2-Carbethoxy-1,2-oxazetidine

G. Pifferi (1) and P. Consonni

Research Laboratories of Lepetit S.p.A., Milan, Italy

Received June 11, 1971

Thus far, little has been reported on 1,2-oxazetidines in the literature (2) and only some polysubstituted compounds have been recently prepared by cycloaddition reactions (3,4,5,6,7). As a continuation of our work on cyclic hydroxylamine derivatives (8,9) and with the aim of synthesizing the parent ring which is of biological interest (10), we describe now the synthesis of 2-carbethoxy-1,2-oxazetidine (IV). In order to prepare the intermediates IIIa,b, the potassium salt of *N*-hydroxyurethan (I) was *O*-alkylated with 2-bromoethanol (a lower yield was reported with 2-chloroethanol (11)) and the alcohol II was then treated with phosphorus tribromide to give *O*-(2-bromoethyl)-*N*-carbethoxyhydroxylamine (IIIa). Treatment of I with 1-bromo-2-chloroethane yielded the chloro-analog IIIb directly. The closure to the four membered ring was effected by heating a dilute suspension of the potassium salt of IIIa (or IIIb) in anhydrous dimethylformamide, according to a procedure already described (8). Infrared analysis of the reaction product revealed a not-related band at 1640 cm^{-1}, while its elemental analysis was in agreement with the formula $C_5H_9NO_3$. The nmr spectrum was consistent with a mixture of about 70% of IV and 30% of an unsaturated compound (12). Owing to thermolability, gas chromatography failed to separate the two substances. However, treatment of the mixture with ethereal hydrogen chloride followed by neutralization with sodium bicarbonate resulted in a substantial recovery of IV, together with small amounts of open chain materials easily removed by distillation.

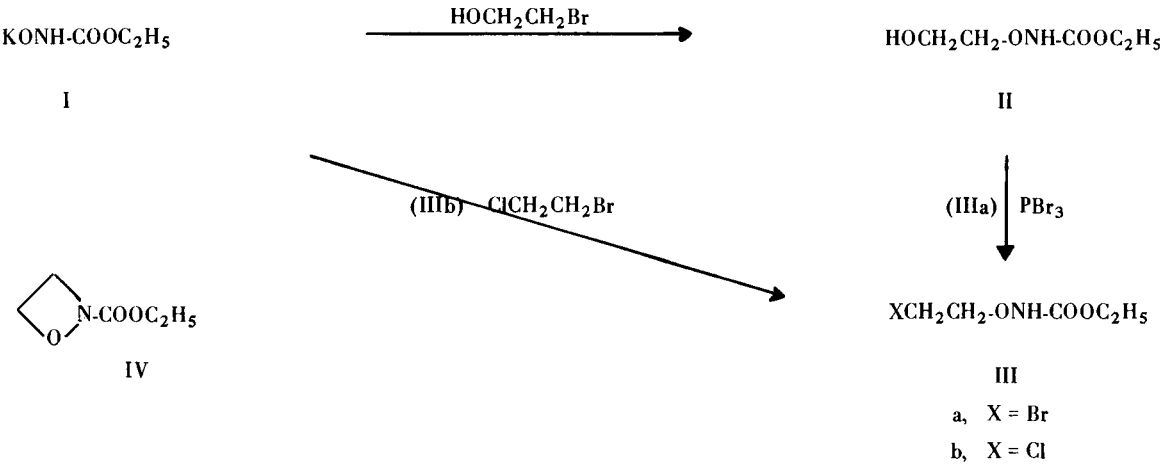
The assigned cyclic structure IV was based on the analytical and spectroscopic data. The mass spectrum at 70 eV showed the molecular peak at m/e 131 and the following fragmentation peaks in accordance with the structure: m/e 103 (M^+-C_2H_4) and 86 (M^+-C_2H_5O) ethyl ester, 72 (M^+-CO_2-CH_3) and 59 (M^+-C_2H_4-CO_2) carbamate (13). The infrared spectrum showed no OH or NH absorptions in the 4000-3000 cm^{-1} region and a medium intensity band at 960 cm^{-1} attributed to the N-O bond (14,15). The nmr spectrum showed, beside the ethyl signals, an A_2B_2 pattern due to the O-CH_2CH_2-N group.

