Nuclear Magnetic Resonance Characteristics of Thiomethylene Groups in a Stereoisomeric Pair of Model Quinolizidines and Some Related Thiospirane *Nuphar* Alkaloids[1]

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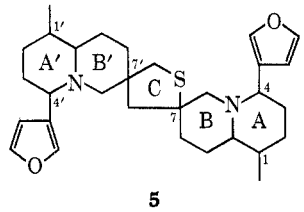
3(e)-Methyl-3(a)-methylthiomethylquinolizidine (**1a**) and 3(a)-methyl-3(e)-methylthiomethylquinolizidine (**1b**) were prepared and their nmr spectra were determined. The chemical shift of the axial thiomethylene in **1a** is found at lower field than the equatorial thiomethylene of **1b**. On the basis of this relationship and reported nmr properties of neothiobinupharidine and thionuphlutine-A and -B, the presence of an equatorial thiomethylene group in each of the latter two alkaloids is proposed.

Axial and equatorial methyl groups attached to *trans*-quinolizidines can be distinguished by nuclear magnetic resonance chemical shift differences.[2] Thus for an axial–equatorial pair of 3-methylquinolizidines, the axial methyl is found at lower field than its equatorial counterpart. A similar relation might be expected for methylene groups as well as methyl groups.

We have prepared the various methylene derivatives **1–4** (Table I) and have studied their nuclear magnetic resonance spectra. The prime objective of this work was to provide experimental evidence which would substantiate an expected relation between chemical shift and the stereochemistry of thiomethylene groups when attached to C-3 of a trans-fused quinolizidine system. Such a demonstrated relation could prove useful in making stereochemical assignments of similarily placed thiomethylene groups in neothiobinupharidine,[3] and thionuphlutine-A and -B;[4] all of these are stereoisomeric *Nuphar* alkaloids which belong to the structural type represented by **5**.



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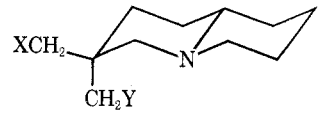
Synthesis and Nmr of Model Compounds.—A mixture containing the stereoisomeric alcohols **2a** and **2b** as well as a number of other partially reduced intermediates had been obtained in the course of following a well-known procedure for the preparation of 3-alkylquinolizidines[5,6] through the reduction of 1-(2-pyridyl)-3,3-dicarbethoxybutane over copper chromite. The two alcohols could be separated by various chromatographic procedures described in the Experimental Section. The mixture of alcohols was converted to a mixture of acetates, **3a** and **3b**, which could be separated by glc. Both acetate isomers absorbed in the ir at 5.75 μ and showed strong Bohlmann bands[2,7,8] in the region of 3.60 μ.

A mixture of liquid tosylates, **4a** and **4b**, was obtained from the mixture of alcohols. Treating the tosylate mixture in 2-methoxyethanol solution with lithium methyl mercaptide gave a mixture of the 3-methyl-3-methylthiomethylquinolizidines, **1a** and **1b**. This sulfide mixture was separated into the pure stereoisomeric sulfides by glc.

A sample of 3(e)-methyl-3(a)-methylthiomethylquinolizidine (**1a**) was prepared from the corresponding pure alcohol **2a** by employing nearly the same scheme as was used in converting the mixture of alcohols to the mixture of sulfides. The only departure was that the tosylate **4a** in methylene chloride solution was treated with methyl mercaptan in place of lithium methyl mercaptide. Resulting was a single sulfide, **1a**, which was identical with one of the two sulfides separated by

TABLE I

NMR CHARACTERISTICS[a,b] FOR AXIAL AND EQUATORIAL 3-CH_3,3-CH_2–X QUINOLIZIDINES



Axial series			Equatorial series		
X = H, Y =	δ, CH_2Y	δ, CH_3[c]	Y = H, X =	δ, CH_2X	δ, CH_3[c]
SCH_3, **1a**	2.80 (s)	0.90	SCH_3, **1b**	2.40 (s)	1.14
OH, **2a**	3.68 (s)	0.74	OH, **2b**	3.32 (s)	1.08
OAc, **3a**	4.22 (AB q, 9 Hz)	0.86	OAc, **3b**	3.80 (s)	1.10
OTs, **4a**	4.14 (AB q, 8 Hz)	0.84	OTs, **4b**	3.68 (s)	1.06

[a] Measured in deuteriochloroform solution relative to tetramethylsilane. [b] s = singlet; q = quartet. [c] All methyl groups were observed as singlets.

