HYDROBORATION OF 1,6-DIMETHYL-3-PIPERIDEINE, 1-METHYL-2-ETHYL-3-PIPERIDEINE, 1-METHYL-6-ETHYL-3-PIPERIDEINE, 1-METHYL-6-PROPYL-3-PIPERIDEINE, AND 1-METHYL-6-ISOPROPYL-3-PIPERIDEINE*

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Hydroboration of the title 1-methyl-6-alkyl-3-piperideines and the subsequent oxidation afforded a mixture of *cis*-1-methyl-6-alkyl-3-piperidinol and both the stereoisomeric 1-methyl-2-alkyl--4-piperidinols. Hydroboration of 1-methyl-2-ethyl-3-piperideine afforded both the 1-methyl--2-ethyl-3-piperidinols along with both the 1-methyl-2-ethyl-4-piperidinols.

In earlier papers[1-3], hydroborations of 1-methyl-3-alkyl-3-piperideines have been reported, leading mainly to *trans*-1-methyl-3-alkyl-4-piperidinols in addition to 1-methyl-3-alkyl-3-piperidinols. Hydroborations of 1-methyl-4-alkyl-3-piperideines[4,5] have been also studied; in this case, 1-methyl-4-alkyl-3-piperidinols (the *trans*-configuration predominated) as the main products were accompanied by lesser amounts of 1-methyl-4-alkyl-4-piperidinols and trace amounts of 1-methyl-3-(1-hydroxyalkyl)piperidines. To obtain an overall picture concerning the substituent effect in hydroborations of 1-methyl-3-piperideines, hydroborations of α-substituted 1-methyl-3-piperideines have been now effected under analogous conditions.

The starting novel 1-methyl-6-alkyl-3-piperideines *Ib–Id* and 1-methyl-2-alkyl--3-piperideines *Va–Vc* have been prepared in fair yields by the sodium borohydride reduction of 2-alkylpyridine methiodides in aqueous sodium hydroxide. These reductions afford always a mixture of compounds *I*, *V*, and 1-methyl-2-alkylpiperidines *VIa–VIc*, the 1-methyl-6-alkyl-3-piperideines *I* being markedly the predominant products. The components of these mixtures were separated by gas chromatography[6] and their structures determined by IR, NMR, and mass spectra. The amino alcohols *II–IV*, *VIII*, and *IX*, obtained by hydroboration, subsequent hydrolysis and oxidation of piperideines *I* or *Va* were isolated from the mixture by GLC. Furthermore, we have examined by GLC as well as NMR spectra the ratio of particular isomers

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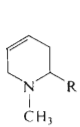
directly in the mixture resulting after the oxidation. For the results of this analysis see Table I. Complete preparative separation of the two configurational isomers *II* and *III* has been achieved in the case of 1-methyl-2-isopropyl-4-piperidinols *IId* and *IIId* only. The structural determination of reaction products has been particularly based on evaluation of IR, mass, and proton NMR spectra. Moreover in the case of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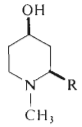
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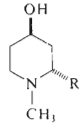
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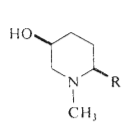
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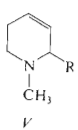
I–*IV* *a*) R = CH_3, *b*) R = CH_3CH_2, *c*) R = $CH_3CH_2CH_2$, *d*) R = CH_3CHCH_3.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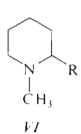
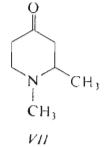

VI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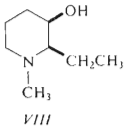
V–*VI* *a*) R = CH_3CH_2, *b*) R = $CH_3CH_2CH_2$, *c*) R = CH_3CHCH_3.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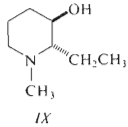
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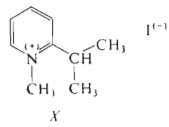
X

1,2-dimethyl-4-piperidinols (*IIa* and *IIIa*), the mixture of the two stereoisomers was oxidised with sodium dichromate in acetic acid to afford 1,2-dimethyl-4-piperidone *VII*) as the single product.

