

HYDROBORATION OF UNSATURATED AMINES. VII.*

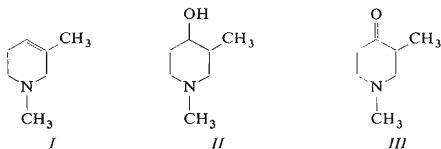
CONFIGURATION OF 1,3-DIMETHYL-4-PIPERIDINOLS
OBTAINED BY HYDROBORATION OF 1,3-DIMETHYL-3-PIPERIDEINE

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In a previous communication¹ we described several methods of hydroboration of 1,3-dimethyl-3-piperideine (*I*). After subsequent oxidation of the reaction mixture 1,3-dimethyl-4-piperidinol (*II*) is formed in addition to a smaller amount of 1,3-dimethyl-3-piperidinol. At a higher temperature 1-methyl-3-hydroxymethylpiperidine is also formed. However, 1,3-dimethyl-4-piperidinol (*II*) always prevailed. In this paper we endeavour to elucidate the configuration of compound *II*.



Hydroboration of 1,3-dimethyl-3-piperideine (*I*) with diborane at 25°C gives pure *trans*-1,3-dimethyl-4-piperidinol (*II*). Hydroboration of compound *I* with triethylamine-borane takes the same course. At a more elevated temperature hydroboration leads to a mixture of *cis* and *trans* isomers of *II*. The formation of the *cis*-isomer *II* is caused probably by the isomerisation of alkylborane formed first by *cis*-addition, and not by direct *trans*-addition. This conclusion is confirmed by the results of the hydroboration of 1-methylcyclohexene carried out by Tichý and coworkers². In order to interpret reliably the NMR spectra of single isomers of *II* and to determine their ratios in the hydroboration mixtures we carried out their independent syntheses. The reduction of 1,3-dimethyl-4-piperidone (*III*) with lithium in liquid ammonia and reduction with lithium aluminium hydride were carried out according to³. We also carried out the hydrogenation of piperidone *III* at room temperature on an Adams catalyst. The separation of isomers *II* by preparative gas chromatography was unsuccessful and therefore we applied chromatography on an alumina column as in³. The determination of the configuration of the stereoisomers of *II* was carried out by NMR spectroscopy, using knowledge following from the study of the NMR spectra of piperidine derivatives⁴⁻⁶. The ratio of *cis* and *trans*-isomers of *II* in mixtures, obtained both by different methods of hydroboration of compound *I* and subsequent

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oxidation of the reaction mixture, and by other methods of reduction of piperidone *III*, was determined by infrared spectroscopy on one hand, and by NMR spectroscopy on the other (see Table I).

In the NMR spectrum of the *cis*-isomer *II* a characteristic doublet was present at 9.06τ due to the protons of the methyl in the position 3 of the piperidine ring and split to a doublet by the geminal proton ($J = 6.6$ c.p.s.). The multiplet centered about 8.19τ was assigned to ring methylene protons in position 5. The lower multiplet centered around 7.59τ was assigned to four methylene protons in the position 2 and 6. The sharp singlet at 7.74τ belongs to the signal of the N-methyl protons. The multiplet at 6.23τ corresponds to the less shielded proton in position 4. This proton is shielded by the electronegative oxygen, and with respect to the equally situated proton in the *trans*-isomer, it is shifted downfield because in view of the conformational equilibrium (*ae* \rightleftharpoons *ea*) it occurs at the average value of the axial and the equatorial position. The shielding of the axial proton is much stronger and its signals may be found in the neighbourhood of 7τ . In the NMR spectrum of the *trans*-isomer *II* the doublet of the methyl at $C_{(3)}$, at 9.04τ , is split by coupling

TABLE I

Ratios of Stereoisomeric 1,3-Dimethyl-4-piperidinols (*II*) in Mixtures after Reductions of 1,3-Dimethyl-4-piperidone (*III*), and after Hydroborations of 1,3-Dimethyl-3-piperidine (*I*)

Reaction	Solvent temp., °C	Composition of the mixture, % IR (NMR)	
		<i>cis</i>	<i>trans</i>
LiAlH ₄ reduction ^a	ether	31.5	68.5
	36	(30.5)	(69.5)
Hydrogenation on PtO ₂ ^b	methanol	73.5	26.5
	22	(74.0)	(26.0)
Reduction with Li in liquid ammonia ^a	ethanol	2.0	98.0
	22	(0)	(100.0)
Hydroboration with B ₂ H ₆ ^c	diglyme	0	100.0
	25	(0)	(100.0)
Hydroboration with B ₂ H ₆	diglyme	18.0	82.0
	160	(17.4)	(82.6)
Hydroboration with (CH ₃) ₃ N.BH ₃ ^c	diglyme	3.5	96.5
	160	(5.4)	(94.3)
Hydroboration with (C ₂ H ₅) ₃ N.BH ₃ ^c	diglyme	0	100.0
	160	(0)	(100.0)

^a See ref. ³; ^b this paper; ^c see ref. ¹.