(1) This work was supported by the McIntire–Stennis Cooperative Forestry Research Program of the U. S. D. A. and the National Institute of Allergy and Infectious Diseases, Grant AI 10188, National Institutes of Helath, U. S. Public Health Service.

(2) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

(3) (a) G. I. Birnbaum, *Tetrahedron Lett.*, 4149 (1965); (b) D. Achmatowicz and J. T. Wróbel, *ibid.*, 129 (1964); (c) O. Achmatowicz, H. Banazek, G. Spiteller, and J. T. Wróbel, *ibid.*, 927 (1964).

(4) R. T. LaLonde, C. F. Wong, and W. P. Cullen, *ibid.*, 4477 (1970).

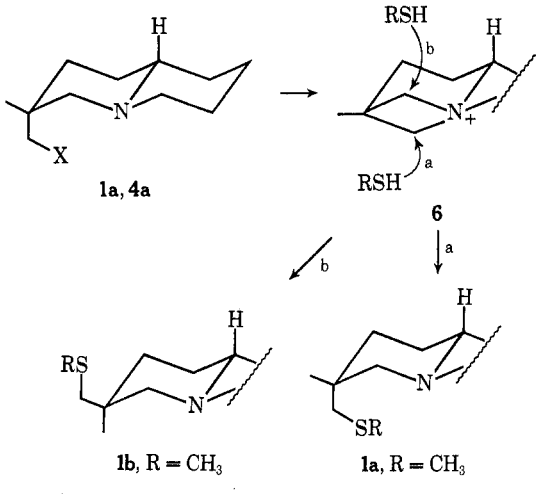
(5) V. Boekelheide and S. Rothchild, *J. Amer. Chem. Soc.*, **71**, 879 (1949).

(6) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955).

(7) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

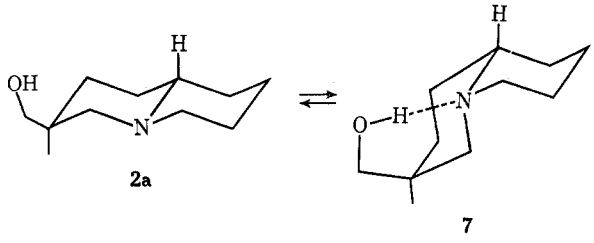
(8) M. W. Wiewiorowski and J. Skolick, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **10**, 1 (1962).

glc from the mixture of sulfides. That the resulting sulfide **1a** possessed the same steric disposition of groups substituted at C-3 as did its alcohol precursor **2a** was demonstrated by the consistency of methyl and thiomethylene chemical shifts with similar data for alcohol, acetate, and tosylate. These data are summarized in Table I. In each case, the methyl groups of the series **1a–4a** were found upfield relative to the methyls of the series **1b–4b**. Had the conversion of tosylate to sulfide taken place by way of an azetidinium ion **5**, possibly the precursor alcohol **2a** would have afforded the equatorial sulfide **1b**. The intermediacy of a structurally



similar azetidinium ion resulting from lupinine derivatives has been observed.[9] However, should such an intermediate intervene and should it have been responsible for the incorporation of an equatorial rather than an axial thiomethylene, then the concomitantly formed axial methyl group should have been observed at low field rather than at high field as was in fact observed.

The stereochemistry of precursor alcohols **2a** and **2b** was established in the following manner. First, the Bohlmann bands displayed by the alcohols (**2a** and **2b**), acetates, and sulfides were of equal intensity. Therefore, the isomer possessing the axial hydroxymethyl group must be a trans-fused quinolizidine and cannot be represented by a cis-fused, hydrogen-bonded structure such as **7** since the latter is expected to display no Bohlmann ir bands or, at best, bands which are less intense than those of the corresponding *trans*-quinolizidine.[8]