The mutual configuration of the two substituents at the piperidine ring carbon atoms has been advantageously determined by means of proton NMR spectra. With 1-methyl-2-alkyl-4-piperidinols *II* and *III*, these spectra especially differ in the chemical shift of proton signals at the carbon atom bearing the hydroxylic function. With the assumption of a chair conformation of the piperidine ring, the signal with the greater shift obviously corresponds to the proton in the equatorial position

while the higher-field signal is attributable to the axial proton. This assignment is also in accordance with the span of these signals which is always much greater in the case of the higher-field signal. With 1,2-dimethyl-4-piperidinols (*IIa* and *IIIa*) it was possible to record at least approximately the coupling constant values, *i.e.*, 4·5 Hz and 9 Hz in the case of the higher-field signal and 3·5 Hz with the lower-field signal. Since the alkyl on the piperidine ring carbon atom assumes in the predominant conformation the equatorial position[7,8], it is obvious that the higher-field signal corresponds to a compound with the *cis*-configuration of the alkyl group and the hydroxylic function while the signal of a higher shift value is attributable to a compound of the opposite configuration. The predominant occurence of the *cis*-isomer of 1-methyl-2-alkyl-4-piperidinol (*II*) in hydroboration products of 1-methyl-6-alkyl--3-piperideines (*I*) might be most likely explained by participation of nitrogen in the diborane addition proper, with the formation of a five-membered ring with a dative B—N bond[3]. Conditions of the present hydroborations do not exert any considerable influence (except for 1,6-dimethyl-3-piperideine *Ia*) on the ratio reaction products. 1-Methyl-6-alkyl-3-piperidinols (*IV*) which are obtained in all hydroborations of piperideines *I* as minor products, are exclusively of the *cis*-configuration. Their IR spectrum exhibits an intramolecular hydrogen bond band (3537 cm^{-1}) indicating that the hydroxylic group is in the axial position. The width of the NMR signal bans at position 3 is 10 Hz only, as the confirmation of the equatorial position of this proton. On the carbon atom attached to the nitrogen atom there was simultaneously found the signal of a single equatorial proton; it is consequently obvious that the

TABLE I

Oxidation Products after Hydroboration of α-Substituted 1-Methyl-3-piperideines

Compound	Hydroboration Method[a]	Yield %)	Amino Alcohols, %			
			II	*III*	*IV*	
Ia	*A*	52	68	14	18	
Ib	*A*	54	75	21	4	
Ic	*A*	53	68	28	4	
Id	*A*	48	76	20	4	
Ia	*B*	72	56	27	17	
Ib	*B*	75	72	18	10	
Ic	*B*	64	68	23	9	
Id	*B*	61	73	23	4	
Va	*A*	42	19	29	8(*VIII*)	44(*IX*)
Va	*B*	58	21	38	8(*VIII*)	33(*IX*)

[a] *A*, with diborane at room temperature; *B*, with triethylamine-borane in refluxing toluene.

alkyl is in the equatarial position, *i.e.*, compounds *IV* virtually possess the *cis*-configuration.

In contrast to the above-discussed hydroborations of piperideines *I*, the hydroboration of 1-methyl-2-ethyl-3-piperideine (*Va*) affords a mixture of four amino alcohols (*IIb*, *IIIb*, *VIII*, *IX*), the constitution and relative configuration of which was inferred from proton NMR spectra similarly to the preceding cases. In oxidation products after the hydroboration of compound *Va*, the overall content of compounds with the hydroxylic function at position β is much higher than after hydroboration of the piperideine *Ib* (almost 52% in the cold). The predominance of *trans*-1-methyl--2-ethyl-4-piperidinol (*IIIb*) over the *cis*-isomer *IIb* and of *trans*-1-methyl-2-ethyl--3-piperidinol (*IX*) over the *cis*-isomer *VIII* might be satisfactorily explained by steric hindrance in the diborane addition to the double bond, due to the alkyl group in the most suitable piperideine ring conformation.

