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New Monohemiaminal Derivatives of Thiobinupharidine and Thionuphlutine B. Role of Circular Dichroism and Mass Spectrometry in Ascertaining the Position of the Hemiaminal Function[1]

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Received April 26, 1974

Spectral properties of four monohemiaminals belonging to the thiaspirane class of nuphar alkaloids are compared and employed in the structure elucidation of three of these compounds. The new monohemiaminals are 6′-hydroxythiobinupharidine and 6-hydroxythionuphlutine B, both isolated from *N. luteum*, and 6′-hydroxythionuphlutine B, prepared from 6,6′-dihydroxythionuphlutine B. The nmr showed that the hemiaminal group in each of the three monohemiaminals was located at one of two C-6 positions. Distinction of a C-6 from a C-6′ hemiaminal was made chiefly by (1) deuteride reduction to singly labeled thiaspirane followed by a mass spectral analysis for the extent of *m/e* 178 to 179 shift; and (2) the CD of the monohemiaminals in acid solution. Singly deuterated thiaspiranes which were labeled at C-6 resulted in *m/e* 178 shifting to 179 by more than 90%. In contrast, thiaspiranes singly labeled at C-6′ resulted in only a 10% shift of *m/e* 178 to 179. The CD of all the C-6′ hemiaminals in acid solution showed positive CD bands in the region of 260–280 nm but the CD of 6-hydroxythiobinupharidine and 6-hydroxythionuphlutine B show positive and negative CD bands, respectively, in the 290–310-nm region.

Two bishemiaminal derivatives of the C_{30} thiaspirane type of Nuphar alkaloid have been reported.[2] These are 6,6′-dihydroxythiobinupharidine (**1**)[3] and 6,6′-dihydroxythionuphlutine B (**2**). A monohemiaminal derivative, 6-hydroxythiobinupharidine (**3**), has also been reported.[5,6] Chief among the methods for ascertaining the number of the hemiaminal functions was a borodeuteride reduction followed by a mass spectral analysis for the presence of a d_1- or d_2-labeled C_{30} thiaspirane. The location of the hemiaminal groups was determined by nmr, which readily allowed a distinction between a C-6 hemiaminal on the one hand and a C-4 or C-10 hemiaminal on the other. However, the distinction between two C-6 positions (C-6 and C-6′) in a monohemiaminal was somewhat more complex because of the symmetry characteristics of the thiaspirane skeleton and it was necessary to rely on subtle differences between α- and β-thiohemiaminals[7] and their stereochemistry. Thus in the case of the monohemiaminal, **3**, the nearly complete replacement of the hemiaminal hydroxyl by equatorial deuterium through sodium borodeuteride hydrogenolysis was the result which necessitated the attachment of the hydroxyl at C-6, not C-6′, since the replacement of hydroxyl by deuterium at C-6′ was known to occur in a completely axial fashion.[5]

Application of CD to α-thioimmonium ions, or α-thiohemiaminals in acid solution, led to the establishment of the absolute configuration of thiobinupharidine and thionuphlutine B[8] and simultaneously gave supporting evidence for the position of the hemiaminal function in 6-hydroxythiobinupharidine. However, the CD results alone did not furnish independent evidence for the presence of a C-6 hemiaminal, as opposed to a C-6′ hemiaminal, since the CD properties of β-thiohemiaminals and β-thioimmonium ions were not known. We have now isolated and prepared two new β-thiohemiaminals and isolated a new α-thiohemiaminal belonging to the thiobinupharidine and thionuphlutine B series. We illustrate here how several spectral characteristics of α- and β-thiohemiaminals differ. However, we emphasize how the CD of these compounds and comparative mass spectra of singly labeled thiaspiranes prepared from the monohemiaminals can be utilized in determining the hemiaminal position in samples obtained in 2–5-mg amounts.

6′-Hydroxythiobinupharidine (4). This compound was isolated from *N. luteum*. Its mass spectrum revealed a parent ion peak at *m/e* 510 which corresponded to a monohemiaminal derivative of a C_{30} thiaspirane type of nuphar alkaloid. The ir revealed the presence of a hydroxyl group. The appearance of Bohlmann bands[9] in the ir indicated the presence of a trans-fused quinolizidine. Since the hydroxyl group could be reduced by hydride reducing agents and hemiaminal derivatives of quinolizidines do not show Bohlmann bands,[10] the evidence for the presence of both hydride-reducible hydroxyl and a trans quinolizidine ring system revealed the dual amine–hemiaminal character of this alkaloid. Conversion of the new monohemiaminal to an am-

Table I
Proton Chemical Shifts[a] in the Nmr of Thiobinupharidine and Thionuphlutine B Hemiaminals

Compd	Proton: CH_3	CH_3S	CH_2N, H_{eq}: C-6	C-6′	HC(OH)N: C-6	C-6′	3F[b]CH: C-4	C-4′	3-Furyl: α	β
6,6′-Dihydroxythiobinupharidine (**1**)	0.82	2.46[c]			4.01[d]	4.26[e]	3.73	3.61	7.35	6.40
6-Hydroxythiobinupharidine, (**3**)	0.88	2.20[c]		2.96	3.98[d]		3.70	2.92	7.22 7.30	6.34
6′-Hydroxythiobinupharidine (**4**)	0.92	2.53[c]	2.83			4.25[e]	2.94	3.62	7.35	6.36
6,6′-Dihydroxythionuphlutine B (**2**)	0.87	2.52[c]			4.10[f]	3.92[f]	3.4–3.7			6.27 6.47
6-Hydroxythionuphlutine B (**8**)	0.88	2.32[c]		2.88	4.08[d]		3.55		7.27	6.22 6.41
6′-Hydroxythionuphlutine B (**14**)	0.89	2.53[c]	2.70			3.94[g]	2.95	3.50	7.30	6.20 5.43

[a] In parts per million from TMS (δ 0.0) in $CDCl_3$. [b] 3F = 3-furyl. [c] AB quartet, J = 11.0–12.0 Hz. [d] Singlet. [e] Doublet, J = 4 Hz. [f] Multiplet. [g] Doublet, J = 2 Hz.

