Chemistry of Isocyanic Acid. I. Reactions of Isocyanic Acid with Carbonyl Compounds

F. W. Hoover, H. B. Stevenson, and H. S. Rothrock

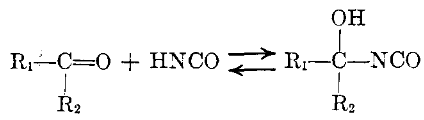
Contribution No. 745 from the Central Research Department, Experimental Station,
E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

Received January 7, 1963

A number of α-hydroxy isocyanates, a new class of compounds, have been synthesized from isocyanic acid and carbonyl compounds such as formaldehyde, chloral, *s*-dichlorotetrafluoroacetone, trifluoroacetaldehyde, and perfluorocyclobutanone. These novel isocyanates undergo most of the normal isocyanate reactions. They can be converted readily to 1,3,5-oxadiazine-2,4-diones and to α-chloro isocyanates, an unusually reactive class of compounds. α-Chloromethyl isocyanate, obtained from hydroxymethyl isocyanate and thionyl chloride, was found to react with styrene to give cinnamyl isocyanate and 3-chloro-3-phenylpropyl isocyanate, with *m*-xylene to give 2,4-dimethylbenzyl isocyanate, and with phenols to give 1,3-oxazinones.

Previously reported chemistry of isocyanic acid, a long known compound,[1] has involved reactions with amines to form ureas[2] and with alcohols to form urethanes[3] and allophanates.[4] Reactions of isocyanic acid with chloral have given cyclic products.[5] The addition of isocyanic acid to Schiff's bases[6] and azines[7] has given heterocyclic structures.

Our studies have led to new chemistry of isocyanic acid which will be reported in this and subsequent papers. In this paper, the addition of isocyanic acid to certain carbonyl compounds to give the hitherto unknown α-hydroxy isocyanates (I) is discussed.



$$R_1-\underset{R_2}{\underset{|}{C}}=O + HNCO \rightleftharpoons R_1-\overset{OH}{\overset{|}{\underset{R_2}{\underset{|}{C}}}}-NCO$$

I

Previous attempts[8] to prepare compounds of this type by the Lossen rearrangement have been unsuccessful.

The formation of hydroxy isocyanates has been found to occur with such carbonyl compounds as formaldehyde, *s*-dichlorotetrafluoroacetone, trifluoroacetaldehyde, 5*H*-perfluoropentanal, perfluorocyclobutanone, chloral, dichloroacetaldehyde, and perfluoroacetone. It appears that most carbonyl compounds capable of forming hydrates undergo this reaction. In general, the carbonyl compounds have electronegative substituents in the α position.

Because of the high reactivity of hydroxy isocyanates, it is usually best to prepare them at temperatures of 0° or below. The extent of the formation of the hydroxy isocyanate on mixing a carbonyl compound with isocyanic acid can be determined readily by near-infrared spectrophotometry. As the reaction proceeds, the absorption band at 1.47 μ (NH of HNCO) decreases, and a band at 1.42–1.44 μ appears as a result of the formation of hydroxyl groups.

Hydroxymethyl Isocyanate (II).—We have found that the addition of monomeric formaldehyde to ethereal solutions of isocyanic acid at about −70° gives hydroxymethyl isocyanate in essentially quantitative yield. Upon removal of the solvent at low temperatures under reduced pressure, hydroxymethyl isocyanate is isolated and is found to melt at about −50°. Infrared examination of this product at −50° showed strong absorption at 2.9 μ (OH) and 4.43 μ (NCO), but none at 5.4 μ to 5.5 μ (CO). This spectrum is consistent with the $HOCH_2NCO$ structure but not with an alternative cyclic structure.

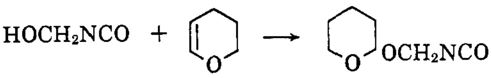
$$CH_2O + HNCO \longrightarrow HOCH_2NCO$$

II

Hydroxymethyl isocyanate polymerizes with explosive violence above 0°. Solutions in diethyl ether are somewhat more stable and remain clear for as long as an hour at room temperature. The formation of a slight turbidity signals an incipient rapid polymerization. No additives were found which would increase the stability of the ether solutions.

Spontaneous polymerization of hydroxymethyl isocyanate gave a friable solid insoluble in water. The elemental analyses of this solid indicated that carbon dioxide was lost during polymerization. The polymers formed with either a basic or acidic catalyst at low temperatures showed a loss of formaldehyde during polymerization. Most of the polymers obtained were of low molecular weight and in no case could be represented by the formula $(HOCH_2NCO)_x$.

Hydroxymethyl isocyanate forms adducts with α,β-unsaturated ethers, such as dihydropyran and butyl vinyl ether, as illustrated by the following reaction.



