thermic reaction occurred. Pyridine (50%) was distilled from the mixture and characterized as the picrate and hydriodide salts. A 2-picoline N-oxide–iodine complex underwent a similar thermal deoxygenation, but at a lower temperature (130°); 2-picoline (50%) was collected and characterized as the picrate. Although there are several reagents suitable for the deoxygenation of pyridine N-oxides,[13] the thermal degradation of iodine complexes may prove useful in selected cases.

(13) G. J. O'Neill, "Deoxygenation of Pyridine N-Oxides," University Microfilms, Ann Arbor, Mich., 1967. See also F. A. Daniher and B. E. Hackley, Jr., *J. Org. Chem.*, **31**, 4267 (1966).

Intramolecular Condensation Reactions of 1,1,3,3-Tetrakis(2-chloroethyl)urea[1]

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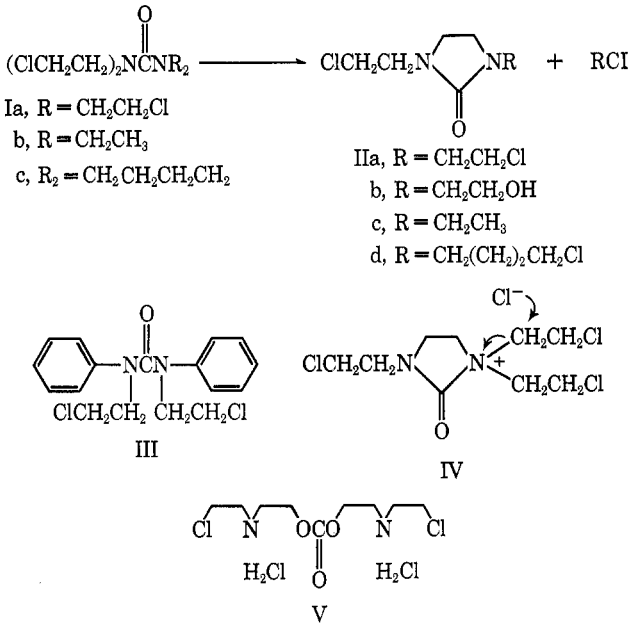
Di- and trisubstituted ureas containing a 2-haloethyl moiety are known to undergo intramolecular alkylation at nitrogen or oxygen, depending on reaction conditions. When the urea is heated in a nonpolar solvent or without solvent, N-alkylation generally occurs and leads to formation of 2-imidazolidinones.[4] By contrast, in aqueous solution, ureas exist in a polarized form,[5] which allows electrophilic attack at oxygen and formation of a 2-amino-2-oxazoline[4b,c,6] or corresponding hydrolysis products.[7] We now report results of a study concerned with subjecting a tetrasubstituted 2-haloethylurea to both intramolecular reaction conditions.

1,1,3,3-Tetrakis(2-chloroethyl)urea (Ia) was prepared in essentially quantitative yield by allowing bis(2-chloroethyl)carbamoyl chloride to react with bis(2-chloroethyl)amine in refluxing benzene. The urea could be purified by column chromatography on Florisil. When an attempt was made to purify Ia by distillation, virtually all of the oily distillate was collected in a single fraction which solidified to colorless prisms, mp 36–37°. Microanalytical data as well as infrared and pmr spectra of the distillate were incompatible with formulation Ia and indicated instead a 1,3-bis(2-chloroethyl)-2-imidazolidinone structure (IIa). This structural assignment was confirmed by the following alternate synthesis.

1,3-Bis(2-hydroxyethyl)-2-imidazolidinone (IIb)[8] was prepared by warming a mixture of 2,2′-(ethylenediimino)diethanol and urea at 190°.[9] Chlorination of IIb utilizing thionyl chloride furnished a crystalline product, mp 35–36°, identical with that isolated from the distillation of urea Ia.



Some aspects of the scope of the cyclization reaction were ascertained by reacting bis(2-chloroethyl)-carbomoyl chloride with diethylamine. The oily product, obtained directly by evaporation of the solvent, was identified as 1-(2-chloroethyl)-3-ethyl-2-imidazolidinone (IIc). Next, bis(2-chloroethyl)carbamoyl chloride was found to react with excess pyrrolidine at room temperature to provide 1-(4-chlorobutyl)-3-(2-chloroethyl)-2-imidazolidinone (IId) in 60% yield.

