HYDROBORATION OF UNSATURATED AMINES. IX.*

HYDROBORATION OF 1-METHYL-4-PROPYL-3-PIPERIDEINE AND 1-METHYL-4-ISOPROPYL-3-PIPERIDEINE

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Hydroboration of the above-mentioned unsaturated amines with diborane in the cold and subsequent oxidation gives rise to a mixture of 1-methyl-4-propyl-3-piperidinol and 1-methyl-4-isopropyl-3-piperidinol of *trans* configuration, in addition to a small amount of the *cis* isomers. On heating 1-methyl-4-propyl-4-piperidinol and 1-methyl-4-isopropyl-4-piperidinol are also formed.

In the preceding paper[1] we described the hydroboration of 3-piperideines substituted at $C_{(4)}$ with a methyl and ethyl group. In order to find a more general effect of the nature of this alkyl group on the ratio of the hydroboration products of 1,4-dialkyl-3-piperideines we carried out this reaction with 4-propyl- (*Ia*) and 4-isopropyl- (*Ib*) derivatives. On reaction with diborane prepared directly in the reaction mixture in the cold, both the unsaturated amines gave mixtures of amino alcohols after oxidation with hydrogen peroxide in alkaline medium. Using gas chromatography we isolated as the main products *trans*-1-methyl-4-propyl-3-piperidinol (*IIa*) or *trans*-1-methyl-4-isopropyl-3-piperidinol (*IIb*), respectively, in addition to a small amount of the *cis* isomers *IIIa*, *IIIb*. The configuration of the products was assigned on the basis of the IR and NMR spectra. Hydroboration of the mentioned unsaturated amines *Ia*, *Ib*, (Table I) carried out by heating with triethylamine-borane also afforded (after oxidation with hydrogen peroxide in alkaline medium) 1-methyl-4-propyl-4-piperidinol (*IVa*) and 1-methyl-4-isopropyl-4-piperidinol (*IVb*) respectively. For the sake of comparison these tertiary amino alcohols *IVa*, *IVb* were prepared from 1-methyl-4-piperidone and propyllithium or isopropyllithium. The starting 1-methyl-4-propyl-3-piperideine and 1-methyl-4-isopropyl-3-piperideine were prepared by reduction of the methiodides of 4-propylpyridine or 4-isopropyl-pyridine with sodium boro-hydride, in analogy to similar cases[2].

For the solution of the configuration of stereoisomeric 1-methyl-4-propyl-3-piperidinols (*IIa*, *IIIa*) and 1-methyl-4-isopropyl-3-piperidinols (*IIb*, *IIIb*) we suppose

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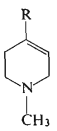
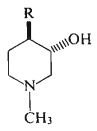
that these bulky alkyl groups in the position 4 will be oriented equatorially. In such a case the hydroxy group proton of the *cis* derivative *IIIa* can form an intramolecular hydrogen bond with the free electron pair of the nitrogen atom. In an IR study based on dilution experiments it was established that the isomeric 1-methyl-4-propyl-3-piperidinol, present in the mixture after hydroboration as the main product, displays at higher concentration intensive bands of intermolecular hydrogen bonds at 3200 and 3400 cm^{-1}. These bands disappear rapidly on dilution and a strong, narrow band at 3630 cm^{-1} appears, which is characteristic of a non-associated hydroxy group. The second stereoisomeric 1-methyl-4-propyl-3-piperidinol gives bands at 3400 and 3520 cm^{-1} in the IR region; on gradual dilution the band at 3400 cm^{-1} disappears, while the relative intensity of the band at 3520 cm^{-1} remains almost unchanged with respect to other absorption bands of the spectrum. In addition to this band a very weak absorption of the free hydroxy group at 3620 cm^{-1} appears. Both the behaviour during dilution and the frequency of the band at 3520 cm^{-1} indicate that it belongs to the hydroxy group bound by an intramolecular hydrogen bridge. Under the given supposition that the propyl group is equatorial, this stereoisomeric amino alcohol should have a *cis*-configuration of the substituents at the carbon atoms 3 and 4, while the first amino alcohol has a *trans* configuration.