This reaction proceeds readily at room temperature with an acidic catalyst such as *p*-toluenesulfonic acid. These adducts are relatively stable, distillable liquids that can be converted to the expected isocyanate derivatives (see Table I).

In general, amines promote the rapid polymerization of hydroxymethyl isocyanate. To obtain good yields of hydroxymethylureas it is necessary to add the hydroxymethyl isocyanate to a solution of amine at low temperature. For example, when an ethereal solution of hydroxymethyl isocyanate was added slowly to an ethereal solution of aniline at −30° N-hydroxymethyl-N′-phenylurea was obtained in high yield. This compound has also been obtained from phenylurea and formaldehyde.[9] On the other hand, when aniline was

---

[1] F. Wöhler, *Ann. Chim. et Phys., Ser. 2*, **27**, 196 (1824).

[2] M. Bogert and G. Scatchard, *J. Am. Chem. Soc.*, **38**, 1606 (1916).

[3] J. Johnson and L. Ferstandig, *Science*, **110**, 441 (1949).

[4] M. A. Spielman, J. D. Barnes, and W. J. Close, *J. Am. Chem. Soc.*, **72**, 2520 (1950); H. W. Blohm and E. I. Becker, *ibid.*, **72**, 5342 (1950).

[5] C. Bischoff, *Ber.*, **5**, 86 (1872).

[6] W. J. Hale and N. A. Lange, *J. Am. Chem. Soc.*, **41**, 379 (1919).

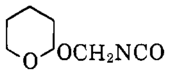
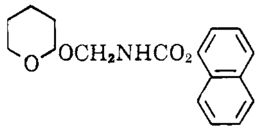
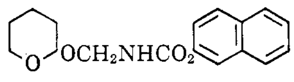
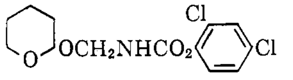
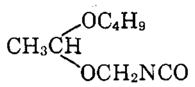
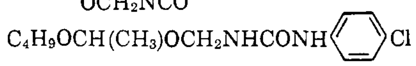
[7] J. R. Bailey and N. H. Moore, *ibid.*, **39**, 279 (1917).

[8] L. W. Jones and D. H. Powers, *ibid.*, **46**, 2518 (1924).

[9] G. Zigeuner, W. Knierzinger, and K. Voglar, *Monatsh.*, **82**, 847 (1951).

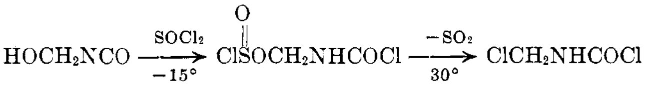
TABLE I

DERIVATIVES OF HYDROXYMETHYL ISOCYANATE

Structure	M.p., °C.	B.p., °C. (mm.) ($n^{25}D$)	Anal. (calcd.)/found C	H	N
		87–88 (15) (1.4499)	(53.48) 53.99	(7.05) 7.12	(8.91) 8.91
	143–147		(54.83) 54.56	(6.02) 6.12	(9.84) 10.09
	81–82		(67.76) 67.38	(6.36) 6.55	(4.65) 4.86
	92–94		(67.76) 67.90	(6.36) 6.39	(4.65) 4.80
	98–100		(48.76) 48.07	(4.72) 4.93	(4.38) 4.44
 $CH_3CH(OC_4H_9)OCH_2NCO$		85–87 (16) (1.4192)	(55.47) 56.10	(8.73) 9.00	(8.95) 8.20
	88–91		(55.90) 55.64	(7.04) 6.86	(9.31) 9.33

added to a solution of hydroxymethyl isocyanate a complicated mixture of products was obtained.

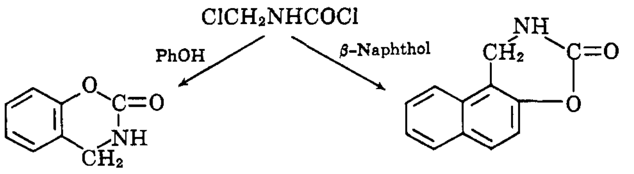
A new synthesis of chloromethyl isocyanate has been uncovered in the reaction of hydroxymethyl isocyanate with thionyl chloride. This reaction takes place in the cold to give first the chlorosulfite which loses sulfur dioxide on warming to room temperature.



$$HOCH_2NCO \xrightarrow[-15^\circ]{SOCl_2} ClS(=O)OCH_2NHCOCl \xrightarrow[30^\circ]{-SO_2} ClCH_2NHCOCl$$

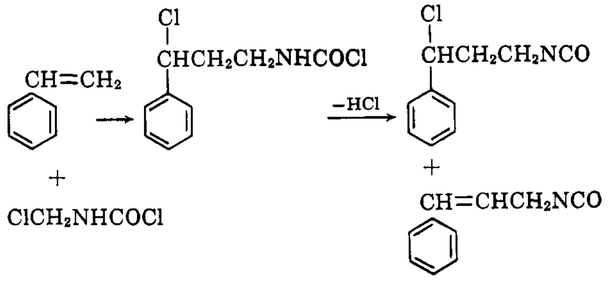
The resulting chloromethylcarbamoyl chloride, m.p. 9–10°, was converted to the known chloromethyl isocyanate[10] by treatment with α-pinene, *d,l*-limonene, acrylonitrile or pyridine. Both chloromethylcarbamoyl chloride and chloromethyl isocyanate are very potent respiratory irritants.

