Thiospiran, C_{30}, *Nuphar* Alkaloids. Structure and Evidence for Intramolecular Sulfur–Immonium Ion Interactions[1]

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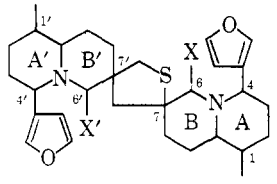
Abstract: Three-dimensional structures of the title alkaloids are proposed on the basis of: (1) showing that the relative configuration of C-1, C-4, and C-10 of the AB and A′B′ quinolizidine systems is the same as the relative configuration of these centers in deoxynupharidine; (2) demonstrating that the carbon atom of the CH_2S group is attached to the A′B′ quinolizidine system in both alkaloids in an equatorial fashion; and (3) showing that the sulfur atom of the CH_2S group is attached in an equatorial fashion to the AB quinolizidine system of thiobinupharidine but is attached in an axial fashion to the AB quinolizidine system of thionuphlutine-*B*. Evidence for the sulfur atom stereochemistry in the AB quinolizidine systems came from an nmr determination of the steric course of sodium borodeuteride reduction of 6,6′-dihydroxythiobinupharidine and 6,6′-dihydroxythionuphlutine-*B*. 6-Hydroxythiobinupharidine was isolated from *Nuphar luteum*. The latter alkaloid, 6,6′-dihydroxythiobinupharidine, 6,6′-dihydroxythionuphlutine-*B*, and two newly synthesized model compounds, 7α-methylthio-7-epideoxynupharidin-6β-ol and 7β-methylthiodeoxynupharidin-6α-ol, in acid solution showed absorption maxima in the region of 290–295 nm (ε 1500–3200). Reduction of all of these compounds with sodium borodeuteride resulted in the incorporation of deuterium stereospecifically. The uv and reduction results are interpreted in terms of sulfur–immonium ion interaction.

The long known antibiotic activity[2] of various preparations of *Nuphar* plant material has been linked to the presence of of C_{30} alkaloids in these preparations. Early investigations of the chemistry of the C_{30} *Nuphar* alkaloids were carried out by Achmatowicz, who isolated a number of sulfur-containing bases.[3] Thiobinupharidine and neothiobinupharidine were among these bases. These are stereoisomers possessing structure **1**.



1, X = X′ = H
2, X = X′ = OH

The gross structure of thiobinupharidine remained uncertain until recently when it was observed[4] that this alkaloid is formed on hydride reduction of 6,6′-dihydroxythiobinupharidine[5] (**2**), a bishemiaminal isolated from a North American *Nuphar*. A second stereoisomeric bishemiaminal, 6,6′-dihydroxythionuphlutine-*B* (**2**), was isolated from the same plant.[2f] On reduction, this second bishemiaminal gave thionuphlutine-*B* (**1**).[5] Therefore three stereoisomeric bisamine alkaloids possessing gross structure **1** are now known.

The structure of neothiobinupharidine has been given three-dimensional expression in **3** as a result of X-ray crystallographic studies.[6,7] We have studied the stereochemistry of thiobinupharidine and thionuphlutine-*B* by other instrumental methods, chemical transformations, and comparisons to model compounds. We report here the evidence which establishes the three-dimensional structures of thiobinupharidine (**4**) and thionuphlutine-*B* (**5**).

Structures **3**–**6** represent four of 2^3 stereoisomers which are possible for gross structure **1**. These four are generated by choosing deoxynupharidine like quinolizidine moieties belonging to the same configurational series as the naturally occurring (−)-deoxynupharidine[8] or (−)-7-epideoxynupharidine[9] and joining these quinolizidine systems together through sulfur in each of four possible ways and in such a manner as to construct the central tetrahydrothiophene ring.

We will present our stereochemical evidence as answers to three questions. (1) Is the configuration at C-1(C-1′), C-4(C-4′), and C-10(C-10′) the same as that found in deoxynupharidine? (2) What is the stereochemistry of the CH_2S attachment to the A′B′ quinolizidine moiety? (3) What is the stereochemistry of the sulfur atom attachment to the AB quinolizidine moiety? In addition, we also present supporting evidence gained through the study of model compounds

(1) Work described herein was initiated under grants from the Federal Water Pollution Control Administration, U. S. Department of Interior, and the McIntire-Stennis Cooperative Forestry Research Program of the U. S. Department of Agriculture. Recent work was supported by the National Institute of Allergy and Infectious Diseases (Grant AI 10188), National Institutes of Health.

(2) (a) A. P. Tatarov, *Farmatsiya (Moscow)*, **8**, 29 (1945); (b) V. G. Drobat'ko, E. Ya. Rashba, B. E. Aizenman, S. I. Novikova, and N. B. Koganskaya, *Antibiotiki*, 22 (1958); *Chem. Abstr.*, **53**, 12589 (1959); (c) S. I. Novikova, *Mikrobiol. Zh. (Kiev)*, **22**, 67 (1960); *Chem. Abstr.*, **60**, 2041 (1964); (d) K. C. Bel'tyukova and L. T. Pastushenko, *ibid.*, **25**, 36 (1963); *Chem. Abstr.*, **59**, 5536 (1963); (e) British Patent 968042 (1964); *Chem. Abstr.*, **61**, 15939 (1964); (f) W. P. Cullen, R. T. LaLonde, C. J. Wang, and C. F. Wong, *J. Pharm. Sci.*, **62**, 826 (1973).

(3) (a) O. Achmatowicz and Z. Bellen, *Rocz. Chem.*, **36**, 1815 (1962); *Tetrahedron Lett.*, 1121 (1962); (b) O. Achmatowicz and J. T. Wrobel, *ibid.*, 129 (1964).

(4) R. T. LaLonde and C. F. Wong, *Phytochemistry*, **11**, 3305 (1972).

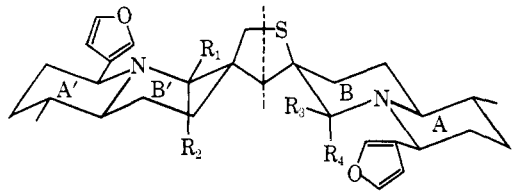
(5) R. T. LaLonde, C. F. Wong, and W. P. Cullen, *Tetrahedron Lett.*, 4477 (1970).

(6) G. I. Birnbaum, *ibid.*, 4149 (1965).

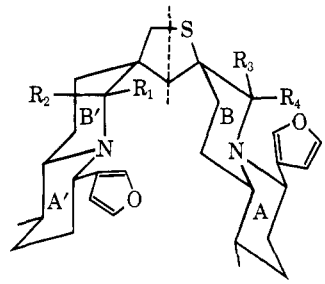
(7) The X-ray study on which the three-dimensional assignment is based shows that both deoxynupharidine moieties belong to the same enantiomeric series but did not settle the problem of which enantiomeric series. We tentatively assume in representing neothiobinupharidine in terms of **3** that the deoxynupharidine moieties of this molecule belong to the same enantiomeric series as (−)-deoxynupharidine itself (ref 8).

(8) (a) C. F. Wong, E. Auer, and R. T. LaLonde, *J. Org. Chem.*, **35**, 517 (1970); (b) K. Oda and H. Koyama, *J. Chem. Soc. B*, 1450 (1970); (c) I. Kawasaki, I. Kusumoto, and T. Kaneko, *Bull. Chem. Soc. Jap.*, **41**, 1264 (1968).

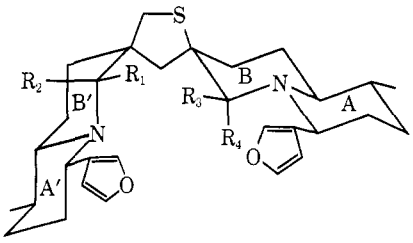
(9) C. F. Wong and R. T. LaLonde, *Phytochemistry*, **9**, 659 (1970).



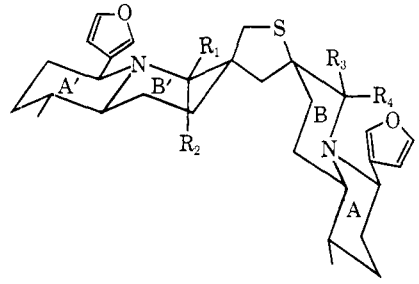
3, $R_1 = R_2 = R_3 = R_4 = H$



4, $R_1 = R_2 = R_3 = R_4 = H$
12, $R_1 = R_4 = H; R_2 = R_3 = D$
14, $R_1 = R_2 = H; R_3$ or $R_4 = OH,H$



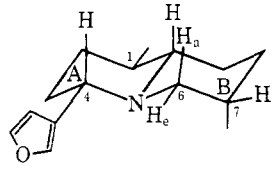
5, $R_1 = R_2 = R_3 = R_4 = H$
13, $R_1 = R_3 = H; R_2 = R_4 = D$



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

and show how the stereochemical evidence can be used in assigning the structure of a monohemiaminal, 6-hydroxythiobinupharidine.

