# Stereochemistry of Ethyl Octahydro-3-methylindolizine-2-carboxylate

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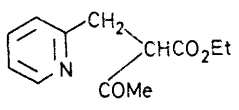
Three of the four possible racemic forms of ethyl octahydro-3-methylindolizine-2-carboxylate have been isolated, and their stereochemistry has been elucidated.

In a previous paper,[1] we described the synthesis of ethyl octahydro-3-methylindolizine-2-carboxylate (4) by the catalytic hydrogenation of the substituted pyridines (1)—(3). Three of the four possible racemic forms of



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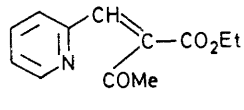

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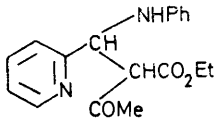

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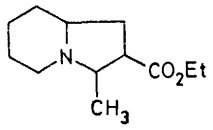


(4)

the octahydroindolizine (4) have now been isolated, and their stereochemistry has been elucidated.

The three samples of the octahydroindolizine (4) were subjected to g.l.c. on Carbowax 20M. In each chromatogram there appeared four components A—D, and when the samples were subjected to g.l.c.–mass spectrometry, these components gave mass spectra which were virtually identical to each other. The components A—D therefore appear to be the four racemates of the octahydroindolizine (4). The relative amounts of the racemates are shown in Table 1, and observed retention times and Kovats indices [2] appear in Table 2. In the

TABLE 1

Relative quantities (%) of the four racemates A—D in different samples of the octahydroindolizine (4), as determined from the gas–liquid chromatograms

| Starting material | Reducing agent | A | B | C | D |
|---|---|---|---|---|---|
| (1) | Pt–$H_2$ | 7 | 88 | Trace | 5 |
| (2) | Pt–$H_2$ | 7 | 88 | Trace | 5 |
| (3) | Pt–$H_2$ | 5 | 93 | Trace | 2 |
| (6) | Pt–$H_2$ | 4 | 96 | | |
| (6) | Na–EtOH | 45 | 52 | | 3 |

chromatogram of the octahydroindolizine obtained from the substituted pyridine (3), the racemates A—D were preceded by a small amount of a fifth component Z. Small quantities of the racemates A, B, and D, and of compound Z, were obtained by preparative g.l.c., and the latter compound was identified as dicyclohexylamine. The origin of the dicyclohexylamine is not apparent from the method of synthesis.

TABLE 2

Observed retention times and Kovats indices for the racemates of ethyl octahydro-3-methylindolizine-2-carboxylate

| Racemate | Observed retention time * (min) | Kovats index † Carbowax 20M 167° | 176° | 187° | SE 301 169° | 180° | 190° |
|---|---|---|---|---|---|---|---|
| A | 3.75 | 1 816 | 1 831 | 1 851 | 1 430 | 1 432 | 1 435 |
| B | 4.80 | 1 903 | 1 921 | 1 940 | 1 464 | 1 468 | 1 474 |
| C | 5.30 | | | | | | |
| D | 6.00 | 1 982 | 2 001 | 2 023 | 1 519 | 1 525 | 1 530 |

* Measured from injection point on a 7 ft × 0.25 in column of Carbowax 20M (15%) on Chrom. W AW/HMDS support at 190° and 60 ml $min^{-1}$ ($N_2$). † Measured (i) on a 7 ft. × 0.25 in. column of Carbowax 20M (15%) on Chrom. W AW/HMDS support, and (ii) on a 5 ft. × 0.25 in. column of SE 301 (10%) on Celite 560 support, both at 60 ml $min^{-1}$ ($N_2$).

One enantiomorph (Ia)—(IVa) from each of the four racemates (I)—(IV) is shown in Figure 1, in the form in

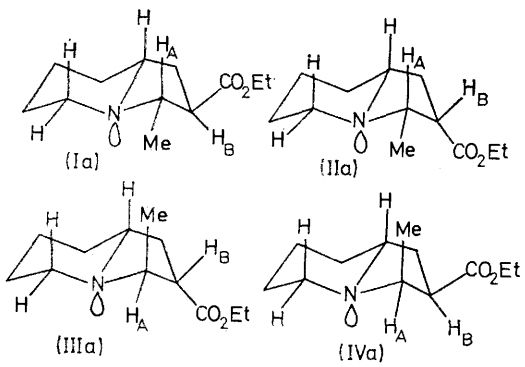


FIGURE 1 One enantiomorph from each of the four racemates of ethyl octahydro-3-methylindolizine-2-carboxylate. The choice of a *trans*-ring junction and the possibility and consequences of a *cis*-junction are discussed in the text

which the ring fusion is *trans*, this being the more favoured form in octahydroindolizine itself.[3] In structures (Ia) and (IIa), the nitrogen lone pair is *trans*-biaxial to three hydrogen atoms, and the racemates (I) and (II) should therefore have a strong Bohlmann band (a C–H stretching band in the region 2 800—2 700 $cm^{-1}$)

