The Preparation of 5-(2-Bromoethyl)-2-iminooxazolidines *via* the Von Braun Cyanogen Bromide Reaction

Marvel L. Fielden

Research Laboratories, A. H. Robins Company, Inc., Richmond Virginia 23220

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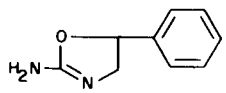
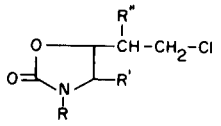
The reaction of certain 1-alkyl-3-pyrrolidinols with cyanogen bromide in ether solution produced 3-alkyl-5-(2-bromoethyl)-2-iminooxazolidines. 5-(2-Bromoethyl)-2-ethyl-2-imino-5-phenyloxazolidine was tested for and found devoid of anorectic activity.

The report of the preparation of the anorectic 2-amino-5-aryl-2-oxazolines (**1**) by the reaction of 1,2-aminoalcohols with cyanogen bromide (1), and our experience with the rearrangement of 3-pyrrolidinols following their reaction with phosgene to give 5-(2-chloroalkyl)-2-oxoazolidinones (2) (**2**) suggested our studying the reaction of 3-pyrrolidinols with cyanogen bromide.



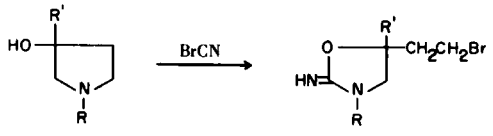
1



2

R = Me, Et, *n*-Bu, $-CH_2C_6H_5$, cyclohexyl
R', R'' = H or CH_3

Based on previous studies with the Von Braun cyanogen bromide reaction (3), it appeared that certain 1-substituted-3-pyrrolidinols would be cleaved by cyanogen bromide in such a manner that they would recyclize to form 5-(2-bromoethyl)-2-iminooxazolidines (**3**).



3

3a R = *i*-pr, R' = H
3b R = Et, R' = C_6H_5

Two compounds of type **3** have been prepared by reacting the appropriate 3-pyrrolidinol with cyanogen bromide in ethyl ether and were isolated as stable hydrobromide salts. Crude yields of these salts were on the order to 50 per cent. No identifiable products were isolated when chloroform or methanol was used as solvent rather than ether.

The nmr spectra of **3a** and **3b** are consistent with the proposed five-membered ring structures. The 3-position hydrogens of compound **3a** show a typical splitting pattern for the AB portion of an ABX system which markedly shifted downfield by protonating the imino group. Similarly, the non-equivalent C-3 protons of **3b** give rise to a typical AB pattern which is shifted downfield, as expected, by protonation of the adjacent nitrogen. In addition, the overall appearance of the nmr spectrum of **3a** is similar to those of the related oxazolidinones (2).

The failure of **3a** to exhibit anorectic activity in rats by the beef broth consumption procedure (4), and our inability to replace the bromine in the molecule with amines (presumably because of intermolecular polymerization) discouraged any further exploration of the reaction in this series.

EXPERIMENTAL (5)

5-(2-Bromoethyl)-2-imino-3-isopropyloxazolidine Hydrobromide (**3a**).

To a cold (dry ice-acetone) solution of 11.7 g. (0.11 mole) of cyanogen bromide in 250 ml. of ethyl ether (anhydrous), was added dropwise with mechanical stirring a solution of 12.9 g. (0.1 mole) 1-isopropyl-3-pyrrolidinol (6) in 50 ml. of ethyl ether (anhydrous). A white solid formed in the reaction mixture. The addition was completed in 0.5 hour, and stirring was continued in the cold (dry ice-acetone) for an additional 0.25 hour. After warming to room temperature, the solid had become an oil or a semisolid. The supernatant was decanted, and the insoluble residue was washed with ethyl ether and the washings combined with the supernatant. The ether solution was carefully treated with hydrogen bromide in ethanol (30%). The initial precipitate was oily but soon solidified, and a white solid continued to precipitate until the ether solution was acidic. The solid was filtered, washed with ethyl ether, and dried *in vacuo*. Yield 16 g. (51%), m.p. 175-179° dec. Recrystallization from 2-propanol-isopropyl ether gave a white crystalline solid, m.p. 179-181° dec.; nmr (deuteriochloroform) of free base, δ 1.17 (d, 6H, *ca.* J = 6.5, $HC(CH_3)_2$), 1.95-2.45 (m, 2H, CH_2CH_2Br),

3.07 (d of d, 1H, *ca.* J = 8.5, J = 7.0, 4), 3.42-3.63 (m, 2H, CH_2CH_2Br), 3.58 (t, 1H, *ca.* J = 8.5, J = 8.5, 4), 3.98 (s, 1H, 2), 4.10 (septet, 1H, *ca.* J = 6.5, $CH(CH_3)_2$), 4.40-4.90 (m, 1H, 5).

Anal. Calcd. for $C_8H_{15}BrN_2O\cdot HBr$: C, 30.40; H, 5.10; N, 8.86; Br, 50.57. Found: C, 30.63; H, 5.09; N, 8.81. Total Br, 50.78; Ionic Br, 25.57.

5-(2-Bromoethyl)-3-ethyl-2-imino-5-phenyloxazolidine Hydrobromide (**3b**).

The above procedure was followed for this analog using 0.05 mole of 1-ethyl-3-phenyl-3-pyrrolidinol (7) and 0.055 mole of cyanogen bromide to give 9 g. (47%) of **3b**, m.p. 138-145° dec. Recrystallization from 2-propanol gave 5.6 g., m.p. 142-145° dec.; nmr (deuteriochloroform): of free base, δ 1.15 (t, 3H, *ca.* J = 7.0, CH_2CH_3), 2.35-3.65 (broad multiplet band, 6H, NCH_2, $-CH_2CH_2$ Br), 3.62 (d, 1H, *ca.* J = 8.0, 4), 3.77 (d, 1H, *ca.* J = 8.0, 4), 4.90 (b, s., 1H, 2), 7.38 (s, 5H, aromatic).

Anal. Calcd. for $C_{13}H_{17}BrN_2O\cdot HBr$: C, 41.29; H, 4.80; N, 7.41; Br, 42.26. Found: C, 41.35; H, 4.98; N, 7.48. Total Br, 42.73; Ionic Br, 21.52.

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(3) For a review see H. A. Hageman, "Organic Reactions," Vol. 7, R. Adams, Ed., John Wiley and Sons, Inc., New York, New York, 1953.

(4) Tested by Dr. R. S. Alphin according to the method of A. P. Roszkowski and N. M. Kelley, *J. Pharmacol. Exptl. Therap.*, **140**, 367 (1963).

(5) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of the compounds were supported by ir, nmr and by mass spectra.

(6) Preparation described by C. D. Lunsford, J. W. Ward, A. J. Pallotta, T. W. Tusing, E. K. Rose and R. S. Murphey, *J. Med. Pharm. Chem.*, 1, 73 (1959).

(7) Preparation described by C. D. Lunsford, U.S. Patent 2,878,264 (1959); *Chem. Abstr.*, 53, 15096d (1959).