Chloromethylcarbamoyl chloride reacted with phenol and naphthol to give cyclic structures.

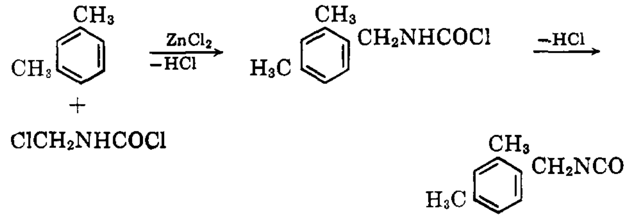


Although the product from naphthol appears to be new, the derivative[11] of phenol has been prepared by another route.

Chloromethylcarbamoyl chloride added readily to styrene in the presence of small amounts of mercuric chloride to give an adduct that lost hydrogen chloride on heating to form cinnamyl isocyanate.



Under mild conditions with zinc chloride as a catalyst, chloromethylcarbamoyl chloride reacted with *m*-xylene to give 2,4-dimethylbenzylcarbamoyl chloride, which was converted to the corresponding isocyanate.



1-Hydroxy-2,2,2-trichloroethyl Isocyanate (III).—The reaction of chloral and isocyanic acid proceeds slowly at 0° but is complete after about seven hours.

$$CCl_3CHO + HNCO \longrightarrow \underset{III}{CCl_3CH(OH)NCO}$$

1-Hydroxy-2,2,2-trichloroethyl isocyanate (III) is a low melting solid (m.p. 25°), recrystallizable from carbon tetrachloride. Above its melting point it is slowly converted to solid products of indefinite composition, which are soluble in acetone but insoluble in carbon tetrachloride.

A new cyclic structure, a 1,3,5-oxadiazine-2,4-dione, was obtained on treatment of 1-hydroxy-2,2,2-trichloroethyl isocyanate with water. This compound was also made from chloral hydrate and isocyanic acid.

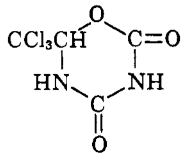
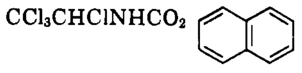
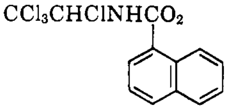
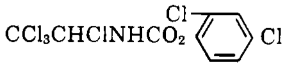
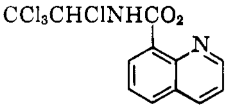
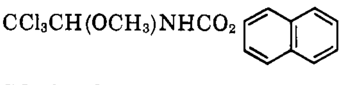
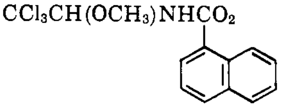
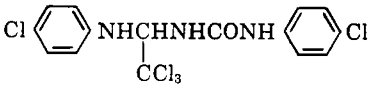
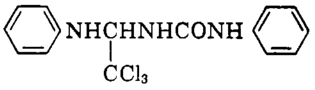
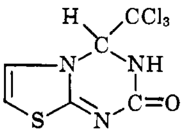
---

[10] G. Schroeter, *Ber.*, **42**, 3356 (1909).

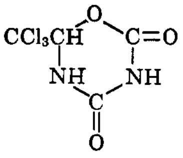
[11] H. Lindemann and W. Schultheis, *Ann.*, **464**, 248 (1928).