[1] J. M. Sprake and K. D. Watson, *J.C.S. Perkin I*, 1976, 5.
[2] L. S. Ettre, *Chromatographia*, 1973, **6**(**11**), 489.
[3] R. Cahill, T. A. Crabb, and R. F. Newton, *Org. Magnetic Resonance*, 1971, **3**, 263.

in their i.r. spectra.[4] In (IIIa) and (IVa) there are only two such hydrogens, and these will be displaced slightly from true axial positions by interaction with the methyl group, so that the racemates (III) and (IV) should give weak Bohlmann bands. The hydrogen atoms $H_A$ and $H_B$ are *trans* to each other in the racemates (I) and (III), and from a model the dihedral angle between them is *ca.* 120°. The vicinal coupling constant in the n.m.r. spectrum is related to dihedral angle, and $J_{AB}$ for (I) and (III) should therefore be *ca.* 0—2 Hz. For the *cis*-isomers (II) and (IV), the dihedral angle is small, and the expected coupling constant $J_{AB}$ is *ca.* 8—10 Hz.

The racemates A and B were found to give a strong Bohlmann band at 2 750 $cm^{-1}$, whereas that for D was much weaker. In order to determine $J_{AB}$ for the three racemates, it was necessary to carry out spin decoupling of the ring-methyl signals, which for A, B, and D appeared at $\tau$ 8.74, 8.89, and 9.09 respectively. When the samples were irradiated at these positions, the $H_A$ signal appeared in the spectrum of A as a singlet at $\tau$ 8.08, but in the spectra of B and D it appeared as a doublet at $\tau$ 7.49 ($J$ 10 Hz) and 6.35 ($J$ 8 Hz) respectively. The racemates A, B, and D therefore correspond to (I), (II), and (IV) respectively (Table 3).

TABLE 3

Assignment of structure to the racemates A, B, and D on the basis of Bohlmann band intensity and n.m.r. coupling constants

| Racemate | $J_{AB}$/Hz | Intensity of Bohlmann band | Assignment |
|---|---|---|---|
| A | 0 | Strong | (I) |
| B | 10 | Strong | (II) |
| D | 8 | Weak | (IV) |

It is possible for the compounds (III) and (IV) to exist in two *cis*-fused conformations, as in Figure 2; (I)

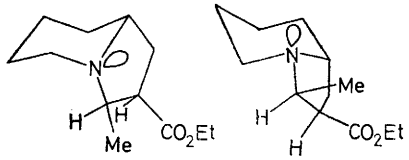
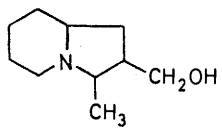



FIGURE 2 *cis*-Fused conformers of (IVa)

and (II) can exist only in the second type of conformation shown in this figure, due to interaction between the ring-methyl group and the axial hydrogens of the piperidine ring. None of the *cis*-fused structures can give rise to Bohlmann bands, since the lone pair on the nitrogen is either in an equatorial position, or *trans*-biaxial to only one hydrogen atom. Since racemates A and B give strong Bohlmann bands, these at least apparently exist substantially in the *trans*-fused forms. Furthermore, only one ring-methyl signal can be discerned in the n.m.r. spectra of each of the racemates, whereas two might be expected if a substantial amount of a *cis*-fused conformation were present, and if interchange between the conformers were slow on the n.m.r. timescale. Such was indeed the case with one of the racemates of 5,7-dimethyloctahydroindolizine studied by Luning and Lundin.[5] There is thus no evidence that racemates (I), (II), or (IV) exist as *cis*-fused forms to any appreciable extent.

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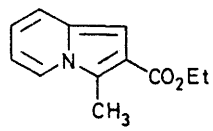


( 6 )

The above assignments of structure are supported by two further pieces of evidence, namely a stereospecific synthesis of the racemate (II), and a consideration of the i.r. spectra of the primary alcohols (5) obtained on lithium aluminium hydride reduction of the esters.

The reduction of ethyl 3-methylindolizine-2-carboxylate (6) [6] with platinum and hydrogen should occur stereospecifically,[5] to give the racemate (II) (B on the above evidence), in which the hydrogen atoms at positions 2,3, and the bridgehead are all *cis*. When the sample of octahydroindolizine obtained by this method was subjected to g.l.c., it was indeed found to consist largely of racemate B (96%), together with a small amount of A (4%).

The indolizine (6) was also reduced with sodium and ethanol, a non-stereospecific reducing agent, in the hope of obtaining a sample of the octahydroindolizine containing a sufficient quantity of racemate C to permit this to be isolated. However, the sample of octahydroindolizine, which was obtained in low yield (6%), contained only the racemates A, B, and D, in the proportions of 45, 52, and 3% respectively.