Conclusively, the hydroboration products of 1-methyl-6-alkyl-3-piperideines *I* contain after hydrolysis and oxidation mainly the amino alcohols formed by the preferential attack of boron on the carbon atom 4. This attack leads finally to the *cis*-compounds *II* as the predominant products. The result of the hydroboration of 1-methyl-2-ethyl-3-piperideine (*Va*) is different since there is formed a considerable amount of amino alcohols *VIII* and *IX* with the hydroxylic function at position 3; the *trans*-isomer *IX* predominates, *i.e.*, the two substituents are again located in equatorial positions. In hydroborations of compound *Va* there are also formed 1-methyl-2-ethyl-4-piperidinols (*IIb*, *IIIb*); the predominance of the *trans*-isomer *IIIb* with the axial hydroxylic function is unusual.

EXPERIMENTAL

All hydroborations and all procedures with the boron-containing products were performed in the nitrogen atmosphere. Temperature data are uncorrected. Gas chromatography was performed on a Chrom II apparatus (column length 170 cm, diameter 0·6 cm, 20% Tridox on porous crushed unglazed tiles Porovina, nitrogen as carrier gas). The apparatus for the preparative gas chromatography was not of commercial origin[6]. NMR spectra were measured on a Varian XL-100-15 apparatus, ^{1}H at 100·1 MHz in deuteriochloroform; 37°C. Assignments were made on the basis of chemical shifts and signal multiplicity. Mass spectra were taken on Gas Chromatograph-Mass Spectrometer LKB 9000 Produkter AB Stockholm. The IR spectra were recorded on a Perkin-Elmer Model 325 apparatus.

Hydroboration of 1,6-Dimethyl-3-piperideine (*Ia*)

A. *With diborane in the cold.* To a solution of sodium borohydride (3·9 g) in diglyme (90 ml) there was added at 25°C over 90 min 1,6-dimethyl-3-piperideine[9] (*Ia*; 6·9 g) and boron trifluoride etherate (19·5 g) in diglyme (30 ml). The reaction mixture was stirred for 2 h, decomposed with 6·8 ml of water and 32 ml of 36% hydrochloric acid, made alkaline with 40% aqueous sodium hydroxide (52 ml), and treated dropwise with 30% hydrogen peroxide (43 ml). The stirring was continued for 3 h, the diglyme layer separated, and the aqueous layer extracted with chloroform.

The combined extracts were mixed with a solution of hydrogen chloride (15 g) in ether and the solvents were evaporated. The residue was dissolved in water (25 ml), the solution extracted with chloroform, the extract dried over anhydrous potassium carbonate, and distilled (b.p. 107 to 110°C/21 Torr) to afford 4·13 g (52%) of a mixture containing 18% of *cis*-1,6-dimethyl-3-piperidinol (*IVa*) and 82% of both the stereoisomers *IIa* and *IIIa* (for the isolation see procedure *B*). On the basis of NMR spectrum integral for the CH—O proton with 1,2-dimethyl-4-piperidinols, the ratio was 68% of *IIa* and 14% of *IIIa*. The NMR data are identical with those of a mixture of 1,2-dimethyl-4-piperidinols obtained by procedure *B*. For $C_7H_{15}NO$ (129·2) calculated: 65·07% C, 11·70% H, 10·84% N; found: 65·17% C, 11·86% H, 10·63% N.

