added 4.0 ml. of 0.096 *N* sulfuric acid to precipitate the barium ions. The barium sulfate was removed by filtration through an asbestos mat. The filtrate was concentrated to dryness *in vacuo* at 50°. The white crystalline product obtained was dissolved in the minimum amount of hot absolute ethanol. The solution was filtered, and upon cooling, fine white needles separated. They were filtered off and dried in a desiccator over phosphorus pentoxide, yield 1.0 g., m. p. 244–245° when heated rapidly. Otherwise, it begins to sinter at 230° and undergoes rearrangement to caffeine. The substance is very soluble in cold water and hot alcohol. Theobromine is quite insoluble in both.

Anal. Calcd. for $C_7H_3ON_4(OCH_3)$: C, 49.5; H, 5.15; OCH_3, 15.95. Found: C, 49.7; H, 5.38; OCH_3, 15.83.

The ethanolic filtrate was diluted with water to a known volume and an aliquot was taken for the determination of the reducing power by the method of Shaffer and Somogyi.[13] Ninety per cent. of the glucose of the original glucoside was accounted for. The reducing value, the rotation of the reaction given above, and a 95% recovery of the aglucon as the methoxy derivative III establishes the formation of glucose.

Rearrangement of the Methoxy-oxy-3,7-dimethylpurine (III) to Theobromine.—Lactim ethers readily undergo rearrangement to the isomeric lactam ($-N{=}C{-}OCH_3 \rightarrow CH_3{-}N{-}C{=}O$) upon heating.[12] This rearrangement was employed to establish the structure of the purine residue III. About 0.2 g. of III was heated in a sealed tube at 290–300° in a lead-bath for one hour. After cooling, the tube was opened and the contents ground up in a mortar. The mixture was heated in a crucible, and the substance that sublimed was collected on the under surface of a watch glass over the crucible. The sublimate was recrystallized from absolute ethanol. It formed fine white needles, m. p. 227–231°, yield 0.15 g. One more recrystallization from the same solvent gave m. p. 230–232°. The substance showed no depression of the melting point when mixed with an authentic sample of caffeine which melted at 232–233°. A methoxyl determination was negative.

(13) Shaffer and Somogyi, *J. Biol. Chem.* **100**, 695 (1933).

The substance formed a mercuric chloride salt, m. p. 246°; reported for caffeine–mercuric chloride salt, m. p. 246°.

Conversion of III to Theobromine.—Ethers of the enolic forms of purines and pyrimidines (lactim ethers) are easily hydrolyzed by dilute acid. A small amount of III was dissolved in water and 0.1 volume of concentrated hydrochloric acid was added. The solution was boiled for five minutes. Upon cooling, it was neutralized with dilute sodium hydroxide and a white crystalline powder separated. This was filtered off and dried. The substance begins to sublime at 300° and melts at 350–355° with decomposition. An authentic sample of theobromine showed this same behavior. The material showed the characteristic solubility of theobromine, and formed an insoluble silver salt when ammoniacal silver nitrate was added to a solution of the substance in dilute ammonia water.

Anal. Calcd. for $C_7H_8O_2N_4$: C, 46.6; H, 4.45. Found: C, 46.8; H, 4.74.

Summary

1. Two purine glucosides, theobromine D-glucoside tetraacetate and hydroxycaffeine D-glucoside tetraacetate were treated with barium methoxide in dry methanol in an attempt to cleave the glucosidic linkage by methanolysis.

2. Methanolysis of theobromine D-glucoside tetraacetate occurred and the products of the cleavage were glucose and a methoxyl derivative of the aglucon. This indicates that the cleavage occurs between the glucosidic oxygen and the aglucon. The cleavage of the glucoside of hydroxycaffeine did not result in products which were indicative of the mechanism of the splitting.

3. An electronic interpretation of this reaction is offered in an attempt to rationalize the results with respect to the present concepts of the various mechanisms involved in the alkaline cleavage of the glycosidic linkage.

MADISON, WISCONSIN RECEIVED JUNE 2, 1949

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORY]

The Reaction of Amides with Isocyanates. II. N-Substituted Amides

BY PAUL F. WILEY

In previous studies[1,2,3] of the reaction of isocyanates with amides in which the amide nitrogen was not substituted the reaction has been shown to occur according to the equation (R′ = H).

$$RCONHR' + R''NCO \longrightarrow RCONCONHR''$$
$$\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\quad R'$$

R = alkyl or aryl
R″ = alkyl or aryl

Recent investigators[4,5,6,7] who have had occasion to use the reaction of nitrogen-substituted amides with isocyanates have generally made no mention of any divergence from the above equation. However, Kühn[1,2] has reported unknown products from formanilide, acetanilide, acetnaphthalide and benznaphthalide and phenyl isocyanate as well as the formation of N,N′-diphenylbenzamidine from benzanilide. A further investigation along the lines of Kühn's[1,2] earlier work has been made in the present study.

