

STUDIES IN THE PYRIDINE SERIES. XLIV.*

SYNTHESIS OF SOME 1-METHYL-4-(HYDROXYALKYL)PIPERIDINES

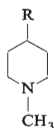
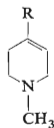
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The amino alcohols *III* have been prepared from the methiodides of the pyridine derivatives *II* by reduction with sodium borohydride. Hydrogenation of the compounds *IIIa–IIIc* afforded the piperidine derivatives *Ia–Ic*.

In connection with the hydroboration of 1-methyl-4-propyl-3-piperidine and 1-methyl-4-isopropyl-3-piperidine¹ we needed for the purpose of comparison 1-methyl-4-(1-hydroxy-1-propyl)piperidine (*Ia*), 1-methyl-4-(2-hydroxy-1-methylethyl)piperidine (*Ib*), and 1-methyl-4-(1-hydroxy-1-methylethyl)piperidine (*Ic*). For the preparation of *Ia* we reduced 4-propionylpyridine with lithium aluminium hydride to 4-(1-hydroxy-1-propyl)pyridine (*IIa*). The methiodide of *IIa* afforded on reduction with sodium borohydride 1-methyl-4-(1-hydroxy-1-propyl)-3-piperidine (*IIIa*), the catalytic reduction of which yielded *Ia*. In an alternative procedure we prepared *IIIa* from 4-propionylpyridine methiodide by reduction with lithium aluminium hydride. The amino alcohols *Ib* and *Ic* were prepared in an analogous manner from the methiodides of the hydroxy derivatives *IIb* and *IIc* by reduction with sodium borohydride and hydrogenation of the resulting 1-methyl-3-piperidine derivatives *IIIb* and *IIIc*. Similarly 1-methyl-4-(2-hydroxy-1-propyl)-3-piperidine (*III'd*) was also prepared.

*I**II**III*

For *I–III*: $a = \text{CH}_3\text{CH}_2-\underset{|}{\text{CH}}-\text{OH}$; $b = \text{CH}_3-\underset{|}{\text{CH}}-\text{CH}_2\text{OH}$; $c = (\text{CH}_3)_2\underset{|}{\text{C}}-\text{OH}$;

$d = \text{CH}_3-\underset{|}{\text{CH}}-\text{CH}_2-$
OH

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EXPERIMENTAL

Gas chromatography was performed on a Chrom II apparatus (column length 170 cm, diameter 0.6 cm, 20% Tridox on Porovina, nitrogen as carrier gas). Thin-layer chromatography was carried out on Silufol UV 254 or on a thin layer of Al_2O_3 . Nuclear magnetic resonance spectra were taken on a Tesla BS 477 (60 Mc) and on a Varian XL-100 apparatus in deuteriochloroform, using tetramethylsilane as internal standard. The melting points are uncorrected.

4-(1-Hydroxy-1-propyl)pyridine (*Ila*)

To a suspension of lithium aluminium hydride (1.9 g) in diethyl ether (50 ml) a solution of 4-propionylpyridine² (13.5 g) in diethyl ether (50 ml) was added dropwise with stirring and the reaction mixture was refluxed for 2 h. Decomposition the reaction mixture according to Mičović and Mihailović³ afforded 6.85 g (50%) of *Ila*, b.p. 128–129°C/3.6 Torr. For $C_8H_{11}NO$ (137.2) calculated: 70.04% C, 8.08% H, 10.21% N; found: 70.23% C, 8.30% H, 10.32% N. NMR spectrum: CH_3 0.84 (t; $J = 7$ Hz), CH_2 1.68 (q; $J = 6$ Hz), $\underline{C}HOH$ 4.54 (s), OH 6.22 (s), $CH=C$ 7.25 (m), $CH=N$ 8.32 (m) p.p.m. (in δ values).

