ANTINEOPLASTIC AGENTS

XV. INTRAMOLECULAR REACTIONS OF N-PHENYL-N′-BIS(2-CHLOROETHYL)UREA[1]

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ABSTRACT

Reaction between phenyl isocyanate and N-bis(2-chloroethyl)amine in cold diethyl ether solution yields N-phenyl-N′-bis(2-chloroethyl)urea. The urea was found to rearrange in ethanol solution or upon warming to, respectively, 2-(N-phenylimino)-3-(2′-chloroethyl)-oxazolidine hydrochloride and 1-phenyl-2-oxo-3-(2′-chloroethyl)imidazolidine. Infrared spectral studies, augmented by mass and proton magnetic resonance determinations provided compelling support for the structural formulations. The oxazolidine reaction sequence was also examined employing 4-nitrophenyl isocyanate, 1-naphthyl isocyanate, and N-bis(2-bromoethyl)amine.

Rapid intramolecular rearrangement of N-bis(2-chloroethyl)amides to 2-(2′-chloroethylamino)ethyl esters, in the presence of water, has been well established (for example, see ref. 1). When rearrangement of N-bis(2-chloroethyl)amides to the corresponding ester derivatives was found to be rather general in scope (1*a*), we decided to extend the study to N-substituted-N′-bis(2-chloroethyl)ureas (I). Major impetus for this course resided with the enhanced potential of N-bis(2-chloroethyl)ureas to undergo one of a variety of possible intra- or inter-molecular reactions combined with the possibility of finding a useful antineoplastic agent among substances of this type and (or) their transformation products.

When the present investigation was begun in 1959, one N-phenyl- and one benz(a)anthracene derivative of N-bis(2-chloroethyl)urea had already been described (2, 3). Both urea derivatives were prepared, employing the corresponding isocyanate and N-bis(2-chloroethyl)amine, and purified under mild conditions employing aprotic solvents. No rearrangement reactions of the ureas were reported and the conditions recorded would not have favored transformations of this type. Subsequently, Popp and Swarz (4*a*) reported a series of urea and thiourea[3] derivatives of N-bis(2-chloroethyl)amine which they considered to be the first examples of N-bis(2-chloroethyl)ureas. Here, the crude reaction products were not further purified.[4] Recently, Khedouri, Kim, and Friedman (4*c*) described a series of N-bis(2-chloroethyl)ureas prepared (in benzene solution) from isocyanate derivatives of aspartic acid, glutamic acid, phenylalanine, methionine, and leucine ethyl esters. A reaction employing ethyl L-leucine isocyanate and N-bis(2-chloroethyl)amine was reported to yield (12 and 70% respectively) a crystalline racemate and the optically active urea. The remaining ureas were oils characterized following column chromatography on Florisil. In each case, treating the urea with water, either alone or containing acid or base, provided a hydrochloride salt which was assigned a carbamate structure (e.g. III*b*).

Addition of phenyl isocyanate to a dry ethereal solution of N-bis(2-chloroethyl)amine

