

The Conformation of Some 1-Azabicycloalkanol

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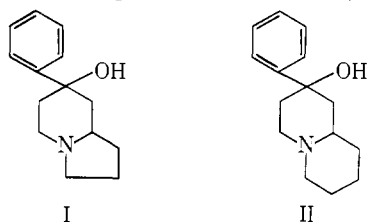
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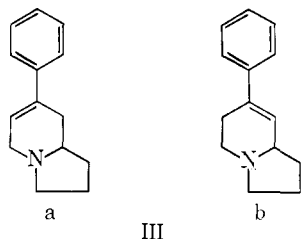
The conformations of the isomer pairs of the 1-azabicycloalkanol I (isomers 1 and 2) and II (isomers A and B) have been established from their ir and pmr spectra. One isomer of each pair (isomers 1 and B) shows some intramolecular H bonding due to the presence of boat forms Ic and IIc, respectively, and has a symmetric free ν_{OH} band profile. The other isomer of each pair (isomers 2 and A) has an asymmetric free ν_{OH} band profile which can be resolved into two symmetric component bands ν_{OH}^I and ν_{OH}^{II} which arise from the three possible (two equivalent) rotational hydroxyl conformations about the C-O bond. The hydroxylic pmr signals are well differentiated, the isomers having the greater downfield chemical shift possessing the equatorial hydroxyl conformation. Both spectroscopic methods give the same conformational assignments of equatorial hydroxyl to isomers 1 (Ia) and B (IIa) and axial hydroxyl to isomers 2 (Ib) and A (IIb). The dissociation constants were measured and are shown to be in agreement with the predicted constants when the intramolecular H-bonded forms of isomer 1 (Ic, d) are considered.

As part of a program on the investigation into the structure-activity relationships of some 1-azabicycloalkane analogs of pethidine-type analgetics,² the conformations of some intermediate 1-azabicycloalkanol have been determined. The compounds were prepared by the addition of phenyllithium to indolizidin-7-one,³ to give 7-phenylindolizidin-7-ol (I), and to quinolizidin-2-one² to give 2-phenylquinolizidin-2-ol (II); each ketone



gave two isomeric alcohols, described as isomers 1 and 2 in the indolizidine series and isomers A and B in the quinolizidine series.

In the indolizidine series, isomer 1 was isolated as the free base, while 2 was fractionally crystallized as the hydrobromide, prepared by treatment with HBr in acetone. This treatment caused partial dehydrogenation of the mixture, with the isolation of some 7-phenylhexahydroindolizinium bromide (III), also ob-



tained by heating isomer 1 with strong aqueous HCl and AcOH and shown to be a single compound by tlc and glpc. The uv spectrum of III showed the expected styrene-type absorption and the nmr spectrum showed a doublet at τ 4.0 ($J = 6$ cps) for the ethylenic proton, indicating structure IIIb for the product.

The ring junction in both isomers 1 and 2 is shown to be predominantly *trans* from the presence of strong bands in the 2700–2800-cm⁻¹ region of the ir spectrum,⁴

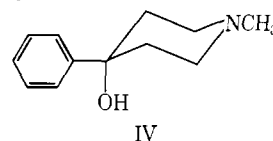
(1) Taken, in part, from Ph.D. thesis (A. E. E. T.), 1966.

(2) A. H. Beckett, R. G. Lingard, and A. E. E. Theobald, *J. Med. Chem.*, **12**, 563 (1969).

(3) F. Lions and A. M. Willison, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 240 (1940).

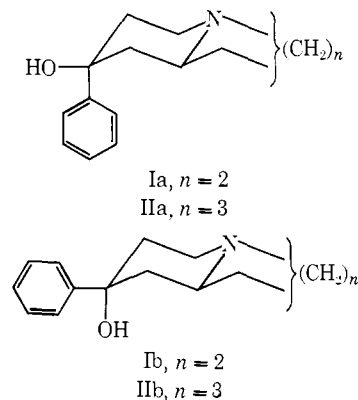
and, assuming all-chair conformations of the fused six-membered rings, the two possible isomeric forms of the indolizidine alcohol are axial phenyl (Ia) and equatorial phenyl (Ib). It seemed likely that acid-catalyzed elimination (predominantly E1⁵) would be faster in Ia than in Ib, due to greater steric acceleration in forming the trigonal carbonium ion, and could be used to assign conformations to isomers 1 and 2. Such an argument would only be valid in the absence of intramolecular H bonding in the corresponding axial hydroxyl boat conformation (*i.e.*, Ic).

Moreover, the rate of elimination of Ib should be similar to that of 1-methyl-4-phenylpiperidin-4-ol (IV) which is not subject to the same conformational restric-



tions as the indolizidinols (I) and will therefore adopt the most stable conformation, *viz.* the chair form and equatorial phenyl/axial hydroxyl.