TABLE II

DERIVATIVES OF CCl$_3$CH(OH)NCO

Structure	M.p., °C.	Anal. (calcd.)/found C	 H	 N	 Cl
CCl$_3$CH(OH)NHCONHC$_6$H$_5$	145			(9.88) 9.97	(37.55) 37.52
CCl$_3$CH(OH)NHCONHC$_6$H$_4$Cl-*p*	183–185			(8.80) 8.79	(44.51) 43.91
(CCl$_3$CH(OH)NH)$_2$CO	173–182[a]	(16.92) 16.35	(1.70) 1.81	(7.90) 8.01	(59.95) 58.75
	190–200[b]	(20.55) 20.68	(1.30) 1.76	(12.00) 12.03	(45.60) 45.50
CCl$_3$CHClNCO	58 (1)[c]			(6.71) 6.85	(67.90) 67.51
CCl$_3$CHClNHCO$_2$CH$_3$	93–94	(19.94) 20.03	(2.09) 2.24	(5.81) 5.87	(58.87) 59.10
CCl$_3$CH(OCH$_3$)NHCO$_2$CH$_3$	64–65	(25.39) 26.08	(3.41) 3.47	(5.92) 5.67	(44.98) 44.73
	158–165	(44.22) 43.91	(2.57) 2.34	(3.97) 3.88	(40.19) 39.95
	175–188	(44.22) 43.61	(2.57) 2.59	(3.97) 4.32	(40.19) 39.99
	135–139	(29.07) 28.52	(1.36) 1.10	(3.77) 3.81	(57.21) 56.90
	121–125			(7.91) 7.87	
	108–110			(4.02) 3.60	(30.60) 30.08
	149–151	(48.30) 48.13	(3.45) 3.42	(4.02) 4.26	
	162–164	(42.13) 41.90	(2.81) 2.90	(9.83) 9.62	
	153–156	(50.23) 49.83	(3.93) 3.95	(11.72) 11.81	
	195 dec.	(26.44) 26.75	(1.48) 1.74	(15.42) 15.25	

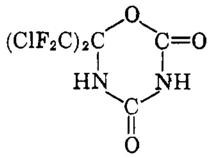
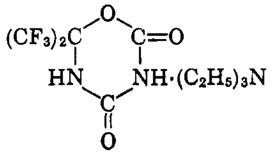
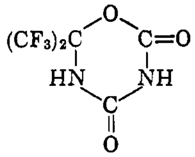
[a] Lit.[15] —190° dec. [b] Depended on the rate of heating. [c] B.p., °C. (mm.).



1-Hydroxy-2,2,2-trichloroethyl isocyanate formed the expected derivatives with aniline and *p*-chloroaniline. With thionyl chloride it gave 1,2,2,2-tetrachloroethylcarbamoyl chloride and 1,2,2,2-tetrachloroethyl isocyanate. Both of these compounds are potent respiratory irritants.

The α-chlorine in 1,2,2,2-tetrachloroethyl isocyanate is highly reactive. Thus, when this compound was treated with alcohols or amines, the first product was the expected derivative of the isocyanate, but when

TABLE III
DERIVATIVES OF VARIOUS HYDROXY ISOCYANATES

Structure	M.p., °C.	Anal. (calcd.)/found			
		C	H	N	F
	98–99	(21.07) 21.36	(0.71) 0.99	(9.83) 9.84	(26.60) 26.35
$(ClF_2C)_2C(OH)NHCO_2C_2H_5$	44–46	(25.02) 25.09	(2.45) 2.56	(4.90) 5.20	(26.40) 26.26
$(ClF_2C)_2C(OH)NHCONHC_6H_5$[a]	75–77			(8.40) 8.84	(22.70) 22.09
$CF_3CH(OH)NHCONHC_6H_5$[a]	145–147			(11.97) 12.20	(24.40) 23.88
$HC_4F_8CH(OH)NHCONHC_6H_5$	125–126			(7.65) 7.62	(41.51) 41.22
	120–121			(11.11) 11.16	(45.22) 44.90
	110–111	(37.40) 37.65	(4.85) 5.09	(11.90) 12.12	(32.27) 31.65

[a] Contained traces of phenylurea.

excess reactant was used the α-chlorine was replaced with an alkoxy or amino group as illustrated by the reaction with methanol.

$$CCl_3CHClNCO \xrightarrow[\text{1 mole}]{CH_3OH} CCl_3CHClNHCO_2CH_3 \xrightarrow[\text{excess}]{CH_3OH} CCl_3CH(OCH_3)NHCO_2CH_3$$

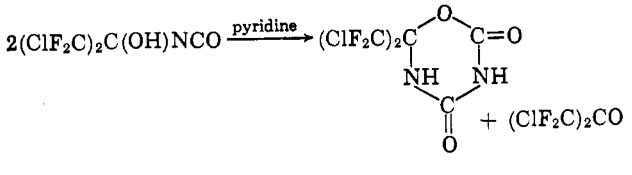
In a similar manner the reaction of 1,2,2,2-tetrachloroethyl isocyanate with water gave $(CCl_3CH(OH)NH)_2CO$.

The derivatives obtained from 1-hydroxy-2,2,2-trichloroethyl isocyanate are listed in Table II.

Bis-(chlorodifluoromethyl)-hydroxymethyl Isocyanate (IV).—Of the various α-hydroxy isocyanates prepared, bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate is one of the most stable at room temperature. It does not undergo polymerization at room temperature and can be distilled under reduced pressure. Examination by near-infrared spectrophotometry of both the product isolated by distillation and equimolar mixtures of isocyanic acid and *s*-dichlorotetrafluoroacetone showed that bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate exists in equilibrium with its precursors. These equilibrium mixtures contained nearly 100% of the hydroxy isocyanate at −20°, 98% at 0°, and 95% at 25°.

