Chem. Thesis

The Action of Hydrogen Peroxide and Alkali on Some Uric Acid Derivatives.

by

Elizabeth Stuart Gatewood

B.S. Barnard College, Columbia University

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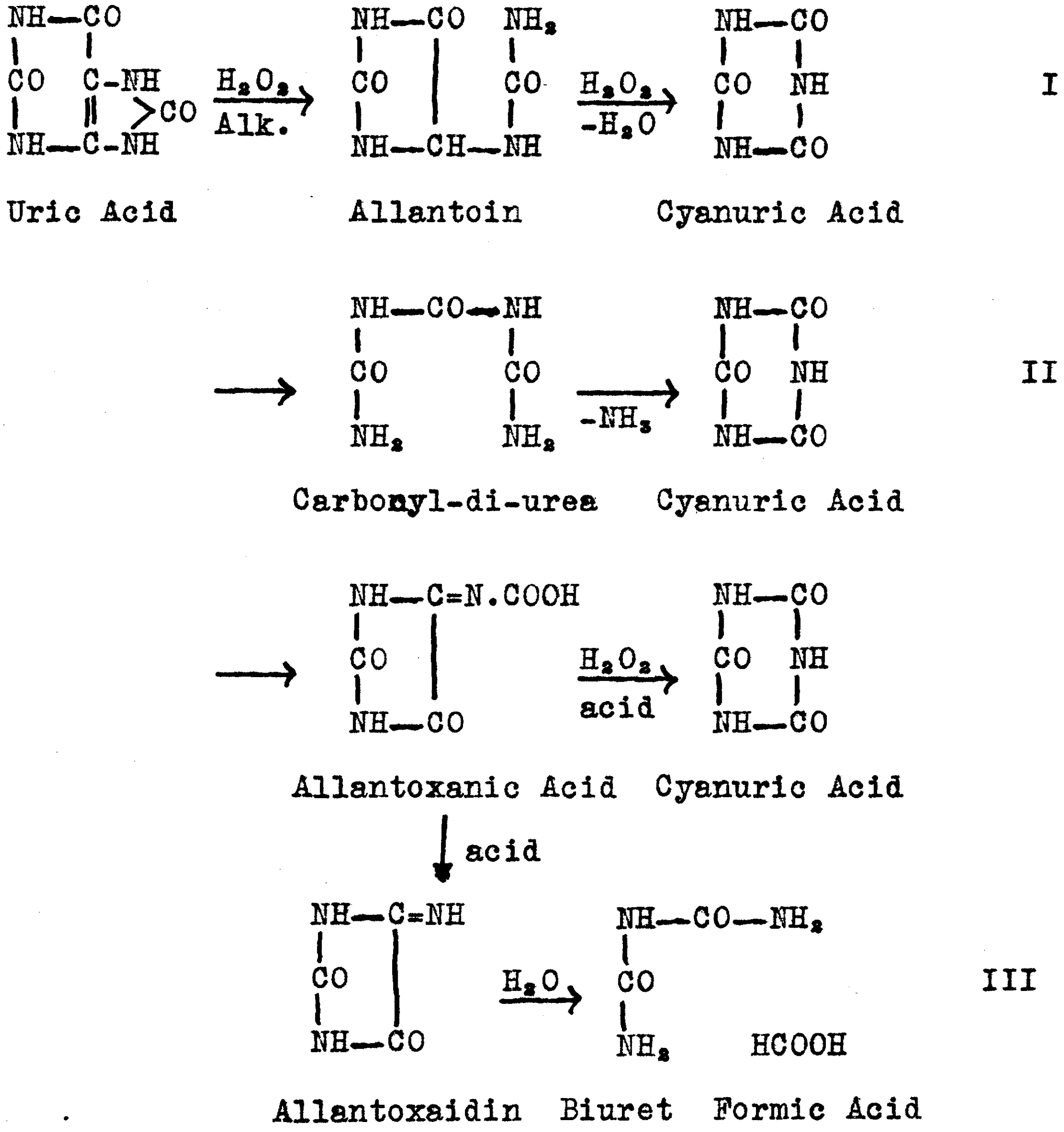
Contents

The Action of Hydrogen Peroxide and Alkali on Some Uric Acid Derivatives.

I. Introduction.

Oxidation of Uric Acid with Hydrogen Peroxide. At the present time the oxidation of uric acid with hydrogen peroxide in alkaline solution[1] may be formulated as follows:



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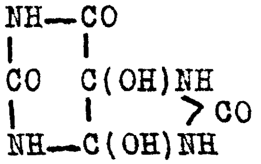
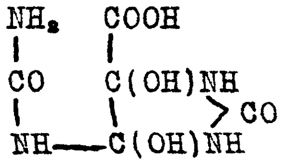
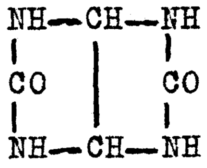
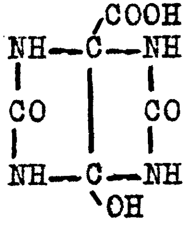
[1] Venable, J.A.C.S. 40, 1099 (1918); Moore and Thomas, J.A.C.S. 40, 1120 (1918).

Each reaction is apparently independent of the other two. Allantoin is formed when the oxidation is carried out in weakly alkaline solution and the solution then slightly acidified; at high temperatures (80° or 90°) it goes over readily to cyanuric acid. Carbonyl-di-urea is also formed at 90° when the alkaline concentration is low. It is transformed in 0.5N alkali to cyanuric acid with or without hydrogen peroxide. Allantoxanic acid is obtained only when the oxidation is carried out in about normal alkali and when the excess peroxide is decomposed by manganese dioxide before acidifying. No intermediates have been found between uric acid and the final oxidation products. Uric acid glycol, and alloxanic acid urea, which, in the permanganate oxidation, Behrend[1] had suggested as possible intermediates, and also glycol uril, have been prepared and treated with hydrogen peroxide, but none of them gave the oxidation products sought. The hypothetical oxyacetylendiurein carboxylic acid, which Behrend[2]









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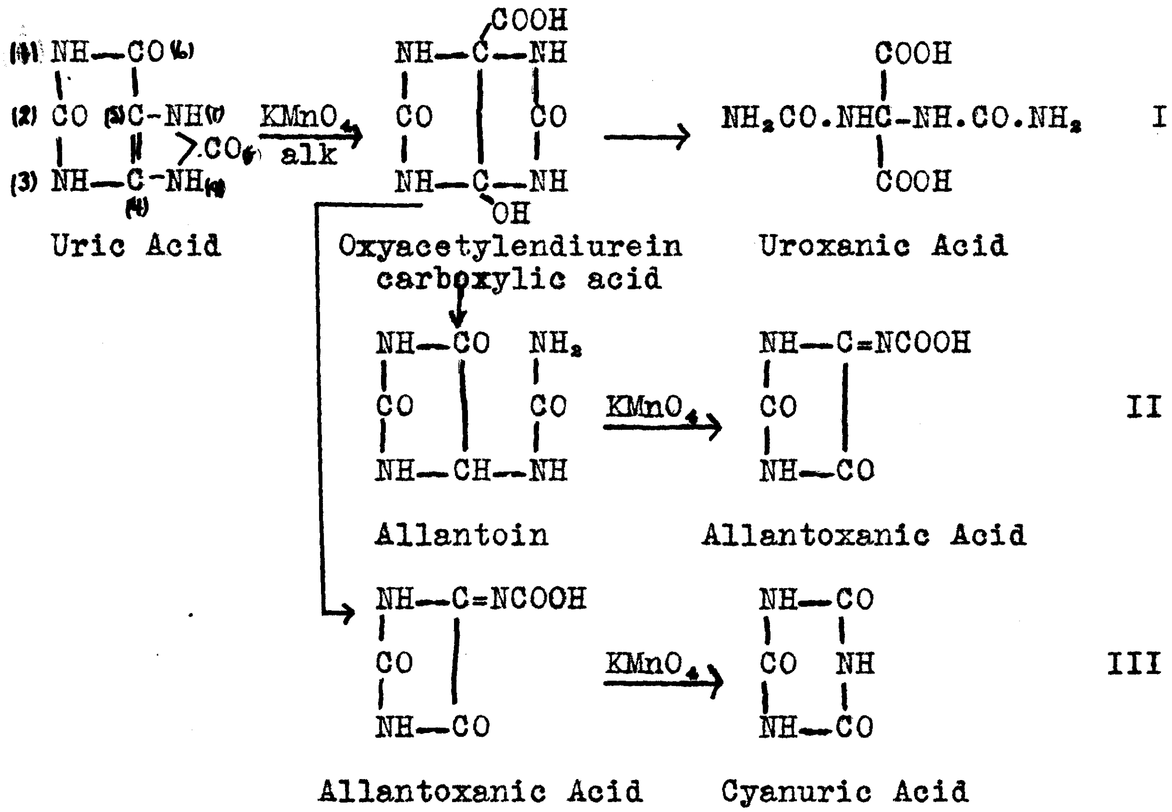
[1] Behrend, Ann. 333, 104 (1904)

[2] Behrend, loc. cit.

also suggested as one intermediate and which Biltz[1] has lately decided is the only intermediate possible in the permanganate oxidation, may very well be the intermediate in the peroxide oxidation also. But there is as yet no experimental proof.

<u>Oxidation of Uric Acid with Potassium Permanganate.</u> The mechanism of the oxidation of uric acid with permanganate in alkaline solution may, according to Biltz,[2] be represented by the following scheme:



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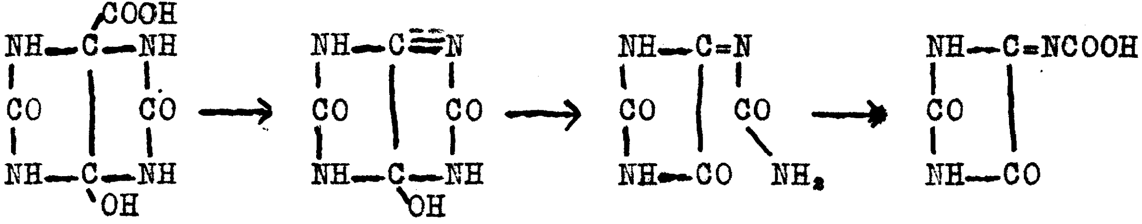
[1] Biltz, Ber. <u>54</u>, 2451 (1921)

[2] Biltz, Ber. <u>53</u>, 1950, 1964, 1967 (1920); Ber. <u>54</u>, 2441, 2451 (1921)

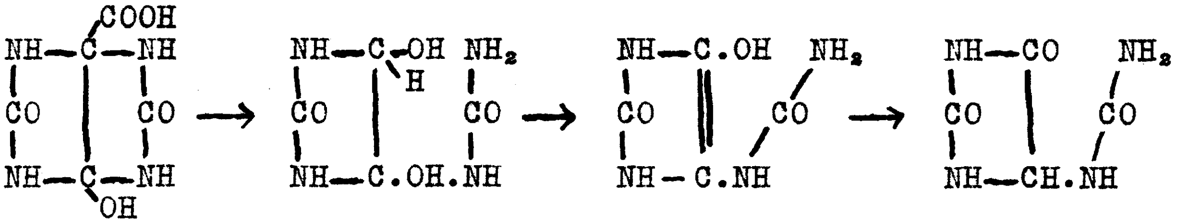
Uric acid is oxidized first to oxyacetylendiurein carboxylic acid, which is formed by an hydroxyl group becoming attached to (4), thus setting a bond free at (5), the latter then attracts the nitrogen at (1) and the ring is reduced to 5 members; a second hydroxyl enters at (6). This intermediate, supposed to exist in the alkaline solution, gives potassium uroxanate on evaporation by double hydrolytic splitting at the lower carbon atom. Allantoin, on the other hand, is formed on acidification by the splitting off of the carboxyl and the scission of one ring. Finally, allantoxanic acid may be obtained when the solution is acidified with acetic acid and treated with alcohol, possibly by the following steps:



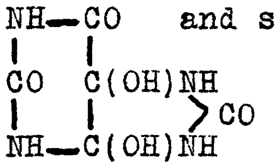
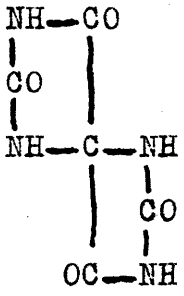
Allantoxanic acid gives cyanuric acid on further oxidation with permanganate.

This symmetrical oxyacetylendiurein carboxylic acid accounts well for the formation af all three products, and Biltz considers it to be the only intermediate necessary in the formation of uroxanic acid and allantoin.

Behrend,[1] however, gives the following possible mechanism for the formation of allantoin:



The symmetrical form of the intermediate also accounts perfectly for the formation of 3-methyl allantoin from 1-methyl uric acid and 7-methyl uric acid and for the 1-methyl allantoin from 3-methyl uric acid and 9-methyl uric acid[2]. It also explains how 1,3 dimethyl allantoin can be obtained from the glycol ethers of both 1,3 dimethyl uric acid and 7,9 dimethyl uric acid[3].

Both uric acid glycol[4]  and spiro dihydantoin,  have been rejected by Biltz as possible intermediates. Uric acid glycol is known[5], but though many attempts have been made, it has never been found possible to obtain it as a direct oxidation product of uric acid. It is also impossible to obtain uroxanic acid or allantoin from it by oxidation. Uric acid glycol in alkaline solution always breaks at the 3-4 bond, and gives the caffolid decomposition.[6]

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[1] loc. cit.

[2] Fischer and Ach, Ber. 32, 2723 (1899).

[3] Biltz, Ber. 54, 2467 (1921)

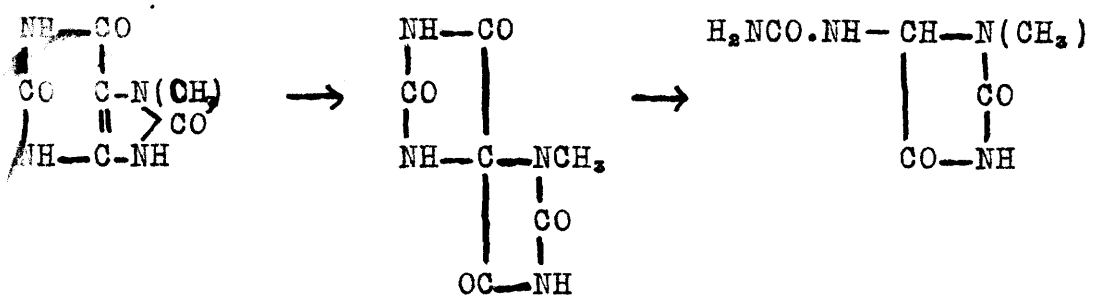
[4] Biltz, Ber. 53, 1965; 54, 2455.

[5] Biltz, B. 43, 1511 (1910); 45, 1679 (1912).

[6] Biltz + Heyn, Ann. 413, 56 (1917).

But from a near relation, uric acid glycol dimethyl ether, Biltz has recently shown that both uroxanic acid[1] and allantoin[2] may be obtained by hydrolysis, so that the intermediate in the uric acid oxidation must be closely related to it.

Spirodihydantoin is also known[3]. Biltz considers it to be too stable to be the intermediate. Furthermore, 3-methyl allantoin is formed from 7-methyl uric acid, and 1-methyl allantoin from 9-methyl uric acid. But, as the following scheme shows, 1-methyl allantoin would be formed from 7-methyl uric acid if spirodihydantoin were the intermediate:



Only one case of the direct formation of biuret by the oxidation of uric acid could be found in the literature. Behrend[4] obtained it by the oxidation of uric acid with permanganate in alkaline solution. The solution was

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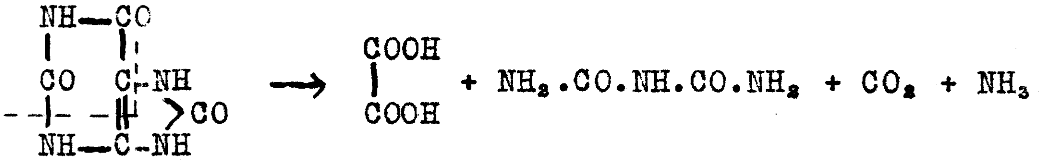
[1] Biltz, Ber. 53, 1964 (1920)

[2] Biltz, Ber. 55, 2465 (1921)

[3] Biltz, Ann. 413, 12, 77 (1917)

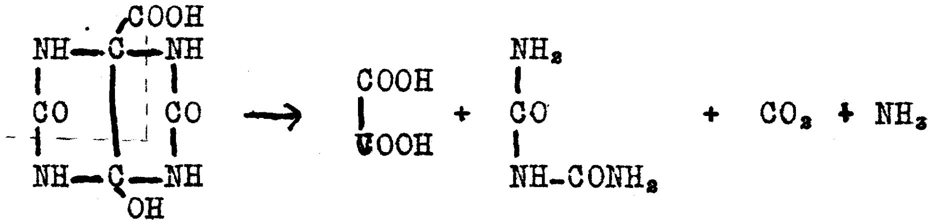
[4] Behrend, Ann. 365, 21 (1909)

warmed until decolorized and then evaporated. Biuret crystallized on cooling. A 28% yield was obtained. The filtrate gave oxalic acid. The reaction might be written thus:



I

or from the intermediate:



II

As the first reaction is just as plausible as the second the formation of biuret throws no light on the nature of the intermediate. Biuret has not been obtained directly by oxidation with hydrogen peroxide.

Action of Alkali on Substituted Uric Acids. Fischer[1] has studied to a slight extent the action of alkali on substituted uric acid, and Strecker[2] and Maly and Andreasch[3] have studied the decomposition of caffein by alkali. No other work of any importance along this line has been done.

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[1] Fischer, Ber. 31, 3266 (1899)

[2] Ann. 123, 361 (1862)

[3] Maly and Andreasch, Monatsch.f.Chem. 4, 369 (1883)

Fischer made no attempt to determine the nature of the decomposition products when the substituted uric acids were decomposed. He merely gave the percentage decomposition, determined by acidifying the alkaline solution and weighing the acids regained, and in a few cases he recorded whether the odor of ammonia or methylamine was noticed. In all cases he used normal potassium hydroxide and heated the solution to 100°. Uric acid itself was 11% decomposed by heating for 36 hours. The monomethyl uric acids were decomposed only slightly; for example, the 7-methyl uric acid is 9.3% decomposed after 16 hours heating. Of the dimethyl uric acids the 1,3 dimethyl was the most unstable; 36.2% decomposition was found after 18 hours. The 7,9 dimethyl uric acid was only decomposed 7.4% after 15 hours. The 1,3,9 trimethyl uric acid far exceeded the other trimethyl uric acids in instability. After only 1 hour's heating, 81.7% was decomposed. A strong odor of methylamine was noticed and much carbon dioxide was liberated on acidifying. The 1,3,7 trimethyl uric acid came next; it was only decomposed 37.8% after 15 hours. Tetramethyl uric acid was decomposed instantly. Fischer[1] believed that a substance of composition, $C_8H_{14}N_4O_2$, analogous to caffeidin, was formed though his analyses, especially

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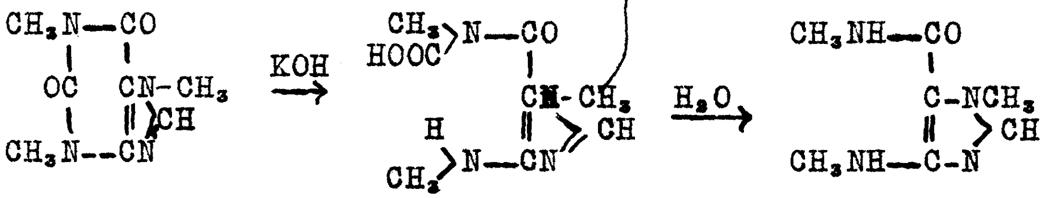
[1] Fischer, Untersuchungen in der Puringruppe, p. 371.

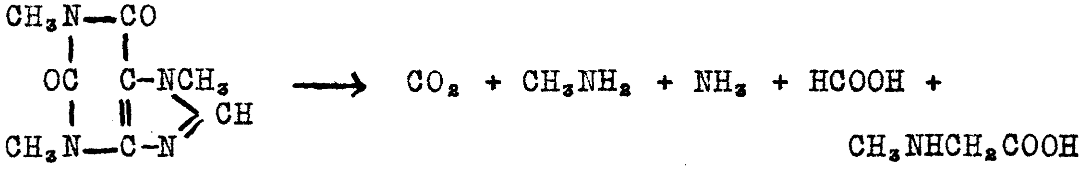
the carbon, were too low. He called the decomposition product tetramethyl ureïdin.

