

## Studies on Orchidaceae Alkaloids

### VI.\* Synthesis and Relative Configuration of 5,7-Dimethyloctahydroindolizines

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The four racemates of 5,7-dimethyl-octahydroindolizine have been synthesized and their relative configuration assigned by NMR- and IR-spectrometry. 5,7-*cis*-9-*trans*-5,7-Dimethyl-octahydroindolizine possessed properties identical with the alkaloid found in *Dendrobium primulinum* Lindl.<sup>2</sup> The preferred conformations of the four racemates and the corresponding methiodides are discussed, as well as the position of the N-CH<sub>3</sub> signal in the NMR-spectrum in view of the spatial relationships of the N-methyl group.

While studying Orchidaceae alkaloids, Lüning and Leander<sup>2</sup> found a 5,7-dimethyl-octahydroindolizine (I) in *Dendrobium primulinum* Lindl. To assign the relative configuration of I, all four racemates isomeric to I have been synthesized and their physical properties compared. To synthesize I, 2,4,6-collidine was reacted with phenyl lithium to form  $\alpha$ -collidyl lithium, subsequent treatment with oxirane in ether yielded 3(4,6-dimethyl-2-pyridyl)propanol (II). Attempts to replace the hydroxyl group with bromine by the action of 48 % hydrobromic acid resulted in the formation of 5,7-dimethyl-2,3-dihydro-1-H-indolizinium bromide (III).

Hydrogenation of III over Adams catalyst at 50 atm. and room temperature gives only one product, which is a stereoisomer of I. The method of preparation demands that it is 5,7,9-*cis*-5,7-dimethyl-octahydroindolizine (IV).

To obtain sufficient amounts of the other three racemates isomeric to IV a less stereospecific hydrogenation of III was devised. Reduction of III with LiAlH<sub>4</sub> gave as a main product an unstable dieneamine (V) which upon catalytic hydrogenation gave a mixture of IV and two of its isomers, but none were identical with I. Birch reduction of V afforded a mixture of unsaturated amines (VI). Catalytic hydrogenation of VI in glacial acetic acid at atmospheric pressure and room temperature gave a high yield of a mixture of the four racemates of 5,7-dimethyl-octahydroindolizine. These were separated by preparative gas chromatography. The racemates are numbered in order of increasing retention times as follows: IV, VII, VIII, IX and were characterized

\* For Paper V of this series, see Lüning.<sup>1</sup>

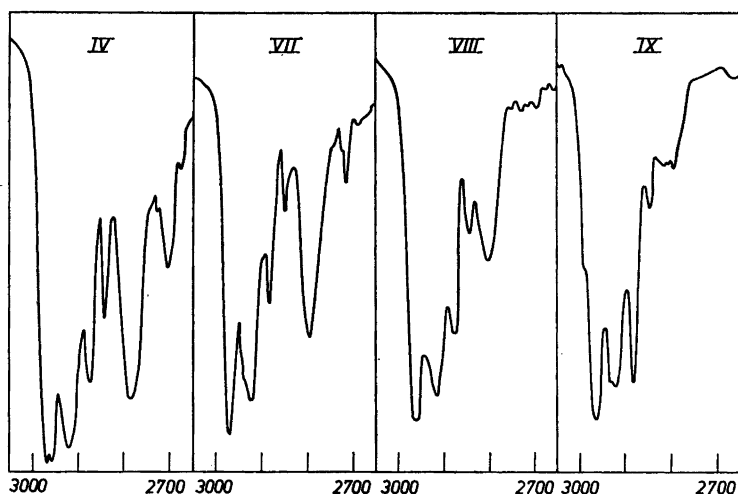


Fig. 1. IR: C—H-stretching bands of the racemates of 5,7-dimethyloctahydro indolizine.

by their IR- and NMR-spectra. Special attention was given to the Bohlmann bands <sup>4-6</sup> in the IR-spectra, which are obtained when two or more  $\alpha$ -hydrogen atoms are *trans* biaxial to the lone electron pair of nitrogen. In the NMR-spectrum the positions of the  $\alpha$ -proton signals as well as those of the methyl doublets were considered. The IR- and NMR-spectra as well as other physical constants of I and IX are identical. The CH-stretching band of the four racemates are presented in Fig. 1 to show the relative intensities of the Bohlmann bands.