B. *With triethylamine-borane at the reflux temperature.* 1,6-Dimethyl-3-piperideine (*Ia*; 6·32 g) was added to a solution of triethylamine-borane (6·55 g) in toluene (65 ml), the whole refluxed for 6 h, and the solvent along with triethylamine evaporated through a column. The product (7 g) was dissolved in acetone (90 ml), the solution treated with 15% aqueous hydrochloric acid (36·5 ml), the whole refluxed for 15 min, and evaporated under diminished pressure. The residual sirupous hydrochlorides of aminoboronic acids (9 g) were diluted with tetrahydrofuran (28·5 ml), made alkaline with 40% aqueous sodium hydroxide (28·5 ml), and oxidized with 30% hydrogen peroxide (28·5 ml). The tetrahydrofuran layer was separated and the aqueous phase extracted with chloroform. The usual isolation process afforded 5·25 g (72%) of the amino alcohol mixture consisting of *cis*-1,6-dimethyl-3-piperidinol (*IVa*; 17%) and both the 1,2-dimethyl-4-piperidinols (83%) in the ratio (*cf.* procedure *A*) 56% of the *cis*-isomer *IIa* and 27% of the *trans*-isomer *IIIa*. By means of GLC (preheater 175°C, column 150°C, flow rate 150 ml of nitrogen per min) there was isolated a mixture of 1,2-dimethyl-4-piperidinols, b.p. 107—109°C/21 Torr. For $C_7H_{15}NO$ (129·2) calculated: 65·07% C, 11·70% H, 10·24% N; found: 65·15% C, 11·87% H, 10·59% N. NMR spectrum: CH_3—C 1·05 (d; 6 Hz) for *IIa*, 1·06 (d; 6 Hz) for *IIIa*; CH_3—N 2·25 (s) for *IIa*, 2·27 (s) for *IIIa*; N—C$\underline{H}_e$H$_a$ 2·84—3·06 (m); CH—O 3·71 (tt; 4·5 Hz; 9 Hz) for *IIa*, 4·02 (qi; 3·5 Hz) for *IIIa* (in δ values) p.p.m.

cis-1,6-Dimethyl-3-piperidinol (*IVa*), b.p. 102—104°C/8 Torr (reported[10] b.p. 120°C/11 Torr and[11] b.p. 65—67°C/8 Torr) was obtained similarly. For $C_7H_{15}NO$ (129·2) calculated: 65·07% C, 11·70% H, 10·84% N; found: 64·89% C, 11·66% H, 10·60% N. NMR spectrum (in δ values): CH_3—C 1·07 (d; 6·5 Hz), C$\underline{H}_a$—CH—C$\underline{H}_2$—C$\underline{H}_2$—C$\underline{H}_a$ 1·35—2·38 (m), CH_3—N 2·22 (s), CH_e—N 2·67—2·89 (m), CH_e—O 3·67—3·93 (m) p.p.m.

1,2-Dimethyl-4-piperidone (*VII*)

The mixture of compounds *IIa* and *IIIa* (0·5 g) in acetic acid (55 ml) was treated with sodium dichromate (1·42 g) in acetic acid (14·8 ml), the whole kept at room temperature for 5 h (*cf.*[12]), diluted with water, made alkaline, and extracted with chloroform. The extract was dried over anhydrous potassium carbonate and distilled (b.p. 75—90°C/9 Torr) to afford 0·31 g (60%) of a mixture containing 22% of 1,2-dimethyl-4-piperidone(*VII*) and 78% of *IIa* + *IIIa*. When a greater amount (2 g) of the oxidised mixture was obtained, 1,2-dimethyl-4-piperidone (*VII*) was isolated by GLC (b.p. 72°C/8 Torr). For $C_7H_{13}NO$ (127·2) calculated: 66·10% C, 10·30% H, 11·01% N; found: 65·97% C, 10·44% H, 11·06% N. NMR spectrum: CH_3—C 1·15 (d; 6·5 Hz), CH_a—CH_2—C—CH_2—CH_a 2·08—2·79 (m), CH_3—N 2·39 (s), N—CH_e 2·93—3·38 (m) p.p.m. (in δ values).

Sodium Borohydride Reduction of 1-Methyl-2-ethylpyridinium Iodide

A solution of 2-ethylpyridine (53·5 g) in methanol (160 ml) was treated with a solution of methyl iodide (93 g) in methanol (80 ml) and the whole refluxed for 28 h. The solvent and excess methyl iodide were evaporated, the residual sirupous 1-methyl-2-ethylpyridinium iodide (109·2 g; 88%)

