

Preparation of Esters of Lactamides.—These were prepared by acylation of the appropriate lactamide with acid anhydrides or chlorides. Acetic and propionic anhydrides were employed to obtain the acetates and propionates, and acid chlorides in conjunction with pyridine were used to prepare the remaining esters by standard procedures. The ester-amides were distilled in an alembic type still¹⁴ at low pressure. Middle fractions or recrystallized materials in the case of solids were used for determination of properties and for analyses. It was necessary to distil the bis-(hexylcarbonate) of 2-hydroxyethyl- and 2-hydroxypropyl lactamides in a centrifugal molecular still. The ester-amides prepared and their properties are shown in Table I. The boiling point curves for N-butyl lactamide 2-ethylhexanoate and the 2-ethylhexanoate and laurate of N,N-dibutyl lactamide are shown in Fig. 1.

Ester-amides by Simultaneous Esterification and Dehydration of Lactic Acid-Amine Salts.—Ethanolamine, 61 g. (1 mole), was added in portions to 112 g. of 80% lactic acid with occasional cooling to remove the heat of neutralization. Then 316 g. (2 moles) of pelargonic acid and 130 ml. of benzene were added to the reaction flask, and the mixture was refluxed under a Barrett-type water trap, which automatically separated water from the water-benzene azeotrope. After two hours, 29 ml. of water and 76 ml. of benzene had been removed from the trap, and the still-pot temperature had risen from 112 to 153°. An additional 40 ml. of water was separated from the reaction mixture as the pot temperature rose to 190° in the next six hours. The reaction mixture was transferred to a Vigreux still and freed of benzene by distillation at 10 mm., a water-bath being used for heating purposes. The ester-amide was then isolated by distillation in an alembic still under high vacuum. The yield of distilled product, N-2-hydroxyethyl lactamide dipelargonate (which solidified in the receiver) was 74%.

N,N-Dibutyl lactamide laurate was prepared by a similar procedure from one mole each of lactic acid, dibutylamine and lauric acid, with xylene as the entraining agent, in 70% yield.

Acknowledgment.—The authors are indebted to Mary Jane Welsh and Ruth Kelly for the ultimate analyses, E. H. Harris, Jr., for assistance in several preparations, and H. B. Knight for the distillation

(14) W. P. Ratchford and C. E. Rehberg, *Anal. Chem.*, **21**, 1417 (1949).

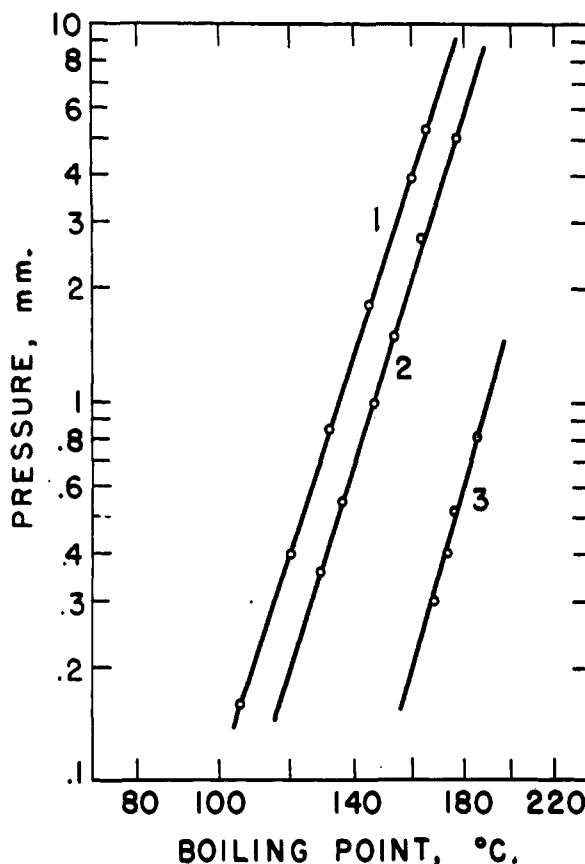


Fig. 1.—Boiling points of lactamide esters: 1, N-butyl lactamide, 2-ethylhexanoate; 2, N,N-dibutyl lactamide, 2-ethylhexanoate; 3, N,N-dibutyl lactamide, laurate.

