

## A New Synthesis of 2-Chloroalkyl Isocyanates

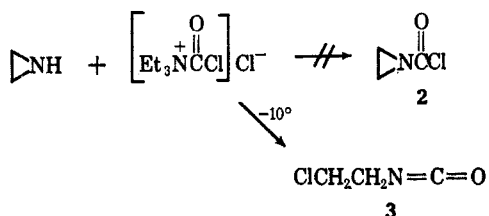
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The reaction of the 1:1 triethylamine-phosgene complex or the 1:1 pyridine-phosgene complex with aziridines gives fair to good yields of 2-chloroalkyl isocyanates. The mechanism and stereochemistry of this ring-opening reaction are discussed.

In an attempt to prepare the unknown compound, 1-(aziridine)carbonyl chloride (2), for use as a synthetic intermediate, an ether solution of aziridine was added with stirring to a slurry of the 1:1 triethylamine-phosgene complex<sup>1</sup> in ether at  $-10^{\circ}$ . Removal of the triethylamine hydrochloride formed in the reaction followed by distillation gave a 53% yield of 2-chloroethyl isocyanate (3) instead of the desired carbonyl chloride.



The known methods<sup>2</sup> for preparing 2-chloroalkyl isocyanates usually involve two or three steps starting from corresponding 2-amino alcohols. The procedures are relatively long, and the reported over-all yields of 2-chloroalkyl isocyanates obtained *via* these methods are usually under 50%. However, Siefken<sup>2c</sup> has reported an 87% yield of 2-chloroethyl isocyanate from ethanolamine using a three-step procedure in which none of the intermediate products were isolated.

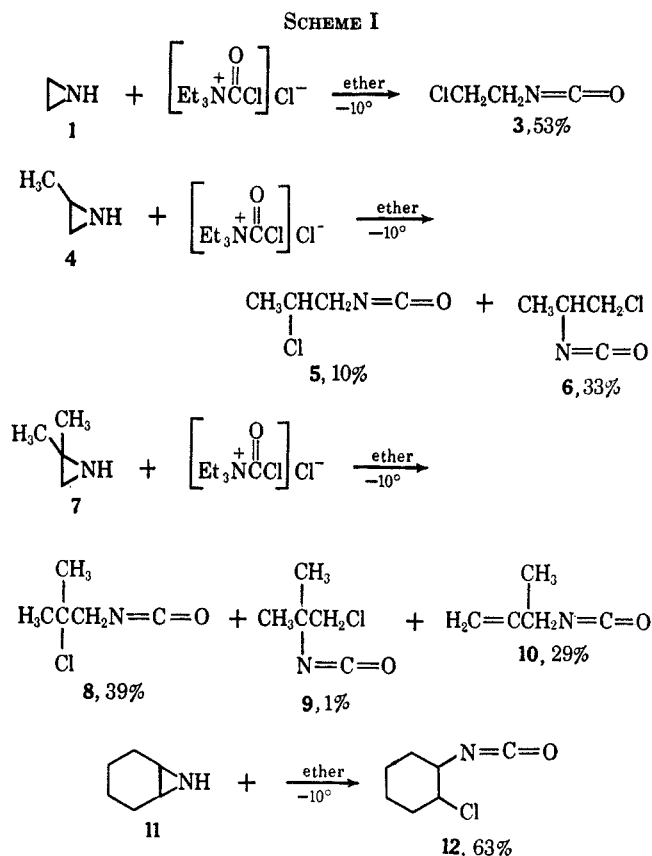
It appeared that the reaction of aziridines having an imino hydrogen with 1:1 tertiary amine-phosgene complexes might provide a new, convenient one-step synthesis of 2-chloroalkyl isocyanates. Therefore, a number of aziridines were subjected to the same conditions to determine the scope of this reaction. The results of these experiments are summarized in Scheme I. All of the aziridines studied gave fair to good yields of 2-chloroalkyl isocyanates. Most of the products were identified by comparison of their infrared and nuclear magnetic resonance (nmr) spectra with authentic samples and by conversion to the corresponding urea derivatives by reaction with aniline. There was no depression of the mixture melting points of these derivatives with authentic samples. The product ratios were determined by nmr spectroscopy.

