

given in Table I. The energies of activation and the log PZ values were determined from the Arrhenius equation. The values of E_{act} are considered to be accurate to ± 0.2 kcal. and the log PZ factors to ± 0.2 .

Dissociation constants. These were determined by potentiometric titration using the same sample of aqueous ethanol

as used in the hydrolyses. The values reported in Table I are the mean of duplicate determination which differed by 0.05 unit.

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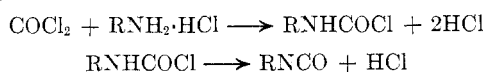
Formation and Properties of Isocyanates Derived from Amino Ester Hydrochlorides

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The usual methods for preparing isocyanates from amino ester hydrochlorides fail in many cases. A new, rapid procedure, uncomplicated by secondary reactions, is described for forming isocyanates derived from 2-, 3-, 6-, and 11-amino ester hydrochlorides. It was found that 2-isocyanato esters are activated towards reaction with active hydrogen compounds.

Although hundreds of isocyanates were known previous to the last twenty years, they were of only little technological interest. More recently, as a result of industrial applications, these substances have become the object of intensive research.¹ One method has dominated their synthesis, *i.e.*, the reaction of phosgene with amine hydrochlorides.

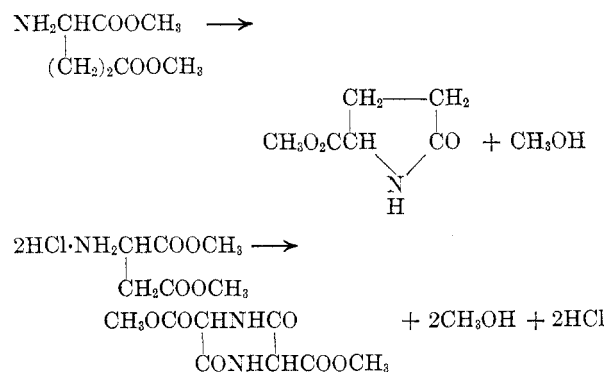


Usually by this procedure, the amine salt is suspended in a refluxing diluent into which phosgene is passed. After allowing a reaction time of several hours, the product is isolated by distillation. However, hydrochlorides of certain amino esters undergo secondary reactions under these conditions. Isocyanates cannot be prepared efficiently, for example, from hydrochlorides of esters of glutamic or aspartic acid by this procedure unless the quantities are small, *i.e.*, less than 0.4 mole. Although isocyanates derived from these and other α -amino esters have been reported in 85–97% yields, they were produced in only 10–20 g. quantities.² Reaction of phosgene with 0.25, 0.5, and 2 moles of dimethyl glutamate hydrochloride gives 80, 60, and 30% yields, respectively. Phosgenation of three moles of diethyl aspartate hydrochloride yields no isocyanate. These results are attributed partly to the competing reaction of cyclization. We have isolated the corresponding pyrrolidone in high yield and small amounts of the diketopiperazine in these two cases, respectively. Indeed, 5-carbomethoxy-2-pyrrolidone is reported to be obtained in 80% yield by heating the base, diethyl glutamate, for twenty minutes.³

(1) A. C. Farthing, *Proc. Chem. Soc. (London)*, 301 (1957).

(2) S. Goldschmidt and M. Wick, *Ann.*, **575**, 217 (1952).

(3) H. M. Chiles and W. A. Noyes, *J. Am. Chem. Soc.*, **44**, 1805 (1922).



Following the method of Siefken,⁴ ethyl isocyanatoacetate can be prepared from twenty moles of glycine ethyl ester hydrochloride in 85% yield by phosgenation in toluene. Similarly, the isocyanate derived from three moles of methionine ethyl ester hydrochloride is obtained in 84% yield. However, reaction of phosgene with one mole of glycine isopropyl or isobutyl ester hydrochloride gives only a 5–10% yield of the isocyanate.