was dissolved in water (285 ml) and sodium hydroxide (17·5 g of pellets in 285 ml of water) and treated with a solution of sodium borohydride (17·5 g) in water (150 ml). The whole mixture was subjected to steam-distillation, the distillate acidified with hydrochloric acid, concentrated under diminished pressure, the concentrate made alkaline, and processed as usual to afford 40·7 g (74%) of a mixture (b.p. 154·5—156·5°C) containing 31% of 1-methyl-2-ethyl-3-piperideine (*Va*), 61% of 1-methyl-6-ethyl-3-piperideine (*Ib*), and 8% of 1-methyl-2-ethylpiperidine (*VIa*). GLC (preheater 165°C, column 125°C, flow rate 130 ml of nitrogen per min) afforded the pure base *Va*, b.p. 42·0—43·5°C/11 Torr. For $C_8H_{15}N$ (125·2) calculated: 76·74% C, 12·08% H, 11·19% N; found: 76·52% C, 12·24% H, 11·16% N. NMR spectrum: CH_3—C 0·90 (t; 7 Hz), N—CH—C= 2·74—3·0 (m), CH_3N 2·34 (s), CH= 5·41—5·88 (m), the other 1·20—2·66 p.p.m. (in δ values). The other isolated product was 1-methyl-6-ethyl-3-piperideine (*Ib*), b.p. 52—53°C/11 Torr. For $C_8H_{15}N$ (125·2) calculated: 76·74% C, 12·08% H, 11·19% N; found: 76·96% C, 12·15% H, 11·16% N. NMR spectrum: CH_3—C 0·92 (t; 7 Hz), CH_3CH_2 1·14—1·18 (m), CH_2—C= 1·92 to 2·16 (m), CH—N 2·20—2·48 (m), CH_3N 2·34 (s), =C—CH_2—N 2·78—3·30 (m), CH= 5·50 to 5·84 (m) p.p.m. (in δ values).

1-Methyl-2-ethylpiperidine (*VIa*)

The base *Va* (1·45 g) was converted to the hydrochloride and its aqueous solution hydrogenated over 45 mg of the Adams catalyst. Usual work-up afforded 1·0 g (68%) of compound *VIa*, b.p. 148—149°C (reported[13], b.p. 150·0—151·5°C). For $C_8H_{17}N$ (127·2) calculated: 75·52% C, 13·47% H, 11·01% N; found: 75·56% C, 13·49% H, 10·84% N. NMR spectrum: CH_3—C 0·88 (t; 7 Hz), CH_3N 2·22 (s), CH_e—N 2·72—2·96 (m), the other 1·15—2·26 p.p.m. (in δ values).

Hydroboration of 1-Methyl-2-ethyl-3-piperideine (*Va*)

The hydroborations were performed analogously to the base *Ia*. Hydroboration at the reflux temperature and the subsequent hydrolysis and oxidation afforded a mixture of four amino alcohols (yield, 58%), b.p. 102—103°C/14 Torr. The following compounds were isolated by means of GLC (preheater 185°C, column 150°C, flow rate 180 ml of nitrogen per min):

cis-1-*Methyl*-2-*ethyl*-3-*piperidinol* (VIII), b.p. 82°C/12 Torr (8%). For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 67·40% C, 11·81% H, 9·92% N. NMR spectrum (in δ values): CH_3—C 0·93 (t; 7 Hz), CH_3N 2·23 (s), CH_e—O 3·79 (m) p.p.m.

trans-1-*Methyl*-2-*ethyl*-3-*piperidinol* (IX), b.p. 92°C/12 Torr (33%). For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 66·83% C, 12·06% H, 9·61% N. NMR spectrum (in δ values): CH_3—C 0·91 (t; 7 Hz), CH_3N 2·26 (s), CH_eN 2·49—2·73 (m), CH_a—O 3·60 (m), the other 1·1—2·28 p.p.m.

Mixture of 1-*methyl*-2-*ethyl*-4-*piperidinols*, b.p. 100—101°C/12 Torr. For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 67·21% C, 11·82% H, 9·98% N. NMR spectrum (in δ values): CH_3—C 0·88 (t; 7 Hz); CH_3N (compound *IIb*) 2·27 (s), CH_3N (compound *IIIb*) 2·29 (s); CH_e—N 2·77—3·07 (m); CH—O (*IIb*) 3·69 (m), CH—O (*IIIb*) 4·05 (m); the other 1·1 to 2·67 p.p.m. On the basis of the NMR spectrum integration of the CH—O proton there was determined 21% of the *cis*-isomer *IIb* and 38% of the *trans*-isomer *IIIb*.