monium–immonium diperchlorate supported the presence of amine and hemiaminal groups. The melting point of this diperchlorate was different from that obtained earlier from 6-hydroxythiobinupharidine.[5]

The sodium borodeuteride reduction of the new monohemiaminal gave a singly labeled thiobinupharidine which was identified by comparative specific rotations, melting points, ir, nmr, and mass spectra. An admixture melting point determination showed no depression. Hydride reduction to unlabeled thiobinupharidine, **6**, would have sufficed to identify the stereoisomeric type of thiaspirane. However, the use of sodium borodeuteride was considered advantageous because we wished to have sufficient labeled material for extensive comparison of the mass spectra of C-6 and C-6′ deuterated thiobinupharidines (see below). Mass spectral differences possibly could allow a determination of the position of the deuterium and thus the position of the hydroxyl group in the precursor monohemiaminal. The singly labeled sample used for comparison was prepared from 6,6′-dihydroxythiobinupharidine. The latter was reduced first with sodium borodeuteride and the resulting 6-hydroxythiobinupharidine-6′-d_1 (**5**), the only monohemiaminal detected in the reaction product, was separated from the mixture of products. The mass, nmr, and uv spectra of this C-6′ labeled hemiaminal were identical with the spectra of 6-hydroxythiobinupharidine except for the absorption bands which would be expected to change as a result of the presence of deuterium. Reduction of the C-6′ labeled hemiaminal with sodium borohydride gave thiobinupharidine-6′-d_1 (**7**). Since 6′-hydroxythiobinupharidine and 6,6′-dihydroxythiobinupharidine both had been reduced to the same labeled thiobinupharidine, it was clear that the first named compound belonged to the thiobinupharidine series.

Significantly, the nmr of the newly isolated hemiaminal displayed a doublet at δ 4.25 which collapsed to a singlet upon addition of deuterium oxide. The chemical shift of this proton was the same as the chemical shift of one of two similar carbinyl hemiaminal protons of 6,6′-dihydroxythiobinupharidine. The nmr also showed an equatorial proton α to nitrogen at δ 2.83. Thus the hemiaminal was not located at C-10, C-10′, C-4, or C-4′, but at C-6 or C-6′. The principal resonances are summarized in Table I along with corresponding data for bishemiaminals and other monohemiaminals of the thiobinupharidine and thionuphlutine B series. As can be seen in Table I, the chemical shift of each monohemiaminal carbinyl proton corresponds to one of two chemical shifts for the pair of similar protons in the bishemiaminals. The carbinyl hemiaminal proton assignments in the thiobinupharidine series are based on the previously reported[5] independent evidence which locates the hemiaminal function in 6-hydroxythiobinupharidine at the C-6 rather than the C-6′ position. These assignments and those in the thionuphlutine B series are supported by the work described below.

Not only do the nmr of 6- and 6′-monohemiaminals show differences, but the mass spectra do also. The *m/e* 178 peak is one of the principal peaks, and is often the base peak, in the mass spectra of the thiaspirane alkaloids.[11] However, 6-hydroxythiobinupharidine shows a weak peak at *m/e* 178 but a much stronger peak at *m/e* 176. The order of peak intensities is reversed in the mass spectrum of 6′-hydroxythiobinupharidine . As shown in Figure 1, the chief source

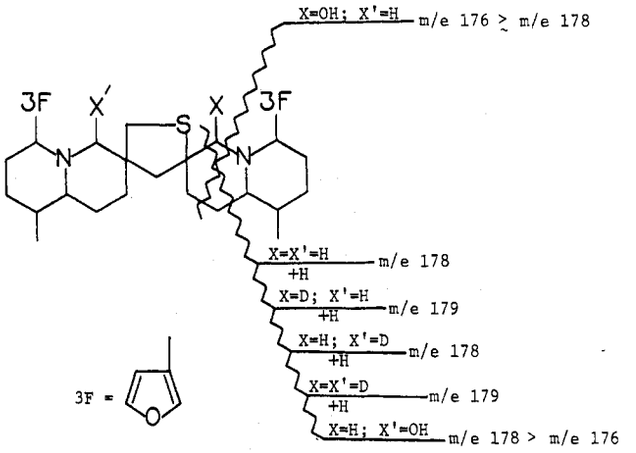


Figure 1. Mass spectral fragmentations of a thiaspirane nuphar alkaloid: the origin of *m/e* 178 and the possible origin of *m/e* 176.

of *m/e* 178 and 176 appears to be from the AB quinolizidine system, the one directly attached to sulfur, rather than the A′B′ quinolizidine ring. That this is the case in the fully reduced thiobinupharidine is evident from the observation that *m/e* 178 is shifted to *m/e* 179 by more than 90% in the mass spectrum of thiobinupharidine-6-d_1,[11] but the same shift occurs to only 9% in the mass spectrum of thiobinupharidine-6′-d_1. These results illustrate the potential usefulness of deuteride reduction and the determination of the *m/e* 178 to 179 shift in distinguishing a C-6 from a C-6′ hemiaminal. This procedure has been used, as described in another section below, in distinguishing C-6 from C-6′ hemiaminals in the thionuphlutine B series.

The uv of 6′-hydroxythiobinupharidine exhibited end absorption in neutral ethanol. However, the addition of perchloric acid resulted in the emergence of a new peak at 279 nm (ε 830) appearing on the long-wavelength slope of the end absorption. In comparison, 6-hydroxythiobinupharidine in acid solution exhibited absorption at 292 nm (ε 3,200).[5] The CD of 6′-hydroxythiobinupharidine in neutral solution exhibited a weak positive band at 250 nm and a moderate negative band at 228 nm. However, as shown in Figure 2, acidification of the solution generated a new positive band at 280 nm and an even stronger positive band at 241 nm. Clearly, a comparison of the curves (Figure 2) of 6,6′-dihydroxythiobinupharidine, 6-hydroxythiobinupharidine, and 6′-hydroxythiobinupharidine, all in acid solution, reveals that both C-6 and C-6′ thiobinupharidine hemiaminals give positive CD bands, but that the C-6 monohemiaminals absorb at longer wavelengths than the C-6′ monohemiaminals.