($J = 6.3$ c.p.s.). The complex multiplet at 8.31τ is again due to the more strongly shielded ring protons in position 5. The singlet of protons of the methyl on nitrogen atom is shifted upfield to a certain extent (7.78τ). The multiplet of protons in the proximity of the electronegative nitrogen is somewhat lowered (7.23τ). The singlet at 7.06τ may be assigned to the hydroxyl proton. The signal of the proton in position 4, which formed a multiplet at 6.23τ in the case of the *cis*-isomer, is shifted to a higher value, 6.94τ , and it partly covers the multiplet of the methylene protons. This upfield shift of the signal of proton in position 4 may be caused by the fixation of its axial, more shielded, position. Hence, the hydroxy group in position 4 is equatorial. As this equatorial position is stabilised the methyl group in position 3 cannot be axial. Thus, the relative configuration is *trans*.

EXPERIMENTAL

The infrared spectra were measured in chloroform on a Zeiss UR 10; the NMR spectra were measured on JNM-3-60 (60 Mc/s) and Tesla BS 487 (80 Mc/s) spectrometers, using hexamethyldisiloxane as internal standard. Gas chromatographic analyses were carried out on a Chrom II apparatus (column length 2 m, diameter 0.6 cm; 15% of Tridox on Cellite, or 20% Carbowax 20 M on Chromosorb W, nitrogen as carrier gas). Thin-layer chromatography and preparative column chromatography was carried out on alumina (activity II according to Brockmann).

cis- and *trans*-1,3-Dimethyl-4-piperidinol (II)

A mixture of 7.65 g (60 mmol) of piperidone III (ref.⁷), 380 mg of platinum oxide, and 80 ml of methanol was hydrogenated at 755 Torr and 22°C for 5 hours, when the theoretical amount of hydrogen was consumed. The catalyst was filtered off and methanol from the filtrate was evaporated using a column. Distillation of the residue gave 6.35 g (82.0%) of liquid, b.p. $87\text{--}90^\circ\text{C}/10$ Torr. Thin-layer chromatography in the system ammonia-saturated methanol-ether (1 : 50) revealed two spots, $R_{F(cis)}$ 0.60, $R_{F(trans)}$ 0.36. For $\text{C}_7\text{H}_{15}\text{NO}$ (129.2) calculated: 65.07% C, 11.71% H, 10.84% N; found: 64.96% C, 11.74% H, 11.02% N.

The separation of amino alcohols II was carried out on a column of alumina of activity II (according to Brockmann). Column length 360 mm, \varnothing 23 mm. To obtain the *cis* isomer the mixture from catalytic hydrogenation of III was used, while for the *trans*-isomer the mixture obtained on reduction of III with lithium in liquid ammonia³ was employed. In both cases the column was loaded with 2.2 g of the mixture of amino alcohols II and elution was carried out gradually with 250 ml of ether, 100 ml of ether containing 0.5% of ammonia-saturated methanol, and 100 ml of ether containing 2% of ammonia-saturated methanol. Fractions of 25 ml each were collected and checked by thin-layer chromatography. Fractions containing a pure product were combined and the solvent evaporated. Distillation of the residues gave 590 mg of the *cis*-isomer II, b.p. $87\text{--}88^\circ\text{C}/10$ Torr (Hickmann flask), and 620 mg of chromatographically pure *trans*-isomer II, b.p. $90\text{--}91^\circ\text{C}/10$ Torr (Hickmann flask).

Determination of Stereoisomers II in Mixtures

A) *Infrared spectroscopy*: In the fingerprint region the *trans*-isomer is characterised by a band at 974 cm^{-1} , and the *cis*-isomer by a band at 988 cm^{-1} . From 0.24M solutions of both isomers mixtures were prepared containing the isomers in various proportions and they were then measured in cells 259 μ thick. After the correction of the measured absorptions and the calculation of reduced extinctions, the dependence of the reduced extinction of the band at 974 cm^{-1} ($E'(974)$) and of the band at 988 cm^{-1} ($E'(988)$) on the ratio of the isomers in the mixture was obtained. Using the least squares of deviations the following dependences were found:

$$E'(974) = -7.1 \cdot 10^{-3} \cdot c_{cis} + 1.108, \quad (1)$$

$$E'(988) = 2.9 \cdot 10^{-2} \cdot c_{cis} + 0.203, \quad (2)$$

where c_{cis} means the percentual content of the *cis*-isomer. From the relatively small scattering of the experimental points about the regression straight lines (1) and (2) it can be concluded that the Lambert-Beer law applies to the given mixtures, and that the values of the measured extinctions are additive. For the proportion of both components the following set of equations applies:

$$E(974) = 1.108 \cdot c_{trans} + 0.398 \cdot c_{cis},$$

$$E(988) = 0.203 \cdot c_{trans} + 2.693 \cdot c_{cis}, \quad (3)$$

where $E(974)$ and $E(988)$ mean total reduced extinctions of the mixture for the corresponding bands, and c_{trans} , c_{cis} mean percentual representation of the *cis* and *trans* isomers in the mixtures of isomeric amino alcohols II. From the mixture of amino alcohols II 0.24M solutions in chloroform were prepared, and after measurement their composition was calculated on the basis of the system of equations (3). The results of measurements are shown in Table I.

B) NMR spectroscopy: In the spectra of mixtures two sufficiently resolved singlets are present, due to the N-methyl groups protons. The ratio of their intensity integrals is the same as that of the corresponding stereoisomers in the mixture. The values given in Table I represent the average of six recordings. The integrals were determined by planimetry.

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