Second, the isomeric alcohol **2a** displayed a strong, broad, intramolecular hydrogen-bonded hydroxyl band at 3260 cm^{-1} which is a frequency lower than the range (3530–3480 cm^{-1}) characteristic of five-membered-ring, hydrogen-bonded hydroxyquinolizidines[10] but within the region (~3300 cm^{-1}) where six-membered-ring, hydrogen-bonded hydroxymethylquinolizidines absorb.[11] A second much weaker free hydroxyl band at 3640 cm^{-1} was also observed. Lowering the concentration 50-fold to 0.01 *M* did not change the relative intensity of the 3260- and 3640-cm^{-1} bands. In contrast, the second isomeric alcohol **2b** showed a sharp band at 3620 cm^{-1} and a broad, intermolecular hydrogen-bonded band in the region of 3100–3500 cm^{-1}. The latter diminished in intensity as the concentration decreased and at a concentration of 0.01 *M* disappeared completely. Therefore the axial hydroxymethyl group was assigned to the isomer **2a** displaying the ir properties of an intramolecular, hydrogen-bonded hydroxyl group. Confirming this stereochemical assignment is the greater mobility of **2a** on both adsorption and gas–liquid columns.

The stereochemistry of thiomethylene groups in **1a** and **1b** follows from the stereochemistry assigned to the precursor alcohols and the conservation of that stereochemistry in the tosylation and nucleophilic displacement steps leading to the respective sulfides. As the data of Table I show, the axial thiomethylene is found at a lower field than is its equatorial counterpart.

Nmr of Thiospirane *Nuphar* Alkaloids.—The chemical shift data for the quinolizidine model sulfides **1a** and **1b** are reproduced in Table II and compared with similar

Table II

Chemical Shift Values for Axial and Equatorial CH_2S and SCH_3

Sulfide	CH_2S δ	CH_2S Assignment	SCH_3 δ
$CH_3SCH_2CH_3$	2.53[a]		2.10
$CH_3S(CH_2)_4CH_3$	2.50[a]		2.08
1a	2.80	Axial	2.14
1b	2.40	Equatorial	2.13
NTBN,[b] **5**	2.69[c]	Axial[d]	
TN-A,[b] **5**	2.32	Equatorial	
TN-B,[b] **5**	2.33	Equatorial	

[a] N. S. Bhacca, L. F. Johnson, and J. N. Schoolery, "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962. [b] NTBN = neothiobinupharidine; TN-A = thionuphlutine-A; TN-B = thionuphlutine-B. [c] Reference 3b. [d] Reference 3a.

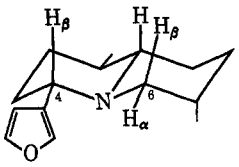
data for simple sulfides and the three known stereoisomeric thiospirane, *Nuphar* alkaloids, **5**. The thiomethylene attached to the A′B′ quinolizidine system of neothiobinupharidine is axial. This assignment of relative stereochemistry follows from an X-ray study of this alkaloid.[3a] In an earlier interpretation[3b] of the nmr of neothiobinupharidine, the resonance reported at δ 3.04, 2.94, 2.83, and 2.69 was attributed to the six protons α to nitrogen. The next higher field resonance band was observed in the region of δ 1.77–1.48. Judging from the chemical shifts of the model sulfides given in Table II, an axial thiomethylene also might come into resonance in the δ 3.04–2.69 region. Reasonably, the reported six-proton resonance in the δ 3.04–2.69 region represents not six protons α to nitrogen but rather two thiomethylene protons plus four protons α to nitrogen. The latter

(9) O. E. Edwards, G. Fodor, and L. Marion, *Can. J. Chem.*, **44**, 13 (1966), and references cited therein.

(10) T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971).

(11) (a) F. Bohlmann, E. Winterfeldt, H. Laurent, and W. Ude, *Tetrahedron*, **19**, 195 (1963); (b) F. Bohlmann, E. Winterfeldt, P. Studt, H. Laurent, G. Boroschewski, and K.-M. Kleine, *Chem. Ber.*, **94**, 3151 (1961).

four would be the two protons α to both nitrogen and the furan ring plus the two equatorial protons attached to C_6 and $C_{6'}$. This reinterpretation of the reported nmr of neothiobinupharidine is based in part on the nmr of deoxynupharidine,[12] **8**, which displays the $C_{4\beta}$



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(axial) proton at δ 2.88, the $C_{6\alpha}$ (equatorial) proton at δ 2.70, but the $C_{6\beta}$ (axial) proton at a much higher field—δ 1.88. The C_{10} (axial) proton also is in the region δ 1.7–1.9. Therefore, either one of the resonances at δ 2.69 or 2.83 reported for neothiobinupharidine would appear to be plausible chemical shift values for the thiomethylene protons of this alkaloid. However, the δ 2.69 band was reported[3b] as strong, integrated for two hydrogens, and was assigned to CH_2N. No integration was given for the resonance band at δ 2.83, but on the grounds that the C_4 proton of deoxynupharidine comes into resonance at δ 2.88 it seems that the reported δ 2.83 could also be attributed to C_4 and $C_{4'}$ protons of neothiobinupharidine. Consequently, the best choice for the thiomethylene resonance would be the δ 2.69 band.

