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

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Hydroboration of the three title unsaturated amines followed by oxidation yielded a mixture of *trans*-1-methyl-3-alkyl-4-piperidinol and a lesser amount of 1-methyl-3-alkyl-3-piperidinol.

In an earlier paper[1], we have reported hydroboration of 1-methyl-4-propyl-3-piperideine and 1-methyl-4-isopropyl-3-piperideine yielding a mixture of both the stereoisomeric 1-methyl-4-alkyl-3-piperidinols (the *trans* isomers predominated). The hydroboration of 1,3-dimethyl-3-piperideine has been also performed[2]. Later on[3], *trans*-1,3-dimethyl-4-piperidinol was shown as the main product of the latter hydroboration.

In the present work, the hydroboration of 1-methyl-3-ethyl-3-piperideine (*Ia*), 1-methyl-3-propyl-3-piperideine (*Ib*), and 1-methyl-3-isopropyl-3-piperideine (*Ic*) has been examined. Hydroborations were performed either at room temperature with diborane prepared directly in the reaction mixture, or by heating with triethylamine-borane in refluxing toluene. The subsequent oxidation of the hydrolysed product afforded in most cases (except for the hydroboration of the piperideine *Ic* by the latter procedure) a mixture of two aminoalcohols, one of which highly predominated. Analogously to hydroboration of 1,3-dimethyl-3-piperideine[2,3], 1-methyl-3-alkyl-4-piperidinol *II* was assumed to represent the main product while 1-methyl-3-alkyl-3-piperidinol *III* was expected as the minor aminoalcohol. For purposes of comparison, the tertiary aminoalcohols *III* were prepared by reaction of 1-methyl-3-piperidone with ethylmagnesium bromide, propylmagnesium bromide[4], and isopropyllithium, resp.

The starting 1-methyl-3-alkyl-3-piperideines *I* were prepared by the sodium borohydride reduction of the corresponding 3-alkylpyridine methiodide. In this reduction, the required 1-methyl-3-alkyl-3-piperideine *I* was accompanied by a lesser

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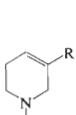
amount of the position isomer, namely, 1-methyl-5-alkyl-3-piperideine *IV*. Reduction of 3-propylpyridine methiodide afforded three bases identified as 1-methyl-3-propyl--3-piperideine (*Ib*), 1-methyl-5-propyl-3-piperideine (*IVb*), and 1-methyl-3-propylpiperidine (*Vb*). In the case of 3-isopropylpyridine methiodide, the reduction afforded two bases only, namely, 1-methyl-3-isopropyl-3-piperideine (*Ic*) and 1--methyl-5-isopropyl-3-piperideine (*IVc*).

On the basis of elemental analysis and NMR spectra, the *trans*-1-methyl-3-alkyl--4-piperidinols *II* were established as the principal hydroboration and oxidation products. In interpretation of spectra, the piperidine ring was assumed in the chair conformation in view of the rapid configurational inversion on the nitrogen atom carrying the N-methyl group in equatorial position. This assumption is fully justified on the basis of literature data[5,6]; the C-alkyl is assumed to prefer in the predominant conformation the equatorial position[7,8]. The NMR signal of the proton at position 4 of 3-alkyl-4-piperidinols lies at a relatively high field value and exhibits a distinctly resolved multiplet[7]. The low chemical shift value of the 3-ethyl derivative *IIa* (3·14 p.p.m.), the 3-propyl derivative *IIb* (3·13 p.p.m.), and the 3-isopropyl derivative *IIc* (3·37 p.p.m.) suggests the axial disposition of this proton.