We have found that isocyanates can be prepared smoothly from hydrochlorides of amino esters in unlimited amounts by a general, *continuous* procedure. By this method, a solution of the salt is passed down a packed, heated column counter-current to a stream of phosgene. The reaction temperature is the reflux temperature of the solvent, 1,2,3-trichloropropane (b.p. 155°). The reaction time within the apparatus is less than one minute. This method is somewhat similar to that described for other continuous reactions.⁵

Methyl, ethyl, isopropyl, *n*-butyl, and isobutyl α -isocyanato esters have been prepared in this way

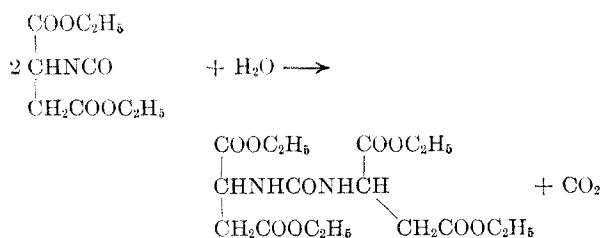
(4) W. Siefken, *Ann.*, **562**, 105 (1949).

(5) C. F. H. Allen, J. R. Byers, Jr., W. J. Humphlett, and D. D. Reynolds, *J. Chem. Educ.*, **32**, 394 (1955). C. F. H. Allen, T. J. Davis, W. J. Humphlett, and D. W. Stewart, *J. Org. Chem.*, **22**, 1291 (1957). C. F. H. Allen and W. J. Humphlett, *Org. Syntheses*, **37**, 2 (1957).

from α -amino mono- or dicarboxylic ester hydrochlorides in good yield. The method proceeds as well with the 3-, 6-, and 11-amino acid derivatives. Glycylglycine methyl ester hydrochloride cleaves under these conditions to form methyl isocyanatoacetate. Cleavage of acylamino compounds by phosgene has been noted previously.⁶

Since suspensions of amine hydrochlorides react slowly with phosgene, solvents for this reaction have been sought.⁷ 1,2,3-Trichloropropane dissolves most amino ester hydrochlorides, allowing a high rate of continuous reaction. With this solvent, a three-liter countercurrent apparatus has a capacity of 605 g. of diethyl α -isocyanatoglutarate prepared per hour. Solubility of the hydrochlorides varies with the ester used. While glycine methyl and ethyl ester hydrochlorides are insoluble in 1,2,3-trichloropropane at 25°, the isopropyl and butyl derivatives are soluble. Dimethyl aspartate hydrochloride dissolves at 90°; the ethyl derivative is soluble at 25°. All other hydrochlorides studied are readily soluble in this solvent. The required ester hydrochlorides were obtained by reaction of the amino acid with thionyl chloride in the appropriate alcohol.⁸ This esterification results in practically quantitative yields and crystalline products. The base, dimethyl glutamate,⁹ in contrast to its hydrochloride, is soluble in most organic solvents. This form gives the isocyanate in 72% yield in continuous synthesis. However, the base is unstable and must be kept at -20° until used. In the preferred procedure, the hydrochloride is employed.

Aliphatic isocyanates are known to be less reactive towards active hydrogen compounds than are aromatic isocyanates.¹ Octadecyl isocyanate emulsified in water is reported to be stable for a day.⁷ The reactivity of aromatic isocyanates is increased by *o*- or *p*-substitution of electron-withdrawing groups.¹⁰ We find that the reactivity of aliphatic isocyanates derived from α -amino esters is increased by the carbonyl group of the ester. Thus, diethyl isocyanatosuccinate reacts completely in a dioxane solution containing 25% water in one hour, forming the urea.



(6) H. Krzikalla, U. S. Patent 2,666,787 (Jan. 19, 1954); *Chem. Abstr.*, **48**, 3995 (1954).

(7) J. H. Saunders and R. J. Slocombe, *Chem. Revs.*, **43**, 203 (1948).

(8) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(9) V. G. Hillmann, *Z. Naturforschung*, **1**, 682 (1946).

(10) R. G. Arnold, J. A. Nelson, and J. J. Verbanec, *Chem. Revs.*, **57**, 47 (1957).