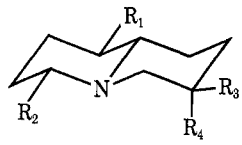
In contrast to the δ 2.69 thiomethylene resonance of neothiobinupharidine, the same group in the stereoisomeric thionuphlutines-A and -B is observed[4] at somewhat higher field—2.32 and 2.33, respectively. On the basis of the low field–high field relation of pairs of equatorial and axial thiomethylene groups, the higher field resonance for the thionuphlutines relative to neothiobinupharidine must mean that the former two alkaloids have an equatorial thiomethylene attached to the A′B′ quinolizidine system. That these equatorial thiomethylene groups are attached to trans-fused quinolizidine systems follows from the following observation. Solutions of thionuphlutine-A and -B and deoxynupharidine which are of equal normality all exhibit Bohlmann bands of equal intensity.

One other point relevant to the use of **1a** and **1b** as models for the thiospirane *Nuphar* alkaloids should be discussed. Conceivably the suitability of **1a** and **1b** might be questioned on the basis that **1a** and **1b** contain no 3-furyl group as do the various stereoisomeric alkaloids **5**. Consequently, the axial and equatorial thiomethylene groups in **5** might be subject to anisotropic effects which the same groups in **1a** and **1b** are not. However, as can be seen from the data given in Chart I, the effect of the 3-furyl group is shielding to nearly the same extent for both axial and equatorial methyl groups and reasonably will be shielding for thiomethylene groups as well. In fact, the magnitude of this effect is observed to be the same for equatorial thiomethylene groups when the model compound **1b** is compared to thionuphlutine-A (-B) (Chart I). The anisotropic effect of the 3-furyl group on an axial thiomethylene awaits an nmr investigation of neothiobinupharidine and a definite assignment of the thiomethylene resonance for this alkaloid. Unfortunately, we have not detected the presence of neothiobinupharidine in any of the species of North American *Nuphar* which have been investigated in our laboratories.

In conclusion, **1a** and **1b** are appropriate models for ascertaining chemical shift differences of axial and equatorial thiomethylene groups. Using these models in conjunction with a reinterpretation of the earlier published nmr data for neothiobinupharidine, the thiomethylene groups of thionuphlutine-A and -B are believed to be equatorial.

CHART I

THE ANISOTROPIC EFFECT OF THE 3-FURYL GROUP ON AXIAL AND EQUATORIAL CH_3 AND CH_2S GROUPS



	CH_3, δ^a
$R_1 = R_2 = R_3 = H$; $R_4 = CH_3$	1.08
$R_1 = R_4 = CH_3$; R_2 = 3-furyl; $R_3 = H$	1.00
$\Delta^{(ax)}_{CH_3} = \delta\ 0.08$	
$R_1 = R_2 = R_4 = H$; $R_3 = CH_3$	0.82
$R_1 = R_3 = CH_3$; R_2 = 3-furyl; $R_4 = H$	0.73
$\Delta^{(eq)}_{CH_3} = \delta\ 0.09$	

$\Delta^{(eq)}_{CH_2S} = \delta^{1b}_{CH_2S,\,eq} - \delta_{TN\text{-}A(-B)^b} = 2.40^a - 2.32^a = \delta\ 0.08$

[a] Measured in deuteriochloroform solution relative to tetramethylsilane. [b] TN-A (-B) = thionuphlutine-A (-B).