In contrast to these results, the reaction of aziridines with phosgene in the absence of base yields  $\beta,\beta'$ -dichloroalkylureas.<sup>3</sup> N,N'-Diethyleneureas are formed when 1 equiv of phosgene is added to a mixture of 2 equiv of a tertiary amine and 2 equiv of an aziridine.<sup>4</sup>

(1) Both 1:1 and 2:1 tertiary amine-phosgene complexes have been reported in the literature: (a) J. Goubeau and G. Winkelmann, *Z. Anorg. Allgem. Chem.*, **271**, 235 (1953); (b) C. Scholtissek, *Chem. Ber.*, **89**, 2582 (1956).

(2) (a) H. Wenker, *J. Am. Chem. Soc.*, **58**, 2608 (1936); (b) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. Soc. Chim. France*, 1611 (1960); (c) W. Siefken, *Ann.*, **562**, 74 (1959).

(3) H. Bestian, *Ann.*, **566**, 210 (1950).



The formation of 2-chloroalkyl isocyanates in these experiments is due to the particular reaction conditions employed. The best yields were obtained when a solution of an equimolar amount of an aziridine in ether was added to a stirred slurry of a 1:1 complex of phosgene and a tertiary amine in ether at or below room temperature. The 1:1 complexes should be prepared *in situ* immediately before use by adding a tertiary amine to a slight excess of phosgene in ether, because they slowly decompose to N,N-dialkyl carbamoyl chlorides and alkyl chlorides<sup>5</sup> even at  $-10^{\circ}$ .<sup>1a</sup>

The prior formation of the 1:1 phosgene-tertiary amine complexes is not required inasmuch as 2-chloroalkyl isocyanates were also obtained when mixtures of an aziridine and a tertiary amine in ether were added to rapidly stirred ether solutions of phosgene. The ratios of isomeric 2-chloroalkyl isocyanates produced by this procedure were somewhat different than those obtained by the first method, but the major and minor products remained the same. However, lower yields were usually obtained by this method. A very low

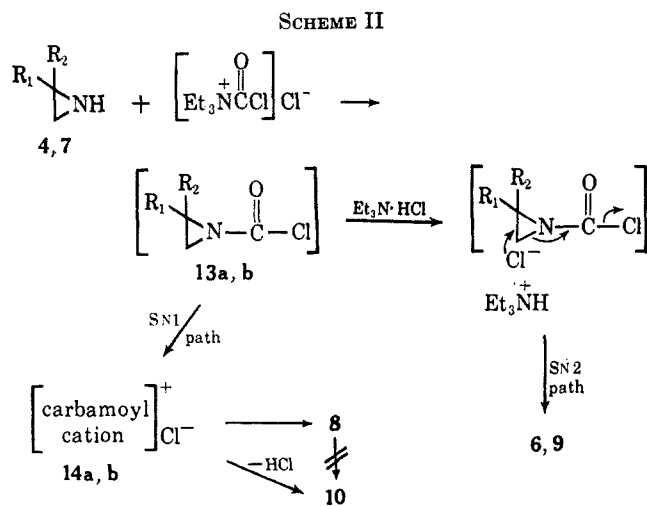
(4) German Patent 863,055 (1953).

(5) The rates of decomposition of the 1:1 complexes of phosgene and aliphatic tertiary amines have not been determined. The 1:1 phosgene-triethylamine complex decomposed to give a 70% yield of N,N-diethylcarbamoyl chloride when stirred in benzene at  $25^{\circ}$  for 24 hr.

yield of 2-chloroethyl isocyanate was also obtained by the direct addition of 0.1 mole of aziridine in ether to 0.14 mole of phosgene in ether in the absence of a tertiary amine.

The mechanism of these ring opening reactions is not known. An attractive explanation involves the formation of transient 1-(aziridine)carbonyl chloride intermediates (13) which subsequently rearrange to 2-chloroalkyl isocyanates. We have no direct evidence for the formation of 1-(aziridine)carbonyl chloride intermediates in these reactions, but other secondary amines give high yields of *N,N*-dialkyl carbonyl chlorides under these same conditions<sup>6</sup> and thiophosgene reportedly reacts with aziridine to give 1-(aziridine)thiocarbonyl chloride.<sup>7</sup> Aziridines and phosgene should react in an analogous fashion to generate 1-(aziridine)carbonyl chlorides. If formed, the carbonyl chlorides must be unstable under these conditions.

