Optical Rotatory Dispersion and Absolute Configuration. Part 35.[1] Chiroptical Properties and Conformation of Indolizidine

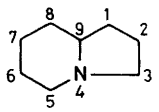
Bjorn Ringdahl, A. Reginald Pinder, Wilfred E. Pereira, Jr., Norman J. Oppenheimer,† and John Cymerman Craig *
Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, San Francisco, California 94143, U.S.A.

^{1}H N.m.r. spectroscopy at 360 MHz confirms that indolizidine is *trans*-fused with the piperidine ring in a chair conformation. The pyrrolidine ring adopts an envelope conformation with the nitrogen atom displaced out of the plane of the four carbon atoms of the ring. An improved synthesis of (+)- and (−)-indolizidine from (−)- and (+)-coniine is described. The o.r.d. and c.d. spectra of indolizidine are compared with those of coniine.

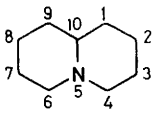
In view of the widespread occurrence of the indolizidine (octahydroindolizine, 1-azabicyclo[4.3.0]nonane) moiety (1) in nature,[2-6] the relationship between its stereochemistry and chiroptical behaviour is of considerable interest.

Although *cis*- and *trans*-fused isomers of hydrindane (bicyclo[4.3.0]nonane) and its substituted derivatives are well known,[7] corresponding stereoisomers of (1) cannot be isolated because rapid inversion of configuration at nitrogen interconverts them, producing an equilibrium mixture. In the studies of this equilibrium in (1) and its derivatives [8] special attention has been given to the Bohlmann bands in the i.r. spectrum, which are obtained when two or more α-hydrogen atoms are *trans* diaxial to the lone electron pair of nitrogen.[9] This criterion is satisfied by (1) only when the rings are *trans*-fused. The i.r. spectrum of (1), in contrast to that of dihydro-β-erythroidine, a model of the *cis*-indolizidine system, showed several fairly intense Bohlmann bands.[8] However, it has been found that in related systems the intensity of Bohlmann bands may be relatively insensitive to the presence of varying amounts of the *cis*-fused isomer in the conformational equilibrium mixture.[10] Aaron and Ferguson [11] reported that the i.r. spectrum of 8-hydroxyindolizidine in dilute carbon tetrachloride solution contained two hydroxy bands, one due to the free hydroxy group of the *trans*-fused isomer and the other due to the intramolecularly hydrogen-bonded hydroxy group of the *cis*-fused isomer, and that the equilibrium mixture contained about 96% of the former. From these observations they calculated the free-energy difference between the *trans* and *cis* conformers of (1) to be −2.4 kcal mol^{-1}, which indicates a strong preference for the *trans* conformation. Although the *trans* junction of (1) seems to have been generally accepted,[12] the empirical nature of the Bohlmann correlation, originally established for the quinolizidine system (2), and the fact that the energy difference between *trans*- and *cis*-(1) was obtained from data on an indolizidine substituted at a carbon next to the ring junction,[11] prompted us to seek independent evidence for the assignment of the ring fusion in (1) by an examination of the 360 MHz ^{1}H n.m.r. spectrum of (1) and its hydrobromide. We were also interested in establishing the conformations of the piperidine and pyrrolidine rings of (1).

(−)-(1) Was first synthesized [13] by cyclization [14] of the *N*-bromo derivative of the hemlock alkaloid (+)-coniine (2-propylpiperidine). Leonard and Middleton [15] obtained (−)-(1) by resolution of the racemic base. Since the optical rotation of (−)-(1) obtained by the two methods agreed, it was concluded [15] that little or no racemization had occurred in the conversion of (+)-coniine into (−)-(1). Moreover, since the chiral centre of coniine is not involved in the cyclization, and since the stereochemistry of (+)-coniine has been correlated with that of D-pipecolic acid (D-piperidine-2-carboxylic acid),[16] it therefore follows that the configurationally related (−)-(1) has the *R* configuration.