In these experiments phenyl isocyanate was the only isocyanate used, and in addition to the amides shown in Table I, N-*n*-butylacetamide, N-isobutylundecylenamide and N-ethylbenzamide were used. The reactions were run using either boiling toluene or xylene as reaction media or no solvent at temperatures varying from 120 to 220°. Table I lists identified products obtained and

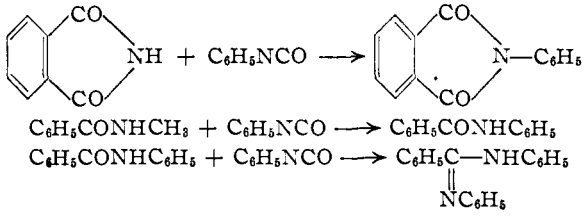
(1) Kühn, *Ber.*, **17**, 2880 (1884).
(2) Kühn, *ibid.*, **18**, 1476 (1885).
(3) Wiley, THIS JOURNAL, **71**, 1310 (1949).
(4) French and Wirtel, *ibid.*, **48**, 1736 (1926).
(5) Lüdke, *Z. physiol. Chem.*, **160**, 215 (1925).
(6) Berchet, U. S. Patent 2,333,914 (November 9, 1943).
(7) Foster, U. S. Patent 2,333,922 (November 9, 1943).

TABLE I

Amide	Solvent or temperature	Time in hours	Yield, %	Product
N-Ethylacetamide	Toluene	24	19.4	1-Acetyl-1-ethyl-3-phenylurea
ϵ-Caprolactam	Toluene	24	92	N-(Phenylcarbamyl)-ϵ-caprolactam
Succinimide	165–180°	7	1.3	1-Succinoyl-3-phenylurea
Acetanilide	Xylene	24	17.3	1-Acetyl-1,3-diphenylurea
N-Methylbenzamide	190°	2	13.2	Benzanilide
Benzanilide	200–220°	4	44	N,N′-Diphenylbenzamidine
Phthalimide	165–180°	4	14	N-Phenylphthalimide

reaction conditions. Of the products reported in Table I, the first three are new. Analyses and method of preparation were felt to be sufficient proof of structure for the first two of these compounds. However, the product obtained from succinimide and phenyl isocyanate did not give an analysis completely consistent with the proposed structure, the yield was very low, and the reaction conditions were severe. It is quite probable that the proposed structure is incorrect, but numerous attempts directed toward an independent synthesis were unsuccessful. The amides used but not listed in Table I could not be caused to react with phenyl isocyanate.

The most generally occurring reaction between substituted amides and isocyanates was the one in accord with the above equation where R′ was alkyl, aryl or acyl. This reaction occurred in all cases where reaction could be made to proceed to any detectable degree in boiling toluene or xylene. Other reactions that occurred were



$$C_6H_5CONHCH_3 + C_6H_5NCO \longrightarrow C_6H_5CONHC_6H_5$$

$$C_6H_5CONHC_6H_5 + C_6H_5NCO \longrightarrow C_6H_5C(=NC_6H_5)-NHC_6H_5$$

These three reactions appear to be quite unlike, but it is probable that the first step in each is an attachment of the isocyanate nitrogen atom to the carbon in the carbonyl group of the amide. Other products were formed in small amounts when ϵ-caprolactam and acetanilide were used at 200°, but these compounds were not identified. The product from acetanilide was a yellow solid melting above 340°. The analysis indicated a molecular formula of $C_{36}H_{28}N_6O_4$, but, due to insolubility of the compound, a molecular weight determination could not be made. The product was undoubtedly the same as that reported by Kühn[2] from the same reaction. From ϵ-caprolactam and phenyl isocyanate at 200° there was obtained a white solid for which the molecular formula $C_{13}H_{14}N_2$ seemed most likely. No satisfactory formula could be postulated for either of these compounds on a basis of the reaction of phenyl isocyanate with the amides. It is probable that they are derived from reaction of phenyl isocyanate with itself.

Reaction of substituted amides with isocyanates is much slower and more difficult to bring about than is the case with unsubstituted amides. In general the completely aliphatic amides in which the nitrogen was relatively basic and little steric hindrance was present, *i. e.*, ϵ-caprolactam, reacted best under mild conditions. Under severe conditions no clear cut pattern of reaction appeared.

Acknowledgment.—I am indebted to Messrs. W. L. Brown, H. L. Hunter and W. J. Schenck for microanalyses.

