

Stereochemistry of Epimeric 1-Hydroxy-*N*-methylquinolizidinium Iodides

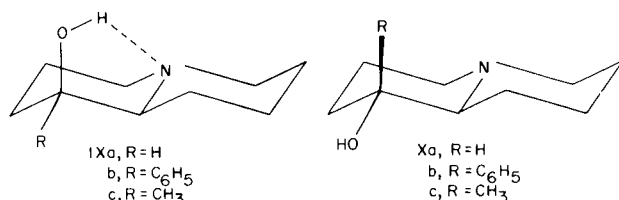
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The methiodides of epimeric 1-hydroxy, 1-hydroxy-1-phenyl, and 1-hydroxy-1-methylquinolizidines were prepared from their respective bases. The previously described but not separated epimeric 1-hydroxy-1-methylquinolizidines were prepared and their configurations elucidated by the use of nuclear magnetic resonance (NMR) and infrared data. Structural assignments of the quinolizidinium iodides were made on the basis of NMR data.

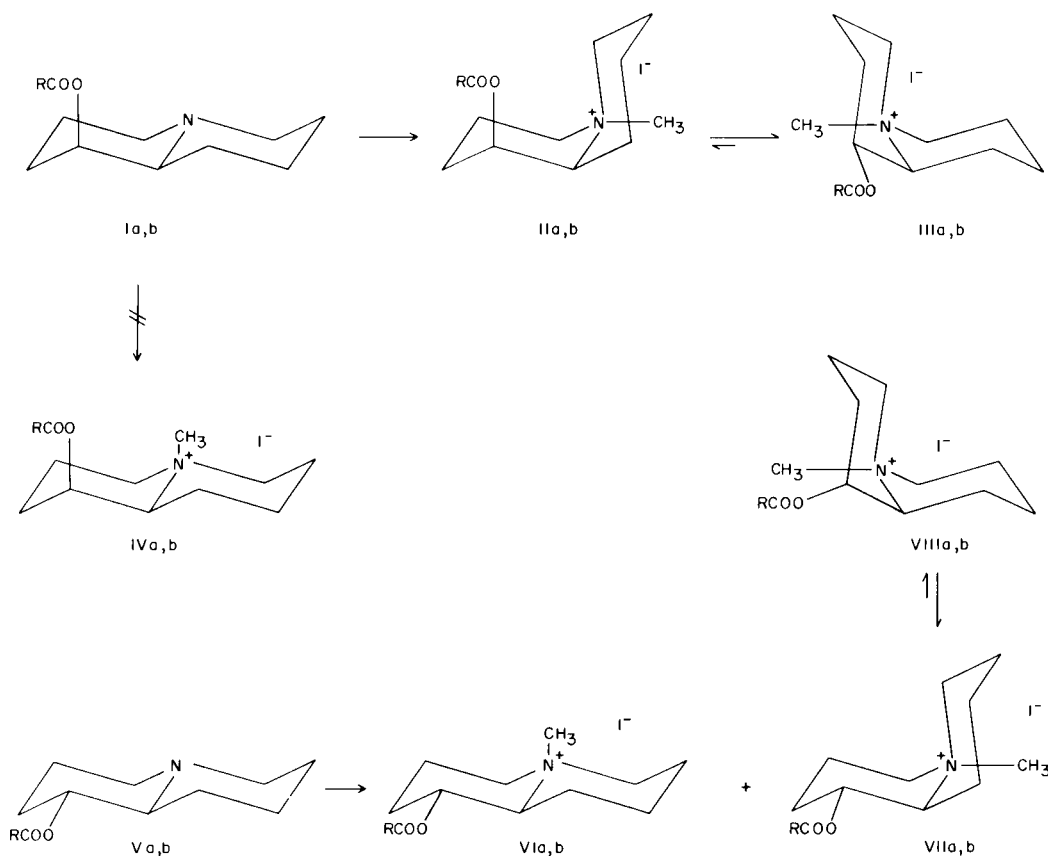
The formation of one quaternary ammonium salt from the reaction of quinolizidin-1(a)-yl acetate (Ia) or propionate (Ib) with methyl halide and the formation of two quaternary ammonium salts from the corresponding equatorial isomers (V) (2) prompted an investigation of other *N*-methylquinolizidinium halides. Conformations II and III, like the *cis*-decalins, are interconvertible. The latter conformation, however, with the bulky ester group in the equatorial position will predominate. Likewise, the axial group in structure IV precludes its formation. It follows also that conformations VI and VII with equatorial substituents are the preferred products from the reaction of V with methyl iodide.