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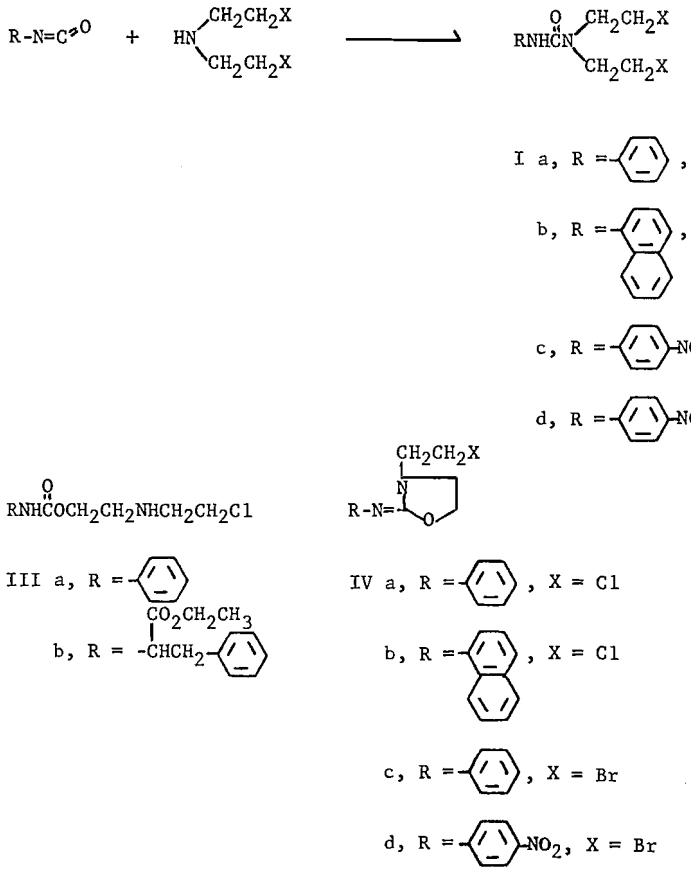
[3]*Interestingly, the principal product from reaction between N-bis(2-chloroethyl)amine and phenyl isothiocyanate in diethyl ether solution has been found (in our laboratory) to be N-bis(2-chloroethyl)amine hydrochloride. The same observation has recently been reported by Berlin and Levi (5). A more detailed study of this unexpected reaction is now in progress.*
[4]*Later (4b), a pure specimen of N-(4-fluorophenyl)-N′-bis(2-chloroethyl)urea was reported.*

was selected for initial study. Conversion to urea I*a* proceeded quite rapidly; the reaction product (I*a*) began to separate from solution within a 3 min period. With several examples described below, the reaction began immediately and was essentially complete within a several minute period. Assignment of an N-phenyl urea structure (I*a*) was considered appropriate on the basis of elemental composition and results of infrared spectral and



proton magnetic resonance (p.m.r.) determinations. The infrared spectrum of urea I*a* exhibited N—H absorption at 3 100 cm^{-1} and carbonyl absorption at 1 670 and 1 635 cm^{-1}. Proton magnetic resonance signals were observed at 3.58 δ (approximately 8 methylene-type protons) and in the region 6.82–7.15 δ (phenyl protons). During purification of urea I*a*, certain conditions such as heating or contact with protic solvents led to new products. Warming (steam bath) the urea caused intramolecular cyclization to imidazolidone II with concomitant loss of hydrogen chloride. In addition to molecular weight determination (by mass spectrometry) and elemental composition, assignment of the imidazolidine structure[5] was suggested by its infrared spectrum (no N—H absorption and a single carbonyl band at 1 685 cm^{-1}) and p.m.r. response. The p.m.r. spectrum of imidazolidine II exhibited a band at 3.53 δ (partially masked triplet) attributable to the 8 aliphatic-type protons and a complex response in the 6.8–7.4 δ region assignable to the aromatic protons.

[5]*An analogous reaction sequence was reported by Gabriel in 1895 (6). Warming N-phenyl-N'-(2-chloroethyl)-urea in ethanol-containing base yielded a product assigned the corresponding imidazolidone structure.*

