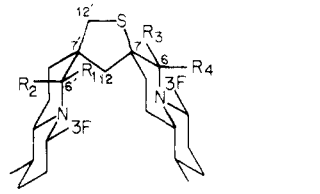
# Preparation and in Vitro Antifungal Activities of Some Quinolizidine Derived Hemiaminals and β-*tert*-Amino Sulfides[1]

Robert Thomas LaLonde,*[2] Amy Inn-Mei Tsai,[2] Chun Juan Wang,[3] Chunfook Wong,[2] and Gigi Lee[3]

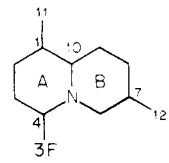
*Departments of Chemistry and Botany, College of Environmental Science and Forestry, State University of New York, Syracuse, New York 13210.* *Received May 30, 1975*

New α-thiohemiaminals, 7α-phenylthio-7-epideoxynupharidin-6-ol, the diasteriomeric 7β-phenylthiodeoxynupharidin-6-ol, and 3-methyl-3-methylthio-4-hydroxyquinolizidine, were prepared and reduced to the corresponding β-*tert*-amino sulfides. The configuration at C-7 of the β-*tert*-amino sulfides was determined by observing the direction of the solvent-induced shift of the C-7 methyl proton resonance. The configuration at C-7 of the new α-thiohemiaminals was established by correlation with the β-*tert*-amino sulfides and confirmed, in the case of the deoxynupharidine derivatives, by circular dichroism and ascertaining the stereochemistry of deuteride incorporation upon sodium borodeuteride reduction of the α-thiohemiaminal. The in vitro antifungal activities of six compounds possessing the quinolizidine skeleton, including all the newly synthesized compounds as well as some previously reported ones, and amphotericin B were tested against several human pathogenic fungi. Besides amphotericin B, only the two deoxynupharidine α-thiohemiaminals were active, especially against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. The observations indicate activity is derived from the 3-furyl group and the functionality from which α-thioimmonium ions can be produced.

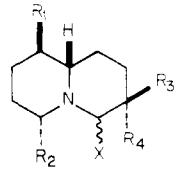
The in vitro activity of the naturally occurring bishemiaminal, 6,6'-dihydroxythiobinupharidine (1), against



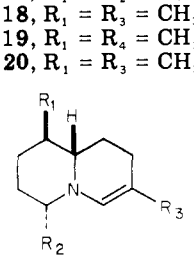
1, $R_1$, $R_2$ = H, OH; $R_3$, $R_4$ = H, OH



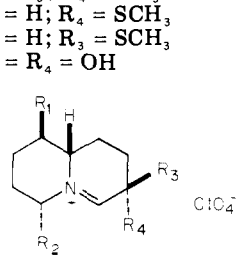
2



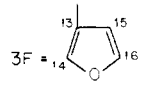
**3**, $R_1 = R_3 = CH_3$; $R_2$ = 3F; X = OH; $R_4 = SCH_3$
**4**, $R_1 = R_4 = CH_3$; $R_2$ = 3F; X = OH; $R_3 = SCH_3$
**5**, $R_1 = R_3 = CH_3$; $R_2$ = 3F; X = OH; $R_4 = SC_6H_5$
**6**, $R_1 = R_4 = CH_3$; $R_2$ = 3F; X = OH; $R_3 = SC_6H_5$
**7**, $R_1 = R_2$ = H; X = OH; $R_3$, $R_4 = CH_3$, $SCH_3$
**9**, $R_1 = R_3 = CH_3$; $R_2$ = 3F; X = H; $R_4 = SC_6H_6$
**10**, $R_1 = R_4 = CH_3$; $R_2$ = 3F; X = H; $R_3 = SC_6H_5$
**11**, $R_1 = R_3 = CH_3$; $R_2$ = 3F; X = β-D; $R_4 = SC_6H_5$
**12**, $R_1 = R_4 = CH_3$; $R_2$ = 3F; X = α-D; $R_3 = SC_6H_5$
**16**, $R_1 = R_2$ = H; X = H; $R_3 = SCH_3$; $R_4 = CH_3$
**18**, $R_1 = R_3 = CH_3$; $R_2$ = 3F; X = H; $R_4 = SCH_3$
**19**, $R_1 = R_4 = CH_3$; $R_2$ = 3F; X = H; $R_3 = SCH_3$
**20**, $R_1 = R_3 = CH_3$; $R_2$ = 3F; X = $R_4$ = OH



**8**, $R_1 = R_3 = CH_3$; $R_2$ = 3F
**15**, $R_1 = R_2$ = H; $R_3 = CH_3$



**13**, $R_1 = R_3 = CH_3$; $R_2$ = 3F; $R_4 = SC_6H_5$
**14**, $R_1 = R_4 = CH_3$; $R_2$ = 3F; $R_3 = SC_6H_5$
**17**, $R_1 = R_2$ = H; $R_3 = SCH_3$; $R_4 = CH_3$



several human pathogenic fungi[4] led us to synthesize and subsequently test simpler quinolizidine analogs containing the hemiaminal group. We report herein the preparation and some identifying chemical and physical properties characteristic of α-thiohemiaminals, an obscure class of compounds. Also we report the antifungal activities of newly synthesized α-thiohemiaminals as well as the antifungal activities of previously prepared, but untested, hemiaminals. Moreover we compare these properties with those of newly and previously prepared β-*tert*-amino sulfides. The antifungal activities were determined and compared in an attempt to ascertain the structural and functional components responsible for antifungal activity of Nuphar hemiaminals.

The atomic framework of the bishemiaminal **1**, as well as other stereoisomers of the thiaspirane Nuphar alkaloid series, consists of two deoxynupharidine skeletons, **2**, joined together directly by one C-12 to C-7' bond and indirectly through a sulfur atom by the C-12' to C-7 link.[5] The structurally abbreviated analogs **3**–**6** and **20** contain the hemiaminal function incorporated into a single deoxynupharidine moiety and, in one case, **7**, into a simple quinolizidine ring.

**Chemistry.** The α-methylthiohemiaminals **3** and **4** had been obtained by treating the enamine, (−)-6-dehydrodeoxynupharidine (**8**),[6] with methyl *p*-toluenethiosulfonate followed by chromatographic separation of the resulting mixture of two diastereomers.[5b] In a similar manner, the α-phenylthiohemiaminals **5** and **6** were obtained from **8** and phenyl benzenethiosulfonate. The most important spectral features of **5** and **6** are given in the Experimental Section and are consistent with the structures proposed.