This hydroxy isocyanate reacted readily with amines and alcohols to form the expected derivatives (see Table III).

Attempts to obtain a linear polyurethane by the use of pyridine as a catalyst led instead to the cyclic structure of the type obtained from chloral.

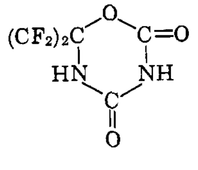


Bis-(trifluoromethyl)-hydroxymethyl Isocyanate (V).

$$(CF_3)_2CO + HNCO \rightleftarrows (CF_3)_2C(OH)NCO$$
$$\text{V}$$

—Bis-(trifluoromethyl)-hydroxymethyl isocyanate is similar to IV in stability. It can be distilled without appreciable decomposition at low temperatures under reduced pressures, but decomposes reversibly at temperatures much above 0°.

On standing in glass containers V is slowly converted to the 1,3,5-oxadiazine-2,4-dione,



an acidic compound that readily forms a salt on treatment with triethylamine in tetrahydrofuran.

Other Hydroxy Isocyanates.—Trifluoroacetaldehyde and 5*H*-perfluorovaleraldehyde reacted rapidly with isocyanic acid at 0° to form the corresponding hydroxy isocyanates. 1-Hydroxy-2,2,2-trifluoroethyl isocyanate from trifluoroacetaldehyde was stable at −20° for several days but polymerized at 0°. On the other hand, the hydroxy isocyanate from 5*H*-perfluorovaleraldehyde was stable for at least three days at 25°. Both hydroxy isocyanates formed ureas with aniline (see Table III). 1-Hydroxy-2,2,2-trifluoroethyl isocyanate reacted slowly with refluxing ethanol to give a mixture of ethyl N-1-hydroxy-2,2,2-trifluoroethylcarbamate and ethyl carbamate.

Experimental

Preparation of Isocyanic Acid.—Isocyanic acid was prepared routinely essentially by a literature method.[12] Cyanuric acid obtained from Eastman Kodak or American Cyanamid was pyrolyzed at 400–550° under a stream of nitrogen. The crude isocyanic acid was collected in traps cooled with Dry Ice–acetone. Redistillation over phosphorus pentoxide gave high purity isocyanic acid with only trace amounts of hydrogen cyanide as indicated by gas chromatography at 22° with a column of Silicone 703 on Columpak.

The purified isocyanic acid could be kept at −50° or below for months without apparent change. However, on warming, it underwent rapid polymerization or trimerization of explosive character so that caution was necessary. By comparison with acetylene or nitrocellulose, isocyanic acid is a mild explosive.

Preparation of α-Hydroxy Isocyanates and Their Derivatives.—The general procedure for preparing α-hydroxy isocyanates comprised mixing isocyanic acid and the carbonyl compound in essentially equimolar quantities at −78° and then allowing the mixture to warm to a temperature of about 0°, depending on the stability of the product. Solvents such as diethyl ether and carbon tetrachloride were used in some cases.

The rate of adduct formation varied with the carbonyl compound. The progress of the reaction was followed by means of near-infrared spectrophotometry.

Hydroxymethyl Isocyanate.—Anhydrous formaldehyde, generated by heating 30 g. (1 mole) of α-polyoxymethylene[13] (formed by base catalysis), was passed into a stirred solution of 39.2 g. (0.91 mole) of isocyanic acid in 200 ml. of anhydrous diethyl ether at −78° over a period of 107 min. Analysis of the reaction mixture at this point by near-infrared showed a strong OH band at 1.42 μ [the optical density of a 1% carbon tetrachloride solution in a 10-cm. cell was 0.528 at room temperature, whereas the optical density at 1.47 μ (HN of HNCO) was only 0.018, indicating that virtually all of the isocyanic acid had reacted].

The solvent was removed at −30° under 0.5-mm. pressure to yield 69 g. (theory 66) of a mobile liquid. On cooling, this liquid formed a crystalline solid at about −52°. Further purification was effected by partial freezing and separation of the solid from the liquid. The resulting solid was triturated with pentane, and residual amounts of pentane were removed by distillation [−29° to −10° (0.5 mm.)]. The final product melted at about −50°. The analysis of hydroxymethyl isocyanate was difficult because of its instability.

Anal. Calcd. for $C_2H_3NO_2$: C, 32.88; H, 4.14; N, 19.17; mol. wt., 73.05. Found: C, 33.55; H, 4.34; N, 19.20; mol. wt., 79, 80 (benzene).

Infrared analysis at −50° showed −NCO (4.43 μ), OH (2.9 μ), and no carbonyl.

