Epimeric 1-Hydroxy-1-substituted Indolizidines (1)

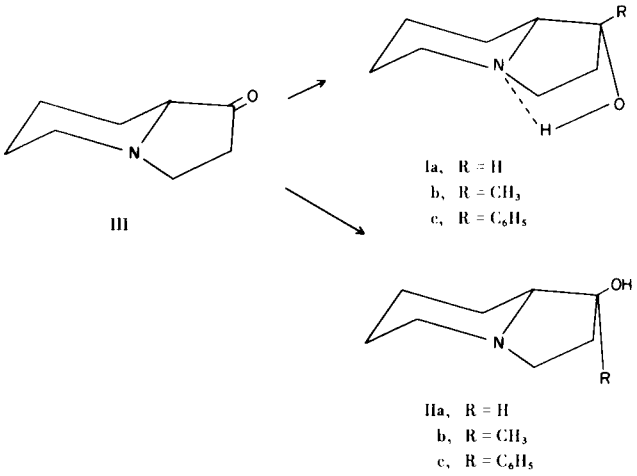
Eugene P. Hibbett (2) and Joseph Sam

Department of Pharmaceutical Chemistry, The University of Mississippi

Epimeric mixtures of 1-hydroxy-1-phenylindolizidines and 1-hydroxy-1-methylindolizidines were obtained from the reaction of 1-ketoindolizidine with the appropriate Grignard reagent. The resulting alcohols were separated by chromatographic and distillation techniques. Infrared data and physical constants were utilized for the elucidation of the structures. Structural assignments of the indolizidinium iodides were made on the basis of nmr data.

The knowledge that many biologically active substances are stereoselective prompted our investigation of epimeric 1-hydroxy-1-methyl (Ib, IIb) and 1-hydroxy-1-phenylindolizidines (Ic, IIc). It was anticipated that these studies might provide information regarding the stereoselectivity of these alcohols and certain of their derivatives on biological activity. Epimers Ic and IIc are analogs of ephedrine (3a), whereas the methiodides of the acetates of Ib and IIb are analogs of methacholine (3b).

Aaron (4,5,6) noted that *trans* ring fusion is the predominant conformation for both the axial hydroxy and the equatorial hydroxy epimers of 1-, 2-, 7-, and 8-hydroxyindolizidines. This conclusion is supported in part by the presence of Bohlmann (7) absorption bands in the 2700-2800 cm^{-1} region of the infrared spectra.



An examination of molecular models reveals that substituents at C-1 (quasi axial or quasi equatorial) on indolizidine occupy similar environments. Consequently, the stereochemistry of Ib and Ic is quite similar to that of the corresponding epimers, IIb and IIc, respectively. Because of this similarity, the separation of the epimers is more difficult than the separation of the corresponding epimers of 1-hydroxy-1-phenylquinolizidine (8). Furthermore, the similarities in the stereochemistry of these compounds provided similar nmr spectra that were of little aid in arriving at the elucidation of the structures.

The epimeric methyl and phenyl alcohols (Ib, Ic, IIb, IIc) were prepared from 1-ketoindolizidine (III) *via* a Grignard reaction. The 1(a)-hydroxy epimers (Ib and Ic) arise from the Grignard reagent attacking the ketone from the "top" side of the molecule. The equatorial hydroxy epimers (IIb and IIc) result from an attack at the "bottom" side. The former approach is hindered by axial and quasi axial hydrogens on C-9 and C-2, respectively. The latter approach is hindered by the quasi equatorial on C-2 and the axial hydrogens on C-3 and C-8, respectively. In addition, the unshared electron pair on the nitrogen through complex formation with the Grignard reagent as noted by Temple and Sam (9) offers significant hindrance to the latter approach. Accordingly, the 1(a)-hydroxyalcohols were found to predominate in a ratio of about 5:1 for the 1-hydroxy-1-phenylindolizidines and 2:1 for the 1-hydroxy-1-methylindolizidines. Melting (or boiling) points, pK_a values and infrared data support the structural assignments of the isomeric alcohols.

Compound IIc melts considerably below (oil at 27°) that of Ic (m.p. 105-106°), whereas Compound Ib boils at a lower temperature (76-79°/3.3 mm) than IIb (98-99°/3.2 mm). The higher m.p. and lower b.p. are attributed to the presence of intramolecular hydrogen bonding.