Attention was next focused on transformation of urea I*a* in a polar medium. As the amide → ester rearrangement noted earlier (1) was found to proceed satisfactorily in ethanol solution, intramolecular rearrangement of urea I*a* was allowed to proceed in this solvent. Here, two prominent reaction pathways would appear likely: rearrangement to carbamate[6] III*a* or oxazolidine IV*a*. Reaction of urea I*a* in ethanol, at room temperature, was found to proceed quite readily and yield (quantitative) a hydrochloride salt. An infrared spectrum of the product revealed a strong ammonium band at 2 750 cm^{-1} and a broad carbonyl-type band at 1 660–1 680 cm^{-1}. Absence of absorption in the vicinity of 1 720 cm^{-1} (8) eliminated the carbamate structure (III) from further consideration. In addition, relatively strong absorption bands at 1 030 and 1 230 cm^{-1} suggested a vinyl ether-type[7] linkage. In keeping with these observations and elemental microanalytical data, the salt was assigned 2-(N-phenylimino)-3-(2′-chloroethyl)oxazolidine (IV*a*) hydrochloride.[8] Although a p.m.r. spectrum of the salt observed in deuterium oxide solution did not provide definitive support for the structural formulation, the complex signals observed at 4.4–4.6 and 4.95–5.15 δ appeared to involve 8 methylene protons and be consistent with oxazolidine IV*a*.

The reaction sequence leading to phenyl oxazolidine IV*a* was also utilized to prepare the 1-naphthyl derivative (IV*b*) and two oxazolidines (IV*c* and *d*) derived from N-bis(2-bromoethyl)ureas. As might be expected, N-phenyl-N′-bis(2-bromoethyl)urea proved too reactive to be conveniently isolated and was instead converted to oxazolidine IV*c*. While reaction of 4-nitrophenyl isocyanate with N-bis(2-chloroethyl)amine led to the most stable urea (I*c*) examined, analogous reaction with N-bis(2-bromoethyl)amine again led to a relatively unstable urea which was more conveniently characterized as oxazolidine IV*d*.

EXPERIMENTAL[9]

N-Phenyl-N′-bis(2-chloroethyl)urea(Ia)

A 20 g (0.112 mole) sample of N-bis(2-chloroethyl)amine hydrochloride (ref. 11, footnote 23) was neutralized with cold (ice bath) 10% sodium hydroxide solution. The amine was extracted with diethyl ether (3 × 100 ml) and the combined extract was washed with water and dried successively over magnesium sulfate and calcium sulfate. The ethereal solution was cooled (ice bath) and a solution of phenyl isocyanate (13.4 g, 0.112 mole) in dry diethyl ether (75 ml) was added. After approximately 3 min, the colorless crystalline product began to separate from solution. Cooling was continued for 30 min before collecting the product; yield 21.2 g (73%), m.p. 72–74°. Four recrystallizations from ethyl acetate – benzene provided an analytical sample as needles melting at 76–78° (lit. (3) m.p. 74–75°); p.m.r. response ($CDCl_3$ solution) 3.58 (8 methylene protons) and 6.82–7.15 (5 phenyl protons) δ; ν_{max}^{KBr} 3 100, 1 670, 1 635, 1 595, 1 440, 760–755, and 695 cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2O$: C, 50.60; H, 5.41; Cl, 27.15; N, 10.72. Found: C, 50.72; H, 5.11; Cl, 27.16; N, 10.92.

1-Phenyl-2-oxo-3-(2′-chloroethyl)imidazolidine(II)

Method A

A 5.0 g specimen of phenyl urea I*a* was heated (steam bath) for approximately 30 h. The remaining pale-yellow residue weighed 4.3 g. Two recrystallizations from ethanol (95%) – methanol yielded a pure specimen

[6]*In this regard, several N-bis(2-chloroethyl)carbamates have been prepared (7), but possible intramolecular rearrangement reactions involving these substances have apparently not been evaluated.*

[7]*For example, see ref. 8, p. 36.*

[8]*Several reactions pertinent to this assignment have been described (6, 9). The products arising from rearrangement of N-phenyl and N-benzyl-N′-(2-chloroethyl)ureas have been assigned oxazoline structures. See also ref. 10.*