The rates of elimination of dilute (1.8×10^{-4} M) solutions in strong aqueous acid were followed by the development of the styrenoid band at 242 m μ . The rates for isomer 2 and the piperidinol IV were almost identical (Figure 1) while dehydration of 1 was more rapid, thus indicating 1 to have the conformation Ia, and 2 the conformation Ib.



(4) A. E. E. Theobald and R. G. Lingard, *Spectrochim. Acta*, **24A**, 1245 (1968).

(5) D. V. Banthorpe, "Elimination Reactions." Elsevier Publishing Co., London, 1963, p 145.

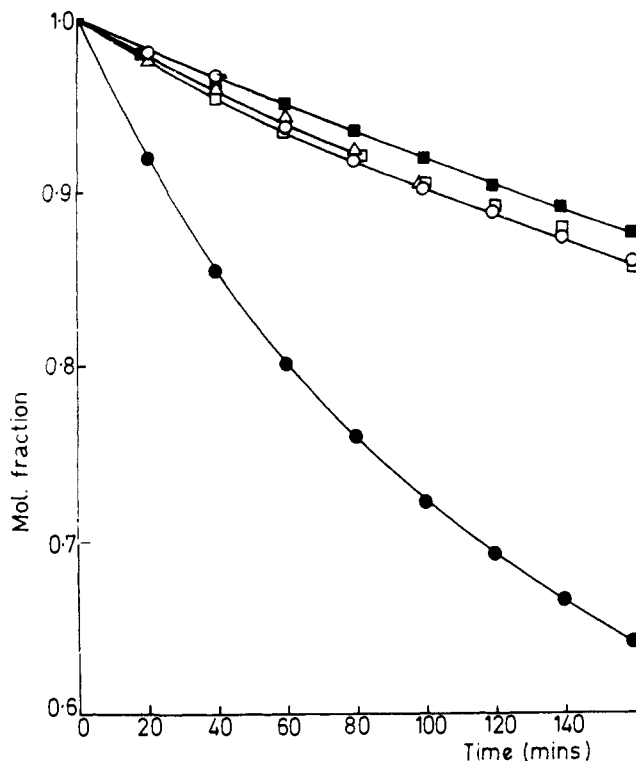


Figure 1.—Elimination rates of tertiary carbinols: isomer 1, ●; 2, ○; A, ■; B, □; IV, △.

Surprisingly, both isomers A and B of 2-phenylquinolizidin-2-ol (II) were dehydrated at almost the same rate as the piperidinol IV. This suggested that intramolecular H bonding might play a part in determining the elimination rates, and also cast some doubt on the validity of conclusions from elimination rates in the indolizidine series. Accordingly, attempts were made to deduce the conformations of the isomeric alcohols spectroscopically.

Several spectroscopic methods are available for the detection of axial and equatorial OH groups in cyclohexane derivatives. The position of the free OH stretching vibrational band, ν_{OH} , is sensitive to steric and electronic effects, and the band for axial tertiary carbinols is at a slightly higher frequency than that for the corresponding equatorial tertiary carbinols in nonpolar solvents.⁶ This difference is attributed to steric rather than to bond polarization factors.

Under high resolution, the ν_{OH} band of a number of primary, secondary, and tertiary alcohols is seen to be asymmetric.⁷ Resolution of the asymmetric band into two symmetric components showed that the frequencies of the resolved bands can be correlated with rotational conformers of the alcohols, and, in examples having adjacent π -electron systems, a shift to lower frequencies was observed as a result of intramolecular OH- π bonding. Aaron and Rader⁸ have shown that an asymmetric ν_{OH} band is given by equatorial cyclohexanols, and a symmetric band by axial cyclohexanols; this approach has been used to distinguish between several axial and equatorial quinolizidinols and indolizidinols.⁹

The chemical shift of the OH proton of cyclohexanols depends on OH conformation as well as solute concentration and H bonding. Huitric, *et al.*,¹⁰ attributed the difference in chemical shift of the OH proton to a difference in the degree of H bonding in some 2-*o*-tolylecyclohexanols. A corresponding difference in chemical shift was noted by Garbisch and Patterson¹¹ for *cis*- and *trans*-4-*t*-butyl-1-phenylecyclohexanols, and by Ouellette¹² for *cis*- and *trans*-4-*t*-butyl-1-ethynylecyclohexanols and 4-*t*-butylecyclohexanols when chemical shifts were extrapolated to infinite dilution. The conformations of a series of 2-aryl-2-hydroxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizines have been deduced by this method.¹³

Thus, from the above data, it seemed that unequivocal conformational assignments could be made to the 1-azabicycloalknols by a combination of ir and pmr spectroscopy, and additional evidence might be furnished by a comparison of dissociation constants.