To exclude confusion of the axial CH—O proton with equatorial CH—N protons in compounds *IIa* and *IIb*, the acetylation was performed resulting in a distinct shift of 3·13 and 3·14 p.p.m. signals to a lower field (4·48 and 4·52 p.p.m.). The somewhat different position of the 3-isopropyl derivative *IIc* 4-proton prompted us to effect oxidation and to reduce the resulting ketone with the formation of a mixture of 1--methyl-3-isopropyl-4-piperidinol *cis* and *trans* isomers. In this mixture, the C-4 proton signal of the equatorial isomer may be observed at 4·06 p.p.m. With the assumption that the predominant disposition of the 3-alkyl group is equatorial, all the three 1-methyl-3-alkyl-4-piperidinols possess exclusively the *trans* configuration. Such an interpretation is also supported by the band width of the C-4 proton signal. This value is 23·5 Hz (measured as distance of external multiplet peaks) in all cases and excludes thus predominance of a conformation with an axial hydroxyl group. This width would be also difficult to explain in the case of a *cis* configuration; moreover, it would be necessary to accept predominance of a conformation with an axial C-alkyl even in the case of the isopropyl group[8,9]. It is noteworthy that the observed band width of the C-4 proton in the *cis* isomer ($\delta = 4{\cdot}06$ p.p.m., *vide supra*) is 8·5 Hz. Using the coupling constant values inferred for related compounds[6,7] and omitting in the first approximation the influence of different substituents, it may be concluded[8] from the just mentioned band widths that the proportion of the compound with the C-4 axial proton in an eventual conformational equilibrium is at least 84% at 37°C, *i.e.*, $\Delta G \approx -1{\cdot}03$ kcal/mol. It must be born in mind, however, that the extreme values of coupling constants applied are only approximate in the present case. As suggested by the almost zero difference between the ethyl derivative *IIa* and the isopropyl derivative *IIc*, the virtual ΔG value will be probably somewhat higher.



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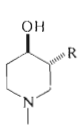

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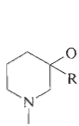

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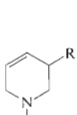

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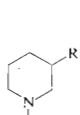
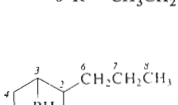
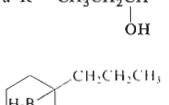


V

I–V *a* R = C_2H_5
b R = $CH_3CH_2CH_2$
c R = $(CH_3)_2CH$
d R = $CH_3CH_2CH(OH)$



VI



VII

Formation of a small amount of compound *III* with the hydroxylic function at position 3 prompted us to take into consideration the primary addition of the boron atom to the C-3 carbon atom followed by rearrangement to the vicinal carbon atom during the work up of the reaction mixture. Such a possibility was rejected since the products did not contain any compound with a hydroxylic function in the side chain as shown by comparison (gas–liquid chromatography and NMR spectra) with 1--methyl-3-(1-hydroxy-1-propyl)piperidine (*Vd*) which was synthesized for this purpose; moreover, it was unequivocally established by the ^{13}C-NMR spectrum of the amine-borane *VI* that the addition of boron occurred on the C-4 carbon atom. The proton NMR spectra of the amine-borane *VI* demonstrate the presence of the dative C—N bond (δ_{CH_3N} = 2·59 p.p.m.) but it is difficult to choose between the intramolecular and intermolecular bond. The easy distillation of compound *VI* along with the earlier observations on the hydroboration of 1,3-dimethyl-3-piperideine[2] appear to favour the former alternative.

Formation of the two amino alcohols *II* and *III* in hydroborations of unsaturated amines *I* could be explained *via* the bicyclic amine-borane *VI* (with a five-membered ring) or *VII* (with a four-membered ring). Owing to the lower stability of the four--membered ring, the amine-borane *VII* may be transformed at elevated temperatures to compound *VI* with the five-membered ring analogously to the thermal isomerisation of products from the hydroboration of 1-alkylcyclohexenes[10]. This explanation is in accordance with data of Table I which indicate that there is formed much less 1-methyl-3-alkyl-3-piperidinols *III* in hydroborations at elevated temperatures

(after hydrolysis and oxidation) than in those at room temperature. The resulting 1-methyl-3-alkyl-4-piperidinols *II* were exclusively of the *trans* configuration in contrast to the hydroboration of 1-methyl-4-alkyl-3-piperideines which also afford a lesser amount of *cis*-1-methyl-4-alkyl-3-piperidinols[1,11]. The exclusive formation of *trans*-amino alcohols *II* does not surprise because of the *cis*-mechanism of the diborane addition to the double bond.