of two products in a centrifugal molecular still. PHILADELPHIA 18, PENNA.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, PHOSPHATE DIVISION, MONSANTO CHEMICAL COMPANY]

The Preparation of Isocyanates by the Thermal Decomposition of Substituted Ureas¹

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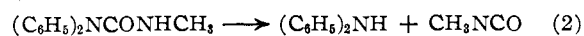
Isocyanates have been prepared in 57–71% yields by the vapor-phase reaction of *sym*-disubstituted ureas with hydrogen chloride. Lower yields were obtained from the vapor-phase reaction of amines and urea or cyanuric acid with hydrogen chloride, and from N-phenylurea with hydrogen chloride.

The thermal dissociation of substituted ureas into the corresponding amines and isocyanates, according to equation 1



has been demonstrated qualitatively both in the liquid phase² and in solution.³ Isocyanates have been identified among the products obtained by the distillation of molten substituted ureas,⁴ and by the treatment of molten ureas with phosphorus

pentoxide⁵ or with dry hydrogen chloride.⁶ As a preparative method for isocyanates, however, the process has been limited to certain trisubstituted ureas which decomposed on heating into a low-boiling isocyanate and a relatively non-volatile secondary amine,⁷ as in equation 2, or to



ureas containing as the only substituent a large tertiary alkyl group, such as the neopentylidimethylcarbinyl group.⁸ The recombination of the

(1) Presented before the Organic Division of the American Chemical Society, Atlantic City, N. J., September 18, 1952.

(2) H. Eckenroth and M. Wolf, *Ber.*, **26**, 1463 (1893).

(3) Y. Iwakura and K. Nagakubo, *Bull. Tokyo Inst. Technol.*, **13**, 25 (1948); *C. A.*, **44**, 3924e (1950).

(4) A. W. Hofmann, *Ber.*, **14**, 2725 (1881).

(5) A. W. Hofmann, *ibid.*, **3**, 653 (1870).

(6) A. Habich and H. Limpricht, *Ann.*, **109**, 101 (1859).

(7) L. Strohmenger, German Patent 748,714; see W. Siefken, *Ann.*, **562**, 75 (1949).

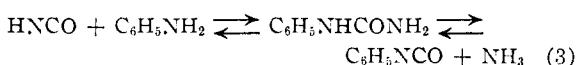
(8) N. M. Bortnick, U. S. Patent 2,611,792 (1952).

dissociation products on cooling has generally limited the recovery of isocyanates from this type of reaction.

In the course of this investigation it was shown by the use of a Victor Meyer type of apparatus that carbanilide and N-phenylurea are largely dissociated in the vapor phase (approximately 99 and 77%, respectively, at 370°). Hydrogen chloride, when added to these vaporized ureas, should combine with the amines formed in the dissociations, and the isocyanates could then be separated from the amine salts.

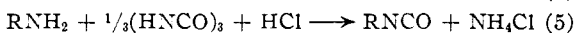
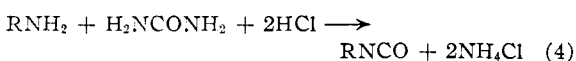
The vaporization of *sym*-disubstituted ureas, followed by cooling in the presence of hydrogen chloride, gave isocyanates in 57–71% yields, along with near-quantitative yields of the corresponding amine salts. An additional nitrogenous substance, possibly an isocyanate polymer, accounted for the remainder of the substituted urea used.

Similar treatment of N-phenylurea gave a 35.9% yield of phenyl isocyanate, along with carbanilide and aniline hydrochloride. Unlike the *sym*-disubstituted ureas, N-phenylurea can dissociate in two ways

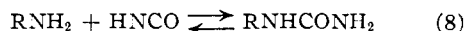


The presence of aniline hydrochloride and carbanilide, along with the major product, phenyl isocyanate, can be accounted for by the assumption of both methods of dissociation and of reactions among the dissociation products.

The successful conversion of substituted ureas into isocyanates led to an investigation of the vapor-phase reaction of amines or amine salts with a small excess of urea or cyanuric acid, according to the over-all equations 4 and 5.