The Bohlmann bands of IV are strong and the NMR-spectrum in trifluoroacetic acid (*cf.* Fig. 2) shows the presence of three axial and one equatorial proton on the carbon atoms adjacent to nitrogen (*cf.* Hamlow *et al.*<sup>7</sup> and Bohlmann *et al.*<sup>8</sup>). Double resonance experiments showed that the 5-methyl group couples with one of the axial protons, and  $\Delta\delta$   $\text{CDCl}_3/\text{C}_6\text{H}_6$  for the 7-methyl group is + 0.06 ppm (*cf.* Williams and Bhacca,<sup>9</sup> and Anderson<sup>10</sup>). These considerations indicate that IV has the conformation depicted in Fig. 3 and that the chemical shifts of the 5- and 7-methyl groups are typical for equatorial methyl groups in these positions.

The Bohlmann bands of VII are weaker than those of IV and the NMR-signals for two of the axial protons on carbon atoms adjacent to nitrogen in VII have been moved to lower field, indicating that these protons are no longer strictly axial. Double resonance shows that one of these protons couples with the 5-methyl group, the signal of which is found at the same position as that in the spectrum of IV. The doublet due to the 7-methyl group in VII, however, is found 0.14 ppm downfield compared to the position of the corresponding signal in IV, indicating that the 7-methyl group is axial<sup>11</sup> in VII. The effect on the  $\alpha$ -protons shows that the 7-methyl group interferes slightly with the hydrogen atoms at the 5- and 9-positions. These facts indicate that VII is the 5,9-*cis*-7-*trans*-isomer with the conformation presented in Fig. 4.

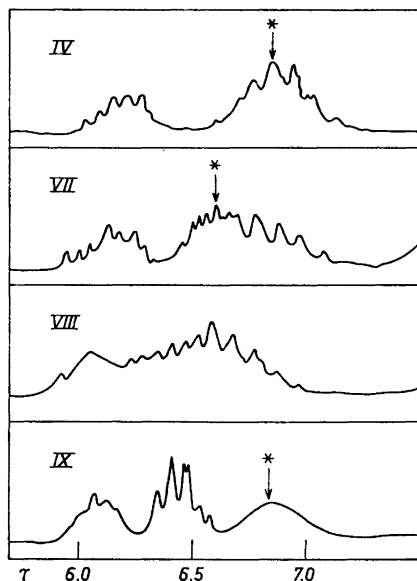


Fig. 2. NMR: Protons on carbon atoms adjacent to nitrogen. Asterisk denotes position of irradiation to obtain decoupling with the 5-methyl group.

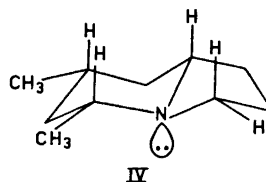


Fig. 3.

In the IR-spectrum of VIII, the Bohlmann bands are even weaker than in that of VII, indicating that less than two  $\alpha$ -protons *trans* biaxial to the lone electron pair of nitrogen are present. The NMR signals due to protons on carbon atoms adjacent to nitrogen are diffuse and spread over the whole area between the band positions for equatorial and axial protons (*cf.* Fig. 2). The signal from the 7-methyl group is situated at the same position as the corresponding one of IV, implying that the 7-methyl group in VIII is equatorial. The signal of the 5-methyl group is split into two doublets, one of which is situated at the position expected for an equatorial 5-methyl group, the other is 0.12 ppm downfield, indicating the presence of an axial 5-methyl group.<sup>11</sup> Since the signal of the 7-methyl group is situated at the position usually ascribed to an equatorial methyl and suffers from no appreciable broadening,

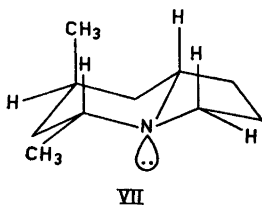


Fig. 4.

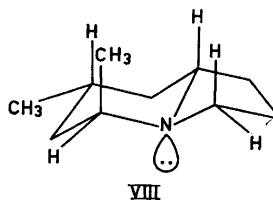


Fig. 5.

the splitting of the signal from the 5-methyl group must be caused by conformational effects on the nitrogen atom. Since there is ample evidence for the presence of an axial 5-methyl group in one conformation of VIII, this must be 7,9-*cis*-5-*trans*-5,7-dimethyl-octahydroindolizine.