TABLE I

Proportion of Amino Alcohols in Hydroborations of 1-Methyl-3-alkyl-3-piperideines *I*

Starting compound	*Ia*[a]	*Ib*[a]	*Ic*[a]	*Ia*[b]	*Ib*[b]	*Ic*[b]
Yield, %	74	44	35	80	64	47
II, %	94	92·5	93	98	99·7	100
III, %	6	7·5	7	2	0·3	0

[a] Cold process; [b] hot process.

EXPERIMENTAL

All the hydroborations and work-ups of boron-containing products were performed in a nitrogen atmosphere. Temperature data are uncorrected. Gas chromatography was performed on a Chrom II apparatus (column length 170 cm, 0·6 cm in diameter, 20% Tridox on Porovina, *i.e.* crushed porous plates, nitrogen as carrier gas). Preparative gas chromatography was carried out on a non-commercial apparatus[12]. The NMR spectra were taken on a Varian XL-100-15 apparatus, ^1H at 100·1 MHz in deuteriochloroform at 37°C. Assignments were made on the basis of chemical shifts and signal multiplicity. Mass spectra were measured on Gas Chromatograph - Mass Spectrometer LKB 9 000 Produkter AB Stockholm.

Hydroboration of 1-Methyl-3-ethyl-3-piperideine (*Ia*)

A. *With diborane at room temperature.* To a solution of sodium borohydride (2·35 g) in diglyme (56 ml) there was added at 25—26°C over 30 min the base *Ia* (4·56 g; separated by gas–liquid chromatography[12] from the reaction mixture after the sodium borohydride reduction of 1-methyl--3-ethylpyridinium iodide[13]) and boron trifluoride etherate (11·8 g) in diglyme (19 ml). The whole was stirred at room temperature for 2 h, decomposed with water (4·1 ml) and conc. hydrochloric acid (20 ml), made alkaline with 40% aqueous sodium hydroxide (32 ml), and treated dropwise with 30% hydrogen peroxide (26·5 ml). The stirring was continued for 3 h, the layers were separated, and the aqueous layer was extracted with chloroform. The organic layers were combined, treated with ethereal hydrogen chloride (15 g of HCl), and evaporated. The residue was dissolved in water (20 ml), the solution washed with chloroform, and the aqueous layer made alkaline. Extraction of this layer with chloroform, drying of the extract with potassium carbonate, and distillation afforded 3·95 g (74%) of a liquid b.p. 113—115°C/20—21 Torr, the composition of which is shown in Table I.

B. *With triethylamine-borane in refluxing toluene.* The base *Ia*[13] (7·0 g) was treated with a solution of triethylamine-borane[27] (6·5 g) in toluene (60 ml) and the whole refluxed for 6 h. The solvent

and triethylamine were evaporated through a column and the crude residue (7·5 g) dissolved in acetone (65 ml). The solution was refluxed with 6·2M-HCl (17 ml) for 20 min and evaporated under diminished pressure. The residue (10 g) was diluted with tetrahydrofuran (18 ml), made alkaline with 40% aqueous sodium hydroxide (18 ml), and oxidised with 30% hydrogen peroxide (18 ml). The tetrahydrofuran layer was separated and the aqueous phase extracted with chloroform. Usual isolation afforded 6 g (80%) of a liquid, b.p. 105–109°C/9 Torr. Fractional distillation yielded the pure *trans*-1-methyl-3-ethyl-4-piperidinol (*IIa*), b.p. 103–105°C/8 Torr. For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N; found: 67·47% C, 12·26% H, 9·79% N. NMR spectrum (p.p.m.): CH_3C 0·90 (t; 6·5 Hz); CH_3N 2·24 (s); CH_{eq}—N 2·66–2·97 (m); CH—O 3·14 (m); and 1·0–2·15. Composition of the reaction mixture after hydroboration is shown in Table I. The minor 1-methyl-3-ethyl-3-piperidinol (*IIIa*) was identified by comparison with the synthetically prepared authentic specimen[4] (elution times).