Configuration of C-1(C-1′), C-4(C-4′), and C-10(C-10′). The intensity of Bohlmann ir absorption is proportional to the number of carbon–hydrogen bonds which are anticoplanar to the nonbonding electron pair of the adjacent quinolizidine nitrogen atom.[10] The C_{15} *Nuphar* alkaloid deoxynupharidine, **7**, possesses three such carbon–hydrogen bonds in a trans-fused quinolizidine ring.[11] We observe that solutions of thiobinupharidine, thionuphlutine-*B*, and deoxynupharidine of equal normality all exhibit Bohlmann bands (3.6–3.7 μ) of equal intensity and complexity. Therefore, both quinolizidine systems of the two C_{30}, sulfur-containing alkaloids are trans-fused.



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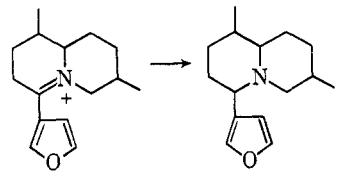
These ir results coupled with some findings[12] of Bohlmann also indicate that the 3-furyl groups are equatorial. Bohlmann found that hydride reduction of a mixture of four stereoisomeric immonium ions **8**



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produced six isomers of **9**, two of which were cis-fused quinolizidines as evidenced by the absence of Bohlmann bands. These two cis-fused quinolizidines must have been formed through inversion of the nitrogen in quinolizidines originally possessing axial 3-furyl groups attached to *trans*-quinolizidines since even the 1,7-diaxial dimethylquinolizidines possess trans-fused rings. The foregoing observation reveals the very strong bias toward the equatorial 3-furyl group. Since the ir of the two C_{30} alkaloids shows no loss of Bohlmann absorption relative to deoxynupharidine, the 3-furyl groups must also be equatorial in the C_{30} alkaloids. Confirming this conclusion is the appearance of the C-4 and C-4′ protons in the δ 2.7–3.1 region, the same region of the nmr spectrum where the resonance of the C-4 axial proton of deoxynupharidine is observed. Moreover in the case of thiobinupharidine, the 100-MHz nmr determined in benzene shows the two C-4 protons as two overlapping quartets both with splittings of 1.5 and 10 Hz. Such a splitting pattern would better be ascribed to an axial C-4 proton split by adjacent axial and equatorial protons than an equatorial C-4 proton split by the same pair.

Evidence for the stereochemistry of the C-1 methyl groups comes from observing the direction of the solvent-induced shift of the C-1 methyl groups in the nmr. We have used this method previously to assign methyl group stereochemistry in both the piperidine and quinolizidine type *Nuphar* alkaloids.[9,13,14] Thus axial and equatorial 1- and 3-methyl quinolizidines undergo downfield and upfield shifts, respectively, on changing the solvent from deuteriochloroform to benzene.[15] The case of deoxynupharidine (**7**) is typical.[9] The C-7 axial methyl is shifted downfield by 4.2 Hz and the C-1 equatorial methyl is shifted upfield by 5.0 Hz on changing the solvent as specified above. The same solvent change results in an upfield shift of 8 Hz for the methyl groups of thiobinupharidine and 7 Hz for the methyl groups of thionuphlutine-*B*. Therefore both methyl groups in both C_{30} alkaloids are equatorial.

(10) (a) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); (b) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962); (c) M. W. Wiewioroski and J. Skolick, *Bull. Acad. Pol. Sci., Ser. Sci.Chim.*, **10**, 1 (1962).

(11) For a review of the evidence see: (a) O. E. Edwards, "Cyclopentanoid Terpene Derivatives," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 6; (b) ref 8a.

(12) F. Bohlmann, E. Winterfeldt, P. Studt, H. Laurent, G. Boroschewski, and K-M. Kleine, *Chem. Ber.*, **94**, 3151 (1961).

(13) C. F. Wong and R. T. LaLonde, *Phytochemistry*, 9,1851 (1970).

(14) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, **94**, 8522 (1972).

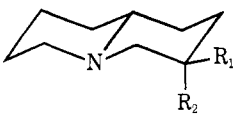
(15) R. T. LaLonde and T. N. Donvito, unpublished work in this laboratory.

In summary, the evidence indicates that all quinolizidines are trans-fused and the methyl and 3-furyl groups are equatorial. Therefore, the relative stereochemistry of C-1, C-4, and C-10 of deoxynupharidine is repeated in the quinolizidine systems of the two C_{30} alkaloids.[16]

Stereochemistry of the CH_2S Attachment to the A′B′ Quinolizidine Ring. The stereochemistry of the CH_2S attachment to the A′B′ quinolizidine ring has been treated earlier.[21] We will review briefly the results here.

An nmr study of a pair of model compounds, 3(e)-methyl-3(a)-methylthiomethylquinolizidine (**10**), and 3(a)-methyl-3(e)-methylthiomethylquinolizidine (**11**), showed that an axial CH_2S came into resonance downfield (23 Hz) relative to its equatorial counterpart. The same low field–high field relationship was observed for three pairs of axial and equatorial 3-oxymethylquinolizidines[21] and is well known for axial and equatorial 3-methylquinolizidines.[10b]

The chemical shifts of the CH_2S groups in neothiobinupharidine, thiobinupharidine, and thionuphlutine-*B* were determined to be δ 2.70, 2.32, and 2.33, respectively. According to X-ray crystallographic studies[6] of neothiobinupharidine (**3**) the CH_2S group attachment to the A′B′ quinolizidine moiety is axial. Therefore, since the CH_2S chemical shift of neothiobinupharidine is downfield by 27 Hz relative to thiobinupharidine and thionuphlutine-*B*, it was reasoned that the CH_2S group of the latter two alkaloids must be affixed in an equatorial fashion to the A′B′ quinolizidines rings as expressed in structures **4** and **5**.[22]



10, $R_1 = CH_3$; $R_2 = CH_2SCH_3$
11, $R_1 = CH_2SCH_3$; $R_2 = CH_3$

Stereochemistry of the Sulfur Attachment to the AB Quinolizidine Ring. The nmr of the C_{15} alkaloid deoxynupharidine, **7**, can serve as a guide to the interpretation of the more complex nmr of the C_{30} sulfur-containing *Nuphar* alkaloids.[23] Deoxynupharidine reveals two protons in the region of δ 2.7–3.1 and a third in the δ 1.7–1.8 region. The two protons at lower field are the C-6 equatorial and the C-4 axial protons. The proton in the higher field region is the C-6 axial proton. Accordingly, the nmr of thiobinupharidine reveals four protons, two C-6 equatorial and two C-4 axial protons, in the region of δ 2.7–3.1. The region δ 1.7–1.8 contains the two C-6 axial protons. The nmr of thionuphlutine-*B* is similar although the two C-6 equatorial and two C-4 axial protons fall in a somewhat extended region, δ 2.42–3.15. The two C-6 axial protons are best accounted for by integrating over the entire region of δ 1.0–2.0.

The sodium borodeuteride reduction of the bishemiaminal alkaloids 6,6′-dihydroxythiobinupharidine and 6,6′-dihydroxythionuphlutine-*B* gave thiobinupharidine-*6,6-d*$_2$ and thionuphlutine-*B*-*6,6′-d*$_2$, respectively.[5] Significantly, the nmr of thiobinupharidine-*6,6′-d*$_2$ shows two C-4 axial and one C-6 equatorial protons in the δ 2.7–3.1 region and one C-6 axial proton in the δ 1.7–1.8 region. In contrast, the nmr of thionuphlutine-*B*-*6,6′-d*$_2$ shows two C-4 axial and two C-6 equatorial protons in the δ 2.42–3.15 region. The region δ 1.0–2.0 contains two fewer protons than the same region in the nmr of the unlabeled sample. Clearly, thiobinupharidine-*6,6′-d*$_2$ contains one C-6 equatorial deuterium and one C-6 axial deuterium while thionuphlutine-*B*-*6,6′-d*$_2$ contains two C-6 axial deuteriums. This result was confirmed by comparing the intensity of the ir Bohlmann bands of labeled and unlabeled alkaloids. The intensity of the Bohlmann absorption of thiobinupharidine-*6,6-d*$_2$ was five-sixths of the absorption of the unlabeled sample while the intensity of the Bohlmann absorption of thionuphlutine-*B*-*6,6′-d*$_2$ was two-thirds of the absorption of the unlabeled sample.