Under similar conditions, the yields of urea formed by isocyanates derived from esters of glutamic acid, glycine, and the branched leucine are 90, 80, and 45-50%, respectively. Reaction with water was stopped after one hour by addition of the much more reactive benzylamine forming a benzyl urea. Activation of the isocyanate group disappears when the carbonyl is separated by more than one methylene group. Isocyanates derived from esters of β -alanine, 6-aminocaproic acid, and 11-amino-undecanoic acid are inert in aqueous dioxane solution under similar conditions. The extent of reaction with water was determined by infrared-spectra analysis based on pure symmetrical and benzyl urea samples.

Other data characteristic of the isocyanates and related compounds are summarized in Table I.

EXPERIMENTAL

Apparatus. A small apparatus suitable for preparing isocyanates in 25-200-g. quantities is made from standard laboratory glassware. For this purpose, a 3-ft. column of $\frac{3}{4}$ -inch internal diameter is packed with $\frac{1}{4}$ -inch glass helices and clamped vertically to a ringstand in a hood. A flask is attached to the bottom of the column to receive the product. A dropping funnel and a reflux condenser are connected to the top of the column. A side-arm located near the bottom allows introduction of phosgene. The column is heated by two lengths of $\frac{1}{2}$ -inch by 6-ft., 288-watt, heating tape connected to variable transformers. A somewhat similar apparatus for countercurrent circulation has been diagrammed.¹¹ A larger apparatus was used more often and is described in detail in the next paragraph. However, the $\frac{3}{4}$ -inch column can be operated in the same way on a smaller scale.

A 5-ft. column of 2-inch internal diameter (volume equal to 3.1 l.), packed with $\frac{1}{4}$ -inch Berl saddles, is useful for preparing 100-5,000-g. quantities of isocyanates. A 3-l. flask is connected to the bottom of the column through a 75/50 ball-and-socket joint. The flask is provided with a stopcock at the bottom for withdrawing the product. A stoppered, second neck on the flask is of advantage. A side-arm tube, $\frac{3}{8}$ in. in internal diameter, located 24 inches from the bottom of the column, allows introduction of phosgene. Phosgene is metered through a calibrated flowmeter.¹² (Bubbling phosgene through sulfuric acid contained in a suitable bottle is an alternative method.) Provision for the release of abnormal pressure is made by a safety valve located between the phosgene tank and the column. Attached to the top of the column through a 75/50 ball-and-socket joint is a head with two openings at its top. Removal of the head allows the column to be packed. One opening at the top of the head serves as an inlet for the solution of amino ester hydrochloride. The solution is, preferably, metered by a calibrated proportionating pump¹³ made of inert materials connected through 19/8 ball-and-socket joints by $\frac{1}{4}$ -inch, heavy-walled, glass tubing to the column head. (Use of a dropping funnel connected at the top of the column can be a substitute method of addition. A constant-rate dropping funnel is more satisfactory.¹⁴ Attached to the other opening of the head through a 29/42 standard tapered joint is a 14-inch reflux condenser of 1-inch internal diameter, packed

(11) C. F. H. Allen, J. R. Byers, Jr., and W. J. Humphlett, *Org. Syntheses*, **37**, 66 (1957).

(12) A Fischer and Porter Co. Precision Bore Flowrator Tube No. 2F 1/4-20-5/35 was used.

(13) Pumps used were Lapp Insulator Co. Lapp Microflo Pulsafeders, Models LS and LS-20, with Teflon heads.