Experimental Section

Spectra were obtained as follows: nmr in $CDCl_3$ solution, 2% TMS (δ 0.0), Varian A-60A, symbols s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; ir in solution as indicated, Perkin-Elmer 137 and 621; mass spectrum at 70 eV and 160–165° with an all-glass heated inlet except where indicated otherwise. Melting points were determined on a Köfler micro hot stage and are uncorrected. Glc conditions were 0.25-in. 5% Carbowax, 195°, He (75% of maximum flow), Varian-Aerograph 200, unless indicated otherwise. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3-Methyl-3-hydroxymethylquinolizidines.—According to the literature procedure,[13] vinylpyridine was treated with the sodium enolate of ethyl methylmalonate to obtain 1-(2-pyridyl)-3,3-dicarbethoxybutane. The last named (200 g, 0.72 mol) in 300 ml of dioxane was heated at 230° under 130 atm of hydrogen with 30 g of copper chromite catalyst. Distillation of the product gave 90 g of 3-methylquinolizindine, bp 90–91° (18.5 mm), $n^{20}D$ 1.4740, and 35 g (26.8%), bp 90–93° (2 mm), of a mixture of hydroxymethylquinolizidines and quinolizidones, ir 6.1–6.2 μ.

A 2-g sample of the higher boiling fraction in CH_2Cl_2 solution was washed with dilute aqueous HCl. The aqueous solution was basified (pH 14) with sodium hydroxide and then extracted repeatedly with CH_2Cl_2. The extract was dried (Na_2SO_4) and the solvent was evaporated to give 1.27 g of residue showing no lactam band at 6.1–6.2 μ. The residue was eluted first with benzene from a column of 38 g of neutral alumina (activity II). Fraction number, weight in milligrams, and volume of eluent in milliliters are as follows: 1, 423, 200; 2, 231, 200; 3, 54, 50; 4, 200 ml. Continued elution with 200 ml of 25% methanol–benzene gave fraction 5, which with fraction 4 amounted to 618 mg. Fractions 2 and 3 consisted of pure 3(e)-methyl-3(a)-

(12) C. F. Wong, E. Auer, and R. T. LaLonde, *J. Org. Chem.*, **35**, 517 (1970).

(13) F. Bohlmann, E. Winterfeldt, G. Boroschewski, R. Meyer-Mader, and B. Gatscheff, *Chem. Ber.*, **96**, 1792 (1963).

hydroxymethylquinolizidine (**2a**): mp 48–50°; glc 6 min. mass spectrum *m/e* (rel intensity) 183 (37), 182 (84), 168 (44), 152 (96), 151 (5), 124 (31), 98 (67), 97 (100), 84 (82), 83 (75), 57 (63), 55 (82); ir (CH_2Cl_2) 3640 (weak), 3260 cm^{-1} (broad and strong), 3.58, 3.62 μ; ir 0.50, 0.25, 0.17, 0.13, 0.12, 0.06, 0.01 *M* in CCl_4 (3-mm cell); observed an invariable intensity of 3260- and 3640-cm^{-1} bands relative to CH bands and a linear plot of concentration *vs.* intensity of the 3260-cm^{-1} band; nmr δ 5.0 (br s, 1 H, OH), 3.68 (s, 2 H, CH_2OH), 2.8 (m, 2 H, NCH eq), 1.0–2.1 (m, 13 H), 0.74 (s, CCH_3 eq). *Fractions* 4 and 5 contained a mixture of the stereoisomeric 3-methyl-3-hydroxymethylquinolizidines, glc 6 and 7.4 min, bp 50° (0.05 mm).

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.56; N, 7.64. Found: C, 72.24; H, 11.70; N, 7.53.

By preparative glc was obtained pure liquid 3(a)-methyl-3(e)-hydroxymethylquinolizidine (**2b**): glc 7.4 min; mass spectrum *m/e* (rel intensity) 183 (39), 182 (84), 168 (14), 152 (92), 151 (53), 124 (30), 98 (59), 97 (100), 84 (78), 83 (74), 57 (58), 55 (95); ir (CH_2Cl_2) 3620 (s) and 3100–3500 cm^{-1}; ir (CCl_4) 0.53–0.01 *M*, 3100–3500-cm^{-1} band absent at 0.01 *M*; nmr 3.32 (s, 2 H, CH_2OH), 1.08 (s, 3 H, CH_3C).

3-Methyl-3-hydroxymethylquinolizidine Acetates.—A 349-mg sample of the mixture of alcohols was treated with 2 equiv of acetyl chloride and an excess of triethylamine in CH_2Cl_2 overnight at 25°. The mixture was treated with aqueous bicarbonate. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The extracts were combined with the original CH_2Cl_2 solution and dried (Na_2SO_4). Evaporation of the solvent gave 422 mg of residue which when passed through neutral alumina (activity I) gave a sample of acetates: ir 1740 cm^{-1}; glc 5 and 5.7 min (0.25-in. 5% Carbowax, 199°, 50% He total flow).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.10; H, 10.27; N, 6.02.