6-Hydroxythionuphlutine B (8). A 2-mg sample of this alkaloid also was isolated from *N. luteum*. There was insufficient material for a combustion analysis. However, the high-resolution mass spectrum indicated that the molecular formula was $C_{30}H_{42}N_2O_3S$. The ir exhibited hydroxyl and Bohlmann band absorption. The nmr (Table I) showed one C-6 hemiaminal proton at δ 4.08 and one C-6 equatorial proton α to nitrogen at δ 2.88. In the mass spectrum *m/e* 176 and 178 were of nearly the same intensity, an observation which suggested that the hemiaminal hydroxyl was at C-6, not C-6′.

Reduction of 6-hydroxythionuphlutine B with sodium borohydride gave thionuphlutine B (**9**), whose tlc properties agreed with those of an authentic sample but differed from those of thiobinupharidine (**6**) and neothiobinupharidine (**10**). Reduction of the monohemiaminal with sodium borodeuteride gave a singly labeled thionuphlutine B. Significantly *m/e* 178 was shifted to *m/e* 179 by more than 90%. This result, coupled with the previously described mass spectral studies of singly labeled thiobinupharidines, meant that the hemiaminal hydroxyl of 6-hydroxythionuphlutine B could be attached to C-6. The CD (Figure 3) confirmed this choice. In acidic ethanol solution, 6-hydroxythionuphlutine B showed a negative CD band at 298 nm. This observation agrees with the negative CD band in the same region exhibited by 6,6′-dihydroxythionuphlutine B (Figure 3) and the fact that the immonium perchlorate derived from 7α-methylthiodeoxynupharidin-6β-ol also gives a negative band in the same region.[8]

The negative CD band exhibited by 7-hydroxythionuphlutine B also confirms that this monohemiminal cannot belong to the stereoisomeric thiobinupharidine series or to a fourth, still unknown, stereoisomeric series represented by structure **12**,[12] since both of the latter two would show positive CD bands in the 300-nm region. While the appearance of the negative CD band at 298 nm does not distinguish 6-hydroxythionuphlutine B from still unknown 6-hydroxyneothiobinupharidine (**13**), the above-mentioned tlc properties of the fully reduced thiaspiranes do. Therefore the structure **8** is assigned to the newly isolated 6-hydroxythionuphlutine B.

6′-Hydroxythionuphlutine B (14). Careful reduction of 6,6′-dihydroxythionuphlutine B (**2**) with sodium borohydride gave a mixture of products of which the major component had tlc properties different from those of the starting bishemiaminal, 6-hydroxythionuphlutine B, and fully reduced thionuphlutine B. There was insufficient material for combustion analysis but the high-resolution mass spectrum indicated that the molecular formula was $C_{30}H_{42}N_2O_3S$. The ir exhibited hydroxyl and Bohlmann band absorption. The mass spectrum showed a strong peak at *m/e* 178 but a weak one at *m/e* 176 and thus indicated that the hemiaminal hydroxyl was located at C-6′. The nmr (Table I) showed one C-6 hemiaminal proton at δ 3.94 and one C-6 equatorial proton α to nitrogen at δ 2.70.

Reduction of this monohemiaminal with sodium borodeuteride gave thionuphlutine B-6′-d_1 (**15**) whose tlc properties were identical with those of an unlabeled sample of thionuphlutine B. The mass spectral study showed that *m/e* was shifted to *m/e* 179 by only 10% and indicated

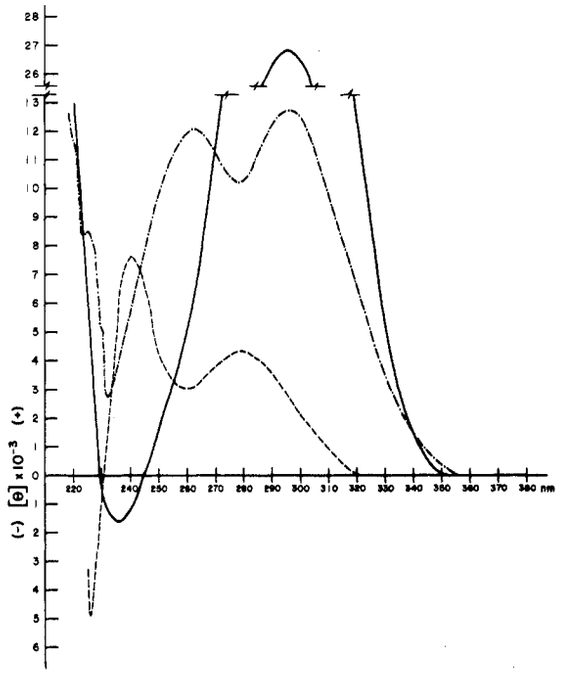


Figure 2. The circular dichroism of 6-hydroxythiobinupharidine (**1**) (——), 6′-hydroxythiobinupharidine (**4**) (– – –), and 6,6′-dihydroxythiobinupharidine (**3**) (— · —) in EtOH with added $HClO_4$.

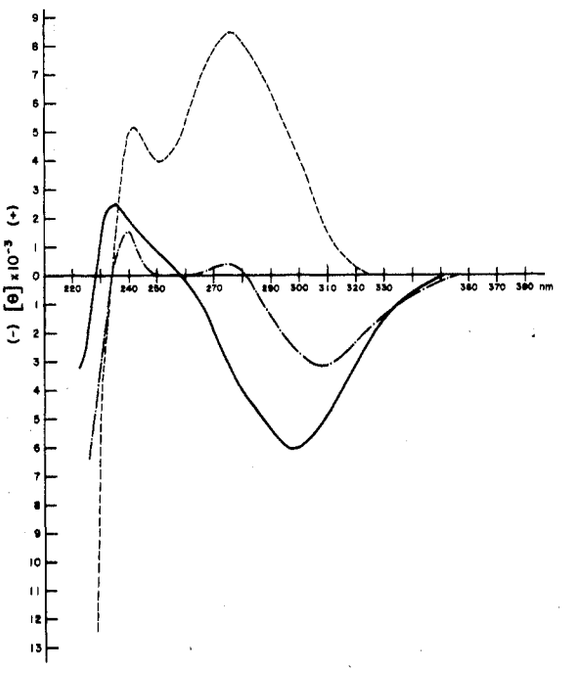
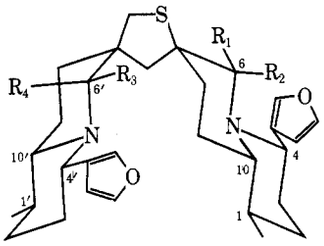
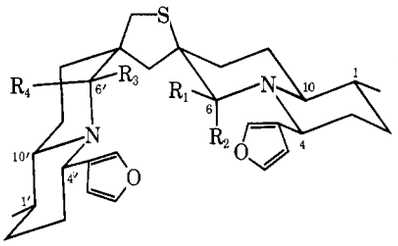