Action of Alkali on Caffein. The decomposition of caffein by alkali has been more thoroughly studied. Maly and Andreasch[1] found that cold dilute alkali changes caffein, $C_8H_{10}O_2N_4$, into caffeïdin carboxylic acid, $C_8H_{12}O_3N_4$, and that this goes over into the caffeïdin, $C_7H_{12}ON_4$, of Strecker[1] on simply boiling with water. No trace of ammonia or methylamine was noticed. When the reaction was carried out at 30°, a slight odor of methylamine developed. The reaction may be represented by the following scheme:



Caffein   Caffeïdin carboxylic acid   Caffeïdin

Schultzen[2] and Strecker and Rosengarten[3] found that caffein on prolonged treatment with barium hydroxide decomposed as follows:



Caffein   Sarkosin

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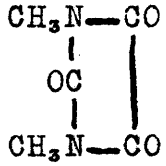
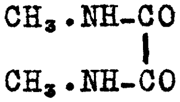
[1] loc. cit.   [3] Strecker + Rosengarten, Ann. 157, 1 (1871)

[2] Schultzen, Zeit.f.Chem. (1867) 614.

On oxidizing caffein with chromic acid[1] in acid solution cholestrophan is formed -  while caffeïdin gives dimethyl oxamid - 

$$\begin{array}{l} CH_3.NH-CO \\ \quad\quad\quad\;\; | \\ CH_3.NH-CO \end{array}$$

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The results confirm the structure given for caffeïdin.

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[1] Maly and Andreasch, Monatsch.f.Chem. <u>4</u>, 369 (1883)

II. General Part.

Only two uric acids containing the phenyl group have been prepared before, the 9-phenyl uric acid and the 1,3,7 trimethyl 9-phenyl uric acid.[1] Besides the actual preparations and the acid oxidation of the former to alloxan and phenyl urea little work has been done on them. The 9-phenyl uric acid is stable toward warm conc. alkali, but the trimethyl phenyl uric acid is immediately decomposed, and much carbon dioxide excapes on acidifying. Fischer believed that the decomposition was similar to that of the tetramethyl uric acid.

In the present work two more methyl phenyl uric acids have been synthesized, the 7-methyl 9-phenyl uric acid and the 1,3-dimethyl 9-phenyl uric acid; and the action of hydrogen peroxide and alkali on these and on the 9-phenyl uric acid has been investigated.

The 9-phenyl uric acid and the 1,3-dimethyl 9-phenyl uric acid were prepared from the corresponding uramils by the action of phenyl isocyanate and subsequent treatment of the pseudo acids formed with hydrochloric acid. The 1,3-dimethyl 9-phenyl pseudo uric acid was also prepared by methylation of 9-phenyl pseudo uric acid with dimethyl sulphate. Biltz[2] has found that the

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[1] Fischer, Ber. <u>33</u>, 1701 (1900)

[2] Biltz, Ann. <u>423</u>, 185 (1921)

pseudo acids methylate much more readily than the corresponding uric acids, and that homogeneous products are always obtained. The methyl groups go in positions (1) and (3). He has prepared in this manner 1,3-dimethyl pseudo uric acid from pseudo uric acid; 1,3-dimethyl 7-alkyl pseudo uric acid from 7-alkyl pseudo uric acid, and 1,3,9-trimethyl pseudo uric acid from both 9-methyl pseudo and 1,9-dimethyl pseudo uric acids. The 9-phenyl pseudo likewise methylated easily to the 1,3-dimethyl 9-phenyl pseudo uric acid. At first it was thought that another methyl phenyl derivative had been formed along with it, as two optically different substances were noticed; but it was found to be only a monohydrate of the 1,3-dimethyl 9-phenyl pseudo uric acid.

The 7-methyl 9-phenyl uric acid was made from 7-methyl uramil[1] by treating with phenyl isocyanate and then boiling the product with hydrochloric acid.

The 9-phenyl pseudo uric acid goes over to the 9-phenyl uric acid quite smoothly on boiling with 20% hydrochloric acid; the 7-methyl 9-phenyl pseudo uric acid is converted even more easily to the uric acid; but the 1,3-dimethyl 9-phenyl pseudo uric acid requires conc. hydrochloric acid and long boiling and even then it is not completely changed.

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[1] Biltz, Ann. 413, 46 (1917)

9-Allyl uric acid was also prepared from uramil and allyl isocyanate. The preparation is quite similar to that of the 9-phenyl uric acid except that the potassium salt of the allyl pseudo uric acid is much more soluble.

Oxidation of 9-Phenyl Uric Acid with Hydrogen Peroxide. 9-phenyl uric acid was oxidized with hydrogen peroxide in dilute alkaline solution. Four products were obtained. From the alkaline solution unsym. phenyl biuret, $C_6H_5NH.CO.NH.CO.NH_2$, formed. It melted at 165° and its properties agreed with those given by Schiff.[1] The solution on acidification gave a substance, $C_8H_9O_2N_3$, melting at 198°, which was isomeric with unsym. phenyl biuret. The total yield of phenyl biuret was usually between 40 and 45% of the theoretical yield when calculated on the basis of 1 mol. of phenyl biuret from 1 mol. of uric acid. The other products identified were phenyl urea,- a 6.5% yield if the uric acid had been completely decomposed to phenyl urea,- and oxalic acid (32%).

The most striking property of the oxidation product melting at 198° was that on treating with ammonia or an organic base (for list see Experimental Part), it

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[1] Schiff, Ann. 352, 79 (1907)

was readily changed into the unsym. phenyl biuret. This change could also be brought about by the combination of hydrogen peroxide and alkali, though neither could produce it alone.

Because of the nature of the catalyst it is very probable that unsym. phenyl biuret is not a direct oxidation product of 9-phenyl uric acid but is formed in the oxidation solution from the product melting at 198° by the action of either the ammonia formed during the oxidation or the hydrogen peroxide and alkali.

The structure of the phenyl biuret obtained from the acidified solution has not been definitely established. One other phenyl biuret besides the unsym. phenyl biuret is known. Schiff[1] and Weith[2] prepared it by the action of phosphorous trichloride on phenyl urea. It melts at 192°. Schiff made one analysis for carbon, hydrogen, and nitrogen which checked well with the calculated values. No other mention of it could be found in the literature. Schiff considers it to be sym. phenyl biuret, $NH_2.CO.NC_6H_5.CO.NH_2$, as that seems to be the only isomer possible or at least probable. The proff of this structure he bases on the following facts:- (1) the method of formation which may be represented by

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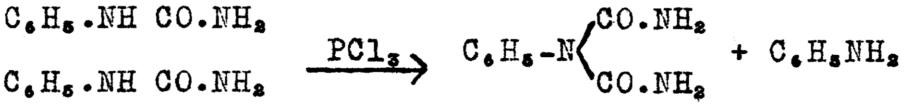
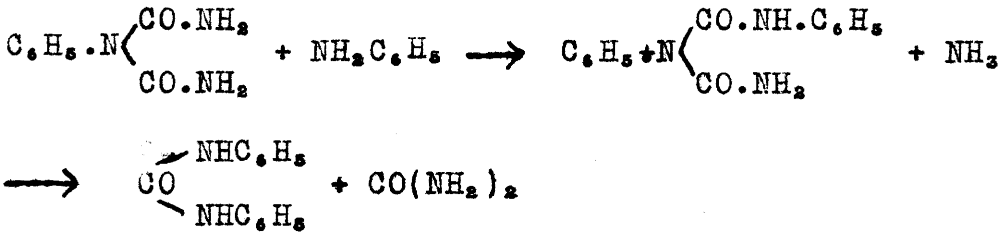
[1] Schiff, Ann. 352, 73 (1907)

[2] Weith, Ber. 10, 1744 (1877)



$$\begin{matrix} C_6H_5.NH\ CO.NH_2 \\ C_6H_5.NH\ CO.NH_2 \end{matrix} \xrightarrow{PCl_3} C_6H_5{-}N\left\langle\begin{matrix} CO.NH_2 \\ CO.NH_2 \end{matrix}\right. + C_6H_5NH_2$$

(2) that it gives the biuret reaction, and (3) that with aniline it goes over into diphenyl urea. Schiff[1] has found that biurets substituted on the end nitrogen do not give the biuret reaction, while those with the central nitrogen substituted do. He represents the formation of diphenyl urea by the following scheme:



$$C_6H_5.N\left\langle\begin{matrix} CO.NH_2 \\ CO.NH_2 \end{matrix}\right. + NH_2C_6H_5 \longrightarrow C_6H_5{+}N\left\langle\begin{matrix} CO.NH.C_6H_5 \\ CO.NH_2 \end{matrix}\right. + NH_3$$

$$\longrightarrow CO\left\langle\begin{matrix} NHC_6H_5 \\ NHC_6H_5 \end{matrix}\right. + CO(NH_2)_2$$

The urea is phenylated by the excess aniline, so that only diphenyl urea is obtained. He considers that the unsym. diphenyl biuret is first formed but that it is unstable and goes over easily to the diphenyl urea. From the unsym. phenyl biuret he is able to isolate the sym. diphenyl biuret when the former is warmed with aniline. This also gives diphenyl urea on longer heating. Both diphenyl biurets have been prepared,[2] but whether the unsym. one is more unstable is not known. Schiff assumes that it is.

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[1] Schiff, Ann. 299, 236 (1897)

[2] Hofmann, Ber. 4, 250.

The phenyl biuret melting at 198°, obtained from the acidified oxidation solution of 9-phenyl uric acid, is not the Schiff phenyl biuret. The latter was prepared and the properties of the two did not agree. Mixed, the melting point was lowered to 160°. The optical properties were not the same. The 198° substance does not give as strong a biuret test. It was also easily isomerized to the unsym. phenyl biuret, as has been said, while Schiff's phenyl biuret is not affected. With aniline the product melting at 198° gives sym. diphenyl biuret, which may be accounted for by the isomerization to the unsym. phenyl biuret by the action of the organic base, and then the further reaction of the latter with aniline. Two analyses, which check, were made and they agree with the calculated values for a phenyl biuret. A molecular weight determination was also made which showed that it is an isomer and not a polymer of unsym. phenyl biuret. If the substance is considered to be sym. phenyl biuret, a mechanism for the oxidation of the three phenyl uric acids can be given. It has not been found possible as yet to explain the course of the oxidation on any other basis. The assumption seems justifiable, as will be shown later.

There is little possibility of either of the two higher melting phenyl biurets having an enol form, for neither gives the ferric chloride test characteristic of enols. Furthermore, a methyl phenyl iso biuret is known[1], and it is very unstable toward dilute hydrochloric acid; it splits methyl chloride and gives unsym. phenyl biuret. The phenyl biuret melting at 198°, however, is obtained from a hydrochloric acid solution. It does not seem likely, either, that the phenyl group should wander from nitrogen to oxygen, and give a substance whose structure is $NH=C(OC_6H_5)NH.CO.NH_2$.

Oxidation of 7-Methyl 9-Phenyl Uric Acid and of 1,3-Dimethyl 9-Phenyl Uric Acid with Hydrogen Peroxide. It was thought that the oxidation of methyl phenyl uric acids might throw light on the course of the reaction and show where the primary splitting of the rings occurs. 7-methyl 9-phenyl uric acid gave on treatment with hydrogen peroxide and dilute alkali ab methyl phenyl urea, $CH_3.NH.CO.NH.C_6H_5$, from both the alkaline and acid solutions. The yield was 44% of the theory. Oxalic acid (28%) was also obtained.

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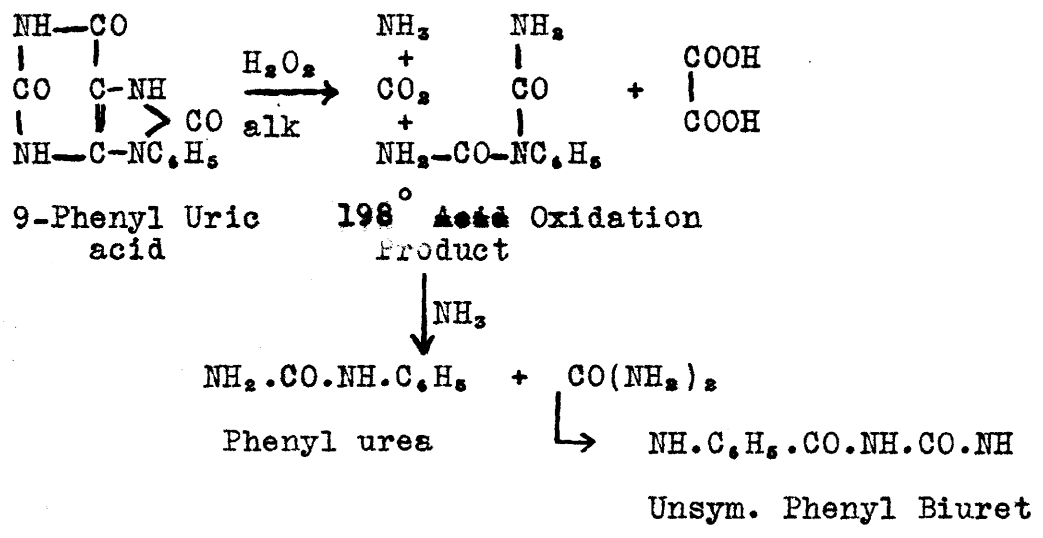
[1] McKee, A.C.J. 26, 209 (1901)

1,3-dimethyl 9-phenyl uric acid when oxidized by peroxide and alkali gave the same methyl phenyl urea as obtained from 7-methyl 9-phenyl uric acid. The yield in this case was 54% of the theory. Oxalic acid in a 51% yield was also found. No biurets were obtained from either of the methyl phenyl uric acids.

No methyl phenyl derivatives of the known oxidation products of uric acid can be considered as intermediates in these oxidations, for none of them accounts for the formation of oxalic acid or for the fact that the same methyl phenyl urea is obtained from both the 7-methyl 9-phenyl uric acid and the 1,3-dimethyl 9-phenyl uric acid. In the mechanism of the reactions given, it is assumed, as said before, that the second oxidation product of 9-phenyl uric acid, melting at 198°, is sym. phenyl biuret. The reactions may be formulated thus:



$$\begin{array}{l} NH\text{—}CO \\ |\quad\;\; | \\ CO\quad C\text{-}NH \\ |\quad\;\; \| \;\; > CO \\ NH\text{—}C\text{-}NC_6H_5 \end{array} \xrightarrow[\text{alk}]{H_2O_2} \begin{array}{l} NH_3 \qquad NH_2 \\ \;+ \qquad\quad | \\ CO_2 \qquad CO \\ \;+ \qquad\quad | \\ NH_2\text{—}CO\text{—}NC_6H_5 \end{array} + \begin{array}{l} COOH \\ | \\ COOH \end{array}$$

9-Phenyl Uric acid

198° ~~Acid~~ Oxidation Product

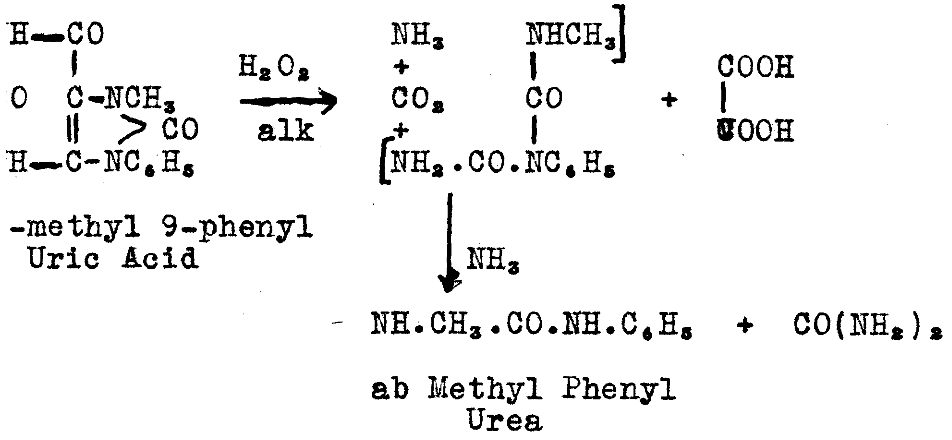
$\downarrow NH_3$

$NH_2.CO.NH.C_6H_5 + CO(NH_2)_2$

Phenyl urea

$\rightarrow NH.C_6H_5.CO.NH.CO.NH$

Unsym. Phenyl Biuret



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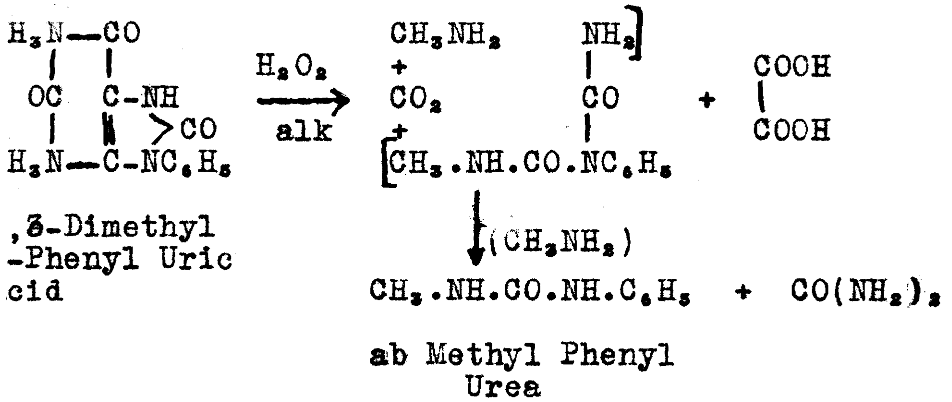


III

If the mechanism is the same in all three ases, as is probable, the splitting indicated is the nly one that will account for all the facts. Methyl henyl biuret is not known. If the change from sym. henyl biuret to unsym. phenyl biuret goes through the tep shown, it might very well be that ammonia would eact with methyl phenyl biuret in the same way, and he products formed could not recombine to give the ther methyl phenyl biuret, $CH_3.NH.CO.NH.CO.NH.C_6H_5$.

This could be tested if it were possible to synthesize the methyl phenyl biuret with the phenyl attached to the central nitrogen. As yet no method has been found.

The mechanism may also be formulated from the hypothetical oxyacetylendiurein carboxylic acid, but a symmetrical formula is not necessary.

Action of Alkali on the Methyl Phenyl Uric Acids. 9-phenyl uric acid and 7-methyl 9-phenyl uric acid proved to be perfectly stable toward sodium or potassium hydroxide. 1,3-dimethyl 9-phenyl uric acid, on the other hand, was very unstable. On boiling a few minutes with 4N sodium hydroxide it was completely decomposed. Methylamine was evolved and much carbon dioxide came off on acidifying in the alkaline solution. This agrees, qualitatively at least, with Fischer's results on the corresponding methyl derivatives.

The acidified solution from 1,3-dimethyl 9-phenyl uric acid gave, on standing some time, a crystalline substance melting at 250°. The empirical composition was found to be $C_{11}H_{11}O_3N_3$. This product was found to be a monobasic acid. The decomposition may be represented as follows: $C_{13}H_{12}O_3N_4 \xrightarrow{alk} C_{11}H_{11}N_3O_3 + CO_2 + CH_3NH_2$. It is in turn decomposed by sodium or potassium hydroxide to phenyl urea, methylamine and oxalic acid.

$C_{11}H_{11}O_3N_3 \longrightarrow C_6H_5.NH.CO.NH_2 + CH_3NH_2 + (COOH)_2$

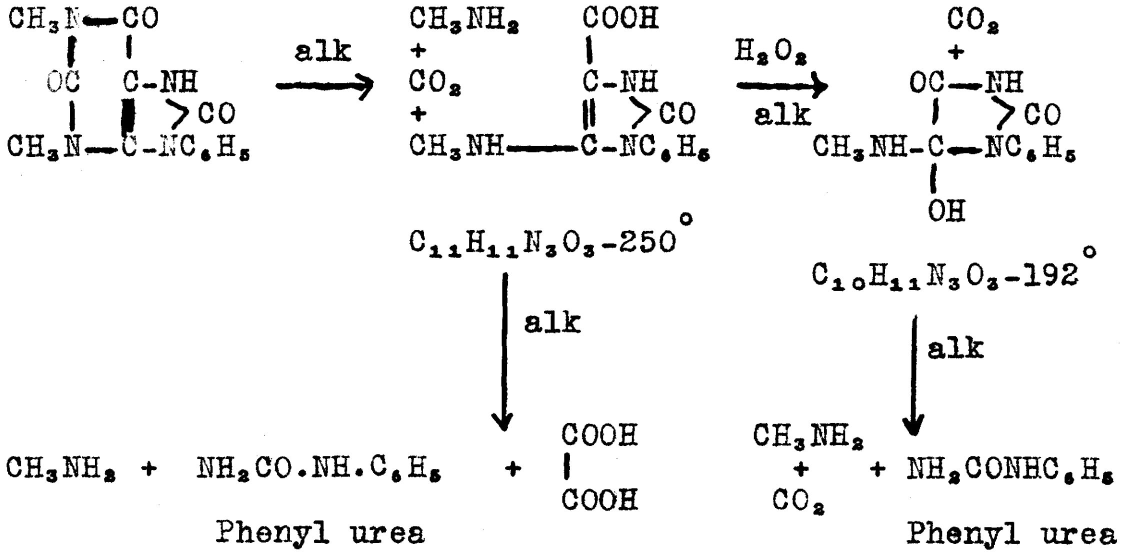
Oxidation of $C_{11}H_{11}O_3N_3$ with Hydrogen Peroxide.

