Hexahydro-1,2-Oxazepine

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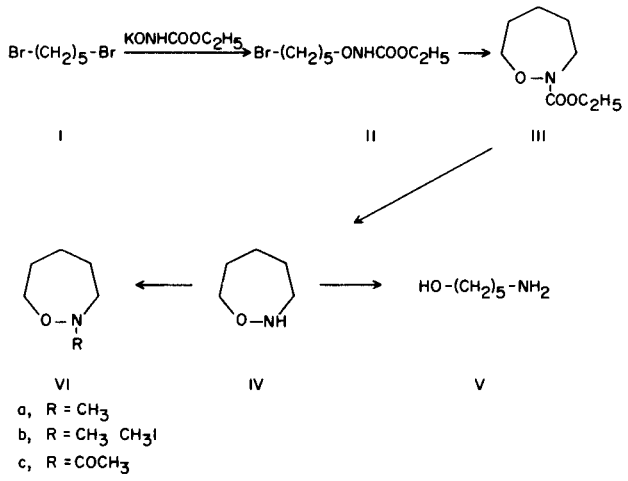
Only a few hexahydro-1,2-oxazepines have been reported in the literature until now. These were obtained by ring expansion of 1-methyl-2-arylpiperidine-1-oxides (1) and 1′-methylanabasine-1′-oxide (2) to give 2,7-disubstituted hexahydro-1,2-oxazepines. We wish now to report the synthesis and characterization of hexahydro-1,2-oxazepine (IV). The method consisted in the cyclization of ethyl (5-bromopentyloxy)carbamate (II) to the hexahydro-2-carbethoxy-1,2-oxazepine (III), followed by the acid hydrolysis and decarboxylation to IV. Compound II was obtained from 1,5-dibromopentane (I) and the potassium salt of *N*-hydroxyurethan. An attempt to synthesize III directly from I and *N*-hydroxyurethan in alcoholic potassium hydroxide according to the procedure of King (3) was unsuccessful. We found that compound II can be converted to III under stringent conditions by warming a dilute suspension of its potassium salt in anhydrous dimethylformamide. If these conditions are not followed, polymerization occurs in preference to cyclization (4). Subsequent hydrolysis of III in 20% hydrochloric acid led to the desired compound IV.

Compound IV, a colorless, volatile base (*p*Ka = 3,6 in MCS/H_2O, 80/20) is soluble in water and in many organic solvents and can be converted to both the hydrochloride and the picrate. The ring structure consistent with NMR and infrared data is also supported by the fact that catalytic hydrogenolysis of IV hydrochloride led to 5-amino-1-pentanol (V). Methylation and acetylation by conventional methods gave the expected *N*-substituted derivatives VIa, b, and c.



EXPERIMENTAL

Melting and boiling points are uncorrected. Distillations were performed *in vacuo* using a bulb tube apparatus (5). Infrared spectra were scanned on a Perkin-Elmer 137 spectrometer; liquid films or Nujol mulls were used. NMR spectra were obtained in deuteriochloroform solution with a Varian A-60 (60 Mc/s) spectrometer. Chemical shifts are reported as τ (ppm) relative to tetramethylsilane. In the NMR spectra the following abbreviations are used: s = singlet; t = triplet; q = quartet; m = multiplet.

Ethyl (5-bromopentyloxy)carbamate (II).

Crude potassium hydroxyurethan (99 g., 0.42 mole, potassium 16.6%) was added in small portions to a stirred solution of 1,5-dibromopentane (I, 96.6 g., 0.42 mole) in 1100 ml. of ethanol. After standing 30 minutes at room temperature, the mixture was refluxed for an hour, then cooled and the precipitate was collected by filtration. The filtrate was concentrated *in vacuo* and ether was added to the residue; the solution was washed with dilute sodium hydroxide, followed by water and dried over sodium sulfate. Following evaporation of the solvent, the residue was distilled, and the fraction boiling at 130-135°/0.5 mm. (37.5 g.; 35%) was collected; IR: 3300 (NH), 1740 (C=O), 1260, 1120 cm^{-1} (C-O ester).

