[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS.]

# THE ACTION OF AMMONIA AND AMINES ON THE SUBSTITUTED UREAS AND URETHANES.

## II. ALLOPHANIC ESTER.

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In a previous paper[1] a study of the action of amines on carbonyl diurethan was presented. It seemed advisable later to follow this with an investigation of the action of amines on allophanic ester, which may be regarded as the mono-carbethoxy derivative of urea, while carbonyl-diurethane is di-carbethoxy urea. We wished not only to ascertain what differences there might be in the course of the reaction, but also to verify the experimental data in the literature which recorded only the formation of a substituted biuret and appeared unnecessarily incomplete.

It will be noted that allophanic ester, $\overset{1}{N}H_2\overset{2}{C}O\overset{3}{N}H\overset{4}{C}OOR$, differs from the carbonyl-diurethane in having at Position 4 only one carboxy group that can enter into reaction; the other point of attack is the amine group at Position 1.

Thus, if the primary amine should react at Position 1, an aryl allophanic ester and ammonia could be obtained.

$$RNH_2 + NH_2CONHCOOC_2H_5 = RNHCONHCOOC_2H_5 + NH_3. \quad (I)$$

On the other hand, if 4 were the point of attack, the result might be a mono-aryl biuret and alcohol.

$$NH_2CONHCOOCH_3 + H_2NR = RNHCONHCONH_2 + C_2H_5OH. \quad (II)$$

As a matter of fact, all of the above products were isolated, which substantiates the validity of the assumptions of these reactions.

At higher temperatures mono- and di-substituted ureas are produced, doubtless because of the continued action of the amines on the biuret.

$$RNHCONHCONHR + RNH_2 = RNHCONH_2 + RNHCONHR. \quad (III)$$

Above 160°, Schiff[2] has found that the monophenyl urea decomposes yielding diphenyl urea, which would account for the relatively small amount of the monophenyl derivative found.

### Experimental Part.

**Preparation of Ethyl Allophanate.**—The literature records many methods for the preparation of this ester, but most of them are unsatisfactory so far as yield is concerned.[3] The greater portion of the allo-

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[1] THIS JOURNAL, **41**, 1004 (1919).

[2] Schiff, *Ann.*, **352**, 83 (1907).

[3] Amato, *Jahresber.* 749 (1873); Saytzeff, *Ann.*, **135**, 230 (1865); Wilm, *ibid.*, **192**, 243 (1878); Schroeter, *Ber.*, **26**, 2172 (1893); Hlasiwetz, *Ann.*, **134**, 116 (1865); *Ann. chim. phys.* [8] **22**, 349, 358 (1911); THIS JOURNAL, **41**, 1005 (1919).

phanic ester used in the following experiments was made by the action of ethyl chloroformate on urea, a method probably first suggested by Wilm and Wischin.[1] Later Schiff repeated this work.[2] When he heated molar mixtures of urea and ethyl chloroformate, he obtained only cyanuric acid, ammonium chloride, ethyl carbonate and a trace of biuret. When the proportions were changed and 2 mols of the urea were used, Schiff obtained a 7.5% yield of the ester, together with cyanuric acid and a trace of biuret. Therefore he concluded that the method was not suitable for the preparation of the ethyl allophanate.

The following modification of the procedure gave good results. One mol. of ethyl chloroformate is poured over 2.1 mols of the urea in a flask connected with a reflux condenser. This mixture is now warmed on a water-bath for 2 or 3 hours, or at least for half an hour after drops cease to fall from the condenser. Water is added to the warm mass and it is filtered with suction and again washed with cold water. When dry it is ready for use. The melting point varies from 189° to 192°, depending upon the purity of the urea. The yield is from 62 to 65%. During the operation no hydrogen chloride was evolved, a fact also observed by Schiff. This explains the role of the second mol of urea, which evidently combines with the acid to form urea hydrochloride. Experiments showed that when pyridine or quinoline was used to take up the acid, there was a decrease in both the purity and the yield of the ester because of the partial decomposition of the ethyl chlorocarformate[3] by the tertiary amine. The method of Billmann,[4] in which urethane is heated with phosphorus pentoxide, is simple, but the yield is somewhat less.