On oxidizing the alkaline decomposition product with peroxide in alkaline solution phenyl urea and oxalic acid also are obtained when the oxidation solution is allowed to stand 3 hours or longer at room temperature. The decomposition is probably due only to the alkali present, as solutions of the same concentration, but without the peroxide, give the same product on longer standing.

When the oxidation solution is allowed to stand at 0°-10° for only five or ten minutes and then acidified and evaporated, it was found possible to isolate an oxidation product of the empirical formula $C_{10}H_{11}O_3N_3$. This substance melted at 192°. It was not formed by the action of the alkali alone as it was never possible to obtain it under the same conditions except for the peroxide. The original 250° substance was always regained. The oxidation product was very unstable toward alkali. On standing 10 or

15 minutes at room temperature with normal potassium hydroxide, phenyl urea separated. No oxalic acid could be found in the mother liquor.

The scheme of decomposition and the proposed structure for the two intermediates may be formulated in the following way:



The decomposition is not like that of caffein or tetramethyl uric acid. Caffein gives a carboxylic compound of the same number of carbon atoms, caffeïdin carboxylic acid. This then gives, on boiling with water, caffeïdin, which has only one carbon less than caffein (See page 9). In the present decomposition, on the other hand, two carbons are lost in the first decomposition, and one in the second. The final product, on complete decomposition, is phenyl urea, while sarkosin is the final product from caffein. It is probable, also, that the decomposition of the trimethyl phenyl uric acid noted by Fischer follows the present course and not that of tetramethyl uric acid.

Uroxanic Acid and Allantoxanic Acid. Attempts were made to oxidize uroxanic acid with hydrogen peroxide in alkaline solution at different temperatures, but the results agreed with those of Venable[1] on sodium uroxanate. It was found to be perfectly stable. But some rather interesting results were obtained in the course of the preparation of uroxanic acid. Potassium uroxanate was obtained by oxidizing uric acid with permanganate in alkaline solution.[2] The mother liquor on evaporation, however, gave a good yield of potassium allantoxanate instead of more uroxanic acid. Biltz was able to get allantoxanic acid by a permanganate oxidation, but his solution was much more concentrated and the acid potassium allantoxanate separated

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[1] Venable, J.A.C.S. 40, 1111 (1918)

[2] Biltz, Ber. 53, 1974 (1920)

only on acidifying and adding alcohol. From 23 grams of uric acid he obtained 2.6 grams of the acid potassium salt. In the present preparations, 2.5 grams of the acid potassium salt of allantoxanic acid were obtained after the potassium uroxanate in from 15 to 19 gram yields had been separated. As the odor of ammonia was always noticed on the evaporation of the mother liquors, attempts were made to see if allantoxanic acid could possibly have been formed from uroxanic acid. Sundwik[1] had obtained slight traces of allantoxanic acid in the course of the oxidation of uric acid to uroxanic acid by alkaline permanganate and so probably did Behrend.[2] Sundwik claimed that by short boiling of a solution of uroxanic acid in alkali he was able to get ammonia and the sodium salt of allantoxanic acid. Biltz[3] was not able to confirm this and he believes that the two substances result from different courses of oxidation. The results obtained from this investigation agreed entirely with those of Biltz.

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[1] Sundwik, Ber. 27, R. 887 (1894)

[2] Behrend, Ann. 333, 141 (1904)

[3] Biltz, Ber. 53, 1939 (1920)

Not a trace of allantoxanic acid was formed. As the yields of allantoxanic acid from the oxidation were so large in comparison with any before obtained by the permanagante oxidation, it would be advisable to study the reaction much more thoroughly.

According to Biltz[1] spirodihydantoin is stable toward permanganate in alkaline solution. It was thought of interest to study the action of hydrogen peroxide and the spirodihydantoin was found to be quite easily attacked. When the oxidation was carried out in very dilute alkali allantoin was obtained and in about normal alkali both allantoin and uroxanic acid were isolated. It was further found that spirodihydantoin was changed by alkali alone at room temperature into uroxanic acid- the presence of the hydrogen peroxide being unnecessary. This is in contradiction to the statement of Biltz regarding the stability of spirodihydantoin toward alkali.

A few preliminary oxidations of uric acid with sodium persulphate were made to see what course the oxidation would take. Allantoin was the only oxidation product found.

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[1] Biltz, Ann. 413, 39 (1917)

III. Experimental Part.

A. Notes on Analytical Work.

Combustions. The analyses for carbon and hydrogen were carried out according to the method of Reimer[1] and Levene.[2] The method differs from the ordinary Liebig method in that cerium dioxide is used as a catalyst; the combustions may therefore be run more rapidly. The catalyst is made by impregnating pure asbestos with very pure cerium nitrate and igniting. About 3cm. are placed after the coarse copper oxide, just before the boat. Lead peroxide in a copper tube is placed at the forward end of the tube to absorb the nitrogen. The oxygen used was preheated by passing over copper oxide and dried by potash, sulphuric acid and calcium chloride. The actual burning of the substances, all of which contained nitrogen, took from twenty-five to thirty-five minutes. The absorption train consisted of a U-tube filled with calcium chloride for absorbing the water, another U-tube filled with soda lime for the carbon dioxide, and a smaller U-tube filled with solid potash and calcium chloride for absorbing any carbon dioxide that passes

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[1] Reimer, J.A.C.S. 37, 1637 (1915)

[2] Levene, J.A.C.S. 40, 460 (1918)

through the soda lime and also any moisture from the soda lime tube as the latter becomes quite hot during the combustion. When the soda lime tube is cold the combustion is over. Oxygen is passed through for one half hour longer and the tubes then weighed.

The regular Dumas method was used for the nitrogen determinations. As many analyses were made, an open tube was used and the carbon dioxide generated outside from manganese carbonate. The substances to be analyzed were weighed into a copper boat and mixed with fine copper oxide.

Potassium Determinations. Potassium was determined as potassium sulphate. A platinum crucible was used; the substance was weighed into it, and carefully ignited. A little pure sulphuric acid was then added and the crucible heated to constant weight.

Hydrogen Peroxide. The hydrogen peroxide used for the oxidation experiments was titrated with potassium permanganate.[1] It was approximately 3%:- (1) 2.93%, (2) 2.96%, (3) 2.916%.

Optical Method. A petrographical microscope was used in determining the optical properties. These constants may be determined nearly as easily as melting points and they furnish a better criteria of the purity

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[1] Coblentz, Volumetric Analysis, p. 106.

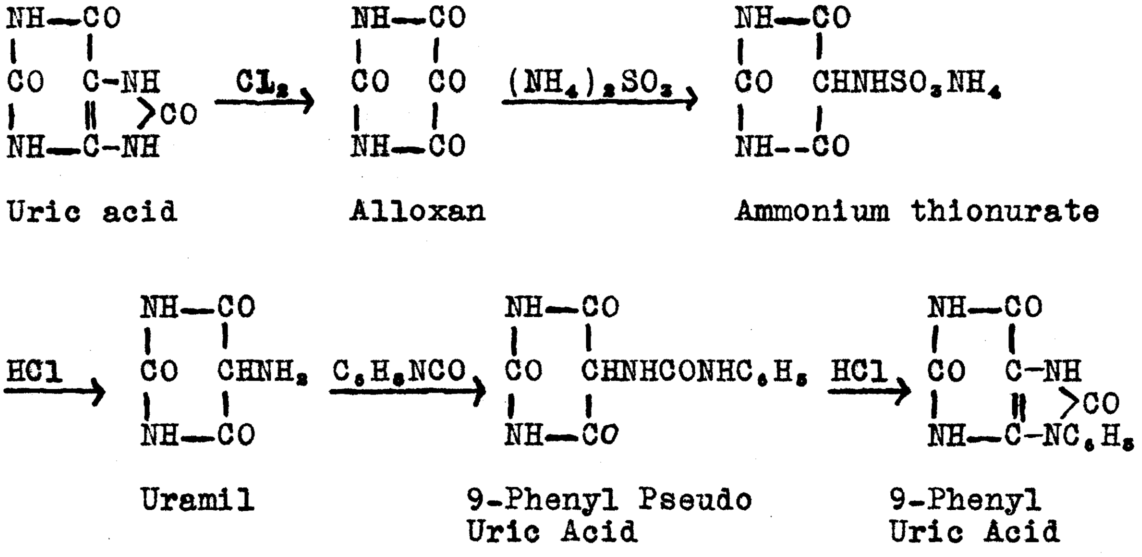
and homogeneity of the product. For purposes of identification they were always determined as a check on mixed melting points and proved invaluable for identifying substances which did not melt below 300°.

B. 9-Phenyl Uric Acid.

1. Preparation.

9-Phenyl Uric Acid was prepared from 9-phenyl pseudo uric acid, following the directions of Fischer.[1] Uric acid was oxidized to alloxan by chlorine. Alloxan on treatment with ammonium sulphite gave thionuric acid, which with hydrochloric acid gave uramil. When uramil was treated with phenyl isocyanate in alkaline solution, 9-phenyl pseudo uric acid was obtained, from which 9-phenyl uric acid was prepared by boiling with hydrochloric acid.

Scheme:-



Uric acid

Alloxan

Ammonium thionurate

Uramil

9-Phenyl Pseudo Uric Acid

9-Phenyl Uric Acid

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[1] Fischer, Untersuchungen in der Puringruppe, p. 543.

Extraction of Uric Acid. 200 grams of snake excrement was boiled with 140 grams of powdered sodium hydroxide and 2.6 liters of water for $\frac{1}{2}$ hour; the solution was filtered hot and the filtrate acidified with hydrochloric acid (commercial acid, s.gr. 1.19, diluted with 3 volumes of water). A heavy white precipitate of uric acid was formed; it was allowed to stand overnight, then filtered and dried at 100°. Six extractions were made. The average yield of uric acid from 200 grams of excrement was 175 grams.

Alloxan. Alloxan was prepared according to the method of Biltz[1] by oxidizing uric acid in glacial acetic acid solution with chlorine. In the first attempts uric acid was used which had been extracted several years before, and it was very hard and dry. No alloxan was obtained. But it was found that when the uric acid was reprecipitated by dissolving in concentrated sulphuric acid on the steam bath and then diluting with water[2], the reaction went very smoothly. When the freshly extracted uric acid was used it was not found necessary to reprecipitate it from sulphuric acid.

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[1] Biltz, Ann. 413, 60 (1917)

[2] Biltz, Ann. 413, 66 (1917)

50 grams of uric acid was placed in a 1-liter short-necked flask fitted with a delivery tube, reaching to the bottom, and an outlet tube. A boiling solution of 150 cc. of glacial acetic acid and 25cc. of water was added and a vigorous stream of chlorine sent in. The flask was shaken continuously and kept warm by partly immersing in warm water. The solution became nearly clear (never entirely so except when small lots, i.e. 10 grams, were used), and a heavy crystalline precipitate of alloxan monohydrate separated. The operation lasted about 15 minutes. The solution was cooled for $\frac{1}{2}$ hour with ice water, filtered, washed with glacial acetic acid and ether and dried in a vacuum desiccator. The yields varied from 31 to 35 grams of alloxan.

Thionuric Acid. Thionuric acid was prepared according to the method of Wöhler and Liebig[1]. Sulphur dioxide was passed into a solution of 75cc. of ammonium hydroxide (15N) and 30cc. of water - cooled with ice - until saturated. The solution was then neutralized with excess ammonium carbonate, and 30 grams of alloxan in 30cc. of water was added. It was heated slowly to boiling and boiled several minutes, then warmed for $\frac{1}{2}$ hour on the steam bath. A heavy precipitate of pearly

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[1] Liebig, Ann. 26, 268 (1838)

scales formed at once. The yield of the ammonium salt of thionuric acid varied from 30 to 40 grams.

Uramil.[1] 30 grams of the dry ammonium salt of thionuric acid was boiled with 120cc. of hydrochloric acid (6N) and 350cc. of water for five minutes. A white precipitate of uramil formed which was filtered and washed with water. Yield, 11 grams. From the same weight of alloxan (30 grams), using thionuric acid which was not dried, yields as high as 25 grams were often obtained.

9-Phenyl Pseudo Uric Acid.[2] 10 grams of finely powdered uramil was added to 140cc. N potassium hydroxide cooled to 0^{o} by an ice and salt mixture, and shaken until almost all had gone into solution. The solution became a deep red violet. 8.3 grams of phenyl isocyanate was added gradually and the solution shaken vigorously after each addition until the oder disappeared. A heavy precipitate of the potassium salt formed which was filtered and washed with cold water. It was then dissolved in hot water and acidified with dilute hydrochloric acid; a heavy white precipitate of the phenyl pseudo uric acid separated at once. The filtrate, on acidifying, gave a little more of the free acid. Total yield, 17 grams.

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[1] Wöhler and Liebig, Ann. 26, 274 (1838)

[2] Fischer, Untersuchungen in der Puringruppe, p. 543.

9-Phenyl Uric Acid.[1] 5 grams of 9-phenyl pseudo uric acid was boiled with 1 liter of 20% hydrochloric acid for $\frac{1}{2}$ hour, or until all had gone into solution, and then boiled $\frac{1}{2}$ hour longer. The solution was evaporated to $\frac{1}{3}$ its volume over a free flame, cooled and filtered. The yields of phenyl uric acid varied from 2.9 to 3.5 grams.

Optical Properties:

Habit: rectangular plates.

Optical Orientation: parallel extinction, γ parallel to elongation.

Indices: $\alpha = 1.525$ ✓ $\gamma = 1.7174$ ✓ (JAC.S - 45, 140.)

2. Oxidation with Hydrogen Peroxide.

Most of the oxidation experiments were carried out in potassium hydroxide solution (0.35 N excess alkali). With sodium hydroxide the same oxidation products were obtained but the yields were not as good. Decomposing the excess peroxide with manganese dioxide and acidifying with acetic acid instead of hydrochloric acid also had no effect on the nature of the acid oxidation product.

In 0.35 N Excess Alkali. 2 grams of 9-phenyl uric acid was dissolved in 2.3 grams of potassium hydroxide

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[1] loc. cit.

and 24cc of water and cooled with ice water. 52cc. of hydrogen peroxide was added. The solution became yellow and an odor of carbylamine soon developed. Several times the potassium salt separated but it gradually went into solution again on longer standing. After one or two days thin transparent crystals had separated which melted at 163°-165°. The yields varied from 0.1 to 0.2 grams. Sometimes it was necessary to add 10cc. more hydrogen peroxide and cool thoroughly before the crystals formed. From the filtrate on acidifying small reddish brown particles separated slowly, which melted at 194°-195°. The yields of the acid oxidation product ranged from 0.27 to 0.46 grams. The amounts of alkaline oxidation product increased as the acid oxidation product diminished.

9-Phenyl Uric Acid	Alk.Oxid.Prod.	Acid Oxid.Prod.
2 grams	0 grams	0.4 grams
2 grams	0 grams	0.46 grams
2 grams	0.09 grams	0.42 grams
2 grams	0.10 grams	0.43 grams
2 grams	0.13 grams	0.27 grams
2 grams	0.17 grams	0.17 grams
2 grams	0.20 grams	0.16 grams
2 grams	0.28 grams	0.31 grams

The mother liquor on evaporation gave more crystals melting at 140°, and weighing from 0.13 to 0.2 grams. Mixed with phenyl urea (147°) it melted at 144°-147°.

The filtrate from this was made alkaline with ammonium hydroxide and a solution of calcium chloride was added. 0.32 grams of calcium oxalate were obtained, 32%.

In Normal Excess Alkali. 2 grams of phenyl uric acid was dissolved in 5.2 grams of potassium hydroxide and 24cc. of water. 60cc. of hydrogen peroxide was then added and the solution cooled in ice water. On standing overnight, a strong odor of carbylamine had developed. A sample gave no precipitate when acidified with hydrochloric acid. One half of the oxidation solution was acidified with hydrochloric acid; on standing reddish crystals separated which when recrystallized once melted at 160°-161°. Mixed with the alkaline oxidation product of the first oxidation in 0.3 N excess alkali, it gave the same melting point- 163°. The other half of the solution was treated with manganese dioxide to decompose the excess of hydrogen peroxide and then made acid with glacial acetic acid. Red spherolitic particles formed which melted at 192°-195°. It was the same as the acid oxidation product from the first oxidation.

Alkaline Oxidation Product. The alkaline oxidation product was found to be unsymmetrical phenyl biuret - $C_6H_5NH.CO.NH.CO.NH_2$. It was recrystallized several times from hot water and dried at 100° for analysis.

I. 0.1422 gr. gave 0.2809 gr. CO_2 and 0.0630 gr. H_2O

0.1271 gr. gave 27.6cc. N_2 at 739 mm. and 23°

II. 0.1483 gr. gave 0.2916 gr. CO_2 and 0.0644 gr. H_2O

0.1299 gr. gave 28.5 cc. N_2 at 738.1 mm. and 24°

	Calc. for $C_8H_9N_3O_2$	Found	
		I	II
C	53.63	53.89	53.62
H	5.03	4.957	4.895
N	23.46	23.66	23.80

Optical Properties.

Habit: thin, rectangular plates

Extinction: parallel

Indices: α = 1.579 γ = 1.67

The unsymmetrical phenyl biuret melts at 164°-165° (uncorrected). It is soluble in hot water, in alcohol and ether. It crystallizes in shining scales. It dissolves readily in normal alkali and with difficulty in dilute hydrochloric acid. It does not give the biuret reaction. These properties agree with those given by Schiff[1] for unsymmetrical phenyl biuret.

It was also prepared synthetically from biuret and aniline. Hofmann[2] obtained only the ab diphenyl biuret by boiling biuret with aniline. But both the

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[1] Schiff, Ann. 352, 79 (1907)

[2] Hofmann, Ber. 4, 265 (1871)

unsymmetrical phenyl and the diphenyl biuret can be made in this way.

Aniline was added to powdered biuret and heated gradually to boiling. The biuret went into solution slowly and a strong odor of ammonia developed. The solution was boiled for a few minutes, then cooled slightly and decanted from the crystalline mass in the bottom of the tube. The precipitate was recrystallized from hot water; shining white scales were obtained on rapid cooling, bunches of needles on slow cooling. It melted at 163°-165° and a mixed melting point with the alkaline oxidation product gave 164°-165°. The optical properties were also the same.

<u>Optical properties.</u> Habit: thin plates

Indices: $\alpha = 1.572$ $\gamma = 1.67$

The decanted solution solidified to a nearly solid mass. It was treated with a little dilute hydrochloric acid to dissolve the aniline; alcohol was added, and the solution filtered. The filtrate on evaporation gave more crystals melting at 165°. The residue was recrystallized from alcohol. Fine white needles were obtained melting at 207°. Hofmann gives for ab diphenyl biuret 210° (corr.)

<u>Optical properties.</u>

Habit: needles

Optical Orientation: parallel extinction, α parallel to elongation

Interference figure: biaxial, large optic angle

Indices: $\alpha = 1.591$ $\gamma \begin{cases} < 1.656 \\ > 1.649 \end{cases}$ (J.A.C.S-45, 145)

The phenyl biuret from the oxidation gave diphenyl biuret on careful warming with aniline.[1] The finely powdered material was moistened with aniline and heated carefully in an aniline bath until all was in solution. On cooling and treating with aqueous alcohol, shining crystals were obtained which melted at 205°. Mixed with diphenyl biuret it melted at 205°-206°. The optical properties were the same.

Acid Oxidation Product. The acid oxidation product is an isomer of unsym. phenyl biuret but it is not the known sym. phenyl biuret - $NH_2CO.N.C_6H_5.CO.NH_2$,[2] for the latter was prepared and its properties are quite different from those of the acid oxidation product. The acid oxidation product was purified by animal charcoal and recrystallizing from hot water several times. It was dried at 110° for analysis.

I. 0.1636 gr. gave 0.3223 gr. CO_2 and 0.0682 gr. H_2O
0.1835 gr. gave 38.2cc. N_2 at 759 mm. and 24°

II. 0.1700 gr. gave 0.3331 gr. CO_2 and 0.0691 gr. H_2O
0.1125 gr. gave 23.3cc. N_2 at 755.7 mm. and 22°

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[1] Schiff, Ann. 352, 80 (1907)

[2] Schiff, Ann. 352, 74 (1907)

	Calc. for $C_8H_9N_3O_2$	Found I	Found II
C	53.63	53.73	53.43
H	5.03	4.665	4.548
N	23.46	23.19	23.21

The molecular weight was determined by the freezing point method. Glacial acetic acid was used as the solvent.