Anal. Calcd. for $C_8H_{16}BrNO_3$: N, 5.51; Br, 31.44. Found: N, 5.32; Br, 30.95.

Hexahydro-2-carbethoxy-1,2-oxazepine (III).

To a stirred solution of II (33 g., 0.13 mole) in 650 ml. of toluene was added an ethanol solution of potassium ethoxide (from 5.1 g. of potassium and 125 ml. of ethanol). After stirring for 30 minutes at room temperature, the mixture was concentrated to 250 ml. *in vacuo* (40°), diluted with 500 ml. of ether and refrigerated for 2 hours. The potassium salt of II was collected on a filter, washed with ether and dried *in vacuo* at room temperature. The salt was suspended in 800 ml. of anhydrous dimethylformamide and the mixture was heated on a hot water bath for 1 hour. The solvent was then evaporated *in vacuo* and the residue was diluted with 500 ml. of anhydrous ether and filtered. The filtrate was evaporated and the residue was distilled, collecting the fraction (9.3 g., 41%) which boiled at 120°/3 mm.; IR; 1700 (C=O), 1200 (C-O ester), 1100, 1070 cm^{-1} (C-O); NMR: 8.70 τ (t, 3H, CH_3), 8.47-7.95 τ (m, 6H, $(CH_2)_3$), 6.55-6.15 τ (m, 2H, CH_2N),

6.15-5.75 τ (m, 2H, CH_2O), 5.78 τ (q, 2H, $COOCH_2$).

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.46; H, 8.73; N, 8.09. Found: C, 55.24; H, 8.78; N, 8.30.

Hexahydro-1,2-oxazepine (IV).

Compound III (3.22 g., 18.6 mmoles) was refluxed in 20% hydrochloric acid (32 ml.) for 3 hours and the solution was concentrated *in vacuo* to dryness. The residue was dissolved in 10 ml. of water, the solution was made basic with 50% sodium hydroxide and the oil which separated was extracted with ether. The organic extract was dried (potassium hydroxide) and evaporated giving an oily residue which was distilled to yield 1.6 g. (85%) of IV, b.p. 65°/30 mm.; IR: 3300 (NH), 1090 cm^{-1} (C-O); NMR: 8.6-7.9 τ (m, 6H, $(CH_2)_3$), 7.1-6.7 τ (m, 2H, CH_2N), 6.3-5.9 τ (m, 2H, CH_2O), 4.2 τ (s broad, 1H, NH).

Anal. Calcd. for $C_5H_{11}NO$: C, 59.38; H, 10.96; N, 13.85. Found: C, 58.98; H, 11.09; N, 13.56.

The Hydrochloride of IV.

This compound which was prepared by the addition of an ether solution of hydrochloric acid to an ether solution of the base, is very hygroscopic and was dried *in vacuo* over potassium hydroxide, m.p. 88-89°; IR: 2800-2000 (NH_2^+), 1580 (NH_2^+), 1070 cm^{-1} (C-O); NMR: 8.45-7.75 τ (m, 6H, $(CH_2)_3$), 6.9-6.59 τ (m, 2H, CH_2N), 6.1-5.6 τ (m, 2H, CH_2O), -2.3 τ (s broad, 2H, NH_2^+).

Anal. Calcd. for $C_5H_{11}NO \cdot HCl$: N, 10.18; Cl, 25.76. Found: N, 10.27; Cl, 25.38.

The Picrate of IV.

The picrate was prepared from a benzene solution of the free base by adding a 1:1 equivalent of picric acid in benzene. The precipitate was collected and crystallized from benzene, m.p. 142-144°.

Anal. Calcd. for $C_{11}H_{14}N_4O_8$: C, 40.01; H, 4.27; N, 16.97. Found: C, 39.74; H, 4.50; N, 17.18.

Hydrogenolysis of IV.