The three racemates A, B, and D were reduced individually to the corresponding primary alcohols with lithium aluminium hydride. Structures (Va)—(VIIIa) (Figure 3) represent one enantiomorph from each of the four possible racemates (V)—(VIII), the conformations shown being those in which the rings are *trans*-fused.

The racemic ester A, which was assigned the structure (I), should give the racemic alcohol (V). Confirmation of this structure was obtained from the i.r. spectrum of the product in dilute solution, which showed a strong Bohlmann band at 2 750 and a sharp peak at 3 630 $cm^{-1}$ characteristic of a free OH group. Intramolecular hydrogen bonding is not possible with this isomer since it cannot exist in the appropriate *cis*-fused conformation (Figure 4) due to steric hindrance between the methyl group and the axial hydrogens of the piperidine ring.

The racemic ester B, which was assigned the structure

[4] (*a*) F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157; (*b*) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.

[5] B. Luning and C. Lundin, *Acta Chem. Scand.*, 1967, **21**, 2136.

[6] J. Hurst, T. Melton, and D. G. Wibberley, *J. Chem. Soc.*, 1965, 2948.

(II), should give the alcohol (VI). A model shows that intramolecular hydrogen bonding is possible in the molecule, and in accordance with this structure, the i.r. spectrum of the product in dilute solution showed a broad, weak absorption band for the OH group at 3 400—3 200, and a strong Bohlmann band at 2 750 $cm^{-1}$.

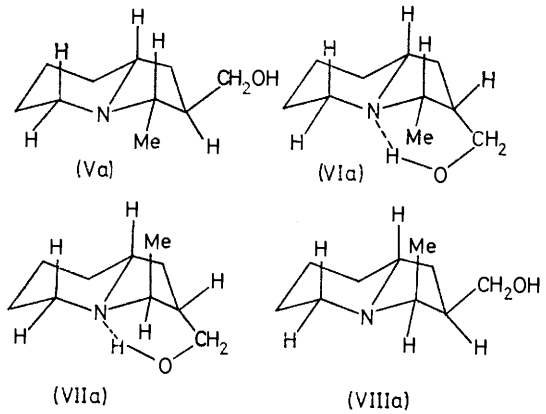


FIGURE 3 One enantiomorph from each of the four racemates of octahydro-2-(hydroxymethyl)-3-methylindolizine

The racemic ester D, which was assigned the structure (IV), should give the alcohol (VIII). Intramolecular hydrogen bonding is not possible in the *trans*-fused form of this molecule (Figure 3), but can occur in the *cis*-fused form (Figure 4). The i.r. spectrum of the product in dilute solution showed both a sharp peak at 3 630, indicative of free OH, and a broad, weak absorption band at 3 400—3 200 $cm^{-1}$ indicative of bonded OH, which suggests that there is a substantial contribution

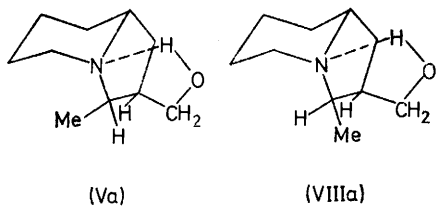


FIGURE 4 *cis*-Fused conformers of (Va) and (VIIIa)

to the equilibrium mixture from the *cis*-fused conformation. The appreciable amount of the *cis*-fused conformation present can be attributed to the stabilising effect of the intramolecular hydrogen bonding.

The isomer (VII), which could not be obtained since the corresponding ester (racemate C) was not available, would be expected to show a weak Bohlmann band and only intramolecular hydrogen bonding in the i.r. spectrum, and would therefore be distinguishable from (V), (VI), and (VIII).

In order to ensure that no epimerisation had occurred during the reduction of the esters, the three isomeric alcohols obtained were subjected to g.l.c. on a variety of columns. In every case, a single peak was obtained. A set of retention times, determined on a Carbowax 20M column, is given in Table 4. It has been shown [7] that the relative retention times of alcohols on a Carbowax column is dependent upon the extent of hydrogen bonding of the alcohol with the Carbowax, and the observed retention times are in accordance with these

TABLE 4

Set of retention times for the alcohols (V), (VI), and (VIII), on a Carbowax column

| Source of alcohol | Structure assigned | Observed retention time * (min) |
|---|---|---|
| B | (VI) | 3.90 |
| D | (VIII) | 5.05 |
| A | (V) | 7.30 |

* Measured from the point of injection on a 7 ft × 0.25 in column of Carbowax 20M (15%) on Chrom. W AW/HMDS support at 192° and 60 ml $min^{-1}$ ($N_2$).

observations, that for the intramolecularly bonded alcohol (VI) being the shortest, and that for the intermolecularly bonded alcohol (V) being the longest.