TABLE I
ISOCYANATES FROM AMINO ESTER HYDROCHLORIDES AND THEIR UREA DERIVATIVES

Acids	Ethyl Ester Hydrochlorides				Isocyanates				Sym. Ureas								
	M.P. ^a	Calcd.		Found	B.P., ^a mm.	n _D ²⁵	Yield, ^f %	M.P.	Calcd.		C	Found					
		C	H						N	H		N	H	N			
Dl-Aspartic acid	96 ^b	42.6	7.2	6.2	42.2	7.0	6.1	87/0.5 132/8	1.4357	91	80 ^k	50.5	7.0	6.9	50.8	6.9	6.5
L-(+)-Glutamic acid	115 ^c				116/2				1.4390	94	96 ^l	52.8	7.5	6.5	52.5	7.4	6.7
Dl-Methionine	76 ^d	39.3	7.6	6.6	39.4	7.6	6.9	98/1	1.4735	82	90 ^l	47.6	6.9	7.4	47.8	7.2	7.2
β-Alanine	58 ^e	49.1	9.3	7.2	49.2	9.5	7.5	77/8	1.4272	92	116 ^m	50.8	7.7	10.8	50.9	8.0	10.9
L-(-)-Leucine	135 ^f	58.7	10.6	5.3	58.8	10.6	4.9	93/8	1.4273	81	113 ^l	59.3	9.4	8.1	59.6	9.5	7.8
11-Aminoundecanoic acid	143 ^g				149/2				1.4450	80	100 ^m	66.9	10.8	5.8	66.9	11.0	5.7
Methyl Ester Hydrochlorides																	
Dl-Aspartic acid	116 ^f	36.5	6.1	7.1	36.8	6.0	6.9	97/1	1.4445	70	135 ^m	44.8	5.7	8.0	45.0	5.7	7.8
L-(+)-Glutamic acid	95 ^g	39.7	6.7	6.6	39.4	6.3	6.3	103/1.5	1.4442	95	118 ^m	47.8	6.4	7.5	47.9	6.3	7.3
β-Alanine	106 ^f	34.4	7.2	10.0	34.7	7.1	10.0	61/6	1.4312	86	88 ^m	46.5	6.9	12.1	46.1	7.3	12.1
6-Aminocaproic acid	125 ^f	46.0	8.8	7.7	46.1	8.8	8.0	68/0.1 123/15	1.4378	74	95 ^m	56.9	8.9	8.9	56.7	8.5	8.8
n-Butyl Ester Hydrochloride																	
Glycine	72 ^h				79/6				1.4301	97	49.5 ^{k,n}						
Isopropyl Ester Hydrochloride																	
Glycine	112 ^f	39.1	7.9	9.1	39.0	7.8	9.2	64/6	1.4188	59	115 ^l	50.8	7.7	10.7	50.4	7.4	11.0
Isobutyl Ester Hydrochloride																	
Glycine	94 ^f	43.0	8.4	8.4	43.4	8.8	8.6	76/6	1.4229	95	86 ^o	54.1	8.4	9.7	54.3	8.2	9.8

^a Melting points are corrected; boiling points are uncorrected. ^b Recrystallized from ethyl acetate. ^c Reported m.p. 113–114°, R. B. Angier *et al.*, *J. Am. Chem. Soc.*, **72**, 74 (1950). ^d Recrystallized from xylene. ^e Reported m.p. 58°, S. K. Mitra, *J. Indian Chem. Soc.*, **15**, 455 (1938). ^f Recrystallized from methyl alcohol-ethyl acetate. ^g ethyl acetate-ether. ^h Reported m.p. 69–71°, W. T. J. Morgan, *J. Chem. Soc.*, 79 (1926). ⁱ Refractive indices were taken of mid-cuts of redistilled isocyanates. ^j Yields include preparation of ester-hydrochlorides. ^k Recrystallized from ether-ligroin (b.p. 35–60°). ^l Methyl alcohol-water. ^m Methyl alcohol. ⁿ The corresponding carboxylic acid melts at 203°, recrystallized from water. *Anal.* Calcd. for C₆H₁₃N₃O₂: C, 34.1; H, 4.6; N, 15.9. Found: C, 34.1; H, 4.9; N, 15.6. ^o Recrystallized from benzene-ligroin (b.p. 35–60°).

with 1/4-inch Berl saddles for efficient condensation of solvent. Waste gases pass from the top of the condenser to a 6-ft. gas trap¹⁶ of 1-inch internal diameter, packed with 1/2-inch Berl saddles. The trap is more effective when ammonia is added in addition to water. Under these conditions, no phosgene can be detected at the bottom of the trap. The column is heated by two 2-inch by 10-ft., 1000-watt and one 1/2-inch by 6-ft., 288-watt heating tapes. The small tape is wound around the upper part of the column. The heating tapes are wrapped with 2-inch asbestos tape. The entire apparatus is set up in a hood.