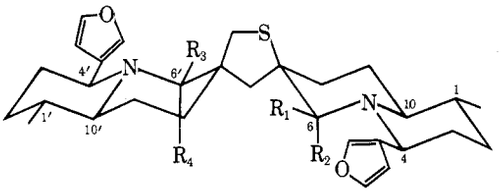
Figure 3. The circular dichroism of 6-hydroxythionuphlutine B (**8**) (——), 6′-hydroxythionuphlutine B (**14**) (- - -), and 6,6′-dihydroxythionuphlutine B (**2**) (— · —) in EtOH with added $HClO_4$.



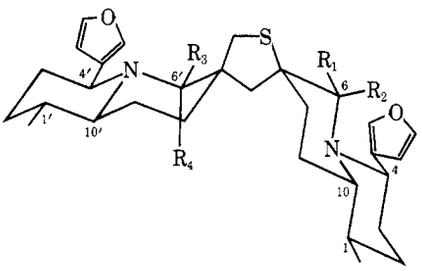
1, R_1+R_2 = OH + H; R_3+R_4 = OH + H
3, R_1+R_2 = OH + H; $R_3 = R_4$ = H
4, $R_1 = R_2$ = H; R_3+R_4 = OH + H
5, R_1+R_2 = OH + H; R_3 = H; R_4 = D
6, $R_1 = R_2 = R_3 = R_4$ = H
7, $R_1 = R_2 = R_3$ = H; R_4 = D



2, R_1+R_2 = OH + H; R_3+R_4 = OH + H
8, R_1+R_2 = OH + H; $R_3 = R_4$ = H
9, $R_1 = R_2 = R_3 = R_4$ = H
11, $R_1 = R_3 = R_4$; R_2 = D
14, $R_1 = R_2$ = H; R_3+R_4 = OH + H
15, $R_1 = R_2 = R_3$ = H; R_4 = D



10, $R_1 = R_2 = R_3 = R_4$ = H
13, R_1+R_2 = OH + H; $R_3 = R_4$ = H



12, $R_1 = R_2 = R_3 = R_4$ = H

thereby that the deuterium label was located at C-6′ and that the hydroxyl group in the precursor hydroxythionuphlutine B was at the same position.

The uv of 6′-hydroxythionuphlutine B was similar to that of 6′-hydroxythiobinupharidine. In neutral solution the former exhibited only strong end absorbtion, but in acidic solution it showed an absorption maximum at 274 nm (ε 940). The CD of 6′-hydroxythionuphlutine B determined in neutral solution showed a negative CD band at 249 nm but in acidic solution positive bands at 275 and 241 nm emerged (Figure 3). These CD results correspond to those observed in the case of 6′-hydroxythiobinupharidine and agree completely with the structure assigned to 6′-hydroxythionuphlutine B (14).

Experimental Section

Spectra were obtained as follows: nmr in solution as indicated, 2% TMS (δ 0.0), on Varian A-60, HA-100, and XL-100 Fourier transform spectrometers, symbols br, d, q, and m refer to broad, doublet, quartet, and multiplet, respectively; ir in KBr and in solution as indicated; mass spectra on a Hitachi Perkin-Elmer RMU6E using a direct inlet probe and other conditions as indicated; high-resolution mass spectra were determined at the High Resolution Mass Spectrometry Laboratory, Battelle's Columbus Laboratories, Columbus, Ohio, AEI MS-9 using a direct inlet probe and other conditions as indicated. Melting points were determined on a Köfler micro hot stage and a Mel-Temp apparatus and are uncorrected. Optical rotations were determined in solution as indicated on a Perkin-Elmer 141 polarimeter. The circular dichroism (CD) was determined on a Jasco Model 5 spectropolarimeter in solution at the concentrations indicated. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Thin layer chromatography was carried out on microscope slides uniformly coated with alumina HF_{254} and using the solvent indicated. The sodium borodeuteride was purchased from Merck, Sharp and Dohme and contained a minimum of 98% deuterium.