N-Hydroxymethyl-N'-phenylurea.—At −35°, a mixture of 26 g. of hydroxymethyl isocyanate and 30 g. of ether was added with stirring over a period of 30 min. to a solution of 47 g. of aniline in 150 ml. of ether. The mixture was allowed to warm to −10° and poured into 500 ml. of cold 5% acetic acid. The solid precipitate was washed with ether and methanol. The analytical sample was recrystallized from methanol (m.p. on rapid heating, 176–182° dec.). The infrared spectrum showed absorption at 3.0, 3.05 μ (NH); 6.03 μ (CO); 6.45 μ (amide II); and 7.6, 13.2 μ (C_6H_5NH).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.51; H, 6.12; N, 16.85.

When aniline was added to hydroxymethyl isocyanate, an unidentified mixture was obtained.

2-Tetrahydropyranyloxymethyl Isocyanate.—A mixture of 135 g. of hydroxymethyl isocyanate, 400 g. of dihydropyran, 185 g. of ether, and 0.5 g. of *p*-toluenesulfonic acid was prepared at −5°. Within a few minutes the temperature rose to 20°. After the mixture had stood about 10 days at 25°, 188 g. of 2-tetrahydropyranyloxymethyl isocyanate, b.p. 87–88° (15 mm.), was obtained (see Table I for analytical data and for information on a similar adduct with butyl vinyl ether).

2-Tetrahydropyranyloxymethyl isocyanate and the adduct from butyl vinyl ether reacted (pyridine catalysis) readily with phenols in ether solution to give a variety of urethanes and with *p*-chloroaniline (see Table I) to form ureas.

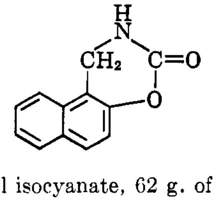
Chloromethylcarbamoyl Chloride and Chloromethyl Isocyanate.—A mixture of 115 g. of hydroxymethyl isocyanate and 100 g. of ether was added at −15° with stirring to a mixture of 205 g. of thionyl chloride, 400 ml. of pentane, and 2 ml. of pyridine. The temperature was maintained at 0° for 1 hr. and at 33–35° for 4 hr., during which time sulfur dioxide was evolved. The pentane and ether were removed under reduced pressure, and the product was recrystallized from pentane–methylene chloride (2:3). The yield of chloromethylcarbamoyl chloride, m.p. 9–10°, was 68%.

Anal. Calcd. for $C_2H_3NOCl_2$: C, 18.77; H, 2.36; N, 10.95; Cl, 55.41. Found: C, 19.41; H, 2.29; N, 11.11; Cl, 53.54.

Treatment of 194 g. of chloromethylcarbamoyl chloride in 100 ml. of xylene with 250 ml. of α-pinene resulted in a mild exothermic reaction (temperature maintained at 25–30° for 2 hr.). On distillation, 66 g. (48%) of $ClCH_2NCO$, b.p. 37–39° (158 mm.) (extrapolated 80°—lit.[10] b.p. 80–81°), $n^{25}D$ 1.4327, was obtained.

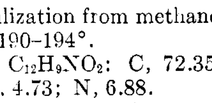
Anal. Calcd. for C_2H_2NOCl: N, 15.31. Found: N, 15.44.

3,4-Dihydro-2*H*-naphtho[1,2-*e*]-1,3-oxazin-2-one.—On mixing 38 g. of chloromethyl isocyanate, 62 g. of pentane–ether (3:1), and 43 g. of β-naphthol at 25°, hydrogen chloride was immediately evolved. After the evolution of hydrogen chloride had ceased (1 day), the solvent was removed under vacuum, and the product extracted with methanol. The solid obtained melted at 175–192°. Recrystallization from methanol gave a 25% yield of the oxazinone, m.p. 190–194°.



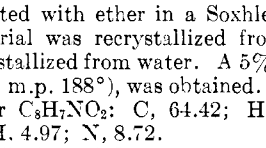
Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.09; H, 4.73; N, 6.88.

3,4-Dihydro-2*H*-benzo-1,3-oxazin-2-one.—A mixture of 38 g. of chloromethyl isocyanate, 62 g. of pentane–ether (3:1), and 28 g. of phenol was allowed to stand 24 hr. at 25° and then refluxed 3 hr. The solid product left after removal of solvent under reduced pressure was extracted with ether in a Soxhlet apparatus, and the extracted material was recrystallized from alcohol–water, sublimed, and recrystallized from water. A 5% yield of product, m.p. 189–191° (lit.[11] m.p. 188°), was obtained.



Anal. Calcd. for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.73; H, 4.97; N, 8.72.

3,4-Dihydro-6,8-dichloro-2(1*H*)-quinazolinone.—A mixture of 8.5 g. of chloromethyl isocyanate and 25 ml. of heptane was added to a mixture of 15 g. of 2,4-dichloroaniline, 50 ml. of ether, and 100 ml. of heptane at −10°. After standing for 16 hr. at 25°, the solid (13 g.) which formed was separated by filtration and recrystallized thrice from dimethylformamide–methanol (2:1). It melted at 258–260°.