Epimeric 1-hydroxyquinolizidines (IXa, Xa) (2,3), 1-hydroxy-1-phenylquinolizidines (IXb, Xb) (4) and 1-hydroxy-1-methylquinolizidines (IXc, Xc) (5) were utilized in these studies. 1-Hydroxy-1-methylquinolizidine was prepared using essentially the same procedure as described by Leonard (5) from 1-ketoquinolizidine *via* the Grignard reaction. The epimeric alcohols (IXc, Xc), separated by gas-liquid chromatography and by fractional recrystallization, were obtained in approximately a 2:3 ratio, respectively.

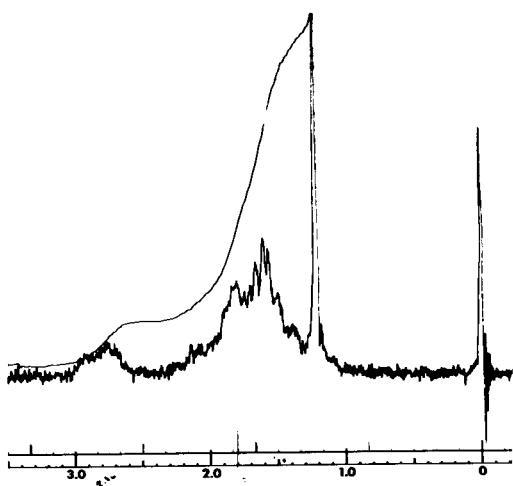
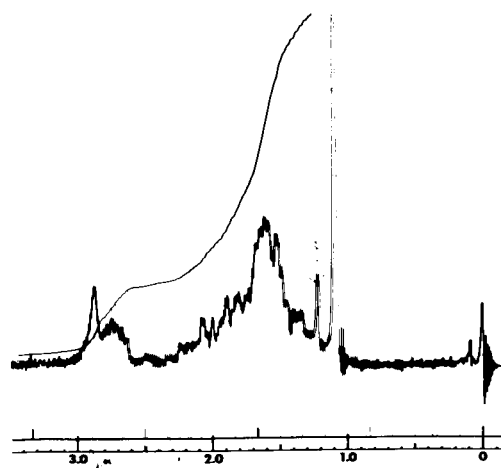