The postulated 1-(aziridine)carbonyl chloride intermediates could rearrange to 2-chloroalkyl isocyanates by either *S<sub>N</sub>1* or *S<sub>N</sub>2* pathways or a combination of the two. 2-Methylaziridine (4) must rearrange predominantly *via* a *S<sub>N</sub>2* process, such as that shown in Scheme II, because the major product 1-chloromethyl-ethyl isocyanate (6) results from attachment of the chlorine atom to the least substituted carbon atom.<sup>8</sup> The minor isomer 5 may arise from a similar displacement reaction at the more hindered carbon atom or from a competing *S<sub>N</sub>1* process.<sup>9</sup> The carbonyl chlorides (13a and b) may dissociate to chloride ions and oxoimino carbonium ions (or carbamoyl cations) which then rearrange as shown in Scheme II. The suggested unimolecular dissociation of the carbonyl chlorides 13a and b is not without precedent.<sup>10</sup>



On the other hand, 2,2-dimethylaziridine (7) appears to rearrange almost exclusively by a *S<sub>N</sub>1* mecha-

(6) For example, the reaction of 0.1 mole of piperidine with 0.1 mole of phosgene-triethylamine complex in ether at  $-10^{\circ}$  gave an 81% yield of *N*-pentamethylenecarbonyl chloride, bp  $112^{\circ}$  (12 mm).

(7) (a) W. Reid, H. Hillenbrand, and G. Oertel, *Ann.*, **590**, 127 (1954); (b) D. A. Tomalia, *J. Heterocyclic Chem.*, **3**, 384 (1966).

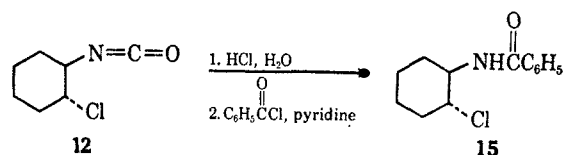
(8) (a) W. J. Gensler, B. A. Brooks, and W. R. Koehler, *J. Org. Chem.*, **30**, 4365 (1965); (b) V. B. Schatz and L. B. Clapp, *J. Am. Chem. Soc.*, **77**, 5113 (1955).

(9) A referee has suggested that 5 and 6 may equilibrate under these conditions. Pure 5 and 6 were separately treated with a mixture of triethylamine, triethylamine hydrochloride, and 1:1 triethylamine-phosgene complex in ether at  $0^{\circ}$  for 2 hr and recovered unchanged.

(10) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **77**, 5995 (1955).

nism. The tertiary carbonium ion (14b) can partition itself between reaction with a chloride ion to give the major product, 2-chloro-2-methyl-*n*-propyl isocyanate (8), and loss of a proton to give methallyl isocyanate (10). The relative amount of 8 was found to increase with temperature. The increased solubility of the tertiary amine hydrochlorides at higher temperatures, and consequent increased chloride ion concentration available for trapping the intermediate carbonium ion (14b) may account for this observation. It was shown that 2-chloro-2-methyl-*n*-propyl isocyanate (8) does not dehydrohalogenate to methallyl isocyanate (10) under these reaction conditions. The 1% yield of 9 is best explained by a competing *S<sub>N</sub>2* reaction.

In order to gain some information about the stereochemistry of the ring opening, the product 12 obtained from 7-azospiro[5.2]octane was studied. Vapor phase chromatographic analysis of the product on three different types of columns showed only one peak which suggests that only one isomer was formed. This assumption is supported by the narrow boiling point range of the product and the sharp melting point of the urea derivative obtained by reaction with aniline. Although the formation of some *cis*-2-chlorocyclohexyl isocyanate has not been conclusively ruled out, the presence of *trans*-2-chlorocyclohexyl isocyanate was demonstrated by converting the product to the known compound, *trans*-2-benzamidocyclohexyl chloride (15).



### Experimental Section

Melting points were taken in capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected. The nmr spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Infrared spectra were recorded by a Perkins-Elmer Model 137 spectrophotometer.

**2-Chloroethyl Isocyanate (3).** **Method A.**—To a dry flamed-out flask was added 75 ml of a diethyl ether solution of phosgene containing 0.85 mequiv of phosgene/ml. A solution of 4.5 g (0.045 mole) of triethylamine in 50 ml of anhydrous ether was added dropwise with stirring and ice-salt-bath cooling to keep the temperature of the mixture between  $-10$  and  $-5^{\circ}$ . To the resulting slurry was added a solution of 1.72 g (0.04 mole) of aziridine in 50 ml of anhydrous ether with rapid stirring and cooling to keep the temperature between  $-10$  and  $-5^{\circ}$ . Stirring was continued for 0.5 hr after completion of the addition, and the mixture was filtered. The solvent was removed by distillation and the residue was distilled at reduced pressure to give 2.25 g (53% yield) of 2-chloroethyl isocyanate, bp  $41^{\circ}$  (16 mm).

