Reductive Aminocyclization of Alkane-2,6-diones to *cis*-6-Alkyl-2-methylpiperidines using Sodium Cyanoborohydride

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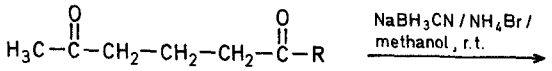
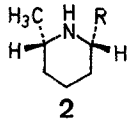
Sodium cyanoborohydride ($NaBH_3CN$) may be used as reagent in the reductive amination of carbonyl compounds[1,2], including the reductive aminocyclization of ketoesters, ketoaldehydes, and diketones. There are only few reports which describe the stereochemistry of the aminocyclized products obtained using $NaBH_3CN$. One of these reports says that the reductive aminocyclization of unsymmetrical alkane-2,5-diones with this reagent gives a 1:1 mixture of *cis*- and *trans*-2,5-dialkylpyrrolidines[3].

As part of a planned synthesis of fire-ant alkaloids[4,5], we performed the reductive aminocyclization of alkane-2,6-diones (**1a–e**). We describe here the experimental results.



1

a R = *n*-C_7H_{15} **d** R = *n*-$C_{13}H_{27}$
b R = *n*-C_9H_{19} **e** R = *n*-$C_{15}H_{31}$
c R = *n*-$C_{11}H_{23}$



2

The methanolic solution of diones **1a–e** is treated with sodium cyanoborohydride and ammonium bromide at room temperature for 4 days, and then stirred at pH 3 for 3 h; work-up involving microdistillation affords the 6-alkyl-2-methylpiperidines **2a–e** in 71–91% yields.

By means of G.L.C. and T.L.C. analysis, the piperidines **2a–e** were found to consist of a single component in all cases. The ^1H- and ^{13}C-N.M.R. spectra of compounds **2a–e** were identical with those of authentic samples of *cis*-6-alkyl-2-methylpiperidines[6].

All melting and boiling points are uncorrected. The ^1H-N.M.R. spectra were measured with a JEOL-PS-100 spectrometer. The ^{13}C-N.M.R. spectra were measured with a JEOL-FX-100 spectrometer using $CDCl_3$ as solvent and the standard (center peak referred to TMS as standard: $\delta = 77.10$ ppm).

6-Alkyl-2-methylpiperidines (2); General Procedure:

A solution of a 2,6-alkanedione (**1a–e**; 0.47 mmol), sodium cyanoborohydride (30 mg, 0.47 mmol), and ammonium bromide (93 mg, 0.95 mmol) in dry methanol (10 ml) is stirred for 4 days at room temperature and then acidified to pH 3 with conc. hydrochloric acid. Stirring is continued for 3 h at room temperature and the mixture evaporated to dryness. The residue is washed with ether (3 × 20 ml), made alkaline to pH 11 with aqueous 10% sodium hydroxide, and extracted with ether (10 × 20 ml). The extract is dried with sodium sulfate and evaporated and the residue is distilled under reduced pressure using a microdistillation apparatus. For identification part of the distillate is converted into the hydrochloride salt, which is recrystallized from ethyl acetate/isopropanol (5/1).

6-Heptyl-2-methylpiperidine (**2a**); yield: 80%; b.p. 68°C (bath)/0.1 torr; m.p. of hydrodrochloride (**2a** · HCl): 156–157°C.

$C_{12}H_{27}N \cdot HCl$	calc.	C 66.81	H 11.99	N 5.93
(233.8)	found	66.40	12.08	5.93

^1H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.94$ (t, $J = 5.25$ Hz, 3H); 1.05 (d, $J = 6.75$, 3H); 1.28 (s, 12H); 1.5–1.9 (m, 7H); 2.4–2.7 ppm (m, 2H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ = 14.00 (q); 22.57 (t); 23.04 (q); 24.83 (t); 25.92 (t); 29.20 (t); 29.74 (t); 31.77 (t); 32.24 (t); 34.42 (t); 37.43 (t); 52.40 (d); 57.07 ppm (d).

2-Methyl-6-nonyl-piperidine (**2b**); yield: 71%; b.p. 93°C (bath)/0.1 torr; m.p. of hydrochloride (**2b** · HCl): 148°C.

$C_{15}H_{31}N \cdot HCl$	calc.	C 68.83	H 12.24	N 5.35
(261.7)	found	68.72	12.43	5.20

^1H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.94$ (t, $J = 5.25$ Hz, 3H); 1.08 (d, $J = 6.75$, 3H); 1.28 (s, 16H); 1.44–1.97 (m, 7H); 2.30–2.70 ppm (m, 2H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ = 14.09 (q); 22.69 (t); 23.08 (q); 24.91 (t); 26.00 (t); 29.36 (t); 29.62 (t); 29.86 (t); 31.92 (t); 32.32 (t); 34.46 (t); 37.50 (t); 52.47 (d); 57.15 (d) ppm (d).

2-Methyl-6-undecylpiperidine (**2c**); yield: 75%; b.p. 115–120°C (bath)/0.1 torr; m.p. of hydrochloride (**2c** · HCl): 152°C.

$C_{17}H_{35}N \cdot HCl$	calc.	C 70.47	H 12.44	N 4.84
(289.9)	found	70.35	12.36	5.30

^1H.N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.95$ (t, $J = 5.25$ Hz, 3H); 1.06 (d, $J = 6.75$ Hz, 3H); 1.28 (s, 22H); 1.40–1.90 (m, 7H); 2.20–2.80 ppm (m, 2H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ = 14.11 (q); 22.69 (t); 23.12 (q); 24.95 (t); 29.67 (t); 29.90 (t); 31.97 (t); 32.32 (t); 37.51 (t); 52.51 (d); 57.19 ppm (d).

2-Methyl-6-tridecylpiperidine (**2d**); yield: 81%; b.p. 138–145°C (bath)/0.1 torr; m.p. of hydrochloride (**2d** · HCl): 148–150°C.

$C_{19}H_{39}N \cdot HCl$	calc.	C 71.81	H 12.60	N 4.41
(318.0)	found	71.40	12.94	4.11

^1H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 0.94 (t, J = 5.25, 3H); 1.08 (d, $J = 6.75$ Hz, 3H); 1.28 (s, 26H); 1.44–1.97 (m, 7H); 2.30–2.70 ppm (m, 2H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ = 13.96 (q); 22.57 (t); 23.00 (q); 24.83 (t); 25.86 (t); 29.24 (t); 29.54 (t); 29.78 (t); 31.81 (t); 32.84 (t); 34.31 (t); 37.39 (t); 52.40 (d); 57.07 ppm (d).

2-Methyl-6-pentadecylpiperidine (**2e**); yield: 91%; b.p. 150–158°C (bath)/0.1 torr; m.p. of hydrochloride (**2e** · HCl): 148–150°C.

$C_{21}H_{43}N \cdot HCl$	calc.	C 72.94	H 12.74	N 3.05
(346.2)	found	71.77	12.96	3.87

^1H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.94$ (t, $J = 5.25$ Hz, 3H); 1.04 (d, $J = 6.75$ Hz, 3H); 1.28 (s, 28H); 1.42–1.90 (m, 7H); 2.30–2.70 ppm (m, 2H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ = 14.03 (q); 22.65 (t), 23.07 (q); 24.87 (t); 25.96 (t); 29.36 (t); 29.67 (t); 29.82 (t); 31.89 (t); 32.32 (t); 34.47 (t); 37.46 (t); 52.43 (d); 57.11 ppm (d).

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[6] Authentic *cis*-6-alkyl-2-methylpiperidines were prepared according to Ref. 4.