The presence of a weak Bohlmann band in the IR-spectrum of VIII implies at least some contribution from a conformation with *trans*-fusion of the rings (*cf.* Fig. 5). In this conformation the axial 5-methyl group interferes with the three axial hydrogen atoms in 1,3-positions. A release of this interaction is possible by inversion of the nitrogen atom resulting in *cis*-fusion of the rings and the appearance of an equatorial nitrogen lone electron pair (*cf.* Fig. 6). A third conformation, with the six-membered ring in flexible conformation and both methyl groups equatorial, would certainly involve broadening of the NMR-signal due to the 7-methyl group. The NMR-signal from the 5-methyl group at  $\tau = 8.61$  should therefore arise from an axial 5-methyl group on a carbon atom attached to a nitrogen atom with an equatorial  $N^+ - H$  bond, an effect which is in the expected direction (*cf.* Jackmann<sup>15</sup>).

The IR- and NMR-spectra of the stereoisomer IX are identical with those of I. IX and I completely lack Bohlmann bands, which is easily explained on basis of the NMR-spectrum which shows one axial, two intermediate, and one equatorial protons on carbon atoms adjacent to nitrogen. Double resonance showed that the axial proton couples with the 5-methyl group. The positions of the methyl signals agree well with those expected for equatorial methyl groups and  $\Delta\delta_{CDCl_3/C_6H_6}$  for the 7-methyl signal is +0.07 ppm. These findings suggest that IX is the 5,7-*cis*-9-*trans*-isomer with the conformation depicted in Fig. 7 and that the structure of I is identical to the one given in Fig. 7 or its mirror image.

Methiodides prepared by treating the bases IV and VII with methyl iodide in acetone actually form mixtures of diastereomers as shown by their NMR-spectra (*cf.* Table 1) and in agreement with earlier findings on analogous compounds.<sup>11,12</sup> It is, however, surprising that VIII and I<sup>2</sup> or XI give only one  $N-CH_3$  singlet each. Assuming that I is the 5,7-*cis*-9-*trans*-isomer, only the conformation depicted in Fig. 7 would be possible in the methiodide but the high  $\tau$ -value, 7.04 of the  $N-CH_3$  singlet, should suggest a *trans*-fusion in the methiodide when compared with the corresponding values obtained with other indolizines,<sup>12</sup> pyrrolizidine,<sup>12</sup> and methyl-quinolizidines.<sup>11</sup> Simple conformational considerations show that methiodides of quinolizidine in their

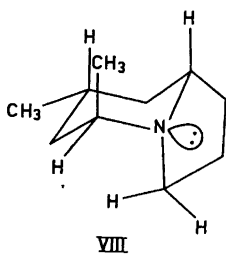


Fig. 6.

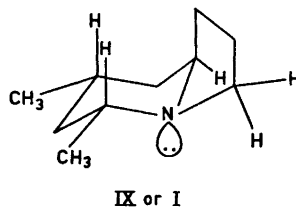


Fig. 7.

Table 1.  $\tau$ -Values of methyl resonances in NMR-spectra of 5,7-dimethyl octahydroindolizinium compounds.

Compound	Base in trifluoroacetic acid		Methiodide in D <sub>2</sub> O		
	5-methyl	7-methyl	5-methyl	7-methyl	N-methyl
IV 5,7,9- <i>cis</i>	8.59	8.96	8.50–8.60 8.60–8.70	9.05 8.97	6.88 7.27
VII 5,9- <i>cis</i>	8.56	8.82	8.64	8.90	6.88 7.28
VIII 7,9- <i>cis</i>	8.50 8.61	8.97	8.48	8.98	7.00
IX (I) 5,7- <i>cis</i>	8.59	8.99	8.69	9.03	7.04

*trans*-fused diastereomers contain an N-methyl group axial to both rings and in their *cis*-fused diastereomers the N-methyl group is axial to one ring and equatorial to the other. This easily explains the difference in chemical shift of the N-methyl signal in *cis*- and *trans*-fused quinolizidines. An analysis of the long range shielding effects according to Jackmann<sup>15</sup> shows that there is only a minor change in the contribution from the bonds in the 5-ring of octahydroindolizine when the N-methyl group alters its position from axial to equatorial with respect to the six-membered ring, in contrast to the contributions from the bonds of the latter.

The nitrogen lone electron pair of IX or I is axial with respect to the six-membered ring, and since the conformation depicted in Fig. 7 is the only possible one, this must be retained in the methiodide, which has an axial N-methyl group, although the rings are *cis*-fused. Any other conformation of this molecule would involve a 1,3-biaxial interaction between the 5- and 7-methyl groups and should be energetically unfavourable.