Finally, N,N′-bis(2-chloroethyl)carbanilide (III), in which the nitrogen atoms are presumably less nucleophilic, was found to be stable at 200°, at which temperature the urea distilled unchanged.

When a Dry Ice trap was placed in the vacuum system during distillation of urea Ia, an 82% yield of 1,2-dichloroethane was collected. Thus imidazolidinone formation may proceed through a quaternary amide which undergoes carbon–nitrogen bond cleavage (IV). There is considerable analogy in the literature for such a proposal.[10] In contrast with the present case, in which intermediate IV arises by alkylation of a secondary amide function, previous examples of N-acylium salts invariably resulted from action of an acylating agent on a tertiary amine.

We next turned attention to transformations of urea Ia in aqueous solution.[11] A mixture of urea Ia and

(1) A preliminary account of this work was presented at the Third Middle Atlantic Regional Meeting of the American Chemical Society, Feb 3, 1968. The present contribution is part XXII of Antineoplastic Agents. For part XXI, see G. R. Pettit and B. J. Danley, *Can. J. Chem.*, **46**, 792 (1968).

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(4) (a) S. Gabriel and R. Stelzner, *Chem. Ber.*, **28**, 2937 (1895); (b) J. P. Picard and A. F. McKay, *Can. J. Chem.*, **31**, 896 (1953); (c) G. R. Pettit, D. S. Blonda, and R. A. Upham, *ibid.*, **43**, 1798 (1965).

(5) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," 3rd ed, Oxford University Press, New York, N. Y., 1966, p 422.

(6) M. E. Kreling and A. F. McKay, *Can. J. Chem.*, **37**, 504 (1959).

(7) E. Khedouri, Y. Kim, and O. M. Friedman, *J. Med. Chem.*, **7**, 653 (1964).

(8) A. B. Steele, U. S. Patent 2,847,418 (Aug 12, 1958).

(9) A. L. Wilson, U. S. Patent 2,517,750 (Aug 8, 1950).

(10) See, *e.g.*, (a) K. C. Murdock, *J. Org. Chem.*, **33**, 1367 (1968); (b) R. F. Meyer and B. L. Cummings, *J. Heterocycl. Chem.*, **1**, 186 (1964); (c) R. C. Clark, A. Mooradian, P. Lucal, and T. J. Slauson, *J. Amer. Chem. Soc.*, **71**, 2821 (1949); (d) J. D. Hobson and J. G. McCluskey, *J. Chem. Soc., C*, 2015 (1967).

(11) Of particular interest here was a recent report concerning changes in biological activity of "aged" bis(2-chloroethyl)carbamates caused by partial conversion into oxazoline derivatives. See R. Wade and F. Bergel, *J. Chem. Soc., C*, 592 (1967).

aqueous ethanol was heated at reflux for 48 hr. Solvent was evaporated and the resulting viscous oil was partially crystallized to provide a hydrochloride salt in 22% yield. Infrared absorption at 1740, 1240, and 990 cm^{-1} indicated carbonate structure V.[12] Further support for carbonate V was provided by hydrolysis (in dilute hydrochloric acid) to 2-[(2-chloroethyl)amino]-ethanol hydrochloride. Formation of carbonate V was a reasonable expectation in view of results of earlier studies in this area.[13]

Experimental Section

Solvent extracts of aqueous solutions were dried over anhydrous magnesium sulfate. Liquid analytical specimens were distilled through a 13-cm Vigreux column. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The infrared spectra of liquids (neat) and solids (KBr) were recorded on a Perkin-Elmer Model 521 spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian HA-100 spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1,1,3,3-Tetrakis(2-chloroethyl)urea (Ia).—Dry benzene solutions (250 and 200 ml, respectively) of bis(2-chloroethyl)-amine (prepared from 17.8 g of the hydrochloride derivative)[13b] and bis(2-chloroethyl)carbamoyl chloride (10.2 g)[14] were combined and warmed at reflux for 14 hr. Precipitated bis(2-chloroethyl)amine hydrochloride, 8.8 g (99%), mp 215–216°, was removed by filtration from the cooled reaction mixture. The filtrate was chromatographed on a Florisil column. The urea was eluted with benzene and, following evaporation *in vacuo* of the solvent, was isolated as a colorless oil, ir (KBr) 1615 cm^{-1} (C=O), nmr δ 3.6 (m).