Hydroboration at room temperature afforded (yield, 42%) a mixture (b.p. 96—98°C/12 Torr) of *IIb*, *IIIb*, *VIII*, and *IX*. *cis*-1-Methyl-2-ethyl-3-piperidinol (8%) was identified by comparison of the elution time with that of compound *VIII*. *trans*-1-Methyl-2-ethyl-3-piperidinol (44%) was identified by comparison with compound *IX*. The mixture of 1-methyl-2-ethyl-4--piperidinols was isolated by means of GLC analogously to the reflux temperature hydroboration. For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 66·81% C, 12·00% H,

9·89% N. The NMR data are identical with those of 1-methyl-2-ethyl-4-piperidinols obtained after the reflux temperature hydroboration; assignments: 19% of *IIb* and 29% of *IIIb*.

Hydroboration of 1-Methyl-6-ethyl-3-piperideine (*Ib*)

The hydroborations were performed analogously to the base *Ia*. The reflux temperature hydroboration followed by hydrolysis and oxidation afforded (yield, 75%) a mixture (b.p. 120–123°C/26 Torr) of three amino alcohols. By means of GLC (preheater 185°C, column 150°C, flow rate 180 ml of nitrogen per min) there was isolated a mixture of 1-methyl-2-ethyl-4-piperidinols. For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 67·18% C, 12·17% H, 9·71% N. The NMR data are identical with those of the product obtained after hydroboration of compound *Va*. On the basis of NMR spectrum integration for the CH—O proton there was inferred 72% of the *cis*-isomer *IIb* and 18% of the *trans*-isomer *IIIb*. *cis*-1-Methyl-6-ethyl-3--piperidinol (*IVb*), b.p. 96°C/14 Torr, was isolated (10%) similarly. For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 67·31% C, 11·83% H, 9·93% N. NMR spectrum (in δ values): CH_3—C 0·88 (t; 7 Hz); CH—N 2·15–2·34 (m), CH_3N 2·25 (s), $C\underline{H}_eH_a$—N 2·70 to 2·91 (m), CH_e—O 3·83 (m), the other 1·15–2·0 p.p.m.

At room temperature, the hydroboration afforded (yield, 54%) a mixture (b.p. 100–101°C/11 Torr) of three amino alcohols. The mixture of 1-methyl-2-ethyl-4-piperidinols was isolated by means of GLC under similar conditions as after the reflux temperature hydroboration. For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 67·31% C, 11·99% H, 10·01% N. The NMR data are identical with those of the mixture of 1-methyl-2-ethyl-4-piperidinols isolated by hydroboration of compound *Va*. By integration of CH—O proton peak there was assigned 75% of the *cis*-isomer *IIb* and 21% of the *trans*-isomer *IIIb*. *cis*-1-Methyl-6-ethyl--3-piperidinol (4%) was identified by comparison of the elution time with that of compound *IVb*.

1-Methyl-2-propylpiperidine (*VIb*)

Hydrogenation of aqueous *Vb* hydrochloride (prepared from 0·8 g of the base[14]) over 24 mg of the Adams catalyst yielded 0·55 g (67%) of the base *VIb*, b.p. 65–66°C/10 Torr (reported[15] b.p. 175·6°C and[16] b.p. 175·5°C. For $C_9H_{19}N$ (141·3) calculated: 76·53% C, 13·56% H, 9·92% N; found: 76·33% C, 13·58% H, 9·73% N. NMR spectrum (in δ values): CH_3—C 0·91 (t; 7 Hz), CH_3N 2·25 (s), CH_e—N 2·72–2·92 (m), the other 1·10–2·30 p.p.m.