Isocyanate yields from these more complex reactions were lower. The preparation of isocyanates by these reactions would seem to proceed through the intermediate formation of a monosubstituted urea



The number of equilibria involved, and hence the number of potential products, possibly accounts for the low isocyanate yields in these reactions (4 and 5). No extensive effort was made to find the conditions which would give the maximum yields, however.

In addition to these results, a few attempts were made to obtain isocyanates by the thermal decomposition of *sym*-disubstituted ureas in the liquid phase, in the presence of hydrogen chloride. In every case the yield was low, of the order of 3 to 7%, and much polymeric material was formed.

Experimental

The Vapor-phase Dissociation of Carbanilide and N-Phenylurea.—A Victor Meyer type of apparatus was con-

structed using a 2-ft. length of 25-mm. Pyrex tubing for the vaporization chamber. The lower 15 in. of the vaporizer was heated in an electric furnace. The maximum increase in gas volume caused by vaporization of the sample was measured over water in a gas buret. The ratios of volume increase to that calculated for an undissociated vapor were 1.07 for naphthalene (standard), 1.99 for carbanilide and 1.77 for N-phenylurea at 370° furnace temperature. These ratios correspond to calculated dissociations of 7, 99 and 77%, respectively.

Description of Apparatus.—The reactor was a horizontal 18-in. length of 25-mm. Pyrex tubing heated by Nichrome ribbon, and packed for 8 in. with 0.25-in. Berl saddles. It was provided with a thermometer opening such that the temperature could be measured at any point in the reactor, with inlets for nitrogen and hydrogen chloride, and a device for introducing a solid sample directly into the heated zone. Exit gases were led into a 2-l. flask which served as a product collector, and were vented through a 1-ft. packed column through which toluene was circulated.

General Procedure.—During the course of an experiment the temperature was held at 350 to 370° except as noted otherwise in the detailed descriptions. Dry nitrogen and hydrogen chloride were swept through the apparatus in a slow stream. The solid sample was dropped in small portions into the heated zone, where it rapidly vaporized and was swept through the reactor. At the completion of an experiment the solids found in the collector were filtered from the toluene, separated into their components and identified insofar as practical. The isocyanate content of the toluene was determined by analysis, as described below. It should be noted that in the presence of hydrogen chloride in the cold the isocyanate was present as the carbamyl chloride, but the two types of compounds are held equivalent for the purpose of this presentation.

The principal experimental difficulty was the plugging of the exit from the reactor by the solid products. A reamer was provided to keep this zone clear. Occasionally an accumulation of solid material developed in the vaporizer portion of the reactor. This solid apparently was polymeric in nature. Little carbonization or tar formation was noted in the reactor beyond the zone in which vaporization occurred.

Identification of Products.—The solid reaction products were treated with water, which would have removed ammonium chloride, amine salts, urea and ammonium cyanate. Except in the case of the water-soluble amines, the amine could be separated and identified by making the water solution basic, extracting with benzene, washing the benzene layer with water to remove ammonia, drying, and treating with phenyl isocyanate. The substituted N-phenylurea thus obtained gave a measure of the amine throughput or formation in the reaction. No attempt was made to separate other water-soluble products.

The water-insoluble solids were triturated with 10% sodium hydroxide solution to remove cyanuric acid. Only traces of this compound were found in any of the experiments. The remaining water- and base-insoluble solids consisted of substituted ureas and possibly polymers; the amount was usually small. In some cases the substituted urea was identified after recrystallization.

The isocyanate content of the toluene solution was most conveniently determined by adding aniline to the solution and weighing the substituted N-phenylurea which was formed. An alternate method, which was less satisfactory because of the small quantities of materials used in most experiments, consisted of removing the solvent and measuring the purity of the crude isocyanate remaining by titration with di-*n*-butylamine.⁹

In some experiments the toluene solution containing excess aniline after separation of the substituted N-phenylurea was evaporated *in vacuo* at 100°. An apparently polymeric nitrogenous mass remained. The weight of this substance was essentially that required to account for the discrepancy in the material balance.

Detailed Procedures.—The melting points are uncorrected. Products were identified by comparison with authentic samples (no depression of melting point in mixture). The following ureas and amine salts were identified at several points during the experiments: carbanilide, m.p. 237.5–239°; N-ethyl-N'-phenylurea, m.p. 98–99.5°; N- α -naph-

(9) Cf. H. E. Stagg, *Analyst*, **71**, 557 (1946).

thyl-N'-phenylurea, m.p. 222–224¹⁰; aniline hydrochloride, m.p. 197–198⁹; and α -naphthylamine, m.p. 48–50⁹.