The most probable diastereomer of the methiodide of VIII would be the one with an axial N-methyl group; the diastereomer with an equatorial N-methyl group would involve a 1,2-*cis*-interaction between the N-methyl and the 5-methyl groups.

These considerations suggest that in the octahydroindolizines a high  $\tau$ -value (7.00–7.30) of the N-methyl group signal corresponds to an axial orientation with respect to the six-membered ring and a low  $\tau$ -value (6.80–6.90) to an equatorial position.

#### EXPERIMENTAL

3-(4,6-Dimethyl-2-pyridyl)propanol (II) was prepared, in analogy with the preparation of 1-pyridyl-2-propanol,<sup>13</sup> from 2,4,6-collidine, phenyl lithium, and oxirane in 62 % yield; b.p. 91°–93°/0.15 mm Hg;  $n_D^{25}$  1.5267. (Found: C 72.6; H 9.02; N 8.52; O 9.86. Calc. for C<sub>10</sub>H<sub>15</sub>NO: C 72.7; H 9.15; N 8.48; O 9.68). NMR in CDCl<sub>3</sub>;  $\tau$  = 3.18 2H doublet;

$\tau = 4.04$  1H singlet;  $\tau = 6.30$  2H triplet,  $J = 6$  cps;  $\tau = 7.15$  2H triplet,  $J = 7$  cps;  $\tau = 7.58$  3H singlet;  $\tau = 7.80$  3H singlet;  $\tau = 8.0$  2H multiplet.

*5,7-Dimethyl-2,3-dihydro-1-H-indolizinium bromide (III)*. II was treated with 48 % hydrobromic acid according to the method described for the preparation of 2-bromoethyl ammonium bromide from ethanolamine.<sup>14</sup> Upon addition of acetone to the concentrated reaction mixture no crystalline precipitate was obtained. The solution was decolorized with active carbon and chromatographed through an  $Al_2O_3$  column. The starting material was eluted with acetone whereas III was eluted with methanol. Recrystallization from ethanol yielded 66 % III, m.p.  $224^\circ-227^\circ$ ; UV  $\lambda_{max}$  217, 267, 272 m $\mu$ . (Found: C 52.7; H 6.24; Br 35.0. Calc. for  $C_{10}H_{14}BrN$ : C 52.6; H 6.19; Br 35.0). NMR in  $CDCl_3$ :  $\tau = 2.20$  2H doublet;  $\tau = 4.95$  2H triplet,  $J = 8$  cps;  $\tau = 6.33$  2H triplet,  $J = 8$  cps;  $\tau = 7.08$  3H singlet;  $\tau = 7.38$  3H singlet;  $\tau = 7.1-7.7$  2H multiplet.

*5,7,9-cis-5,7-Dimethyloctahydro indolizine (IV)*. In 75 ml ethanol 0.25 g III was hydrogenated over Adams catalyst at 50 atm. and room temperature for 18.5 h. The reaction mixture was evaporated to dryness and 1 ml of 30 % sodium hydroxide added; this solution was extracted with ether, giving, after evaporation, a quantitative yield of one product (GLC). The mass spectrum of this product was almost identical with that of I; parent peak: 153. *Hydrobromide* from ethanol m.p.  $214^\circ-218^\circ$ . (Found: C 51.6; H 8.31; N 5.92; Br 35.5. Calc. for  $C_{10}H_{20}BrN$ : C 51.3; H 8.60; N 5.98; Br 34.1). *Methiodide* from acetone m.p.  $204^\circ-207^\circ$ . (Found: C 44.2; H 7.71; N 4.47; I 43.6. Calc. for  $C_{11}H_{22}IN$ : C 44.7; H 7.51; N 4.77; I 43.0). NMR properties are found in Fig. 2 and Table I, Bohlmann band in IR in Fig. 1. 7-Methyl NMR signal  $\tau_{CDCl_3} = 9.08$ ,  $\tau_{C_4H_4} = 9.14$ .

*LiAlH<sub>4</sub> reduction of III*. To a solution of  $LiAlH_4$  (0.38 g; 0.01 mole) in 22 ml ether, III (0.23 g; 0.001 mole) was added. The mixture was stirred for 1 h, cooled to  $0^\circ$  and treated with successive additions of 0.4 ml water, 0.3 ml 20 % sodium hydroxide, and 1.4 ml of water. The white solid was filtered off and the ethereal solution evaporated, leaving a quantitative yield of a mixture (V) of amines which was analysed by GLC-MS. The mixture consisted of two amines with molecular ions  $m/e$  149 and in the ratio 1:5. After 12 h at  $-20^\circ$ , GLC showed only decomposition products.