1-Methyl-4-(1-hydroxy-1-propyl)-3-piperidine (*IIla*)

A. A mixture of 4-(1-hydroxypropyl)pyridine (*Ila*) (6.12 g), dissolved in methanol (20 ml) and methyl iodide (10 g) in methanol (10 ml) was refluxed for 20 h. Evaporation of the solvent and methyl iodide afforded the syrupy methiodide (12.4 g; 99%). The solution of the crude methiodide (12.4 g) in water (30 ml) was mixed with a solution of 1.9 g of sodium hydroxide in 30 ml of water and then treated with 1.9 g of sodium borohydride in 15 ml of water. After the reaction was over, the mixture was stirred for further 30 min and then extracted with chloroform. The extract was dried over potassium carbonate and distilled to give 4.51 g (68%) of *IIla*, b.p. 119–121°C/8 Torr. For $C_9H_{17}NO$ (155.2) calculated: 68.81% C, 11.23% H; found: 68.94% C, 11.03% H. NMR spectrum: $\underline{C}H_3CH_2$ 0.81 (t; $J = 7.5$ Hz), $\underline{C}H_2CH_3$ 1.48 (q; $J = 7$ Hz), $\underline{C}H_2CH_2$ 1.83–2.67 (m), CH_3N 2.27 (s), $\underline{C}HOH$ 3.82 (t; $J = 6.5$ Hz), OH 4.11 (s), $-CH=$ 5.52 (s), $N-CH_2CH=$ 2.85 (m) p.p.m. (in δ values).

B. 1-Methyl-4-propionylpyridinium iodide (14.2 g) was added to a suspension of lithium aluminium hydride (9.5 g) in diethyl ether (150 ml) and the mixture refluxed for 4 h. Working up the reaction mixture according to ref.³ gave 2.15 g (26%) of *IIla*, b.p. 118–120°C/8 Torr, identical with the product of the foregoing reduction.

1-Methyl-4-(1-hydroxy-1-propyl)piperidine (*Ia*)

A solution of base *IIla* (3.7 g) in methanol (100 ml) was hydrogenated in the presence of Adams catalyst (117 mg). The usual work-up furnished 3.0 g (80%) of the title product, b.p. 115–116°C/10 Torr. For $C_9H_{19}NO$ (157.25) calculated: 68.74% C, 12.18% H, 8.91% N; found: 68.54% C, 12.32% H, 8.91% N. NMR spectrum: $\underline{C}H_3CH_2$ 0.92 (t; $J = 5.5$ Hz), CH_3N 2.20 (s), $\underline{C}HOH$ 3.2 (m), OH (4.1) (s) p.p.m. (in δ values).

1-Methyl-4-(2-hydroxy-1-methylethyl)-3-piperidine (*IIlb*)

A solution of crude 4-(2-hydroxy-1-methylethyl)pyridine methiodide⁴ (52 g) in water (120 ml) was treated with sodium hydroxide (8 g) in water (120 ml) and subsequently with sodium borohydride (8 g) in water (60 ml). The reaction mixture was stirred for 30 min, whereupon it was worked up in the same manner as in the preparation of compound *IIla* to yield 17.3 g (60%) of *IIlb*, b.p. 118–122°C/8 Torr. For $C_9H_{17}NO$ (155.2) calculated: 69.63% C, 11.03% H, 9.02% N;

found: 69.33% C, 11.08% H, 9.32% N. NMR spectrum: $\text{CH}_3\text{—C}$ 1.02 (d; $J = 7$ Hz), $\text{N—CH}_2\text{—CH}_2\text{—C—CH}$ 2.00—2.62 (m), $\text{CH}_3\text{—N}$ 2.33 (s), $\text{CH—CH}_2\text{—N}$ 2.91 (m) $\text{CH}_2\text{—O}$ 3.24—3.62 (m), OH 4.15 (s), —CH= 5.44 (m) p.p.m. (in δ values).

1-Methyl-4-(2-hydroxy-1-methylethyl)piperidine (*Ib*)

The hydrogenation of *IIIb* was carried out analogously as the preparation of *Ia*. Yield 78.7% of *Ib*, b.p. 122—124°C/8 Torr. For $\text{C}_9\text{H}_{19}\text{NO}$ (157.3) calculated: 68.74% C, 12.18% H, 8.91% N; found: 68.90% C, 12.38% H, 8.96% N. NMR spectrum: $\text{CH}_3\text{—C}$ 0.90 (d; $J = 7$ Hz), $\text{CH}_2\text{—CH}(\text{CH})\text{CH}_2$ and 2 H $\text{CH}_2\text{—N—CH}_2$ 1.20—2.50 (m), $\text{CH}_3\text{—N}$ 2.23 (s), 2 H $\text{CH}_2\text{—N—CH}_2$ 2.75—2.98 (m) OH 3.35 (s), $\text{CH}_2\text{—O}$ 3.50 p.p.m. (in δ values).