The configuration at C-7 in the new pair of α-thiohemiaminals was determined in the same manner as it had been previously in the case of **3** and **4**.[5b] Thus the sodium borohydride reduction of **5** gave **9**. α-Thiohemiaminal **6** was first converted to the corresponding immonium perchlorate, **14** (vide infra), which, when treated with sodium borohydride, gave **10**. The presence of an equatorial C-7 methyl in **9** and an axial C-7 methyl in **10** was ascertained first by observing the direction of the benzene-induced shift of the C-7 methyl proton magnetic resonance ($^1$H NMR) signal. Relative to the chemical shift determined in deuteriochloroform, the C-7 methyl resonance of **9** was shifted upfield while the C-7 methyl resonance of **10** was shifted downfield. Consequently, a C-7 equatorial methyl was assigned to **9** and a C-7 axial methyl was assigned to **10**. The C-1 methyl resonances of **9** and **10** both were shifted upfield as expected. The direction of the benzene-induced shifts obserbed for equatorial and axial methyl resonances is typical of those which we have observed for several other methyl-substituted quinolizidines and piperidines of the Nuphar alkaloid class.[7]

The relative configuration at C-7 in **9** and **10** follows from the above described $^1H$ NMR observations and the presence of trans-fused quinolizidine rings as demonstrated by the appearance of Bohlmann infrared (ir) bands. These bands were observed to be as intense as those shown by (−)-deoxynupharidine. The absolute stereochemistry followed from the correlation of (−)-deoxynupharidine with (−)-6-dehydrodeoxynupharidine (**8**).[6]

Confirmation of the stereochemistry at C-7 in **5** and **6** came from two independent sources, the stereochemistry of the sodium borodeuteride reduction of the C-6 hemiaminal and the study of the circular dichroism (CD). Thus reduction of the hemiaminal **5** with sodium borodeuteride in methanol gave 7$\alpha$-phenylthio-7-epideoxynupharidine-6$\beta$-$d_1$ (**11**). The 100-MHz $^1H$ NMR of this sample revealed the C-6 equatorial proton ($\delta$ 3.21) as a broad singlet imposed on a doublet of a doublet, the latter portion of the signal resulting from geminal coupling to the residual C-6 axial proton and long-range W coupling to the C-8 equatorial proton. The doublet of a doublet portion of the signal amounted to approximately one-tenth of the total signal. Only a small remnant of the C-6 axial doublet at $\delta$ 1.71 could be detected but since it appeared in the region occupied by many other resonances an estimate of its integrated intensity was not possible. However, the $^1H$ NMR analysis of the $\delta$ 3.21 region showed that approximately 90% of the deuterium at C-6 must be axial. Thus sodium borodeuteride reduction of **5** gave **11** to the extent of 90%.

Similar sodium borodeuteride reduction of the immonium perchlorate, **14**, derived from **6** gave predominantly 7$\beta$-phenylthiodeoxynupharidine-6$\alpha$-$d_1$ (**12**). The C-6 equatorial proton, appearing at $\delta$ 2.87 as a doublet of a doublet in the $^1H$ NMR of **10**, was largely absent in the spectrum of **12**. Less than 0.1 proton could be detected in the $\delta$ 2.87 region. The C-6 axial proton appearing at $\delta$ 1.88 in the $^1H$ NMR of **10** collapsed to a singlet in **12**. Therefore the sodium borodeuteride reduction of the immonium perchlorate occurred in an equatorial fashion to an extent greater than 90%. Thus the sodium borodeuteride reductions of the $\alpha$-thioimmonium perchlorate of **6** and the $\alpha$-thiohemiaminal **5** were highly stereospecific, a result which, when correlated with our earlier findings,[5b] indicates the trans orientation of phenyl sulfide to deuterium atom.

In neutral solution, the hemiaminals **5** and **6** gave respectively relatively weak negative and positive CD bands at 260 nm ($\theta$ 2000–3000)[8] (Figure 1). These bands are attributed to the chiroptical properties of the C-7 phenyl sulfide group.[9,10] However, in acid solution the hemiaminal **5** displayed somewhat stronger new negative bands at 295 and 250 nm and a positive band at 276 nm. $\alpha$-Thiohemiaminal **6**, which is stereoisomeric with **5** at C-7, displayed in acid solution new positive CD bands at 295 and 270 nm and a very strong positive band at 246 nm (Figure 1). Their appearance and sign are consistent with $\alpha$-thioimmonium ion formation and the previously observed relation[11] between C-7 configuration and the sign of the CD band in the 290–310-nm region.

The crystalline perchlorates **13** and **14** were obtained from **5** and **6**, respectively, by treating the hemiaminals with aqueous perchloric acid. Evidence for the presence of the immonium ion was the observation of (1) the C=N$^+$ bands in the 5.95–6.05-$\mu$m region of the ir; (2) C-6 aldimmonium $^1H$ NMR signals in the region $\delta$ 7.55–7.85; and (3) C-6 aldimmonium $^{13}C$ nuclear magnetic resonance ($^{13}C$ NMR) signals at 172.6 and 172.4 ppm, respectively, for **13** and **14**. The position of the observed ir immonium absorption is typical[12] while the aldimmonium protons appear about 0.5 ppm upfield from those of similar aldimmonium ions.[13] The $^{13}C$ NMR resonances appear to fall in the right general region for doubly bonded carbon but appropriate models for comparison are lacking.

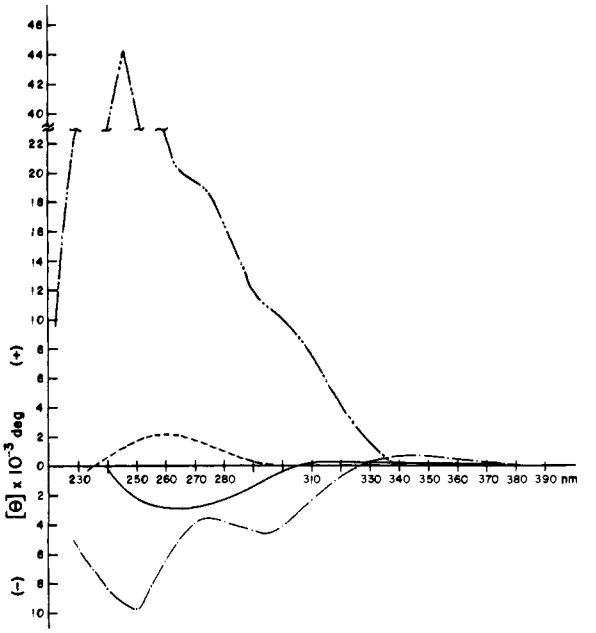



**Figure 1.** The circular dichroism of 7$\beta$-phenylthiodeoxynupharidin-6-ol (**6**) in acid solution (- · · -) and in neutral solution (- - -); and 7$\alpha$-phenylthio-7-epideoxynupharidin-6-ol (**5**) in acid solution (- · -) and in neutral solution (—).

3-Methyl-4-ketoquinolizidine was treated with diisobutylaluminum hydride according to the method of Bohlmann[14] to generate 3-methyl-3-dehydroquinolizidine (**15**) which, without isolation, was treated immediately with methyl *p*-toluenethiosulfonate to obtain 3-methyl-3-methylthio-4-hydroxyquinolizidine (**7**) consisting largely, if not entirely, of the 3$\beta$-methylthio isomer since reduction with sodium borohydride gave 3$\alpha$-methyl-3$\beta$-methylthioquinolizidine (**16**) as the only detectable product in 83% yield. The appearance of Bohlmann ir bands and the downfield shift of the methyl $^1H$ NMR signal upon changing the solvent from deuteriochloroform to deuteriobenzene indicated the axial C-3 methyl in a trans-fused quinolizidine. The $\alpha$-thiohemiaminal **7** in acid solution gave a band at 293 nm in the characteristic 290–310-nm ultraviolet region. Also the derived crystalline immonium perchlorate, **17**, showed a single absorption of the >C=N$^+$ < group in the appropriate spectral regions of ir, $^1H$ NMR, and $^{13}C$ NMR.