1-Methyl-3-propyl-3-piperideine (*Ib*)

A solution of 3-propylpyridine (23·8 g; prepared from 3-propionylpyridine[14] by a modified Kizhner–Wolff reduction analogously to ref.[15]) in methanol (55 ml) was treated with methyl iodide (36 g) in methanol (27 ml), the whole refluxed for 22 h, and evaporated to afford 48 g (94%) of a hygroscopic sirup which was dissolved in water (120 ml). To this aqueous solution there was added sodium hydroxide (7·5 g) in water (120 ml) and sodium borohydride (7·5 g) in water (65 ml), and the whole was steam-distilled. The bases were separated from the distillate by the addition of potassium hydroxide, dried over potassium hydroxide pellets, and distilled to afford 12·44 g (45%) of a liquid, b.p. 170–171°C, containing 4·5% of 1-methyl-3-propylpiperidine, 11% of compound *IVb* and 84·5% of compound *Ib*. Pure *Ib* was obtained by gas–liquid chromatography (preheater 165°C, column 130°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: 77·44% C, 12·51% H, 9·93% N. NMR spectrum: CH_3—C 0·90 (t; 7 Hz); C—CH_2—C—C= 1·40 (m); CH_3—N 2·35 (s); N—CH_2——C= 2·78 (m); CH= 5·42 (m); and 1·75–2·58 p.p.m.

1-Methyl-5-propyl-3-piperideine (*IVb*)

A mixture of lithium aluminium hydride (25·7 g) and diethyl ether (490 ml) was refluxed for 1 h, treated with 3-propylpyridine methiodide (85·3 g), the whole refluxed for additional 8 h, decomposed with dilute hydrochloric acid (98 ml of the conc. acid and 325 ml of water), and the layers separated. The aqueous phase was made alkaline with 40% aqueous sodium hydroxide and steam-distilled. The bases were separated from the distillate by the addition of potassium hydroxide, dried over potassium hydroxide pellets, and distilled to afford 26·75 g (59%) of a liquid, b.p. 74–77°C/20 Torr, containing 75% of compound *Ib*, 3% of 1-methyl-3-propylpiperidine (*Vb*), and 22% of 1-methyl-5-propyl-3-piperideine (*IVb*). Pure *IVb* was obtained by a threefold gas–liquid chromatography (preheater 160°C, column 130°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: 77·62% C, 12·22% H, 10·09% N. NMR spectrum (p.p.m.): CH_3C 0·90(t; 7 Hz); C—CH_2—C—C= 1·33 (m); CH_3N 2·35 (s); CH=CH 5·65 (b s); and 1·80–3·20.

1-Methyl-3-propylpiperidine (*Vb*)

Hydrogenation of the aqueous hydrochloride (obtained from 2 g of compound *Ib*) over the Adams catalyst (60 mg) and usual work-up afforded 1·1 g (54%) of the base *Vb*, b.p. 70–71°C/21 Torr. For $C_9H_{19}N$ (141·3) calculated: 76·53% C, 13·56% H, 9·92% N; found: 76·51% C, 13·51% H,

10·08% N. NMR spectrum (p.p.m.): CH_3C 0·88 (t; 6·5 Hz); CH_3N 2·24 (s); CH_{eq}—N 2·62—2·94 (m); and 1·0—2·0.