Experimental[8]

1-Acetyl-1-ethyl-3-phenylurea.—A solution of 11.9 g. (0.1 mole) of phenyl isocyanate and 8.7 g. (0.1 mole) of N-ethylacetamide in 200 cc. of dry toluene was refluxed for twenty-four hours. The solvent was removed by evaporation under reduced pressure. The residue was separated further by distillation *in vacuo* removing material boiling at 55–60° at 0.5 mm. pressure. The semi-solid substance remaining was crystallized twice from alcohol. The yield of 1-acetyl-1-ethyl-3-phenylurea, m. p. 54–58°, was 4.0 g. (19%). Three recrystallizations from alcohol changed the melting point to 55–58°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.80; N, 13.59. Found: C, 63.86; H, 6.80; N, 13.57.

N-Phenylcarbamyl-ϵ-caprolactam.—A solution of 11.3 g. (0.1 mole) of ϵ-caprolactam and 11.9 g. (0.1 mole) of phenyl isocyanate in 200 cc. of dry toluene was refluxed for twenty-four hours. Removal of the solvent by reduced pressure evaporation left a colorless liquid residue which crystallized on cooling. The solid melted at 62–67° and weighed 22.7 g. Recrystallization of the product from alcohol gave a yield of 21.6 g. (92%) of white crystalline material, m. p. 67–69°. A small portion was recrystallized three times from alcohol, m. p. 67–69°.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.95; N, 12.06. Found: C, 67.00; H, 6.67; N, 12.03.

1,1-Succinoyl-3-phenylurea.—A mixture of 11.1 g. (0.1 mole) of succinimide and 11.9 g. (0.1 mole) of phenyl isocyanate was refluxed for seven hours. The temperature of the reaction mixture ranged from 166 to 178°. The cooled reaction mixture was dissolved in absolute alcohol, and the resulting solution was diluted with dry ether. The supernatant liquid was decanted, and the residue was dissolved in boiling alcohol, treated with charcoal, and recrystallized five times. The product crystallized in shiny white crystals, m. p. 118–120°. The yield was 0.3 g. (1.3%).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.58; N, 12.84. Found: C, 60.17; H, 4.43; N, 13.28.

1-Acetyl-1,3-diphenylurea.—A solution of 6.7 g. (0.05 mole) of acetanilide and 5.95 g. (0.05 mole) of phenyl isocyanate in 100 cc. of dry xylene was refluxed for twenty-four hours. Cooling the reaction mixture caused deposition of 4.4 g. of acetanilide, m. p. 100–105°. After the mixture was filtered, the solvent was removed from the

(8) Melting points are uncorrected.

filtrate by reduced pressure evaporation. The residue was shaken thoroughly with water, and the mixture was allowed to stand overnight. The water was poured off, and the remaining solid was crystallized from alcohol. There was obtained 2.2 g. (17%) of 1-acetyl-1,3-diphenylurea, m. p. 103–105° (lit. 105°).

N-Methylbenzamide and Phenyl Isocyanate.—A mixture of 13.5 g. (0.1 mole) of N-methylbenzamide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated slowly to about 190° and maintained at that temperature for about two hours. The cooled reaction mixture solidified. Five recrystallizations from alcohol gave 2.6 g. (13%) of benzanilide, m. p. 160–162°, and no depression in melting point upon admixture with benzanilide.

N-Phenylphthalimide.—A mixture of 29.4 g. (0.2 mole) of phthalimide and 23.8 g. (0.2 mole) of phenyl isocyanate was refluxed for four hours. The cooled reaction mixture was broken up and boiled in alcohol. The alcohol was removed by filtration. The residue was dissolved in boiling acetic acid and treated with charcoal. This was followed by three recrystallizations from acetic acid. The product was a white solid, m. p. 204–206°, crystallizing in long white needles (lit. m. p. 204°). A yield of 6.2 g. (14%) was obtained.

Anal. Calcd. for $C_{14}H_9NO_2$: N, 6.28. Found: N, 6.25.

N,N'-Diphenylbenzamidine.—A mixture of 11.9 g. (0.1 mole) of phenyl isocyanate and 19.7 g. (0.1 mole) of benzanilide was heated at 200–220° for four hours. The solid obtained on cooling was recrystallized three times from absolute alcohol. The yield of white solid, m. p. 130–132°, was 12.1 g. (44%). A product melting at 140–144° was obtained after five more recrystallizations from alcohol. Kühn[2] reported a melting point of 145°.

Anal. Calcd. for $C_{19}H_{16}N_2$: N, 10.29. Found: N, 10.46.