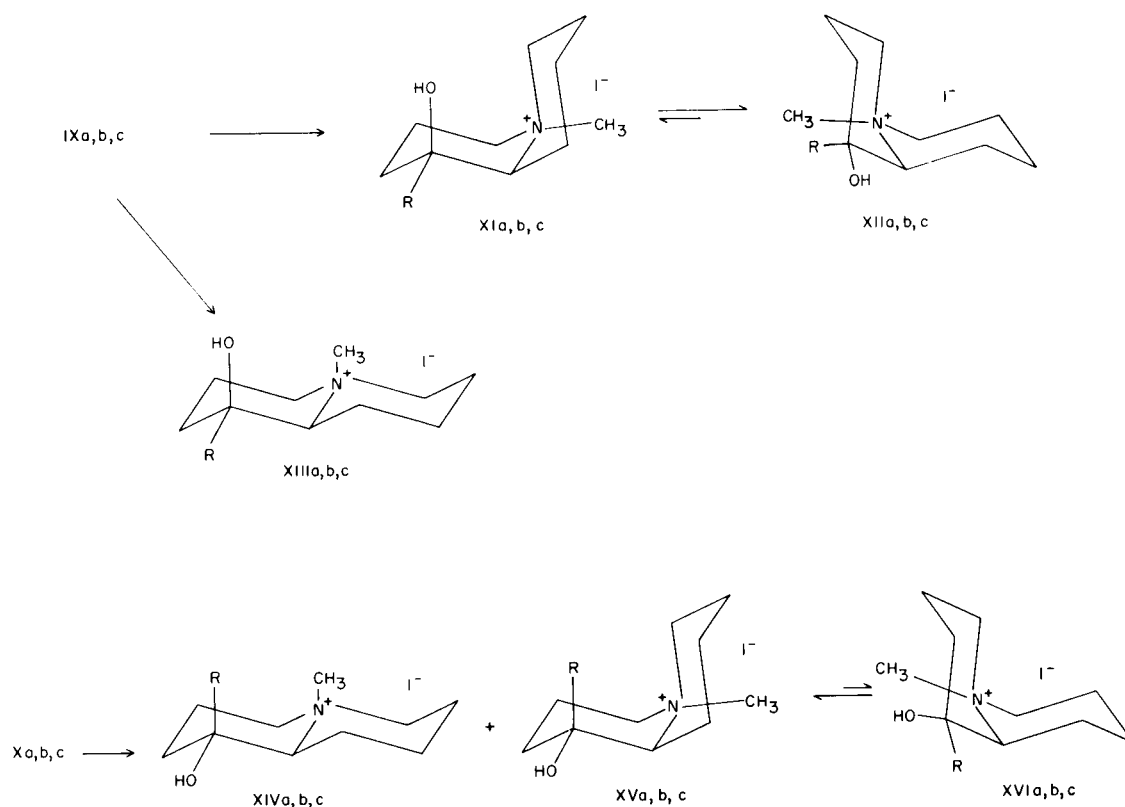
1(a)-Hydroxy-1(e)-methylquinolizidine (IXc) melts considerably lower (46-48°) than its epimer (Xc, m.p. 96-97°). The difference in melting points may be ascribed to intramolecular hydrogen bonding in IXc and intermolecular hydrogen bonding in Xc. The infrared spectra (Table 1) of 1(a)-hydroxy-1(e)-methylquinolizidine (IXc) shows a single, broad (strong) hydroxyl absorption at 3480 cm⁻¹, attributed to an intramolecularly hydrogen bonded hydroxyl group, which is consistent with the findings of Sam and England (4) for *cis*-1-hydroxy-1-phenylquinolizidine. The infrared spectra of Xc shows sharp (weak) free hydroxyl absorption at 3620 cm⁻¹, intermolecular hydroxyl absorption at 3200 cm⁻¹, and none of the broad absorption at 3480 cm⁻¹ as seen in IXc. The presence of "Bohlmann bands" (6,7) in the infrared spectra of both epimers is indicative of *trans*-ring fused structures.

The NMR spectral data of compounds IXc and Xc were in good agreement with the structural assignments made on the basis of the physical data previously described. The primary differences in the NMR spectra of compounds IXc and Xc are produced by the tertiary hydroxyl and methyl groups. Epimer Xc (Fig. 2) shows a single signal at 1.22 δ (3 protons) which is due to the C-1 methyl group. The equatorial methyl group of epimer IXc (Fig. 3) gives a signal at 1.09 δ slightly upfield from that caused by epimer Xc. The hydroxyl signals of the two compounds are significantly different. Epimer Xc (Fig. 2) shows a broad hydroxyl signal at 2.86 δ consistent with intermolecular proton exchange, whereas epimer IXc (Fig. 3) shows a

Figure 1. (a, R=CH₃; b, R=C₂H₅)

sharp peak at 2.88 δ consistent with an intramolecularly bonded system.

Figure 2. NMR spectrum of *trans*-1(e)-hydroxy-1(a)-methylquinolizidine (Xc) in CDCl₃ (10%).Figure 3. NMR spectrum of *trans*-1(e)-hydroxy-1(a)-methylquinolizidine (IXc) in CDCl₃ (10%).