## I. Ethyl Allophanate and Amines.

Hofmann[5] found that this ester reacts with aqueous ammonia at 100° to give the biuret and alcohol. However, anhydrous liquid ammonia, or liquid ammonia containing 2% of water is without effect, since the ester can be recovered unchanged. This is in decided contrast to the ease with which carbonyl-diurethane reacts under like conditions.

**1. Aniline and Ethyl Allophanate.**—Hofmann also showed[5] that aniline at its boiling-point reacted with ethyl allophanate to give diphenyl biuret. He assumed, though without any evidence, that monophenyl biuret was first formed. On the contrary, the experimental results indicate that phenyl allophanic ester is the primary product.

After ethyl allophanate was heated with slightly more than one mol of aniline at 120–125° for one hour, the reaction product was extracted with

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[1] Wilm and Wischin, *Ann.*, **147**, 155 (1868).

[2] Schiff, *ibid.*, **291**, 372 (1896).

[3] Hopkins, *J. Chem. Soc.*, **117**, 278 (1920).

[4] Billmann, *Ber.*, **50**, 508 (1917).

[5] Hofmann, *ibid.*, **4**, 265 (1871).

a cold dilute solution of sodium hydroxide. Ethyl-phenyl allophanate was precipitated (m. p. 105°) when the filtrate was acidified. Its identity was proven by comparison with a known sample of the ester, which had been made by the action of phenyl isocyanate on urethane.[1]

**Diphenyl Biuret.**—The allophanic ester (one mol) and aniline (2 mols) were heated at 125° for one hour. After the residue had been treated with dil. alkali to remove the soluble phenyl allophanic ester, it was crystallized repeatedly from alcohol, from which the biuret separated as a mass of white needles, with a silky luster. It melted at 209–10°.

Calc. for $C_{14}H_{13}O_2N_3$: N, 16.47. Found: 16.44, 16.63.

**Monophenyl Urea and Diphenyl Urea.**—When a mixture of the ester and aniline was heated at 160° to 170°, both monophenyl urea and diphenyl urea were formed. They were separated by the differences in their solubilities and were identified by analysis and by comparison with a known sample of each compound.

2. ***o*-Anisidine and Ethyl Allophanate.**—*o*-Anisyl-allophanic ethyl ester ($o$-$CH_3OC_6H_4NHCONHCOOC_2H_5$) was formed when the allophanic ester was heated with *o*-anisidine at 130° to 140° for 2 hours. It dissolved in a dilute solution of sodium hydroxide and crystallized from alcohol in fine needles, which melted at 125°. It is insoluble in water but very soluble in acetone and in benzene. The same compound was made by the action of ethyl chlorocarbonate on mono-*o*-anisyl urea.

**Di-*o*-Anisyl Biuret,** $NH(CONHC_6H_4OCH_3)_2$.—This was the main product isolated when 2 mols of the amine were used and the temperature varied from 130° to 140°. It crystallized from acetone or from alcohol in white needles which melted at 211–2° with partial sublimation.

Calc. for $C_{16}H_{17}O_4N_3$: N, 13.33. Found: 13.15.

Di-*o*-anisyl urea was the only product formed when the compounds were heated at 175° for 2 hours. Crystallized from alcohol, it melted at 182°.[2]

Calc. for $C_{15}H_{16}O_3N_2$: N, 10.29. Found: 10.24.

3. ***o*-Toluidine and Ethyl Allophanate.**—**Ethyl-*o*-tolyl-allophanate,** $o$-$C_7H_7NHCONHCOOC_2H_5$.—Equal mols of the ester and *o*-toluidine heated between 115° and 116° for 4 hours gave the substituted ester. It was soluble in dil. alkali, melted at 133° and was identical with the ester prepared from the *o*-tolyl urea and ethyl chlorocarbonate.[3] When 2 mols of *o*-toluidine were used at temperatures varying from 160–190° 3 compounds could be isolated: monotolyl urea (m. p. 189°); di-*o*-tolyl urea (m. p. 245–7°); and di-*o*-tolyl biuret, which formed white needles when crystallized from alcohol, and melted at 204–5°.