Phenyl Isocyanate and Acetanilide at 200°.—A mixture of 13.5 g. (0.1 mole) of acetanilide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated at 200–210° for four hours. The product was broken up and boiled with 150 cc. of alcohol. This mixture was cooled and filtered. There was obtained 5.3 g. of a yellow solid which melted at about 350°. This product was recrystallized four times from boiling nitrobenzene. The final compound melted at 340–375° with decomposition.

Anal. Calcd. for $C_{36}H_{28}N_5O_4$: C, 72.72; H, 4.74; N, 11.77. Found: C, 72.79; H, 4.66; N, 11.85.

Phenyl Isocyanate and ε-Caprolactam at 200°.—A mixture of 11.3 g. (0.1 mole) of ε-caprolactam and 11.9 g. (0.1 mole) of phenyl isocyanate was heated at 190–210° for four hours. The cooled reaction mixture was dissolved in boiling alcohol and filtered. The cooled filtrate deposited 1.7 g. of white crystals melting at 202–205°. Charcoaling and concentrating the filtrate gave only a black non-crystallizable oil. Five recrystallizations of the solid product from alcohol gave a sample, m. p. 209–210°.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.79; H, 7.07; N, 14.12; mol. wt., 198. Found: C, 78.28, 78.65, 79.21; H, 7.30, 6.48, 7.24; N, 14.53, 14.74; mol. wt., 232.

Summary

1. Under mild conditions some nitrogen substituted amides react with phenyl isocyanate to form 1,1-disubstituted-3-phenylureas, and some do not react.

2. The products obtained under severe conditions are varied and not predictable.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF GEORGIA SCHOOL OF MEDICINE]

Chemotherapeutic Agents from Heterocyclic Amines. I. Amine Arsenicals[1]

BY DAVID FIELDING MARSH[2] AND ROBERT A. WOODBURY

The replacement of the amide NH_2 group of sulfanilamide by an NHR radical in which R represents a heterocyclic nucleus has led to compounds which are more potent and are useful for a greater variety of infections.[3] It seemed advisable to utilize these heterocyclic nuclei as substituents in other series of compounds characterized by chemotherapeutic activity.

Gough and King[4] showed the trypanocidal activity of *p*-arsenosobenzamide, and Eagle, Doak, Steinman and Hogan[5] have exhaustively investigated simple derivatives and homologs of this compound and have indicated their favorable treponemicidal activity.

The present communication reports the preparation of *p*-arsenosobenzamidoheterocycles by the reaction of *p*-dichloroarsylbenzoyl chloride with the required amine in benzene followed by hydrolysis of the *p*-arsenosobenzamidoheterocycles.

Experimental Part

Preparation of Amides.—The amine (0.2 mole), recrystallized from benzene before use, was dissolved in 250–600 ml. of warm benzene in an erlenmeyer flask and 12 ml. of freshly distilled *p*-dichloroarsylbenzoyl chloride[6] was added with shaking. The mixture was refluxed for twenty minutes to an hour and the supernatant liquid decanted into a beaker. The material which adhered to the flask was dissolved in warm 95% ethanol. On cooling, the desired *p*-arsenosobenzamide separated and was removed by filtration. Partial evaporation of the filtrate yielded some *p*-arsenosobenzoic acid. The by-product amine hydrochloride can be obtained by complete evaporation of the filtrate. The yields of amide were 35–45%, based on the amount of amine used. By recrystallizing the residual material from absolute methanol instead of 95% ethanol it was possible to prepare the dichloroarsylbenzamides. The decanted benzene contained some of the corresponding dichloroarsylbenzamide along with some unreacted amine. The products are white amorphous powders that are tinged slightly yellow or pink if

(1) Presented on the program of the Medicinal Division at the American Chemical Society meeting, New York, September 11, 1944.

(2) Present address: Department of Pharmacology, West Virginia University School of Medicine, Morgantown, West Virginia.

(3) Fosbinder and Walton, THIS JOURNAL, **61**, 2032 (1939); and Roblin, Williams, Winnek and English, *ibid.*, **62**, 2002 (1940).

(4) Gough and King, *J. Chem. Soc.*, 669 (1930).

(5) (a) Doak, Eagle and Steinman, THIS JOURNAL, **62**, 3012 (1940); (b) Steinman, Doak and Eagle, *ibid.*, **66**, 192 (1944); and (c) Eagle, Hogan, Doak and Steinman, *J. Pharmacol.*, **81**, 142 (1944).

(6) Prepared by the method of Lewis and Cheetham, THIS JOURNAL, **43**, 2117 (1921), from *p*-carboxyphenylarsonic acid which was synthesized either by their method or from *p*-cyanophenylarsonic acid prepared by the method of Linsker and Bogert, *ibid.*, **65**, 932 (1943).