Isolation of 6′-Hydroxythiobinupharidine (4). As described earlier,[4] elution of a *Nuphar luteum* extract from alumina, using first hexane and then C_6H_6, gave fractions (A1–A7) yielding thiobinupharidine and neothiobinupharidine. Continued elution with 100 ml of 20% CH_2Cl_2–C_6H_6 gave fraction A8; two 300-ml portions of 50% CH_2Cl_2–C_6H_6 gave fractions A9 and A10; three 200-ml portions of CH_2Cl_2 gave fractions A11–A13; and finally 400 ml of MeOH gave fraction A14. Fraction A11 (136 mg) was chromatographed on a column of neutral alumina (activity 2.5) using C_6H_5N–EtOEt–hexane (3:10:37). Sixty-one (B1–B61), 5-drop fractions were taken after the first Dragendorff active substance was detected in the effluent. Continued elution with two 15-ml portions and then one 30-ml portion of the same solvent gave B62, 63, and 64, respectively. Finally the column was eluted with 50 ml of MeOH, which gave 32.8 mg of brown oil. Combined B62–63 gave 57 mg of **4**: tlc (C_5H_5N–EtOEt–hexane, 6:20:74) R_f 0.36; $[\alpha]^{25}D$ + 34° (*c* 10 mg/ml, 95% EtOH); uv (neutral 95% EtOH) λ_{max} 204 nm (ε 35,000); uv (acidic 95% EtOH) $\lambda_{max\,1}$ 204 nm (ε 29,000), $\lambda_{max\,2}$ 279 (830); ir (CCl_4) 2.75 (w, OH), 3.59 (m, Bohlmann bands), 11.45 μ (s, 3-furyl); nmr (60 MHz, $CDCl_3$) δ 0.92 (d, *J* = 3 Hz, 6 H, C-1 CH_3), 2.46 (absent when D_2O is added, d, *J* = 4 Hz, 1 H, OH), 2.16, 2.36, 2.69, 2.90 (AB q centered at δ 2.53, *J* = 11.5 Hz, CH_2S), 2.83 (d of d, *J* = 11 and 1.5 Hz, 1 H, C-6 H_{eq}), 2.94 (br t, 1 H, C-4 H_{ax}), 3.62 (t, 1 H, C-4′ H_{ax}), 4.25 (br d but br s on addition of D_2O, 1 H, HOC-6 H), 6.36 (br s, 2 H, β-furyl H), 7.35 (m, 4 H, α-furyl H); mass spectrum (70 eV, 120°) *m/e* (rel intensity) 510 (7.7) (M^+), 509 (1.5) ($M^+ - H$), 508 (1.5) ($M^+ - H_2$), 492 (60) ($M^+ - H_2O$), 262 (15), 230 (69), 178 (100), 176 (13), 136 (8), 107 (40), 94 (26), 81 (18); high-resolution mass spectrum (70 eV, 200°) obsd/calcd mass (formula), 492.2782/492.2810 ($C_{30}H_{40}N_2O_2S$); CD (*c* 0.3 mg/ml, neutral 95% EtOH *l* = 0.1 dm) $[\theta]_{270}$ ±0°, $[\theta]_{258}$ + 530°, $[\theta]_{250}$ +850°, $[\theta]_{244}$ 530°, $[\theta]_{240}$ ±0°, $[\theta]_{232}$ −2650°, $[\theta]_{288}$ −5900°, $[\theta]_{225}$ 5100°; CD (*c* 0.3 mg/ml, acidic 95% EtOH, *l* = 0.1 dm) $[\theta]_{320}$ ±0°, $[\theta]_{300}$ +2110°, $[\theta]_{288}$ +3810°, $[\theta]_{380}$ +4350°, $[\theta]_{266}$ +3400°, $[\theta]_{260}$ +3070°, $[\theta]_{250}$ +4250°, $[\theta]_{248}$ +5300°, $[\theta]_{241}$ +7650°, $[\theta]_{234}$ +4040°, $[\theta]_{230}$ −960°, $[\theta]_{266}$ −4900°, $[\theta]_{225}$ −3200°.

A 10-mg sample of 4 was treated with 0.2 ml of *M* aqueous $HClO_4$ (2 equiv) and sufficient acetone to obtain a homogeneous solution. The solvent was evaporated and the residue was recrystallized from MeOH, giving the immonium ammonium diperchlorate: mp 216–220°; ir (KBr) Bohlmann bands absent, 6.02 μ (m, > C=N^+<).

Anal. Calcd for $C_{30}H_{42}N_2O_{10}SCl_2$: C, 51.93; H, 6.11; N, 4.04; S, 4.62. Found: C, 51.77; H, 6.06; N, 4.06; S, 4.56.

Thiobinupharidine-6′-d_1 (7) from 6′-Hydroxythiobinupharidine (4). To a solution of 8 mg of 4 in methanol at 0° was added 20 mg of $NaBD_4$. After 10 min the solvent was vacuum evaporated and the residue was mixed with 1 ml of H_2O and 1 ml of CH_2Cl_2. The H_2O layer was extracted repeatedly with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and the solvent was vacuum evaporated to afford 6 mg of colorless residue which was taken up in 20 ml of C_6H_6. The resulting solution was passed through 6 g of neutral alumina. Vacuum evaporation of the C_6H_6 gave 5.3 mg of colorless, oily 7 which in time became crystalline: mp 130–132.5°; $[\alpha]D$ +6.5 (*c* 4.8 mg/ml, 95% EtOH); ir (CCl_4) 3.60 (s, Bohlmann bands), 4.92 μ (w, CD); nmr (100 MHz, C_6D_6) same as that of thiobinupharidine except δ 3.16 (br s, 1.82 H including δ 3.10, C-6′ H_{eq}), 3.10 (d of d, 1.82 H including δ 3.16, C-6 H_{eq}), 1.41

(d, C-6′ H_{ax} absent); mass spectrum *m/e* (rel intensity) 495 (45) (M^+, 11% d_0, 83% d_1, 6% d_2), 360 (15), 231 (24), 230 (57), 179 (23), 178 (100), 136 (9), 107 (22), 94 (14), 81 (10), 79 (8).

Thiobinupharidine-6′-d_1 (7) from 6,6′-Dihydroxythiobinupharidine (1). One or two particles of $NaBD_4$ were added at one time to a solution of 18 mg of 1 in 5 ml of MeOH. Addition of $NaBD_4$ (five particles) was continued until the presence of thiobinupharidine was detected by tlc (20 drops of *t*-BuOH in 10 ml of C_6H_6). At this point, tlc showed the presence of three components, 6,6′-dihydroxythiobinupharidine (R_f 0.36), 6-hydroxythiobinupharidine (R_f 0.56), the major component, and thiobinupharidine (R_f 0.85). Processing the reaction mixture in the usual manner[13] gave 16 mg of residue, which was separated on a column of 6 g of neutral alumina (activity 2.5). The column was eluted with 20 ml of C_6H_6, giving fraction 1; 29 ml of C_6H_6 which contained 5 drops of *t*-BuOH–10 ml of C_6H_6, giving fraction 2; the latter solvent collected in 13 3-drop fractions, giving fractions 3–15; and 15 ml of the same solvent, giving fraction 16. Fractions 1 and 16 consisted of 4 mg of thiobinupharidine-6,6′-d_2 and 0.7 mg of dihydroxythiobinupharidine, respectively. Combined fractions 3–15 yielded 8 mg of **5**: ir (CH_2Cl_2) 2.80 (OH), 2.43–2.52 (CH), 2.61 (Bohlmann bands), 4.90 (CD), and 11.45 μ (3-furyl); uv (acidic, MeOH) 292 nm (ϵ 3400); nmr (60 MHz, $CDCl_3$) δ 2.95 (br d, 1 H, C-6 H_{eq}), 1.4 (d, J = 11 Hz) absent; mass spectrum *m/e* (rel intensity) 511 (11) (M^+, 6% d_0, 87% d_1, 7% d_2), 493 (100), 231 (67), 230 (65), 229 (53), 228 (92), 179 (17), 178 (16), 177 (24), 176 (96), 136 (15), 107 (40), 94 (40), 81 (25), 79 (30).

