The Synthesis and Ring Opening of *N*-Substituted-2-oxo-6-azaspiro[2,5]octanes

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N-Substituted-4-piperidones have been reacted with trimethyl sulfoxonium iodide to give the title compounds. These undergo ring opening with lithium aluminum hydride-aluminum chloride to give piperidine-4-methanols which were converted to the chloromethylpiperidines.

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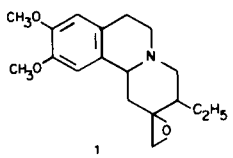
In connection with our studies of **1** (1) it was necessary to prepare model compounds in the piperidine series. *N*-benzyl-, *N*-(2-phenylethyl)-, and *N*-methyl-4-piperidones (**2**) were reacted with trimethyl sulfoxonium iodide to give the epoxides **3**. The *N*-methyl-2-oxo-6-azaspiro[2,5]-octane (**3**, R = CH_3) was obtained only in low yield, probably due to its high water solubility. The other two epoxides were obtained in good yield.

Reduction of the epoxides (**3**) with lithium aluminum hydride-aluminum chloride mixtures, where the ratio of aluminum chloride to lithium aluminum hydride was 4:1 or greater gave, by Bly's procedure (2), the primary alcohols **4**. In one run a small amount of what was believed to be the isomeric *N*-benzyl-4-methyl-4-hydroxypiperidine was obtained. The spectroscopic properties of the crude alcohols were consistent with the assigned structure (**4**) and treatment with thionyl chloride gave the chloromethyl compounds (**5**) which were characterized as the hydrochloride salts. The *N*-unsubstituted chloromethylpiperidine (**5**, R = H) was obtained from the known piperidine-4-methanol (3).



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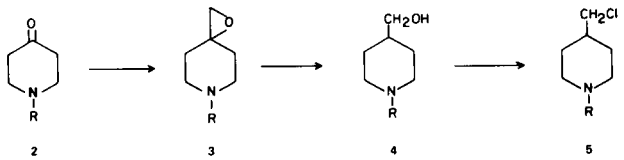

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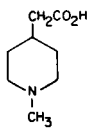

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In the course of preparing the related *N*-methyl-4-(2-hydroxyethyl)-piperidine (4) from ethyl (*N*-methyl-4-piperidyl)acetate (5), we had occasion to prepare **6** by hydrolysis of the ester.

EXPERIMENTAL

N-Benzyl-2-oxo-6-azaspiro[2,5]octane (**3**, R = $CH_2C_6H_5$).

To a solution of sodium hydride (1.5 g., 0.035 mole), which had been washed with hexane and dried *in vacuo*, and trimethyl sulfoxinium iodide (4.8 g., 0.02 mole) in dimethyl sulfoxide (30 ml.) was added a solution of *N*-benzyl-4-piperidone (**2**, R = $CH_2C_6H_5$) (3.8 g., 0.02 mole) in dimethyl sulfoxide (30 ml.). The resulting solution was stirred 30 minutes at room temperature, one hour at 50°, and then poured over ice. Chloroform extraction yielded an oil, distillation gave 2.6 g. (65%), b.p. 110° (0.25 mm), reported (6), b.p. 93° (0.06); ir: 3010, 1250 cm^{-1}; nmr: 7.2 (s, 5H), 3.4 (s, 2H), 2.4 (m, 6H), 2.0-1.0 (m, 4H); ms: 203 (12), 202 (9), 172 (8), 134 (7), 112 (9), 91 (25), 58 (40), 43 (100), 42 (10).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.86; H, 8.37; N, 6.89. Found: C, 76.86; H, 8.37; N, 6.95.

N-(2-Phenylethyl)-2-oxo-6-azaspiro[2,5]octane (**3**, R = $CH_2CH_2C_6H_5$).

This compound, b.p. 123° (0.4 mm), was prepared from *N*-(β-phenylethyl)-4-piperidone (**2**, R = $CH_2CH_2C_6H_5$) in a similar manner as described above, in 65% yield, ir: 3050, 1240 cm^{-1}; nmr: 7.1 (s, 5H), 2.7-2.2 (m, 10H), 2.0-1.0 (m, 4H); ms: 217 (1), 216 (1), 134 (11), 126 (24), 96 (11), 91 (21), 63 (10), 58 (34), 43 (100), 42 (13).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.43; H, 8.75; N, 6.45. Found: C, 77.29; H, 8.94; N, 6.39.

N-Methyl-2-oxo-6-azaspiro[2,5]octane (**3**, R = CH_3).

This compound, isolated as a picrate, m.p. 162-164°, from ethanol, was prepared from *N*-methyl-4-piperidone (**2**, R = CH_3) in a similar manner as described above, in 15% yield.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.49; N, 15.73. Found: C, 43.84; H, 4.43; N, 15.60.

4-Chloromethylpiperidine (**5**, R = H).

A solution of piperidine-4-methanol (**4**, R = H) (3) (10 g., 0.09 mole) in chloroform (50 ml.) was saturated with gaseous hydrogen chloride, cooled in ice, and thionyl chloride (12 g., 0.1 mole) was added dropwise. The mixture was refluxed 2 hours, cooled and extracted with 5% hydrochloric acid. The aqueous extracts were evaporated to dryness and the residue dissolved in ethanol. Ether was added and the solution cooled.