Hydroborations of 1-Methyl-3-propyl-3-piperideine (*Ib*)

Both the hydroborations were performed analogously to those of compound *Ia* (in the hydroboration in refluxing toluene, the reaction time was 7 h) to afford (after hydrolysis and oxidation) as the principal product (hot process) *trans*-1-methyl-3-propyl-4-piperidinol (*IIb*), m.p. 35—37°C, b.p. 125—126°C/10 Torr. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·78% C, 12·22% H, 9·11% N. NMR spectrum (p.p.m.): CH_3—C 0·91 (t; 6·5 Hz); CH_3—N 2·23 (s); CH_{eq}—N 2·66—2·95 (m); CH—O 3·13 (m); and 1·1—2·15. Composition of reaction mixtures after the hot (yield, 64%) and cold (44%) hydroborations is shown in Table I. The minor component *IIIb* was determined as earlier[4].

1-Methyl-3-isopropylpyridinium Iodide

A solution of 3-isopropylpyridine (57 g; prepared analogously to 4-isopropylpyridine[16]) in methanol (130 ml) was treated with methyl iodide (86 g) in methanol (65 ml), the whole refluxed for 14 h, and evaporated to afford 114 g (92%) of the title methiodide, m.p. 85°C (ethyl acetate–2-propanol, 7 : 1). For $C_9H_{14}IN$ (263·1) calculated: 41·08% C, 5·36% H, 48·23% I, 5·32% N; found: 40·91% C, 5·48% H, 48·37% I, 5·13% N.

1-Methyl-3-isopropyl-3-piperideine (*Ic*)

To a solution of 1-methyl-3-isopropylpyridinium iodide (110 g) in water (95 ml) there was added sodium hydroxide (17·2 g) in water (95 ml) and then sodium borohydride (17·2 g) in water (140 ml). The mixture was steam-distilled and the basic layer separated. The aqueous layer of the distillate was acidified with hydrochloric acid, the aqueous hydrochloride solution concentrated, and the concentrate made alkaline with 40% aqueous sodium hydroxide. The base was separated by the addition of potassium hydroxide, combined with the above basic layer and distilled to afford 34·4 g (59%) of a liquid, b.p. 168—171°C, containing 16% of 1-methyl-5-isopropyl-3-piperideine[17] (*IVc*) and 84% of the isomer *Ic*. Pure *Ic* was isolated by means of gas–liquid chromatography (preheater 165°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: 77·89% C, 12·53% H, 9·80% N. NMR spectrum (p.p.m.): $(CH_3)_2C$ 1·01 (d; 7 Hz); CH_3—N 2·35 (s); =C—CH_2—N 2·82 (m); CH= 5·44 (m); and 1·80—2·60.

1-Methyl-3-isopropylpiperidine (*Vc*)

An aqueous solution of the hydrochloride prepared from 2 g of the base *Ic* was hydrogenated over the Adams catalyst (60 mg) and processed as usual to afford 1·2 g (59%) of the base *Vc*, b.p. 54—55°C/10 Torr. For $C_9H_{19}N$ (141·3) calculated: 76·53% C, 13·56% H, 9·92% N; found: 76·80% C, 13·86% H, 10·01% N. NMR spectrum (p.p.m.): $(CH_3)_2C$ 0·89 (d; 6·5 Hz); CH_3—N 2·24 (s); CH_{eq}—N 2·60—2·96 (m); and 1·10—2.0.

Hydroborations of 1-Methyl-3-isopropyl-3-piperideine (*Ic*)

The hydroborations were performed analogously to those of compound *Ib* to afford after the subsequent hydrolysis and oxidation as the principal product *trans*-1-methyl-3-isopropyl-4-piperi-

dinol (*IIc*) in 47% yield (hot process; b.p. 114°C/10 Torr) and 35% yield (cold process, b.p. 145 to 147°C/37 Torr), *cf.* Table I. For $C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N; found: 69·08% C, 12·47% H, 8·63% N. NMR spectrum (p.p.m.): CH_3C 0·85 (d; 7 Hz) and 0·96 (d; 7 Hz); CH_3N 2·24 (s); CH_{eq}—N 2·58—2·90 (m); CH—O 3·37 (m); and 1·30—2·20. The minor component *IIIc* was identified by comparison of elution times with those of an authentic specimen.