[9]*Melting points were observed employing a Kofler melting point apparatus and are corrected. Dr. R. A. Hill of this laboratory provided the infrared and proton magnetic resonance spectra. The p.m.r. spectra were obtained using a Varian Associates Model A-60 NMR Spectrometer. When deuterium oxide was employed as solvent, a sealed capillary tube containing tetramethylsilane (TMS) was added to the sample tube. Otherwise, enough tetramethylsilane was added to the solution (containing approximately 10% by weight of sample) to standardize the instrument. Scanning was performed from low to high field at a rate of 120 c.p.s. per min and measurements are reported in δ (p.p.m.) units with respect to TMS. Elemental compositions were determined in the microanalytical laboratory of Dr. A. Bernhardt, Max-Planck Institute, Müilheim, Germany. Molecular weight determinations (by mass spectrometry) were provided by Dr. R. Ryhage, Karolinska Institutet, Stockholm, Sweden.*

of colorless leaflets melting at 94–94.5°; p.m.r. response ($CDCl_3$ solution) 3.53 (partially masked triplet corresponding to 8 protons) and 6.8–7.4 (5 phenyl protons) δ; ν_{max}^{KBr} 2 900 (weak), 1 685, 1 594, 1 505, 1 490, 1 285, 1 150, and 755 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}ClN_2O$(225): C, 58.78; H, 5.83; Cl, 15.79; N, 12.47. Found: C, 58.77; H, 5.65; Cl, 15.75; N, 12.61; molecular weight, 225.

Method B

When the urea (I*a*, 0.3 g) was heated at 140° for 24 h in a sublimation tube (at 0.1 mm), 0.1 g, m.p. 92–93°, of the imidazolidone (II) was collected. Found: C, 58.66; H, 5.75; Cl, 16.02; N, 12.23.

2-(N-Phenylimino)-3-(2'-chloroethyl)oxazolidine(IVa) Hydrochloride

A solution of N-phenyl urea I*a* (1.0 g) was prepared in absolute ethanol (10 ml) at room temperature. Before concentration (*in vacuo*, at room temperature) to a viscous oil, the clear solution was allowed to stand approximately 15 h. The oil crystallized during an overnight drying (*in vacuo*) period. An infrared spectrum of the crude product indicated conversion to the oxazolidine was essentially complete, as absorption attributable to N—H or carbonyl was not observed. Three recrystallizations from ethanol – ethyl ether yielded an analytical sample as colorless needles; m.p. 96–97°; p.m.r. response (D_2O solution) 4.25–4.6, 4.95–5.15, and 7.60 δ; ν_{max}^{KBr} 3 400 (weak), 2 750, 1 670 (broad), 1 590, 1 510, 1 275, 1 230, 1 080, 1 030, 980, 900, and 755 cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2O$: C, 50.60; H, 5.41; Cl, 27.15; N, 10.72. Found: C, 50.64; H, 5.40; Cl, 26.99; N, 10.70.

N-(1-Naphthyl)-N'-bis(2-chloroethyl)urea(Ib)

Preparation of urea I*b* (14.8 g, 85% yield, m.p. 123–126°) was accomplished using 1-naphthyl isocyanate (9.5 g) and the amine corresponding to 10 g of N-bis(2-chloroethyl)amine hydrochloride in dry diethyl ether (300 ml) as illustrated for synthesis of phenyl urea I*a*. Recrystallization (three times) from acetone afforded an analytical sample as colorless crystals melting at 124–125°; p.m.r. response ($CDCl_3$ solution) 3.64 and 7.02–7.70 (complex) δ; ν_{max}^{KBr} 3 120, 1 670, 1 630, 1 595, 1 515, 1 500, 790, and 770 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O$: C, 57.90; H, 5.18; Cl, 22.78; N, 9.00. Found: C, 57.75; H, 5.31; Cl, 22.81; N, 8.97.

Naphthyl urea I*b* did not exhibit any change in its infrared spectrum after storage in a sealed container for approximately 1 year.