I. 0.0776 gr. in 10cc. glacial acetic gave 0.192° low'ng

II. 0.1360 gr. in 10cc. glacial acetic gave 0.311° low'ng

Calc. for $C_8H_9N_3O_2$	Found I	Found II
179	146.5	158.1

The results are low, due to the fact that the stirrer broke, so the solution could not be stirred adequately. Nevertheless they are close enough to show that the acid oxidation product is not a polymer but an isomer of phenyl biuret.

Optical Properties. Habit: long needles

Extinction: 32°-33°

Indices: $\alpha = 1.559$ $\gamma = 1.73+$ (J.A.C.S.)- 45, 148)

The pure oxidation product melts 196°-197.5° with decomposition. It is soluble in hot water and alcohol but not as soluble as the unsym. phenyl biuret is. It dissolves in alkali and is regained on evaporation or acidifying. It gives a weak biuret reaction.

The test was made following the directions of Schiff.[1] 1 gram of copper sulphate was dissolved in 100 grams of water. 1 mg. of the substance was mixed with a few drops of water and 1-2 drops of the copper sulphate solution was added drop by drop. The color changed from blue to violet but it was not the red violet given by biuret. When boiled with aniline the acid oxidation product gave ab diphenyl biuret. 0.1 gram was boiled with aniline under an air reflux for a few minutes. A little dilute hydrochloric acid was added to remove the aniline, and then alcohol. A precipitate of very fine needles was formed which melted at 198°-202°. Mixed with the original material it melted at 180°; with diphenyl biuret (207°) it melted at 209°.

A little of the oxidation product was suspended in water, and a drop of ammonium hydroxide (15 N) was added. The solution was warmed and filtered. Bunches of crystals separated on cooling which melted at 163°-165°! Mixed with the alkaline oxidation product, unsym. phenyl biuret, it melted at 163°-164°. The optical properties were the same. The acid oxidation product was isomerized by the ammonia to unsym. phenyl biuret. This reaction will be discussed in detail later.

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[1] Schiff, Ann. 352, 84 (footnote)

Sym. phenyl biuret was prepared according to Schiff's directions[1], which consisted in treating phenyl urea with phosphorous trichloride. Several attempts proved unsuccessful but finally a little of the phenyl biuret was obtained.

10 grams of phenyl urea was powdered and dried at 110°-115°. It was placed in a small flask connected with a reflux and 10cc. of phosphorous trichloride was added. The thick mass formed was refluxed on the water bath for 3 hours; it gradually became a colorless syrupy liquid. As much as possible was poured off while still warm. It was washed with ligroin and a little ice was added to decompose any phosphorous trichloride. It was then neutralized with solid sodium bicarbonate, while cooling. A granular mass resulted which was dried in the vacuum desiccator. It was boiled with a little benzene to dissolve any aniline, which was then poured off and the residue boiled several times with water. The first filtrate gave a white crystallize precipitate, part of which melted at 120° and the rest at 170°. It gave a strong biuret reaction. It was recrystallized from water in two lots. From the first a substance melting at 139°-140° was obtained. It did not give the biuret reaction and mixed with phenyl urea it melted at 142-145°. It was unchanged phenyl urea. From the second,

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[1] Ann. 352, 73 (1907)

crystals separated which softened at 175° and melted at 190°. It gave a strong biuret reaction. The second filtrate gave crystals which melted at 120°-122° and gave the biuret test. On recrystallization only phenyl urea was obtained.

The sticky mass left in the flask was also washed with ligroin and ice and neutralized with sodium bicarbonate. It was necessary to add a little water, or otherwise it was impossible to remove the residue from the flask. After standing overnight the liquid was poured off from the solid mass and evaporated on the water bath to dryness. The residue was boiled with alcohol, evaporated to dryness and then taken up with a little water. On cooling crystals melting at 184°-185° formed, which gave a good biuret reaction. The solid mass was boiled with water 4 times. The first filtrate gave a few crystals melting at 128°-130°, which gave the biuret test. Only phenyl urea was obtained on recrystallizing. The other filtrates gave phenyl urea back.

The properties of the sym. phenyl biuret agreed with those given by Schiff[1]. It melted when pure at 190° (uncorr.). It was readily soluble in hot water and in alcohol. When boiled with aniline for a short time and

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[1] loc. cit.

then treated with alcohol, white needles melting at 238°-240° were obtained. Mixed with diphenyl urea these melted at 238°-240°.

Optical Properties of Sym. Phenyl Biuret.

Habit: short, thick prisms

Extinction: 32°-34°

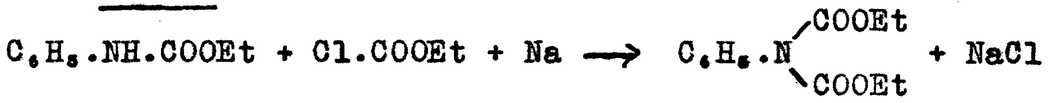
Indices: $\alpha = 1.5316$ $\gamma = 1.649+$ (J.a.c.s - 45, 148)

The optical properties do not agree with those of the acid oxidation product. Mixed melting point of sym. phenyl biuret (190°) and the acid oxidation product (197°) gave 160°. When the phenyl biuret was suspended in water, a few drops of ammonia added and the solution warmed, the original material was regained on cooling. It melted at 185°-189°; mixed with sym. phenyl biuret at 188°-190°. This experiment was repeated several times with the same results. Hence the acid oxidation product is not sym. phenyl biuret.

Several other attempts were made to synthesize sym. phenyl biuret as the method of Schiff gave only a very small quantity. The first consisted in heating dicarboxy ethyl aniline with ammonia under various conditions; but instead ot the ester groups being replaced by amino groups the substance split at the C-N bond and gave only phenyl urethane.

Dicarboxy ethyl aniline was prepared by the method of Diels and Narviosky[1].

Scheme:



$$C_6H_5.NH.COOEt + Cl.COOEt + Na \longrightarrow C_6H_5.N\begin{matrix} \diagup COOEt \\ \diagdown COOEt \end{matrix} + NaCl$$

Phenyl Urethane

Chlorformic ester   Dicarboxy ethyl aniline

10 grams of phenyl urethane were dissolved in 100cc. of absolute ether. 2.5 grams of sodium sand (made by melting sodium under xylene, shaking vigorously, pouring off the xylene and washing with ether) was added and the mixture refluxed for 10 hours on a luke warm water bath. Then 6.5 grams ethyl chlor formate was added slowly from a dropping funnel and the solution boiled 5 hours more. It was cooled and filtered by suction and the filtrate was evaporated. Large colorless crystals separated, which were recrystallized from a mixture of acetone and petroleum ether. Yield, 7 grams. The dicarboxy ethyl aniline melted at 58°-60°.

It was heated with liquid ammonia, an alcoholic solution of ammonia and conc. aqueous ammonia. 0.5 grams of dicarboxy ethyl aniline was allowed to stand with liquid ammonia overnight in a dewar flask. When all the ammonia had evaporated, a yellow oil remained, which solidified after standing several days. It melted at 51°.

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[1] Diels and Narviosky, Ber. 37, 3681 (1904)

Phenyl urethane melts at 51°-52°. 0.5 grams was heated with an alcoholic solution of ammonia for 50 hours at 80° in a sealed tube. On evaporation crystals melting at 50° were obtained. 0.5 grams was heated with alcoholic ammonia for 48 hours at 160°-180° in a sealed tube. Crystals formed on evaporation which melted at 51°. 0.5 grams was allowed to stand with conc. aqueous ammonia (15 N) for several days. Oily drops formed. On evaporation of the water a thick syrup was obtained from which crystals melting at 60°-65° separated. Mixed with the original material it melted at 60°.

The action of brombenzene on biuret in the presence of copper sulphate was also tried. 5 grams of biuret was dissolved in 10cc. of water and 10 grams of brombenzene and 0.5 grams of powdered copper sulphate were added. The mixture was refluxed several hours. The brombenzene was then decanted and the precipitate recrystallized from water. Biuret was regained, so the substance did not react.

Isomerism of the Oxidation Products. It was found that ammonia and many organic bases catalyse the change of the acid oxidation product to unsym. phenyl biuret. The inorganic bases, sodium, potassium, barium and silver hydroxides did not, nor did benzyl amine or pyridine.

Preparation of bases. The inorganic bases, including ammonium hydroxide, the aniline, ethyl amine, pyridine and benzylamine were all chemically pure. The other bases used were prepared in the laboratory. Methyl amine was prepared from methyl amine hydrochloride, freed from ammonium chloride, by boiling with alkali and absorbing the methyl amine evolved in water. Dimethyl amine was prepared free from ammonia by the method of Baeyer[1], using nitroso-dimethylaniline. 4 grams of nitroso-dimethylaniline was added to a boiling solution of 20 grams of sodium hydroxide in 180 grams of water. The solution turned a bright reddish yellow. The dimethylamine evolved was absorbed in dilute hydrochloric acid. The distillate was then boiled with alkali and the gas absorbed in water.

Tetramethyl ammonium hydroxide was prepared from tetramethyl ammonium iodide. 2 grams was warmed with 10cc. of absolute methyl alcohol. 0.55 grams of solid potassium hydroxide (1 equiv.) was added. Potassium iodide precipitated immediately. It was filtered and water added to the solution of the tetramethyl ammonium hydroxide.

Trimethyl sulphonium hydroxide was made from trimethyl sulphonium iodide by treating it with moist silver oxide[2].

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[1] Baeyer, Ber. 7, 964 (1874)

[2] Holleman, Organic Chemistry, p. 82.

Tetraethyl phosphonium hydroxide was prepared according to the directions of Cahours and Hofmann[1] by adding 1 gram of triethyl phosphin to 1.7 grams of ethyl iodide in 5cc. of absolute ether. The solution was allowed to stand in ice water. A crystalline precipitate of tetraethyl phosphonium iodide separated— 0.27 grams. An aqueous solution was treated with moist silver oxide and the silver iodide removed by filtering. A solution of tetraethyl phosphonium hydroxide remained.

Diphenyl iodonium hydroxide[2] was prepared by shaking together 2 grams of iodobenzene, 2.2 grams of iodosobenzene, 2.1 grams silver oxide and 10cc. of water for 3 hours on the shaking machine. The solution was then filtered, a little sulphurous acid was added, the solution filtered again and potassium iodide added to the filtrate. A heavy yellowish precipitate of diphenyl iodonium iodide, formed which weighed 1.2 grams and melted at 166°-167°. On recrystallizing from alcohol it melted at 173°-174° (uncorr.) and gave a deep red melt. A solution of diphenyl iodonium hydroxide was obtained by dissolving the iodide in water, treating with silver oxide and filtering off the silver iodide precipitate.

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[1] Cahours and Hofmann, Ann. 104, 15 (1857)

[2] Hartmann and Meyer, Ber. 27, 508 (1894)

Each reaction with the acid oxidation product was carried out in the same manner. A little of the powdered product, melting at 197°-198°, was suspended in water and warmed. Then a few drops of the base were added and the solution heated once to boiling and filtered immediately onto a watch glass. The crystalline product formed on cooling was filtered and its melting point found. It was identified by a mixed melting point when possible.

Base	Product	Melting Pt.	Mixed M. Pt.
NH_4OH	Unsym.Ph.Biuret	164°	163°-164°
CH_3NH_2	"	164°	163°-164°
$C_2H_5NH_2$	"	165°	163°-164°
$(CH_3)_2NH$	"	164°-165°	165°-166°
$(CH_3)_4NOH$	"	165°	164°-165°
$NaOH$	Acid Oxid.Prod.	197°-199°	198°-200°
KOH	"	198°-200°	198°-200°
Ag_2O	"	198 -200	198 -199
$Ba(OH)_2$	"	198°	198°
$C_6H_5NH_2$	ab Diph.Biuret	203°	205
$C_6H_5CH_2NH_2$	?	80°-85°	---
$(CH_3)_2SOH$	Unsym.Ph.Biuret	162°-164°	163°-164°
$(C_2H_5)_4POH$	"	164 -166	165 -166°
$(C_6H_5)_2IOH$	"	165°	165 -166
C_5H_5N	Acid Oxid.Prod.	196 -200°	198

The acid oxidation product was also treated with dilute hydrochloric acid. On cooling crystals of the original material, melting at 200°, were regained. Mixed with the original substance it melted at 198°-200°.

The alkaline oxidation product (165°) was warmed with dilute hydrochloric acid. Crystals melting at 165° were obtained. It was treated with normal potassium hydroxide, warmed and acidified. The original material was regained. On standing overnight with potassium hydroxide (4 N) the unsym. phenyl biuret was found to be unchanged.

The acid oxidation product in aqueous and in alcoholic solution gave no color with ferric chloride, so it was not the enol form - $NH=C(OH)NC_6H_5CO.NH_2$.

The effect of ultra violet light was tried on the two isomers, both in the dry state and in alcoholic solution. Dry powdered unsym. phenyl biuret (M.P. 165°) was subjected to ultra violet rays (110 volts) at a distance of 20cm. from the source. After 8 hours exposure the substance melted at 164°-165°; mixed with the original material, at 164°-165°. Therefore no change had taken place. Dry powdered acid oxidation product was exposed to ultra violet rays - 20cm. from the source-for 8 hours. No change occurred; the material melted at 198°-200°, mixed with the original at 197°. 0.05 gram of unsym. phenyl biuret was dissolved in 2cc. of absolute alcohol. It dissolved quite readily. It was poured into a small quartz tube and exposed to ultra violet light for 24 hours. The solution on evaporation gave crystals melting at 157°-161°, mixed with phenyl biuret it melted at

160°-162°. 0.05 gram of the acid oxidation product was dissolved in 3cc. of absolute alcohol. It was necessary to warm to get it into solution. After subjecting this solution in a quartz tube to the rays for 24 hours, a few crystals had separated. They melted at 198°-200°. The filtrate on evaporation gave more material, melting at the same temperature. Ultra violet light has therefore no effect on either product.

Attempts were made to oxidize the two oxidation products with hydrogen peroxide in 0.5 N alkali. The alkaline oxidation product was not effected. The acid oxidation product was changed to the alkaline oxidation product, i.e., unsym. phenyl biuret. Neither peroxide nor potassium hydroxide alone was able to do this - only the combination.

0.5 gram of unsym. phenyl biuret was added to 9cc. water, and 0.8 gram of potassium hydroxide. Only part of it went into solution. It was cooled by ice water and 28cc. of hydrogen peroxide was added. An immediate precipitate was formed which did not lessen on standing. A sample was filtered; the residue melted at 163°-165°. After 3 days the entire solution was filtered. 0.36 gram of the phenyl biuret was regained. On acidifying the filtrate and evaporating 0.04 gram more was obtained. It melted at 162°-164°. No trace of phenyl urea was found.

0.5 gram of the acid oxidation product was dissolved in 0.8 gram potassium hydroxide and 9cc. of water. It was cooled with ice water and 28cc. of hydrogen peroxide was added. A heavy precipitate formed immediately. A little was filtered off - it melted at 164°-165° ! Mixed with unsym. phenyl ~~urea~~ biuret it melted at 164°. The rest of the oxidation solution was allowed to stand. After two days its was filtered. 0.2 gram of unsym. phenyl biuret was obtained. Mixed melting point gave 165°. On acidifying the filtrate a small amount of unchanged acid oxidation product was obtained - 0.01 gram. It melted at 198°-200°. 0.05 gram of the acid oxidation product was mixed with 0.9cc. of water, and 2.8cc. of hydrogen peroxide was added. After standing 1 hour none had dissolved. It was filtered. The residue melted at 198°-200°. 0.05 gram was treated in the same way and allowed to stand overnight. No change was apparent. The substance melted at 198°-200°.

0.05 gram was mixed with 0.9cc. of water and 0.08 gram potassium hydroxide. All dissolved. On the addition of 2.8cc. of water nothing separated. After standing 1 hour the solution was acidified with hydrochloric acid. The precipitate melted at 198°-200°. 0.05 gram was heated as before and allowed to stand overnight. 0.04 gram of the original material was regained on acidifying. It melted at 198°-200°.

It was also found that when the acid oxidation product was suspended in a little water and a drop or two of conc. ammonium hydroxide, part went into solution; but on standing in the cold for a short time a flocculent precipitate separated which melted at 165°. The filtrate on evaporation gave a substance melting from 180° to 195°. It was probably a mixture of unsym. phenyl biuret and the acid oxidation product.

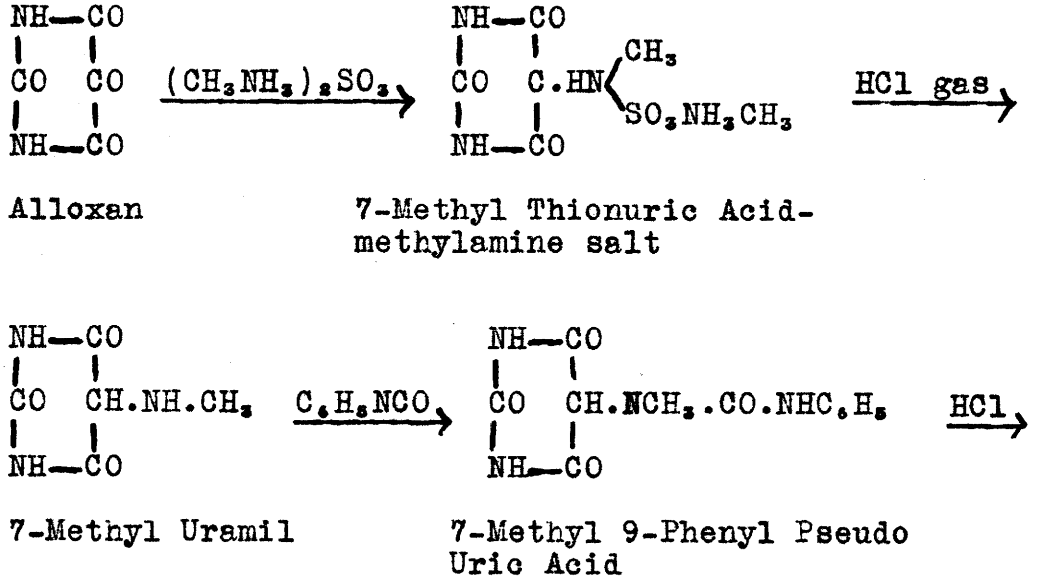
C. 7-Methyl 9-Phenyl Uric Acid.

1. Preparation.

a. First Attempts.

7-methyl uramil, the starting point in the preparation of 7-methyl 9-phenyl uric acid, has been made by several investigators. Fischer's method[1], consisting in the action of methylamine sulphite on alloxan to give a solution of methyl thionuric acid and the subsequent decomposition of this by hydrochloric acid to give 7-methyl uramil, was attempted repeatedly without success. Miss Thomas[2] was also unable to repeat his work.

Scheme:

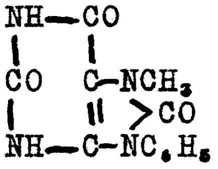


Alloxan

7-Methyl Thionuric Acid-methylamine salt

7-Methyl Uramil

7-Methyl 9-Phenyl Pseudo Uric Acid



7-Methyl 9-Phenyl Uric Acid

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[1] Fischer, Untersuchungen in der Puringruppe, p. 251

[2] Private communication

The methylamine solution used was prepared by dissolving 190 grams of methylamine hydrochloride in water in a large flask, to which was attached a reflux condenser to prevent dilution of the distillate. From the top of the latter a delivery tube passed into an empty receiver to catch any of the solution that drew back; this was connected to an Erlenmeyer flask containing 250cc. of water to absorb the gas and this is turn to a small flask with a little water to absorb any gas that passed through. 125 grams of sodium hydroxide dissolved in water was then added slowly to the hydrochloride from a dropping funnel and the solution heated gradually to boiling. It was boiled hard until the methylamine solution started to run back. About 375cc. of the methylamine solution was obtained. It contained 23.25% methylamine according to specific gravity measurements.

60 grams of the methylamine solution was cooled with ice and saturated with sulphur dioxide, and then neutralized with methylamine. 30 grams of alloxan in 60cc. of water was added and the mixture was warmed on the water bath at 70°-75°. After about an hour and a half a precipitate began to form (Fischer says the solution remains clear). After 3 hours there was still a

heavy precipitate. The solution was well cooled and saturated with dry hydrochloric acid gas, prepared by dropping conc. sulphuric acid on hydrochloric acid (s.gr. 1.19) and dried by passing through a sulphuric acid wash bottle. Prolonged treatment did not cause the precipitate to redissolve though it became less. (Fischer states that a precipitate is formed on passing in the gas and on longer treatment redissolves.) The solution was allowed to stand overnight and then a greater part of the hydrochloric acid was evaporated off on the water bath at 40°. The residue was diluted with water and filtered. 15 grams of the substance was obtained. Fischer ways that his product was impure 7-methyl uramil,- it was mixed with some uramil and with alloxantin, and the latter was removed by boiling with water. He does not purify his substance or analyse it, but uses the impure product to make 7-methyl pseudo uric acid; he also obtained some of the pseudo uric acid. The two were easily separated and identified.