The above-described sample of **4** in 1 ml of MeOH was treated with 20 mg of $NaBH_4$ and the resulting mixture was stored under N_2 at 25° for 2 days. Thereafter tlc (20 drops of *t*-BuOH–10 ml of C_6H_6) showed only thiobinupharidine (R_f 0.85). Processing the reaction mixture in the usual manner[13] gave 11 mg of residue, which was chromatographed on 5 g of neutral alumina (activity 2). Elution of the column with 30 ml of C_6H_6 gave 8 mg of colorless, oily thiobinupharidine-6′-d_1 which in time became crystalline: mp 131–132.5°; admixture with a sample from $NaBD_4$ reduction of 6′-hydroxythiobinupharidine, mp 130–132.5°; ir (CCl_4) and nmr (100 MHz C_6D_6) identical with spectra of a sample from $NaBD_4$ reduction of 6′-hydroxythiobinupharidine; mass spectrum *m/e* (rel intensity) 495 (30) (M^+, 9% d_0, 89% d_1, and 2% d_2), 360 ((13), 231 (22), 230 (47), 179 (25), 178 (100), 136 (10), 107 (23), 94 (15), 81 (11), 79 (11).

6′-Hydroxythionuphlutine B (14) from 6,6′-Dihydroxythionuphlutine B (2). A solution of 15 mg of **2**[2] in 5 ml of MeOH was treated with particles of $NaBH_4$ at −77° until **2** was no longer observed in the tlc [20% acetone–hexane, R_f 0.36 (6′-hydroxythionuphlutine B), 0.46 (6-hydroxythionuphlutine B), 0.71 (thionuphlutine B)]. Processing the reaction mixture in the normal manner[13] gave 12.5 mg of oily residue which was chromatographed on 7 g of neutral alumina (activity 3). Elution with 20 ml of C_6H_6 gave 6.2 mg of thionuphlutine B.[2] Continued elution with 20% acetone–hexane gave 7.9 mg of impure **14** which was applied, in a minimum amount of C_6H_6, to a column of 10 g of neutral alumina (activity 2). Elution with 10% acetone–hexane continued until the effluent was Dragendorff active; thereafter, 32 10-drop fractions were taken. Fractions 16–32 were combined to give 4.5 mg of pure **14**: tlc (20% acetone–hexane) R_f 0.5; ir (CH_2Cl_2) 2.75, 2.60 (m, Bohlmann band), 11.45 μ (3-furyl); uv (neutral 95% EtOH) end absorption; uv (acidic 95% EtOH) λ_{max} 205 nm (ϵ 24,400), $\lambda_{max\,2}$ 274 (940); nmr (100 MHz, $CDCl_3$) δ 0.89 (d, J = 6 Hz, 6 H), 2.31, 2.45, 2.63, 2.75 (AB q centered at δ 2.53, J = 12 Hz, 2 H, CH_2S), 2.70 (d of d, J = 11 and 2 Hz, 1 H, C-6 H_{eq}), 2.95 (m, 1 H, C-4H), 3.50 (m, 1 H, C-4′ H), 3.94 (d, J = 4 Hz, 1 H, C-6′ H), 6.20 (m, 1 H, β-furyl H), 6.43 (m, 1 H, β-furyl H), 7.30 (m, 4 H, α-furyl H); mass spectrum (70 eV, 110°) *m/e* (rel intensity) 510 (0.5) (M^+), 509 (0.5) ($M^+ - H$), 508 (0.5) $M^+ - H_2$), 492 (100) ($M^+ - H_2O$), 262 (14), 230 (60), 228 (22), 178 (74), 176 (13), 136 (5), 107 (37), 94 (30), 81 (18); high-resolution mass spectrum (70 eV, 150°) obsd/calcd mass (formula), 510.2846/510.2916 ($C_{30}H_{42}N_2O_3S$), 509.2656/509.2838 ($C_{30}H_{41}N_2O_3S$), 508.2710/508.2759 ($C_{30}H_{40}N_2O_3S$), 492.2756/492.2810 ($C_{30}H_{40}N_2O_2S$); CD (*c* 0.28 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{288}$ ±0°, $[\theta]_{276}$ −450°, $[\theta]_{266}$ −810°, $[\theta]_{257}$ −2520°, $[\theta]_{249}$ $[\theta]_{243}$ −2780°, $[\theta]_{238}$ −990°, $[\theta]_{236}$ 990°, $[\theta]_{231}$ 3680°, $[\theta]_{228}$ 7360°, $[\theta]_{227}$ 4850°; CD (*c* 0.28 mg/ml, acidic 95% EtOH, *l* = 0.1 dm), $[\theta]_{325}$ ±0°, $[\theta]_{313}$ +900°, $[\theta]_{298}$ +4500°, $[\theta]_{288}$ +6750°, $[\theta]_{277}$ +8450°, $[\theta]_{274}$ +8450°, $[\theta]_{263}$ +6460°, $[\theta]_{257}$ +4670°, $[\theta]_{250}$ +3960°, $[\theta]_{241}$ +5210°, $[\theta]_{238}$ +4140°, $[\theta]_{234}$ ±0°, $[\theta]_{230}$ −4120°, $[\theta]_{228}$ −12,500°, $[\theta]_{225}$ −18,000°.