(1)



(2)

The Hofmann–Löffler reaction [14] is an important method of preparing both mono- and bi-cyclic pyrrolidines, its main drawback being that the desired tertiary amine is almost invariably contaminated with considerable amounts of the starting secondary amine.[14] Disproportionation reactions of the intermediate carbon and ammoniumyl radicals were suggested to account for the formation of the by-products.[17] Another possibility is, however, pointed out below.

Chiroptical techniques are valuable tools in the determination of the three-dimensional structure of chiral compounds, especially when simple model compounds of known conformation and configuration are available. We have therefore examined the o.r.d. and c.d. spectra of (+)-(1) and (−)-(1).

Results and Discussion

Synthesis of Indolizidine.—When the synthesis of (1) was repeated by the published method [18] (heating *N*-bromoconiine in sulphuric acid, treatment with alkali, and steam distillation of the product), the resultant base was found by g.l.c. analysis to contain 30—40% of coniine. Since evolution of bromine and sulphur dioxide was observed during the heating step, it was possible that the presence of coniine in the product could be due to a reduction of *N*-bromoconiine by sulphur dioxide, produced (along with bromine) by the oxidation of hydrobromic acid, the formation of which has been previously reported in this reaction,[18] by hot sulphuric acid.

The reaction was therefore repeated in a stream of dry nitrogen to remove the sulphur dioxide formed, and the crude product then consisted of indolizidine of >95% purity by g.l.c., with <5% of coniine present. Purification by removal of coniine as the *N*-benzoyl derivative afforded pure (1) (single peak on g.l.c.). The material was identical (g.l.c., m.p. and mixed m.p. of picrate) with a sample of (±)-(1) prepared from 2-(3-hydroxypropyl)pyridine by the method of Reinecke and Kray.[19]

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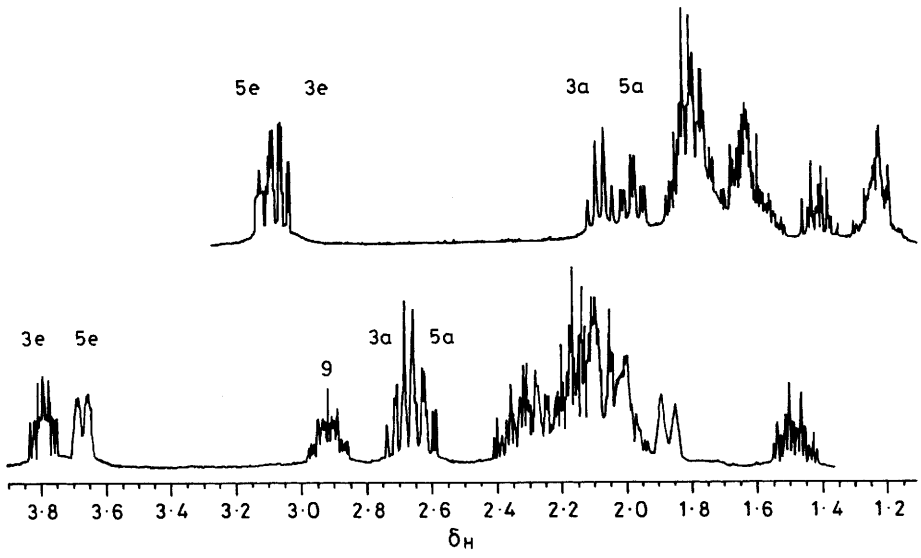

Figure 1. 360 MHz ^{1}H n.m.r. spectrum of indolizidine (upper) and indolizidine hydrobromide (lower) in deuteriochloroform

Application of the modified method to optically pure [20] (+)-coniine and (−)-coniine [21] gave (−)-(1) of $[\alpha]_D$ −10.2 ± 0.6° and (+)-(1) of $[\alpha]_D$ +9.3 ± 0.6°.