Infrared Studies.—In a preliminary experiment, solutions of the isomers of alcohols I and II were scanned in the ν_{OH} and ν_{CH} regions (3650–2600 cm^{-1}). The spectra (Figures 2 and 3) showed that one isomer of

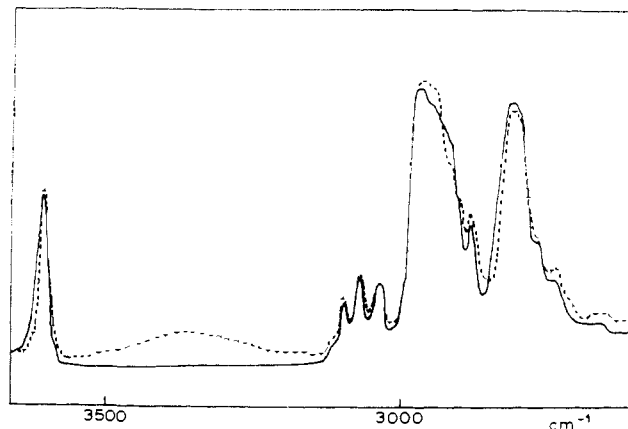


Figure 2.—Infrared spectrum of 7-phenylindolizidin-7-ol in 0.1% solutions of CCl_4 : isomer 1, - - - - -; isomer 2, —.

each pair (isomer 1 and isomer B, respectively) exhibited a weak bonded ν_{OH} band at about 3360 cm^{-1} . Dilution studies indicated that the band profile remained unchanged and that the band intensity followed the Beer-Lambert-Bouguer law precisely, thus indicating the bonding to be intramolecular. A similar intramolecular bonding was reported by Lyle¹⁴ for 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol and shown to be due to a boat form of the piperidine ring, stabilized by intramolecular bonding between the nitrogen and OH group. The compound was also reported to be remarkably resistant to acetylation, a property also possessed by the indolizidinol (1).

It seems likely that the two isomers (I, isomer 1; II, isomer B) showing intramolecular bonding contain significant amounts of the boat forms (Ic and IIc).

(6) A. R. H. Cole and G. T. A. Miller, *J. Chem. Soc.*, 1218 (1959).

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(8) H. S. Aaron and C. P. Rader, *J. Amer. Chem. Soc.*, **85**, 3046 (1963).

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(10) A. C. Huitric and J. B. Carr, *ibid.*, **26**, 2648 (1961); A. C. Huitric, W. G. Clarke, K. Leigh, and D. C. Staiff, *ibid.*, **27**, 715 (1962); A. C. Huitric, W. S. Stayropoulos, and B. J. Nist, *ibid.*, **28**, 1539 (1963).

(11) E. W. Garbisch and D. B. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963).

(12) R. J. Ouellette, *ibid.*, **86**, 4378 (1964).

(13) H. Bruderer, M. Baumann, H. Uskokovic, and A. Rossi, *Helv. Chim. Acta*, **47**, 1852 (1964).

(14) R. E. Lyle, *J. Org. Chem.*, **22**, 1280 (1957).

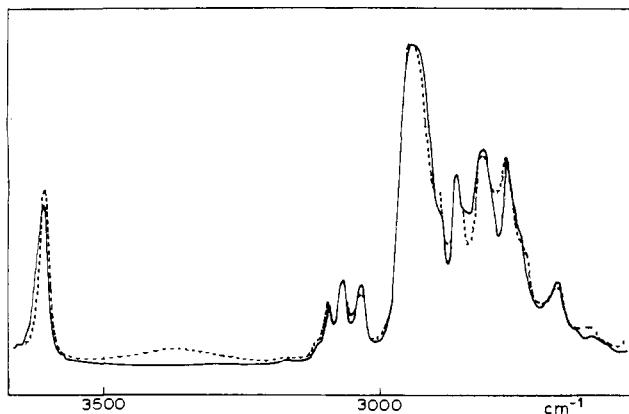
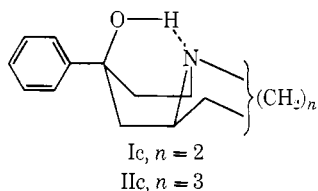
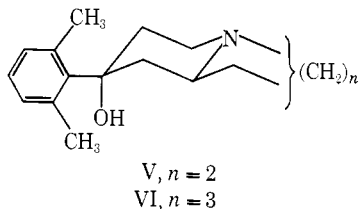


Figure 3.—Infrared spectrum of 2-phenylquinolizidin-2-ol in 0.1% solutions of CCl_4 : isomer A, —; isomer B, - - - -.



respectively) in solution. The corresponding chair forms of these isomers must therefore have the equatorial OH conformation (Ia, IIa).