EXPERIMENTAL

All boiling points are uncorrected. Infrared spectra were measured with a Perkin-Elmer 137 spectrometer as liquid films. Nmr spectra were recorded on a Varian A-60 (60 Mc/s) instrument in deuteriochloroform solution. Chemical shifts are reported as τ (ppm) relative to tetramethylsilane as an internal standard.

N-Carbethoxy-*O*-(2-hydroxyethyl)hydroxylamine (II).

Crude potassium hydroxyurethan (I) (210 g., potassium = 18%) was added in small portions to a stirred solution of 2-bromoethanol (113 g., 0.9 mole) in 0.9 l. of ethanol and the mixture was re-



fluxed for four hours. After cooling, the precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether, washed three times with a saturated solution of sodium chloride and dried over sodium sulfate. Evaporation of the solvent left an oil (92 g.) in which tlc indicated the presence of equal amounts of II and *N*-hydroxyurethan which were easily separated by column chromatography on silica gel (0.05-0.2 mm., 1400 g.). Elution with benzene-ethyl ether (8:2) removed *N*-hydroxyurethan; further elution with methanol and evaporation of the solvent gave crude II, which was distilled *in vacuo* using a bulb tube apparatus (16), yield 37.7 g. (28%) of II, b.p. 120°/0.4 mm. (11); ir: 3320 (OH and NH), 1710 (C=O), 1260, 1120 and 1070 cm^{-1} (C-O); nmr: 8.71 (triplet, 3H, $CH_3C(H_2)$), 6.4-5.3 (multiplet, 5H, CH_2-CH_2 and OH), 5.73 (quartet, 2H, CH_2O-CO), 1.23 τ (broad singlet, 1H, NH).

O-(2-Bromoethyl)-*N*-carbethoxyhydroxylamine (IIIa) from II.

A solution of 10 ml. of phosphorus tribromide in 140 ml. of carbon tetrachloride was added dropwise with stirring to a solution of 42.4 g. of II in 560 ml. of the same solvent. The solution was allowed to stir at room temperature for four hours, then anhydrous sodium bicarbonate (70 g.) was added in small portions. The mineral salts were removed by filtration, the filtrate was evaporated and the residue distilled *in vacuo* using a bulb tube apparatus (16) to give 23 g. (38%) of IIIa, b.p. 110°/0.1 mm.; ir: 3250 (NH), 1730 (C=O), 1260 and 1115 cm^{-1} (C-O); nmr: 8.70 (triplet, 3H, CH_3-$C(H_2)$), 6.42 (triplet, 2H, CH_2Br), 5.81 (triplet, 2H, $CH_2ON<$), 5.75 (quartet, 2H, CH_2OCO), 1.78 τ (singlet, 1H, NH).

Anal. Calcd. for $C_5H_{10}BrNO_3$: N, 6.60; Br, 37.68. Found: N, 6.59; Br, 37.48.

O-(2-Chloroethyl)-*N*-carbethoxyhydroxylamine (IIIb) from I.

Crude potassium hydroxyurethan (241 g., potassium = 18%) was added in small portions to a stirred solution of 1-bromo-2-chloroethane (143 g., 1 mole) in 1 l. of ethanol and the mixture was refluxed for three hours. After cooling, the precipitate was removed by filtration, the filtrate was concentrated *in vacuo* and ether was added to the residue. The solution was washed with 500 ml. of a saturated solution of sodium chloride, dried over sodium sulfate and the solvent evaporated. The residual oil was chromatographed through a 1500 g. column of silica gel, with benzene-ethyl ether (95:5) as eluent. The fractions shown to be identical by tlc (R_f = 0.5 on silica gel HF and benzene-ethyl ether 1:1) were combined, concentrated and the residue was distilled to give 59 g. (35%) of IIIb, b.p. 82-83°/0.5 mm. (11); ir: 3290 (NH), 1730 (C=O), 1260 and 1120 cm^{-1} (C-O); nmr: 8.69 (triplet, 3H, $CH_3C(H_2)$), 6.24 (triplet, 2H, CH_2Cl), 5.82 (triplet, 2H, $CH_2ON<$), 5.72 (quartet, 2H, CH_2OCO), 1.90 τ (singlet, 1H, NH).