(a) **Carbanilide**.—From 41 g. of carbanilide (prepared from phenyl isocyanate and aniline) in a run of 5.5 hours duration there was obtained 24 g. of aniline hydrochloride, a 96% yield. After aniline treatment of the toluene solution 23.6 g. of carbanilide was obtained, corresponding to a 57.6% yield of phenyl isocyanate. Also isolated from the solution was 9.5 g. of an inert liquid containing 11.05% nitrogen.

(b) **sym-Diethylurea**.—From 81.5 g. of Sharples *sym*-diethylurea, in a run of 4.5 hours duration, there was obtained 53.2 g. (93.0%) of ethylamine hydrochloride, m.p. 107–108⁹, and, after aniline treatment, 72.9 g. of N-ethyl-N'-phenylurea, corresponding to a 63.3% yield of ethyl isocyanate. A residue weighing 15.1 g. and containing 15.29% nitrogen was also obtained from the toluene solution.

(c) **sym-Dicyclohexylurea**.—From 58.7 g. of *sym*-dicyclohexylurea, prepared from cyclohexyl isocyanate and cyclohexylamine, m.p. 227–227.5¹¹ in a run of 5.5 hours duration there was obtained 34 g. (96.2%) of cyclohexylamine hydrochloride, m.p. 205¹². The yield of cyclohexyl isocyanate as determined by titration of the crude isocyanate and toluene distillate with dibutylamine was 23.4 g., or 71.5%.

(d) **N-Phenylurea**.—From 48.4 g. of N-phenylurea, prepared from phenyl isocyanate and ammonia, m.p. 145–147⁹, there was obtained 10.5 g. (22.8%) of aniline hydrochloride and 5.1 g. (13.5%) of carbanilide. Treatment of the toluene solution with aniline gave 27.1 g. of carbanilide, corresponding to a yield of 35.9% of phenyl isocyanate.

(e) **Urea and Aniline Hydrochloride**.—From a mixture of 7.4 g. of urea and 13.3 g. of aniline hydrochloride (1.2:1 molar ratio) in a run of one hour duration there was obtained, after treatment with aniline, 6.1 g. of carbanilide, corresponding to a 28.0% yield of phenyl isocyanate, based on the aniline hydrochloride.

(f) **Urea and α -Naphthylamine**.—From a mixture of 8.4 g. of urea and 16.5 g. of du Pont α -naphthylamine (1.2:1 molar ratio) there was obtained after aniline treatment 9.0 g. of N- α -naphthyl-N'-phenylurea.¹⁰ The recovery of α -

naphthylamine was 5.2 g., 31.5%. The yield of α -naphthyl isocyanate, based on amine used, was 43.5%.

(g) **Urea and α -Naphthylamine Hydrochloride**.—From a mixture of 10.1 g. of urea and 24.9 g. of α -naphthylamine hydrochloride (1.2:1 molar ratio) in a run of 3.5 hours duration, there was obtained a recovery of 3.6 g. of α -naphthylamine, 18.1%, and, after aniline treatment, 12.4 g. of N- α -naphthyl-N'-phenylurea.¹⁰ The corresponding yield of α -naphthyl isocyanate was 41.5%, based on amine hydrochloride used. A residual material containing 14.04% nitrogen was also isolated from the toluene solution.

(h) **Cyanuric Acid and α -Naphthylamine**.—From 6.0 g. of cyanuric acid¹³ and 17.2 g. of α -naphthylamine (1.2:1 equivalent ratio) in a run of one hour time at 415–425⁹ there was obtained, following aniline treatment, 2.2 g. of N- α -naphthyl-N'-phenylurea.¹⁰ The recovery of amine was 5.5 g., 31.9%. The corresponding yield of α -naphthyl isocyanate was 10.3%, based on amine. The accumulation of solids in the vaporization zone was excessive in this experiment.