The above results must mean that one set of two hemiaminal functions was reduced in the same steric mode but the second set of two hemiaminal functions was reduced in a different steric mode. Some agent must have induced the variable steric mode of deuterium incorporation in the second set of hemiaminal functions. We propose that this agent is the C-7 sulfur atom which interacts with C-6 in a three-membered ring during the course of immonium ion reduction and thereby induces the usual stereochemical results consistent with nucleophilic attack occurring with neighboring group participation. Therefore, the bishemiaminal which underwent reduction with the incorporation of one axial and one equatorial deuterium must contain an equatorial sulfur bonded to the AB quinolizidine system. This bishemiaminal was 6,6′-dihydroxythiobinuphari-

(16) We assume that both sets of C-1, C-4, and C-10 centers of thiobinupharidine and thionuphlutine-*B* belong to the same configurational series (1*R*, 4*S*, 10*S*) as (−)-deoxynupharidine., This assumption is made on the basis of: (1) the correlations of (−)-deoxynupharidine with (−)-nupharolutine[14,17] and (−)-7-epideoxynupharidine,[9,18] correlations which demonstrate that other quinolizidine type *Nuphar* alkaloids belong to the same 1*R*, 4*S*, 10*S* series as (−)-deoxynupharidine, (2) the X-ray study which indicates that both deoxynupharidine moieties of neothiobinupharidine belong to the same configurational series,[6,7] and (3) the structurally apparent but as yet unproven biogenetic scheme in which the C_{30} sulfur alkaloids are formed through oxidative elaboration of C-7 and the C-7 methyl groups of two (−)-deoxynupharidine molecules. The configurations of a number of the piperidine type *Nuphar* alkaloids also have been related to (−)-deoxynupharidine.[18-20]

(17) J. T. Wrobel, A. Iwanow, C. Braekman-Danhaux, T. I. Martin, and D. B. MacLean, *Can. J. Chem.*, **50**, 1831 (1972).

(18) R. T. LaLonde, E. Auer, C. F. Wong, and V. P. Muralidharan, *J. Amer. Chem. Soc.*, **93**, 2501 (1971).

(19) I. Kawasaki, S. Matsutani, and T. Kaneko, *Bull. Chem. Soc. Jap.*, **36**, 1474 (1963).

(20) Y. Arata and T. Ohashi, *Chem. Pharm. Bull.*, **13**, 1247 (1965).

(21) R. T. LaLonde, C. F. Wong, and H. G. Howell, *J. Org. Chem.*, **36**, 3703 (1971).

(22) The suitability of the pair of model compounds, **10** and **11**, for comparison with *Nuphar* alkaloids has been discussed with regard to the presence or absence of the 3-furyl group.[21] The anisotropic effect of the 3-furyl group is observed to shield axial and equatorial methyls or CH_2S groups to the same extent (5–6 Hz). Another point regarding model compound suitability is that the model quinolizidine pair contain only one quinolizidine system attached to the CH_2S in question, whereas the alkaloids which are being compared contain two quinolizidine systems, the second system (AB) being attached to the sulfur atom. The question arises whether or not this second quinolizidine system might have some affect on the chemical shift of the CH_2S groups. Comparison of the chemical shifts of the methyl groups attached to sulfur in the models **17** and **18** shows that the equatorial CH_3S in **18** comes into resonance 4 Hz downfield from the axial CH_3S in **17**. Therefore, the second quinolizidine system (AB) can be expected to have roughly one-sixth of the effect in the opposite direction compared to the quinolizidine system (A′B′) attached directly to the carbon of CH_2S. Since the magnitude of the A′B′ quinolizidine influence is so much greater than that of the AB system the model pair **10** and **11** appear to be appropriate for assigning CH_2S stereochemistry based on chemical shift differences.

(23) Proton assignments in the nmr of deoxynupharidine have been made[8a] and confirmed in deuterium labeling studies.[18,24]

(24) R. T. LaLonde, J. T. Woolever, E. Auer, and C. F. Wong, *Tetrahedron Lett.*, 1503 (1972).

dine and accordingly thiobinupharidine-6,6′-d_2 would possess structure **12** and the unlabeled compound structure **4**. The bishemiaminal which underwent reduction with the incorporation of only axial deuterium must contain an axial sulfur atom attached to the AB quinolizidine system. This bishemiaminal was 6,6′-dihydroxythionuphlutine-*B* and accordingly thionuphlutine-*B*-6,6′-d_2 would possess structure **13** and the unlabeled compound, structure **5**.

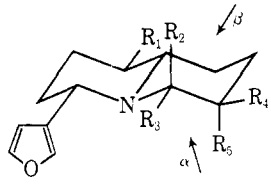
The reduction of the C-6′ hemiaminal group would seem to be directed sterically by the attack of the deuteride on the lesser hindered, convex, β surface of the two bishemiaminals. Even in the case of the reduction of a simple deoxynupharidine derivative, such as Δ^6-dehydrodeoxynupharidine, in which the shielding effect of a second quinolizidine is absent, the predominant direction of catalytic or hydride reduction is from the side (β) opposite the 3-furyl group. Alternatively, the direction of the C-6′ hemiaminal reduction might be directed by sulfur–immonium ion interaction through a four-membered ring. Regardless of the rationale used to explain the steric mode of C-6′ reduction, it should be emphasized that it is the C-6′ hemiaminal centers in both bishemiaminals which are reduced in the same steric mode since the nmr results indicate that the CH_2S group is attached to the A′B′ quinolizidine moiety with the same stereochemistry in both thiobinupharidine and thionuphlutine-*B*. Therefore we propose that the three-dimensional structures of thiobinupharidine and thionuphlutine-*B* are **4** and **5**, respectively.[25]

6-Hydroxythiobinupharidine. An appreciation for the role of intramolecular sulfur in directing the stereochemical course of deuteride reduction of immonium ions was helpful in determining the structure of 6-hydroxythiobinupharidine (**14**).[26] The latter, whose isolation procedure and spectral properties are detailed in the Experimental Section, is the first monohemiaminal of the thiospiran *Nuphar* alkaloid series. Sodium borohydride reduction converted this monohemiaminal to thiobinupharidine and thus established the three-dimensional skeleton. The identification of thiobinupharidine was made by admixture melting point and rotation and comparison spectra. The position of the hemiaminal function could be located at C-6 or C-6′ as a result of the nmr which displayed a singlet at δ 3.98 which was assigned to the hemiaminal α proton (HOC*H*N<). Therefore, of the six possible positions (C-4, C-4′, C-10, C-10′, C-6, and C-6′) the hemiaminal hydroxyl group must have been located at one or the other of the C-6 positions. The presence of one fully reduced C-6 position was supported by the appearance of a one-proton doublet of a doublet (J = 2.5 and 12 Hz) at δ 2.96. This resonance was assigned to a C-6 equatorial proton on the basis of the splitting pattern and a comparison of chemical shift with the same proton in deoxynupharidine.[8a,18] The splitting is rationalized by geminal coupling to the C-6 axial proton and W-mode coupling to the C-8 equatorial proton. The mass spectrum (Experimental Section) was fully consistent with a C-6 hemiaminal structure. Therefore the structure problem was resolved into one of ascertaining whether the hemiaminal hydroxyl group was located at C-6 or C-6′. The distinction was achieved by determining the stereochemistry of deuteride reduction of the hemiaminal.

The monohemiaminal was treated with sodium borodeuteride to obtain a singly labeled thiobinupharidine (24% d_0, 76% d_1). Spin decoupling experiments performed on the d_1 sample in deuteriobenzene showed that the δ 1.41 doublet (C-6′, axial proton) and the δ 3.16 doublet of a doublet (C-6′, equatorial proton) were coupled. The C-6 axial proton appeared at δ 1.91 as a singlet (~0.8 H) imposed on a doublet (~0.2 H). The doublet portion of the signal resulted from coupling to some residual C-6 equatorial proton. Under conditions whereby the C-6′ equatorial proton was decoupled from the C-6′ axial proton, the residual C-6 equatorial proton at δ 3.10 could be observed clearly. The latter signal had an integrated intensity of about 0.2 proton appearing as a doublet of a doublet which resulted from incomplete incorporation of deuterium in the reduction product. This finding means that a C-6 position was reduced stereospecifically with the introduction of an equatorial deuterium. The conversion of the monohemiaminal, **14**, to thiobinupharidine-d_1 with the incorporation of equatorial deuterium must mean that the hemiaminal hydroxyl is located at C-6 not C-6′, since reduction of 6,6′-dihydroxythiobinupharidine with sodium borodeuteride resulted in the incorporation of equatorial deuterium at C-6 but axial deuterium at C-6′.

The stereochemistry of deuteride reduction of the sulfur-containing hemiaminals is a significant topic not only in relation to structure determination but also because it related to the existence of sulfur–immonium ion interaction. This topic is treated further in the section immediately following along with spectral evidence for such interaction.