**Antifungal Properties.** Although the examination of the separate diastereomeric $\alpha$-thiohemiaminals and sulfides is of obvious interest, the study of mixtures of two diastereomers or the more readily available of two diastereomers was considered the most expeditious approach in the initial phase of exploring the antifungal activities. Accordingly, the $\alpha$-thiohemiaminals **6** and a mixture of **3** and **4**, the $\alpha$-hydroxyhemiaminal **20**, and the $\beta$-*tert*-amino sulfides comprised of a mixture of **11** and **12** and a mixture of **18** and **19** were tested immediately as they became available over the period of several months. In this first series of tests,[15] the activities of the above materials were determined against two isolates each of *Histoplasma capsulatum* and *Blastomyces dermatitidis* and one isolate each of *Sporotrichum schenckii*, *Tricophyton rubrum*, and *Microsporum gypseum*. Only the $\alpha$-thiohemiaminals, **6**,

Table I. Simultaneous Determination of the Sensitivities of *Histoplasma* and *Blastomyces* to Compounds 6, 3 and 4, 7, and Amphotericin B as Expressed by the Total Increments of the Colony Diameter (in mm)[a] on Sabouraud Dextrose Agar at 25°C (Mycelial Phase)

| | | *Histoplasma capsulatum* | | | | | | *Blastomyces dermatitidis* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Isolate 1098 | | | Isolate 1106 | | | Isolate 1099 | | | Isolate 1107 | | |
| Compd | μg/ml | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 6 | 100 | 0[b] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| | 80 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 3 | 7 |
| | 60 | 0 | 2 | 8 | 0 | 0 | 0 | 0 | 6 | 9 | 0 | 10 | 14 |
| | 40 | 6 | 9 | 13 | T[c] | T | 5 | T | 10 | 14 | T | 15 | 18 |
| | 20 | 8 | 14 | 18 | 6 | 11 | 15 | 7 | 14 | 18 | 7 | 18 | 22 |
| | 10 | 10 | 19 | 25 | 9 | 19 | 25 | 12 | 20 | 27 | 13 | 26 | 32 |
| 3 and 4 | 100 | 0 | 0 | 4 | 0 | 0 | 2 | 0 | 7 | 14 | 0 | 10 | 19 |
| | 80 | T | 4 | 8 | T | T | 5 | 7 | 11 | 17 | 7 | 14 | 17 |
| | 60 | T | 7 | 9 | T | 5 | 8 | 8 | 15 | 20 | 11 | 18 | 20 |
| | 40 | 6 | 10 | 11 | 7 | 12 | 18 | 11 | 20 | 27 | 17 | 24 | 26 |
| | 20 | 9 | 13 | 15 | 8 | 15 | 20 | 13 | 23 | 29 | 19 | 26 | 27 |
| | 10 | 10 | 17 | 22 | 13 | 22 | 27 | 16 | 25 | 35 | 18 | 28 | 32 |
| 7 | 100 | 8 | 15 | 30 | 9 | 17 | 26 | 13 | 25 | 33 | 16 | 31 | 40 |
| | 80 | 9 | 18 | 30 | 10 | 19 | 26 | 13 | 25 | 33 | 18 | 29 | 40 |
| | 60 | 9 | 18 | 30 | 10 | 19 | 27 | 13 | 25 | 32 | 20 | 31 | 40 |
| | 40 | 9 | 19 | 30 | 10 | 21 | 28 | 13 | 26 | 34 | 20 | 33 | 40 |
| | 20 | 10 | 18 | 31 | 11 | 20 | 26 | 15 | 26 | 35 | 21 | 34 | 40 |
| | 10 | 11 | 20 | 31 | 11 | 21 | 26 | 16 | 28 | 38 | 20 | 33 | 40 |
| Ampho- | 100 | T | 8 | 14 | T | 6 | 10 | 0 | 0 | 2 | 0 | 6 | 11 |
| tericin B | 80 | 4 | 10 | 14 | 5 | 7 | 12 | 0 | 0 | 2 | T | 10 | 15 |
| | 60 | 4 | 9 | 13 | 6 | 9 | 13 | 0 | 0 | 4 | T | 10 | 14 |
| | 40 | 5 | 11 | 16 | 6 | 9 | 13 | 0 | 2 | 4 | T | 14 | 13 |
| | 20 | 8 | 12 | C[d] | 6 | 7 | C | 0 | C | C | T | C | C |
| | 10 | 8 | 14 | 19 | 7 | 12 | 17 | 0 | 6 | 11 | T | 9 | 15 |
| | 1 | 9 | 19 | 28 | 9 | 18 | 24 | 7 | 10 | 19 | T | 19 | 32 |
| Solvent | | 14 | 23 | 29 | 14 | 23 | 27 | 16 | 31 | 35 | 22 | 34 | 40 |
| control | | 12 | 21 | 28 | 14 | 25 | 31 | 14 | 27 | 34 | 20 | 35 | 40 |

[a] Average of two cultures. [b] 0 = no growth. [c] T = trace of growth. [d] C = contaminated.

and the mixture of **3** and **4** showed in vitro activity against *H. capsulatum* and *B. dermatitidis*, **6** being active at 40 μg/ml through 3 and 2 weeks, respectively, against the first and second organisms. On a weight basis, this activity is roughly twice that reported earlier[4] for the bishemiaminal, 6,6'-dihydroxythiobinupharidine (**1**). However, on a mole basis, the activities of **1** and **6** are roughly the same. The mixture of **3** and **4** was slightly less active than **6** against the same two organisms, *H. capsulatum* being inhibited through 2 weeks at a test substance concentration of 60 μg/ml. Similarly the growth of *B. dermatitidis* was inhibited through 2 weeks when the mixture of **3** and **4** was used at a concentration of 80 μg/ml. The mixture of **3** and **4** and the single diastereomer **6** were also active at levels of 40–80 μg/ml through 2 weeks against *S. schenckii* and *T. rubrum*. The organisms were insensitive to the α-hydroxyhemiaminal **20** and the two mixtures of β-*tert*-amino sulfides **11** and **12** and **18** and **19**. The solitary exception was *T. rubrum* whose growth was inhibited through 2 weeks when a mixture of **11** and **12** was used at a concentration of 80 μg/ml.

Once the activity of α-thiohemiaminals had been ascertained, their activities in relation to a well-known active compound were determined in a single experiment. Table I presents the results of this second experiment. The activities of **6**, a mixture of **3** and **4**, **7**, and amphotericin B were tested simultaneously against *H. capsulatum* and *B. dermatitidis*. Under our laboratory conditions, **6** and the mixture of **3** and **4** were more effective than amphotericin B in inhibiting the growth of the four cultures tested; but the α-thiohemiaminal **7**, which lacks the ring A methyl and 3-furyl groups, is much less active than the α-thiohemiaminals **3** and **4**, **6**, and amphotericin B. For **6** at 60 μg/ml, total inhibition of *H. capsulatum* no. 1106 was achieved through 3 weeks although total inhibition of no. 1098 lasted only 1 week. *B. dermatitidis* was more resistant to **6**; at 60 μg/ml, the inhibition was only 1 week of duration. Qualitatively the results of the second experiment support those of the first series of tests.