Figure 4. (a, R = H; b, R = C₆H₅; c, R = CH₃)

The existence of *cis*-ring fusion in the quaternary ammonium salts of certain quinolizidines has been noted by others (2,7). Johnson and co-workers (8) have discussed the kinetics of quaternization of quinolizidine and methylquinolizidine by methyl iodide and have calculated the free-energy differences for *cis-trans* interconversions (ring fusion). Williamson and co-workers (9) have assigned the stereochemistry of *cis*- and *trans*-ring

fused *N*-methylquinolizidinium ions on the basis of the NMR line widths at half-height of the angular *N*-methyl group, and have indicated the chemical shifts for *trans*-ring fused and *cis*-ring fused *N*-methylquinolizidine as 2.86 δ and 3.05 δ , respectively.

The methiodides of the six epimeric alcohols (IXa, b, c and Xa, b, c) were prepared by refluxing the alcohols in various solvents with an excess of methyl iodide.

TABLE I

Infrared Spectral Data (cm⁻¹) for Epimeric 1-Hydroxy-1-methylquinolizidines (15% CHCl₃ solution)

Epimer	Free OH	H-bonding		Bohlmann bands (6)
		Intra	Inter	
IXc	-	3480 (strong)	-	2700-2800
Xc	3620 (weak)	-	3200 (strong)	2700-2800

The NMR spectra of the methiodides of IXa and Xa are shown in Figures 5 and 6, respectively. The principal difference between the two spectra lies in the nature of the *N*-methyl signals. The NMR spectrum (Fig. 5) of the methiodide of IXa shows a single

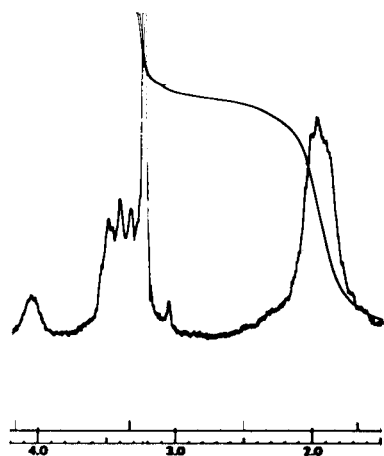


Figure 5. NMR spectrum of *cis*-1(a)-hydroxy-*N*-methylquinolizidinium iodide (XIIa) in D₂O (10%).

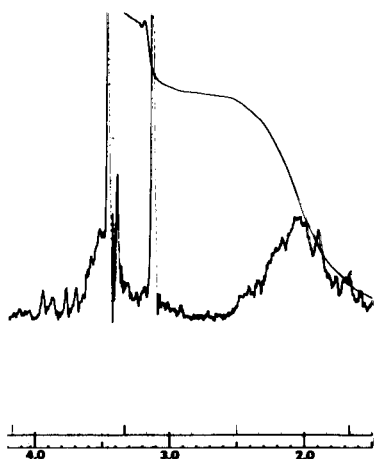


Figure 6. NMR spectrum of a mixture of *cis* and *trans*-1(e)-hydroxy-*N*-methylquinolizidinium iodide (XVa and XIVa) in D₂O (10%).

signal at 3.23 δ which is due to the *N*-methyl group and integrates to three protons. The single *N*-methyl signal is attributed to the *cis*-fused structure (XIIa) based on the previously described work with quaternary salts of the related esters (2). The methiodide of Xa (prepared in acetonitrile) presents a different picture (Fig. 6) in the *N*-methyl region, one signal appearing at 3.12 δ and a second at 3.46 δ . The signals at 3.12 δ and 3.46 δ each integrate to approximately 1.5 protons, indicating the

