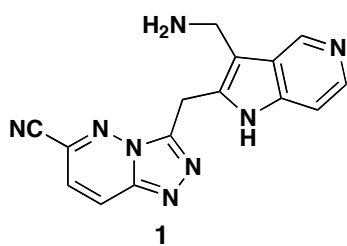
Question 4 (20 points). Propose mechanisms for the formation of benzothiazoles and quinazolines using a heterocycle you probably have never seen before: "Appel Salt".



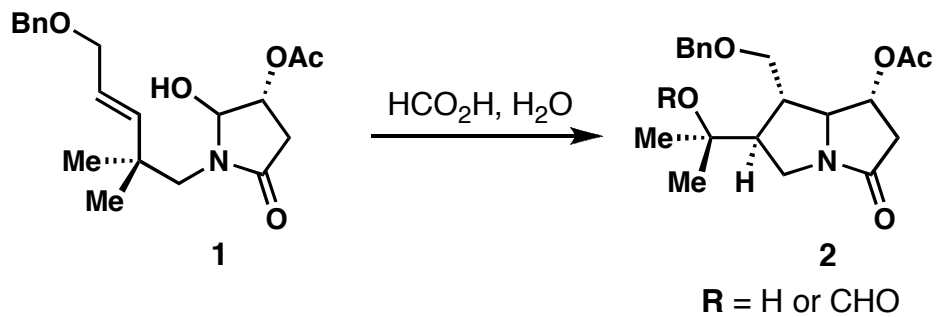
Question 5 (50 points). Show how nitramine and nitrarine are derived from L-lysine in Nature (25 points each).



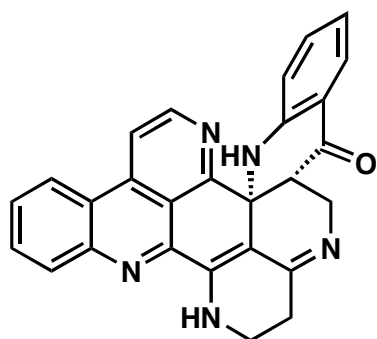
Question 6 (60 points). Propose syntheses of the following nitrogen-rich, medically relevant compounds (20 points each).



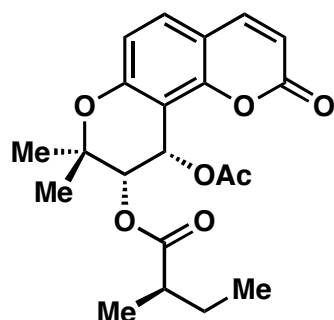
Question 7 (20 points). Please write a logical mechanism for the transformation 1 → 2.



Question 8 (40 points). Propose total syntheses of the following natural products via aromatic heterocycles (20 points each).



Eudistone A



(9S,10S)-(-)-Visnadin

Question 9 (50 points). Deduce the structures of the following heterocycles (5 points each).

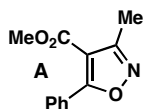
1. Ethyl acetoacetate, 3-hydroxybenzaldehyde, and thiourea are refluxed in THF for 12 hrs with a catalytic amount of ytterbium triflate (0.1 equiv.). $C_{14}H_{16}N_2O_3S$

2. 2-Bromo-nitrobenzene is treated with 3 equiv. vinyl magnesium chloride in THF at $-70\text{ }^\circ\text{C}$ and stirred for 3 hours. C_8H_6NBr

3. 3-Phenylpyridine is refluxed with sodium amide in toluene. $C_{11}H_{10}N_2$.

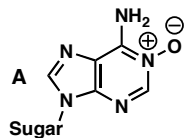
4. 3-Aminoacetanilide is heated with vinyl phenyl ketone in acetic acid. $C_{17}H_{14}N_2O$

5. Isoxazole **A** is treated with Raney Nickel and hydrogen, followed by P_4S_{10} and chloranil. $C_{12}H_{11}NO_2S$



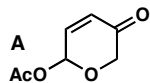
6. Ethyl cyanoaminoacetate is heated neat with methyl phenyl-dithioacetate. $C_{13}H_{14}N_2O_2S$

7. Pyrimidine **A** is treated with i) dimethylsulfate, ii) dimethylamine, and then iii) refluxed in methanol with dimethylammonium iodide. $C_6H_6N_5O$



8. Histidine is treated with acetic anhydride and pyridine. $C_9H_{12}N_3O_2$

9. Pyran **A** is heated with acrolein. $C_8H_8O_3$



10. 3-Oxo-benzofuran is heated with isatin-7-carboxylic acid in an aqueous solution of potassium hydroxide. $C_{17}H_9NO_5$

Bonus Question (25 points): Propose a plausible biosynthetic hypothesis for the natural product eilatin from tryptophan and catechol. For the answer, see *Tetrahedron Lett.* **1993**, 1827 – 1830.