1.2 grams of the product obtained was treated with 5cc. of water and 0.92 grams of potassium cyanate to see if it would give 7-methyl pseudo uric acid.[1] The solution was warmed on the water bath for 20 minutes,

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[1] Fischer, *Untersuchungen in der Puringruppe*, p. 282.

and shaken constantly. A deep red color developed which gradually became yellow and then nearly white. The solution was allowed to stand overnight; it was then diluted and warmed on the water bath. No residue ~~had~~ formed as in Fischer's preparation. On cooling and acidifying nothing precipitated, so no methyl pseudo uric acid had been formed and the original material was not even impure 7-methyl uramil.

4 grams were added to 60cc. of normal potassium hydroxide at 0° and the solution was shaken until almost all the material had dissolved. A purplish red color developed. 3 grams of phenyl isocyanate was added gradually with shaking and cooling. After a short time the solution began to thicken. When all had been added, the solution was filtered. The filtrate on acidifying became barely cloudy. The residue was boiled with water, filtered and acidified. A precipitate of shining flakes came down which melted at 145°-150°. Analysis showed it to be ab methylphenyl urea - $CH_3.NH.CO.NH.C_6H_5$. On recrystallization it melted at 149°-150°. It was dried to constant weight over sulphuric acid in a vacuum desiccator for analysis.

I. 0.1790 gr. gave 0.4177 gr. CO_2 and 0.1060 gr. H_2O

0.1717 gr. gave 29.2 cc. N_2 at 750.17 mm. and 25°

II. 0.1552 gr. gave 0.3640 gr. CO_2 and 0.0928 gr. H_2O

0.1470 gr. gave 24.1 cc. N_2 at 748.74 mm. and 24°

Calc. for $C_8H_{10}ON_2$		Found	
		I	II
C	63.98	63.96	63.62
H	6.713	6.689	6.625
N	18.66	18.60	18.65

Optical Properties. Habit: thin transparent plates

Extinction: parallel (J.A.C.S - 45, 142)

Indices: $\alpha = 1.513$ $\gamma = 1.632$

The residue insoluble in water was boiled with alcohol. All dissolved. Needle shaped crystals came out on cooling, which melted at 232°-235°. It was recrystallized and dried in a vacuum desiccator for analysis. The pure substance melted at 236°-238°. It was sym. diphenyl urea.

I. 0.1570 gr. gave 0.415 gr. CO_2 and 0.0766 gr. H_2O

0.1821 gr. gave 22.10 cc. N_2 at 753.48 mm. and 24.5°

II. 0I1420 gr. gave 0.3805 gr. CO_2 and 0.0728 gr. H_2O

0.2113 gr. gave 25.50 cc. N_2 at 753.25 mm. and 25°

Calc. for $C_{13}H_{12}ON_2$		Found	
		I	II
C	73.55	73.15	73.24
H	5.701	5.459	5.736
N	13.20	13.27	13.39

Optical Properties.

Habit: needles

Optical Orientation: parallel extinction, α parallel to elongation

Interference figure: biaxial, 1 brush

Indices: $\alpha = 1.583$ ✓ $\gamma = 1.74$ (?) ✓ JACS. 45, 144

It appears that there was little or no 7-methyl uramil in hand. The source of the methylphenyl urea is not definitely known - it was not always obtained. The diphenyl urea came from the hydrolysis of the phenyl isocyanate[1].

Finally, as the substance gave a blue purple precipitate with barium hydroxide[2], it was thought probable that most of it might be alloxantin mixed with a little uramil and 7-methyl uramil. To separate the alloxantin[3] 2 grams were boiled with water and filtered hot. A crystalline precipitate came down at once. It weighed 1 gram, and became pink at 90°-100°, a deep red orange by 210°, and melted with decomposition at 215°-220°. Pure alloxantin decomposes at 170°. A solution of it gave a heavy purple precipitate with barium hydroxide. But so did the residue. It was again boiled with water, filtered and

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[1] Beilstein, Handbuch Vol. II, p. 374.

[2] Beilstein, Handbuch Vol. I, p. 1401.

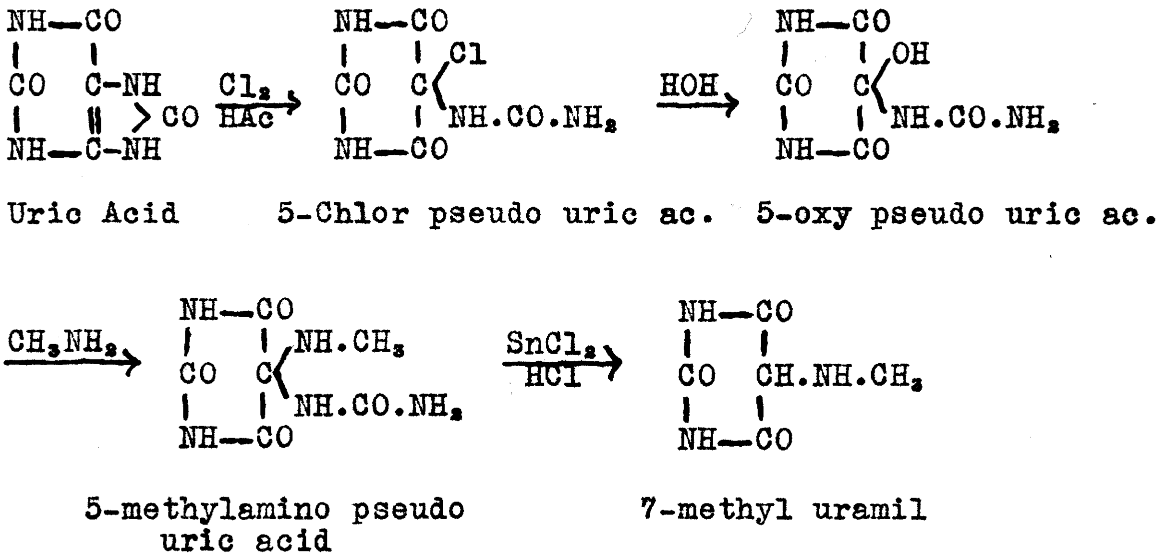
[3] Fischer, Untersuchungen in der Puringruppe, p. 282.

cooled. More crystals identical with those from the first filtrate formed. A residue of only 0.2 gram was left. Apparently most of the product was alloxantin. 7-methyl uramil does not melt[1] but turns violet and decomposes slowly at 250°. It is not readily soluble in water.

b. Method.

The method for preparing 7-methyl uramil finally used was that of Biltz[2]. It consisted in treating uric acid with chlorine, whereby 5-chlor pseudo uric acid was formed. The 5-oxy pseudo uric acid, made by the action of water on the chlor compound, gave 5-methyl amino pseudo uric acid by treating with methylamine, and this finally was reduced to 7-methyl uramil by stannous chloride in acid solution.

Scheme:



Uric Acid 5-Chlor pseudo uric ac. 5-oxy pseudo uric ac.

5-methylamino pseudo uric acid 7-methyl uramil

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[1] Biltz, Ber. 46, 3679 (1913) [2] Biltz, Ann. 413, 23, 29, 46 (1917)

Purification of Uric Acid. The uric acid used must be pure. It was purified by boiling a solution of 100 grams of uric acid in 70 grams of sodium hydroxide and 1.4 liters of water. On filtering while hot and saturating with carbon dioxide, a heavy precipitate of acid sodium urate was formed. This was filtered and the wet residue heated to boiling with 400cc. of dilute hydrochloric acid. A fine white precipitate of uric acid was obtained which was filtered by suction, washed with water, alcohol and ether and dried to constant weight at 110°. Yield, 55 grams.

5-Chlor Pseudo Uric Acid. 5-chlor pseudo uric acid was prepared by mixing 10 grams of pure uric acid with 80cc. of glacial acetic acid (freshly distilled - B.P. 117°) and 1 cc. of water (measured with a pipette) in a mortar. The mixture was poured into a 250cc. wide mouthed Erlenmeyer flask fitted with a delivery tube for chlorine and a long outlet tube to carry off the unused gas. It was cooled to about 12° by ice water and chlorine from a cylinder, dried by sulphuric acid and calcium chloride, was passed in in a vigorous stream. The temperature was kept at 7°-10° and the solution was shaken continuously. Some of the acetic acid crystallized, but it soon redissolved. After 20 minutes the solution began to thicken with crystals and after $\frac{1}{2}$ hour it was almost solid. The chlorine was stopped and the preparation, closed by a small calcium chloride tube, was left in ice water for an hour. By then the crystals appeared entirely homogeneous under the microscope. Glacial acetic acid was added, the solution was filtered quickly, washed with a little glacial acetic acid and much ether, and dried in a desiccator for a short time. The yield of chlor pseudo uric acid was 9 grams. It became pink at 120°, red at 140°, and part melted at 240° leaving a dark mass on the sides of the tube which did not melt.

5-Oxy Pseudo Uric Acid. 5-oxy pseudo uric acid was made by adding 18 grams of the chlor pseudo uric acid to 80cc. of ice water. The needles decomposed at once and a heavy precipitate, consisting of crystals of no definite shape, formed and settled rapidly. After a few minutes it was filtered by suction, washed with water, alcohol and ether and dried in a vacuum desiccator. Yield, 9 grams.

5-Methylamine Pseudo Uric Acid. The oxy pseudo uric acid acid was changed into the methylamine derivative by cooling 10 grams in 60cc. of water and adding 5.2 grams of 33% methylamine solution from a dropping funnel, shaking constantly. A pinkish precipitate formed. The solution was acidified with dilute acetic acid and left in ice water for 1 hour. It gradually became a deep pink. On filtering and washing with alcohol and ether, a yield of 7 grams was obtained, which melted at 186°-187° with a deep red melt.

7-Methyl Uramil. A clear boiling solution of 14 grams of stannous chloride in 28cc. conc. hydrochloric acid was added to 7 grams of methylamine-pseudo uric acid. The solution was milky in appearance. (Biltz says it should be clear.) It was covered with a watch glass and boiled 5 minutes. Then the solution was poured slowly into 250cc. of cold water; a white precipitate settled rapidly. It was left in the ice box overnight, then filtered. A soft white precipitate of methyl uramil was obtained, weighing 4 grams. It turned pink at 205° and became deeper in color but did not melt.

7-Methyl 9-Phenyl Pseudo Uric Acid. 7-Methyl 9-Phenyl pseudo uric acid was prepared by cooling 60cc. of normal potassium hydroxide to 0° and adding 5 grams of 7-methyl uramil, shaking until practically all dissolved. To the solution 5 grams of phenyl isocyanate was added in small portions, shaking after each addition until the odor disappeared. The temperature was kept at 0°-5°. The solution became purplish but very little precipitate separated. It was filtered and the slight residue was boiled with water. 0.1 gram of material was obtained which did not melt. The part that did not dissolve in water was boiled with alcohol, and gave crystals melting at 238°-240°; mixed with diphenyl urea they melted at 235°-238°. The filtrate on acidifying with hydrochloric acid gave a heavy precipiate, weighing 7 grams, which melted melted at 245°-250° and gave a yellow melt. Of the pseudo uric acids known up to now, the 7-methyl pseudo is the only one that does not give a characteristic deep red color on melting. The 7-methyl 9-phenyl pseudo uric acid makes the second exception. The potassium salt of 7-methyl 9-phenyl pseudo uric acid is also more soluble than the potassium salt of 9-phenyl pseudo uric acid; just as that of the 7-methyl pseudo uric acid is more soluble than the potassium salt of pseudo uric acid.[1]

Optical Properties.

Habit: needles

Optical Orientation: parallel extinction, γ parallel to elongation

Indices: $\alpha = 1.636$ $\gamma = 1.714+$ (J.A.C.S. 45, 141)

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[1] Fischer, Untersuchungen in der Puringruppe, p. 253.

7-Methyl 9-Phenyl Uric Acid. 3 grams of the methyl phenyl pseudo uric acid was boiled with 600cc. of 35% hydrochloric acid. Much of it did not appear to dissolve. It was boiled down to $\frac{1}{5}$ of its volume and filtered hot. 1.55 grams of precipitate was obtained which on recrystallization gave a mat of fine glistening needles. It did not melt below 295°. The filtrate on further evaporation and cooling gave 0.78 grams of precipitate which when recrystallized proved to be the same as the residue. The total yield was 2.12 grams, 76%. It gave the murexid test with potassium chlorate, hydrochloric acid and ammonia. Evidently the 7-methyl 9-phenyl pseudo uric acid is changed by hydrochloric acid to the methyl phenyl uric acid much more easily than the 9-phenyl pseudo uric acid. It was recrystallized from water for analysis;—much water was necessary as it is not very soluble,—and dried to constant weight at 100°.

I. 0.2140 gr. gave 0.4412 gr. CO_2 and 0.0833 gr. H_2O

0.1437 gr. gave 28.3 cc. N_2 at 753.29 mm. and 26°

II. 0.2052 gr. gave 0.4225 gr. CO_2 and 0.0765 gr. H_2O

0.1581 gr. gave 30.4 cc. N_2 at 773.26 mm. and 26°

	Calc. for $C_{12}H_{10}O_3N_4$	Found I	Found II
C	55.81	56.22	56.14
H	3.903	4.355	4.172
N	21.70	22.00	21.72

Optical Properties.

Habit: needles

Optical Orientation: parallel extinction, γ parallel to elongation.

Indices: $\alpha = 1.557+$ $\gamma = 1.674$ (J.a.c.s. 45, 141)

7-methyl 9-phenyl uric acid is quite stable toward 4 N sodium hydroxide. 0.15 gram was heated to boiling with 7cc. of 4 N alkali. On acidification an immediate precipitate of unchanged acid was formed - 0.13 gram.

2. Oxidation with Hydrogen Peroxide.

To 0.5 gram of 7-methyl 9-phenyl uric acid in 6cc. of water 2.2 grams of solid potassium hydroxide was added. A white precipitate formed - probably the potassium salt. On the addition of 40cc. of 3% hydrogen peroxide the precipitate did not entirely dissolve, so after standing 15-20 minutes it was warmed carefully until all had gone into solution,-the temperature rose to about 40°. It was cooled with ice water for 2 hours and then left at room temperature. After 3 days a sample gave only a very slight precipitate on acidifying. The solution was evaporated by drawing air through. 0.06 gram of precipitate was obtained which melted at 145°-150°. On recrystallization from hot water, good crystals were formed which melted at 145°-150°; mixed with ab methyl phenyl urea it softened at 145° and melted at 148°-150°.

The optical properties of the two were identical. Therefore the alkaline oxidation product was ab methyl phenyl urea.

Optical Properties. Habit: plates

Extinction: parallel

Indices: $\alpha = 1.513$ $\gamma = 1.636$

The alkaline filtrate stood one day longer and then as no more precipitate formed, it was acidified with dilute hydrochloric acid. After standing several hours, crystals began to form which did not look homogeneous - some were like the original methyl phenyl uric acid. They were filtered off. Weight, 0.15 gram. The substance did not melt. It was recrystallized from water, using 3 lots of water. The first gave crystals immediately. They were not homogeneous under the microscope; part melted at 215°, the rest did not melt. It was probably a mixture of the acid oxidation product and some unchanged methyl phenyl uric acid. The other two lots gave 0.03 gram of unchanged acid. The acid filtrate was evaporated further in a vacuum desiccator. It gave 0.02 gram of crystals melting at 145°-148°; mixed with methyl phenyl urea it melted at 146°-147°. Total yield of methyl phenyl urea was 0.1 gram. Theory, 0.3 gram.

Optical Properties. Habit: square plates

Extinction: parallel

Indices: α = 1.513 γ = 1.636+

The mother liquor was evaporated until potassium chloride started to crystallize. It was then made alkaline with ammonia and a solution of calcium chloride was added. 0.07 gram of calcium oxalate separated. Theory, 0.25 gram.

D. 1,3-Dimethyl 9-Phenyl Uric Acid.

1. Preparation.

a. First attempts.

1,3 dimethyl 9-phenyl uric acid and the corresponding uric acid have not been prepared before, but the starting point, 1,3 dimethyl alloxan, has. Fischer[1] made it by oxidizing caffein with potassium chlorate, reducing the oxidation solution to amalinic acid by hydrogen sulphide and then oxidizing this with chlorine to dimethyl alloxan. The method was tried but the yields were poor. It was especially difficult to separate the amalinic acid from the precipitated sulphur, as the former is not very soluble in water.

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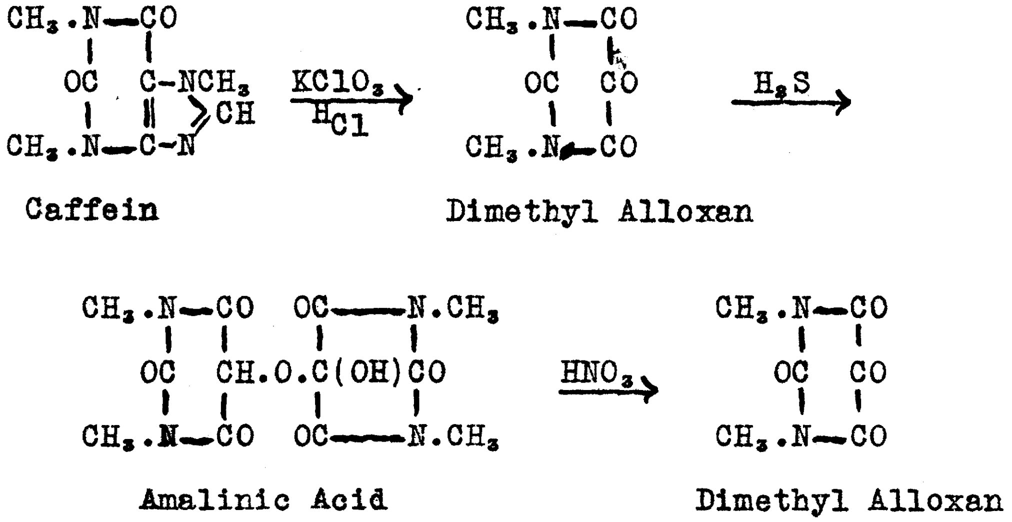
[1] Fischer, Untersuchungen in der Puringruppe, p. 88, 128.

Scheme:



Caffein

Dimethyl Alloxan

Amalinic Acid

Dimethyl Alloxan

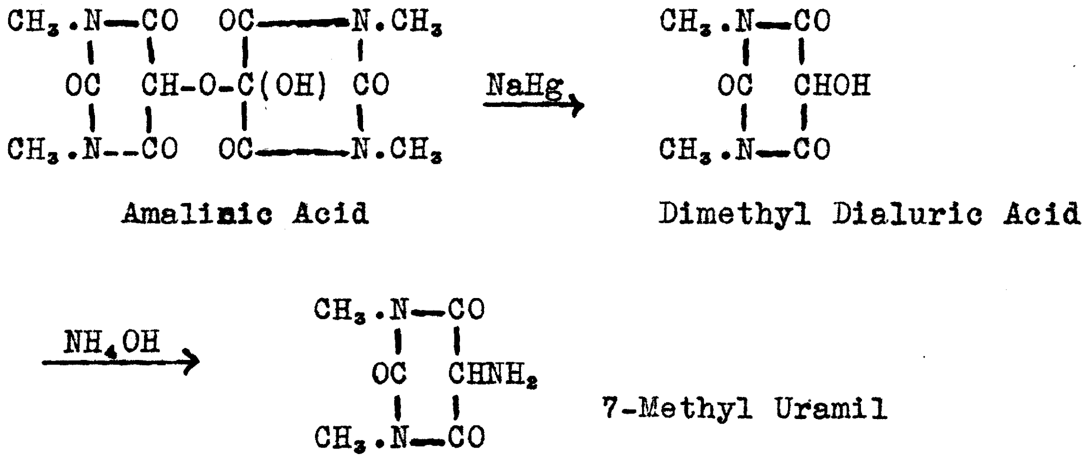
Amalinic Acid. 7 grams of potassium chlorate was added in small portions to a solution of 15 grams of caffein in 20 grams of hydrochloric acid and 45 grams of water, warmed to 50°. After a short time a heavy precipitate of chlor caffein separated which on shaking and adding the rest of the potassium chlorate gradually disappeared. The solution was a clear yellow at the end. The operation lasted about $1\frac{1}{2}$ hours. The solution was then diluted with the same volume of water. A little sulphurous was added to destroy the excess chlorine, and hydrogen sulphide was passed in until the solution was saturated. A heavy precipitate of amalinic acid and free sulphur was formed. The amalinic acid was extracted by boiling with a large amount of water - about 500cc.