formation of a 50:50 mixture of *trans*-ring fused (XIVa) and *cis*-ring fused (XVa) salts from 1(e)-hydroxyquinolizidine (Xa). The signal at 3.12 δ is attributed to the *trans*-fused isomer (XIVa) and that at 3.46 δ to the *cis*-fused isomer (XVa) on the basis of the observations of Williamson and co-workers (9) that unsubstituted *cis*-fused *N*-methylquinolizidinium ions absorb downfield from the *trans*-fused isomer by 0.2 PPM. It was observed that the *cis*-fused isomer (XVa) could be removed preferentially by recrystallization of the mixture from acetone (Fig. 7). The *trans*-fused methiodide (XIVa) also was prepared in anhydrous benzene and was obtained in quantitative yield as a white crystalline solid. None of the corresponding *cis*-fused isomer was obtained. Johnson and co-workers (8) experienced an increased of *cis* over *trans*-ring fused products when methanol was used rather than acetonitrile for the formation of the methiodides of several different alkyl quinolizidines. These results were explained by suggesting that the hydrogen-bonded lone-pair has greater steric requirements than the unsolvated lone-pair.

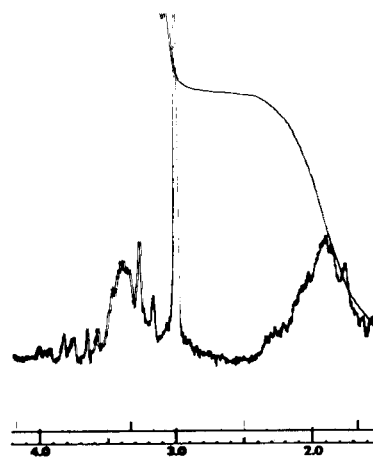


Figure 7. NMR spectrum of *trans*-1(e)-hydroxy-*N*-methylquinolizidinium iodide (XIVa) in D₂O (10%).

In view of this work, it was anticipated that the preparation of the methiodide of Xa in methanol would produce a different ratio of the *cis*:*trans*-fused isomers from that in acetonitrile or benzene. The reaction, however, yielded a white solid (XIVa) whose NMR spectrum was similar to that of the methiodide formed in benzene, showing the presence of no more than 1% of the *cis*-fused compound (XVa). The results obtained in methanol must be due to some unknown steric requirement of the solvated hydroxyl group. The importance of the hydrogen-bonded hydroxyl group was substantiated by other work done in this laboratory which has shown that the corresponding esters give a 50:50 mixture of *cis*-fused and *trans*-fused

TABLE II

Infrared Spectral Data (cm^{-1}) for Aromatic Substituted Quinolizidines (Nujol Mull)

Epimer	Aromatic Absorption (a)
1 (e)-hydroxy-1(a) phenylquinolizidine (b)	760, 697
1 (a)-hydroxy-1 (e) phenylquinolizidine (b)	740, 704
1 (a)-phenylquinolizidin-1 (e)-yl acetate and propionate (c)	762, 697
1 (e)-phenylquinolizidin-1 (a)-yl acetate and propionate (c)	750, 697
2 (a)-phenylquinolizidin-2 (e)-yl acetate and propionate (c)	770, 702
2 (e)-phenylquinolizidin-2 (a)-yl acetate and propionate (c)	762, 695
1 (e)-hydroxy-1 (a)phenyl- <i>N</i> -methylquino- lizidinium iodide	775 (d), 740 (d), 701
1 (a)-hydroxy-1 (e)phenyl- <i>N</i> -methylquino- lizidinium iodide	758, 704

(a) Axial phenyl groups always exhibit bands at higher wave numbers in the 775-740 region than the corresponding equatorial epimer. (b) Ref. 1. (c) Unpublished. (d) Indicative of both structures XVb and XVIb.

products in both polar and non-polar solvents when reacted with methyl iodide.