The infrared spectrum showed a band at  $4.4 \mu$  and was identical with a spectrum of an authentic sample prepared by the procedure of Wenker.<sup>2a</sup> Reaction with aniline in ether gave  $\alpha$ -phenyl- $\beta$ -( $\beta$ -chloroethyl)urea, mp  $124^{\circ}$  (lit.<sup>2a</sup> mp  $124^{\circ}$ ). There was no depression of a mixture melting point with an authentic sample.

**Method B.**—A solution of 4.3 g (0.1 mole) of aziridine and 8.4 g of pyridine in 100 ml of anhydrous ether was added dropwise, with stirring and ice-bath cooling to keep the temperature below  $10^{\circ}$ , to a mixture of 9.0 ml of phosgene and 100 ml of anhydrous ether. After completion of the addition, stirring was continued for 0.5 hr and the mixture was filtered. The solvent and then the residue were distilled to give 4.0 g (37.7% yield) of 2-chloroethyl isocyanate, bp  $42^{\circ}$  (16 mm).

***trans*-2-Chlorocyclohexyl Isocyanate (12).**—An ether-phosgene solution (100 ml, 0.95 mequiv/ml) was cooled to  $-10^{\circ}$  and a

solution of 5.4 g (0.054 mole) of triethylamine in 50 ml of anhydrous ether was added dropwise with stirring and cooling to keep the temperature between  $-10$  and  $-5^{\circ}$ . To the resulting slurry was added dropwise with stirring 4.8 g (0.05 mole) of 7-azaspiro[5.2]octane<sup>11</sup> in 50 ml of anhydrous ether. Stirring was continued at  $-10^{\circ}$  for 0.5 hr after the addition was completed. The solution was filtered and distilled to give 5.0 g (63% yield) of *trans*-2-chlorocyclohexyl isocyanate, bp  $107^{\circ}$  (20 mm). Vapor phase chromatographic analysis of this product on three different types of columns showed only one peak. The addition of 0.5 g of aniline to a solution of 0.8 g (0.005 mole) of this distillate in 1:1 chloroform-hexane gave white crystals which were washed with hexane and dried to give 1.15 g of crystals, mp  $154$ – $155^{\circ}$ . Crystallization from ethanol did not raise the melting point of this product, N-phenyl-N'-*trans*-2-chlorocyclohexylurea.

*Anal.* Calcd for  $C_{13}H_{17}ClNO_2$ : C, 61.8; H, 6.7; Cl, 14.0; N, 11.1. Found: C, 62.1; H, 6.9; Cl, 13.8; N, 11.0.

The structure of 12 was proven by conversion to *trans*-2-benzamidocyclohexyl chloride<sup>12</sup> as follows. A solution of 0.8 g (0.005 mole) of 2-chlorocyclohexyl isocyanate (12) in 2 ml of dioxane was added dropwise to a mixture of 2 ml of concentrated HCl, 5 ml of water, and 5 ml of dioxane. After stirring for 1 hr at  $25^{\circ}$ , 4 g of pyridine, 15 ml of water, and 0.84 g (0.006 mole) of benzoyl chloride were added. After 1 hr the solution was diluted with 25 ml of  $H_2O$  and the solid was collected and dried, mp  $162$ – $165^{\circ}$ . Crystallization from benzene gave 0.4 g of *trans*-2-benzamidocyclohexyl chloride, mp  $165.5$ – $166.5^{\circ}$  (lit.<sup>12</sup> mp  $164.5$ – $165.5^{\circ}$ ).

**Reaction of 2-Methylaziridine with Phosgene.**—2-Methylaziridine (2.28 g, 0.04 mole) was treated with the 1:1 phosgene-triethylamine complex according to method A to give 2.2 g (43% yield) of a mixture of the isomeric isocyanates 5 and 6, bp  $49$ – $51^{\circ}$  (11 mm), the infrared spectrum of which showed a band at  $4.4 \mu$ . The nmr spectrum of the mixture in  $CCl_4$  showed doublets at  $\tau$  8.64 and 8.47 ( $J = 6.3$  cps) in a ratio of 78:22, respectively, and a group of peaks in the  $\tau$  5.6–6.5 region. 1-Chloromethylethyl isocyanate (6) and 2-chloro-*n*-propyl isocyanate (5) were independently synthesized<sup>2b</sup> and their nmr spectra found to be identical with those of the major and minor products, respectively.