Manifestation of Sulfur–Immonium Ion Interactions. Steric Course of Deuterium Introduction. The observation of stereospecific incorporation of deuterium upon treating the thiospiran hemiaminal alkaloids with sodium borodeuteride prompted us to examine the reduction using the pair of model β-methylthiohemiaminals **15** and **16**. The latter pair was obtained in the following manner. Treatment of the enamine, (−)-Δ^6-dehydrodeoxynupharidine,[18] in absolute ethanol or benzene solution, with methyl *p*-toluenethiosulfonate



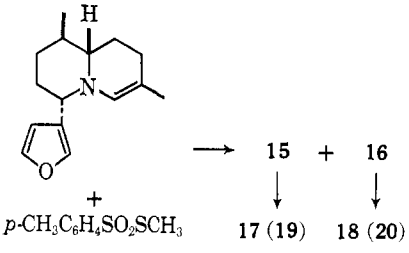
15, $R_1 = R_4 = CH_3$; $R_2 = OH$; $R_3 = H$; $R_5 = SCH_3$
16, $R_1 = R_5 = CH_3$; $R_2 = H$; $R_3 = OH$; $R_4 = SCH_3$
17, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$; $R_5 = SCH_3$
18, $R_1 = R_5 = CH_3$; $R_2 = R_3 = H$; $R_4 = SCH_3$
19, $R_1 = R_4 = CH_3$; $R_2 = D$, $R_3 = H$; $R_5 = SCH_3$
20, $R_1 = R_5 = CH_3$; $R_2 = H$, $R_3 = D$; $R_4 = SCH_3$
21, $R_1 = R_5 = CH_3$; $R_2 = R_5 = OH$

(25) After the work had been submitted for publication we learned through personal communication with Professor D. B. MacLean that he and his coworkers had determined the structure of thiobinupharidine by X-ray crystallographic studies and that his structure was in accord with ours. We thank Professor MacLean for disclosing his results to us prior to publication.

(26) A preliminary account of the structure of 6-hydroxythiobinupharidine was given at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 27–Sept 1 1972, Abstract ORGN-072.

in the presence or absence of various tertiary amines gave mixtures of the hemiaminals **15** and **16** in yields ranging from 12 to 41%. Yields of 50% could be obtained consistently by carrying out the reaction in benzene in the presence of neutral alumina. The stereoisomeric hemiaminals were separated by elution chromatography.

The structures assigned to the model hemiaminals are consistent with spectral properties which are given in the Experimental Section. The model hemiaminal

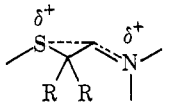


15 is believed to possess an axial C-6 hydroxyl group because its ir shows both free and hydrogen bonded hydroxyl group bands. In contrast, the ir of **16** reveals only a hydrogen bonded hydroxyl group when determined at a similar concentration. Moreover, the assigned stereochemistry of hydroxyl groups in **15** and **16** corresponds to the stereochemistry of deuterium introduction by deuteride reduction of the hemiaminals.

The configuration at C-7 in the model hemiaminals follows from the configuration of this same center in the products of hemiaminal reduction. Treatment of **15** and **16** with sodium borohydride in methanol gave respectively 7α-methylthio-7-epideoxynupharidine (**17**) and 7β-methylthiodeoxynupharidine (**18**). Both gave evidence for possessing *trans*-quinolizidine ring systems by displaying strong Bohlmann absorption.[10] The stereochemistry at C-7 of **17** and **18** was assigned by nmr chemical shift differences. The compound having the lower field singlet methyl resonance (δ 1.32) was assigned structure **18**; that with the higher field singlet methyl resonance (δ 1.12) was assigned structure **17**. These stereochemical assignments were supported by the direction of the benzene-induced shifts of the methyl groups. The deuteriochloroform to benzene solvent change resulted in the upfield shift (8 Hz) of the equatorial C-7 methyl of **17** and a downfield (-6 Hz) of the C-7 axial methyl of **18**. The C-1 equatorial methyls of both compounds were shifted upfield (7 Hz).

Sodium borodeuteride reduction of the model hemiaminal containing the axial methylthio group (*i.e.*, **15**) gave the methylthiodeoxynupharidine (**19**) possessing axial deuterium at C-6. In contrast, the model hemiaminal containing the equatorial methylthio group (*i.e.*, **16**) gave the methylthiodeoxynupharidine (**20**) possessing equatorial deuterium at C-6. Configurational assignments at C-6 were made on the basis of the nmr in relation to the previously studied nmr of deoxynupharidine and C-6-labeled deoxynupharidine.[8a,18] The nmr, determined in benzene, of 7α-methylthio-7-epideoxynupharidine-6β-d_1 (**19**) showed the C-6 equatorial proton as a broad singlet while the region where the axial C-6 proton is usually found was lacking one proton. The nmr of 7β-methylthiodeoxynupharidine-6α-d_1 (**20**) showed that the C-6 equatorial proton was nearly absent while the region where the C-6 axial proton is expected contained the full complement of protons. Clearly, the direction of the deuteride attack of the substrate molecules is from the side opposite from the sulfur atom. This result is consistent with that observed in the deuteride reduction of the C_{30} hemiaminals and therefore lends support to the stereochemical assignment of the sulfur atom in the C_{30} compounds.

The sulfur–immonium interaction which directs the course of hydride reduction may take the form of the ion expressed as **22** or, perhaps, a fully developed



22

episulfonium ion[27] derived from **22**. Interestingly, the hemiaminal **15** is reduced nearly 800 times faster than the hemiaminal **16**. Possibly this difference reflects the increased steric opposition to α (bottom side) hydride attack, as opposed to β (top side) hydride attack, on an episulfonium-like intermediate formed from **16**.

Uv Spectra of the β-Thiohemiaminals. In the course of investigating 6-hydroxythiobinupharidine (**14**), we discovered that the alkaloid, in acid solution, produced an absorption band at 292 nm (ϵ 3200). Upon further investigation of the other known bishemiaminal, sulfur-containing alkaloids, and newly synthesized model compounds we observed that this interesting uv spectral property is common to all of these compounds. In neutral solution these hemiaminals give only strong end absorption or high intensity maxima at about 210 nm. When acid is added the 290–295-nm band (ϵ 1500–3200) appears; upon adding base the band disappears but reappears on reacidification.

The bisamine thiospiran alkaloids, **1**, do not give the 290–295-nm band and simple immonium ions show moderate or strong absorption between 222 and 232 nm,[28] a region below that observed for the acid-induced absorption of the sulfur-containing hemiaminals.

We attribute the 290–295-nm absorption to sulfur–immonium ion interaction. In the case of the two model compounds **15** and **16** and the monohemiaminal, **14**, this nonbonded sulfur–immonium ion interaction, which we designate as S–$C_{>C=\overset{+}{N}<}$,[29] likely involves the sulfur in a three-membered ring as depicted in **22**. Because of the similarity in the uv properties, we also prefer to ascribe the acid-induced band of the bishemiaminal sulfur alkaloids to sulfur–immonium ion interaction involving a three-membered ring. Interestingly, the immonium perchlorate derived from diol **21**,[14] the oxygen analog of the immonium ion derived from **15**, displays only the normal, low wavelength absorption characteristic of simple immonium ions. The different participating abilities of sulfur and oxygen in the excited states of chromophores have been observed previously in the case of bicyclic ketones.[29a]

(27) For a recent review and a comment regarding the possible role of episulfonium ions in the addition of electrophilic sulfur reagents to enamines, see W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, **8**, 482 (1969).

(28) G. Opitz, H. Hellmann, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 117 (1959).

(29) A similar interaction, designated S–$C_{C=O}$, has been observed for various sulfur containing ketones, see (a) A. Padwa and A. Battisti, *J. Amer. Chem. Soc.*, **94**, 521 (1972); (b) L. A. Paquette and L. D. Wise, *ibid.*, **89**, 6659 (1967); (c) N. J. Leonard, T. W. Milligan, and T. L. Brown, *ibid.*, **82**, 4075 (1960).

Experimental Section

Spectra were obtained as follows: nmr in solution is as indicated, 2% TMS (δ 0.0), on Varian A60 and HA100 spectrometers by Mary Lou Green, Hazel Jennison, and Al Vulcano, symbols d, q, and m refer to doublet, quartet, and multiplet, respectively; ir in solution as indicated, Perkin-Elmer 137 and 621; low resolution mass spectra (ms) on a Hitachi-Perkin-Elmer RMU6E by Hazel Jennison using the direct inlet at 110–130°, 70 ev, chamber temperature 160°; high resolution mass spectra by R. Foltz and J. Hoyland, The High Resolution Mass Spectrometry Laboratory, Battelle's Columbus Laboratories, Columbus, Ohio, AEIMS-9. Melting points were determined on a Köfler micro hot stage and Mel-Temp apparatus and are uncorrected. Optical rotations were determined in solution as indicated on a Perkin-Elmer 141 polarimeter. Tlc was performed using alumina, Type E, GF-254, silica gel GF-254, and the solvent systems indicated.