Filtration and recrystallization from chloroform-ether gave 2.0 g. (17%) of the hydrochloride salt, m.p. 128-130°; ir: 2600 cm^{-1}.

Anal. Calcd. for $C_6H_{13}Cl_2N$: C, 42.40; H, 7.65; N, 8.24. Found: C, 42.49; H, 7.66; N, 8.26.

N-Benzyl-4-chloromethylpiperidine (**5**, R = $CH_2C_6H_5$).

A mixture of lithium aluminum hydride (0.27 g., 0.0072 mole) and aluminum chloride (1.3 g., 0.0096 mole) in anhydrous ether (50 ml.) was cooled in an ice/salt bath and the epoxide (**3**, R = $CH_2C_6H_5$) (0.8 g., 0.0039 mole) in anhydrous ether (30 ml.) was added dropwise. The mixture was stirred 30 minutes cold, one hour at room temperature and then the excess reducing agent destroyed with 15% sodium hydroxide. The ether was decanted from the solids, dried and evaporated to give an oil which was distilled to give 0.55 g. (65%) of **4** (R = $CH_2C_6H_5$), b.p. 122-123° (0.3 mm); ir: 3350 cm^{-1}; nmr: 7.2 (s, 5H), 5.3 (s, 1H), 4.9 (s, 1H), 4.7 (s, 1H), 3.9 (s, 2H), 3.4 (s, 2H), 2.5-2.2 (m, 4H), 2.1 (s, 3H); ms: 205 (2), 204 (3), 203 (5), 148 (7), 135 (15), 134 (97), 128 (13), 92 (11), 91 (100), 44 (10). In one run a small amount of what was believed to be *N*-benzyl-4-methyl-4-hydroxypiperidine, b.p. 103° (1.0 mm); nmr: 7.2 (s, 5H), 4.7 (s, 2H), 3.4 (s, 2H), 2.6-2.1 (m, 7H), 1.7 (s, 3H) was obtained.

A solution of the *N*-benzyl-4-hydroxymethylpiperidine (**4**, R = $CH_2C_6H_5$) (2.3 g., 0.011 mole) in benzene (50 ml.) was cooled in an ice bath and treated with freshly distilled thionyl chloride (3 ml.). The mixture was stirred 30 minutes in the cold, at room temperature for 4 hours and the benzene removed *in vacuo*. The tan solid was recrystallized from 2-propanol to give 2.4 g. (86%) of **5** (R = $CH_2C_6H_5$) hydrochloride, m.p. 137-139°; ir: 2450, 670 cm^{-1}; nmr: 7.8 (m, 2H), 7.6 (m, 3H), 5.3 (s, 1H), 5.1 (s, 1H), 4.5 (d, 2H), 4.1 (s, 2H), 3.4 (broad s, 2H), 2.8 (m, 5H).

Anal. Calcd. for $C_{13}H_{19}Cl_2N$: C, 60.04; H, 7.31; N, 5.38. Found: C, 60.02; H, 7.28; N, 5.28.

N-(2-Phenylethyl)-4-chloromethylpiperidine (**5**, R = $CH_2CH_2C_6H_5$).

N-(-phenylethyl)-4-hydroxymethylpiperidine (**4**, R = $CH_2CH_2C_6H_5$) was prepared from **3** (R = $CH_2CH_2C_6H_5$), as described above, in 70% yield, b.p. 133° (0.5 mm); ir: 3350 cm^{-1}; nmr: 7.1 (s, 5H), 5.2 (s, 1H), 4.9 (s, 1H), 4.7 (s, 1H), 3.9 (s, 2H), 2.7-2.1 (m, 11H); ms: 219 (8), 200 (1), 148 (64), 129 (13), 128 (100), 110 (13), 105 (91), 104 (12), 98 (11), 91 (11), 83 (20), 79 (14), 77 (14), 44 (16). Treatment with thionyl chloride, as described above, gave, after recrystallization from benzene, an 85% yield of **5** (R = $CH_2CH_2C_6H_5$) hydrochloride, m.p. 82-85°; ir: 2250, 675 cm^{-1}.

Anal. Calcd. for $C_{14}H_{21}Cl_2N$: C, 61.31; H, 7.72. Found: C, 61.34; H, 7.79.

(*N*-Methyl-4-piperidyl)acetic Acid (**6**).

A solution of ethyl (*N*-methyl-4-piperidyl)acetate (5) (25 g., 0.135 mole) in 1:1 hydrochloric acid (120 ml.) was refluxed overnight. The water was removed *in vacuo*, yielding a yellowish oil which was recrystallized from ethanol-ethyl acetate to give 20 g. (80%) of **6** hydrochloride, m.p. 144-146°; ir: 1725, 2700, 3500 cm^{-1}; nmr: 3.1 (m, 3H), 2.7 (s, 3H), 2.2-1.0 (m, 10H).

Anal. Calcd. for $C_8H_{16}ClNO_2$: C, 49.63; H, 8.27; N, 7.24. Found: C, 49.52; H, 8.54; N, 7.16.

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