White crystals of amalinic acid separated on cooling. Yield, 3 grams.

Dimethyl Alloxan. Dimethyl alloxan was prepared by suspending 4 grams of amalinic acid in 20cc. of water and passing in chlorine. A clear solution resulted which was evaporated in vacuo. After 2 days large crystals of dimethyl alloxan separated, which weighed 2 grams. This was worked up into dimethyl thionuric acid and dimethyl uramil by the same method as given below.

Two or three efforts were made to reduce amalinic acid to dimethyl dialuric acid by sodium amalgam and by treating the latter with ammonium hydroxide to get 7-methyl uramil ,[1] but they were not successful.

Scheme:



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[1] Biltz, Ber. 46, 3670 (1913)

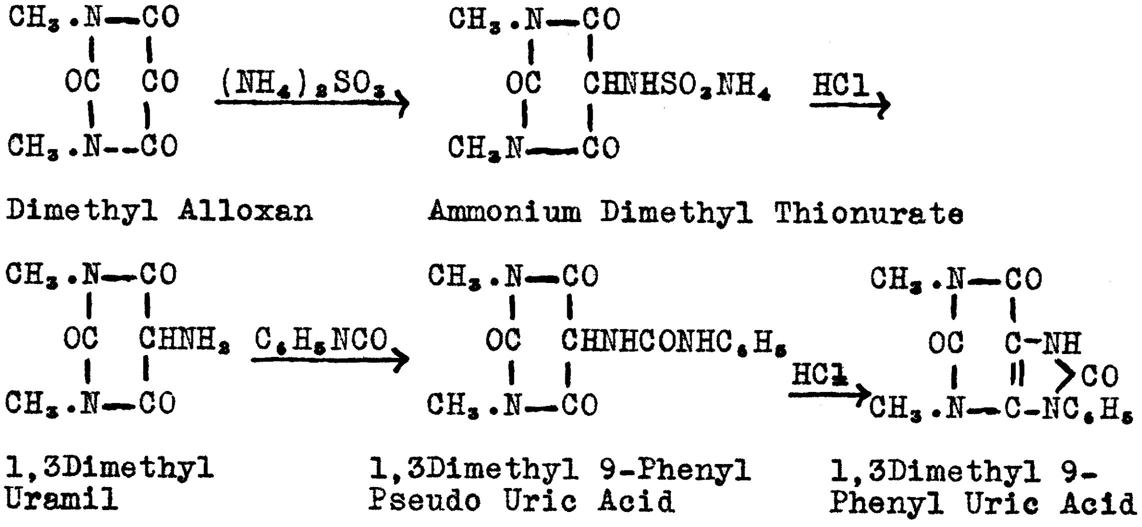
Dimethyl Dialuric Acid. 10 grams of amalinic acid was mixed with 10cc. of water, making a thick paste. The sodium amalgam used for the reduction was made by warming 150 grams of mercury in an evaporating dish to about 80° on the water bath and adding 5 grams of dry sodium in small pieces. There was a vigorous reaction at first; the solution became gradually thicker until at the end it was a solid mass. 97 grams of the amalgam was added to the amalinic acid in small portions. The solution became first reddish, then a deep purple, and finally a dirty gray. When all the amalgam had been added the solution was thick with precipitate. An excess of boiling concentrated hydrochloric acid was added until the precipitate dissolved. It was then quickly filtered and cooled with ice. The solution remained clear, so crystallization was started by scratching a little in a test tube and seeding the solution. A small crystalline precipitate of 0.65 grams resulted, which melted at 219° with a deep red melt.

Dimethyl Uramil. 0.5 grams of dimethyl dialuric acid was mixed with 4cc. of hot water and 1.5cc. of ammonium hydroxide. The solution became first purple and then yellow, and all dissolved. It was acidified with dilute acetic acid and warmed on the water bath. A crystalline precipitate of dimethyl uramil separated but it only weighed 0.03 gram.

b. First Method.

The method given by Biltz[1] for making dimethyl alloxan was the one finally used. It consisted in oxidizing caffein by potassium chlorate, reducing the oxidation solution to amalinic acid by stannous chloride, and then oxidizing the amalinic acid to dimethyl alloxan by fuming nitric acid. This procedure gave much better results than Fischer's method. From the dimethyl alloxan dimethyl thionuric acid and dimethyl uramil were obtained, and the latter with phenyl isocyanate gave the desired 1,3 dimethyl 9-phenyl pseudo uric acid and 1,3 dimethyl 9-phenyl uric acid.

Scheme:



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[1] Biltz, Ber. 45, 3674 (1912)

Amalinic Acid. 100 grams of caffein were worked up at a time, the oxidations being carried out in 25 gram lots and then combined. A solution of 25 grams of caffein in 35 grams of conc. Hydrochloric acid and 75cc. of water was warmed on the steam bath to 40°. 10 grams of finely powdered potassium chlorate was added in very small portions, with constant shaking. The temperature was kept below 55°. A heavy mass of chlorcaffein came out after about $\frac{3}{4}$ hour; the solution became nearly solid with it. After 2 hours all the chlorate had been added; the solution was a clear yellow and smelt strongly of chlorine. It was cooled with water and combined with three other oxidation solutions in a 2 liter Erlenmeyer flask. The combined solutions were then cooled with ice water and air was drawn through for 2 hours to get rid of the chlorine and to precipitate any apocaffein that had formed. Usually about 5 grams was obtained; it melted at 143°-144° and gave a white precipitate with barium hydroxide.[1] It was filtered off and a cold solution of 54 grams of stannous chloride in 40cc. hydrochloric acid and 40cc. of water was added gradually through a thistle tube, the solution being kept cold and stirred by a current of air. The operation lasted 2 hours.

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[1] Fischer, Untersuchungen in der Puringruppe, p. 103-104.

The solution was allowed to stand $\frac{1}{2}$ hour in ice water, and then the amalinic acid was filtered and dried. Yield, 47 grams. The filtrate on standing overnight in the ice box usually gave a little more precipitate.

Dimethyl Alloxan. Dimethyl alloxan was prepared by gradually adding fuming nitric acid to a paste of 46 grams of amalinic acid and 40cc. of water, while warming on the water bath. After about 7cc. of the acid had been added the solution fumed strongly and then cleared. It was filtered when necessary and evaporated in a vacuum desiccator. A thick mass of large clear crystals separated, weighing 37 grams. The filtrate on longer standing gave about 8 grams more. Often the yield was not as large, due either to too much water being used in the beginning or to too short evaporation. But the solution worked up into dimethyl thionuric acid just as well as the crystals and they were often used instead of waiting for the dimethyl alloxan to crystallize, the amount of ammonia used being calculated on the basis of the calculated yield.

Dimethyl Thionuric Acid.[1] The ammonium salt was prepared according to Fischer's directions. 120cc. of

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[1] Fischer, Untersuchungen in der Puringruppe, p. 171.

ammonium hydroxide (15 N) and 20cc. of water were cooled by ice water and saturated with sulphur dioxide. The solution was neutralized with an excess of ammonium carbonate. To this 37 grams of powdered dimethyl alloxan (or the solution of oxidized amalinic acid) was added; it became nearly solid. On warming on the steam bath for 1 hour the solution cleared. After standing overnight at room temperature a heavy precipitate of the ammonium salt of dimethyl thionuric acid had separated. It was filtered by suction. Yield, 51 grams. The filtrate on further evaporation gave 4 grams more.

1,3 Dimethyl Uramil.[1] 204 grams of conc. Hydrochloric acid was added to 5 grams of ammonium dimethyl thionurate and the solution allowed to stand for 3 hours at room temperature. Water was added until the inorganic ammonium salts which had separated were dissolved and then the solution was carefully neutralized with ammonium carbonate(about 120 grams were necessary). The dimethyl uramil was precipitated as a foamy mass. When exactly neutral the uramil was filtered quickly, washed with water, alcohol and ether and dried in a vacuum desiccator. Yield, 40 grams. As dimethyl uramil when moist turns red very rapidly in the air,

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[1] Fischer, Untersuchungen in der Puringruppe, p. 172.

it is necessary to work as fast as possible. Even then the preparation is usually quite pink. Once or twice small quantities which had been washed only with water and dried in the air remained perfectly white, but when large quantities were tried they became a deep red. It was probably because the small amounts had been dried almost completely by the suction, whereas the large quantities of course were not.

The yields of all these substances varied somewhat-from 100 grams of caffein, at different times, the following yields were obtained:- 65, 47, 57, 45, 59 and 53 grams of amalinic acid; 48, 32, 30, 47, and 57 grams of dimethyl alloxan; 50, 63, 64, 44 and 65 grams of ammonium dimethyl thionurate; and 35, 50, 32, 24, and 40 grams of dimethyl uramil.

1,3 Dimethyl 9-Phenyl Pseudo Uric Acid. 1,3 dimethyl uramil[1] is very unstable toward alkali; it is even decomposed by ammonium carbonate. So the first attempts to make 1,3 dimethyl 9-phenyl pseudo uric acid were with water instead of alkali as the solvent. A little of the 1,3 dimethyl 9-phenyl pseudo uric acid was obtained but the yields were very poor. It was soon found that alkali could be used if it was first

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[1] loc. cit.

cooled to about 0° and if the addition of the phenyl isocyanate began immediately after the dimethyl uramil had been added. This procedure gave very good yields indeed.

With Water as Solvent. 1 gram of phenyl isocyanate was added to 1 gram of dimethyl uramil in 10cc. of water. The solution became purple. It was warmed on the water bath at 35°-45° and shaken constantly. The color deepened at first and then became lighter. After 20 minutes it was a light pink and there was no odor of the isocyanate. A thick precipitate had formed which was filtered and dried. It weighed 1.16 grams. Part of the residue dissolved on boiling with hot water and the filtrate gave 0.13 gram of a white crystalline precipitate, melting at 182°-190°. The residue insoluble in water gave on boiling with alcohol 0.4 gram of diphenyl urea, melting at 239°-240°. The original filtrate gave on acidifying clusters of small crystals, weighing 0.3 gram, which also melted at 183°-190° with a deep red melt. On recrystallizing,0.1 gram of pure 1,3 dimethyl 9-phenyl pseudo uric acid, melting at 192°, was obtained.

With Potassium Hydroxide as Solvent. 30 grams of dimethyl uramil was finely powdered and added to 360cc. of normal potassium hydroxide cooled to 0° by ice and salt. A deep red solution resulted. 30 grams of phenyl iso cyanate was added in small portions and the solution shaken vigorously after each addition until the odor had gone. The temperature was kept at 0°-4°. The operation took from $\frac{3}{4}$ to 1 hour. The solution was light pink and thick with precipitate. It was filtered and the residue washed with water. The filtrate and wash water were both acidified. A slight precipitate was obtained. The potassium salt was not very soluble, in which respect it resembles that of 9-phenyl pseudo uric acid. The salt was dissolved in hot water (about 500cc.), cooled slightly and made acid with dilute hydrochloric acid, which must be added gradually; and the solution must not be stirred. A heavy white precipitate of the 1,3 dimethyl 9-phenyl pseudo uric acid separated. It was allowed to stand overnight and then filtered. Yield, 33 grams. Little diphenyl urea is obtained if the reaction has been carried out properly.

From 10 grams of uramil yields of 16, 11, 9, 12 and 13 grams were obtained; from 30 gram-lots yields of 28, 31, 37, 30 and 33 grams. Vigorous shaking, low temperature, and the gradual addition of the isocyanate favor good yields.

The 1,3 dimethyl 9-phenyl pseudo uric acid was recrystallized twice from hot water for analysis. It crystallized in colorless plates which melted at 189°-189.8°, and gave the characteristic deep red melt. It was dried to constant weight over sulphuric acid in a vacuum desiccator.

I. 0.2054 gr. gave 0.4008 gr. CO_2 and 0.0947 gr. H_2O
0.1599 gr. gave 28.8 cc. N_2 at 758.95 mm. and 25°

II. 0.2075 gr. gave 0.4064 gr. CO_2 and 0.0922 gr. H_2O
0.1471 gr. gave 27.2 cc. N_2 at 757.57 mm. and 29°

	Calc. for $C_{13}H_{14}O_4N_4$	Found	
		I	II
C	53.76	53.22	53.39
H	4.863	5.158	4.971
N	19.32	19.95	20.02

Optical Properties.

Habit: plates

Extinction: 25°-27°

Interference Figure: biaxial, large optic angle

Indices: $\alpha = 1.525$ $\gamma = 1.647$ (J.A.C.S. 45, 143)

1,3 Dimethyl 9-Phenyl Uric Acid. Dimethyl phenyl uric acid was prepared by boiling the pseudo uric acid with conc. hydrochloric acid and evaporating.

5 grams of 1,3 dimethyl 9-phenyl pseudo uric acid was dissolved in 1 liter of hydrochloric acid (sp. gr. 1.19) and boiled with a free flame until crystallization started. It was then evaporated on the steam bath to about $\frac{1}{3}$ of its volume, cooled and filtered. The yields varied from 1.3 grams to 1.6 grams, but the product was always mixed with a little unchanged dimethyl phenyl pseudo uric acid, as shown by its turning pink or red at 190°-200°. It is purified by boiling with a little water several times. The uric acid is difficultly soluble in water, while the pseudo acid dissolves quite readily. When pure, dimethyl phenyl uric acid remained perfectly white when heated to 300° and showed no signs of melting. The yield of the pure acid was about 1 gram. On evaporating the filtrate further a little more of the unchanged pseudo acid was regained - from 0.5 to 1 gram in all.

The 1,3 dimethyl 9-phenyl uric acid was recrystallized from much water and dried to constant weight at 110° for analysis.

I. 0.1551 gr. gave 0.2278 gr. CO_2 and 0.0670 gr. H_2O

0.1455 gr. gave 27cc. N_2 at 757.58 mm. and 26°

II. 0.1721 gr. gave 0.3623 gr. CO_2 and 0.0661 gr. H_2O

0.1341 gr. gave 24.3cc. N_2 at 757.24 mm. and 23°

	Calc. for $C_{13}H_{12}O_3N_4$	Found I	Found II
C	57.32	57.63	57.42
H	4.44	4.83	4.298
N	20.60	20.24	20.42

Optical Properties.

Habit: hexagonal or rectangular plates

Optical Orientation: sym. extinction, α parallel to elongation.

Interference Figure: biaxial, large optic angle, off the field.

Indices: α = 1.55+ γ = 1.684 (J.A.C.S 45, 143)

1,3 dimethyl 9-phenyl uric acid is difficultly soluble in water and alcohol. It is decomposed readily by warm alkali but is stable toward sodium bicarbonate. No sodium salt could be prepared. On titrating with 0.094 normal sodium hydroxide, the addition of 0.5cc. caused a deep pink color to develop. For the 0.11 gram of the acid used 4.35cc. of sodium hydroxide would be an equivalent if the acid were monobasic. On boiling the solution after the addition of $\frac{1}{2}$ cc. the acid did not dissolve; $1\frac{1}{2}$ equivalents (6.53 cc.) had to be added before solution took place. On cooling crystals separated which did not melt below 300°, apparently gave no residue on platinum foil and on igniting in a crucible no residue was left.

Weight of crucible	19.1861 gr.
Weight of crucible + substance . . .	19.2267 gr.
Weight of substance	0.0406 gr.
Weight of crucible after ignition .	19.1863 gr.
Increase in weight	0.0002 gr.

Therefore the free dimethyl phenyl uric acid separated out from the alkaline solution. It gave the murexid test with potassium chlorate, hydrochloric acid and ammonia.

As the yields of the dimethyl phenyl uric acid were very poor, many attempts were made to improve the method or to find another. Hydrochloric acid of all concentrations was tried but the concentration used above was found to be the best. The yields with the other concentrations were poorer and more of the pseudo remained unchanged.

Wt. dimethyl phenyl pseudo uric acid	Am't HCl	Conc.	Yield of dimethyl phenyl uric acid	Unchanged dimethyl phenyl pseudo uric acid
5 gr.	1 liter	35%	1 to 1.5 g.	0.5 gr.
5 gr.	1 liter	30%	0.5 to 1 g.	-----
5 gr.	1 liter	25%	0.7 g.	1 gr.
5 gr.	1 liter	20%	0.53 g.	1 gr.
5 gr.	1 liter	10%	0.24 g.	3.5 gr.

A saturated solution of hydrochloric acid was also tried in both an open vessel and in sealed tubes. The pseudo acid was decomposed to a substance melting at 125°-135° and phenyl urea. The solution was made by saturating cold conc. hydrochloric acid (sp.gr.1.19) with dry hydrogen chloride. The specific gravity of the resulting solution was 24° Baume, which corresponds to about a 39.1% solution. 1 gram lots of the methyl phenyl pseudo uric acid were added to 10cc. of the saturated solution, the tubes were sealed and the solutions heated to different temperatures and for different times. The tube was then opened and the solution evaporated. In the first experiment the solution did not clear; in the second it cleared only on warming.

Temp.	Time	Products	Unchanged 1,3 Dimethyl 9-phenyl pseudo uric acid
20°	3 days	0.46 g.- m.p.125-127°	0.13 g.
20°	5 days	0.23 g.- m.p.127-130°	——
70-80°	1½ hrs	0.03 g.-no m.p.	
100°	3 hrs	0.47 g.phenyl urea	
70-80° (open vessel)	15 min.	0.1 g. m.p. 125°	0.03 g.

Oxalic acid, both crystalline and anhydrous,[1] was also tried, but dimethyl phenyl uric acid could not be obtained. Decomposition resulted.

10 grams of crystalline oxalic acid was fused on an oil bath and 1 gram of the dimethyl phenyl pseudo uric acid was added and the mixture quickly heated to 160°-165°. The solution cleared about 130° and the oxalic acid sublimed rapidly. Alcohol was added to the hot melt. 0.26 gram of precipitate melting at 216°-218° resulted. From the filtrate on cooling crystals melting at 130°-132° were obtained.

10 grams of anhydrous oxalic acid was heated to 120° and 1 gram of dimethyl phenyl pseudo uric acid was added and the mixture heated rapidly to 165°. On the addition of alcohol, 0.4 gram of a crystalline precipitate melting at 128°-130° was obtained. The filtrate gave 0.4 gram more of the same product.

This decomposition product was not the same as the one, melting at 125°, obtained from the saturated hydrochloric acid treatment, for a mixed melting point lowered the melting point to 85°-100°.

c. Second Method.

Biltz[2] has found that the pseudo uric acids can be methylated with dimethyl sulphate much more readily

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[1] Fischer, Untersuchungen in der Puringruppe, p. 179.

[2] Biltz, Ann. 423, 186 (1921)

than the corresponding uric acids and a uniform product is obtained. The methyl groups always enter in positions (1) and (3).

The reaction has been found to go just as well when the 9-phenyl pseudo uric acid was methylated. The 1,3-dimethyl 9-phenyl uric acid was obtained. It agreed in melting point and optical and chemical properties with that obtained by the first method. By the second method another substance was also obtained, which, though it gave the same melting point and did not lower the melting point when mixed with first product, had quite different optical properties. It was finally proved to be only the monohydrate of 1,3 dimethyl 9-phenyl pseudo uric acid.

Methylation of 9-Phenyl Pseudo Uric Acid with Dimethyl Sulphate. 5 grams of powdered 9-phenyl pseudo uric acid (1 mol) was dissolved in 40cc. of 2N sodium hydroxide (3.5 mols) and cooled to 0° by an ice and salt mixture. 11 grams of dimethyl sulphate (4 mols) was added and the flask was stoppered and vigorously shaken. The temperature was kept around 0°. After $\frac{1}{2}$ hour a heavy crystalline precipitate separated. The solution was shaken $\frac{1}{2}$ hour longer and then filtered. The residue was quite soluble in water; it gave a residue on platinum foil and turned pink about 150° but did not melt. On boiling with water for a few minutes a heavy precipitate came out which weighed 1.15 grams and melted at 185°-190° with a deep red melt. Mixed with the dimethyl phenyl pseudo uric acid from the first method it melted at 190°-192°. The filtrate on acidification gave an immediate precipitate of dimethyl phenyl pseudo uric acid which weighed 3.9 grams and melted at 192°. Total yield, 5 grams. It can be recrystallized from hot water but more easily from alcohol.

Monohydrate of 1,3 Dimethyl 9-Phenyl Pseudo Uric Acid. If the precipitate obtained in the second method from the alkaline solution is dissolved in water and allowed to stand at room temperature instead of warming, good crystals separated out slowly. These melted at 190° and when mixed with dimethyl phenyl pseudo uric acid at 190° also, but the two substances did not have the same optical properties.

Optical Properties.