Hydroboration of 1-Methyl-6-propyl-3-piperideine (*Ic*)

The hydroborations of *Ic*[14] (b.p. 171–172°C) were performed analogously to the base *Ia*. The reflux temperature hydroboration followed by hydrolysis and oxidation afforded a mixture of three amino alcohols (b.p. 127–133°C/26 Torr; yield, 64%). The mixture of 1-methyl-2-propyl--4-piperidinols, b.p. 131 to 132°C/25 Torr, was isolated by means of GLC (preheater 185°C, column 155°C, flow rate 180 ml of nitrogen per min). For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·76% C, 12·36% H, 9·12% N. NMR spectrum (in δ values): CH_3—C 0·80–1·00 (m); CH_3N 2·27 (s) (for *IIc*), CH_3N 2·29 (s) (for *IIIc*); CH—O 3·66 (m) (for *IIc*), CH—O 4·03 (m) (for *IIIc*); the other 1·1–3·1 p.p.m. By integration of CH—O proton peak there was assigned 68% of the *cis*-isomer *IIc* and 23% of the *trans*-isomer *IIIc*. *cis*-1-Methyl-6-propyl-3-piperidinol (*IVc*), b.p. 125–126°C/25 Torr, was isolated (9%) similarly. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·41% C, 12·21% H, 8·68% N. NMR spectrum (in δ values): CH_3—C 0·91 (m), CH—N 2·18–2·35 (m), CH_3N 2·25 (s), $C\underline{H}_eH_a$—N 2·70–2·93 (m), CH_e—O 3·75–3·91 (m), the other 1·05–2·05 p.p.m.

At room temperature, the hydroboration also afforded three amino alcohols (b.p. 120—123°C/15 Torr; yield, 53%). 1-Methyl-2-propyl-4-piperidinol was isolated by means of GLC analogously to the reflux temperature hydroboration. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·75% C, 12·31% H, 8·64% N. The NMR data are identical with those of the mixture of 1-methyl-2-propyl-4-piperidinols isolated after the reflux temperature hydroboration (68% of *IIc* and 28% of *IIIc*). *cis*-1-Methyl-6-propyl-3-piperidinol (4%) was identified by comparison of the elution time with that of compound *IVc*.

1-Methyl-2-isopropylpyridinium Iodide (*X*)

A solution of 2-isopropylpyridine (26·5 g; prepared by reduction of 2-(2-hydroxy-2-propyl)-pyridine[17] with zinc and formic acid[18]) in methanol (60 ml) was treated with methyl iodide (40 g) in methanol (30 ml), the whole refluxed for 20 h, and evaporated to remove the solvent and excess methyl iodide. Yield, 55·25 g (96%) of the iodide *X*, m.p. 117—118°C (ethyl acetate–acetone). For $C_9H_{14}IN$ (263·1) calculated: 41·08% C, 5·36% H, 48·23% I, 5·32% N; found: 40·98% C, 5·46% H, 47·94% I, 5·07% N.

Sodium Borohydride Reduction of the Quaternary Iodide *X*

A solution of the iodide *X* (53·2 g) in water (46 ml) was diluted with aqueous sodium hydroxide (from 8·4 g of NaOH and 46 ml of water), treated with a solution of sodium borohydride (8·4 g) in water (70 ml), and the whole steam-distilled. Usual work-up of the distillate yielded 22·5 g (79%) of a mixture (b.p. 75—82°C/22 Torr) containing 30% of 1-methyl-2-isopropyl-3-piperideine (*Vc*), 67% of 1-methyl-6-isopropyl-3-piperideine (*Id*), and 3% of 1-methyl-2-isopropylpiperidine (*VIc*). The base *Vc*, b.p. 70°C/22 Torr, was isolated in pure state by means of GLC (preheater 175°C, column 135°C, flow rate 130 ml of nitrogen per min). For $C_9H_{17}N$ (139·2) calculated: 77·63% C, 12·30% H, 10·06% N; found: 77·41% C, 12·36% H, 9·81% N. NMR spectrum (in δ values): CH_3—C 0·82 (d; 7 Hz) and 0·96 (d; 7 Hz), CH_3N 2·32 (s), CH—N and CH_eH_a—N 2·70—3·05 (m), CH= 5·42—5·92 (m), the other 1·90—2·55 p.p.m. Base *Id*, b.p. 73—74°C/22 Torr, For $C_9H_{17}N$ (139·2) calculated: 77·63% C, 12·30% H, 10·06% N; found: 77·81% C, 12·21% H, 10·28% N, NMR spectrum (in δ values): CH_3—C 0·90 (d; 7 Hz) and 0·94 (d; 7 Hz), CH_3N 2·27 (s), =C—CH_2—N 2·80—3·36 (m), CH= 5·50—5·85 (m), the other 1·80—2·35 p.p.m.

