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Stereochemistry of *cis*- and *trans*-1-Hydroxy-1-phenylquinolizidines (1)

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cis and *trans*-1-Hydroxy-1-phenylquinolizidines were prepared from 1-ketoquinolizidine and isolated by column chromatography. Infrared and nuclear magnetic spectral data were utilized for the elucidation of the structures.

The importance of stereochemical features of biologically active substances (3) prompted our investigation of *cis*- and *trans*-1-hydroxy-1-phenylquinolizidine (I and II, respectively). It was speculated that the title compounds would provide additional clues to structure-activity relationships in the cardiovascular field inasmuch as they are conformational analogs of the potent vasopressor, epinephrine (III). It was of interest therefore, to determine if the orientation of the aromatic group in compounds I and II has any particular effect on the biological activity of the compounds. In *cis*-1-hydroxy-1-phenylquinolizidine (I) the phenyl group is *trans* to the nitrogen whereas in the *trans* isomer the phenyl group is in a 60° skew conformation relative to the nitrogen. Furthermore, the overall shape of the two molecules is quite different with the *cis* isomer being somewhat planar whereas the *trans* isomer is non-planar.

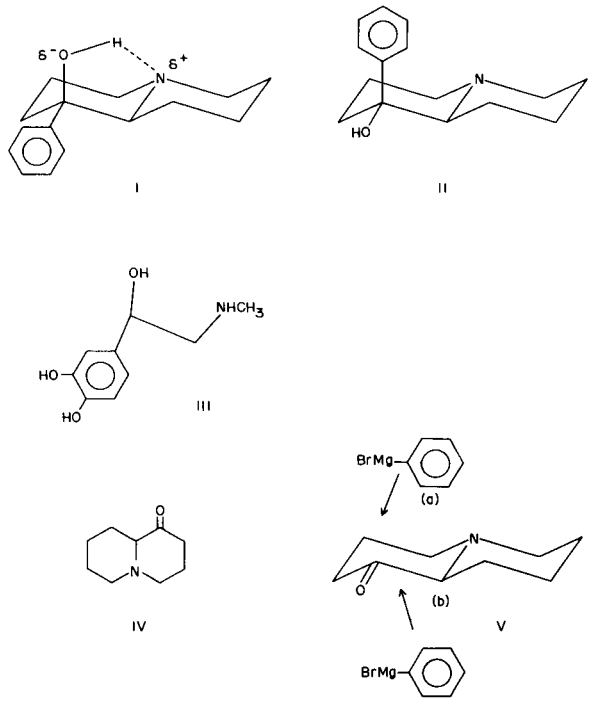
Mason's recent work (4) indicated that 1-ketoquinolizidine (IV) exists predominately in the bicyclic *trans* fused chair-chair conformation (V). Aaron and associates (5) have shown that the ring fusion in both *cis*- and *trans*-1- and 3-hydroxyquinolizidines is *trans*. This conclusion is also supported by the presence of Bohlmann (6) absorption bands in the 2700-2800 cm^{-1} region and by Cookson's (7) analogy with the decalin system.

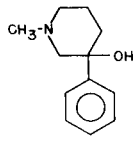
Epimeric phenyl alcohols, for which structures I and II have been assigned, were prepared from 1-ketoquinolizidine (IV), via a Grignard reaction. The *cis* racemate (I) would arise from the phenylmagnesium bromide approaching the ketone from the "bottom" (Vb). The *trans* racemate (II) would result from the phenylmagnesium bromide approaching the ketone from the "top" (Va).

The former approach is hindered by a 1:3:5 arrangement of axial hydrogens on C_2, C_4 and C_9 respectively. The latter approach is hindered by the axial C_3 and C_8 hydrogens and the electron density associated with *p* electron pair of the nitrogen. The two alcohols were obtained in approximately a 2.5:1 *cis*:*trans* ratio. Melting point, infrared and nuclear magnetic resonance data support the conformational assignments of these epimeric alcohols.

