Heterocyclic Chemistry – Final Exam

June 7th, 2005

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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  ____< (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.  

```
  O
  Me
  O
  Me
  Me
  O
  Me
  Me

isorobustin
```

B.  

```
  HN
  \[\text{Ring} \]\n  S
  \[\text{Ring} \]\n  N
  \[\text{Ring} \]
  O
  Me
```

C.  

```
  OH
  EtO₂C
  NH
  Me
  N
  H

monastrol
```

D.  

```
  \[\text{Ring} \]
  Me
```
E. Indoxacarb

G. Indoxacarb

H. Indoxacarb
Question 2 (40 points). Propose a biogenetic hypothesis for the formation of phlegmariurine C from 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.
**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 CHCl₃/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.
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 Mel. (5 points)

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

C. \((C_9H_10N_6O_2)\) By the following sequence of transformations on 1,2-dimethyl-5-nitroimidazole: 1. DMFDMA, heat, 2. Ac₂O, heat, 3. guanidine. (10 points)

D. \((C_{12}H_{11}NO_3)\) Formed upon reaction of benzoyl chloride and EtO₂CCH₂NC in the presence of KO-t-Bu. (5 points)

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

```
A \(\xrightarrow{P_2O_5} \xrightarrow{\Delta} \xrightarrow{\text{HCl}}\)
```

```
\[
\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{CO}_2\text{Et}
\end{array}
\]
```

```
\[
\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{CO}_2\text{Et}
\end{array}
\]
```

```
\[
\begin{array}{c}
\text{Me} \\
\text{HO}
\end{array}
\]
```

```
\[
\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{CO}_2\text{Et}
\end{array}
\]
```

```
\[
\begin{array}{c}
\text{EtO}_2\text{C} \\
\text{CO}_2\text{Et}
\end{array}
\]
```
F. \( \text{C}_{12} \text{H}_8 \text{N}_2 \text{O} \) Formed by simply heating the following compound (5 points):

\[
\text{H}N\text{Bu}_2\text{S}_2\text{eqquiv. } n\text{-BuLi, -78 °C to rt then MeI, -65 °C} \rightarrow \text{C}_{12} \text{H}_6 \text{NS}
\]

G. \( \text{C}_{13} \text{H}_9 \text{NO} \) Derived from 2-chlorobenzophenone by treatment with hydroxylamine followed by 50% KOH in MeO(CH\(_2\))\(_2\)OH at reflux. (10 points)

H. (10 points)

I. (10 points)

J. (10 points)

\[
\text{EtO}_2\text{OP} + \text{HNTs} + \text{OHC} \rightarrow \text{C}_{7} \text{H}_6 \text{N}_2 \text{S} \text{NaH (2 equiv)}
\]
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 ^1H 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)?

\[ \text{Isomacrorine} \quad \text{Isolongistrobine (proposed structure)} \]

\[ \text{^1H NMR spectrum of isolongistrobine} \]

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