The NMR spectrum (Fig. 8) of the methiodide of 1 (e)-hydroxy-1 (a)-methylquinolizidine (Xc) presented a similar picture to that of 1 (e)-hydroxy-*N*-methylquinolizidinium iodide (XIVa, XVa), the primary difference being a doublet, centered at 1.30 δ , attributed to the C-1 methyl group. The presence of two signals with slightly different chemical shifts ($\Delta \delta = 0.4 \delta$) at 1.30 δ is due to the presence of both structures XIVc and XVc which are responsible also for *N*-methyl signals at 3.07 δ and 3.45 δ , respectively. The differences in chemical shift of the two methyl signals at 1.30 δ is not sufficient to indicate that the *cis* methiodide exists in form XVIc even though the methyl group has been shown to be thermodynamically more demanding than the hydroxy group by some workers (10); however, the steric requirements of non-bonded lone-pair electrons also should be considered (11).

The NMR spectrum (Fig. 9) of the methiodide of 1 (a)-hydroxy-1 (e)-methylquinolizidine (IXc) is similar

to that for 1 (a)-hydroxy-*N*-methylquinolizidinium iodide (XIIa). The singlets at 3.22 δ and 1.31 δ are indicative of a single component, which in view of the previous argument, preferably would exist as structure XIIc.

1 (e)-Hydroxy-1 (a)-phenylquinolizidine (Xb, oil at 27°) formed a methiodide (a mixture of XIVb and XVb) immediately upon addition of methyl iodide to a solution of the alcohol in anhydrous ether (m.p. 250-253°). 1 (a)-Hydroxy-1 (e)-phenylquinolizidine (IXb, m.p. 114-115°) did not form a methiodide as readily as did the equatorial hydroxy derivative. Refluxing in acetonitrile was necessary before methiodide formation was evident. The difficulty incurred in formation of the methiodide may be ascribed to the intramolecularly hydrogen bonded axial alcohol, hindering the attack of the methyl iodide.

The NMR spectrum (Fig. 10) of the methiodide of 1 (a)-hydroxy-1 (e)-phenylquinolizidine exhibits a single *N*-methyl signal at 3.58 δ and the NMR spectrum (Fig. 11) of the methiodide of 1 (e)-hydroxy-1 (a)-phenylquinolizidine shows a single *N*-methyl signal downfield at

TABLE III
1-Substituted-1-Hydroxy-*N*-Methylquinolizidinium Iodides

No.	Reaction Solvent	Recryst. Solvent	Yield %	M.P. °C	Molecular Formula	Analysis, %							
						Calcd.			Found				
					C	H	N	I	C	H	N	I	
XIIa	CH ₃ OH, C ₆ H ₆	acetone	40	265-267	C ₁₀ H ₂₀ INO	40.42	6.78	4.71	42.70	40.08	6.70	4.62	42.66
XIVa	CH ₃ OH, C ₆ H ₆	acetone	100	245 dec.	C ₁₀ H ₂₀ INO	40.42	6.78	4.71	42.70	40.64	7.06	4.63	43.76
XIVa + XVa	CH ₃ CN	-	100	oil	C ₁₀ H ₂₀ INO	-	-	-	-	-	-	-	-
XIIIb	CH ₃ CN	acetone	100	255 dec.	C ₁₆ H ₂₄ INO	51.48	6.48	3.75	34.00	51.65	6.25	3.67	34.40
XVIIb + XVb	(C ₂ H ₅) ₂ O	ethanol-ether	100	274-275	C ₁₆ H ₂₄ INO	51.48	6.48	3.75	34.00	51.72	6.22	3.80	34.39
XIIc	C ₆ H ₆	acetone	100	210-212	C ₁₁ H ₂₂ INO	42.45	7.13	4.50	40.78	42.39	7.26	4.56	40.99
XIVc + XVc	C ₆ H ₆	acetone	50	302 subl.	C ₁₁ H ₂₂ INO	42.45	7.13	4.50	40.78	42.57	7.21	4.62	40.92

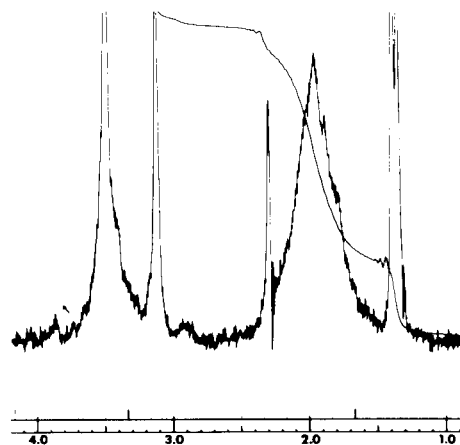


Figure 8. NMR spectrum of *cis* and *trans*-1(e)-hydroxy-1(a)-methyl-*N*-methylquinolizidinium iodide (XIVc and XVc) in D₂O (10%).