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[1] Dains, Greider, Kidwell, THIS JOURNAL, 41, 1008 (1919).

[2] Conrad and Limpach, *Ber.*, 21, 1654 (1888); Muhlhauser, *Ann.*, 207, 245 (1881).

[3] Piccard, *J. Chem. Soc.*, 81, 1571 (1902); THIS JOURNAL, 41, 1010 (1919).

Calc. for $C_{16}H_{17}O_2N_3$: N, 14.84. Found: 14.36.

The last 2 compounds were separated with difficulty by repeated fractional crystallization from alcohol.

4. ***m*-Toluidine and Ethyl Allophanate.**—No *m*-tolyl-allophanic ester could be found, when the same experimental conditions that were successful in the case of *o*-toluidine were used. Three products were isolated: *m*-tolyl urea (m. p. 143°); di-*m*-tolyl urea (m. p. 217°); and di-*m*-tolyl biuret. The last of the three is difficultly soluble in the usual organic solvents, but could be crystallized from alcohol from which it separated as a cotton-like mass of white needles, which melted at 179–9°.

Calc. for $C_{16}H_{17}O_2N_3$: N, 14.84. Found: 14.65, 14.75.

5. ***m*-Nitro-aniline and Ethyl Allophanate.**—Equal mols of the ester and *m*-nitro-aniline were dissolved in kerosene and heated for 2 hours at 125°. The residue was partly soluble in cold solution of sodium hydroxide from which acid precipitated ethyl *m*-nitrophenyl allophanate, the same as that which had been obtained previously by Piccard from *m*-nitrophenyl-hydroxy-oxamide.[1] This crystallized from alcohol in yellow needles which melted at 189–90°.

Calc. for $C_{10}H_{11}O_5N_3$: N, 16.60. Found: 16.71.

**Di-*m*-nitrophenyl Biuret.**—When heated at 145°, the same components gave the biuret in the form of yellow crystals difficultly soluble in alcohol; they melted at 215–16°.

Calc. for $C_{14}H_{11}O_6N_5$: N, 20.30. Found: 20.29.

At higher temperatures mononitro-phenyl urea was obtained as yellow crystals (m. p. 165°), soluble in hot water and di-*m*-nitro-diphenyl urea (m. p. 133–4°).

Calc. for $C_{13}H_{10}O_5N_4$: N, 18.54. Found: 18.30.

6. ***p*-Bromo-aniline and Ethyl Allophanate.**—The reaction followed in the main the lines suggested for aniline, although great difficulty was experienced in separating the products on account of their comparative insolubility in most organic solvents. Below 120°, no action seems to occur.

**Di-*p*-bromo-diphenyl Biuret.**—In one case, after the components had been heated for 2 hours at 120°, a product was obtained which was washed with hot water, hot alcohol and hot acetic acid. The residue, crystallized from boiling nitrobenzene, separated in small plates with a pearly luster, which began to decompose at 280°.

Calc. for $C_{14}H_{11}O_2N_3Br_2$: N, 10.26. Found: 10.20.

Heated at 140°, *p*-bromo-aniline and the ester gave mono-*p*-bromophenyl urea, difficultly soluble plates which decomposed above 270°.

Calc. for $BrC_6H_4NHCONH_2$: N, 13.03. Found: 13.00.

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[1] Piccard, *J. Chem. Soc.*, **81**, 1569 (1902).

At 150° the formation of di-*p*-bromo-diphenyl urea occurred.

Calc.: N, 7.57. Found: 7.46.