Although amphotericin B had limited effects on the two isolates of *H. capsulatum*, it was very active against *B. dermatitidis*, especially isolate no. 1099 whose growth was inhibited through 1 week when the amphotericin B concentration was 10 μg/ml. In general amphotericin B was less effective in its antifungal activities than previously reported.[16] Several factors should be taken into consideration: the potency of amphotericin B in the lot used, the effect of the solvent system, the amount of inoculum, the resistant characters of the cultures, and other laboratory conditions.

In concluding, we observe that only the α-thiohemiaminals possessing the C-1 equatorial methyl and the C-4 equatorial 3-furyl groups are active antifungal agents and that these agents are more effective in vitro against *H. capsulatum* than amphotericin B. Since we observe that α-thiohemiaminals undergo weak acid promoted conversion to α-thioimmonium ions and the tests were carried out in the pH range of 5.0–6.5, it seems reasonable that the structural and functional components necessary for activity are the ring A methyl and 3-furyl groups and functionality capable of generating an α-thioimmonium ion in acid solution. Additional studies dealing with the activity dependence on pH and ring A modifications, especially those which affect conformation, should provide interesting tests of this proposal. Also, now that the requirement for the presence of the α-thiohemiaminal function is fully appreciated, attention can be given to the influence of C-7 configuration on antifungal activity.

## Experimental Section

Spectra were obtained as follows: proton magnetic resonance ($^1$H NMR) in solution as indicated, 2% $Me_4Si$ (δ 0.0 ppm), on

Varian A-60 and XL100 FT spectrometers, symbols br, s, d, t, m, ax, and eq referring to broad, singlet, doublet, triplet, multiplet, axial, and equatorial, respectively, and $J$ signifying the splitting values; pulsed, proton decoupled $^{13}C$ nuclear magnetic resonance ($^{13}C$ NMR)[17] in $CD_3CN$, $Me_4Si$ ($\delta$ 0.0 ppm) relative to $CD_3CN$ ($\Delta_{CD_3CN}^{Me_4Si}$ = 1.29 ppm), $CD_3CN$ lock; ir in KBr and liquid film using Perkin-Elmer 137 and 621 infrared spectrometers; mass spectra (MS)[17] on a Hitachi Perkin-Elmer RMU-6E using a direct inlet probe at 110 and 120° and a chamber voltage of 70 eV; circular dichroism (CD) on a Jasco Model 5 spectropolarimeter in solution at the concentrations indicated, only the wavelength of peaks, troughs, and shoulders being reported here.[17] Melting points were determined on a Kofler micro hot stage and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Thin-layer chromatography (TLC) was carried out on microscope slides uniformly coated with 0.25 mm of alumina $HF_{254}$, E. Merck, and using the solvents indicated. Woelm neutral alumina ($Al_2O_3$) of the indicated activity was used in elution chromatography. The $NaBD_4$ was purchased from Merck Sharp & Dohme and contained a minimum of 98% deuterium.

**7α-Phenylthio-7-epideoxynupharidin-6-ol (5) and 7β-Phenylthiodeoxynupharidin-6-ol (6).** A $C_6H_6$ solution (45 ml) containing 488 mg of 6-dehydrodeoxynupharidine (2.1 mmol), 541 mg of phenyl benzenethiosulfonate (2.2 mmol), and 2.5 g of $Al_2O_3$ (activity 3) was stored in the dark under $N_2$ at 25° for 16 hr. The reaction mixture was concentrated on the rotary evaporator and added to a 3-cm diameter column containing 60 g of $Al_2O_3$ (5% $H_2O$) which was eluted successively with 200 ml of $C_6H_{14}$, 100 ml of 10% $C_6H_6$–$C_6H_{14}$, 250 ml of $C_6H_6$, 200 ml of 10% $Et_2O$–$C_6H_6$, and 100 ml of 20% $C_6H_6$–$Et_2O$ and 150 ml of MeOH. Fractions, 1, 2, and 5–7 consisted of 35 ml each of $C_6H_6$ effluent. Fractions 3 and 4 consisted of 60 ml each of $C_6H_6$. Fractions 8–10 consisted of 35 ml each of 10% $C_6H_6$–$Et_2O$. Combination of fractions 2 and 3 yielded 213 mg (28.4%) of pure liquid 7β-phenylthiodeoxynupharidin-6-ol (6): TLC ($C_6H_6$) $R_f$ 0.3; ir (liquid film) 2.87 (OH), 6.32, 6.68 (Ar), 11.49 (3-furyl), 12.7, 13.4, 14.5 μm (Ar); $^1H$ NMR (60 MHz) $\delta$ 0.92 (d, $J$ = 3 Hz, 3 H, C-1 $CH_3$), 1.14 (s, 3 H, C-7 $CH_3$ ax), 2.60 (br, m, 1 H, C-10 H), 3.18 (br s, 1 H, C-6 OH and disappearing on addition of $D_2O$), 3.77 (d of d, $J$ = 5 and 9 Hz, 1 H, C-4 H), 4.07 (br s, 1 H, C-6 H and sharpening on addition of $D_2O$), 6.24 (m, 1 H, β-furyl H), 7.2–7.5 (m, 7 H, phenyl and α-furyl H); MS $m/e$ (% rel intensity) 357 (32) ($M^+$), 248 (100), 231 (25); CD ($c$ 0.35 mg/ml, neutral MeOH, $l$ = 0.1 dm) $[\theta]_{256}$ +2060°; CD ($c$ 0.12 mg/ml, $HClO_4$ in MeOH, $l$ = 0.1 dm) $[\theta]_{295}$ +10890°, $[\theta]_{270}$ +19360°, $[\theta]_{246}$ +44200°.

Fractions 8–10 were combined to obtain 36 mg of pure 7α-phenylthio-7-epideoxynupharidin-6-ol (5) (4.8%): TLC ($C_6H_6$) $R_f$ 0.09; ir (liquid film) 2.90 (OH), 6.0, 6.3, 6.68 (Ar), 11.49 (3-furyl), 12.7, 13.4, 13.8, 14.8 μm (Ar); $^1H$ NMR (60 MHz) $\delta$ 0.94 (s, 6 H with $\delta$ 0.96 d, C-7 $CH_3$ eq), 0.96 (d, $J$ = 4.5 Hz, 6 H with $\delta$ 0.94 s, C-1 $CH_3$), 2.38 (br m, 1 H, C-10 H), 3.39 (br s, 1 H, C-6 OH), 3.66 (t, $J$ = 7 Hz, 1 H, C-4 H), 4.40 (br s, 1 H, C-6 H), 6.62 (m, 1 H, β-furyl), 7.2–7.6 (m, 7 H, phenyl and α-furyl H); MS $m/e$ (% rel intensity) 357 (10) ($M^+$), 248 (30), 231 (100); CD ($c$ 0.40 mg/ml, neutral MeOH, $l$ = 0.1 dm) $[\theta]_{262}$ −2940°; CD ($c$ 0.23 mg/ml, $HClO_4$ in MeOH, $l$ = 0.1 dm) $[\theta]_{340}$ +700°, $[\theta]_{295}$ −4520°, $[\theta]_{276}$ −3430°, $[\theta]_{250}$ −9690°.