2-Carbethoxy-1,2-oxazetidine (IV).

A solution of 27 g. (0.13 mole) of IIIa in 310 ml. of anhydrous toluene was added to an ethanolic solution of potassium ethoxide (from 3.91 g. of potassium and 80 ml. of ethanol) and the mixture was evaporated to half volume *in vacuo* at room temperature. Ether (500 ml.) was added and the potassium salt of IIIa was quickly collected on a filter and dried *in vacuo*. The crude salt (20 g.) was suspended in 370 ml. of anhydrous DMF and heated at 90-95° for one hour. The reaction mixture was cooled, ether was added (700 ml.) and the mineral salts were removed by filtration. The ethyl ether was evaporated at normal pressure and dimethyl formamide was then removed by heating under a moderate vacuum. Fractional distillation of the residue gave 8 g. (47%) of crude IV, b.p. 84°/5 mm.

An analytical sample of IV was prepared by adding 7.5 ml. of a 3% ether solution of hydrogen chloride to an ether solution of 2 g. of crude product. The precipitate was filtered off and the filtrate was carefully neutralized with solid sodium bicarbonate. The mineral salts were discarded, the solvent evaporated and the oily residue, containing some IIIb, was twice distilled *in vacuo* in a bulb tube apparatus to give 0.25 g. of IV, b.p. 130°/20 mm; ir: 1710 (C=O), 1300 and 1050 (C-O), 960 cm^{-1} (N-O); nmr: 8.65 (triplet, 3H, CH_3-$C(H_2)$), 5.66 (quartet, 2H, CH_2OCO), 5.5-4.80 τ (multiplets, 4H, CH_2-CH_2).

Anal. Calcd. for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 46.00; H, 6.99; N, 10.45.

Acknowledgment.

The authors are indebted to Dr. L. Zerilli for the mass spectrum, to Dr. B. Gioia for the nmr spectrum, to Mr. G. Tuan for the ir spectra and to Mr. A. Restelli for the microanalyses.

REFERENCES

(1) Present address: Research Laboratories I. S. F. - Italseber, Milan.

(2) A. Weissberger "The Chemistry of Heterocyclic Compounds", Interscience, New York, 1964, Vol. 19, Part 2, p. 981.

(3) V. A. Ginsburg, S. S. Dubov, A. N. Medvedev, L. L. Martynova, B. I. Tetel'baum, M. M. Vasil'eva and A. Ya. Yakubovich, *Dockl. Akad. Nauk. SSSR.*, **152**, 1104 (1963); *Chem. Abstr.*, **60**, 1570 (1964).

(4) R. W. Hoffman, *Angew. Chem.*, **76**, 346 (1964).

(5) R. E. Banks, R. M. Haszeldine, D. R. Taylor, *J. Chem. Soc.*, 5602 (1965).

(6) R. A. Falk and J. D. Readio, *J. Org. Chem.*, **34**, 4088 (1969).

(7) D. H. Coy, R. M. Haszeldine, M. J. Newlands and A. E. Tipping, *Chem. Commun.*, 456 (1970).

(8) G. Pifferi and P. Consonni, *J. Heterocyclic Chem.*, **6**, 111 (1969).

(9) G. Pifferi, P. Consonni and R. Monguzzi, *ibid.*, **8**, 911 (1971).

(10) T. Sheradsky, U. Reichman and M. Frankel, *J. Org. Chem.*, **33**, 3619 (1968).

(11) B. J. R. Nicolaus, G. Pagani and E. Testa, *Helv. Chim. Acta*, **45**, 358 (1962).

(12) The infrared absorption at 1640 cm^{-1} has been attributed to the C=N stretching vibration of an heterocyclic compound presently under investigation.

(13) H. Budzikiewicz, Ci. Djerassi, D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, Inc., San Francisco, p. 501.

(14) L. D. Quin and G. L. Roof, *J. Org. Chem.*, **27**, 4451 (1962).

(15) L. D. Quin and F. A. Shelburne, *ibid.*, **30**, 3135 (1965).

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