Reduction of 6,6′-Dihydroxythiobinupharidine.[30] **A. With $NaBH_4$.** A 43-mg sample of the bishemiaminal in MeOH was treated with 47 mg of $NaBH_4$ at 25° for 15 hr. Evaporation of the solvent at reduced pressure, addition of water to the resulting residue, and extraction of the mixture with CH_2Cl_2 produced an extract which was dried (Na_2SO_4). Removal of the CH_2Cl_2 at reduced pressure gave a residue which was eluted from neutral alumina (10 g, activity IV) with benzene. In this manner was obtained 38 mg of thiobinupharidine: mp 131–132°; $[\alpha]^{25}D$ +7.8 (MeOH, *c* 0.18); uv (EtOH, neutral) λ 215 sh nm (ε 13,000); uv (EtOH, H^+) λ 215 sh nm (ε 13,000); ir (CCl_4, *c* 0.0358 *M*) 3.6 (Bohlmann bands) (integrated intensity 2440–2852 cm^{-1} = 1.1 relative to deoxynupharidine [CCl_4, *c* 0.765 *M*], 6.69 and 11.47 μ (3-furyl); nmr ($CDCl_3$) δ 0.93 (d, 6 H, $HCCH_3$), 1.7–1.8 (m, 4 H, C-6 H axial, C-6′ H axial, and others), 2.32 (ABq, 2 H, CH_2S), 2.75–3.1 (m, 4 H, C-4 H axial, C-4′ H axial, C-6 H equatorial and C-6′ H equatorial), nmr (C_6H_6, 100 MHz), δ 2.80 (q, *J* = 1 and 10 Hz, 1 H, C-4 H or C-4′ H axial), 2.83 (q, *J* = 1 and 10 Hz, C-4′ H or C-4 H axial), 6.39 (m, 2 H, 3-furyl β H), 7.30 (m, 4 H, 3-furyl α H); nmr (C_6H_6) δ 0.82 (d, 6 H, $HCCH_3$); ms *m/e* (rel intensity) 494 (39) (M^+), 493 (7), 461 (4), 447 (4), 359 (15), 230 (53), 178 (100), 136 (8), 107 (18), 94 (15), 81 (8); high-resolution ms obsd/calcd (formula) 494.29673/494.29688 ($C_{30}H_{42}N_2O_2S$).

A solution of 37 mg of thiobinupharidine in 20 ml of MeOH was treated with 2 equiv of 0.02 *N* aqueous $HClO_4$. The mixture was concentrated to 0.5 ml. The resulting precipitate (44 mg) was recrystallized from MeOH to obtain 11 mg of thiobinupharidine monoperchlorate monohydrate, mp 266–267°.

Anal. Calcd for $C_{30}H_{42}N_2O_2S \cdot H_2O \cdot HClO_4$: C, 58.75; H, 7.40; N, 4.57; S, 5.23. Found: C, 58.78; H, 7.30; N, 4.55; S, 4.78.

The mother liquor was evaporated to dryness and the residue was recrystallized from EtOH. Thereby was obtained 28 mg of thiobinupharidine diperchlorate.

Anal. Calcd for $C_{30}H_{42}N_2O_2S \cdot 2HClO_4$: C, 51.64; H, 6.65; N, 4.02. Found: C, 51.23; H, 6.49; N, 3.96.

B. With $NaBD_4$. A solution of 66 mg of 6,6′-dihydroxythiobinupharidine in EtOH was treated with 66 mg of $NaBD_4$ at 25° for 20 hr. The solvent was evaporated at reduced pressure and the residue was processed as described above in the $NaBH_4$ reduction. In this manner was obtained 17 mg of thiobinupharidine-*6,6′-d_2*. A better yield was obtained by reducing the bisimmonium hydrochloride. Thus 116 mg of 6,6′-dihydroxythiobinupharidine was treated with 2 equiv of HCl in MeOH. The solvent was removed at reduced pressure and the residue was treated with 114 mg of $NaBD_4$ in 0.5 ml of MeOH at 25° for 18 hr. Water (20 ml) was added and the mixture was evacuated at 25° for 30 min to remove the bulk of the MeOH. The resulting aqueous mixture was extracted with CH_2Cl_2. The combined extract was dried (Na_2SO_4). Removal of solvent at reduced pressure gave 101 mg of oil which was chromatographed on 5 g of alumina (neutral, activity II) using 30 ml of Et_2O–hexane (5:95) (fraction 1), 20 ml of the same solvent (fraction 2), and 20 ml of MeOH (fraction 3). Fraction 1 yielded 60 mg of thiobinupharidine *6,6′-d_2*: ir (CCl_4) 4.9 μ (C–D), the ratio of integrated intensities 2440–2852 cm^{-1} (Bohlmann absorption) for thiobinupharidine-*6,6′-d_2* and thiobinupharidine was equal to 0.84; nmr ($CDCl_3$) δ 2.7–3.1 (m, 3 H, C-4 H axial, C-4′ H axial, and C-6 H equatorial), 1.7–1.8 (m, 3 H, C-6 H axial and others); ms *m/e* (rel intensity) 496 (15) (M^+) (6% d_0, 24% d_1, 71% d_2), 495 (7), 463 (2), 449 (2), 361 (10), 231 (35), 179 (100), 136 (11), 107 (33), 94 (80), 81 (27).

Reduction of 6,6′-Dihydroxythionuphlutine-*B*.[30] **A. With $NaBH_4$.** A solution of 47 mg of 6,6′-dihydroxythionuphlutine-*B* in methanol was reduced with 50 mg of $NaBH_4$ according to the procedure described above. In this manner was obtained 34 mg of thionuphlutine-*B*: $[\alpha]^{25}D$ −131° (MeOH, *c* 0.8); uv (EtOH, neutral) λ 210 sh nm (ε 30,000); uv (EtOH, H^+) λ 217 sh nm (ε 15,000); ir (CCl_4, *c* 0.0362) 3.6–3.7 (Bohlmann bands) (integrated intensity 2440–2852 cm^{-1} = 1.05 relative to deoxynupharidine [CCl_4, *c* 0.0766 *M*]), 6.68 and 11.47 μ (3-furyl); nmr ($CDCl_3$) δ 0.91 (d, 6 H, $HCCH_3$), 1.0–2.0 (m, 24 H, C-6 H axial, C-6′ H axial, and others), 2.33 (ABq, 2 H, CH_2S), 2.42–3.15 (m, 4 H, C-4 H axial, C-4′ H axial, C-6 H equatorial, and C-6′ H equatorial), 6.23 (m, 1 H, 3-furyl β H), 6.43 (m, 1 H, 3-furyl β H), 7.22 (m, 2 H, 3-furyl α H), 7.31 (m, 2 H, 3-furyl α H); nmr (C_6H_6) δ 0.80 (d, 6 H, $HCCH_3$); ms *m/e* (rel intensity) 494 (33) (M^+), 461 (6), 447 (7), 359 (18), 230 (100), 178 (37), 136 (11), 107 (28), 94 (21), 81 (12); high resolution ms obsd/calcd (formula) 494.29879/494.29663 ($C_{30}H_{42}N_2O_2S$).

Anal. Calcd for $C_{30}H_{42}N_2O_2S$: C, 72.83; H, 8.56; N, 5.67; S, 6.48. Found: C, 72.96; H, 8.71; N, 5.78; S, 5.66.

B. With $NaBD_4$. A solution of 47 mg of 6,6′-dihydroxythionuphlutine-*B* in 2 ml of ethanol was treated with 64 mg of $NaBD_4$ at 25° for 12 hr. Processing the reaction mixture as described above and chromatography of the crude reduction product on alumina (neutral, activity III, benzene) gave 22 mg of thionuphlutine-*B-6,6′-d_2*: ir (CCl_4) 4.9 μ (C–D), the ratio of integrated intensities 2440–2852 cm^{-1} (Bohlmann absorption) for thionuphlutine-*B-6,6′-d_2* and thionuphlutine-*B* was equal to 0.65; nmr ($CDCl_3$) δ 2.42–3.15 (m, 4 H, C-4 H axial, C-4′ H axial, C-6 H equatorial, and C-6′ H equatorial), 1.0–2.0 (m, 22 H); ms (rel intensity) 496 (39) (M^+) (1% d_0, 38% d_1, 61% d_2), 495 (26), 463 (4), 449 (5), 361 (18), 231 (100), 179 (70), 136 (26), 107 (76), 94 (60), 81 (40).