Fractions 4–7 (combined, 264 mg) consisted of mixtures of 7α-phenylthio-7-epideoxynupharidin-6-ol and 7β-phenylthiodeoxynupharidin-6-ol. Rechromatography as above gave an additional 78 mg (10.4%) of the former and 93 mg (12.4%) of the latter.

**Immonium Perchlorate, 14, from 7β-Phenylthiodeoxynupharidin-6-ol (6).** A solution of 54 mg of 6 (0.15 mmol) in 2 ml of absolute EtOH was treated with 0.76 ml of 0.2 $M$ aqueous $HClO_4$. The resulting white solid was recrystallized from $Me_2CO$. Thereby was obtained 50 mg (75.8%) of white crystalline immonium perchlorate 14: mp 241–244°; ir (KBr) 5.98 (s, C=N+), 6.26 (Ar), 6.69 (Ar), 11.49 (3-furyl), 12.32, 12.41, 13.04, 13.38, 14.38, 14.50 μm; $^1H$ NMR (60 Hz, $CD_3CN$) $\delta$ 1.03 (d, $J$ = 5.5 Hz, 3 H, C-1 $CH_3$), 1.38 (s, 3 H, C-7 $CH_3$), 3.67 (br m, 1 H, C-10 H), 5.05 (d of d, $J$ = 6.5 and 14.5 Hz, 1 H, C-4 H), 6.62 (q, $J$ = 1 Hz, 1 H, β-furyl H), 7.38 (m, 5 H, phenyl H), 7.58 (br s, 1 H, α-furyl or C-6 H), 7.72 (t, $J$ = 1.5 Hz, 1 H, α-furyl H), 7.81 (br s, 1 H, α-furyl or C-6 H); $^{13}C$ NMR $\delta$ 18.4 (C-11, eq $CH_3$), 22.5 (C-12, $CH_3$), 172.6 (C-6). Anal. ($C_{21}H_{26}NO_5SCl$) C, H, N, S.

**Immonium Perchlorate, 13, from 7α-Phenylthio-7-epideoxynupharidin-6-ol (5).** A solution of 78 mg of 5 (0.22 mmol) in 2 ml of absolute EtOH was treated with 1.09 ml of 0.2 $M$ aqueous $HClO_4$. The resulting clear solution was concentrated on the rotary evaporator to an oil which was dissolved in 2 drops of $Me_2CO$. A few drops of $Et_2O$ were added and the resulting crystalline solid was recrystallized from $Me_2CO$–EtOEt. Thereby was obtained 38 mg (39.3%) of crystalline immonium perchlorate 13: mp 174–181°; ir (KBr) 5.98, 6.05 (C=N+), 6.68 (Ar), 11.47 (3-furyl), 12.30, 13.2, 13.5, 14.25, 14.40 μm; $^1H$ NMR (60 Hz, $CD_3CN$) $\delta$ 0.93 (m, 3 H, C-1 $CH_3$ eq), 1.43 (s, 3 H, C-7 $CH_3$), 3.57 (br m, 1 H, C-10 H), 5.01 (d of d, $J$ = 4 and 12 Hz, 1 H, C-4 H), 6.63 (q, $J$ = 1 Hz, 1 H, β-furyl H), 7.53 (s, 5 H, phenyl H), 7.73 (t, $J$ = 1.8 Hz, 2 H, α-furyl H), 7.84 (br s, 1 H, C-6 H); $^{13}C$ NMR $\delta$ 18.0 (C-11, $CH_3$ eq), 21.9 (C-12, $CH_3$), C-6 (172.4). Anal. ($C_{21}H_{26}NO_5SCl$) C, H, N, S.

**Conversion of the Immonium Perchlorate Salt, 14, of 7β-Phenylthiodeoxynupharidin-6-ol to 7β-Phenylthiodeoxynupharidine (10).** A solution of 45 mg of the title immonium salt (0.10 mmol) in 15 ml of MeOH was treated with 87 mg of $NaBH_4$ (2.3 mmol) and the resulting mixture was kept at 25° for 4 days and then concentrated at the rotary evaporator. The residue was chromatographed on 10 g of $Al_2O_3$ (activity 2) eluting with $C_6H_6$, the first 45 ml of which produced 32 mg (91.2%) of 10: TLC ($C_6H_6$) $R_f$ 0.74; TLC (50% $C_6H_6$–$C_6H_{14}$) $R_f$ 0.62; ir (liquid film) 3.6 (Bohlmann band), 6.29 (Ar), 6.69 (Ar), 11.48 (3-furyl), 12.74, 12.92, 13.41, 14.28, 14.5 μm (Ar); $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 0.92 (m, 3 H, C-1 $CH_3$ eq), 1.28 (s, 3 H, C-7 $CH_3$ ax), 1.88 (d, $J$ = 11.5 Hz, 1 H, C-6 H ax), 2.87 (d of d, $J$ = 11.5 and 2 Hz, 1 H, C-6 H eq), 2.94 (d of d, $J$ = 7.5 and 6 Hz, 1 H, C-4 H), 6.37 (m, 1 H, β-furyl H), 7.2–7.7 (m, 7 H, α-furyl and phenyl H); $^1H$ NMR (100 MHz, $C_6D_6$) $\delta$ 0.72 (d, $J$ = 5.6 Hz, 3 H, C-1 $CH_3$ eq), 1.44 (s, 3 H, C-7 $CH_3$ ax), 2.00 (d, $J$ = 11.5 Hz, 1 H, C-6 H ax), 2.76 (m, 1 H, C-4), 3.04 (d of d, $J$ = 11.5 and 2 Hz, 1 H, C-6 H eq), 6.25 (m, 1 H, β-furyl H), 7.2–7.3 (m, phenyl H), 7.51 (m, 2 H, α-furyl H); MS $m/e$ (% rel intensity) 341 (26) ($M^+$), 232 (100). Anal. ($C_{21}H_{27}NOS$) C, H, N, S.