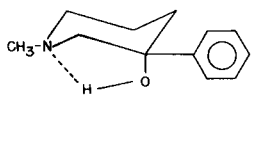
trans-1-Hydroxyquinolizidine melts 8-9° below its *cis* epimer (5, 8). *trans*-1-Hydroxy-1-phenylquinolizidine (II) likewise melts considerably below (oil at 27°) its *cis* isomer (I, m.p., 114-115°). This is presumably partly due to the formation of partial ionic charges on the oxygen and nitrogen atoms of the intramolecularly hydrogen bonded isomer (I). This situation is imposed upon the molecule by a 1:3 type $N:C_1$-OH relationship. Also, the general planar nature of compound I would give rise to a "closer packing" of the molecules to form a more stable crystal lattice than the molecules of compound II.

The infrared spectral data obtained on compounds I and II are also in keeping with the structural assignments which have been made. For example, compound I gives a single but broad hydroxyl absorption with the maximum occurring at 3480 cm^{-1}. This is attributed to intramolecular hydrogen bonding of the type shown in I and is in good keeping with 3496 cm^{-1} O-H···N absorption found in compounds of type VI (VII) as reported by Hite, Smissman and West (9). These authors also reported that compound VIII showed both free hydroxyl absorptions





VI



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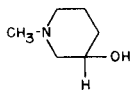

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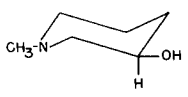
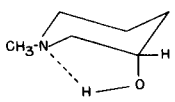


IX



X

at 3623 cm^{-1} and O-H···N absorption at 3539 cm^{-1}. The free hydroxyl absorption is attributed to structure IX whereas the hydrogen bonded absorption is attributed to structure X.

In contrast to the infrared spectrum of compound I, compound II shows strong intermolecular hydrogen bonding at 3430 cm^{-1} which agrees with the intermolecular hydrogen bonding data reported by Aaron and associates (5b) for *trans*-1-hydroxyquinolizidine. Compound II also exhibits weak fundamental free hydroxyl absorption at 3620 cm^{-1} which is similar to that observed by Hite and associates (9) for compound IX.

cis-1-Hydroxy-1-phenylquinolizidine (I) shows the Bohlmann (6) absorption bands at 2770 and 2820 cm^{-1}; the *trans* isomer (II) also shows these bands at 2770 and 2810 cm^{-1} thus indicating the presence of a *trans* fused ring system in both compounds. Aaron and associates (5b) also observed these bands with 1-, 2-, and 3-hydroxyquinolizidines.

The nuclear magnetic resonance spectra of compounds I and II are shown in Figures I and II, respectively. The most significant difference between those two spectra lies in the nature of the aromatic proton region. The *cis* isomer (I, Fig. I) shows one major family of signals at 7.4 δ which integrates to five protons using the hydroxyl proton at 3.44 δ as reference. This type of signal would be expected due to the fact that equatorially oriented phenyl group is not inhibited in its rotation; one would not expect it to be especially influenced by the tertiary nitrogen.

The *trans* isomer (II, Fig. II) has a distinctly different absorption in the aromatic region. The aromatic signal has been split into two families of peaks occurring at 7.23 δ and 7.75 δ which integrates to three and two protons respectively. Increasing the temperature to 70° did not cause these peaks to collapse into one. The most plausible explanation for this behavior is consistent with the structure assignments that have been made. Not only is there a restriction to the rotation of the phenyl group imposed upon the molecule due to the interaction of the C_3 and C_8 hydrogens, but also a restriction due to the electron cloud associated with the tertiary nitrogen. Scale molecular models dramatically illustrate these interactions.

The sharp hydroxyl absorption at 3.44 δ for compound I is consistent with strong intramolecular hydrogen bonding; likewise, the broad hydroxyl absorption at 3.42 δ for compound II is in keeping with strong intermolecular exchange of the proton.