## EXPERIMENTAL

$^1H$ N.m.r. spectra were recorded for solutions in carbon tetrachloride, with a Bruker Spectrospin HFX 90 MHz instrument, with benzene as internal standard.

Gas–liquid chromatograms were recorded on a Pye-Unicam 104 model 64 instrument.

*Reduction of Ethyl 3-Methylindolizine-2-carboxylate* (6).—(a) A solution of ethyl 3-methylindolizine-2-carboxylate [6] (20.3 g) in glacial acetic acid (100 ml) was shaken with platinum dioxide (1.0 g) in the presence of hydrogen at 3 atm. until the uptake of hydrogen ceased (12 h). The catalyst was removed and the filtrate was evaporated to dryness under reduced pressure. The residue was treated with 10% sodium hydroxide solution, and extracted with chloroform (2 × 100 ml). The combined chloroform extracts were dried ($K_2CO_3$) and evaporated to dryness under reduced pressure. Distillation of the residue at 96—102° and 1.5 mmHg gave ethyl octahydro-3-methylindolizine-2-carboxylate (16.9 g, 80%).

(b) Sodium (6.9 g, 0.30 g atom) was added in small portions to a stirred, boiling solution of the indolizine (20.3 g, 0.10 mol) in ethanol (600 ml). The mixture was cooled, diluted with water, and neutralised with 10% hydrochloric acid. The ethanol was removed by distillation, and the aqueous residue was made alkaline with sodium hydroxide solution and extracted with chloroform (2 × 60 ml). The dried chloroform extracts ($K_2CO_3$) were evaporated to dryness under reduced pressure to give a tarry residue, which was dissolved in glacial acetic acid (100 ml) and hydrogenated in the presence of platinum dioxide (1.0 g). Removal of the solvent and distillation of the residue under reduced pressure gave ethyl octahydro-3-methylindolizine-2-carboxylate (1.3 g, 6%).

*G.l.c. of Samples of Ethyl Octahydro-3-methylindolizine-2-carboxylate* (4).—The samples of the octahydroindolizine were chromatographed on a 7 ft × 0.25 in column of Carbowax 20M (10%) on Chrom. W AW/HMDS support, with column temperatures of 190—196° and nitrogen flow rates of 60 ml $min^{-1}$.

G.l.c.–mass spectrometry was carried out using the above column conditions. The mass spectra of the four components A—D proved to be identical, *m/e* 211 ($M^+$, 13%),

[7] H. S. Aaron, C. P. Rader, and G. M. Wicks, jun., *J. Org. Chem.*, 1966, **31**, 3502.

210 (13), 196 (100), 182 (34), 166 (33), 138 (11), 111 (45), and 96 (32). Component Z gave a mass spectrum identical to that of dicyclohexylamine.

The relative quantities of the racemates were determined from their peak areas on the chromatograms by cutting out the peaks and weighing them, and also by taking the product of peak height and peak width at half peak height. Each procedure was repeated three times, and an average of the results was taken. The results obtained by the different methods were within $\pm 2\%$ of each other, and are shown in Table 1.

Small quantities of the racemates A, B, and D, and component Z, were obtained by preparative g.l.c. on a 15 ft × 3/8 in column of Carbowax 20M (10%) on Chrom. W AW/HMDS support at 190°, with a flow rate of nitrogen of 400 ml $min^{-1}$.

Component Z was confirmed to be dicyclohexylamine from the i.r. and n.m.r. spectra, which were identical to those of an authentic sample.

Racemate A had $\tau$ 5.83 (2 H, q, $COCH_2$), 6.75—8.57 (13 H, m, ring protons), 8.68 (3 H, t, $CH_2CH_3$), and 8.74 (3 H, d, $CH_3$); racemate B had $\tau$ 5.81 (2 H, q, $COCH_2$), 6.63—8.52 (13 H, m, ring protons), 8.67 (3 H, t, $CH_2CH_3$), and 8.89 (3 H, d, $CH_3$); and racemate D had $\tau$ 5.83 (2 H, q, $COCH_2$), 6.15—8.59 (13 H, m, ring protons), 8.70 (3 H, t, $CH_2CH_3$), and 9.09 (3 H, d, $CH_3$).

*Conversion of the Racemic Esters to the Corresponding Primary Alcohols.*—The racemates A, B, and D were reduced individually to octahydro-2-(hydroxymethyl)-3-methylindolizine [1] with lithium aluminium hydride (3 mol. equiv.) in tetrahydrofuran. Each of the products gave one peak only when subjected to g.l.c. on Carbowax 20M, SE 301, Apiezon L, or HI-EFF 1B.

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