I



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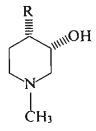

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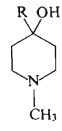

IV

I—IV, $a = n\text{-}C_3H_7$; $b = i\text{-}C_3H_7$

TABLE I
Yields (%) of the Hydroboration of Amines

Amine	Procedure[a]	Total	*II*	*III*	*IV*
Ia	A	43	93·5	5·4	1·1
Ia	B	55	73	22	5
Ib	A	61	97	3	—
Ib	B	73	90·4	9	0·6

[a] A Hydroboration with diborane in the cold; B hydroboration with triethylamine–borane under heating.

Under this supposition the configuration of this stereoisomeric pair may also be solved by NMR spectra. The hydrogen atom in the position 3 of the piperidine ring is in the *cis* derivative equatorial, so that its signal may be expected at a lower field than the signal of the axial proton in the *trans* derivative[3,4]. The proton in the position 3 is in *cis* derivative splitt by two *ae* and one *ee* coupling constants, while in the compound with the *trans* configuration the proton in the position 3 is splitt by two *aa* and one *ae* coupling constants. Hence, it may be expected that the total width of the multiplet of this proton will be distinctly greater in *trans* derivative than in *cis* derivative[5]. Further, the proton in the position 4 is axial in both stereoisomeric 1-methyl-4-propyl-3-piperidinols. However, in the *trans* derivatives it is *syn*-clinal, in the *cis* derivative *anti*-periplanar with respect to the hydroxy group. Its signal should lie at a lower field in the case of the *cis* isomer than in the case of the *trans* isomer[6-8].

The analysis of the NMR spectra of both 1-methyl-4-propyl-3-piperidinols *IIa* and *IIIa* showed that the signal of the proton in the position 3 is at 3·31 p.p.m. for the product prevailing after hydroboration, and that the width of this multiplet is approx. 23 Hz at the half height of the signal. The methods of multiple resonance (decoupling and INDOR) demonstrated that the signal of proton 4 is in the region of about 1·23 p.p.m. The second stereoisomeric 1-methyl-4-propyl-3-piperidinol gives a signal of the proton in the position 3 at 3·67 p.p.m., and the width of the band at the half-height of the signal is 7–8 Hz. The signal of the hydrogen at $C_{(4)}$ was located at 1·51 p.p.m. by multiple resonance. The comparison of these results with the above mentioned effects of the change of configuration on the NMR spectrum makes it possible to assign – in accordance with the results of IR spectra measurements – the *trans* configuration to the main product of hydroboration, (*i.e.* 1-methyl-4-propyl-3-piperidinol, *IIa*), and the *cis* configuration to the minor product of the reaction (*IIIa*).

Similar results were obtained by the analysis of the NMR spectra of both 1-methyl-4-isopropyl-3-piperidinols *IIb*, *IIIb*. The proton in the position 3 gives in the case of the minor component (amino alcohol) a multiplet centered about 3·87 p.p.m. with a band width of 8 Hz at the half-height of the signal, and the signal of the proton 4 was located by the method of double resonance at 1·50 p.p.m.. The main product of hydroboration of 1-methyl-4-isopropyl-3-piperideine gives the signal of the proton 3 at 3·54 p.p.m., in the form of a multiplet with a band width at the half-height of the signal 23 Hz; the signal of proton 4 was found by double resonance and INDOR experiments in the region of 1·17 p.p.m.. On the basis of the mentioned assumptions the *cis* configuration can again be assigned to the minor amino alcohol component, and the *trans* configuration to the main product of hydroboration of 1-methyl-4-isopropyl-3-piperideine.

The starting assumption of the equatorial position of the propyl or the isopropyl group in the position 4 is confirmed by the chemical shifts of the proton at carbon 4. Their relatively low values in the case of the *trans* derivatives (1·23 or 1·17 p.p.m.) agrees with the fact that this proton is axial. In addition to this in the case of the equatorial proton no reason is obvious for the differing values of the shift of its

signal in the *cis* derivative with respect to the *trans* derivative, as in both stereoisomers it is *syn*-clinal with respect to the hydroxy group.

TABLE II

NMR Spectra of Amino Alcohols (in deuteriochloroform, chemical shifts in δ, p.p.m.)