1-Methyl-2-isopropylpiperidine (*VIc*)

Aqueous *Vc* hydrochloride (prepared from 2·0 g of the base) was hydrogenated over 60 mg of the Adams catalyst to yield 1·5 g (74%) of the base *VIc*, b.p. 69°C/16 Torr (reported[19], b.p. 165—167°C). For $C_9H_{19}N$ (141·3) calculated: 76·53% C, 13·56% H, 9·92% N; found: 76·48% C, 13·62% H, 10·03% N. NMR spectrum (in δ values): CH_3—C 0·85 (d; 7 Hz) and 0·88 (d; 7 Hz), CH_a—N 1·90—2·25 (m), CH_3N 2·21 (s), CH_e—N 2·77—2·98 (m), the other 1·04—1·85 p.p.m.

Hydroboration of 1-Methyl-6-isopropyl-3-piperideine (*Id*)

The hydroborations were performed analogously to the base *Ia*. At the reflux temperature, the hydroboration afforded after the subsequent hydrolysis and oxidation a mixture (yield, 61%) of three amino alcohols, b.p. 124—129°C/20 Torr. A mixture of 1-methyl-2-isopropyl-4-piperidinols (b.p. 126—127°C/19 Torr) was obtained by means of GLC (preheater 200°C, column 155°C, flow rate 200 ml of nitrogen per min). For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·76% C, 12·24% H, 8·99% N. On the basis of integration of CH—O proton NMR spectrum the following assignment was made: 73% of the *cis*-isomer *IId* and 23% of the

trans-isomer *IIId*. Repeated separations (accompanied by considerable loss) afforded the following compounds. *cis*-1-Methyl-2-isopropyl-4-piperidinol (*IId*), b.p. 129°C/20 Torr. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 69·03% C, 12·24% H, 9·20% N. NMR spectrum (in δ values): CH_3—C 0·79 (d; 7 Hz) and 0·86 (d; 7 Hz), CH_3N 2·24 (s), CH_e—N 2·94—3·13 (m), CH_a—O 3·66 (m), the other 1·05—2·28 p.p.m. *trans*-1-Methyl-2-isopropyl--4-piperidinol (*IIId*), b.p. 127°C/20 Torr. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·43% C, 12·41% H, 9·02% N. NMR spectrum (in δ values): CH_3—C 0·85 (d; 6·5 Hz) and 0·89 (d; 6·5 Hz), CH_3N 2·27 (s), CH_e—N 2·53—2·75 (m), CH_e—O 4·14 (m), the other 1·45—2·30 p.p.m. *cis*-1-Methyl-6-isopropyl-3-piperidinol (*IVd*), b.p. 123°C/19 Torr, was isolated (4%) similarly. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·43% C, 12·39% H, 9·02% N. NMR spectrum (in δ values): CH_3C 0·86 (d; 7 Hz) and 0·88 (d; 7 Hz), CH_3N 2·21 (s), CH_e—N 2·74—2·95 (m), CH_e—O 3·81 (m), the other 1·1—2·5 p.p.m.

At room temperature, the hydroboration afforded (yield, 48%) a mixture (b.p. 114—121°C/17 Torr) of the amino alcohols *IId*, *IIId*, and *IVd*. The mixture of 1-methyl-2-isopropyl-4-piperidinols was isolated by means of GLC analogously to the reflux temperature hydroboration experiment. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% H; found: 68·85% C, 12·03% H, 9·07% N. By integration of CH—O proton NMR spectrum, the following assignment was made: 76% of *IId* and 20% of *IIId*. *cis*-1-Methyl-6-isopropyl-3-piperidinol (4%) was identified by comparison of the elution time with that of compound *IVd*.

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