The reaction of 2-methylaziridine (4) with phosgene according to method B (using triethylamine as the base) gave a 25.2% yield of isomeric products 6 and 5. Nmr analysis of the mixture showed the presence of 75% of 6 and 25% of 5.

**Reaction of 2,2-Dimethylaziridine with Phosgene.**—Method A was used starting with 5.68 g (0.08 mole) of 2,2-dimethylaziri-

dine<sup>13</sup> and 8.33 g (0.0825 mole) of triethylamine. After removal of the solvent, a portion of the crude material was analyzed by nmr in  $CCl_4$  to determine the product ratios, and the material was distilled to give 2.2 g of material, bp  $38$ – $40^{\circ}$  (40 mm), 1.4 g, bp  $40$ – $63^{\circ}$  (40 mm) and 2.8 g of material, bp  $63$ – $67^{\circ}$  (40 mm). The nmr spectrum of the low-boiling fraction in  $CCl_4$  showed singlets at  $\tau$  8.24, 6.20 and a complex peak at 5.04 in the relative ratio of 3:2:2. Reaction of the low boiling fraction with aniline gave crystals, mp  $126$ – $127^{\circ}$ , from 2:1 hexane-ethanol. The infrared spectrum of these crystals was identical with that of N-methallyl-N'-phenylurea prepared from methallyl isocyanate and aniline. There was no depression of a mixture melting point.

*Anal.* Calcd for  $C_{11}H_{14}N_2O$ : C, 69.5; H, 7.4; N, 14.7. Found: C, 69.6; H, 7.4; N, 14.8.

The nmr spectrum of the high-boiling fraction in  $CCl_4$  showed singlets at  $\tau$  8.4 and 6.55 in the ratio of 3:1 and a trace of the other isomer having singlets at  $\tau$  8.58 and 6.47 in the ratio of 3:1. The peaks of the minor isomer correspond to those of 1-methyl-1-chloromethyl ethyl isocyanate (9) which was prepared from 2-amino-2-methylpropanol by the method of Wenker,<sup>2a</sup> bp  $67^{\circ}$  (40 mm). This isocyanate (9) reacted with aniline to give a urea derivative, mp  $110^{\circ}$ . The major product must be the other isomer 2-chloro-2-methyl-*n*-propyl isocyanate (8). This was confirmed by conversion to N-phenyl-N'-(2-chloro-2-methyl-*n*-propyl)urea as follows. Addition of 0.19 g of aniline to 0.26 g of the high-boiling fraction in 4 ml of 50:50 hexane-chloroform gave crystals, mp  $130$ – $134^{\circ}$ . Two crystallizations from benzene raised the melting point to  $133$ – $134^{\circ}$ .

*Anal.* Calcd for  $C_{11}H_{16}ClN_2O$ : C, 58.2; H, 6.6; Cl, 15.6; N, 12.4. Found: C, 58.7; H, 6.6; Cl, 15.2; N, 12.2.

The per cent yield of the three products based on nmr analysis of the crude material and the total weight of isolated products is 29.4% 10, 38.4% 8, and 1% 9. Substitution of pyridine for the triethylamine gave similar results. However, when the reaction was run at  $20$ – $25^{\circ}$  using pyridine as the base, the ratios of the products changed to 26 mole % 10, 72 mole % 8, and 2 mole % 9. The total yield of isocyanates obtained was 6.7 g.

**Registry No.**—3, 1943-83-5; 5, 10146-78-8; 6, 10146-79-9; 8, 10146-80-2; 9, 10146-81-3; urea derivative of 9, 10146-82-4; 10, 10182-00-0; 12, 10146-83-5; N-phenyl-N'-*trans*-2-chlorocyclohexylurea, 10146-84-6; N-methallyl-N'-phenylurea, 10182-01-1; N-phenyl-N'-(2-chloro-2-methyl-*n*-propyl)urea, 10146-85-7.

(11) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1040 (1964).

(12) (a) W. S. Johnson and E. N. Schubert, *J. Am. Chem. Soc.*, **72**, 2187 (1950); (b) O. E. Paris and P. E. Fanta, *ibid.*, **74**, 3010 (1952).

(13) This compound was prepared by the method of K. N. Campbell, A. H. Summers, and B. K. Campbell, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 148.