Since axial and equatorial tertiary alcohols are known to have ν_{OH} band maxima at slightly different frequencies, an attempt was made to assign conformations on this basis. For this, reference compounds of similar structure and known conformation were required, and the analogous compounds, 7-(2,6-dimethylphenyl)indolizidin-7-ol (V) and 2-(2,6-dimethylphenyl)quinolizidin-2-ol (VI) were prepared, in which the aryl group



must be equatorial because of its bulky character. The piperidinol IV, having predominantly the axial OH conformation, was used as a third reference compound.

However, only very small differences in free ν_{OH} band maxima were apparent (all being within the range 3611–3608 cm^{-1}), but in some cases the bands were asymmetric. Using a Beckman DK-2 spectrophotometer, all compounds showed symmetric free ν_{OH} bands with reproducible band maxima at either 3611 (I, isomer 1; II, isomer B) or 3618 cm^{-1} (I, isomer 2; II, isomer A; IV–VI), the frequencies being comparable with those reported by Cole⁶ for tertiary carbinols (Table I). This discrepancy between instruments is due to the poorer resolution obtainable on the DK-2, giving an “average” band profile. Under high resolution (SP 100) where the spectral band width is less than the half-band height ($\Delta\nu_{1/2}$), the observed band profile is a close approximation to the true band profile.

The free ν_{OH} band profiles were determined under high resolution for the compounds in both CCl_4 and CS_2 ; representative band profiles are shown in Figures

TABLE I

FREE ν_{OH} BAND FREQUENCIES OF SOME 1-AZABICYCLOALKANOLS

Compound	Free ν_{OH}		OH conformation
	μ	cm^{-1}	
I, isomer 1	2.769	3611	Equatorial
I, isomer 2	2.764	3618	Axial
II, isomer A	2.763	3619	Axial
II, isomer B	2.769	3611	Equatorial
IV	2.763	3619	Axial
V	2.764	3618	Axial
VI	2.764	3618	Axial

4 and 5. The free ν_{OH} bands of the compounds previously thought to have the axial OH conformation were asymmetric, while the bands for the intramolecularly bonded isomers appeared symmetric.

It seemed highly probable that the asymmetric bands were due to the overlap of several symmetric component bands⁷ which might be correlated with the rotational conformations of the OH group. Using a spectral band width of 2 cm^{-1} for bands of natural $\Delta\nu_{1/2}$ of 20–30 cm^{-1} , the observed band profile is probably only slightly convoluted by the “instrument function,” although several small sources of error may contribute to the distortion of the true band shape.¹⁵ The observed asymmetric bands were separated into two component bands by a graphical procedure,¹⁶ and the areas of the observed and component bands were determined by graphical integration; these were also computed from the integrated Lorentz function as a test of band shape. As the spectral band width was considerably narrower than the half-band width, no intensity corrections¹⁷ were made.

The frequencies of the observed and component band maxima and apparent integrated absorption intensities (B) are given in Table II. The calculated band areas differ from those obtained graphically; this discrepancy is probably due to (a) the band profiles not being strict Lorentz functions, and (b) the instrumental scan limit at 3650 cm^{-1} , the high-frequency “wing” of all bands being cut off, thus making the assignment of a base line less precise. However, in the case of symmetric ν_{OH} bands such as that of isomer I (Figure 4), the observed and computed curves are in very close agreement.

In all cases, the asymmetric band could be graphically resolved into two symmetric component bands, $\nu_{\text{OH}}^{\text{I}}$ and $\nu_{\text{OH}}^{\text{II}}$. The smaller, high-frequency bands ($\nu_{\text{OH}}^{\text{I}}$) had maxima between 3621.5 and 3615 cm^{-1} ($\epsilon_{\text{max}}^{\text{I}}$ 15–23.5) in CCl_4 and between 3615 and 3611 cm^{-1} ($\epsilon_{\text{max}}^{\text{I}}$ 9–19) in CS_2 . The larger, low-frequency bands ($\nu_{\text{OH}}^{\text{II}}$) had maxima between 3607 and 3605 cm^{-1} ($\epsilon_{\text{max}}^{\text{II}}$ 31.5–51.5) in CS_2 . The symmetric free ν_{OH} band of the intramolecularly bonded isomers (isomers I, B) was in the same frequency range as the $\nu_{\text{OH}}^{\text{II}}$ band in both solvents.