Separation of the mixture of acetates by glc gave pure 3(e)-methyl-3(a)-acetoxymethylquinolizidine (**3a**) [glc 5.0 min (0.25-in. 5% Carbowax, 199°, 50% He total flow; ir 5.75 μ; nmr 4.22 (q, 2 H, J = 9 Hz CH_2OAc), 0.86 (s, 3 H, $CH_3C<$)], and 3(a)-methyl-3(e)-acetoxymethylquinolizidine (**3b**) [glc 5.7 min; ir 5.75 μ; nmr δ 3.80 (s, 2 H, eq CH_2OAc), 1.10 (s, ax CH_3)].

Treatment of 18 mg of 3(e)-methyl-3(a)-hydroxymethylquinolizidine with acetyl chloride and triethylamine in the manner described above gave 20 mg of pure 3(e)-methyl-3(a)-acetoxymethylquinolizindine (**3a**): glc 5 min; ir 5.75 μ; nmr δ 4.22 (AB q, J = 9 Hz).

3-Methyl-3-hydroxymethylquinolizidine *p*-Toluenesulfonates.—A 259-mg sample of the alcohol mixture in 2 ml of CH_2Cl_2 was treated with 270 mg of *p*-toluenesulfonyl chloride for 14 hr. The solvent was evaporated and the residue was stored at 0° for 30 hr but no crystalline material formed. Therefore the residue was treated with 10 ml of saturated aqueous bicarbonate and then extracted with CH_2Cl_2 (three 20-ml portions). The combined extracts were dried. Evaporation of the solvent left 384 mg of brown, oily tosylate: nmr δ 7.9 (m, 4 H, SO_2Ar-*o*-H), 7.40 (m, 4 H, SO_2Ar-*m*-H), 4.14 (AB q, J = 8 Hz, 2 H, ax CH_2OTs), 3.68 (s, 2 H, eq CH_2OTs), 2.50, 2.46 (2 s, 6 H, CH_3ArSO_2), 0.84 (s, 3 H, eq $CH_3C<$), and 1.06 (s, 3 H, ax $CH_3C<$).

A 31-mg sample of 3(e)-methyl-3-(a)-hydroxymethylquinolizidine in 0.5 ml of benzene was treated with 33 mg of *p*-toluenesulfonyl chloride at 70–75° for 0.5 hr and at 25° for 14 hr. Removal of solvent by evaporation produced an oil which on cooling gave crystalline 3(e)-methyl-3(a)-hydroxymethylquinolizidine *p*-toluenesulfonate hydrochloride (**4a**): mp 165–166° (transition point, 126°) (CH_2Cl_2–hexane); nmr δ 4.66, 4.52, 4.38, 4.02 (AB q, 2 H, CH_2OTs), and 0.95 (s, 3 H, ax $CH_3C<$); mass spectrum (unheated, direct inlet) *m/e* (rel intensity) 337 (9), 336 (14), 182 (77), 166 (100); ir OH and Bohlmann bands absent, 4.22, 4.35, 6.24, 6.89, 7.40, 8.40, 8.51, 10.25, 10.48 μ.

Anal. Calcd for $C_{18}H_{28}NSO_3Cl$: C, 57.81; H, 7.55; N, 3.75. Found: C, 57.84; H, 7.31; N, 3.50.

A sample of the hydrochloride was treated with aqueous sodium bicarbonate and shaken with CH_2Cl_2. The extract was dried and the solvent was evaporated to obtain the liquid, free base: nmr δ 4.14 (AB q, J = 8 Hz, 2 H, ax CH_2OTs) and 0.84 (s, 3 H, eq CH_3C); mass spectrum *m/e* (rel intensity) 337 (9), 336 (16), 182 (84), 166 (100); ir OH band absent, 3.40, 3.50, 3.60 (strong, Bohlmann), 6.24, 6.20, 6.89, 6.91, 7.32, 8.40, 8.50, 10.30, 10.50 μ.