A solution of IV hydrochloride (0.5 g.) in 20 ml. of ethanol was hydrogenated with 10% palladium on charcoal (0.5 g.) at 4 atmospheres and room temperature for 2 hours. The catalyst was then removed by suction and the solvent was evaporated. The viscous residue was dissolved in a few ml. of water and the solution was made alkaline with 30% sodium hydroxide. The mixture was then extracted three times with ether and the extracts, after drying over sodium sulfate, were evaporated. The residue was distilled to give 0.2 g. of 5-amino-1-pentanol (V), b.p. 110°/5 mm. Compound V was characterized by the formation of the chloroplatinate derivative, m.p. 183-184° (from ethanol); lit. m.p. for 5-amino-1-pentanol chloroplatinate, 185-186° (6).

Hexahydro-2-methyl-1,2-oxazepine (VIa).

To a solution of IV (0.4 g., 4 mmoles) in 2 ml. of 99% formic acid was added 0.56 ml. of 38% formaldehyde dropwise at room temperature. The mixture was heated at 60° for 2 hours and then at 80° for 3 hours. After concentrating the reaction mixture *in vacuo*, an excess of 50% sodium hydroxide was added to the residue and the mixture was extracted with ether. The extract was dried (potassium hydroxide), the solvent was removed by evaporation and the residue was distilled to give 0.39 g. (85%) of VIa, b.p. 60°/40 mm.; IR: no NH absorptions were observed in the range 3500-3000 cm^{-1}, 1070 cm^{-1} (C-O); NMR: 8.5-7.9 τ(m, 6H, $(CH_2)_3$), 7.5-7.05 τ (m, 2H, CH_2N), 7.42 τ (s, 3H, CH_3N), 6.3-5.95 τ (m, 2H, CH_2O).

Anal. Calcd. for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.40; H, 11.50; N, 11.98.

Hexahydro-2-methyl-1,2-oxazepine methiodide (VIb).

A solution of IV hydrochloride (0.55 g., 4 mmoles) in 5 ml. of methanol was boiled with methyl iodide (5 ml.) and sodium bicarbonate (0.7 g.) for 3 hours. The mixture was concentrated, the residue was added to methylene chloride and the insoluble sodium salts were filtered off. The solvent was removed by evaporation and the residue was crystallized from ethanol, 0.52 g. (51%), m.p. 125°.

Anal. Calcd. for $C_7H_{16}INO$: C, 32.70; H, 6.27; N, 5.45; I, 49.35. Found: C, 32.56; H, 6.07; N, 5.38; I, 49.00.

Hexahydro-2-acetyl-1,2-oxazepine (VIc).

To a mixture of IV hydrochloride (0.55 g., 4 mmoles) and anhydrous triethylamine (1.1 ml., 8 mmoles) in 7 ml. of methylene chloride was added dropwise a solution of acetyl chloride (0.28 ml., 4 mmoles) in 5 ml. of methylene chloride. After stirring for 1 hour at room temperature and for 2 hours at 40°, the solvent was removed by evaporation and the residue was taken up with ether and filtered. The filtrate was concentrated and the oily residue was distilled giving compound VIc, 0.46 g. (81%), b.p. 100°/3 mm; IR: 1650 (C=O), 1030 cm^{-1} (C-O); NMR: 8.55-8.05 τ (m, 6H, $(CH_2)_3$), 7.96 τ (s, 3H, CH_3CO), 6.6-6.2 τ (m, 2H, CH_2N), 6.2-5.9 τ (m, 2H, CH_2O).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.36; H, 9.33; N, 9.82.

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REFERENCES

(1) L. D. Quin and F. A. Shelburne, *J. Org. Chem.*, 30, 3135 (1965).

(2) W. Carruthers and R. A. W. Johnstone, *J. Chem. Soc.*, 1653 (1965).

(3) H. King, *ibid.*, 432 (1942).

(4) J. D. Roberts and M. C. Caserio "Basic Principles of Organic Chemistry", W. A. Benjamin, Inc. New York, N. Y. 1965, p. 111.

(5) G. Pifferi, A. De Ros and M. Borbonese, *Il Farmaco, Ed. Pr.*, 22, 210 (1967).

(6) S. Keimatsu and R. Takamoto, *J. Pharm. Soc. Japan.*, 544, 73 (1927).

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