**Conversion of the Immonium Perchlorate Salt, 14, of 7β-Phenylthiodeoxynupharidin-6α-ol to 7β-Phenylthiodeoxynupharidine-6α-$d_1$ (12).** To a solution of 19 mg of the title immonium salt (0.043 mmol) in 7 ml of MeOH was added in a portionwise manner 66 mg of $NaBD_4$ (0.16 mmol) over a period of 36 hr and the resulting mixture was kept at 25° for an additional 100 hr. The mixture was concentrated at the rotary evaporator and the residue was chromatographed on 4 g of $Al_2O_3$ (activity 2) eluting with $C_6H_6$, the first 30 ml of which produced 14 mg (94.7%) of 7β-phenylthiodeoxynupharidine-6α-$d_1$: TLC (50% $C_6H_6$–$C_6H_{14}$) $R_f$ 0.62; $^1H$ NMR (100 MHz, $C_6D_6$) $\delta$ 0.71 (d, $J$ = 6 Hz, 3 H, C-1 $CH_3$ eq), 1.43 (s, 3 H, C-7 $CH_3$ ax), 1.97 (s, 0.9 H, C-6 H ax), 2.00 (d, $J$ = 11.5 Hz, 0.1 H, C-6 H ax), 2.75 (m, 1 H, C-4), 3.02 (d of d, $J$ = 11.5 and 2 Hz, 0.15 H, C-6 H eq), 6.23 (m, 1 H, β-furyl H), 7.0–7.3 (m, phenyl H), 7.48 (m, 2 H, α-furyl H); MS $m/e$ (% rel intensity) 242 ($M^+$, 2% $d_0$, 98% $d_1$), 233 (100).

**Conversion of 7α-Phenylthio-7-epideoxynupharidin-6-ol (5) to 7α-Phenylthio-7β-epideoxynupharidine (9).** To a solution of 39 mg of 5 (0.11 mmol) in 7 ml of MeOH was added 64 mg of $NaBH_4$ (1.7 mmol). TLC ($C_6H_6$) indicated the disappearance of 5 ($R_f$ 0.09) within 5 min. The reaction mixture was kept at 25° for 16 hr and concentrated at the rotary evaporator. Chromatography of the residue on 10 g of $Al_2O_3$ (activity 2) eluted with 60 ml of $C_6H_6$ gave, in combined fractions 2, 3, and 4 (total 50 ml $C_6H_6$), 35 mg (94.0%) of 9: TLC (50% $C_6H_6$–$C_6H_{14}$) $R_f$ 0.44; ir (liquid film) 3.6 (Bohlmann band), 6.32, 6.69 (Ar), 11.47 (3-furyl), 12.72, 13.38, 14.22, 14.45 μm (Ar); $^1H$ NMR (100 MHz, $C_6D_6$) $\delta$ 0.87 (d, $J$ = 6 Hz, 3 H, C-1 $CH_3$), 0.96 (s, 3 H, C-7 $CH_3$ eq), 1.71 (d, $J$ = 11.5 Hz, C-6 H ax), 2.15 (d of t, $J$ = 4 and 6 Hz, 1 H, C-10 H), 2.82 (d of d, $J$ = 10 and 4 Hz, 1 H, C-4 H), 3.21 (d of d, $J$ = 11.5 and 2 Hz, 1 H, C-6 H eq), 6.65 (m, 1 H, β-furyl H), 7.0–7.3 (m, phenyl H), 7.52 (m, 2 H, α-furyl H); MS $m/e$ (% rel intensity) 341 (23) ($M^+$), 232 (100). Anal. ($C_{21}H_{27}NOS$) C, H, N, S.

**Conversion of 7α-Phenylthio-7-epideoxynupharidin-6-ol (5) to 7α-Phenylthio-7-epideoxynupharidine-6β-$d_1$ (11).** To a solution of 26 mg of 5 (0.073 mmol) in 7 ml of MeOH was added 24 mg of $NaBD_4$ (0.57 mmol). The reaction mixture was kept

at 25° for 2 hr and then concentrated at the rotary evaporator. Chromatography of the residue on 6 g of $Al_2O_3$ (activity 2) eluted with 30 ml of $C_6H_6$ gave 7 mg (28%) of 7α-phenylthio-7-epideoxynupharidine-6β-*d*1: $^1H$ NMR (100 MHz, $C_6D_6$) δ 0.85 (d, $J$ = 6 Hz, 3 H, C-1 $CH_3$), 0.91 (s, 3 H, C-7 $CH_3$ eq), 2.12 (t of d, $J$ = 4 and 6 Hz, 1 H, C-10 H), 2.80 (d of d, $J$ = 10 and 4 Hz, 1 H, C-4 H), 3.17 (br s, 0.9 H, C-6 H eq), 3.21 (d of d, $J$ = 11.5 and 2 Hz, 0.1 H, C-6 H eq), 6.64 (m, 1 H, β-furyl H), 7.01 (m, 5 H, phenyl H), 7.49 (m, 2 H, α-furyl H); MS *m/e* (% rel intensity) 342 ($M^+$, 7% $d_0$, 90% $d_1$, 3% $d_2$), 233 (100).

**3-Methyl-3-methylthio-4-hydroxyquinolizidine (7).** An $Et_2O$ solution (10 ml) containing 736 mg of 3-methyl-4-ketoquinolizidine (4.41 mmol), obtained[18] as a side product in the catalytic reduction of 1-(2-pyridyl)-3,3-dicarbethoxybutane to 3-methylquinolizidine, was stirred with 8.5 ml of a 20% solution of diisobutylaluminum hydride (approximately 1.7 g, 12 mmol) in $C_6H_{14}$ at −50° under $N_2$ for 1.5 hr and then treated with 16 ml of 10% aqueous HCl at −20° and concentrated at the rotary evaporator at 25°. The acidic aqueous solution was basified with KOH pellets and extracted repeatedly with $Et_2O$. The resulting ether solution (35 ml) was stirred with 1.01 g of methyl *p*-toluenethiosulfonate (5.0 mmol) in the presence of 2.5 g of $Al_2O_3$ (activity 3) at −20° under $N_2$ for 1 hr and at 25° overnight. The mixture was concentrated at the rotary evaporator and then chromatographed repeatedly on $Al_2O_3$ (activities 2 and 3) using $C_6H_6$. In this manner was obtained 271 mg of material which was chromatographed on $Al_2O_3$ (20 g, 5% $H_2O$) using $C_6H_6$–$Et_2O$ (9:1) in several 5-ml fractions. Fractions 2–13 were combined to obtain 169.7 mg (17.9%) of pure 3-methyl-3-methylthio-4-hydroxyquinolizidine: TLC ($C_6H_6$–$Et_2O$, 9:1) $R_f$ 0.87; mp 35–37°; ir (liquid film) 2.95 μm (OH); $^1H$ NMR (60 MHz, $CDCl_3$), δ 1.29 (s, C-3 $CH_3$), 1.44 (s, C-3 $CH_3$), 1.98 (s, 1 H with δ 2.03, C-3 $SCH_3$), 2.03 (s, C-3 $SCH_3$), 2.69 (m, 3 H, C-6 $CH_2$ and C-10 CH), 3.28 (s, 1 H, OH, and disappearing upon addition of $D_2O$), 3.53 (s, 0.1 H, C-4 H), 4.06 (s, 1 H, C-4 CH); uv (95% EtOH, neutral) end absorption only at 220 nm; uv (95% EtOH, acidic) $\lambda_{max}$ 293 nm (ε 1200).

Repeated treatment of 3-methyl-3-methylthio-4-hydroxyquinolizidine with EtOH followed by vacuum evaporation gave 3-methyl-3-methylthio-4-ethoxyquinolizidine: MS *m/e* (% rel intensity) 244 (2) ($M^+$), 150 (100).