## II. Methyl Allophanate and Aromatic Amines.

**Preparation.**—The methyl ester was made by the action of methyl chlorocarbonate (one mol) on urea (2 mols), according to the procedure used in the preparation of the ethyl derivative. The maximum yield obtained was 75%, but the product was of a high degree of purity. It is only slightly soluble in hot water, but can be readily recrystallized from dil. alcohol or from acetone.

1. **Aniline and Methyl Allophanate.**—While the action in the main is analogous to that of the ethyl ester, yet one interesting difference presented itself in that the methoxy-group showed less stability than the ethoxy toward the amine.

Although a great variety of temperatures were chosen, methylphenyl allophanate was not isolated in any experiment. This is singular, because the first product of the action of amines on the ethyl ester is the corresponding ethylaryl allophanate.

**α-Phenyl Biuret,** $C_6H_5NHCONHCONH_2$.—Molar quantities of the methyl ester and aniline were heated at 150° for 2 hours. The melt was extracted with a dilute solution of sodium hydroxide and the filtrate treated with dil. acid. The precipitated biuret can be crystallized from alcohol, acetone, or hot water, from which it separates in shining scales, which usually melt at 164°, 165° or 167°. However, after further recrystallization if the crystals are dried at 100° they melt and darken at 155°. Piccard and Carter[1] give the melting-point at 156°, as does also McKee,[2] who obtained it by the action of hydrogen chloride on methylphenyl-isobiuret. Schiff,[3] who prepared it from phenyl-hydroxy-oxamide, says that the true melting-point is 165°.

Calc. for $C_8H_9O_2N_3$: C, 53.62; H, 5.08; N, 23.46. Found: C, 46.18; H, 5.33; N, 23.58.

Molar weight (McCoy's method in absolute alcohol).

Calc.: 179. Found: 179.91, 187.

Heated with aniline the α-phenyl biuret gave ammonia and diphenyl biuret.

**Other Products.**—Diphenyl biuret was produced at all temperatures from 150° to 170°, while above this point diphenyl urea was the main product. Monophenyl urea was isolated in only one case. Evidently the amount formed with the methyl-ether is less than that produced with the ethyl ester.

2. ***o*-Toluidine and Methyl Allophanate. *o*-Tolyl Biuret,** $C_7H_7$-

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[1] Piccard and Carter, *J. Chem. Soc.*, **79**, 846 (1900); **81**, 1563 (1902).

[2] McKee, *Am. Chem. J.*, **26**, 254 (1901).

[3] Schiff, *Ann.*, **352**, 79 (1907).

NHCONHCONH$_2$. This was found in various amounts when temperatures ranging from 140–170° were employed. It was soluble in alkali and crystallized from dil. alcohol in fine white needles, which melted and sublimed at 179–180°. It corresponded in every way to the biuret obtained by Piccard and Carter[1] from *o*-tolyl-hydroxyl-oxamide. The other products isolated were di-*o*-tolyl biuret, *o*-tolyl urea and di-*o*-tolyl urea. No methyltolyl allophanate was found.

### III. Aniline and Ethyl Benzoyl Allophanate, $C_6H_5CONHCONHCOOC_2H_5$.

For comparison, the action of aniline on an acyl derivative of allophanic ester was tried. Thus, benzoyl-allophanic ester and aniline when heated at 150° gave benzoyl-phenyl urea (m. p. 209°).

Calc., $C_{14}H_{12}O_2N_2$: N, 11.65. Found: 11.56.

This same urea had been obtained previously by the action of aniline on benzoyl urethane[2] and on ethyl-benzoyl-thioncarbamate,[3] $C_6H_5CONH$-$CSOC_2H_5$.

**Phenyl hydrazine and Ethyl Allophanate, 1-Phenyl-4-carbethoxy-semicarbazide,** $C_6H_5NHNHCONHCOOC_2H_5$.—Below 140° there was no reaction between the components; at that temperature, however, the new ester was formed with the elimination of ammonia but no alcohol, and after repeated crystallization from alcohol, it was obtained in the form of small white scales, melting at 175–6°.

Calc. for $C_{10}H_{13}O_3N_3$: N, 18.93. Found: 19.18.