Isolation of 6-Hydroxythiobinupharidine. Powdered dry rhizomes of *Nuphar luteum*,[31] 1465 g, were moistened with 3.5 l. of 10% aqueous NH_3 and then extracted with CH_2Cl_2 (6 × 3 l.), with mechanical shaking. Evaporation of the CH_2Cl_2 extract yielded 30.3 g of brown liquid. This was dissolved in 1 l. of CH_2Cl_2 and the resulting solution was washed with 10% H_2SO_4 (3 × 900 ml). The combined acid was cooled to 0° and basified with aqueous NH_3 (1:1) to pH 10. The cloudy, aqueous NH_3 solution was extracted with CH_2Cl_2 (4 × 500 ml) and the combined CH_2Cl_2 extract was dried (Na_2SO_4). Evaporation of the CH_2Cl_2 gave 15 g of dark brown resin which was eluted from 500 g of Alumina Woelm neutral (activity II). The amounts, solvents employed, and the resulting fractions, in parentheses, were: 150 ml of hexane (A 1-6), 3 l. of 5% ether–hexane (A 7-46), 400 ml of 10% ether–hexane (A 47-48), 1.1 l. of 20% ether–hexane (A 49-56), 1.8 l. of 50% ether–hexane (A 57-68), 2100 ml of ether (A 69-80), 800 ml of 10% CH_2Cl_2–ether (A 81-84), 800 ml of 20% CH_2Cl_2–ether (A 85-86), 400 ml of 50% CH_2Cl_2–ether (A 87), 1 l. of CH_2Cl_2 (A 88-89), 400 ml of 10% MeOH–CH_2Cl_2 (A 90), 900 ml of 20% MeOH-CH_2Cl_2 (A 91-94), 1.5 l. of MeOH (A 95-96).

Combined fractions A 57-58, 743 mg, tlc (Alumina 30% ether–hexane) R_f 0.13 and 0.03, was eluted from 25 g of alumina (activity II). The employed solvents, amounts, and corresponding fraction number, in parentheses, were: 70 ml of hexane (B 1-2), 50 ml of 5% ether–hexane (B 3), and 800 ml of 10% ether–hexane (B 4-27). Combined fractions B 11-19, 402 mg, tlc Alumina (15:1:84, ether–hexane–CH_2Cl_2) R_f 0.3 and 0.43, was rechromatographed from alumina (activity II) with 125 ml of hexane (fraction C 1), 200 ml of hexane–C_6H_6 (1:5) (C 2), 50 ml of C_6H_6 (C 3), 350 ml of 5% ether–C_6H_6 (C 4), 150 ml of 10% ether–C_6H_6 (C 5), 100 ml of 20% ether–benzene (C 6), 100 ml of 50% ether–C_6H_6 (C 7). Rechromatography of fraction C 4, 230 mg, tlc alumina (5% CH_3CN–C_6H_6) R_f 0.95 and 0.56, on alumina (activity II, 10 g) using 125 ml of 5% CH_3CN in C_6H_6 gave fraction D, 191 mg, tlc (5% CH_3CN–C_6H_6) R_f 0.56, silica gel (1:5:1 acetone–C_6H_6–hexane), R_f 0.2 and 0.68.

A 143-mg sample of fraction D (~0.3 mmol) was treated with 120 ml of 0.005 *M* aqueous $HClO_4$ (0.6 mmol). The water was evaporated and the granular residue was recrystallized from a large volume of MeOH containing a trace of acetone. Cooling at 0–5° gave 120 mg of 6-hydroxythiobinupharidine diperchlorate (colorless needles): mp 256–258° (softening), 265° (liquid), 273° dec; ir (KBr) 4.35 (>N^+H–), 6.02 (C=N^+<), 6.64, 11.43 μ (furan); Bohlmann band at 3.56 μ was absent.

(30) The isolation procedure is disclosed in ref 2f.

(31) The plant material was collected near Galwiecie in the State of Bialostock, Poland, and was obtained through the help of Dr. Leokadia Witkowska-Zük, Faculty of Forestry, The University of Agriculture, Warsaw, Poland. We thank Dr. Witkowska-Zük for her assistance.

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, 52.06; H, 6.21; N, 3.98; S, 4.57.

A 0.005 *M* aqueous $HClO_4$ solution (6 ml, 0.03 mmol) was added to 14 mg of fraction D (0.03 mmol) dissolved in 5 ml of MeOH. The solvents were evaporated and the residue was twice recrystallized from acetone, washed, and dried to give 10 mg of 6-hydroxythiobinupharidine monoperchlorate: mp 238–242°; ir (KBr) 5.99 (C=N⁺<), 3.59 (Bohlmann band), 11.45 μ. Treatment of the monoperchlorate with aqueous NH_3 gave the free base: tlc silica gel (1:5:1 acetone–C_6H_6–hexane) R_f 0.68 only; ir 2.79 (OH), 3.57 (weak, Bohlmann), 6.67 and 11.43 μ (furan); ms 510 (M^+).

A 122-mg sample of 6-hydroxythiobinupharidine diperchlorate was basified with dilute aqueous NH_3 and then extracted with CH_2Cl_2 (3 × 20 ml). The combined CH_2Cl_2 extract was dried (Na_2SO_4). Evaporation of the solvent gave 85.6 mg of free base which was chromatographed from alumina (activity II, 3 g) using 10% ether–benzene to obtain 82 mg of 6-hydroxythiobinupharidine as a glass-like solid: $[\alpha]^{26}D$ +33 (CH_2Cl_2, *c* 36 mg/ml); uv (95% EtOH, neutral) shoulder at 250 nm imposed on end absorption; $\lambda_{max\ 1}$ (95% EtOH, acidic) 209 nm (ε 22,300), $\lambda_{max\ 2}$ 292 (ε 3200); ir (CH_2Cl_2) 3.59 (Bohlmann band), 6.26, 6.66, 6.90, 7.26, 8.61, 9.06, 9.41, 9.67, 9.74, 11.46 μ; nmr (100 MHz, $CDCl_3$) δ 0.88 (d, *J* = 5 Hz, 6 H, 2x HCCH_3), 2.20 (ABq, *J* = 12 Hz, 2 H, CH_2S), 2.31 (OH, exchangeable with D_2O), 2.92 (q, *J* = 5 and 8 Hz, 1 H, C-4 or C-4′ H), 2.96 (s, *J* = 12 Hz, 1 H, C-6′ H_{eq}), 3.70 (q, *J* = 6 and 8 Hz, 1 H, C-4′ or C-4 H), 3.98 (s, 1 H, HOC-6 H), 6.34 (m, 2 H, β-furyl H), 7.22 and 7.30 (m, 4 H, α-furyl H); nmr (100 MHz, C_6D_6) δ 0.76 (d, *J* = 6 Hz, 6 H, 2x HCCH_3), 2.10 (ABq, *J* = 12 Hz, 2 H, CH_2S), 2.76 (m, 1 H, C-4 or C-4′ H), 3.14 (q, *J* = 2.5 and 12 Hz, 1 H, C-6 H_{eq}) 3.86 (q, *J* = 6 and 8 Hz, 1 H, C-4′ or C-4 H), 4.24 (s, 1 H, HOC-6 H), 6.36 (sharp m, β-furyl H), 6.43 (sharp m, 2 H with 6.36, β-furyl H), ~7.18 (m, α-furyl H); ms (70 ev, DI probe 110°) *m/e* (rel intensity) 510 (10) (M^+), 494 (19), 493 (35), 492 (87) ($M^+ - H_2O$), 464 (12), 445 (11), 231 (24), 230 (100), 229 (42), 228 (62), 214 (13), 200 (8), 178 (35), 177 (24), 176 (89), 149 (17), 136 (12), 107 (28), 97 (26), 95 (13), 94 (28), 81 (40), high resonance ms (DI probe 285°, 500 ev) obsd/calcd mass (formula) 492.2794/492.2810 ($C_{30}H_{10}N_2O_2S$), 230.1546/230.1545 ($C_{13}H_{20}NO$), 176.1072/176.1075 ($C_{11}H_{14}NO$).

Sodium Borohydride Reduction of 6-Hydroxythiobinupharidine. A 26-mg sample of the title alkaloid in 5 ml of MeOH was treated with 100 mg of sodium borohydride at room temperature for 20 hr. Water was added and the solution extracted with CH_2Cl_2. The CH_2Cl_2 was evaporated to obtain a residue which was eluted from alumina (activity II, 1 g) with 50 ml of hexane and 50 ml of 10% ether–hexane. The latter eluent produced 19 mg of thiobinupharidine: $[\alpha]^{25}D$ +8° (MeOH, *c* 14 mg/1 ml); ir (CCl_4) 3.6 (Bohlmann), 6.69, and 11.47 μ (furan) and identical with the ir of an authentic sample;[5] nmr ($CDCl_3$, 60 MHz) identical with spectrum of authentic sample;[5] ms (DI probe 110°, 70 ev) *m/e* (rel intensity) 494 (33) (M^+), 359 (15), 230 (49), 178 (100), 136 (10), 107 (23), 94 (22), 81 (14).