Habit: needles

Optical Orientation: parallel extinction, α parallel to elongation

Indices: $\alpha = 1.583$ $\gamma \begin{matrix} > 1.768 \\ < 1.8 \end{matrix}$ J.A.C.S 45, 143

Birefringence: strong

If a little of the precipitate was dissolved in cold water and acidified a product was obtained which on recrystallization gave a mixture of crystals melting at 189°-190°. The optical properties of one kind agreed with those of the dimethyl phenyl pseudo uric acid and the optical properties of the other were like the above.

The dimethyl phenyl pseudo uric acid from the first method also gave a mixture of the two kinds of crystals on recrystallizing slowly from water.

Some of the pure material with the higher indices was boiled a short time with concentrated hydrochloric acid and evaporated. A mixture of crystals of the lower indices and of dimethyl phenyl uric acid was obtained.

When the material with the higher indices was recrystallized from alcohol, only the crystals with the lower indices were obtained.

All of these properties point to the fact that the second substance of higher indices was a hydrate of dimethyl phenyl pseudo uric acid. It was finally proved to be the monohydrate, by heating at 95°-100° to constant weight.

0.2352 grams lost 0.0137 grams H_2O

Calc. for $C_{13}H_{12}O_3N_4 + 1\ H_2O$	Found
5.842	5.824

M.pt. before heating . . 190°-191.5°

M.pt. after heating . . 187°

Mixed m.pt. . . . . 188°

The optical properties of the substance both after heating and on recrystallizing from alcohol were the same as those of dimethyl phenyl pseudo uric acid. On recrystallizing from water the monohydrate was regained.

2. Oxidation with Hydrogen Peroxide.

The oxidation experiments were carried out in various concentrations of alkali- 0.3 N, 0.5 N and N excess alkali- and at two different temperatures- 25° and 40°-50°. In all cases ab methyl phenyl urea was obtained. In two of the experiments, one when the excess alkali was 0.5 N and one when it was 1N, a little of a substance melting at 177°-180° was obtained from the acid solution along with the methyl phenyl urea. Methyl phenyl urea was also obtained when the excess peroxide was decomposed by manganese dioxide before acidifying.

(1)2 grams of dimethyl phenyl uric acid was mixed with 24cc. of water in an Erlenmeyer flask. 9 grams of solid potassium hydroxide (1N excess) was added and then 140cc. of 3% hydrogen peroxide. The solution was allowed to stand at room temperature. After 5 or 10 minutes bubbles of gas came off and a slight odor developed. Samples were withdrawn every day and tested for unchanged acid. After 8 days no precipitate formed on acidifying. So the whole solution was made acid with hydrochloric acid. After several hours, 0.13 gram of the original material was regained. The solution was evaporated at 40°. Not very much had evaporated after two days, so air was drawn through the solution. 0.2 gram of an oxidation product, melting at 143°, was obtained. Mixed melting point and optical properties showed it to be methyl phenyl urea. The mother liquor on evaporation to dryness and dissolving the inorganic salts in water gave a little of a substance melting at 165°. On recrystallizing it melted at 170°-175° with decomposition.

(2) 2 grams of dimethyl phenyl uric acid was dissolved in 24cc. of water and 9 grams of potassium hydroxide, and 140cc. of hydrogen peroxide was added. After standing 10 days at room temperature colorless crystals began to separate from the alkaline solution.

On standing overnight 0.085 gram had formed. It melted at 147°-150° and mixed with the acid oxidation product (143°) at 148°-150°. The two products were the same. 10cc. more peroxide was added to the oxidation solution and it was evaporated further by a current of air. 0.145 gram of the methyl phenyl urea was precipitated. The filtrate was acidified - much gas was evolved. On evaporating, 0.34 gram of crude acid oxidation product melting at 137°-140° was obtained. It was quite brown, while the methyl phenyl urea from the alkaline solution was nearly white. Total yield of oxidation products, 0.57 gram. On recrystallizing it melted at 148°-150° and mixed with methyl phenyl urea (149°-150°) at 148°-148.5°. Percentage yield, 54%. The optical properties were the same.

Optical Properties.

Habit: octagonal plates

Optical Orientation: sym. extinction, α parallel to elongation

Interference figure: biaxial, large optic angle

Indices: $\alpha = 1.583$ $\gamma = 1.632$

From the mother liquor 0.48 gram of calcium oxalate was obtained. Yield, 51%.

3. Action of Alkali.

2 grams of dimethyl phenyl uric acid was powdered and added to 100cc. of 4N sodium hydroxide. The solution was heated gradually to boiling and boiled a few minutes. It was then filtered through glass wool if necessary, cooled slightly and acidified with dilute hydrochloric acid. After standing several hours (sometimes longer) a crystalline substance began to separate. The solution was left overnight and then filtered. From 1.3 to 1.4 grams was obtained— 80% yield of $C_{11}H_{11}N_3O_3$. It was recrystallized from water; bunches of needles melting at 249°-250° with a clear yellow melt ~~were~~ obtained. It was recrystallized again and dried over sulphuric acid in the vacuum desiccator for analysis.

I. 0.1541 gr. gave 0.3174 gr. CO_2 and 0.0677 gr. H_2O

0.1411 gr. gave 22.9 cc. N_2 at 23.5° and 759.12 mm.

II. 0.1511 gr. gave 0.3100 gr. CO_2 and 0.0653 gr. H_2O

0.0965 gr. gave 15.8 cc. N_2 at 23° and 759.12 mm.

Another preparation was analysed for carbon and hydrogen.

III. 0.1548 gr. gave 0.3194 gr. CO_2 and 0.0658 gr. H_2O

IV. 0.1612 gr. gave 0.3312 gr. CO_2 and 0.0709 gr. H_2O

	Calc. for $C_{11}H_{11}N_3O_3$	Found			
		I	II	III	IV
C	56.62	56.22	55.95	56.28	56.04
H	4.756	4.919	4.835	4.756	4.921
N	18.03	18.14	18.34		

Optical Properties.

Habit: Rectangular plates

Optical Orientation: parallel extinction, γ parallel to elongation

Interference figure: biaxial, large optic angle

Indices: $\alpha = 1.571$ $\gamma = 1.620$

Birefringence: strong

The substance was monobasic.

0.1 gr. required 4.65 cc. of 0.094 N sodium hydroxide

4.65 cc. of NaOH 0.0177 gr. NaOH

0.1 gr., if monobasic, would require 0.0171 gr. NaOH

It gave no residue on igniting in a platinum crucible. The other products of decomposition, methylamine and carbon dioxide, were also determined.

200 grams of powdered dimethyl phenyl uric acid was added to 100cc. of 4N sodium hydroxide (free from carbonate) in an Erlenmeyer flask fitted with an air reflux. A small U-tube containing glass beads and 2cc. of dilute hydrochloric acid was attached to the latter. This solution was heated slowly to boiling and boiled 1 minute. Air was then passed through for ½ hour. Bubbles of white fumes passed through the hydrochloric acid solution. 10% chlorplatinic acid was added to the contents of the U-tube. No precipitate formed. It was

evaporated in the desiccator. Orange crystals separated, which were washed with absolute alcohol. The substance~~s~~ blackened at 225°-230° and the black ~~was~~ residue melted by 285°. A mixed melting point with methylamine chlorplatinate gave a blackening at 221° and melting at 240°. One product of decomposition was therefore methylamine. Under the microscope a mixture of the ammonia and methyl amine chlorplatinates was observed. The trace of ammonia would account for the slightly high melting point as ammonium chlorplatinate does not melt.

Optical Properties. Habit: hexagonal plates

Optical Orientation: isotropic

Indices: (1) = 1.74

(2) > 1.8

Optical Properties of $(CH_3NH_3)_2PtCl_6$:

Habit: thin hexagonal plates

Optical Oriantation: isotropic

Index: 1.74

Optical Properties of $(NH_4)_2PtCl_6$:

Habit: thick hexagonal plates

Optical Orientation: isotropic

Index: > 1.8 J.A.C.S. 45, 105

The alkaline solution was poured into a distilling flask which was fitted with a dropping funnel having a capillary tube as the end of the stem, and a tube for passing air through the solution. Both the dropping funnel stem and the tube reached to the bottom of the flask. To the side arm a sulphuric acid wash bottle, a calcium chloride tube, and a weighed soda lime and a calcium chloride-potash tube were attached. 70cc. of dilute hydrochloric acid was dropped in at such a rate that the bubbles passed slowly through the sulphuric acid wash bottle. When about neutral much carbon dioxide was evolved, and the soda lime tube became quite hot. The solution was then heated to boiling, boiled hard for a minute, and then kept just below boiling. Air, dried by soda lime, was passed through until the soda lime tube had cooled, and then after removing the flame for 15 minutes more.

2.00 gr. gave 0.470 gr. CO_2; calc. for 1 mol., 0.32 gram. 0.72 gr. of $C_{11}H_{11}N_3O_3$ separated from the acid solution on standing. Yield, 42%. It melted at 248°.

When 1 gram of the decomposition product, $C_{11}H_{11}N_3O_3$, was carefully warmed with 4cc. of sodium hydroxide (4N) to just below boiling, a strong ammoniacal odor developed. On cooling, 0.01 gram of crystals had separated, which melted at 142°. Mixed with phenyl urea they melted at 146°. Yield, 13%.

Optical Properties.

Habit: plates

Optical Orientation: parallel extinction, γ parallel to elongation

Indices: α = 1.602 γ = 1.627

Birefringence; very weak

Optical Properties of Phenyl Urea (Kahlbaum) J.A.C.S - 45, 144

Habit: plates

Optical Orientation: parallel extinction, γ parallel to elongation

Interference Figure: biaxial, large optic angle

Indices: α = 1.602 γ = 1.627

Birefringence: weak

To further identify as phenyl urea, a derivative was made. 0.05 gram was boiled with aniline under an air reflux. The solution was diluted with 15cc. of dilute hydrochloric acid; a precipitate of fine needles separated. It was recrystallized from 60% alcohol. It melted at 236°-238°. Mixed with diphenyl urea (238°) it melted at 237°-238°. The optical properties were identical.

On acidifying the alkaline filtrate from which the phenyl urea had separated with acetic acid and adding calcium chloride, 0.06 gram of calcium oxalate was obtained. Yield, 13%.

0.1 gram of $C_{11}H_{11}N_3O_3$ was warmed until nearly boiling with 4N potassium hydroxide and the gas given off was collected in a little dilute hydrochloric acid in a small U-tube. Air was passed through for 15 minutes after the flame was removed. The contents of the U-tube were treated with chlorplatinic acid. On evaporation orange crystals separated which melted at 228°-230°; mixed with methylamine chlorplatinate at 230°. The alkaline solution gave 0.01 gram of phenyl urea, melting at 144°. Yield, 17%.

$C_{11}H_{11}N_3O_3$ was found to be stable toward alkali in the cold if allowed to stand a short time. On acidifying almost all of the substance was regained. But if it was allowed to stand several days with warmed alkali it was decomposed to phenyl urea. 0.1 gram was dissolved in 8.7cc. of water and 0.4 gram of potassium hydroxide. The solution was evaporated in a vacuum desiccator for several days. 0.02 gram of phenyl urea ~~was~~ separated - 35% - and 0.02 gram of calcium oxalate was obtained - 40% yield.

When 0.1 gram was dissolved in 8.2 cc. water and 0.4 gram potassium hydroxide at room temperature and then evaporated to dryness at 30°-40°, the residue gave, after dissolving the inorganic salt, 0.03 gram of phenyl urea, 52%, and 0.035 gram of calcium oxalate, 63%.

With barium hydroxide $C_{11}H_{11}N_3O_3$ gave only once a little of a substance melting at 191°-192°. Though many attempts were made it could not be obtained again.

0.5 gram was heated with 1.5 gram of barium ~~chloride~~ hydroxide and 10cc. of water on the water bath at 80° for 15 minutes. All did not dissolve. It was evaporated in the vacuum desiccator until nearly dry, then taken up with water. Dilute sulphuric acid was added to precipitate the barium. The filtrate was evaporated on the steam bath to a small volume and then in the desiccator. Crystals separated which weighed 0.02 gram and melted on recrystallization at 191°-192°.

<u>Optical Properties</u>. Habit: long needles
Extinction: parallel
Interference figure: biaxial, 1 brush
Indices: $\alpha = 1.560$

Mixed with phenyl hydantoin (m.p. 190°-191°) it melted at 170°, so it was not phenyl hydantoin.

1 gram was warmed for 15 minutes with 3 grams of barium hydroxide and 30cc. of water at 80°. The solution was treated as before. 0.07 gram of crystals was obtained which did not melt. The filtrate gave 0.01 gram of $C_{11}H_{11}N_3O_3$ back.

<u>Oxidation with Hydrogen Peroxide.</u> $C_{11}H_{11}N_3O_3$ was oxidized with peroxide in alkaline solution. An oxidation product melting at 192° was isolated when the cold oxidation solution was only allowed to stand 5-10 minutes. On longer standing only phenyl urea and oxalic acid could be obtained.

2 grams $C_{11}H_{11}N_3O_3$ was added to 24cc. of water and cooled thoroughly by ice water. 8 grams of solid potassium hydroxide and 140cc. of 3% hydrogen peroxide were added. After 24 hours the solution was acidified with dilute hydrochloric acid. No precipitate formed. On evaporating at 30°, 0.8 gram of phenyl urea was obtained. Yield, 40%. The filtrate gave 0.3 gram of calcium oxalate. Yield, 31%.

0.5 gram was treated with 6cc. of water, cooled, and 2 grams of potassium hydroxide and 35cc. of hydrogen peroxide were added. After 3 hours it was acidified and evaporated. A 69% yield of phenyl urea was obtained.

0.5 gram was heated with 6cc. of water, cooled thoroughly and 1.48 gram of potassium hydroxide and 35cc. of hydrogen peroxide added. After 10 minutes, as a sample gave no precipitate on acidifying, the solution was made acid. After standing in ice water for several hours it was evaporated in a desiccator. 0.41 gram of oxidation product was obtained. The product was not homogeneous. The crystals were separated mechanically. One melted at 195°, the other at 163°. The higher melting one was much more soluble in water. Both were recrystallized from water. The first then melted at 197°-198°, and the second at 185°-187°.

Optical Properties of 197°-198°.

Habit: large rectangular plates

Optical Orientation: parallel extinction, α parallel to elongation

Interference figure: biaxial, large optic angle

Indices: $\alpha = 1.544$ $\gamma = 1.583$

Birefringence: weak

Optical Properties of 185°-187°.

Habit: small thin plates

Optical Orientation: extinction, 35°-40°, α parallel to elongation

Indices: $\alpha = 1.556$ $\gamma = 1.696$

1 gram of $C_{11}H_{11}N_3O_3$ was added to 12cc. of water and cooled to 5°. 2.9 grams potassium hydroxide and 70cc. of hydrogen peroxide were added. After 5 minutes the solution was acidified and allowed to stand several hours in ice water. It was then evaporated in the vacuum desiccator over sulphuric acid. After 5 days 0.61 grams of a light brown product melting at 195° and 0.03 gram of one melting at 177°-178° were isolated. The latter on recrystallization melted at 193°. The optical properties of the 195° substance were the same as in the other oxidation. But the other substance gave different optical properties from the 187° substance obtained before.

Optical properties of 193°. Habit: very fine needles
Extinction: parallel
Indices: $\alpha = 1.602$
$\gamma \begin{matrix} > 1.667 \\ < 1.674 \end{matrix}$
Birefringence: weak

The 195° product was the only one ever formed in any amount. It was recrystallized twice using animal charcoal, and twice from hot water alone. When pure it melted at 192°.

I. 0.1151 gr. gave 0.2300 gr. CO_2 and 0.053 gr. H_2O

II. 0.1108 gr. gave 0.2195 gr. CO_2 and 0.049 gr. H_2O

III. 0.1296 gr. gave 20.7cc. N_2 at 754.67 mm. and 26°

	Calc. for $C_{10}H_{11}O_3N_3$	Found		
		I	II	III
C	54.28	54.49	54.04	---
H	5.012	5.181	4.950	---
N	18.99,	---	---	17.51

The nitrogen is much too low, but the carbon and hydrogen check very well. $C_{10}H_{11}O_3N_3$ is the empirical formula that agrees best.

When 0.5 gram of $C_{11}H_{11}N_3O_3$ was heated with 9.5cc. water and 1.4 gram potassium hydroxide and allowed to stand in ice water 10 minutes, 0.34 gram of unchanged $C_{11}H_{11}N_3O_3$ was regained.

The 191°-192° product from the action of barium hydroxide was not the same as the oxidation product, as it lowered the melting point to 170°.

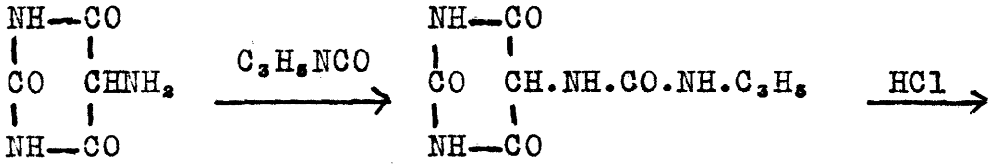
When the 192° oxidation product was allowed to stand at room temperature with a little normal potash good crystals of phenyl urea separated after about 10 minutes. It melted at 144° and mixed with phenyl urea (Kahlbaum) at 144°-146°. The oxidation product is evidently much more unstable toward alkali than $C_{11}H_{11}N_3O_3$. No oxalic acid could be found in the filtrate.

E. 9-Allyl Uric Acid

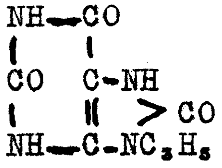
1. Preparation

Neither 9-allyl pseudo uric acid nor 9-allyl uric acid have been prepared before. Venable[1] tried to make the 9-allyl uric acid by the methylation method of Fischer, using allyl iodide in place of methyl iodide, but without success. The method used for making 9-phenyl pseudo uric acid was used. It consisted in treating uramil in alkaline solution with allyl isocyanate.

Scheme:



Uramil 9-Allyl Pseudo Uric acid



9-Allyl Uric Acid

The silver cyanate used for making allyl isocyanate was prepared by dissolving 25 grams potassium cyanate in water and adding a solution of 50 grams silver nitrate in water. A heavy white precipitate of silver cyanate was obtained, weighing 43.5 grams. It was necessary to dry it in the dark as it turned brown on exposure to the light. The allyl iodide used was purified by shak-

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[1] Venable, private communication.

ing with potassium hydroxide to take out the free iodine, washing with water, drying over calcium chloride and distilling; the fraction boiling at 101°-102° was used, It was practically colorless.

Allyl isocyanate[1] was made by adding 15 grams of allyl iodide (1 mol) to 20 grams of finely powdered silver cyanate (1½ mols) in a distilling flask. The heat of the reaction was sufficient to carry over the allyl isocyanate. It boiled at 83°-87° (C&H-87°). The distillate was pale yellow. Yield, 11 grams. The isocyanate has a very strong odor and attacks the eyes.

To make the 9allyl pseudo uric acid, 5 grams of uramil were added to 100cc. N potassium hydroxide cooled to 0°. Part dissolved on shaking, giving a purple red solution. 3 grams of allyl isocyanate were added in small portions, and shaken after each addition until the odor had gone. The operation lasted about an hour. No potassium salt separated, so it was much more soluble that the potassium salt of the 9-phenyl pseudo uric acid. The solution was filtered and acidified with hydrochloric acid. It turned yellow and a heavy precipitate separated, which was filtered off. Yield, 3 grams. The filtrate on longer standing gave

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[1] Cahours and Hofmann, Ann. 102, 297; Menne, B. 33, 660.

more crystals, weighing 0.5 gram. The product was recrystallized from much hot water; it was insoluble in alcohol and ether. Colorless needles resulted which turned pink at 170°, and melted at 227°-228° with decomposition. It was recrystallized again from hot water and dried at 100° for analysis.

I. 0.1618 gr. gave 0.2361 gr. CO_2 and 0.0726 gr. H_2O

0.1231 gr. gave 24.9cc. N_2 at 769.3 mm. and 23°

II. 0.1700 gr. gave 0.2469 gr. CO_2 and 0.0771 gr. H_2O

0.1218 gr. gave 25.2cc. N_2 at 754.34 mm. and 23°

Calc. for $C_8H_{10}O_4N_4 + 1H_2O$		Found	
		I	II
C	39.32	39.8	39.61
H	4.96	4.985	5.04
N	22.95	22.85	23.02

Optical Properties.

Habit: needles

Optical Orientation: parallel extinction, α parallel to elongation

Indices: α = 1.591 γ = 1.69 (J.A.C.S. 45, 144)

9-Allyl Uric Acid. 9-Allyl Pseudo uric acid was converted into 9-allyl uric acid by boiling 3 grams with 600cc. of 20% hydrochloric acid until in solution and then boiling 15 minutes longer. The solution was evaporated rapidly on the steam bath to $\frac{1}{3}$ its volume, cooled and filtered. 2 grams 9-allyl uric acid, in the form of glistening leaves, were obtained. It was recrystallized from hot water. It did not melt by 300°. No change in weight was observed on drying at 100°-140°, so it was recrystallized again and dried at 110° for analysis.