The resolved $\nu_{\text{OH}}^{\text{I}}$ and $\nu_{\text{OH}}^{\text{II}}$ bands can be correlated with the rotational conformers of the OH group about the C–O bond, and intramolecular H bonding between the OH group and the aromatic π electrons. Possible rotational conformations of the alcohols are shown in Table III, assuming all-chair ring conformations. For the axial hydroxyl isomers (Ib, IIb), conformations I,

(15) K. S. Seshadri and R. N. Jones, *Spectrochim. Acta*, **19**, 1013 (1963).

(16) Y. Armand and P. Arnaud, *Ann. Chim. (Paris)*, **9**, 433 (1964).

(17) D. A. Ramsay, *J. Amer. Chem. Soc.*, **74**, 72 (1952).

TABLE II
 CHARACTERISTICS OF THE FREE ν_{OH} BAND AND COMPONENT BANDS

Compound	Obsd free O-H band ^d					Component band I ^d					Component band II ^d				
	$\nu_{OH}^{(a)}$	$\epsilon_{max}^{(b)}$	$\Delta\nu_{1/2}^{(c)}$	$B_{obsd}^{(a)}$	$B_{obsd}^{(a)}$	ν_{OH}^{II}	ϵ_{max}^{II}	$\Delta\nu_{1/2}^{II}$	B_{obsd}^{II}	B_{obsd}^{II}	ν_{OH}^{II}	ϵ_{max}^{II}	$\Delta\nu_{1/2}^{II}$	B_{obsd}^{II}	B_{obsd}^{II}
I, isomer 1 ^a	3605.5	71	14.5	3.85	3.22						3605.5	71	14.4	3.85	3.22
I, isomer 2 ^a	3605	65	17.5	4.15	3.00	3615.5	23.5	15	1.30	1.10	3605.5	59.5	14.5	2.88	1.87
V ^a	3605	41	22	3.24	2.45	3621.5	15	23	1.25	0.95	3605	35	15.5	1.95	1.46
II, isomer A ^a	3605	57	18.5	3.82	2.22	3615	16.6	16	0.96	0.76	3605	51.5	14.5	2.70	1.48
II, isomer B ^a	3606	68	14.5	3.57	3.04	3606	68	14.5	3.57	3.04	3606	68	14.5	3.57	3.04
VI ^a	3608	60	16.5	3.58	3.09	3619.5	17.3	27	1.68	1.26	3608	51	13.5	2.49	1.53
I, isomer 1 ^b	3593	55.5	20.5	4.12	2.89						3593	55.5	20.5	4.12	2.89
I, isomer 2 ^b	3594.5	54.5	27	5.32	4.05	3611	19.0	37.5	1.73	1.68	3594.5	44	19	3.08	2.35
V ^b	3597	34	34.5	4.24	2.91	3615.5	11.8	17.5	0.75	0.68	3597.5	31.5	25.5	2.91	2.14
II, isomer A ^b	3593.5	53	37	7.06	3.77	3611.5	9.0	20	0.65	0.51	3593.5	50.5	23.6	4.31	3.28
II, isomer B ^b	3595.5	55	20.5	4.08	2.96						3595.5	55	20.5	4.08	2.96
VI ^b	3595.5	45	26	4.23	3.38	3614.5	9.3	23.5	0.79	0.51	3595.5	44	22	3.50	2.86

^a Solutions in CCl₄. ^b In CS₂. ^c Apparent band characteristics, indicated by a superscript a in parentheses. ^d ν_{OH} = frequency of band maximum, ϵ_{max} = decadic extinction coefficient at the band maximum, $\Delta\nu_{1/2}$ = band width in cm⁻¹ at half-height, B_{obsd} = apparent integrated band intensity calculated from Lorentz function, B_{obsd} = apparent integrated band intensity obtained from graphical integration.