1-Methyl-3-isopropyl-3-piperidinol (*IIIc*)

A solution of 1-methyl-3-piperidone[18] (4 g) in pentane (4 g) was added at 0°C under argon over 15 min into a solution of isopropyllithium[19] (4·3 g) in pentane (96 ml), the whole stirred for 30 min at 0°C and for 1 h at room temperature, decomposed with water (22 ml) and 40% aqueous sodium hydroxide (5 ml), and the layers separated. The aqueous phase was extracted with chloroform, the extract combined with the pentane layer, dried over potassium carbonate, and evaporated to afford 3·7 g (66%) of a liquid, b.p. 76—80°C/11 Torr, containing 62% of the hydroxy derivative *IIIc* and 38% of the unreacted 1-methyl-3-piperidone. Pure *IIIc* was isolated by means of gas–liquid chromatography (preheater 180°C, column 150°C, flow rate 135 ml of nitrogen per min), b.p. 88—89°C/15 Torr. For $C_9H_{19}NO$ (157·3) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·59% C, 11·92% H, 8·80% N. NMR spectrum (p.p.m.): $(CH_3)_2C$ 0·94 (d; 7 Hz); $N—CH_a—CO$ 1·90 (d; $^2J = 11·5$ Hz); $N—CH_{eq}—CO$ 2·52 (dt; $^2J = 11·5$ Hz; $^4J = 1·7$ Hz); CH_3N 2·26 (s); $N—CH_{eq}—C—C$ 2·75 (m); and 1·1—1·95.

Acetoxy Derivatives

trans-1-*Methyl*-3-*ethyl*-4-*acetoxypiperidine*. A mixture of acetic anhydride (20 ml), fused sodium acetate (2 g), and *trans*-1-methyl-3-ethyl-4-piperidinol (*IIa*; 1 g) was refluxed (bath temperature 175°C) for 70 min, poured onto ice (30 g), the whole stirred for 1 h, treated with saturated aqueous sodium hydrogen carbonate (10 ml), stirred for 1 h more, treated with additional 10 ml of the above saturated solution, stirred for 45 min at room temperature, and extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and distilled to afford 0·65 g (50%) of the acetate, b.p. 93°C/8 Torr or b.p. 95°C/9 Torr. For $C_{10}H_{19}NO_2$ (185·3) calculated: 64·83% C, 10·34% H, 7·56% N; found: 64·62% C, 10·46% H, 7·27% N. NMR spectrum (p.p.m.): $CH_3—C$ 0·88 (t; 7 Hz); $CH_3—CO$ 2·05 (s); $CH_3—N$ 2·27 (s); $CH_{eq}—N$ 2·60—3·05 (m); CH—O 4·48 (m); and 1·0—2·30.

trans-1-*Methyl*-3-*propyl*-4-*acetoxypiperidine*, b.p. 105°C/14 Torr, was prepared in 59% yield analogously to the preceding paragraph. For $C_{11}H_{21}NO_2$ (199·3) calculated: 66·29% C, 10·62% H, 7·03% N; found: 66·21% C, 10·78% H, 6·89% N. NMR spectrum (p.p.m.): $CH_3—C$ 0·89 (t; 6·5 Hz); $CH_3—CO$ 2·0 (s); $CH_3—N$ 2·39 (s); $CH_{eq}—N$ 2·90—3·18 (m); CH—O 4·52 (m); and 1·0—2·50 (traces of free acetic acid).