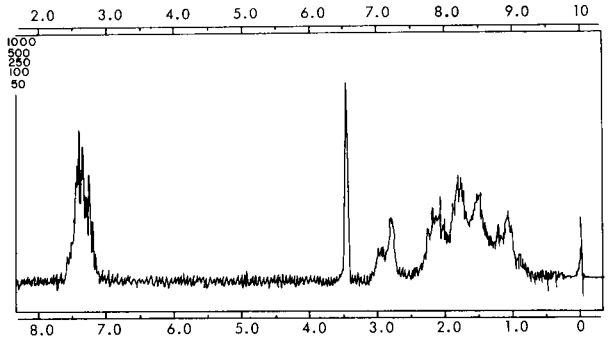


Figure I. Nmr spectrum of cis-1-hydroxy-1-phenylquinolizidine in $CDCl_3$ (10%)

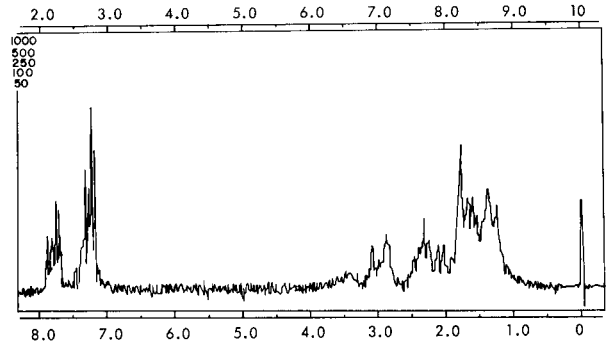


Figure II. Nmr spectrum of trans-1-hydroxy-1-phenylquinolizidine in $CDCl_3$ (10%)

EXPERIMENTAL (10)

cis and *trans*-1-Hydroxyphenylquinolizidine (I and II).

The procedure described by Leonard (11) for the preparation of 1-hydroxy-1-methylquinolizidine was essentially followed. A solution of 10.0 g. (0.065 mole) of 1-ketoquinolizidine in 50 ml. of anhydrous ether was added dropwise over a period of 30 minutes to an ethereal solution of phenylmagnesium bromide (prepared from magnesium turnings, 4.78 g., 0.196 g.-atom, bromobenzene, 29.2 g., 0.190 mole and 150 ml. anhydrous ether). The resulting yellow solution was stirred at room temperature for 1 hour, refluxed gently for 3 hours and further stirred at room temperature for an additional 12 hours.

The yellow Grignard complex was maintained at a temperature less than 25° and decomposed by the slow addition of 150 ml. of 15 per cent sodium hydroxide. The ether layer was separated and the milky aqueous layer thrice extracted with 200 ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. The ether was removed via flash evaporation; the resulting thick syrup (14.9 g.) solidified upon further evacuation at 0.3 mm. The solid was triturated repeatedly with cold petroleum ether; 4.7 g. of solid remained which melted at 97-100°. The latter was treated with activated charcoal and recrystallized from petroleum ether (30-60°) to give the *cis*-alcohol melting at 114-115°. An infrared spectrum (10

TABLE I

Infrared Spectral Data for *cis*- and *trans*-1-Hydroxy-1-phenylquinolizidines (10 per cent chloroform solution)

Epimer	Free OH	H-bonding		Bohlmann (6) bands
		Intra	Inter	
cis	-	3480 cm^{-1}	-	2770, 2820 cm^{-1}
trans	3620 cm^{-1}	-	3430 cm^{-1}	2770, 2810 cm^{-1}

per cent chloroform solution) gave the spectral data recorded in Table I. Thin-layer chromatograms (50:50 benzene-ethanol and 4:1:1 butanol, acetic acid and water) showed a single component to be present.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.87; H, 9.15; N, 6.06. Found: C, 77.72; H, 8.97; N, 6.24.