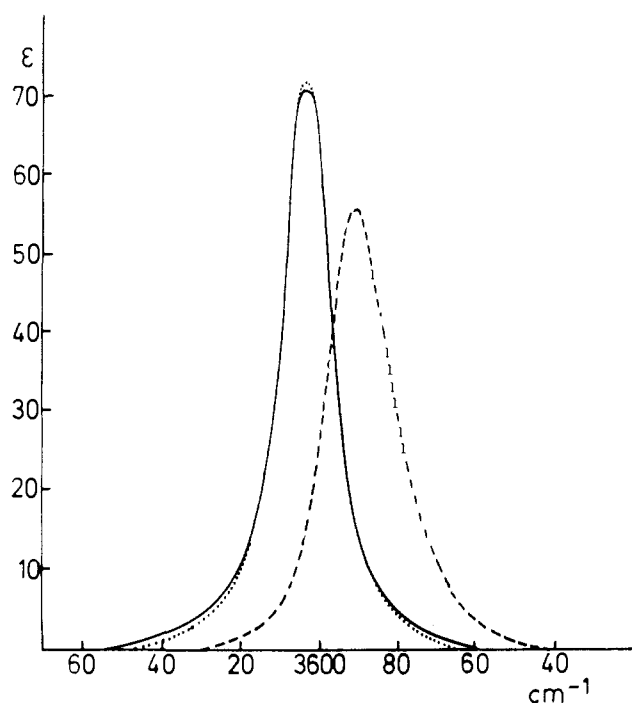


Figure 4.— ν_{OH} band profile of 7-phenylindolizidine (I, isomer 1) in CCl₄ (—) and CS₂ (---) also showing the computed Lorentz curve (.....).

2a, and **2b** are possible, and since **2a** and **2b** are equivalent only two bands are possible. Intramolecular OH- π interaction is also possible in rotational conformations **2a** and **2b** which would displace the free ν_{OH}^{II} band to lower frequencies. The observed displacement of the ν_{OH}^{II} band in CS₂ ($\Delta\nu = 7.5$ - 12.5 cm⁻¹) together with the smaller displacement of the ν_{OH}^I band in the same solvent ($\Delta\nu = 3.5$ - 6.0 cm⁻¹) is supporting evidence for this, and the observed displacements are consistent with those reported¹⁸ for similar systems. A similar conformational arrangement is possible with the 2,6-dimethylphenyl homologs (V, VI) where the proportion of rotational conformation **1** would be greater due to steric restriction of rotation in the aromatic ring.

Pmr Studies.—From the data available, equatorial OH protons show a greater downfield chemical shift

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TABLE III
 ROTATIONAL CONFORMATIONS OF TERTIARY CARBINOLS

Type	Ia IIa	II, IIb	V VI	ν_{OH} , cm ⁻¹
1 (ν_{OH}^I)				3611-3622
2a (ν_{OH}^{II})				3605-3607 (CCl ₄) 3593-3598 (CS ₂)
2b (ν_{OH}^{II})				3605-3607 (CCl ₄) 3593-3598 (CS ₂)

than the corresponding axial OH protons. Ouellette¹² has shown that the difference in chemical shift is still apparent on extrapolation to infinite dilution; thus the effect is at least partially intramolecular and cannot be entirely due to shielding by a geminal substituent, as the spatial relationship between the axial or equatorial OH and substituent is identical in both conformations. Possibly, the difference in chemical shift is at least partially due to rotational conformations of the OH group about the axial and equatorial C-O conformations.

As the chemical shift difference seemed to be a general effect in unsubstituted, 1-alkyl-, and 1-aryl-cyclohexanols, the conformation of the 1-azabicycloalkanol might be deduced from chemical shifts of the OH protons. The spectra for solutions of the 1-azabicycloalkanol (I, isomers **1** and **2**; II, isomers A and B; 15% w/v) in CDCl₃ were determined, and the OH proton signals were identified by exchange with D₂O. These signals are well differentiated in each isomeric pair (Table IV), and the isomer having the greater downfield shift was assigned the equatorial OH conformation.

Although the spectra were determined for solutions of similar concentration, the possibility of a reversal of signal position upon dilution could not be ignored. The spectra of the isomeric 7-phenylindolizidine-7-ol were run at several concentrations, when a linear relationship between concentration and chemical shift was found for each isomer. Furthermore, although

TABLE IV
OH PROTON CHEMICAL SHIFTS

Compound	τ_{OH}	OH conformation
I, isomer 1	6.82	Equatorial
I, isomer 2	7.42	Axial
II, isomer A	7.79	Axial
II, isomer B	7.15	Equatorial

due to the presence of a significant amount of the intramolecularly bonded boat form Id in which bonding of the OH is to the protonated nitrogen.

The agreement between calculated and experimental values for the quinolizidine isomers A and B shows that insignificant amounts of the intramolecularly

TABLE V
DISSOCIATION CONSTANTS OF AZABICYCLOALKANOLS

Secondary azabicycloalkanol	pK_a^a	Tertiary azabicycloalkanol	pK_a		Δ^c	Found ^d $\Delta(\text{ax} - \text{eq})$
			Calcd ^b	Found		
Indolizidin-7-ol	8.96	I, isomer 1 (Ia)	8.56	8.92	0.36	0.09
	9.53	I, isomer 2 (Ib)	9.13	9.01	0.12	
Quinolizidin-2-ol	9.20	II, isomer B (IIa)	8.80	8.88	0.08	0.20
	9.53	II, isomer A (IIb)	9.13	9.08	0.05	

^a Values taken from ref 8. ^b Calculated assuming a ΔpK_a of -0.4^{19} for the introduction of C_6H_5 . ^c Difference between experimental and calculated pK_a values. ^d Difference between pK_a values for axial and equatorial OH compounds.

these plots are convergent, they do not cross on extrapolation to infinite dilution, showing that the chemical shift relationship holds over the experimental concentration range. The conformational assignments made here are in agreement with those from the ir studies.