**Preparation of the Immonium Perchlorate Salt from 3-Methyl-3-methylthio-4-hydroxyquinolizidine (7).** A solution of 96.8 mg of **7** (0.45 mmol) in 2 ml of 95% EtOH was treated with 2.75 ml of 0.2 *M* aqueous $HClO_4$. The resulting solution was concentrated at the rotary evaporator to a light yellow oil which was dissolved in several drops of $Me_2CO$ and 1 ml of $Et_2O$. Thereby a white crystalline solid formed and this was recrystallized from $Me_2CO$–$Et_2O$ to obtain 70 mg (52.3%) of the immonium perchlorate: mp 106–110°; ir (KBr) 6.00 μm ($N^+$=C), 8.8–9.6 ($ClO_4^-$); $^1H$ NMR (60 MHz, $CD_3CN$) δ 8.35 (s, 1 H, $^+$N=CH), 4.5–3.5 (m, 3 H, C-6 $CH_2$ and C-10 CH), 2.17 (s, 3 H, C-3 $SCH_3$), 1.55 (s, 3 H, C-3 $CH_3$); $^{13}C$ NMR ($CD_3CN$) δ 11.9 (C-3 $SCH_3$), 23.2 (C-3 $CH_3$), 45.4 (C-3), 61.8 (C-6 and C-10), 175.9 (C-4). Anal. ($C_{11}H_{20}ClNO_4S$) C, H, N, S.

**Conversion of 3-Methyl-3-methylthio-4-hydroxyquinolizidine (7) to 3α-Methyl-3β-methylthioquinolizidine (16).** A solution of 54.9 mg of **7** (0.26 mmol) in 1 ml of MeOH was stirred with 58.0 mg of $NaBH_4$ (1.53 mmol) at 25° overnight. The solvent was removed at the rotary evaporator, the residue was treated with $C_6H_6$, and the resulting mixture was put on a column of 12 g of $Al_2O_3$ (activity 3) which was eluted with $C_6H_6$ in one fraction. The eluent showed one spot on TLC ($C_6H_6$) which on evaporation of $C_6H_6$ gave 42.1 mg (82.6%) of liquid 3α-methyl-3β-methylthioquinolizidine: $^1H$ NMR (60 MHz, $CDCl_3$) δ 2.00 (s, 3 H, C-3 $SCH_3$), 1.41 (s, 3 H, C-3 $CH_3$); $^1H$ NMR ($C_6D_6$) δ 1.82 (s, 3 H, C-3 $SCH_3$), 1.50 (s, 3 H, C-3 $CH_3$); $^{13}C$ NMR ($CDCl_3$) δ 9.9 (C-3 $SCH_3$), 23.4 (C-3 ax $CH_3$); MS *m/e* (% rel intensity) 199 (15) 98 (100). Anal. ($C_{11}H_{21}NS$) C, H, N, S.

**Determination of Antifungal Properties.** The following is typical of the procedures[4] used for preparing solutions of the test compounds and reference solvents for in vitro antifungal screening. A 50-mg sample of 7β-phenylthiodeoxynupharidin-6-ol (**6**) was dissolved in a mixture of 30 mg of HOAc and 5.5 ml of $Me_2SO$. The solution then was diluted to 50 ml with water. The solvent used for control and further dilution of the solution of **6** contained 60 mg of HOAc and 11 ml of $Me_2SO$ in a total volume of 103 ml of water. Both solution and solvent were sterilized by filtration through a Seitz filter. The sterile test solution was diluted with the sterile solvent to the desired concentrations and each of these was added to sterile, melted (50°) Sabouraud dextrose agar, whose pH had previously been adjusted to 7.0–7.5 with 0.1 *N* NaOH, to make the final concentrations 100, 80, 60, 40, 20, and 10 μg/ml of **6** in the test medium. These and the solvent were distributed into sterile quadrant plates. The final pH of the agar after admixture with the test solution was 6.0–6.5.

In the order given, the test substance, the weight of each in milligrams, and the volume of added $Me_2SO$ in milliliters are: a mixture of **3** and **4**, 50, 1; the compound **6**, 46, 5; a mixture of **18** and **19**, 46, 1; **20**, 43, 1. Each of these solutions contained 30 mg of HOAc and was diluted initially with water to a concentration of 1000 μg/ml of test compound. The solvents used for control and dilution contained the same concentrations of HOAc and $Me_2SO$ as the corresponding test solutions. Each concentration, the solvent control, and a control (blank) were tested in duplicate.

The seven fungi used in this study were *Histoplasma capsulatum* Darling (isolates 1098 and 1106), *Blastomyces dermatitidis* Gilchrist & Stokes (isolates 1099 and 1107), *Microsporum gypseum* (Bodin) Guiart & Grogorakis (1102), *Sporotrichum schenckii* Hektoen & Perkins (1109), and *Trichophyton rubrum* (Castellani) Sab. (1112).

The section of a quadrant plate was center-inoculated with a 2 × 2 mm portion of a 2-week-old mycelial culture. The plates then were sealed with masking tape and incubated at 25°C. The linear expansion of each colony was measured weekly up to the end of the third or fourth week.

The experiment in which the activities of **6**, a mixture of **3** and **4**, **7**, and amphotericin B were compared simultaneously (Table I) involved the following modifications of the typical procedure described above. Solutions of test compounds were filter-sterilized. Amphotericin B (Type I, Fungizone, batch no. 91830-001, potency 972 μg/mg) was weighed and dissolved in filter-sterilized solvent and thereafter distributed into melted Sabouraud dextrose agar to make final concentrations of 100, 80, 60, 40, 20, 10, and 1 μg/ml. The pH of the agar used for each test was adjusted to 6 prior to the addition of the test compound and was 5.0–5.5 after the addition of the test compound. Two isolates each of *H. capsulatum* and *B. dermatitidis* were used for this experiment and the diameter of each colony was measured weekly for 3 weeks.

## References and Notes

(1) Support of this work by the National Institutes of Health, U.S. Public Health Service (Grant No. AI10188), is gratefully acknowledged. The authors are grateful also to the National Science Foundation for an equipment grant to the Department of Chemistry, State University of New York, College of Environmental Science and Forestry, toward the purchase of the XL-100-15 spectrometer and the VFT 100 computer used in this study.
(2) Department of Chemistry.
(3) Department of Botany.
(4) W. P. Cullen, R. T. LaLonde, C. J. Wang, and C. F. Wong, *J. Pharm. Sci.*, **62**, 826 (1973).
(5) (a) G. I. Birnbaum, *Tetrahedron Lett.*, 4149 (1965); (b) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Am. Chem. Soc.*, **95**, 6342 (1973); (c) J. T. Wrobel, B. Bobeszko, T. I. Martin, D. B. MacLean, N. Krishnamachari, and C. Calvo, *Can. J. Chem.*, **50**, 1831 (1972).
(6) R. T. LaLonde, E. Auer, C. F. Wong, and V. P. Muralidharan, *J. Am. Chem. Soc.*, **93**, 2501 (1971).
(7) R. T. LaLonde, T. N. Donvito, A. I-M. Tsai, and C. F. Wong, *Org. Magn. Reson.*, **7**, 191 (1975).
(8) For comparison, the ORD of (−)-deoxynupharidine in neutral solution is a plain negative curve in the region 220–350 nm. In acid solution a plain positive curve is obtained.
(9) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy", Wiley, New York, N.Y., 1962, Chapter 17.
(10) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry", Holden-Day, San Francisco, Calif., 1965, Chapter 11.
(11) R. T. LaLonde and C. F. Wong, *J. Org. Chem.*, **38**, 3225