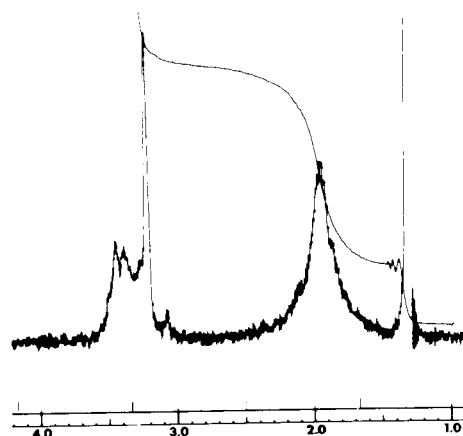


Figure 9. NMR spectrum of *cis*-1(a)-hydroxy-1(e)-methyl-*N*-methylquinolizidinium iodide (XIIc) in D₂O (10%).

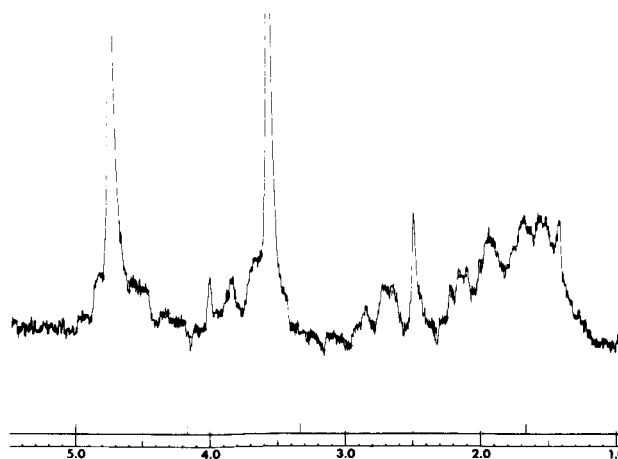


Figure 10. NMR spectrum of *trans*-1(a)-hydroxy-1(e)-phenyl-*N*-methylquinolizidinium iodide (XIIIb) in D₂O (10%).

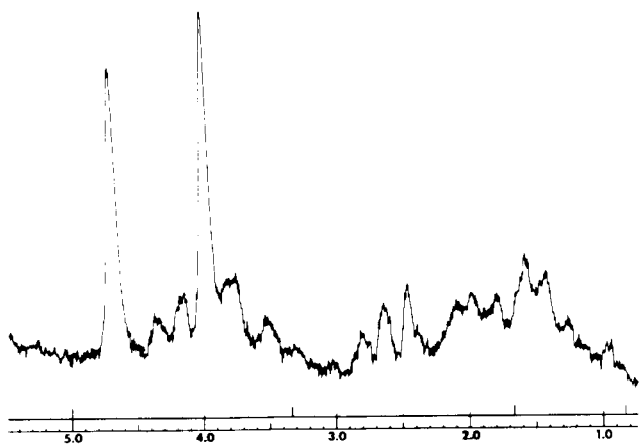


Figure 11. NMR spectrum of *cis*-1(e)-hydroxy-1(a)-phenyl-*N*-methylquinolizidinium iodide (XVb) and *cis*-1(a)-hydroxy-1(e)-phenyl-*N*-methylquinolizidinium iodide (XVIb) in D₂O (10%).

4.01 δ , indicative of the *trans* (XIIIb) and *cis* (XVb, XVIb) structures, respectively (9). The different results obtained with the phenyl alcohols from that of the other alcohols may be due to steric and electronic properties associated with the phenyl group.