Dissociation Constants.—Differences in the pK_a values of axial and equatorial OH isomers of indolizidinols and quinolizidinols have been reported,⁹ and the equatorial isomers of quinolizidin-2-ol and indolizidin-7-ol had lower pK_a values than the corresponding axial isomers ($\Delta pK_a = 0.33$ and 0.57 , respectively). Larger differences were noted between the isomers of quinolizidin-1-ol, quinolizidin-3-ol, and indolizidin-8-ol, in which the axial isomer is more basic than the corresponding quinolizidin-2-ol and indolizidin-7-ol. This increased basicity was attributed to intramolecular bonding to N. The influence of intramolecular bonding on pK_a depends on whether such bonding is more important in the free base (base weakening) or the cation (base strengthening)¹⁹ and although evidence for bonding in the base is given, intramolecular bonding in the cation would be responsible for the reported increase in base strength.

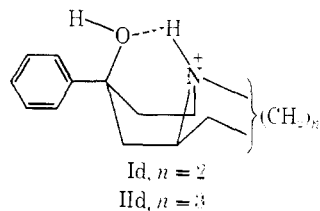
The pK_a values for the indolizidine alcohols (I, isomers 1, 2) and quinolizidine alcohols (II, isomers A, B) were found to lie within the narrow range 8.88–9.08 (Table V) and the ΔpK_a values for isomer pairs are smaller than those reported for the analogous secondary alcohols, although the axial OH isomers have the higher pK_a . The inductive and resonance effects of the phenyl group, although base weakening, should have a small effect on N due to their relatively large separation by a three-carbon chain, and any effect the aromatic group may have would be transmitted equally in both isomers. Assuming a ΔpK_a of 0.4 for the introduction of a phenyl group α to an alkylamine,¹⁹ and applying this to the reported pK_a values of indolizidin-7-ol and quinolizidin-2-ol, the predicted pK_a values of isomers 1 and 2, A and B (Table V) agree reasonably well with the experimental values, except for isomer 1 where the experimental value is 0.36 unit higher. This indicates that the smaller ΔpK_a between 1 and 2 than predicted is due mainly to 1 being a stronger base than predicted, and this in turn is most probably

bonded form IIId are present, and that isomer B (IIa) has the predicted base strength.

Summary.—Both spectroscopic methods give the same conformational assignments to the isomeric alcohols (I, isomer 1 = Ia; I, isomer 2 = Ib; II, isomer A = Iib; II, isomer B = IIa). The ν_{OH} frequencies in the ir spectra are insufficiently differentiated under high resolution to be of use in conformational assignment, but the band profile, symmetric or asymmetric, can be used for this purpose. Thus the isomers having asymmetric bands (isomers 2 and A) are those having the axial OH conformation (Ib, Iib), the asymmetry being due to differing populations in the two allowable rotational conformations of the OH about the C–O bond. Those isomers showing symmetric ν_{OH} bands (isomers 1 and B) also exhibit intramolecular H bonding to some extent, which is only possible in the boat forms Ic and IIc, which in turn are derived from the chair forms Ia and IIa. Furthermore, intramolecular OH– π interaction is possible with the aromatic group in all cases and accounts for the relatively low frequency of the resolved $\nu_{\text{OH}}^{\text{II}}$ bands associated with the rotational conformations 2a, b (Table III). Thus the axial Ph, equatorial OH conformation can be assigned to 1 (*i.e.*, Ia) in the indolizidine series, and isomer B (*i.e.*, IIa) in the quinolizidine series, and the conformations Ib and Iib to 2 and A in the indolizidine and quinolizidine series, respectively. This assignment by means of band asymmetry is opposite to that of Aaron and Rader for secondary carbinols, but in the case of the tertiary carbinols additional factors must be considered: (a) the rotational conformers (Table III) give rise to component bands at lower frequencies than secondary carbinols, and (b) the type 1 rotational conformer is absent due to strong intramolecular bonding of OH to N, leaving two equivalent type 2 rotational conformers which give rise to a single symmetric band corresponding to $\nu_{\text{OH}}^{\text{II}}$ (Table II).