Substance	CH_3-C	CH_3-N	CH—O OH	Others
				1·03—1·54 (m)
IIa	0·91 (t; $J = 7$)	2·26 (s)	3·31 (m)	1·56—2·06 (m)
			4·03 (s)	2·58—3·00 (m)
IIb	0·85 (d; $J = 7$)	2·26 (s)	3·54 (m)	1·05—2·30 (m)
	0·95 (d; $J = 7$)		3·74 (s)	2·68—3·06 (m)
IIIa	0·90[a]	2·23 (s)	3·67 (m)	1·07—1·80 (m)
			2·71 (s)	1·80—2·97 (m)
IIIb	0·89 (d; $J = 7$)	2·24 (s)	3·87 (m)	1·37—2·10 (m)
	0·96 (d; $J = 6·5$)		2·78 (s)	2·70—3·00 (m)

[a] A poorly resolved triplet.

EXPERIMENTAL

All temperature data are uncorrected. Gas chromatography was carried out with Chrom 2 apparatus (Laboratorní přístroje, Prague). Preparative gas chromatography was carried out on an apparatus of non-commercial origin[9] (Tridox on Pórovina as stationary phase). The NMR spectra were measured on Varian XL-100 and Tesla BS 477 spectrographs. Mass spectra were measured with a Gas-Chromatograph-Mass Spectrometer Type 9000 LKB Producter AB Stockholm, and the obtained values were in all instances in agreement with the supposed structures. The IR spectra were measured in tetrachloromethane on a Perkin-Elmer 325 apparatus.

1-Methyl-4-propyl-3-piperideine (*Ia*)

A solution of 45 g of 4-propylpyridine[10] in 100 ml of methanol was mixed with a solution of 68·5 g of methyl iodide in 50 ml of methanol and refluxed for 10 hours. After evaporation of the solvent and excess methyl iodide a syrupy product was obtained, 97·5 g (99%). A solution of 95 g of the crude 1-methyl-4-propylpyridinium iodide in 240 ml of water was mixed with a solution of 15·1 g of sodium hydroxide in 240 ml of water, and a solution of 15·1 g of sodium borohydride in 124 ml of water was added and the reaction mixture steam distilled. The base was salted out and dried over potassium hydroxide, b.p. 94°C/34 Torr, or 72°C/15 Torr and 66°C/10 Torr; yield 40·6 g (74%). For $C_9H_{17}N$ (139·25) calculated: 77·63% C, 12·30% H, 10·06% N; found: 77·74% C, 12·28% H, 10·11% N. NMR spectrum: $C\underline{H}_3CH_2CH_2$ 0·85 (t, $J = 6·5$ Hz), CH_3N 2·3 (s), $N—C\underline{H}_2CH$ 2·87 (m), $CH_3—C\underline{H}_2—CH_2$ 1·06—1·68 (m), CH—C—CH_2—CH_2——N 1·70—2·65 (m), —CH= 5·36 (m) p.p.m. (in δ values).

1-Methyl-4-isopropyl-3-piperideine (*Ib*)

This was prepared in a similar manner as the preceding isomer, from 4-isopropylpyridine[11] transformed to its methiodide, by reduction with sodium boro-hydride, b.p. 64—66°C/10 Torr, yield 74%. For $C_9H_{17}N$ (139·25) calculated: 77·63% C, 12·30% H, 10·06% N; found: 77·61% C, 12·35% H. 9·98% N. NMR spectrum: CH_3—C 1·02 (d; J = 7 Hz), CH_3—N 2·32 (s), N—CH_2——CH 2·87 (m), CH_2—N 2·50 (m), CH—C—CH_2 2·0—2·38 (m), —CH= 5·37 (m) p.p.m. (in δ values).

Hydroboration of 1-Methyl-4-propyl-3-piperideine (*Ia*)

A. *With diborane in the cold*: To a solution of 6·3 g of sodium boro-hydride in 150 ml of diglyme 14 g of the base *Ia* and 31·7 g of boron trifluoride etherate in 50 ml of diglyme were added over 90 min at 25°C. After 2 h stirring the mixture was decomposed with 52 ml of conc. hydrochloric acid diluted with 11 ml of water, then alkalised with 85 ml of 40% sodium hydroxide, and additioned with 70 ml of 30% hydrogen peroxide. After 3 hours stirring and standing overnight the diglyme layer was separated and the aqueous layer extracted with chloroform. The combined extracts were mixed with a solution of 30 g of gaseous hydrogen chloride in ether, the solvents were evaporated and the residue dissolved in water (40 ml) and extracted with chloroform. The extract was dried over potassium carbonate and distilled, b.p. 109—110·5°C/8 Torr, yield, 6·85 g (43%). For $C_9H_{19}NO$ (157·3) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·74% C, 12·13% H, 9·19% N. According to NMR it is *trans*-1-methyl-4-propyl-3-piperidinol (*IIa*).