Thionuphlutine B-6′-d_1 (15) from 6′-Hydroxythionuphlutine B (14). A solution of 0.5 mg of 14 in MeOH at 25° was treated with 5 mg of $NaBD_4$ until tlc (15% acetone–hexane) showed no remaining **14**. Processing the reaction mixture in the normal manner[13] gave 0.1 mg of residue which was chromatographed on 1 g of neutral alumina (activity 3). Elution with 25 ml of C_6H_6 afforded 0.1 mg of **15**: tlc (10% EtOEt–hexane) R_f 0.50, (40% isooctane–CH_2Cl_2) R_f 0.35, (10% CH_2Cl_2–C_6H_6) R_f 0.52, (C_6H_6) R_f 0.35, which in each case was the same as that for an authentic sample of thionuphlutine B; mass spectrum *m/e* (rel intensity) 495 (31) (M^+, 11% d_0, 89% d_1), 360 (13), 231 (26), 230 (52), 179 (26), 178 (100), 136 (11), 107 (24), 94 (15), 81 (4).

6-Hydroxythionuphlutine B (8). Fraction A66 (53 mg), obtained in the same elution chromatography from which 6-hydroxythiobinupharidine was obtained,[5] was eluted from a column of 20 g of neutral alumina (activity 2) with 30 ml of hexane, to give fraction E1, and then with 5% acetone in hexane, which contained 60 drops of *t*-BuOH per 100 ml of solvent. Fractions E2–33, each containing 20 drops of the latter solvent, were taken. Fractions E19–25 were combined to obtain 2 mg of **8**: tlc (10% acetone–hexane and 60 drops of *t*-BuOH/100 ml) R_f 0.32; ir (CCl_4) 2.66 (OH), 3.55 (Bohlmann band), 6.65 and 11.51 μ (3-furyl); nmr (100 MHz, $CDCl_3$) δ 0.88 (d, J = 5 Hz, 6 H, C-1 and C-1′ CH_3), 2.32 (AB q, J = 12 Hz, 2 H, CH_2S), 2.88 (2, H, C-6′$_{eq}$ and C-4′ H), 3.55 (1 H, C-4 H), 4.08 (1 H, >NCHOH), 6.22 and 6.41 (2 H, β-furyl H), 7.27 (4 H, α-furyl H); mass spectrum *m/e* (rel intensity) 510 (2), 493 (10), 492 (21), 477 (1.5), 461 (2), 359 (5.5), 230 (100), 228 (15), 178 (45), 176 (30), 136 (7), 107 (18), 94 (14), 81 (13); high-resolution mass spectrum (70 eV, 160°) obsd/calcd mass (formula) 510.2883/510.2916 ($C_{30}H_{42}N_2O_3S$), 509.2827/509.2828 ($C_{30}H_{41}N_2O_3S$), 508.2745/508.2759 ($C_{30}H_{40}N_2O_3S$), 493.2830/493.2889 ($C_{30}H_{41}N_2O_2S$), 492.2750/492.2810 ($C_{30}H_{40}N_2O_2S$); CD (*c* 1.0 mg/ml, 95% EtOH + 3 drops of aqueous 1 *N* HCl) $[\theta]_{350}$ ±0°, $[\theta]_{330}$ −1430°, $[\theta]_{314}$ −4100°, $[\theta]_{298}$ −6010°, $[\theta]_{280}$ +4100°, $[\theta]_{270}$ +1840°, $[\theta]_{258}$ ±0°, $[\theta]_{245}$ +1530°, $[\theta]_{235}$ +2550°, $[\theta]_{230}$ +1530°, $[\theta]_{228}$ ±0°, $[\theta]_{222}$ −3260°, $[\theta]_{220}$ −1530°.

By similar, repeated elution chromatography of fractions A63–65[5] an additional 2-mg sample of **8** was obtained.

Thionuphlutine B (9) from 6-Hydroxythionuphlutine B (8). A solution of 0.5 mg of **8** in MeOH at 25° was treated with 5 mg of $NaBH_4$ for 30 min. Thereafter the MeOH was vacuum evaporated and the residue was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated for studies of tlc properties: tlc (10% EtOEt–hexane) R_f 0.50, (40% isooctane–CH_2Cl_2) R_f 0.35, (CH_2Cl_2–C_6H_6) R_f 0.52, (C_6H_6) R_f 0.35, which in each case was the same as that for an authentic sample of thionuphlutine B obtained from reduction of 6,6′-dihydroxythionuphlutine B[2] but different from that of thiobinupharidine [tlc (10% EtOEt–hexane) R_f 0.61, (40% isooctane–CH_2Cl_2) R_f 0.56, (10% CH_2Cl_2–C_6H_6) R_f 0.70, (C_6H_6) R_f 0.50] and different from that of neothiobinupharidine [tlc (10% EtOEt–hexane) R_f 0.2, (40% isooctane–CH_2Cl_2) R_f 0.12, (10% CH_2Cl_2–C_6H_6) R_f 0.18, (C_6H_6) R_f 0.16]; mass spectrum *m/e* (rel intensity) 494 (26), 359 (11), 231 (15), 230 (47), 179 (14), 178 (100), 136 (11), 107 (22), 94 (27), 81 (14).

Thionuphlutine B-6-d_1 (11) from 6-Hydroxythionuphlutine B (8). A solution of 2 mg of **8** in 5 ml of methanol was treated with 10 mg of $NaBD_4$, the reaction mixture was processed in the usual manner,[13] and the crude **11** was purified on a column of alumina (activity 2) using 10% EtOEt–hexane as the eluting solvent to obtain pure **11**: ir (CCl_4) 3.56 (Bohlmann bands), 4.9 (CD), 6.17 and 11.47 μ (3-furyl); mass spectrum *m/e* (rel intensity) 495 (25) (M^+), 462 (3), 448 (4), 360 (13), 231 (34), 179 (100), 136 (12), 107 (26), 94 (17), 81 (12), 79 (13).

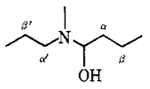
Registry No.—**1**, 30343-70-5; **2**, 30343-71-6; **3**, 50478-55-2; **4**, 52002-85-4; **4** immonium ammonium perchlorate, 52002-88-7; **5**, 52002-89-8; **7**, 52079-26-2; **8**, 52002-90-1; **9**, 30343-74-9; **11**, 52079-24-0; **14**, 52002-84-3; **15**, 52079-25-1.