Anal. Calcd for $C_9H_{16}Cl_4N_2O$: C, 34.84; H, 5.16; Cl, 45.80; N, 9.03. Found: C, 35.07; H, 5.35; Cl, 45.64; N, 9.24.

1,3-Bis(2-chloroethyl)-2-imidazolidinone (IIa). A. From 1,1,3,3-Tetrakis(2-chloroethyl)urea.—Distillation of urea Ia (12 g) *in vacuo* provided, after a few drops of forerun, a single fraction, bp 136–142° (0.6 mm), which solidified on cooling: mp 36–37°; yield 7.8 g (95%); ir (KBr) 1680 cm^{-1} (C=O); nmr δ 3.5–3.9 (m).

Anal. Calcd for $C_7H_{12}Cl_2N_2O$: C, 39.81; H, 5.68; Cl, 33.65; N, 13.26. Found: C, 40.05; H, 5.41; Cl, 33.20; N, 12.92.

B. From 1,3-Bis(2-hydroxyethyl)-2-imidazolidinone (IIb).—An intimate mixture of 2,2′-(ethylenediimino)diethanol (11 g)[15] and urea (4.5 g) was warmed in a test tube immersed in an oil bath at 200° until evolution of ammonia stopped (*ca.* 2 hr). The oil was transferred to a round-botton flask and distilled. After starting diol had been removed at 152–158° (0.2 mm), 1.2 g (9%) of the desired 1,3-bis(2-hydroxyethyl)-2-imidazolidinone (IIb) was collected as a viscous liquid, bp 185–190° (0.2 mm) [lit.[8] bp 187–191° (0.2 mm)]. Thionyl chloride (0.75 ml) dissolved in chloroform (5 ml) was added dropwise to a solution of IIb (0.6 g) in the same solvent (10 ml). The reaction mixture was heated at reflux for 4 hr, cooled, and concentrated *in vacuo*. The resulting discolored oil was dissolved in methyl ether, washed with ice–water, and dried. Imidazolidinone IIa was precipitated by adding petroleum ether and chilling to yield 0.45 g (62%), mp 34–36°, mmp, with product from A above, 35–36°. The infrared spectra of imidazolidinone IIa specimens prepared by methods A and B were identical.

1-(2-Chloroethyl)-3-ethyl-2-imidazolidinone (IIc).—A mixture of bis(2-chloroethyl)carbamoyl chloride (10.2 g) and diethylamine (10.0 g) in dry benzene (150 ml) was heated at reflux for 2 hr. Precipitated diethylamine hydrochloride was removed and the filtrate was washed successively with dilute hydrochloric acid, water, aqueous sodium bicarbonate, and water. Following concentration *in vacuo*, the oily residue was purified by distillation. The major fraction was collected at 94–95° (2 mm), yield 6.4 g (73%). An infrared spectrum of the distilled specimen was identical with that of crude material, ir (KBr) 1680 cm^{-1} (C=O), nmr δ 1.1 (t, 3, CH_2CH_3) and 3.1–3.6 (m, 10).

Anal. Calcd for $C_7H_{13}ClN_2O$: C, 47.59; H, 7.41; Cl, 20.09; N, 1.584. Found: C, 47.69; H, 7.26; Cl, 20.21; N, 16.01.

1-(4-Chlorobutyl)-3-(2-chloroethyl)-2-imidazolidinone (IId).—A solution of bis(2-chloroethyl)carbamoyl chloride (10.2 g) in benzene (50 ml) was added dropwise with stirring and cooling (cold-water bath) to a solution of pyrrolidine (8.5 g) in the same solvent (150 ml). After addition was complete, the reaction mixture was stirred for 30 min. The benzene solution was decanted from a layer of oily pyrrolidine hydrochloride. The salt was extracted with benzene and the combined extract was washed once with water and concentrated *in vacuo* to a mobile oil. The oil was chromatographed on a Florisil column and the product was eluted with benzene to provide 8.2 g (69%) of analytically pure imidazolidinone IId, ir (neat) 1680 cm^{-1} (C=O), nmr δ 1.6–1.9 (m, 4) and 3.1–3.9 (m, 12).

Anal. Calcd for $C_9H_{16}Cl_2N_2O$: C, 45.20; H, 6.70; Cl, 29.70; N, 11.71. Found: C, 45.33; H, 6.90; Cl, 29.75; N, 11.93.