The infrared spectral data obtained on compounds Ib, Ic, IIb and IIc are also in keeping with the structural assignments which have been made. For example, compounds Ib and Ic, due to intramolecular hydrogen bonding, give strong, broad hydroxyl absorptions with maximum occurring at 3420 and 3430 cm^{-1}, respectively (Table I).

In contrast to the infrared spectra of compounds Ib and Ic, compounds IIb and IIc show strong hydroxyl absorptions at 3370 and 3440 cm^{-1}, respectively. This is attri-

TABLE I

Infrared Spectral Data (cm^{-1}) (a) and pK_a Values for Epimeric 1-Hydroxy-1-substitutedindolizidines

Epimer	Free OH	H-bonding Intra	H-bonding Inter (b)	pK_a values
Ib (c)	-------	3420	----	9.9 (d)
IIb (c)	3590	----	3370	8.8 (d)
Ic (e)	----	3430	----	8.6 (f)
IIc (e)	3600	----	3440	7.7 (f,g)

(a) All of the compounds exhibit Bohlmann bands (7) in the 2700-2800 region. (b) Eliminated in dilute solutions. (c) Infrared determined in 10% chloroform solution. (d) Ionic strength at pK_a point, 0.005. (e) Infrared determined in 10% carbon tetrachloride solution. (f) Ionic strength at pK_a point, 0.05. (g) Due to low water solubilities, the pK_a values were determined in 60% ethanol solutions.

buted to intermolecular hydrogen bonding. Compounds IIb and IIc also exhibit weak fundamental free hydroxyl absorptions at 3590 and 3600 cm^{-1}, respectively.

Each of the four alcohols (Ib, Ic, IIb, IIc) shows the Bohlmann (7) absorption bands in the 2700-2800 cm^{-1} region of the infrared spectra, indicative of a *trans* fused ring system.

The pK_a measurements for compounds Ib, Ic, IIb, and IIc were also in keeping with the assigned structures. The pK_a values for compounds Ib and Ic were 9.9 and 8.6 respectively, whereas the pK_a values for their corresponding epimers, IIb and IIc, were 8.8 and 7.7, respectively (Table I). These findings are in agreement with the results of others (10), who observed that in isomeric amino compounds, the isomer which is capable of intramolecular hydrogen bonding will have the higher pK_a value.

The *cis* and *trans* fused conformations of indolizidine are not isolable due to the fact that rapid inversion at the tertiary nitrogen results in an equilibrium mixture. However, quaternization of the nitrogen results in immobilization at the nitrogen, and the resulting salts should exist as isolable *cis* and *trans* ring fused conformers. That such is the case has been observed by Meyer (11) who reported the existence of both *cis* and *trans* ring fusion in the methiodides of indolizidine. Similar observations in other bicyclic systems with bridgehead nitrogens have been reported by others (12,13,14).

Meyer (11) has indicated the chemical shifts for the *N*-methyl protons of *cis* and *trans* ring fused *N*-methylindolizidinium salts as 3.12 δ and 2.82 δ, respectively. These assignments are based upon calculated differences in the extent of shielding of the angular *N*-methyl protons. In the analogous quinolizidine system, Williamson (15) on the basis of the nmr line widths at half-height of the angular *N*-methyl group, assigned the *cis* fused configuration to that isomer with the higher delta value.

The methiodides of the six epimeric alcohols (Ia, Ib, Ic, IIa, IIb, IIc) were prepared by refluxing the alcohols in benzene with an excess of methyl iodide (Figure II).

The principal difference in the nmr spectra of the methiodides lies in the nature of the *N*-methyl signals (Table II). The nmr spectrum of the methiodide of Ia shows one *N*-methyl signal at 3.38 δ which integrates to two protons and a second signal at 3.57 δ which integrates to one proton. The conformer with the *N*-methyl signal farther downfield is assigned the *cis* configuration based on the observation of Meyer (11) that the *N*-methyl signal of the *cis* fused conformer will absorb downfield from the *trans* fused conformer by about 0.2 ppm. The methiodide of IIa presents a somewhat different picture, in that the *cis* fused conformer whose *N*-methyl signal appears at 3.23 δ predominates over the *trans* fused conformer whose *N*-methyl signal appears at 2.90 δ.