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.
(2) R. T. LaLonde, C. F. Wong, and W. P. Cullen, *Tetrahedron Lett.*, 4477 (1970).
(3) 6,6′-Dihydroxythiobinupharidine had originally been named 6,6′-dihydroxythionuphlutine A (ref 2) but the latter name was dropped when it was discovered (ref 4) that thionuphlutine A and thiobinupharidine were identical.
(4) R. T. LaLonde and C. F. Wong, *Phytochemistry*, **11**, 3305 (1972).
(5) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, **95**, 6342 (1973).
(6) T. I. Martin, D. B. MacLean, J. T. Wróbel, A. Iwanow and W. Starzec [*Can. J. Chem.*, **52**, 2705 (1974)] have recently reported the structure

of this same monohemiaminal which they refer to as thionupharoline. We wish to thank Professor MacLean for communicating his results to us prior to publication.

(7) We erroneously referred to α-thiohemiaminals as β-thiohemiaminals in an earlier paper (ref 5). The α and β positions of a hemiaminal are designated as follows. The α and β positions of the corresponding immonium ion are similarly designated.



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(12) Conceivably an A'B' quinolizidine moiety belonging to the same absolute configurational series as (−)-deoxynupharidine combined with an AB hemiaminal belonging to the enantiomeric deoxynupharidine series could also give a C_{30} thiaspirane possessing a negative CD band in the 300-nm region. However, (+)-deoxynupharidine has never been reported nor has its incorporation in any of the Nuphar alkaloids been observed. Therefore we assume that all quinolizidine moieties of the thiaspiranes belong to the same enantiomeric series as (−)-deoxynupharidine.

(13) The work-up procedure is the same as that described above in the conversion 6'-hydroxythiobinupharidine to thiobinupharidine-6'-d_1.

Reaction of Phosgene with *N*-Methyleneaniline Derivatives

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Received May 7, 1974

The reaction of *N,N'*-diphenylmethylenediamine (**1**) and 1,3,5-triphenylhexahydro-*s*-triazine (**2**) with phosgene is accompanied by cleavage of a carbon–nitrogen bond to give *N*-chloromethyl-*N*-phenylcarbamoyl chloride (**5**) and 1,3,5-trisaza-1,3,5-triphenyl-1,5-bis(chloroformyl)pentane (**7**), respectively. 4-Aminobenzylaniline upon reaction with phosgene produces *N*-phenyl-*N*-4-isocyanatobenzylcarbamoyl chloride in high yield, which on reaction with hydrogen chloride undergoes a carbon–nitrogen bond cleavage to give phenyl isocyanate and 4-isocyanatobenzyl chloride.

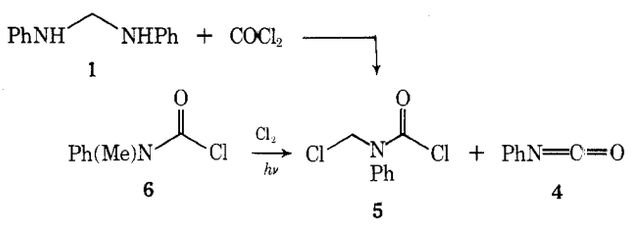
The reaction of aniline with aqueous formaldehyde in the presence of mineral acids to give diphenylmethane derivatives proceeds in two steps. Initially, phenyl-*N,N*-acetals of formaldehyde are formed, which rapidly rearrange in the presence of the acid catalyst to give benzylamines and finally diphenylmethane derivatives.[1] These di- and oligomeric amines are the precursors of commercially important di- and polyisocyanates. It is of interest to study the reaction of the intermediate products with phosgene, because small amounts could be present in the polyamine mixture.

Reaction of aniline with aqueous formaldehyde in the absence of acid produces a mixture of phenyl-*N,N*-acetals (aminals) in which *N,N'*-diphenylmethylenediamine (**1**) and 1,3,5-triphenylhexahydrotriazine (**2**) could be detected by nmr spectroscopy. Using a ratio of aniline–formaldehyde of 10:1 only one methylene signal at δ 4.45 (attributed to **1**) was present, while a solution prepared from a ratio of aniline–formaldehyde of 2:1 showed two methylene signals at δ 4.4 and 4.75 ppm (attributed to **1** and **2**; ratio approximately 1:1).

In order to investigate the reaction of *N*-methyleneanilines with phosgene, model compounds **1** and **2** were synthesized independently.[2] The model compound selected for the benzylamine intermediates, *p*-aminobenzylaniline (**3**), was prepared by reduction of the Schiff base[3] derived from *p*-nitrobenzaldehyde and aniline (Scheme III). The literature procedure,[4] using 4-nitrobenzyl chloride and aniline, followed by reduction did not produce **3** in our hands.

The model compounds with the exception of **2** are secondary amines, and formation of disubstituted carbamoyl chlorides is expected in their reaction with phosgene.[5] However, complications could arise due to the lability of the carbon–nitrogen bonds in phenyl-*N,N*-acetals of formaldehyde, and to a lesser degree in benzylamines. When **1** was treated with excess phosgene, a mixture of products was obtained which contained phenyl isocyanate (**4**) and the novel *N*-chloromethyl-*N*-phenylcarbamoyl chloride (**5**). The latter compound was synthesized independently in 80% yield by monochlorination of *N*-methyl-*N*-phenylcarbamoyl chloride (**6**) (Scheme I). Initial attack of phosgene on one of the nitrogens of **1** leads to the formation of hydrogen chloride, which cleaves the other carbon–nitrogen bond. This pathway explains both of the observed reaction products.

Scheme I



The reaction of **2** with phosgene gave **5**, the novel biscarbamoyl chloride **7** and a third unknown product of intermediate molecular weight as observed by gel permeation chromatography. Since the center nitrogen atom in **7** is the most likely site of attack of phosgene, the unknown compound could have the biscarbamoyl chloride structure **8** (see Scheme II), based on comparative gel permeation chromatography with **5** and **7**. The nmr spectrum of the biscarbamoyl chloride **7** shows, as expected, only one signal for the methylene protons at δ 4.85 ppm; the mass spectrum of the compound shows, due to its thermal lability, only fragments (HCl, $PhNCH_2$, PhNCO, PhN, etc.) and no molecular ion peak.