The compound is isomeric with the 1,1-phenyl-carbethoxy-semicarbazide, $C_6H_5N(COOC_2H_5)NHCONH_2$, which can be synthesized by the action of ethyl chlorocarbonate on the monophenyl-semicarbazide and which melts at 171–5°.[4] The mode of formation of the ester melting at 176°, shows conclusively that it must be an isomer and not identical with the 1,1-phenyl-carbethoxy-semicarbazide.

Heated above its melting-point the 1-4 ester lost alcohol, the ring closed and 1-phenyl-urazole was formed, while with ammonia it gave a compound melting at 195°, which is being investigated.

**1-Phenyl-urazole,** $C_6H_5N$-$NHCONHCO$ (m. p. 263–4°) is formed quantitatively whenever phenylhydrazine and the ester are heated above 140°. It was identified by comparison with a known sample of the urazole and by the synthesis of its acetyl derivative (m. p. 169°).

**Phenyl Hydrazine and Methyl Allophanate.**—The same interesting reactivity of the methoxy group was noted in the case of methyl ester. The intermediate 1,4-phenyl-carbomethoxy-semicarbazide could not be

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[1] Piccard and Carter, *J. Chem. Soc.*, 81, 1563 (1902).

[2] Wheeler and Johnson, *Am. Chem. J.*, 24, 208 (1900).

[3] Wheeler and Merriam, This Journal, 23, 289 (1901).

[4] Wheeler and Beardsley, *Am. Chem. J.*, 27, 269 (1902); Acree, *Ber.*, 37, 618 (1904).

isolated. When the mixture was heated at 150° for a short time no change occurred, but longer heating at this temperature, or for a few minutes at 153°, gave the 1-phenyl-urazole as the sole product.

## Summary.

(1) A study has been made of the progressive action of primary amines on methyl and ethyl allophanate which has resulted in the isolation of aryl allophanic esters, mono- and di-aryl biurets and mono- and di-substituted ureas.

(2) Phenylhydrazine has been found to give 1-phenyl-4-carbethoxy-semicarbazide and 1-phenyl-urazole. The investigation is being continued in this laboratory.

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[CONTRIBUTION FROM THE LABORATORY OF WERNER DRUG AND CHEMICAL CO.]

# THE METHIODIDES OF THE CONDENSATION PRODUCTS OF SOME CYCLIC ALDEHYDES WITH QUINALDINE AND ALPHA PICOLINE, AND THEIR POSSIBLE VALUE AS INDICATORS IN ACIDIMETRY.

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The aqueous solution of the methiodide of 2(3-methoxy-4-hydroxy-styryl)quinoline when treated with sodium hydroxide solution was found to give a deep fuchsine-colored fluid, instead of the anticipated precipitate of the quaternary-ammonium hydroxide. As the hydrochloride of 2(3-methoxy-4-hydroxy-styryl)quinoline under like conditions gave but a milky emulsion of the free base, the color noted must be due to the auxochrome effect of the methyl group attached to nitrogen.

Following up these results, the methiodides of the condensation products of various cyclic aldehydes with quinaldine were prepared, and their behavior with sodium hydroxide determined. The methiodides of the condensation products of quinaldine with benzaldehyde, furfural, *o*-hydroxy-benzaldehyde, *p*-hydroxy-benzaldehyde, protocatechuic aldehyde, and also the condensation product of piperonal with $\alpha$-picoline, were prepared and studied.

The results secured showed that in order that the methiodides of compounds of this type have the properties of an indicator, that there be a phenolic hydroxyl group attached to the neucleus of the aldehyde used in its preparation. Thus in the case of the methiodides of 2-styryl-quinoline, 2($\beta$-furfuryl-vinyl)quinoline, 2(4,3-methylene-dioxyl)pyridine, the yellow-aqueous solutions of these salts were rendered colorless upon the addition of sodium hydroxide solution, but the methiodides of 2(2-hydroxy-styryl)quinoline and of 2(4-hydroxy-styryl)quinoline gave a blood-red