Magnetic Resonance Data.—Proton magnetic resonance studies on quinolizidine (2), which exists almost entirely in the *trans* conformation,[22] and its ring-deuteriated and ring-methylated derivatives have shown [23,24] that the resonances of equatorial protons α to the nitrogen are at substantially lower field than those of α-axial protons.

The 360 MHz ^{1}H n.m.r. spectra of (1) and its hydrobromide in deuteriochloroform solution are shown in Figure 1. On the basis of the results obtained [24] for (2) and its protonated form,[23] the low-field resonance of (1) and the two low-field resonances of (1)·HBr, the former corresponding to two protons and each of the latter to one proton, can be assigned to the equatorial protons at C-3 and C-5 (3-H_e and 5-H_e). The resonances at δ 2.1—1.9 for (1), corresponding to two protons, are assigned to 3-H_a and 5-H_a, by analogy with the assignment in quinolizidine [24] and substituted indolizidines.[8]

The strong shielding of the 9-H resonance in the free base (δ <1.9) relative to its chemical shift in (1)·HBr (δ 2.92) is analogous to the shielding experienced by the bridgehead proton resonance of quinolizidine [24] and therefore suggests that 9-H occupies an axial position. The coupling constants of the 9-H resonance of (1)·HBr are also only consistent with 9-H being axial to the two adjacent methylenes (see Table). Furthermore, based on the expected shielding of axial protons relative to the corresponding equatorial protons, the resonances centred at δ 2.67 in (1)·HBr, corresponding to two protons, must be due to axial protons α to the nitrogen.[25] Since both (1) and (1)·HBr have 3 α-axial and 2 α-equatorial protons and since there are no resonances between the positions expected for α-axial and α-equatorial protons, as has been observed for *cis*-fused substituted indolizidines,[3] these results suggest that (1) and (1)·HBr exist predominantly in the *trans*-fused conformation in solution at room temperature.

The assignment of the *trans* ring fusion to (1) and the preference of its pyrrolidine ring to adopt an envelope conformation with the nitrogen displaced out of the plane occupied by C-1, C-2, C-3, and C-9 was confirmed by evaluation of coupling constants from the spin-decoupled and expanded spectra of (1) (Table). Thus, the equatorial proton

Table. Chemical shifts and coupling constants for α-protons of indolizidine and indolizidine hydrobromide

Proton	Chemical shift (δ/p.p.m.)	Coupling constants (*J*/Hz) ^2J [a]	^3J	$^3J_{NH}$
		Indolizidine		
5_e	3.11	−11.2	3.0, 3.6	—
3_e	3.06	−9.2	9.2, 1.8	—
5_a	1.98	−11.2	11.2, 3.4	—
3_a	2.08	−9.2	8.9, 8.9	—
		Indolizidine hydrobromide		
5_e	3.67	−11.5	3.0,[b] 3.0 [b]	2.5
3_e	3.79	−10.5	9.5, 3.5	5.2
9	2.92	—	10.9, 10.9, 3.2, 6.4	10.9
5_a	2.64	−11.5	11.1, 3.2	9.9
3_a	2.68	−10.5	11.5, 11.5	7.7

[a] ^2J Is assumed to be negative. [b] Values are ±0.5 Hz.

5-H_e appears at lowest field as a broad doublet with a separation of 11.2 Hz, which corresponds to the expected value [25,26] of the geminal coupling constant between methylene protons adjacent to nitrogen in a six-membered ring of chair conformation. This resonance is further split by small coupling to the 6-H_e and 6-H_a resonances.