2-[N-(1'-Naphthyl)imino]-3-(2'-chloroethyl)oxazolidine(IVb) Hydrochloride

A solution of naphthyl urea I*b* (0.5 g) in absolute ethanol (10 ml) was allowed to stand at room temperature 5 h. Addition of dry diethyl ether (100 ml) precipitated 0.28 g of colorless crystals. An infrared spectrum of the crude product exhibited no absorption in the N—H stretching region. Three recrystallizations from ethyl alcohol – ethyl ether led to needles melting at 147–151°. Further recrystallization (using the same solvent) did not improve the melting point. The p.m.r. spectrum (D_2O) displayed a series of complex responses at 4.38–4.55, 4.86–5.15, and 7.70–8.23 δ. The infrared spectrum (ν_{max}^{KBr}) of oxazolidine IV*b* exhibited principal absorption bands at 2 700 (broad), 1 660 (broad), 1 270, 1 105, and 1 030 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O$: C, 57.90; H, 5.18; Cl, 22.78; N, 9.00. Found: C, 57.53; H, 5.31; Cl, 22.84; N, 8.86.

N-(4-Nitrophenyl)-N'-bis(2-chloroethyl)urea(Ic)

Employing the amine from 5.45 g of N-bis(2-chloroethyl)amine hydrochloride, and *p*-nitrophenyl isocyanate (5.0 g), preparation of *p*-nitrophenyl urea I*c* was accomplished in 79% yield (7.4 g, m.p. 137–140°). In this case, the colorless urea began to separate from solution within a few seconds after initiation of the reaction. On exposure to the atmosphere, the colorless product became pale yellow. Following three recrystallizations from ethyl acetate – hexane a pure specimen melted at 142–144° (cf. ref. 4*a*); p.m.r. response (CH_3CN solution) 3.65 and a quartet (J = 10 c.p.s.) at 7.38, 7.53, 7.85, and 8.0 (4 phenyl protons) δ; ν_{max}^{KBr} 3 100, 1 642, 1 610, 1 590, 1 545, and 1 500 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}Cl_2N_3O_3$: C, 43.15; H, 4.28; Cl, 23.17; N, 13.73. Found: C, 43.36; H, 4.22; Cl, 23.16; N, 13.63.

The *p*-nitrophenyl urea (I*c*) remained unchanged (as evidenced by its infrared spectrum) during storage in a sealed container for over 2 years.

2-(N-Phenylimino)-3-(2'-bromoethyl)oxazolidine(IVc) Hydrobromide

A dry ethereal solution of N-bis(2-bromoethyl)amine from 15 g of the corresponding hydrobromide derivative (12) was allowed to react at 0–5° with phenyl isocyanate (5.75 g) as described for preparation of urea I*a*. The solid product (12.5 g, 75%) which separated displayed an infrared spectrum consistent with that expected for *N-phenyl-N'-bis(2-bromoethyl)urea*. However, during a 4-day period at room temperature, the urea rearranged to oxazolidine IV*a* hydrobromide. An infrared spectrum (in potassium bromide) of the product indicated conversion to the oxazolidine was complete. Four recrystallizations of the new product from ethanol (95%) – diethyl ether led to a pure sample of colorless needles; m.p. 118–119° and ν_{max}^{KBr} 2 900 (broad), 1 670 (broad), 1 595, 1 512, 1 280, 1 075, 975, 750, and 690 cm^{-1}. The p.m.r. spectrum (in D_2O) exhibited complex responses at 4.0–4.55 and 5.0–5.17 δ, and a sharp band at 7.62 δ.

Anal. Calcd. for $C_{11}H_{14}Br_2N_2O$: C, 37.74; H, 4.03; Br, 45.65; N, 8.01. Found: C, 37.94; H, 3.87; Br, 45.92; N, 7.95.