B. *With triethylamine-borane under heating*: A solution of 8·25 g of triethylamine-borane in 76 ml of toluene was mixed with 10 g of base *Ia* and the mixture refluxed for 7 h. After distillation of the solvent and the triethylamine through a column the residual crude product (10·8 g) was dissolved in acetone (115 ml) and boiled with 46 ml of 15% HCl for 15 min. The reaction mixture was evaporated *in vacuo* and the syrupy residue of the hydrochlorides of boronic acids (15·4 g) was mixed with 36 ml of tetrahydrofuran and alkalized (36 ml of 40% sodium hydroxide) and oxidized with 36 ml of 30% hydrogen peroxide. After the separation of the tetrahydrofuran layer the aqueous layer was extracted with chloroform. The conventional isolation procedure gave 6·2 g (55%) of a product, b.p. 119—124°C/16 Torr. According to gas chromatography it is a mixture of 73% of *trans* (*IIa*), 22% of *cis*-1-methyl-4-propyl-3-piperidinol (*IIIa*), and 5% of 1-methyl-4-propyl-4-piperidinol (*IVa*). Using preparative gas chromatography substance *IIIa* was obtained in a 90% purity and its structure proved by NMR and IR spectroscopy (Table II), b.p. 108°C/8 Torr.

Hydroboration of 1-Methyl-4-isopropyl-3-piperideine (*Ib*)

The procedure was analogous as above. The main product, *IIb*, isolated after hydroboration in the cold had b.p. 113—115°C/8 Torr. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·85% C, 12·23% H, 8·71% N. From the mixture after hydroboration with triethylamine-borane at elevated temperature substance *IIIb* was isolated in 90% purity, b.p. 115°C/10 Torr.

1-Methyl-4-propyl-4-piperidinol (*IVa*)

To a suspension of 3·55 g of lithium in 50 ml of diethyl ether a solution of 3·13 g of propyl bromide in 100 ml of diethyl ether was added at —30°C. After addition of 1·8 g of 1-methyl-4-piperidone[12] in 20 ml of diethyl ether the mixture was stirred at —30°C for 2 h, then refluxed under stirring

for 11 hours, decomposed with sodium hydroxide, extracted with chloroform, the extract dried over potassium carbonate and distilled. B.p. 106—109°C/12 Torr, yield, 1·0 g (40%). For C_9H_{19}. .NO (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·82% C, 12·26% H, 9·03% N. NMR spectrum (in δ values): $C\underline{H}_3CH_2$ 0·91 (t; $J = 7$ Hz), $CH_2\underline{CH}_2CH_3$ 1·2—2·0 (m), CH_2—N 2·0—3·0 (m), OH 2·5 (s), CH_3—N 2·25 (s) p.p.m.

1-Methyl-4-isopropyl-4-piperidinol (*IVb*)

A solution of 1-methyl-4-piperidone (6 g) in pentane was added to a solution of 3·2 g isopropyllithium[13] in pentane kept under argon at −45°C. The reaction mixture was stirred at −45°C for 30 minutes and then until the temperature rose to 20°C. The stirring was continued at this temperature for another hour. The reaction mixture was decomposed under cooling with 15 ml of water and 3·5 ml of 40% sodium hydroxide and then worked up in the usual manner. Yield, 3 g of a mixture, b.p., 104—106°C/15 Torr, containing 45% of the unreacted amino ketone. Preparative gas chromatography gave a product boiling at 105—108°C/18 Torr, m.p. 60—62°C. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 69·03% C, 12·39% H. 8·64% N. NMR spectrum: CH_3—C 0·92 (d; $J = 7$ Hz), CH_3—N 2·29 (s), CH_2—N 2·08—2·78 (m), other 1·35—1·88 (m) p.p.m. (in δ values).

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