*Catalytic hydrogenation of V*. The mixture V was dissolved in glacial acetic acid and hydrogenated over Adams catalyst at atmospheric pressure and room temperature. A quantitative yield of saturated bicyclic amines was obtained, and analysis by GLC-MS showed the presence of 99 % IV and 0.5 % of each of two further amines with mass spectra almost identical to I and IV, but no component with the same retention time as I.

*Birch reduction of V*. A solution of V (3.27 g; 0.022 mole) in 250 ml of ether was added to a solution of lithium (2.4 g; 0.34 mole) in 500 ml of liquid ammonia over a period of 20 min. After another 40 min, ammonium chloride (22 g) was added in small portions. The ammonia was allowed to evaporate and remaining material was extracted with ether until the extracts were negative to the Dragendorff reagent. The ethereal solution was concentrated and the remaining mixture of amines analyzed by GLC-MS showing the reaction product (VI) to consist of three unsaturated bicyclic amines (M.W. 151) and IV in the ratio 2:2:10:1. The mixture was not investigated further but was used directly in the subsequent reaction.

*Catalytic reduction of VI*. The reaction mixture VI was treated with 75 ml glacial acetic acid and the solution was hydrogenated over Adams catalyst at atmospheric

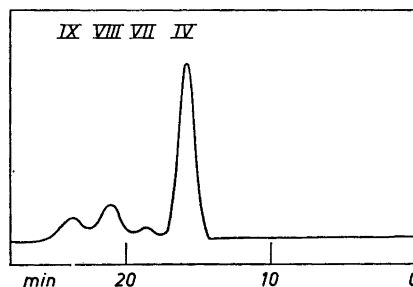


Fig. 8. Gas chromatogram showing relative amounts of racemates of 5,7-dimethyloctahydro indolizine obtained by synthesis.

pressure and room temperature; the hydrogen uptake was 380 ml (0.017 mole). After removal of the catalyst, the solution was evaporated to 5 ml, 5 ml water added and solid sodium hydroxide until strongly alkaline. The amines were extracted with ether, the ether evaporated, leaving 3.0 g crude amines, (overall yield, based on III was over 70 %) which were analyzed with GLC-MS showing the presence of four components IV, VII, VIII, and IX in the ratio shown in Fig. 8, all with practically identical mass spectra. IX had the same retention time as I. The four racemates were separated by preparative GLC on a 20 % SE-52 column (length 2.9 m, width 8 mm) at 100°. NMR spectral data see Fig. 2 and Table 1, IR C-H-stretching bands see Fig. 1.

*5,9-cis-7-trans-5,7-Dimethyloctahydro indolizine (VII)*; methiodide m.p. 285°(decomp.).  
*7,9-cis-5-trans-5,7-Dimethyloctahydro indolizine (VIII)*; hydrobromide, m.p. 113°-115°; methiodide, m.p. 266°-267°.

*5,7-cis-9-trans-5,7-Dimethyloctahydro indolizine (IX)*; hydrobromide, m.p. 191°-193° (racemate; m.p. of I hydrobromide is 206°-207°); methiodide, m.p. 259°-262° (I methiodide, m.p. 264°-265°). NMR-, IR-, and Mass spectra as well as retention times in GLC are identical for IX and I. 7-Methyl NMR signal:  $\tau_{\text{CDCl}_3} = 9.08$ ;  $\tau_{\text{C}_6\text{H}_6} = 9.15$ .

The NMR spectra of the methiodides were measured on the unseparated reaction mixtures obtained by adding methyl iodide to acetone solutions of the bases. The reaction mixtures were evaporated to dryness and washed with ether to remove any unreacted base, and then the measurement was performed in D<sub>2</sub>O solution. NMR spectra of the bases were measured in CDCl<sub>3</sub> or benzene, and those of the protonated species in trifluoroacetic acid on a Varian HA 100 spectrometer. Mass spectra were measured on an LKB 9000 mass spectrometer equipped with a GLC-inlet system. Melting points are corrected, boiling points uncorrected, IR-spectra were measured in CCl<sub>4</sub> on a Perkin Elmer 221 instrument and the UV-spectra were measured in ethanol on a Beckman DK2 spectrometer.

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