Sodium Borodeuteride Reduction of 6-Hydroxythiobinupharidine. A 38-mg sample of the title compound in 10 ml of MeOH was treated with 100 mg of sodium borodeuteride in the manner described above for sodium borohydride treatment. In this way was obtained 34 mg of thiobinupharidine-6-d_1: ms (DI probe 110°, 70 ev) *m/e* (rel intensity) 495 (34) (M^+), 494 (14), 360 (12), 359 (7), 231 (29), 230 (30), 179 (100), 178 (34), 136 (11), 107 (24), 94 (23), 81 (16); ms % isotopic composition 24% d_0, 76% d_1; nmr (C_6D_6, 100 MHz) δ 1.41 (d, *J* = 11.5 Hz, C-6′ H_{ax} and s when the sample was irradiated at C-6′ H_{eq} resonance frequency), 1.91 (s, ~0.7 H, C-6 H_{ax}), 1.91 (d, *J* = 10, ~0.3 H, C-6 H_{ax}), 2.18 (br s, 2 H, C-7 -CH_2-C-7′), 2.29 (ABq, *J* = 12 Hz, 2 H, C-7′ -CH_2S-C-7), 2.81 (q, *J* = 9.5 and 4 Hz, 2 H, C-4 and C-4′ H), 3.10 (q, *J* = 10 and 2 Hz, ~0.3 H, C-6 H_{eq}), 3.16 (q, *J* = 11.5 and 2 Hz, 1 H, C-6′ H_{eq} and d when sample was irradiated at C-6′ H_{ax} frequency).

Preparation of 7β-Methylthiodeoxynupharidin-6α-ol and 7β-Methylthio-7-epideoxynupharidin-6β-ol. A solution of 412 mg of Δ⁶-dehydrodeoxynupharidine[18] in 20 ml of anhydrous C_6H_6 was treated with 383 mg of methyl *p*-toluenethiosulfonate in the presence of 2 g of alumina (neutral, activity III) at 25° under nitrogen overnight. The solvent was evaporated and the residue was chromatographed on a column of alumina (60 g, neutral, 5%, H_2O) 3 cm in diameter. The column was eluted with: 120 ml of C_6H_6–hexane, 1:9 (fraction 1); 70 ml of C_6H_6 (fraction 2); 200 ml of C_6H_6 (fraction 3); 100 ml of C_6H_6 (fraction 4); 200 ml of C_6H_6–ether, 9:1 (fraction 5). Fraction 4 was pure 7β-methylthiodeoxynupharidin-6α-ol: uv $\epsilon_{210}^{C_2H_5OH}$ end absorption, λ_{max} C_2H_5OH (H^+) 294 nm (ε 2460); ir (CCl_4) 2.85 (s, br; H bonded OH), 11.45 μ (3-furyl), Bohlmann bands absent; nmr ($CDCl_3$) δ 0.90 (d, *J* = 4 Hz, 3 H, C-1 CH_3), 1.38 (s, 3 H, C-7 CH_3), 1.85 (s, 3 H, CH_3S), 2.88 (d, *J* = 1 Hz, 1 H, OH, exchanged by addition of D_2O), 3.76 (m, 1 H, C-4 H), 4.15 (d, *J* = 1 Hz, 1 H, C-6 H), 6.4 (m, 1 H, β H of 3-furyl), 7.4 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.82 (d, *J* = 4 Hz, 3 H, C-1 CH_3), 1.35 (s, 3 H, C-7 CH_3), 1.52 (s, 3 H, CH_3S), 2.98 (d, *J* = 1.5 Hz, 1 H, OH, exchanged by addition of D_2O), 3.90 (m, 1 H, C-4 H), 4.27 (br s and sharpening after D exchange at OH, 1 H, C-6 H), ms *m/e* (rel intensity) 295 (100) (M^+), 280 (13.5), 278 (31), 266 (50), 248 (84), 231 (41.5), 218 (39.5), 192 (47), 175 (13), 176 (13.5), 164 (22.5), 136 (18), 107 (91), 94 (70), 81 (46).

An 84-mg sample of fraction 4 was treated with 0.2 *M* aqueous $HClO_4$ (1 equiv) and sufficient C_2H_5OH for homogeneity. The solvent was evaporated at 40° to obtain 35 mg of crystalline immonium perchlorate of 7β-methylthiodeoxynupharidine-6α-ol: mp 179–180°; ir (KBr) 6.02 μ.

Anal. Calcd for $C_{16}H_{24}NO_5SCl$: C, 50.90; H, 6.40; N, 3.71; S, 8.49. Found: C, 50.92; H, 6.43; N, 3.85; S, 8.69.

Fraction 6 was pure 7α-methylthio-7-epideoxynupharidin-6β-ol: mp 79–80°; uv $\epsilon_{210}^{C_2H_5OH}$ end absorption, λ_{max} (C_2H_5OH, H^+) 295 (ε 1610); ir (CCl_4) 2.75 (s, sharp, free OH), 2.86 (s, br, H bonded OH), 11.46 μ (3-furyl), Bohlmann bands absent; nmr δ 0.95 (d, *J* = 4.5 Hz, 3 H, C-1 CH_3), 1.23 (s, 3 H, C-7 CH_3), 1.87 (s, 3 H, CH_3S), 4.23 (br s, 1 H, C-6 H), 6.5 (m, 1 H, β H of 3-furyl), 7.37 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.84 (d, *J* = 4 Hz, 3 H, C-1 CH_3), 1.13 (s, 3 H, C-7 CH_3), 1.70 (s, 3 H, CH_3S), 3.55 (m, 1 H, C-4 H), 4.5 (d, *J* = 4.5 Hz and s after D exchange at OH, 1 H, C-6-H); ms *m/e* (rel intensity) 323 (7), 308 (4), 295 (74) (M^+), 280 (13), 278 (23), 277 (38), 264 (36), 248 (66), 231 (78), 216 (39), 192 (34.5), 176 (29), 164 (44), 136 (19), 107 (100), 94 (87), 81 (52).

A 77-mg sample of fraction 6 was treated with $HClO_4$ in aqueous ethanol. The solvent was evaporated at 40° to obtain 40 mg of crystalline immonium perchlorate of 7α-methylthio-7-epideoxynupharidin-6β-ol: mp 155–158°; ir (KBr) 6.00 μ.

Anal. Calcd for $C_{16}H_{24}NO_5SCl$: C, 50.90; H, 6.40; N, 3.71; S, 8.49. Found: C, 50.92; H, 6.43; N, 3.85; S, 8.69.

7α-Methylthio-7-epideoxynupharidine. A 65-mg sample of 7α-methylthio-7-epideoxynupharidin-6β-ol in 1 ml of CH_3OH was treated with 50 mg of $NaBH_4$. After 5 min the tlc (alumina, 5:95 EtOEt–C_6H_6) indicated no hemiaminal (R_f 0.54) and only 7α-methylthio-7-epideoxynupharidine (R_f 0.8). The solvent was evaporated. Water (5 ml) was added and the mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was dried (Na_2SO_4). Evaporation of the solvent gave 52 mg of colorless oil which was dissolved in C_6H_6. The benzene solution was passed through a column of 5 g of Al_2O_3. The column was washed with another 50 ml of C_6H_6. Evaporation of the C_6H_6 gave 48 mg of 7α-methylthio-7-epideoxynupharidine: ir (CCl_4) 3.4–3.4 (s), 3.62 (Bohlmann), 11.40 μ (s, 3-furyl); nmr ($CDCl_3$) δ 0.29 (d, *J* = 4.5 Hz, 3 H, C-1 CH_3), 1.12 (s, 3 H, C-7 CH_3), 1.62 (d, *J* = 12.5 Hz, 1 H, C 6 H_{ax}) (s, 3 H, CH_3S), 2.89 (br d, *J* = 12.5 Hz, 1 H, C-6 H_{eq}), 2.95 (m, H, C-4 H), 6.46 (m, 1 H, β H of 3-furyl), 7.30 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.82 (d, *J* = 5 Hz, 3 H, C-1 CH_3), 0.98 (s, 3 H, C-7 CH_3), 1.57 (d, *J* = 12.5 Hz, C-6 H_{ax}), 1.70 (s, 3 H, CH_3S), 2.82 (m, 1 H, C-4 H), 3.05 (d of d, *J* = 12.5 and 2.5 Hz, 1 H, C-6 H_{eq}); ms *m/e* (rel intensity) 279 (18) (M^+), 264 (6), 250 (2), 233 (100), 178 (32), 164 (29), 144 (34), 136 (36), 107 (34), 96 (44), 94 (48), 88 (34), 81 (29).

To 70 mg of 7α-methylthio-7-epideoxynupharidine in 10 ml of CH_3OH was added 1.3 ml of 0.2 *M* aqueous $HClO_4$. The solvent was evaporated at 40° and the resulting residue was recrystallized twice from CH_3OH. Thereby was obtained the crystalline hydroperchlorate: mp 230–236° (dried overnight at 25° over P_2O_5); ir (KBr) 3.24 (s), 3.4–3.5 (s), 11.45 μ (s).