Anal. Calcd. for $C_8H_6N_2OCl_2$: C, 44.26; H, 2.79; N, 12.91; Cl, 32.67. Found: C, 44.11; H, 3.02; N, 12.76; Cl, 32.55.

The infrared spectrum showed absorption at 3.0 μ (NH), 3.23 μ (=CH), 3.36 μ (saturated CH), 6.05 μ (>CO), 6.23–6.45 μ,

---

[12] F. Zobrist and H. Schinz, *Helv. Chim. Acta*, **35**, 2380 (1952); M. Linhard, *Z. anorg. allgem. Chem.*, **236**, 200 (1938).

[13] I. F. Walker, "Formaldehyde," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1953, p. 129.

6.53 μ (conjugated >C=C< and NH), and 12.12 μ (probably C–Cl) consistent with this structure.

Cinnamyl Isocyanate and 3-Chloro-3-phenylpropyl Isocyanate.—A mixture of 36 g. of chloromethylcarbamoyl chloride, 58 g. of styrene, 100 ml. of methylene chloride, and 2 g. of mercuric chloride was refluxed for 37 hr. The volatiles were removed at 45° (1 mm.). Toluene (100 ml.) was added and the mixture refluxed for 20 hr. to remove hydrogen chloride. Fractionation gave 1, b.p. 75–76° (0.35), $n^{25}\text{D}$ 1.5597, and 2, b.p. 76–83° (0.28 mm.), $n^{25}\text{D}$ 1.5408. Infrared and elemental analyses indicated that fraction 1 was 70% cinnamyl isocyanate and 30% 3-chloro-3-phenylpropyl isocyanate and fraction 2 was 15% cinnamyl isocyanate and 85% 3-chloro-3-phenylpropyl isocyanate.

2,4-Dimethylbenzylcarbamoyl Chloride and 2,4-Dimethylbenzyl Isocyanate.—A mixture of 508 g. of *m*-xylene, 300 ml. of methylene chloride, 135 g. of chloromethylcarbamoyl chloride, and 2 g. of zinc chloride was refluxed (57–58°) for 26 hr. when the evolution of hydrogen chloride had virtually ceased. The zinc chloride was removed by adding phosphorus pentoxide (2 g.), refluxing, and filtering. Removal of solvent at 50° (1 mm.) left 92 g. of crude 2,4-dimethylbenzylcarbamoyl chloride, m.p. 64–77°, after one recrystallization from heptane.

This carbamoyl chloride was refluxed for 24 hr. with 200 ml. of toluene to remove the hydrogen chloride. On distillation, 55.7 g. of 2,4-dimethylbenzyl isocyanate, b.p. 80–81° (0.2 mm.), $n^{25}\text{D}$ 1.5240, was obtained.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.57; H, 6.97; N, 9.13.

The infrared spectrum was consistent with this structure.

A mixture of 9 g. of 2,4-dimethylbenzyl isocyanate and 50 ml. of methanol gave methyl 2,4-dimethylbenzylcarbamate, m.p. 70.5–71.5°, after recrystallization from methanol.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.46; H, 7.95; N, 7.27.

The infrared spectrum was in good agreement with this structure.

1-Hydroxy-2,2,2-trichloroethyl Isocyanate.—This compound was prepared routinely in essentially quantitative yields by allowing a mixture of chloral and a 40% ethereal solution of isocyanic acid (reactants in equimolar amounts) to stand overnight. When no solvent was used, the hydroxy isocyanate was obtained as a solid at 0°. This solid melted about 25° and underwent an exothermic reaction above its melting point to give a mixture of unidentified acetone-soluble products.

Reaction of 1-hydroxy-2,2,2-trichloroethyl isocyanate with amines in ether at −10° gave the expected ureas (see Table II). The 1,3,5-oxadiazine-2,4-dione was obtained in 30% yield by stirring a mixture of 10.5 g. (0.055 mole) of hydroxy isocyanate, 1 g. (0.055 mole) of water, and 9 ml. of 1,2-dimethoxyethane at 0° for 1 hr. It was identified by its infrared spectrum (two carbonyls at 5.57 μ and 5.8 μ, NH at 3.1 μ and 3.25 μ) and elemental analysis.

1,2,2,2-Tetrachloroethylcarbamoyl Chloride, 1,2,2,2-Tetrachloroethyl Isocyanate, and Their Derivatives.—1,2,2,2-Tetrachloroethylcarbamoyl chloride was prepared by the procedure used for chloromethylcarbamoyl chloride. Conversion to the isocyanate was effected by refluxing a toluene solution. The overall yield of isocyanate from chloral was about 75%.