(i) **Urea and Ethylamine Hydrochloride**.—From 23.8 g. of urea and 26.9 g. of ethylamine hydrochloride (1.2:1 molar ratio) in a run of one hour duration, at 370–380⁹, there was obtained, after aniline treatment, 4.9 g. of N-ethyl-N'-phenylurea. The corresponding yield of ethyl isocyanate was 9.1%, based on the amine hydrochloride fed. The solids found in the collector, weighing 40.9 g., were all water-soluble. The unchanged ethylamine hydrochloride was not determined, so the actual yield of isocyanate, based on amine consumed, may have been larger than 9.1%.

(j) **Urea and Cyclohexylamine Hydrochloride**.—From 25.4 g. of urea and 47.5 g. of cyclohexylamine hydrochloride, in a run of three hours duration, there was obtained, following aniline treatment, 10.7 g. of N-cyclohexyl-N'-phenylurea, m.p. 149–150¹¹. The corresponding yield of cyclohexyl isocyanate, based on amine hydrochloride fed, was 14.0%. No cyclohexylamine could be isolated from the 34.9 g. of water-soluble solids found in the collector. The toluene solution decolorized bromine in carbon tetrachloride, indicating an unsaturated compound, possibly cyclohexene.

(10) A. E. Dixon, *J. Chem. Soc.*, **79**, 102 (1901).

(11) A. Skita and H. Rolfes, *Ber.*, **53**, 1242 (1920).

(12) O. Wallach, *Ann.*, **343**, 40 (1905).

(13) R. J. Slocombe, E. E. Hardy, J. H. Saunders and R. L. Jenkins, *THIS JOURNAL*, **72**, 1888 (1950).

ANNISTON, ALABAMA

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin. X. Dethiogliotoxin and Related Compounds¹

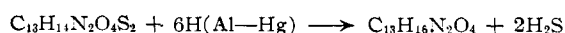
By JOHN R. JOHNSON AND JAMES B. BUCHANAN²

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Dethiogliotoxin, C₁₃H₁₆N₂O₄, which is formed by desulfurization of gliotoxin with amalgamated aluminum, has been converted smoothly by hot aqueous hydrochloric acid into a new crystalline compound, C₁₃H₁₄N₂O₂, named anhydrodethiogliotoxin. On heating with acetic anhydride, anhydrodethiogliotoxin furnishes the compound C₁₃H₁₂N₂O₂, which has been identified as *dl*-2,3-dimethylpyrazinoindole-1,4-dione and is identical with the product obtained by direct reduction of gliotoxin with phosphorus and hydriodic acid. Anhydrodethiogliotoxin is tentatively formulated as a hydroxyindoline derivative. The action of amalgamated zinc and dilute hydrochloric acid on gliotoxin furnishes a compound C₁₃H₁₈N₂O₃, which differs from dethiogliotoxin in having one less oxygen atom. With hydrogen at low pressure over Raney nickel, in the presence of aqueous ethanol and triethylamine, gliotoxin is converted to a compound C₁₃H₂₀N₂O₄, which corresponds formally to a tetrahydro derivative of dethiogliotoxin. New structures are proposed for dethiogliotoxin and gliotoxin.

The action of amalgamated aluminum on gliotoxin under mild conditions brings about elimination of the sulfur atoms as hydrogen sulfide and furnishes a colorless, crystalline sulfur-free product of the molecular formula C₁₃H₁₆N₂O₄, which is designated as dethiogliotoxin.³ This compound appears to be formed by simple reductive desul-

furization in which the two sulfur atoms of gliotoxin are replaced by two hydrogen atoms



(1) Preceding paper, *THIS JOURNAL*, **73**, 3749 (1951).

(2) The Wm. S. Merrell Company Fellow, 1948–1949.

(3) J. D. Dutcher, J. R. Johnson and W. F. Bruce, *THIS JOURNAL*, **67**, 1736 (1945). In the present paper the name *dethiogliotoxin* is used instead of *dethiogliotoxin*, in conformity with recent recommendations for nomenclature of such compounds.

Dethiogliotoxin, like gliotoxin itself, is strongly levorotatory and its ultraviolet absorption spectrum is similar to that of gliotoxin. Since it seems likely that the desulfurization is effected without any profound structural alteration, the study of dethiogliotoxin is expected to contribute significantly to establishing the structure of gliotoxin.

Dethiogliotoxin reacts rapidly with hot methan-