The reaction of indolizidine with methyl iodide is reported (11) to result in the formation of the *cis* and *trans* fused conformers in a ratio of 1:1. The fact that one

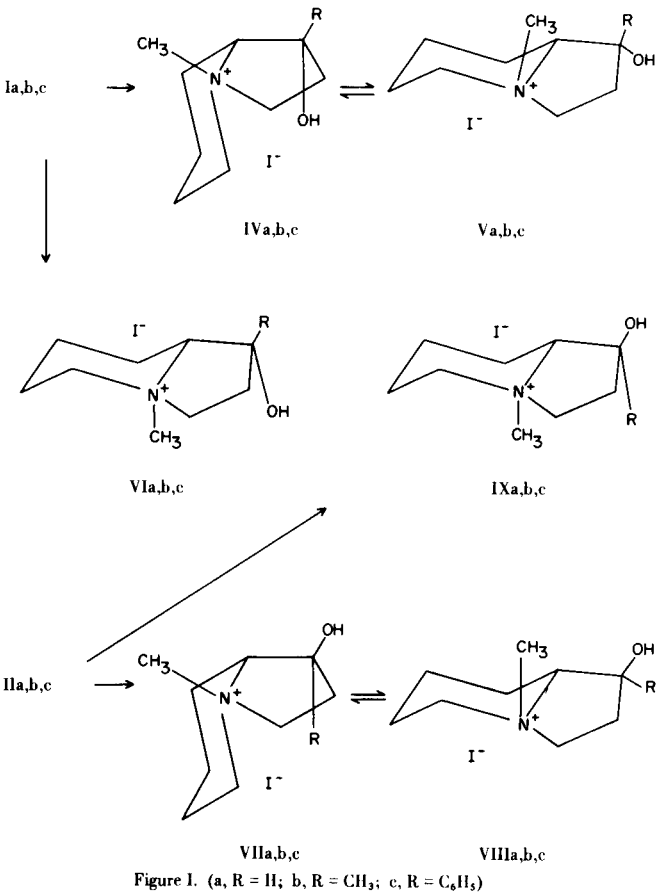


Figure I. (a, R = H; b, R = CH_3; c, R = C_6H_5)

TABLE II

NMR Spectral Data of the Methiodides of 1-Hydroxy-1-substitutedindolizidines

Compound No.	*N*-methyl Proton δ	Number of Protons
VIa	3.38	2
IVa or Va	3.57	1
VIb	3.41	2.5
IVb or Vb	3.62	0.5
VIc	3.69	2.5
IVc or Vc	3.80	0.5
IXa	2.90	1
VIIa or VIIIa	3.23	2
IXb	3.31	1
VIIb or VIIIb	3.76	2
IXc	3.85	2
VIIc or VIIIc	3.95	1

conformer predominates in the 1-substituted indolizidines reported here is not surprising. Apparently this is due to the substituents at C-1 presenting steric or electronic effects which result in the transition states of the *cis* and *trans* fused conformers having different stabilities.

The nmr spectra of the methiodides of 1(a)-hydroxy-1(e)-methylindolizidine (Ib) and 1(a)-hydroxy-1(e)-phenylindolizidine (Ic) were analogous to that of 1(a)-hydroxy-*N*-methylindolizidinium iodide, with the *trans* fused conformer predominating in both instances in ratios of 5:1. The methiodide of Ib exhibited one *N*-methyl signal which appeared at 3.41 δ and a second *N*-methyl absorption at 3.62 δ; likewise, the methiodide of Ic exhibited one *N*-methyl signal at 3.69 δ and a second at 3.80 δ (Table II).

The nmr spectrum of the methiodide of 1(e)-hydroxy-1(a)-methylindolizidine (IIb) was similar to that of 1(e)-hydroxyindolizidinium iodide in that the *cis* fused conformer predominated in a ratio of 2:1, with one *N*-methyl signal appearing at 3.31 δ and a second at 3.76 δ. Conversely, the *trans* fused conformer predominates with the methiodide of epimer IIc, which has *N*-methyl signals which appear at 3.85 δ and 3.95 δ. This anomaly is apparently due to some obscure steric and/or electronic effects.

Elemental analyses of the compounds described herein are listed in Table III.

EXPERIMENTAL (16)

1-Hydroxy-1-methylindolizidine (Ib, IIb).

Sixteen g. (60%) of 1-hydroxy-1-methylindolizidine (17) was obtained from 24 g. (0.17 mole) of 1-ketoindolizidine *via* the Grignard reaction according to the method described by Leonard and associates (18). The epimeric alcohols contained in the viscous golden oil were separated by means of a Nester-Faust Annular Teflon spinning band distillation column. The first component collected contained 8.1 g. of colorless oil which distilled at 76-79°/3.3 mm. and was indicated by glc to be 99% epimerically pure. Infrared data (Table I) indicated this component to be 1(a)-hydroxy-1(e)-methylindolizidine (Ib) which was characterized as the methiodide (Table III).