1-Methyl-3-isopropyl-4-piperidone

To a solution of *trans*-1-methyl-3-isopropyl-4-piperidinol (*IIc*; 3·3 g) and N,N'-dicyclohexylcarbodiimide (20·9 g) in dimethyl sulfoxide (51 ml) there was added 100% phosphoric acid[20] (5·1 g) and the whole shaken for 30 min under cooling with tap water. The reaction mixture was kept at room temperature for 64 h, decomposed with a mixture of methanol (90 ml) and water (60 ml), kept for additional 30 min[21], filtered (to remove N,N'-dicyclohexylurea, m.p. 230°C), the solid washed with 80% aqueous methanol and 80% aqueous acetic acid, the filtrate and washings combined, made alkaline with 25% aqueous ammonia, and extracted with dichloromethane.

The extract was dried over anhydrous magnesium sulfate and distilled to afford 13·8 g of a liquid, b.p. 89°C/21 Torr, *i.e.*, a solution of the product in dimethyl sulfoxide. The liquid was acidified with dilute hydrochloric acid and continuously extracted with benzene for 4 h. The aqueous phase was separated and made alkaline to afford 0·65 g (20%) of an oil, b.p. 89°C/21 Torr, which was identified as 1-methyl-3-isopropyl-4-piperidone by mass spectrometry, $M^+ = 155$. The aqueous layer was extracted with dichloromethane, the extract evaporated, and the residue distilled (b.p. 89°C/21 Torr) to afford almost exclusively dimethyl sulfoxide (containing 1—2% of the required piperidone). Other oxidation methods[22—25] were not successful. For $C_9H_{17}NO$ (155·2) calculated: 69·63% C, 11·04% H, found: 69·33% C, 11·09% H, NMR spectrum: $(CH_3)_2C$ 0·92 (d; 6·5 Hz); CH_3N 2·39 (s); and 1·50—3·0 p.p.m. (traces of dimethyl sulfoxide).

Reduction. A solution of 1-methyl-3-isopropyl-4-piperidone (300 mg) in diethyl ether (2 ml) was added to a suspension of lithium aluminium hydride (38 mg) in diethyl ether (2 ml), the whole refluxed for 90 min, decomposed successively with water (0·3 ml), 15% aqueous sodium hydroxide (0·3 ml), and water again (0·9 ml), and filtered through a sintered glass funnel. The filtrate was dried over potassium carbonate and distilled (b.p. 111—113°C/10 Torr) to afford 180 mg (59%) of a liquid, identified by NMR spectrum and gas–liquid chromatography as a 37 : 63 mixture of *cis*- and *trans*-1-methyl-3-isopropyl-4-piperidinol (the preparative separation by gas–liquid chromatography failed). For $C_9H_{19}NO$ (157·3) calculated: 68·74% C, 12·18% H, 8·91% N; found: 68·87% C, 12·28% H, 8·68% N. M^+ (mass spectrometry): 157.

3-(1-Hydroxy-1-propyl)pyridine

Into a suspension of lithium aluminium hydride (3·1 g) in diethyl ether (80 ml) there was added dropwise with stirring a solution of 3-propionylpyridine[14] (22 g) in diethyl ether (80 ml), the whole refluxed for 2 h, and processed[26] to afford 15·1 g (67%) of 3-(1-hydroxy-1-propyl)pyridine, b.p. 122°C/0·9 Torr. For $C_8H_{11}NO$ (137·2) calculated: 70·04% C, 8·08% H, 10·21% N; found: 70·14% C, 8·27% H, 10·01% N. NMR spectrum (p.p.m.): CH_3 0·91 (t; $J = 7·5$ Hz); CH_2 1·77 (m); CHOH 4·60 (t; 6·5 Hz); CH (β) 7·23 (m); CH (γ) 7·70 (dt; $J_{45} = 8$ Hz; $J_{24} = J_{46} = 2$ Hz); CH (α) 8·24—8·45 (m).