The same assignments can also be made from the OH proton signal in the pmr spectra (Table IV). The dissociation constants are also in the order expected; the axial OH is associated with the higher pK_a of the pair. The experimentally determined pK_a of 1 is significantly greater than predicted; this is probably due to a contribution from the intramolecularly bonded

cation Id. A similar bonded form II_d can be invoked



for the corresponding quinolizidine isomer B, but here the difference between calculated and experimental pK_a values is small, and the proportion of II_d in the sample would not be highly significant. The corresponding intramolecularly bonded base II_c was also shown to be present in small amounts, from the ir spectrum (Figure 3).

Experimental Section

All compounds have been described previously.²

Dissociation constants were determined by potentiometric titration at $25 \pm 0.1^\circ$. The amines or salts were dissolved in freshly boiled and cooled distilled H_2O to give solutions of similar ionic strength ($\mu = 0.005$). The solutions were titrated with 0.1 *N* HCl or NaOH (prepared by ion exchange) added from a micrometer syringe. Titrations were performed under N_2 and pH values were measured with an EIL Vibron electrometer and pH accessory, or a Pye Dynacap meter. The electrode system and meters were standardized with 0.05 *M* potassium hydrogen phthalate and 0.05 *M* borax solutions immediately before and after each titration. The pK_a values were determined from the pH readings at increments of 10% over the range 20–80% neutralization.²⁰

Pmr spectra were determined for 15% w/v solutions in $CDCl_3$ (Me_4Si) on a Perkin-Elmer R10 spectrometer. Hydroxyl pmr signals were located by exchange with added D_2O .

Ir spectra were obtained on a Unicam SP100 spectrometer. Preliminary spectra (*e.g.*, Figures 2 and 3) in the 3600–2600- cm^{-1} region were obtained using 1-cm Infracil cells containing 0.1–0.2% w/v solutions in dry CCl_4 . The ν_{OH} band profiles were obtained for 0.004 *M* solutions in dry CCl_4 and CS_2 using a slow scan (2 cm^{-1}/min) over the range 3650–3550 cm^{-1} with a calculated spectral band width of 2 cm^{-1} ,²¹ and recorded on an expanded scale of 1.6 $cm/10 cm^{-1}$. Before use, solvents were dried over

(20) A. Albert and E. P. Serjeant "Ionisation Constants of Acids and Bases," Methuen, London, 1962, Chapter 2.

(21) Unicam Instruments Ltd., "Spectral Slitwidth Data for the SP100 Spectrophotometer."

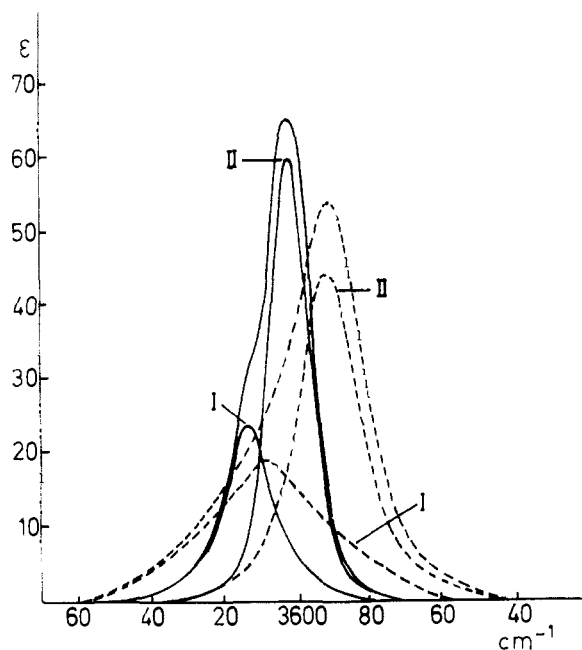


Figure 5.— ν_{OH} band profiles of 7-phenylindolizidin-7-ol (I, isomer 2) showing component bands I and II in CCl_4 (—) and CS_2 (---).

P_2O_5 and redistilled. The cell compartments were continuously flushed with dry air during scanning, and the spectrometer wave number calibration was periodically checked on the water vapor spectrum.

Spectra in the ν_{OH} region were also obtained on a Beckman DK2 spectrometer, using the PbS detector, and 0.003 *M* solutions in a 4-cm silica cell.

The ν_{OH} band profiles (Figures 4 and 5) were plotted as decadic molecular coefficient (ϵ) vs. wave number, and the asymmetric bands were resolved into two component bands by a graphical method.¹⁸ The areas of the observed and component bands were determined graphically, and computed from the integrated Lorentz function (1) as a test of band shape.

$$B = \frac{\pi}{2cl} \Delta\nu_{1/2} 2.303 \log \left(\frac{I_0}{I} \right)_{\max}$$

$$= \frac{\pi}{2} \Delta\nu_{1/2} 2.303 \epsilon_{\max} \quad (1)$$