Infrared studies indicate that both *cis* structures (XVb and XVIb) are formed from 1(e)-hydroxy-1(a)-phenylquinolizidine (Xb). Phenylquinolizidines exhibit two strong absorption bands in the infrared (Table II) in the 704-697 cm^{-1} and 775-740 cm^{-1} regions typical of compounds bearing a monosubstituted benzene ring (12). In quinolizidines bearing an axial phenyl group, the absorption in the 775-740 cm^{-1} region is observed at higher wave numbers than that of the corresponding equatorial isomer. The infrared spectrum of the methiodide of Xb (Nujol mull) showed absorption bands at 775 cm^{-1} and 740 cm^{-1} indicating that both XVb and XVIb exist in the solid form.

EXPERIMENTAL (13)

1-Hydroxy-1-methylquinolizidine.

Eighteen grams (84%) of 1-hydroxy-1-methylquinolizidine were obtained from 20 g. (0.13 mole) of 1-ketoquinolizidine via the Grignard reaction according to the method described by Leonard (5). The viscous yellow oil, which solidified upon standing, was chromatographed using an Aerograph Autoprep model A-700 fitted with a 16 ft. x 1/4 in. column packed with 10% carbowax on chromosorb W. A flow rate of 60 ml./min. and a column temperature of 190° were maintained. Two peaks were observed; the area of the first peak (retention time 360 sec.) was about 2/3 that of the second peak (retention time 570 sec.). The sample

collecting bottles were kept cold in an acetone-dry ice bath and up to 250 μl . samples were injected. The samples were difficult to collect and only about 25% of the first component and 45% of the second component could be collected in this manner. Recrystallization of the fraction having the greater retention time from petroleum ether (30-60°) yielded snow white needles, m.p. 96-97°. Infrared data (Table I) indicated this component to be 1(e)-hydroxy-1(a)-methylquinolizidine.

Anal. Calcd. for C₁₀H₁₉NO: C, 70.96; H, 11.31; N, 8.28
Found: C, 70.74; H, 11.25; N, 8.39.

Recrystallization of the epimer with the shorter retention time from acetone yielded white crystals, m.p. 46-48°. Infrared data (Table I) indicated this component to be 1(a)-hydroxy-1(e)-methylquinolizidine.

Anal. Calcd. for C₁₀H₁₉NO: C, 70.96; H, 11.31; N, 8.28.
Found: C, 70.79; H, 11.19; N, 8.14.

The epimeric alcohols were also separated by fractional recrystallization. The crude Grignard product when recrystallized five times from petroleum ether, (b.p. 30-60°) provided a 60% yield of 1(e)-hydroxy-1(a)-methylquinolizidine, m.p. 96-97°. The axial hydroxy compound was obtained in 30% yield by recrystallizing the residue from the combined mother liquors from acetone five or six times. Elution chromatography utilizing a grade IV neutral alumina column was found to be most satisfactory. The axial isomer was obtained by eluting with petroleum ether (30-60°) and the equatorial isomer by eluting with acetone or ethanol.

1-Hydroxy-*N*-methylquinolizidinium Iodides (Table III).

The various hydroxyquinolizidine methiodides were prepared by refluxing the base in dry solvents with an excess of methyl iodide. When dry benzene or ether was used as a solvent the solution was refluxed until precipitation was complete and then the solid was collected and recrystallized. When acetonitrile or methanol was used as a solvent, the mixture was refluxed for twelve hours and then evaporated under reduced pressure. The resulting product was washed with anhydrous ether to remove any trace of unreacted starting material and recrystallized.

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(13) All melting points were taken on a Thomas-Hoover apparatus and are corrected. Infrared spectra were determined on a

Perkin-Elmer Model 137B and Model 137G spectrophotometers using the technique described in the text. The NMR spectra were determined with a Varian A-60A spectrometer using tetramethylsilane as the internal standard. Chemical shifts are recorded as δ values.

Received June 10, 1968

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