The above product formed a picrate from an ethanolic solution of picric acid with difficulty (considerably heating was required) which was recrystallized from ethanol to give a product melting at 188.5-189.5°.

Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.77; H, 5.25; N, 12.17. Found: C, 54.98; H, 5.33; N, 12.12.

The mother liquors from the above treatments with petroleum ether were combined, concentrated, and fractionally distilled. The first fraction, 1.0 g., 60-68°/0.25 mm., was a clear golden liquid which was identified by its refractive index and infrared spectrum (liquid film) to be primarily 1-ketoquinolizidine. The second fraction, 5.1 g., 120°/0.25 mm. was a thick golden syrup which showed no tendency to solidify after standing at room temperature for 10 days. Cooling to 0° likewise failed to induce crystallization. This fraction showed strong hydroxyl absorption (liquid film) and immediately formed a precipitate with picric acid which was recrystallized from ethanol to give a picrate of the *trans* alcohol melting at 239-240°.

Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.77; H, 5.25; N, 12.17. Found: C, 55.21; H, 5.36; N, 11.96.

In order to obtain a pure sample of the *trans* epimer for instrumental analysis the above syrup, b.p. 120°/0.25 mm., was chromatographed using a 54 x 2.7 cm. column packed with 300 g. of Woelm Grade IV neutral alumina. The syrup (4.35 g.) was dissolved in a minimum amount of petroleum ether and placed on the column. Elution was begun taking 10 ml. cuts at a flow rate of 5.0 ml./min. Fractions 1-60 were eluted with petroleum ether, fractions 61-100 with anhydrous diethyl ether, and fractions 101-140 with methanol. Fractions 16-18 were combined (193 mg.) and was shown by its spectrum to be biphenyl (12). Fractions 23-25 (300 mg.) were identified by melting point and infrared analysis to be the previously isolated *cis* alcohol. Fractions 76-95 (1.81 g.) were identified as the *trans* alcohol. Fraction 80 was taken to be representative of this sample and was used to obtain the infrared data recorded in Table I and the NMR spectrum recorded in Figure II. The deeply colored and obviously highly impure material eluted with methanol was not characterized.

REFERENCES

(1) Taken from the dissertation presented by J. D. England, January, 1966, to the Graduate School of the University of Mississippi in partial fulfillment of the requirements for the Ph.D. degree.

(2) National Institutes of Health Predoctoral Fellow, 1963-1966. Present address, Harding College, Searcy, Arkansas.

(3) R. B. Barlow, "Introduction to Chemical Pharmacology," Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1964.

(4) S. F. Mason, K. Schofield and R. J. Wells, *Proc. Chem. Soc.*, 337 (1963); *Chem. Abstr.*, 60, 3978 (1964).

(5a) H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.*, 85, 3046 (1963). (b) H. S. Aaron, G. E. Wicks, Jr. and C. P. Rader, *J. Org. Chem.*, 29, 2248 (1964). (c) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *ibid.*, 29, 2252 (1964).

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

(7) R. C. Cookson, *Chem. and Ind.*, 337 (1953).

(8a) G. A. Swan, *J. Chem. Soc.*, 2051 (1958). (b) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *J. Am. Chem. Soc.*, 77, 439 (1955).

(9) G. Hite, E. D. Smissman, and R. West, *ibid.*, 82, 1207 (1960).

(10) All melting points were taken on a Thomas-Hoover Uni-melt melting point apparatus and are corrected. Infrared spectra were determined on a Beckmann IR-7 spectrophotometer using the technique indicated in the text. The NMR spectra were taken using a Varian Model A-60A instrument.

(11) N. J. Leonard, R. W. Fulmer, and A. S. Hay, *J. Am. Chem. Soc.*, 78, 3457 (1956).

(12) L. R. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1964, p. 89.

Received September 28, 1966 University, Mississippi 38677