The equatorial proton 3-H_e appears as a doublet of triplets. The positions of the carbon atoms C-1 and C-3 are fixed by the chair conformation of the piperidine ring as shown in Figure 2. The observed pattern for 3-H_e suggests that the hydrogens on C-2 and C-3 are nearly eclipsed and that C-1, C-2, C-3, and C-9 are virtually *in a common plane*. The splitting pattern can then be interpreted as arising from geminal coupling and coupling to one of the vicinal methylene protons both with *J* 9.2 Hz, as well as a smaller coupling to the other methylene proton. The observed value for the geminal coupling constant agrees well with that found (−9.5 Hz) for the geminal coupling between the C-3 methylene protons of 2,2-dideuterioindolizidine.[27]

The axial proton 5-H_a appears as a doublet of triplets due to the large geminal coupling and coupling to 6-H_a as well as a

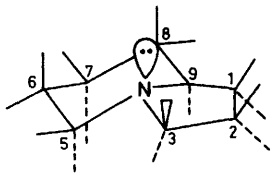

Figure 2. The molecular conformation of (*S*)-(+)-*trans*-indolizidine

smaller coupling to 6-H_e. The axial proton 3-H_a, appearing as a quartet, indicates that the geminal and the two vicinal coupling constants are of similar magnitude. This can only be satisfied if C-1, C-2, C-3, and C-9 are nearly coplanar, giving dihedral angles between 3-H_a and the C-2 methylene protons of *ca.* 30 and 150°. Only minor conformational changes of the pyrrolidine ring are associated with protonation of the nitrogen, as indicated by a similar analysis of the coupling constants of the hydrobromide salt (Table). This conclusion is in agreement with a recent *X*-ray crystallographic structure of indolizidine alkaloids [5] which reveals that in the crystal the carbon atoms 1, 2, 3, and 9 of the pyrrolidine ring are essentially coplanar (within ±0.17 Å), with the nitrogen atom puckered out of the plane (Figure 2).

Chiroptical Data.—The o.r.d. spectrum of (*R*)-(−)-coniine showed a plain negative curve, descending steeply below 230 nm with a barely visible positive Cotton effect (C.e.) centred at 205 nm (confirmed by a positive c.d. maximum at 205 nm [28]). In the hydrochloride, the C.e. disappeared and an almost flat plain negative o.r.d. curve was seen down to 200 nm.

Cyclization of (*R*)-(−)-coniine to (*S*)-(+)-(1) resulted in a plain positive o.r.d. curve for both the base and the hydrochloride. However, the sign of the C.e. remained positive ($[\theta]_{206}$ + 580) with little change either in the wavelength or the intensity of the ellipticity. Since the configurationally related (*R*)-(−)-coniine and (*S*)-(+)-(1) gave c.d. maxima of the same sign and similar wavelength and magnitude for the n ⟶ σ* transitions of the nitrogen chromophore, the oppositely signed o.r.d. curves for the two compounds, as well as the change of sign of the D-line rotation, must reflect a change in the net vector of the rotational contributions from the σ ⟶ σ* transitions of their carbon skeletons below 200 nm. Whereas, in the case of coniine, the three-carbon chain attached to the chiral centre will, for minimum energy, be orientated away from the piperidine ring, in (1) it is constrained by the ring fusion (Figure 2). From these and previous [28,29] results it appears that the indolizidine system has its own unique chiroptical identity and cannot be treated as a simple pyrrolidine or piperidine chromophore. Since the *trans*-indolizidine system of the *S* configuration gives a positive c.d. for the longest-wavelength transition of the nitrogen chromophore, this fact may be useful in assigning the absolute configuration of substituted *trans*-fused indolizidines.

Experimental

O.r.d. and c.d. measurements were carried out on a Jasco ORD-CD5 spectropolarimeter at 20 °C. Enantiomers gave essentially (±5%) mirror image o.r.d. and c.d. curves. Optical rotations at the sodium D line were measured with a Perkin-Elmer 141 polarimeter in a 1 dm tube. Gas chromatography was performed on a Varian 2100 instrument using a 2 m Carbowax 20M (10%) column at a temperature of 120 °C.