Reagents. 11-Aminoundecanoic acid was obtained from Organic Research Chemicals Ltd., Bucks, England, and 6-aminocaproic acid from Columbia Organic Chemicals Co., Inc. Other amino acids, 1,2,3-trichloropropane, and thionyl chloride were Eastman White Label products. Ethyl isocyanatoacetate (carbethoxymethyl isocyanate) was a redistilled Eastman product, b.p. 67°/11 mm., n_D^{25} 1.4195.

General procedure. Amino ester hydrochlorides. These were prepared by modifications of the method of Brenner and Huber.⁸ In a typical synthesis of diethyl glutamate hydrochloride, commercial absolute ethyl alcohol (8 l., 137 moles) was placed in a 12-l. round flask equipped with a mechanical stirrer. Thionyl chloride (2 l., 27.8 moles) was added from a dropping funnel during 1 hr., with stirring, the temperature of the mixture being kept below 25° by a Dry Ice-acetone bath. When the addition was complete, L-(+)-glutamic acid (1471 g., 10 moles) was added. The mixture was stirred at 50° for 3 hr., forming a yellow solution. (Alternatively, the mixture could be stirred overnight at room temperature.) The volatile components were removed *in vacuo* by a water pump. When crystallization began, 1,2,3-trichloropropane (4 l.) was added and the remainder of the thionyl chloride and alcohol removed. Heat was applied to aid the removal, but the temperature of the solution was not allowed to rise above 40°. (Excessive heating at this point caused the solution to darken, resulting in lower yields of isocyanate, with tar formation.) The solution was diluted to 8 l. with 1,2,3-trichloropropane and used for the isocyanate synthesis. Hydrochlorides of glycine isopropyl ester or leucine ethyl ester were diluted to one half of this concentration and warmed to 45° to maintain a solution. Preparation of glycine isopropyl, isobutyl, or *n*-butyl ester hydrochloride required 10 moles of alcohol and 2.7 moles of thionyl chloride per mole of glycine. Reaction time was 1-3 days at 45° or until solution occurred. (These ester derivatives were also prepared, in 65-80% yield after 3-hr. reaction time, in 2.75 moles of alcohol per mole of glycine catalyzed by anhydrous hydrogen chloride. The unchanged glycine hydrochloride was separated by fractional crystallization.) All other amino ester hydrochlorides were obtained by the procedure described for ethyl glutamate hydrochloride.

Samples of the hydrochlorides were isolated by diluting their 1,2,3-trichloropropane solutions with ether and collecting the precipitate. Since certain previously reported melting points have been lower or sirups noted, melting points and recrystallization data are given in Table I.

Isocyanates. In a typical continuous preparation, the column was heated with variable transformer settings to the top, middle, and bottom heating tapes at 85, 100, and 100 volts, respectively. 1,2,3-Trichloropropane was added slowly to wet the column. After 30 min., when the solvent began to reflux, phosgene was added at a rate to provide a phosgene/amine molar ratio of about 2 (Flowrator reading of 3.5). The solution of diethyl glutamate hydrochloride in 1,2,3-tri-

chloropropane was added at a rate of 490 ml./hr. (*i.e.*, 147 g. of diethyl glutamate hydrochloride/hr.). A brown solution of the isocyanate collected in the flask at the bottom of the column. When the addition was complete, the column was rinsed with 300 ml. of solvent. The collected effluent was distilled *in vacuo* to remove the solvent, b.p. 39-44°/7 mm. The distilled solvent, which was dry and contained some phosgene, was used repeatedly with little loss. The isocyanate was distilled from the residue. The apparatus was used in continuous preparations of 130-5500 g. of isocyanate from 0.5-21 l. of diethyl glutamate hydrochloride solution. At addition rates of solution of 500-1920 ml./hr., yields were 91-94%. Addition of 2400 ml./hr., or preparation of 605 g. of isocyanate/hr. in 88% yield, is about the capacity of the column. Higher rates gave increased amounts of 5-carbethoxy-2-pyrrolidone, m.p. 55°,³ recrystallized from ether. The same procedure was used to prepare the other isocyanates of Table I.