1-Methyl-3-(1-hydroxy-1-propyl)-3-piperideine (*Id*)

3-(1-Hydroxy-1-propyl)pyridine (12·7 g) in methanol (40 ml) was combined with methyl iodide (21 g) in methanol (20 ml), the mixture refluxed for 20 h, evaporated, the residual sirup (24 g; 93%) dissolved in water (60 ml), the aqueous solution combined with sodium hydroxide (3·7 g) in water (60 ml) and sodium borohydride (3·7 g) in water (30 ml). When the reaction was complete, the mixture was stirred for additional 30 min, and extracted with chloroform. The extract was dried over potassium carbonate and distilled to afford 6·5 g (51%) of a liquid, b.p. 126—128°C/ /27 Torr, containing compounds *Id* and *Vd* in the ratio 92 : 8. Pure *Id*, b.p. 124°C/23 Torr, was obtained by gas–liquid chromatography (preheater 185°C, column 150°C, flow rate 200 ml of nitrogen per min, elution time 12 h). For $C_9H_{17}NO$ (155·2) calculated: 69·63% C, 11·04% H, 9·02% N; found: 69·37% C, 11·02% H, 9·31% N. NMR spectrum (p.p.m.): CH_3—C 0·88 (t; 7 Hz); CH_3—CH_2 1·53 (m); CH_2—CH_2 2·06—2·80 (m); CH_3—N 2·34 (s); N—CH_{eq}—C= 3·0—3·25 (m); CH—OH 3·88 (t; $J = 6·5$ Hz); CH= 5·61 (m).

1-Methyl-3-(1-hydroxy-1-propyl)piperidine (*Vd*)

A solution of compound *Id* (1·5 g) in ethanol (40 ml) was hydrogenated over the Adams catalyst (45 mg) and processed as usual to afford 0·95 g (63%) of compound *Vd*, b.p. 113°C/14 Torr. For

$C_9H_{19}NO$ (157·25) calculated: 68·74% C, 12·18% H, 8·91% N. Found: 68·39% C, 11·92% H, 8·72% N. NMR spectrum (p.p.m.): CH_3—C 0·95 (t; $J = 7·5$ Hz); CH_3—N 2·26 (s); CH_{eq}—N 2·50—2·95 (m); CH—OH 3·24—3·59 (m); and 1·30—2·39 (diastereoisomeric mixture).

1-Methyl-1-aza-7-bora-3-propylbicyclo[2.2.1]heptane (*VI*)

A mixture of compound *Ib* (8 g), triethylamine-borane (6·7 g), and toluene (60 ml) was refluxed (bath temperature 145°C) for 6 h, the solvent and triethylamine evaporated through a column (bath temperature below 170°C), and the residue distilled at 60—90°C/1·1—1·4 Torr to afford 5·6 g (63%) of a liquid. Fractionation afforded pure *VI*, b.p. 74—76°C/1·3 Torr; yield, 5·6 g (63%). For $C_9H_{22}BN$ (155·1) calculated: 69·29% C, 14·32% H, 9·24% N; found: 69·01% C, 14·03% H, 9·01% N. NMR spectrum (p.p.m.): CH_3—C 0·87 (m); CH_3—N 2·59 (s). ^{13}C-NMR spectrum (in hexadeuteriobenzene at 25·2 MHz, δ in p.p.m. with respect to tetramethylsilane): C-1 67·38, C-2 40·95, C-3 29·50, C-4 24·72, C-5 61·23, C-6 35·52, C-7 21·81, C-8 14·72, C-9 44·25.

Hydrolysis and oxidation. To a solution of compound *VI* (2·25 g) in acetone (25 ml) there was added dropwise 15% dilute hydrochloric acid (10 ml), the whole refluxed for 80 min, and evaporated. The residue (3·1 g; 97%) was diluted with tetrahydrofuran (10 ml) and 30% aqueous sodium hydroxide (10 ml) and treated dropwise over 20 min with 30% hydrogen peroxide (10 ml). The resulting mixture was refluxed with stirring for 5 h and the layers were separated. The aqueous phase was extracted with chloroform. Usual work-up yielded 1·25 g (57%) of the oxidation product b.p. 123—124°C/10 Torr, identified as compound *IIb* by comparison of elution times and analysis.

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