N.m.r. spectra at 360 MHz were obtained at 35 °C on a Bruker HXS-360 n.m.r. spectrometer equipped with a Nicolet 1180 computer/Fourier transform system and a computer-controlled homonuclear decoupling accessory. Quadrature detection was used and 16 K Fourier transforms were obtained with a spectral width of 3 610 Hz. Typically, 64 transients were accumulated for the 20 mM solutions with 2.7 s between pulses. A 60° pulse was used, thus equilibrium intensities were observed for all the resonances. The samples were prepared in $CDCl_3$ (Aldrich) and 0.1 mM Me_4Si was used as an internal reference.

(±)-*Indolizidine from* (±)-*Coniine.*—A hypobromite solution prepared from bromine (3 g) and a cold (ice–salt) solution of sodium hydroxide (5 g) in water (80 ml) was added during 10 min to cooled (ice–salt) shaken (±)-coniine (5.4 g) and the cooled mixture was shaken for a further 15 min. The lower layer (*N*-bromoconiine) was run off cautiously into cooled (−10 °C) and swirled conc. sulphuric acid (20 ml). The mixture was heated at 140—150 °C (bath) for 75 min while a current of dry nitrogen was passed through the hot sulphuric acid solution. The reaction flask was cooled, the contents poured onto ice and basified with a large excess of potassium hydroxide, and the base was isolated by the procedure of Löffler and Kaim.[18] The product (2.7 g, 50%) showed two peaks on g.l.c.: indolizidine (>95%, R_t 3.8 min) and coniine (<5%, R_t 4.7 min).

The crude product was shaken with benzoyl chloride (2 ml) and 2M-sodium hydroxide (25 ml) for 15 min at 0 °C, then acidified (2M-hydrochloric acid) and extracted with diethyl ether. The aqueous layer was basified at 0 °C with solid potassium hydroxide, and the liberated base was extracted with diethyl ether. The combined extracts were dried (KOH) and the solvent was removed under reduced pressure at room temperature. Distillation of the residue gave pure (±)-indolizidine, b.p. 58—59 °C/18 mmHg, which showed a single peak on g.l.c. The picrate had m.p. 232 °C (decomp.), undepressed on admixture with an authentic sample (lit.,[19] 230—231 °C). The hydrobromide (recrystallized from EtOH–Et_2O) had m.p. 198—199 °C (lit.,[30] 196 °C) and the deuteriobromide (prepared using 47% deuterium bromide in D_2O) had >99% isotopic purity by n.m.r. spectroscopy and m.p. 200—201 °C (from EtOH–Et_2O), undepressed on admixture with the protio compound.

(+)-*Indolizidine from* (−)-*Coniine.*—A similar reaction carried out with (−)-coniine [21] (shown to be 99% optically pure by g.l.c. of the *N*-trifluoroacetyl-L-prolyl derivative) [20] afforded (+)-indolizidine, b.p. 59—60 °C/19 mmHg; $[\alpha]_D^{23}$ +9.3 ± 0.6° (*c* 1.77, EtOH) [lit.,[31] $[\alpha]_D^{25}$ +3.2° (*c* 1.76, EtOH)], and which showed a single peak on g.l.c. O.r.d. (*c* 2.1, 95% ethanol): $[\alpha]_{340}$ +75.6° and $[\alpha]_{215}$ +262.4°. O.r.d. of hydrochloride (*c* 0.5, 95% ethanol): $[\alpha]_{340}$ +19.9° and $[\alpha]_{200}$ +139.3°. Picrate m.p. 224 °C (decomp.).

(−)-*Indolizidine from* (+)-*Coniine.*—By the same method, (+)-coniine [21] of 99% optical purity gave (−)-indolizidine, b.p. 59—60 °C/19 mmHg; $[\alpha]_D^{23}$ −10.2 ± 0.6° (*c* 1.76, EtOH) [lit.,[15] $[\alpha]_D^{27}$ −7.89° (no solvent given)], and which showed a single peak on g.l.c. Picrate m.p. 224 °C (decomp.) [lit.,[13] 225 °C (decomp.).]

Acknowledgements

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