Ureas. Symmetrical ureas were prepared from the corresponding isocyanates by standing 24 hr. in an acetone-water solution. They were precipitated by dilution with water. Ethyl isocyanatoacetate gave a urea, m.p. 147°, recrystallized from ether.

Anal. Calcd. for C₉H₁₆N₂O₅; N, 12.1. Found: N, 12.1.

Benzyl ureas were prepared in a few minutes in an acetone-benzylamine solution. 1-Benzyl-3-carbethoxymethylurea was recrystallized from methyl alcohol-water, m.p. 96°.

Anal. Calcd. for C₁₂H₁₆N₂O₄; N, 11.8. Found: N, 12.0.

1-Benzyl-3-(1,2-dicarbethoxyethyl)urea was recrystallized from ether-ligroin (b.p. 35-60°), m.p. 82°.

Anal. Calcd. for C₁₆H₂₂N₂O₆; N, 8.7. Found: N, 8.5.

1-Benzyl-3-(1,3-dicarbethoxypropyl)urea, recrystallized from ether, melted at 91°.

Anal. Calcd. for C₁₇H₂₄N₂O₆; N, 8.3. Found: N, 8.1.

1-Benzyl-3-(2-carbethoxyethyl)urea was recrystallized from methyl alcohol, m.p. 83°.

Anal. Calcd. for C₁₃H₁₈N₂O₅; N, 11.2. Found: N, 10.9.

1-Benzyl-3-(1-carbethoxyisovaleryl)urea was recrystallized from ligroin (b.p. 66-75°), m.p. 49°.

Anal. Calcd. for C₁₈H₂₄N₂O₅; N, 9.6. Found: N, 9.6.

1-Benzyl-3-(10-carbethoxydecyl)urea, recrystallized from ethyl alcohol, melted at 97°.

Anal. Calcd. for C₂₁H₃₀N₂O₆; N, 7.7. Found: N, 7.7.

1-Benzyl-3-(5-carbomethoxyamyl)urea, recrystallized from ethyl alcohol, melted at 90°.

Anal. Calcd. for C₁₆H₂₂N₂O₆; N, 10.0. Found: N, 9.8.

Reactivity of isocyanates. Comparison of the rates of reaction of redistilled isocyanates with water was made by dissolving 0.05 mole of the isocyanate in 100 ml. of 1,4-dioxane and adding 35 ml. of water. (The undecanoate required 150 ml. of dioxane.) After 1 hr. at 25°, benzylamine (6 ml., 0.055 mole) was added to stop the reaction with water. After standing for 10 min., the solvent was removed *in vacuo*, and the residue dried for 4 hr. at 1 mm. and 100°. The contents of symmetrical and benzyl ureas in the mixture were found by infrared-spectra analysis based on 14.3 μ peak of the out-of-plane deformation of the C-H bonds of the phenyl group. Ureas derived from isocyanates of the ethyl esters of aspartic, glutamic, and 11-undecanoic acids; β -alanine; and the methyl ester of 6-aminocaproic acid were examined in dioxane. The leucine derivative was assayed in carbon disulfide, and the glycine derivative in a pressing.

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(14) W. J. Humphlett, *Org. Chem. Bulletin*, Vol. 27, No. 3 (1955), published by the Research Laboratories of the Eastman Kodak Co.

(15) C. F. H. Allen, *Org. Syntheses*, Coll. Vol. II, 3 (1943).