(1973).
(12) S. K. Malhotra in "Enamines", A. G. Cook, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 1.
(13) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, New York, N.Y., 1969, p 191.
(14) F. Bohlmann, H. J. Mueller, and D. Schumann, *Chem. Ber.*, **106**, 3026 (1973).
(15) A condensation of raw data substantiating the activities of all compounds tested in the initial phase is available on request.
(16) G. Hildick-Smith, H. Blank, and I. Sarkany, "Fungus Diseases and Their Treatment", Little, Brown and Co., Boston, Mass., 1964, pp 387–389.
(17) Detailed MS, CD, and $^{13}C$ NMR data are available on request.
(18) R. T. LaLonde, C. F. Wong, and H. G. Howell, *J. Org. Chem.*, **36**, 3703 (1971).

# Cycloalkanones. 8. Hypocholesterolemic Activity of Long-Chain Ketones Related to Pentadecanone

Steven D. Wyrick,[1] Iris H. Hall,* C. Piantadosi, and Charles R. Fenske

*Division of Medicinal Chemistry, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514.*
*Received June 5, 1975*

Aliphatic analogs of 2,8-dibenzylcyclooctanone which includes $C_{15}$–$C_{18}$ ketones have been investigated for hypocholesterolemic activity in rats. The position of the carbonyl group in the chain for maximum activity appears to be the 2 position. 2-Hexadecanone reduced serum cholesterol levels significantly without altering serum triglyceride levels. This drug was not estrogenic at effective doses which is in contrast to the cyclooctanones which possess this activity.

It has recently been demonstrated that aliphatic ketone analogs related to 2,8-dibenzylcyclooctanone are effective hypocholesterolemic agents (i.e., 8-pentadecanone).[2] The aliphatic ketones do not have the estrogenic and antifertility characteristics which are associated with the cyclooctanones.[2] Further expansion of this aliphatic chain to include $C_{15}$–$C_{18}$ ketones and the importance of position of the ketone in the carbon chain have now been examined. Separation of the hypocholesterolemic effect from the uterotropic effect has been achieved in a $C_{16}$ ketone, while preserving the hypocholesterolemic activity.

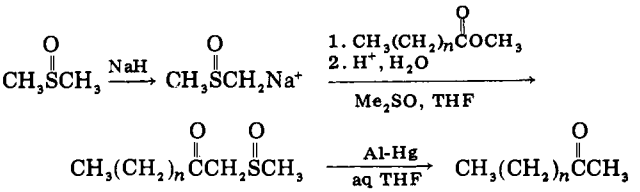
## Experimental Section

All melting points were determined on the Thomas-Hoover melting point apparatus and were corrected. Infrared spectra were obtained on the Perkin-Elmer 257 spectrophotometer. All thin-layer chromatography was carried out on silica gel G coated microslides. Column chromatography was performed using 70–230 mesh silica gel 60. Elemental analyses were determined by M-H-W Laboratories, Garden City, Mich., and were correct within 0.4% of the theoretical values.

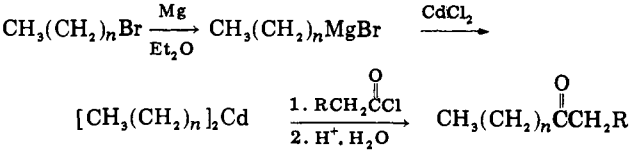
**2-Pentadecanone** (1). This compound was purchased from Calbiochem and was used in biological studies after proven pure by TLC and infrared spectroscopy. This ketone is a colorless semisolid at 25°.

**Synthesis of β-Keto Sulfoxides. General Procedure.**[3] A weighed amount of a 50% w/w dispersion of sodium hydride in mineral oil was placed in a three-neck round-bottom flask and washed with petroleum ether. The hydride was allowed to settle and the petroleum ether was decanted off. This washing procedure was repeated three times, and the flask was then evacuated with a water aspirator, and a nitrogen atmosphere was established. Dry dimethyl sulfoxide (about 100 ml/4.0 g of sodium hydride) was then added through a dropping funnel over a 15-min period with stirring. The temperature was then slowly raised to and maintained at 60–63° for 1.0 hr by which time a cloudy gray-green solution of methylsulfinyl carbanion was obtained. The reaction was diluted with an equal volume of dry tetrahydrofuran and cooled to 0° and 0.5 equiv of the appropriate methyl ester (based on 1 equiv of sodium hydride) was added dropwise either neat or as a THF solution. After stirring for 1.0 hr at room temperature, the entire mixture was poured into 600 ml of water and the pH adjusted to 3–4 (pH paper) using concentrated HCl. The resulting suspension was extracted with chloroform, the chloroform extracts were dried over anhydrous $Na_2SO_4$ and filtered, and the solvent was removed in vacuo to leave the crude β-keto sulfoxide as a yellow solid. Recrystallization from ethyl acetate–benzene (10:1) afforded pure β-keto sulfoxide in 35–70% yield (Scheme I, Table I).

Scheme I



Scheme II



**Reduction of β-Keto Sulfoxides. General Procedure.**[3] A weighed amount of the above β-keto sulfoxide was dissolved in 10% aqueous tetrahydrofuran (about 600 ml/20 g). To this solution was added aluminum amalgam (10:1 molar ratio) prepared as follows. Aluminum foil was cut into 4 × 0.5 in. strips. Each strip was separately dipped into 2% aqueous mercuric chloride for 15 sec, rinsed with absolute ethanol and then anhydrous diethyl ether, and cut into 0.5 in. squares directly into the reaction vessel containing the β-keto sulfoxide solution. The reaction was then mechanically stirred under spontaneous reflux for 1.0 hr. The solid residue was filtered, the filtrate evaporated, and the residue was taken up in diethyl ether and extracted with 50 ml of water. The ether solution was dried over anhydrous $Na_2SO_4$ and filtered, and the ether was removed in vacuo leaving the crude ketone. Purification by recrystallization or column chromatography afforded the pure ketone in about 50–60% yield (Scheme I, Table I).

**Synthesis of Hexadecanone Isomers. General Procedure.**[4] To a weighed amount of dry magnesium turnings covered with sufficient dry diethyl ether was added 1 equiv of the appropriate alkyl halide dropwise neat or in ether solution. Addition and reflux were maintained at approximately the same rate. Upon reaction of all the magnesium, the reaction was cooled to 5–10° and 1 equiv of anhydrous cadmium chloride (previously dried to constant weight) was added over a 5–10-min period. The mixture was then stirred under reflux for 1.0 hr. At this time 0.8 equiv of the appropriate acid chloride in dry diethyl ether was added dropwise