N,N′-Bis(2-chloroethyl)carbanilide (III).—A solution of phosgene (2.0 g) in dry benzene (25 ml) was added dropwise with stirring to a solution of N-(2-chloroethyl)aniline (prepared from 15.4 g of the corresponding hydrochloride derivative)[16] in the same solvent (200 ml). After addition was complete, the mixture was heated at reflux for 5 hr, cooled, and filtered. The precipitated amine hydrochloride weighed 7.2 g (95%), mp 161–163°. Concentrating the filtrate provided a colorless, viscous oil which distilled unchanged at 195–200° (13 mm), ir 1715 cm^{-1} (C=O), nmr δ 7.4 (m, 10), 4.0 (t, 4), and 3.6 (t, 4).

Anal. Calcd for $C_{17}H_{18}Cl_2N_2O$: C, 60.54; H, 5.34; Cl, 21.07; N, 8.30. Found: C, 60.32; H, 5.62; Cl, 21.30; N, 8.13.

Bis{2-[(2-chloroethyl)amino]ethyl}carbonate (V).—Urea Ia (2.0 g) in 50% aqueous ethanol (30 ml) was heated at reflux for 48 hr. The reaction mixture was then concentrated *in vacuo* to a solid residue. Recrystallization from absolute ethanol afforded 0.52 g (22%), mp 200–201°, of carbonate V. Two additional recrystallizations from ethanol provided an analytically pure sample: mp 204–205°; ir 1740 cm^{-1} (C=O); nmr (DMSO-d_6) δ 4.5 (t, 4), 4.0 (t, 4), 3.4 (m, 8), and 2.5 (m, 4).

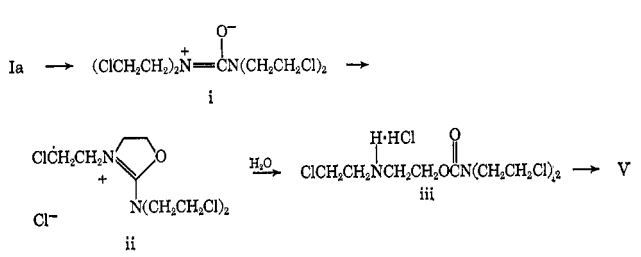
Anal. Calcd for $C_9H_{20}Cl_4N_2O_3$: C, 31.22; H, 5.78; Cl, 41.04; N, 8.09. Found: C, 31.31; H, 5.85; Cl, 41.10; N, 8.13.

Hydrolysis of Bis{2-[(2-chloroethyl)amino]ethyl}carbonate (V).—Carbonate V (0.10 g) was heated at reflux in 10% hydrochloric acid (10 ml) for 24 hr. Following concentration *in vacuo*, an infrared spectrum of the oily hydrochloride was found to be identical with that of an authentic specimen[17] of 2-[(2-chloroethyl)amino]ethanol hydrochloride.

Registry No.—Ia, 22794-66-7; IIa, 3367-18-8; IIc, 22794-68-9; IId, 22794-69-0; III, 22794-70-3; V, 22866-45-1.

(12) K. Nakanishi, "Infrared Absorption Spectra," Holden-Day, Inc., San Francisco, Calif., 1962, p 45.

(13) Carbonate V probably arises from stepwide production (Ia → i → ii) and hydrolysis (iii) of oxazoline derivatives, as presented in Ia → V. The reaction sequence resembles that proposed by Ross to explain an analogous rearrangement of N,N-bis(2-chloroethyl)amides. See (a) W. C. J. Ross and J. C. Wilson, *J. Chem. Soc.*, 3616 (1959); (b) G. R. Pettit, D. S. Blonda, and E. C. Harrington, *Can. J. Chem.*, **41**, 2962 (1963).



(14) A. F. Childs, L. J. Goldsworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Selton, and A. L. L. Thompsett, *J. Chem. Soc.*, 2174 (1948).

(15) I. G. Farbenindustrie, French Patent 801,121 (July 28, 1936); *Chem. Abstr.*, **31**, 111 (1937).

(16) R. S. Tipson, *J. Org. Chem.*, **27**, 1449 (1962).

(17) G. R. Pettit and M. R. Chamberland, *Can. J. Chem.*, **44**, 813 (1966).