The final component collected contained 2.9 g. of colorless oil which distilled at 98-99°/3.2 mm. and was indicated by glc to be 96% epimerically pure. Infrared data (Table I) indicated this component to be 1(e)-hydroxy-1(a)-methylindolizidine (IIb), which was characterized as the methiodide (Table III).

1-Hydroxy-1-phenylindolizidine (Ic, IIc).

Ten g. (65%) of 1-hydroxy-1-phenylindolizidine was obtained from 10 g. (0.072 mole) of 1-ketoindolizidine according to the method of Villani and coworkers (19). A portion of the epimeric mixture (4.04 g.) contained in the resulting golden waxy solid was separated by means of elution chromatography. A column 36 cm. x 2.7 cm. was packed with 160 g. of Woelm neutral alumina, intermediate between grades II and III (4.5% water). The epimeric mixture was dissolved in a minimum amount of ether, then placed on the column and eluted with anhydrous ether; 10 ml. fractions at a flow rate of about 6 ml. per minute were collected. Fractions 1-8 contained no product; fractions 9-12 contained only one component (1.11 g.) as indicated by tlc (aluminum oxide G; ether). Infrared date (Table I) indicated this component to be 1(e)-hydroxy-1(a)-phenylindolizidine (IIc), which was characterized as the picrate (Table III).

Fractions 13-15 contained two components, 1.57 g., as indicated by tlc. Fractions 16-20 contained only one component, 0.91 g. Infrared data (Table I) indicated this component to be 1(a)-hydroxy-1(e)-phenylindolizidine (Ic), which was characterized as the picrate (Table III).

Alternately, it was observed that the crude Grignard product, when recrystallized from petroleum ether (b.p. 30-60°), gave a 33% yield of 1(a)-hydroxy-1(e)-phenylindolizidine.

1-Hydroxy-1-substituted-*N*-methylindolizidinium Iodides (Table III).

The various hydroxyindolizidine methiodides were prepared by refluxing the base in anhydrous benzene with an excess of methyl iodide. The solid which precipitated was collected and recrystallized.

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TABLE III

1-Hydroxy-1-substitutedindolizidines

No.	M.p. or B.p., °C	% Yield (Recrystallization Solvent) (a)	Molecular Formula	Analysis, % Calcd. C	H	N	I	Found C	H	N	I
Ia	90/6 mm.	17	$C_8H_{15}NO$ (b)								
Ia (methiodide)	310-312 dec.	100 (E-Et)	$C_9H_{18}INO$	38.17	6.41	4.95	44.82	38.19	6.84	4.45	44.58
IIa	106/6 mm.	50	$C_8H_{15}NO$ (b)								
IIa (methiodide)	319-320 dec.	92 (A)	$C_9H_{18}INO$	38.17	6.41	4.95	44.82	38.30	6.41	5.08	44.80
Ib	76-79/3.3 mm.	51	$C_9H_{17}NO$								
Ib (methiodide)	306-307 dec.	100 (E-PE)	$C_{10}H_{20}INO$	40.41	6.78	4.71	42.70	40.21	6.75	4.89	42.69
Ib (picrate)	141-142	-(IP)	$C_{15}H_{20}N_4O_8$	46.86	5.24	14.58	---	47.42	5.46	14.23	---
IIb	98-99/3.2 mm.	18	$C_9H_{17}NO$								
IIb (methiodide)	306-307 dec.	100 (A)	$C_{10}H_{20}INO$	40.41	6.78	4.71	42.70	40.25	6.69	4.70	42.68
Ic	107-108	39 (PE)	$C_{14}H_{19}NO$	77.38	8.81	6.45	---	77.26	8.58	6.55	---
Ic (methiodide)	194-195	76 (E-PE)	$C_{15}H_{22}INO$	50.14	6.17	3.90	35.32	49.60	6.34	4.05	34.89
IIc	semisolid	9	$C_{14}H_{19}NO$								
IIc (methiodide)	218-219	42 (E)	$C_{15}H_{22}INO$	50.14	6.17	3.90	35.32	49.96	6.12	3.87	35.40
IIc (picrate)	199-202 dec.	-(IP)	$C_{20}H_{22}N_4O_8$	53.81	4.97	12.55	---	54.05	5.08	12.55	---

(a) E = ethanol; Et = ethyl ether; A = acetone; IP = isopropanol; PE = petroleum ether (30-60°). (b) Ref. 6.

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