Anal. Calcd for $C_{16}H_{26}NO_5SCl$: C, 50.58; H, 6.90; N, 3.69; S, 8.46. Found: C, 50.38; H, 6.84; N, 3.70; S, 8.61.

7α-Methylthio-7-epideoxynupharidine-6β-d_1. A 35-mg sample of 7α-methylthio-7-epideoxynupharidin-6β-ol (**8**) was treated with 25 mg of $NaBD_4$ in CH_3OH. Processing in the manner described for the unlabeled sample gave 20 mg of 7α-methylthio-7-epideoxynupharidine-6α-d_1: ir (CCl_4) 3.5–3.6 (s), 3.62 (Bohlmann), 4.92 (m), 11.45 μ (s); nmr ($CDCl_3$) δ 0.92 (d, *J* = 4.5 Hz, 3 H, C-1 CH_3), 1.12 (s, 3 H, C-7 CH_3), 1.83 (s, 3 H, CH_3S), 2.88 (br s, 1 H, C-6 H_{eq}), 2.95 (m, 1 H, C-4 H), 6.46 (m, 1 H, β H of 3-furyl), 7.30 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.82 (d, *J* = 5 Hz, 3 H, C-1 CH_3), 1.0 (s, 3 H, C-7 CH_3), 1.70 (s, 3 H, CH_3S), 2.82 (m, 1 H, C-4 H), 2.97 (br s, 1 H, C-6 H_{eq}); ms *m/e* (rel intensity) 280 (18) (M^+) (13% d_0 and 87% d_1), 265 (5), 251 (2), 234 (100), 179 (33), 164 (26), 145 (30), 136 (44), 107 (38), 97 (42), 94 (81), 88 (26), 81 (31).

7β-Methylthiodeoxynupharidine. A solution of 35 mg of 7β-methylthiodeoxynupharidin-6α-ol in 2 ml of CH_3OH was treated with 25 mg of $NaBH_4$ at 25° for 24 hr. Tlc (alumina, C_6H_6) indicated about one-third of the hemiaminal (R_f 0.33) had been reduced to the amine (R_f 0.75). The CH_3OH was evaporated and was replaced by 2 ml of C_2H_5OH and 60 mg of $NaBH_4$ was added and additional small amounts of $NaBH_4$ were added periodically during the course of 60 hr. After a total of 70 hr, a tlc of the reaction mixture still showed a trace of starting hemiaminal. The solvent was evaporated and the residue in C_6H_6 was passed through a column of 3 g of neutral alumina. The first 50-ml fraction yielded 20 mg of 7β-methylthiodeoxynupharidine: ir (CCl_4) 3.40, 3.50 (s), 3.62 (s, Bohlmann), 11.45 μ; nmr ($CDCl_3$) δ 0.92 (d, 3 H, C-1 CH_3), 1.32 (s, 3 H, C-7-CH_3), 1.90 (s, 3 H, CH_3S), 1.78 (d, J = 10.5 Hz, 1 H, C-6 H_{ax}), 2.75 (d of d, J = 10.5 and 2.0 Hz, 1 H, C-6 H_{eq}), 2.97 (m, 1 H, C-4 H), 6.36 (m, 1 H, β H of 3-furyl), 7.3 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.82 (unresolved d, 3 H, C-1 CH_3), 1.42 (s, 3 H, C-7 CH_3), 1.74 (s, 3 H, CH_3S), 1.93 (d, J = 10.5 Hz, 1 H, C-6 H_{ax}), 2.84 (m, 1 H, C-4 H), 3.04 (d of d, J = 10.5 and 2.0 Hz, 1 H, C-6 H_{eq}); ms *m/e* (rel intensity) 279 (14) (M^+), 264 (6), 250 (5), 233 (100), 178 (38), 164 (24), 144 (25), 136 (36), 107 (38), 96 (49), 94 (52), 88 (37), 81 (28).

A solution of 7β-methylthiodeoxynupharidine in 10 ml of C_2H_5OH was treated with 1.4 ml of 0.2 *M* aqueous $HClO_4$. Evaporation of the solvent left a residue which on two recrystallizations from C_2H_5OH gave 50 mg of the crystalline hydroperchlorate: mp 185–197°; ir (KBr) 3.22 (s), 3.4–3.5 (s), 3.55–4.0 (m), 11.45 μ (s).

Anal. Calcd for $C_{16}H_{26}NO_5SCl$: C, 50.58; H, 6.90; N, 3.69; S, 8.46. Found: C, 50.40; H, 6.88; N, 3.58; N, 3.58; S, 8.60.

7β-Methylthiodeoxynupharidine-6α-d_1. A solution of 35 mg of 7β-methylthiodeoxynupharidin-6α-ol in 2 ml of absolute C_2H_5OH was treated at 12-hr intervals over the course of 80 hr with small portions of $NaBD_4$ (200 mg). The reaction mixture was processed as in the reductions described above to obtain 25 mg of colorless oil: tlc (alumina, C_6H_6) R_f 0.33 (**16**) and 0.75 (**20**). This oil in benzene was passed through a column of 3 g of alumina (neutral, activity II). The first 50-ml fraction gave 18 mg of 7β-methylthiodeoxynupharidine-6α-d_1: ir (CCl_4) 3.4–3.5 (s), 3.61 (s, Bohlmann), 4.93 (w), 11.45 μ (s); nmr ($CDCl_3$) δ 0.92 (br s, 3 H, C-1 CH_3), 1.33 (s, 3 H, C-7 CH_3), 1.89 (s, 3 H, CH_3S), 2.75 (d, J = 10.5 Hz, 0.2 H, C-6 H_{eq}), 2.98 (m, 1 H, C-4 H), 6.39 (m, 1 H, β H of 3-furyl), 7.31 (m, 2 H, α H of 3-furyl); nmr (C_6H_6) δ 0.82 (unresolved d, 3 H, C-1 CH_3), 1.43 (s, 3 H, C-7 CH_3), 1.74 (s, 3 H, CH_3S), 1.93 (d, J = 10.5 Hz, 0.25 H and s, 0.75 H, C-6 H_{ax}), 2.85 (m, 1 H, C-4 H), 3.04 (d of d, J = 10.5 and 2.0 Hz, 0.25 H, C-6 H_{eq}); ms *m/e* (rel intensity) 280 (15) (M^+) (21% d_0, 79% d_1), 265 (6), 250 (2), 234 (100), 179 (33), 164 (28), 145 (31), 136 (26), 107 (41), 97 (37), 94 (52), 88 (30), 81 (27).

Asymmetric Synthesis of Chiral Sulfoxides. II.[1] An Intramolecular O → N Sulfinyl Migration

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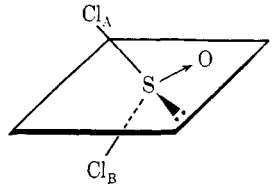
Abstract: The conversion of a 1,2,3-oxathiazolidine 2-oxide (**1**) derived from *l*-ephedrine to methyl aryl sulfoxides *via* sulfinamides (**3**) was studied in detail. The stereochemistry of sulfinyl transfer in an O-sulfinylated ethanolamine (**7**) was investigated. This rearrangement proceeds *via* two competitive paths: intramolecular and intermolecular. The intramolecular path yields a sulfinamide (**3**) with retention of configuration at sulfur.

Chiral menthyl arenesulfinates are converted stereospecifically[2,3] to sulfoxides. This approach to open-chain optically pure sulfoxides, though elegant, is limited. Only *R* aryl alkyl sulfoxides can be prepared in optically pure form because the less soluble diastereomer of the known menthyl arenesulfinates (*l* isomer) is always of the same absolute configuration at sulfur.[3] Furthermore, the diastereomeric mixtures of low molecular weight alkanesulfinates (*e.g.*, menthyl, cedryl, and bornyl methane- to propanesulfinates) are oils at room temperature. These oils proved difficult to separate.[4] While a more recent approach *via* organolithium reactions with deoxyephedrine sulfinamides can lead to either enantiomer of any open-chain sulfoxide, it is restricted to the synthesis of *optically pure* sulfoxides *lacking α hydrogens*.[5,6]

This paper describes the results of one aspect of a possible general approach designed to circumvent the above difficulties. Originally, we envisioned our method to be applicable to the synthesis of molecules containing many different chiral atoms; for example, sulfoxides, selenoxides, phosphine oxides, arsine oxides, silanes, germanes, and the intriguing possibility of a suitable chiral stannane.[7]

Our plan is based on the distinction between the two enantiotopic (prochiral) chlorine atoms (Cl_A and Cl_B) of thionyl chloride by a chiral ethanolamine. Equations 1–4 describe the overall approach.



The following features were anticipated to make the above scheme attractive. (1) Any chiral ethanolamine could be a suitable reagent for reaction 1. (2) The epimerization of sulfinyl sulfur (S=O) by hydrogen chloride (reaction 2) was studied by Herbrandson and Dickerson[8] and Mislow.[9a] That is, if reaction 1 would

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