2-[N-(4'-Nitrophenylimino)]-3-(2'-bromoethyl)oxazolidine(IVd) Hydrobromide

Reaction between the amine from N-bis(2-bromoethyl)amine hydrobromide (12.0 g) and *p*-nitrophenyl isocyanate (6.32 g) in diethyl ether (150 ml) was conducted as noted in the case of urea I*a*. The colorless solid which began to separate immediately (from the reaction mixture) was collected after 20 min. On exposure to the atmosphere urea I*d* (12.6 g, 83%), m.p. 121–124°, became pale yellow. The infrared spectrum (in potassium bromide) was in complete accord with a N-(4-nitrophenyl)-N'-bis(2-bromoethyl)urea (I*d*) structure. The urea was found to rearrange readily in polar solvents (such as acetone) and was, therefore, more conveniently characterized as the oxazolidine derivative (IV*d*). A 1.0 g specimen of urea I*d* was dissolved in 25 ml of warm ethanol. Immediately after dissolution the crystalline oxazolidine began to separate. Following a 12 h period at room temperature, the product (0.72 g) was collected. Three recrystallizations from ethanol – ethyl ether yielded an analytical sample of yellow platelets melting over the range 134–144° with sintering from 120°; ν_{max}^{KBr} 2 890 (broad), 1 685, 1 590, 1 520, 1 340, 1 250, and 1 075 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}Br_2N_3O_3$: C, 33.44; H, 3.32; Br, 40.45; N, 10.63. Found: C, 33.52; H, 3.38; Br, 40.42; N, 10.54.

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REFERENCES

1. (*a*) G. R. PETTIT, D. S. BLONDA, and E. C. HARRINGTON. Can. J. Chem. **41**, 2962 (1963). (*b*) F. BERGEL. J. Pure Appl. Chem. **6**, 351 (1963).
2. O. M. FRIEDMAN and A. M. SELIGMAN. J. Am. Chem. Soc. **70**, 3082 (1948).
3. R. PREUSSMANN. Arzneimittel-Forsch. **8**, 9 (1958); Chem. Abstr. **52**, 9439 (1958).
4. (*a*) F. D. POPP and H. SWARZ. J. Org. Chem. **26**, 4764 (1961). (*b*) F. D. POPP and D. W. ALWANI. Can. J. Chem. **42**, 1506 (1964). (*c*) E. KHEDOURI, Y. KIM, and O. M. FRIEDMAN. J. Med. Chem. **7**, 653 (1964).
5. A. Y. BERLIN and I. S. LEVI. Zh. Obshch. Khim. **33**, 846 (1963).
6. S. GABRIEL and R. STELZNER. Chem. Ber. **28**, 2937 (1895).
7. R. RAILEANU and E. CIORANESCU. Acad. Rep. Populare Romine Studii Cercetari Chim. **11**, 433 (1963); Chem. Abstr. **60**, 15938 (1964). M. H. BENN, A. M. CREIGHTON, L. N. OWEN, and G. R. WHITE. J. Chem. Soc. 2365 (1961). T. F. NOGRADY. J. Org. Chem. **26**, 4177 (1961).
8. K. NAKANISHI. Infrared absorption spectroscopy. Holden-Day, Inc., San Francisco. 1962. p. 47.
9. A. F. MCKAY. J. Org. Chem. **16**, 1395 (1951). A. F. MCKAY, M. A. WEINBERGER, J. P. PICARD, W. G. HATTON, M. BEDARD, and H. E. ROONEY. J. Am. Chem. Soc. **76**, 6371 (1954). R. B. MOFFETT. J. Med. Chem. **7**, 319 (1964). F. F. EBETINO. J. Org. Chem. **29**, 2582 (1964). F. L. SCOTT and D. F. FENTON. Tetrahedron Letters, 1681 (1964).
10. M. R. KAMAL and J. E. WICKLATZ. Can. J. Chem. **42**, 1500 (1964).
11. G. R. PETTIT, M. F. BAUMANN, and K. N. RANGAMMAL. J. Med. Pharm. Chem. **5**, 800 (1962).
12. G. R. PETTIT, M. R. CHAMBERLAND, D. S. BLONDA, and M. A. VICKERS. Can. J. Chem. **42**, 1699 (1964).