4-(1-Hydroxy-1-methylethyl)pyridine Methiodide

A mixture of base *IIC*⁵ (27.4 g), methanol (80 ml), and methyl iodide (91 g) was refluxed for 7 h. After distilling off the excess methyl iodide and methanol, the yellow product separated out in a yield of 52 g (93.5%), m.p. 135—136°C (ethanol). For $\text{C}_9\text{H}_{14}\text{INO}$ (279.1) calculated: 38.73% C, 5.05% H, 5.02% N; found: 38.85% C, 5.10% H, 5.02% N.

1-Methyl-4-(1-hydroxy-1-methylethyl)-3-piperidine (*IIIc*)

A solution of 28 g of above methiodide in 70 ml of water, mixed with 4.2 g of sodium hydroxide in 70 ml of water, was reduced with 4.2 g of sodium borohydride in 34 ml of water. After stirring for 30 min, the reaction mixture was extracted with chloroform. The isolation in the usual manner afforded 11.1 g (71.6%) of *IIIc*, b.p. 62—63°C/10 Torr. For $\text{C}_9\text{H}_{17}\text{NO}$ (155.2) calculated: 69.63% C, 11.03% H, 9.02% N; found: 69.46% C, 12.24% H, 9.01% N. NMR spectrum: $\text{CH}_3\text{—C}$ 1.30 (s), $\text{CH}_2\text{—C}$ 2.10—2.30 (m), $\text{CH}_3\text{—N}$ 2.32 (s), $\text{CH}_2\text{—CH}_2\text{—N}$ 2.40—2.60 (m), OH 2.84 (s), $\text{CH—CH}_2\text{—N}$ 2.93 (m), —CH= 5.65 (m) p.p.m. (in δ values).

1-Methyl-4-(1-hydroxy-1-methylethyl)piperidine (*Ic*)

A solution of *IIIc* (3.1 g) in ethanol (75 ml) was hydrogenated in the presence of Adams catalyst (90 mg) for 4 h. Working up the reaction mixture afforded 3 g (95.5%) of product *Ic*, b.p. 103 to 104°C/11 Torr, which was chromatographically homogeneous according to thin-layer chromatography. For $\text{C}_9\text{H}_{19}\text{NO}$ (157.2) calculated: 68.74% C, 12.18% H, 8.90% N; found: 68.51% C, 12.46% H, 9.07% N. NMR spectrum: $\text{CH}_3\text{—C}$ 1.16 (s), $\text{CH}_3\text{—N}$ (2.23 (s), $\text{CH}_2\text{—CH—CH}_2$ and 2 H $\text{CH}_2\text{—N—CH}_2$ 1.10—2.40 (m), 2 H $\text{CH}_2\text{—N—CH}_2$ 2.76—3.02 (m), OH 3.07 (s) p.p.m. (in δ values).

1-Methyl-4-(2-hydroxy-1-propyl)-3-piperidine (*IIIId*)

A solution of crude 4-(2-hydroxy-1-propyl)pyridine methiodide⁶ (27.9 g) in water (60 ml) was mixed with sodium hydroxide (4 g) in water (60 ml) and subsequently with sodium borohydride (4 g) in water (30 ml). The mixture was stirred for 30 min (foaming), extracted with chloroform and the chloroform extract distilled to yield 7.65 g (49.5%) of product *IIIId*, b.p. 116—118°C/13 Torr. For $\text{C}_9\text{H}_{17}\text{NO}$ (155.2) calculated: 69.63% C, 11.04% H, 9.02% N; found: 69.47% C, 11.08% H, 8.72% N. NMR spectrum: $\text{CH}_3\text{—C}$ 1.17 (d; $J = 7$ Hz), $\text{CH}_2\text{—CH}_2$ 1.70—2.60 (m), $\text{CH—CH}_2\text{—C}$ 2.10 (badly resolved doublet; $J = 7$ Hz), $\text{CH}_3\text{—N}$ 2.34 (s), $\text{N—CH}_2\text{—CH}$ 2.92 (m), OH 3.75 (s), CH—O 3.87 (sextet; $J = 7$ Hz), —CH= 5.46 (m) p.p.m. (in δ values).

NMR spectra were measured by Dr P. Trška and analyses were performed in the Analytical Laboratories (headed by Mr L. Helešić) of our Department.

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