The isocyanate was generally quite reactive and could be converted to carbamates by refluxing in ether with an equivalent amount of alcohol. Refluxing with excess alcohol led to replacement of the α-chloro group with an alkoxy group (Table II).

Admixture of the isocyanate with amines in aromatic hydrocarbon solvents gave the corresponding ureas (Table II). With excess amine, the α-chloro group was replaced with an amine group.

The reaction of the isocyanate with 2-aminothiazole proceeded rapidly in tetrahydrofuran at room temperature to give the bicyclic derivative shown in Table II in high yield. This reaction is analogous to that reported[14] for CH_3OCF_2NCO.

The isocyanate reacted with 2,4-dichlorophenol, α-naphthol, β-naphthol, and 8-quinolinol in ether or benzene under reflux with triethylamine as a catalyst. No reaction occurred without catalyst.

The urea $(CCl_3CHOHNH)_2CO$ was obtained by treatment of the isocyanate with aqueous acetone. This compound was obtained previously from chloral and urea.[15]

Bis-(chlorodifluoromethyl)-hydroxy Isocyanate (IV).—A mixture of *s*-dichlorotetrafluoroacetone (4.5 g.) and 1.2 g. of isocyanic acid prepared at −78° was allowed to warm slowly to room temperature. Distillation of the product gave 2.4 g. of bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate, b.p. 26–27° (7 mm.). Near-infrared absorption at 1.42 μ (OH) in carbon tetrachloride, infrared absorption at 2.9 μ (OH), 4.43 μ (NCO) as well as proton and fluorine resonance data were consistent with the proposed structure.

Anal. Calcd. for $C_4HNO_2F_4Cl_2$: N, 5.80. Found: N, 6.03.

Bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate was converted to a urea by reaction with aniline. Aniline was added dropwise at −5° to a stirred mixture of 9.7 g. of bis-(chlorodifluoromethyl)-hydroxymethyl isocyanate and 25 ml. of ether. After allowing the mixture to stand overnight, the solvent was removed under reduced pressure leaving 2.9 g. (95%) of crude 1-[bis-(chlorodifluoromethyl)-hydroxymethyl]-3-phenylurea, m.p. 60–70°. A small amount of phenylurea impurity was removed by treating the product with a diethyl ether–petroleum ether (10 ml.:40 ml.) mixture in which phenylurea is only slightly soluble. Recrystallized (from carbon tetrachloride), the product melted at 75–77°.

When a drop of pyridine was added to 1.63 g. of IV, an exothermic reaction occurred with the formation of a viscous liquid which solidified on cooling. After recrystallization from benzene, it melted at 98–99°. Elemental analyses (see Table IV) and the infrared spectrum [3.07 μ, 3.22 μ (NH), 5.58 μ, 5.78 μ (>C=O), 8.9 μ (C—F and C—O)] were in accord with the oxadiazine-2,4-dione structure.

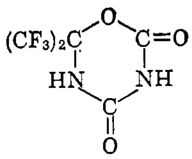
Reaction of IV with ethanol in ether occurred rapidly to form the carbamate. Proton magnetic resonance indicated the presence of NH, OH, and C_2H_5 groups. The infrared spectrum was also consistent with the carbamate structure and indicated strong internal hydrogen bonding.

Bis-(trifluoromethyl)-hydroxy Isocyanate (V).—This compound was prepared by essentially the same procedure used for IV. It distilled at about 2° (3 mm.). Some decomposition to its precursors occurred when higher pressures and temperatures were employed. The distilled product melted about −40°.

Anal. Calcd. for $C_4HF_6NO_2$: N, 6.70. Found: N, 7.12.

The proton magnetic resonance spectrum of the pure compound showed a single peak at 4.07 p.p.m. [downfield from the external standard, tetramethylsilane (5%) in carbon tetrachloride, used in these n.m.r. studies].

On standing for a week in a glass container, V was converted to



The proton magnetic resonance spectrum showed a single peak at 9.5 p.p.m.

The infrared spectrum (3.1 μ, 3.2 μ (NH's); 5.52 μ, 5.70 μ (>C=O); 8-μ region (C—F and C—O) was in good agreement with the structure.

The addition of 2.2 g. (0.02 mole) of triethylamine to a mixture of 2.5 g. (0.01 mole) of 6,6-bis-(trifluoromethyl)-1,3,5-oxadiazine-2,4-dione and 5 ml. of tetrahydrofuran at 25° gave an immediate precipitate of a 1:1 derivative. Proton magnetic resonance in "D" acetone showed broad absorption at 8 p.p.m., a quadruplet at 3.2 p.p.m., and a triplet at 1.3 p.p.m.

---

[14] J. C. Kauer and A. K. Schneider, *J. Am. Chem. Soc.*, **82**, 852 (1960).

[15] O. Jacobson, *Ann.*, **157**, 247 (1871).