3-Methyl-3-methylthiomethylquinolizidine.—A 384-mg sample of 3-methyl-3-hydroxymethylquinolizidine *p*-toluenesulfonate in 2 ml of 2-methoxyethanol was added to a solution of lithium methyl mercaptide prepared by treating 91 mg of lithium hydride with 2 ml of methanethiol and 1 ml of 2-methoxyethanol. The mixture was stored at 50° for 17 hr and at 100° for 2 hr.[14] The reaction mixture was added to 20 ml of benzene and the resulting mixture was passed through 20 g of neutral alumina (activity II). The alumina was washed thoroughly with 150 ml of benzene. Evaporation of the benzene produced 207 mg of oily residue which was chromatographed on a 1-cm-diameter column containing 10 g of neutral alumina (activity II). The chromatography was monitored by glc (0.25-in. 5% Carbowax, 175°, He 75% total flow). Elution with hexane gave a 31-mg fraction and then a 46-mg fraction consisting of two components having glc retention times of 6.65 and 8.95 min. Continued elution with 25% benzene–hexane gave a 77-mg mixture rich in the 6.65-min component. The 46-mg fraction was rechromatographed on 4 g of neutral alumina (activity II) to obtain an analytical sample.

Anal. Calcd for $C_{12}H_{23}NS$: C, 67.55; H, 10.86; N, 6.56; S, 15.03. Found: C, 67.35; H, 11.01; N, 6.50; S, 15.15.

Preparative glc of the 77 mg, 25% benzene–hexane fraction gave 3(e)-methyl-3(a)-methylthiomethylquinolizidine (**1a**) [glc 6.65 min (0.25-in. 5% Carbowax, 175°, He 75% total flow); uv λ_{max} 220 mμ; mass spectrum *m/e* (rel intensity) 213 (M^+, 59), 198 (100), 167 (51), 166 (100), 152 (28), 150 (20), 138 (38), 136 (22), 110 (20), 98 (100); ir (neat) 3.42, 3.51 (s, CH), 3.59, 3.62 (Bohlmann), 6.95, 7.31, and 8.90 μ; nmr δ 2.80 (s, 2 H, CH_2SCH_3), 2.68 (m, 1 H, eq CHN), 2.49 (m, 1 H, eq CHN), 2.13 (s, 3 H, CH_3S), 1.1–2.0 (m, 13 H), 0.90 (s, 3 H, ax CH_3C)] and 3(a)-methyl-3(e)-methylthiomethylquinolizidine (**1b**) [glc 8.95 min; mass spectrum *m/e* (rel intensity) 213 (M^+, 42), 198 (66), 167 (43), 166 (100), 152 (22), 150 (18), 138 (32), 136 (18), 110 (17), 98 (100); ir (neat) 3.42, 3.51 (CH), 3.59 3.62 (Bohlmann), 7.0 μ; nmr δ 2.66 (m, 2 H, eq CHN); 2.40 (s, 2 H, eq CH_2S), 2.13 (s, 3 H, CH_3S), 2.0–1.22 (m, 13 H), 1.14 (s, 3 H, ax CH_3)].

3(e)-Methyl-3(a)-methylthiomethylquinolizidine (1a).—A 59-mg sample of the hydrochloride salt of 3(e)-methyl-3(a)-hydroxymethylquinolizidine *p*-toluenesulfonate in a 0.5-ml solution of methyl mercaptan in methylene chloride was heated at 80–90° for 12 hr in a sealed glass tube. The volatiles were removed by evaporation. The nmr of the 57 mg of residue indicated the presence of only starting *p*-toluenesulfonate ester. The residue was treated with 5 ml of saturated, aqueous bicarbonate and then dissolved in CH_2Cl_2 to recover the *p*-toluenesulfonate ester as the free base. The base (42 mg) in CH_2Cl_2 was heated with 1 ml of methanethiol for 16 hr at 80–90° in a sealed glass tube. The volatiles were removed by evaporation. An nmr of the resulting residue (23 mg) showed no starting *p*-toluenesulfonate ester but the presence of the axial CH_2SCH_3 group (δ 2.80). Glc demonstrated the presence of 3(e)-methyl-3(a)-methylthiomethylquinolizidine (6.6 min, 0.25-in. 5% Carbowax, 175°, 75% He total flow). The isomeric sulfide (8.95 min) could not be detected in the product mixture by glc or nmr.

Registry No.—**1a**, 31819-27-9; **1b**, 31819-28-10; **2a**, 31819-29-1; **2b**, 31819-30-4; **3a**, 31883-37-1; **3b**, 31819-31-5; **4a**, 31819-32-6; **4a** HCl, 31819-33-7; **4b**, 31819-34-8.

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