I. 0.1726 gr. gave 0.2919 gr. CO_2 and 0.0615 gr. H_2O
0.1075 gr. gave 25.2 cc. N_2 at 767.1 mm. and 19°

II. 0.1966 gr. gave 0.3349 gr. CO_2 and 0.0636 gr. H_2O
0.1053 gr. gave 24.5 cc. N_2 at 767.9 mm. and 25°

	Calc. for $C_8H_8N_4O_3$	Found I	Found II
C	46.16	46.13	46.34
H.	3.874	3.959	3.620
N	26.93	27.03	26.80

Optical Properties.

Habit: plates

Optical Orientation: symmetrical extinction, γ parallel to elongation

Indices: $\alpha = 1.75$ $\gamma \begin{matrix} > 1.775 \\ < 1.8 \end{matrix}$

Interference figure: uniaxial

2. Preliminary Oxidation with Hydrogen Peroxide.

(1) 0.5 gram of 9-allyl uric acid was added to 6cc. water, and 0.23 gram solid sodium hydroxide and

13cc. of hydrogen peroxide were added to this. (0.3 N excess alkali). The solution was kept at room temperature. A decided odor developed after several hours. On standing 2 days a sample with hydrochloric acid gave no precipitate. Manganese dioxide was added to ~~of~~ the oxidation solution until all the oxygen had been evolved. It was filtered, cooled, and made acid with glacial acetic acid. No precipitate separated, but the solution became cloudy upon scratching. After 24 hours small spherolitic particles had formed which melted at 235° with vigorous evolution of gas.

(2) 0.5 gram of 9-allyl uric acid was added to 6cc. of water and then 0.35 gram potassium hydroxide was added. The solution was cooled and treated with 13cc. of hydrogen peroxide. (0.3 N excess alkali). No precipitate formed on acidifying a sample after 2 days, and so the excess peroxide was decomposed by manganese dioxide. The solution was filtered, cooled, and made acid with glacial acetic acid. After 2 days white crystals separated, which turned light brown at 230° and melted at 236°.

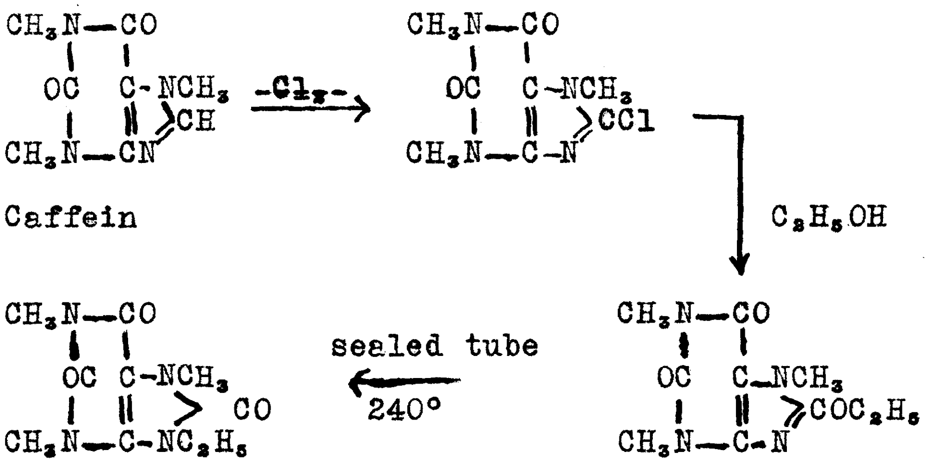
The same oxidation product was obtained when the reaction was carried out in either sodium or potassium hydroxide. There was not a sufficient amount to work with.

F. 9-Ethyl Trimethyl Uric Acid

1. <u>Preparation</u>.

9-ethyl trimethyl uric acid was prepared according to the method of Biltz[1] which consisted in heating 8-chlor caffein with ethyl alcohol, and then isomerizing the 8-ethoxy caffein so obtained by heating in a closed tube to ethyl trimethyl uric acid.

<u>Scheme</u>:



<u>8-chlor caffein</u>. 8-chlor caffein was made by following the directions of Fischer[2]. 20 grams of powdered caffein were heated to boiling with 160 grams chloroform in a large test tube (8" x 1½") provided with a delivery tube and an outlet tube. Dry chlorine gas

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[1] Biltz, Ann. <u>414</u>, 455 (1918)

[2] Fischer, <u>Untersuchungen in der Puringruppe</u>, p. 92.

was passed in; the solution cleared and then a heavy white precipitate formed which gradually turned red, then white again and finally disappeared. The reaction was then ended. The chloroform was evaporated in the air, leaving a light yellow residue. This was boiled with water and filtered. A yield of 15 grams of chlorcaffein was obtained.

8-Ethoxy caffein. 8-ethoxy caffein was prepared according to Biltz.[1] 6 grams of finely powdered chlor-caffein was added to a solution of 4 grams of potassium hydroxide in 40 grams of absolute alcohol and heated under reflux on the steam bath for 15 minutes. The potassium chloride was filtered off and the filtrate cooled with ice and salt. 4.1 grams of crude ethoxy caffein resulted. It was recrystallized from boiling absolute alcohol. 3 grams of ethoxy caffein melting at 139° was obtained.

9-Ethyl Trimethyl Uric Acid. 1cc. of absolute alcohol was next added to 3 grams of the powdered ethoxy caffein and the solution was heated in a sealed tube in an oil bath for 4 hours at 240°. The contents were boiled twice with 6cc. of alsolute alcohol. On cooling 2.3 grams of 9-ethyl trimethyl uric acid separated. M.pt. 195°.

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[1] loc. cit.

The ethyl trimethyl uric acid was purified[1] by treating 3 grams in water with barium hydroxide in slight excess (litmus) and evaporating on the water bath to dryness. The residue was twice evaporated with alcohol and then boiled 20 minutes with chloroform. On filtering, evaporating the filtrate and recrystallizing from hot water 1.5 grams of thin colorless plates were obtained. They melted at 200° (uncorr.), which agrees with that of Biltz for the pure acid— 203° (corr.)

2. Preliminary Oxidation with Hydrogen Peroxide.

0.5 gram of 9-ethyl trimethyl uric acid was added to a solution of 0.68 gram potassium hydroxide in 10cc. water. It was found necessary to warm before all would go into solution, and no precipitate formed on cooling. 13cc. of hydrogen peroxide was then added. After 43 hours a sample gave no precipitate when acidified with hydrochloric acid. Manganese dioxide was added to 12cc. of the solution to decompose the excess hydrogen peroxide. The solution was then filtered, cooled and acidified with glacial acetic acid. It became cloudy on scratching. After 2 days the solution had evaporated to dryness, leaving a mixture of large colorless crystals and long needles. The large crystals

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[1] Biltz, Ann. <u>414</u>, 58

gave a small residue on platinum foil. They softened at 227°, and turned brown and gradually decomposed up to 300°. The long needles melted before 100° and gave considerable residue on platinum foil. It was potassium acetate which dissolved in its water of crystallization on warming.

The other 12cc. of the oxidation solution was cooled and acidified with hydrochloric acid. It became cloudy on scratching. After 2 days a mixture of small crystals and potassium chloride formed. The small crystals were soluble in water.

No attempts were made to identify the oxidation products, as the amounts were too small.

G. Uroxanic Acid and Allantoxanic Acid.

1. Preparation.

Uroxanic acid was prepared by oxidizing uric acid with potassium permanganate in alkaline solution according to the directions of Biltz,[1] with the single change that stirring was accomplished by drawing air through the solution instead of using a mechanical stirrer. The results did not agree with his. He obtained uraxanic acid from both the precipitate on evaporation and from the mother liquor. But in the present work the first oxidation gave uroxanic acid and an unknown acid salt; the second a potassium salt melting at 120°-125° which was identified as being mostly the acid potassium uroxanate, and acid potassium allantoxanate; the third, uroxanic acid and acid potassium allantoxanate.

Oxidation of Uric Acid with Potassium Permanganate.

(1) 25 grams of uric acid mixed with 62cc. of warm water were dissolved in a solution of 50 grams of potassium hydroxide in 500cc. of water in a 2 liter flask, with constant shaking and warming. The solution was cooled to about 0° by an ice and salt mixture. The flask was fitted with a thermometer, a thistle tube and a tube to connect to the suction pump. A solution of

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[1] Biltz, Ber. 53, 1952 (1920)

16 grams of potassium permanganate in 350cc. water was then added gradually through the thistle tube, the solution being mixed by drawing air through and the temperature kept at about 3°. In about an hour all had been added. The solution was allowed to stand overnight. (In the preparation given by Biltz the solution stood only 4 hours.) The manganese dioxide was filtered off the next morning and washed twice with hot water. The filtrate was then evaporated on the steam bath to about 100cc. The little manganese dioxide that had separated was filtered off and the filtrate was cooled with ice water. A heavy precipitate - white and crystalline - of potassium uroxanate formed, weighing 15 grams. This was dissolved in 200cc. water at 90°, cooled to about 40° and acidified with conc. hydrochloric acid. A crystalline precipitate of uroxanic acid came down. 2 grams were obtained. It melted at 161°-162° with foaming, which agreed with that obtained by Biltz[1], though the yield of uroxanic acid from potassium uroxanate was less.

Optical Properties.

Habit: small tetrahedrons, not well formed

Indices: α = 1.5316- γ = 1.6005 (J.a.c.s 45, 145)

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[1] Biltz, Ber. 53, 1955 (1920)

The mother liquor on further evaporation gave more precipitate which on dissolving in a minimum amount of warm water, cooling, and acidifying, gave 2.5 grams of a substance which did not melt, so it was not uroxanic acid. Biltz got only uroxanic acid on evaporation of the mother liquor and acidifying.

Optical Properties.

Habit: long rectangular plates, γ parallel to elongation

Extinction: parallel

Indices: $\alpha = 1.559+$ $\gamma = 1.6289-$

Potassium Determination.

0.1021 gr. gave 0.0702 gr. K_2SO_4

Found K = 30.87

This oxidation product was not obtained again, though at least six similar oxidations were made.

(2) The procedure was exactly the same as in (1) except that the solution was allowed to stand only 4 hours after all the permanganate was added. The manganese dioxide was then filtered off and the filtrate evaporated on the water bath to 100cc. The solution was filtered again to get rid of the little manganese dioxide that had separated and cooled with ice water. 19 grams of a heavy crystalline precipitate were obtained.

It was dissolved in 70cc. of hot water, cooled to 35° and acidified with conc. hydrochloric acid. A precipitate separated slowly which did not look like uroxanic acid under the microscope. Weight, 3.25 grams. It melted at 120°-125° with foaming and gave a residue on platinum foil.

Optical Properties.

Habit: hexagonal and octagonal plates, α parallel to elongation

Extinction: symmetrical

Indices: α = 1.513- γ = 1.545-

Potassium Determination.

0.2042 gr. gave 0.0779 gr. K_2SO_4

0.1408 gr. gave 0.0541 gr. K_2SO_4

Calc. for $C_5H_7O_6N_4K$ K = 15.15

Found K = 17.13, 17.26

0.2 gram of the substance was mixed with 2cc. of 10% hydrochloric acid and stirred occasionally. The crystals under the microscope changed in form. The solution was cooled with ice and filtered. The crystals melted at 162°-163°; mixed with uroxanic acid, at 160°. Therefore, the substance melting at 125° was the acid potassium salt of uroxanic acid, mixed probably with a little of the neutral salt, which would account for the large percentage of potassium. The solution of the neutral salt, from which the acid salt was obtained, was probably too concentrated.

The mother liquor was evaporated. A strong odor of ammonia developed. It was cooled and filtered. A heavy precipitate was obtained which on recrystallization from warm water gave a good crystalline product.

Optical Properties.

Habit: long needles, γ parallel to elongation
Extinction: parallel
Indices: $\alpha = 1.4676$ $\gamma = 1.620+$ (J.A.C.S - ~~p~~ 45, 145)

The rest was dissolved in hot water, cooled to 35° and acidified. An immediate precipitate of long needles in radiating clusters formed, weighing 2.85 grams. It did not melt and gave a residue on platinum foil. It was recrystallized from water. It did not lose weight when heated at 110°. It was dried to constant weight over sulphuric acid in a vacuum desiccator for analysis.

I. 0.1695 gr. gave 33.1cc. N_2 at 769.4 mm. and 24.5°
0.1790 gr. gave 0.1493 gr. CO_2 and 0.0265 gr. H_2O (white ash in boat)
0.1501 gr. gave 0.0654 gr. K_2SO_4

II. 0.1500 gr. gave 29.6cc. N_2 at 768.23 mm. and 25°
0.1458 gr. gave 0.1211 gr. CO_2 and 0.0184 gr. H_2O (white ash in boat)
0.1672 gr. gave 0.0692 gr. gr. K_2SO_4

Calc. for $C_4H_2N_3O_4K$		Found	
		I	II
C	24.78	22.75	22.65
H	1.03	1.65	1.412
N	21.54	22.00	22.14
K	20.01	19.57	19.72

The carbon is low, as 1 mol. of CO_2 was held by the potassium as K_2CO_3. Calculated on this basis, which is not accurate, of course, C = 25.82, 25.72.

Optical Properties.

Habit: long slender needles

Optical Orientation: parallel extinction, α parallel to elongation

Indices: $\alpha = 1.513$ $\gamma = 1.69$

Birefringence: strong

These agree with the optical properties given by Moore and Thomas[1] for the acid potassium salt of allantoxanic acid.

(3) The procedure was the same as in (2) On evaporation to 100cc. and cooling 9 grams of precipitate was obtained. It was dissolved in warm water, cooled and acidified. A precipitate of star-shaped crystals formed, weighing 2.5 grams. They melted at 162°-163°, and mixed with uroxanic acid at 162°. The mother liquor was evaporated as before. A strong odor of ammonia was noticed. On cooling, a heavy precipi-

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[1] Moore and Thomas, J.A.C.S. <u>40</u>, 1129 (1918)

tate was obtained, which was dissolved in 50cc. warm water (50°) and acidified. 2.5 grams of acid ~~of~~ potassium allantoxanate resulted. It turned pink at 240° but did not melt. Its optical properties were the same as those of the second product from (2).

Identification of Allantoxanic Acid. To further identify as acid potassium allantoxanate the free acid and allantoxaidin were prepared.

Allantoxanic Acid.[1] 0.25 gram of the acid potassium salt was treated with 3cc. of 10% hydrochloric acid and stirred. After 10 minutes the long needles had changed to small rectangular plates under the microscope. The solution was cooled with ice for ½ hour and then filtered. 0.14 gram was obtained, melting at 253°-254° with decomposition.

Allantoxaidin.[2] 0.14 gram of allantoxanic acid was warmed on the water bath with 0.38cc. of water. A vigorous evolution of carbon dioxide began when the temperature reached 40°. The solution was warmed to 70°. A second crystalline product then began to form before all the first had dissolved. It was warmed until gas had stopped coming off, and then cooled with ice water. Yield, 0.05 gram. Theoretical, 0.084 gram.

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[1] Biltz, Ber. 53, 1978 (1920)

[2] Biltz, Ber. 53, 1981 (1920)

The product turned light brown at 270° and melted at 273°-274° (uncorr.) with decomposition, which agrees with the melting point given by Biltz.

2. Oxidation with Hydrogen Peroxide.

Oxidation of Uroxanic Acid.

(1) 0.5 gram of uroxanic acid was dissolved in 12cc. water and 0.45 gram of potassium hydroxide. 15cc. of 3% hydrogen peroxide was added and the solution allowed to stand at 20° for 27 hours. (Excess alkali 0.12 N) Then one half of the solution was evaporated until almost dry on the water bath, cooled with ice and filtered - 0.4 gram. This was dissolved in a little water and acidified. 0.15 gram of precipitate formed which melted at 162°, and mixed with uroxanic acid at 162°.

The other half was acidified with hydrochloric acid. A precipitate of the characteristic stars of uroxanic acid formed. It melted at 162°, and mixed with uroxanic acid - 162°. The mother liquor, which weighed 0.07 gram, on further evaporation gave only potassium chloride.

(2) 0.5 gram of uroxanic acid was dissolved in 15cc. of water and 0.4 gram of potassium hydroxide (.09 N excess). 15cc. of 3% hydrogen peroxide was

added and the solution kept at 50°-60° for 20 hours. The solution was then made acid, and 0.08 gram of uroxanic acid, melting at 163°, was regained. The mother liquor on evaporation gave potassium chloride.

(3) 0.5 gram of uroxanic acid was dissolved in 15cc. of water and 0.4 gram of potassium hydroxide. 15cc. of hydrogen peroxide was added and the temperature kept at 80°-90°. A sample was acidified every half hour - uroxanic acid was obtained each time. After two hours the solution was evaporated until almost dry. It gave 0.44 gram of a potassium salt melting at 235°. On dissolving in water and acidifying 0.08 gram of uroxanic acid, melting at 162°, was regained.

Oxidation of Acid Potassium Allantoxanate. The acid potassium aslt of allantoxanic acid, obtained from 1 (2) was oxidized with hydrogen peroxide according to Venable's directions for the sodium salt.[1] A good yield of cyanuric acid was obtained which was identified by its optical properties and by the Wöhler test.

Oxidation of the Unknown Potassium Salt from the First Preparation of Uroxanic Acid. 1 gram of the substance was dissolved in 0.5 gram of potassium hydroxide and 25cc. of water. 25cc. of 3% hydrogen peroxide was

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[1] Venable, J.A.C.S. 40, 1117 (1918)

added. The temperature was kept at 40° for two hours and then at room temperature over night. On evaporating one half to dryness, 0.58 gram of residue resulted, which on dissolving in water and acidifying gave 0.05 gram of cyanuric acid - identified by the Wöhler test and by its optical properties. The other half was acidified with hydrochloric acid. 0.035 gram of cyanuric acid was obtained.

3. Action of Alkali on Uroxanic Acid.

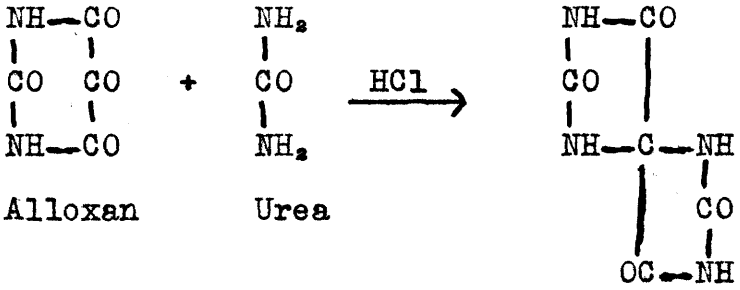
0.5 gram of uroxanic acid was dissolved in a solution of 1 gram of potassium hydroxide in 20cc. of water (the concentration was the same as that of the oxidation solution in (3)). The solution was warmed on the water bath. On evaporating and cooling, a potassium salt separated, which was dissolved in warm water, cooled and acidified. Characteristic star shaped crystals of uroxanic acid formed, which weighed 0.22 gram, and melted at 162°. The filtrate was evaporated. There was no odor of ammonia. A slight precipitate formed, which was filtered, dissolved in water and acidified. A very slight amount of precipitate formed, but it was not enought for a melting point determination. The experiment was repeated with the same results - most of the uroxanic acid was regained. There was no odor of ammonia on evaporating the mother liquor, and no trace of allantoxanic acid was found on acidifying.

H. Spirodihydantoin

1. Preparation.[1]

Spirodihydantoin was prepared from alloxan and urea by the action of hydrochloric acid gas.

Scheme:



Spirodihydantoin

It was found that along with the spirodihydantoin cyanuric acid and at least two other substances were formed, of which Biltz makes no mention; and some difficulties were met with in separating them.

Action of Hydrochloric Acid on Alloxan and Urea. 2 grams of alloxan was finely powdered and mixed well with 4 grams of urea in a mortar. The mixture was put in a large test tube (8" x 1½") provided with an inlet tube for the hydrogen chloride and an outlet tube for fumes. The hydrogen chloride, made from dropping conc. sulphuric acid on hydrochloric acid (s.gr. 1.19), was

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[1] Biltz, Ann. 413, 80 (1917)

passed in and the tube heated at 145°-150° in an oil bath. The mixture turned red, and then foamed up with a vigorous evolution of dense fumes. When the mass had settled and the fumes practically ceased, the reaction was ended. The yellow-brown mass after cooling was taken up with a little water (40-50cc), boiled and filtered, (Filtrate (1)) The residue was boiled again with more water (100cc.) and filtered (Filtrate (2)); and the small residue left was then boiled again with water (Filtrate (3)).

Filtrate (1) gave an immediate orange precipitate and, on cooling, bunches of light yellow crystals. These were separated mechanically. The yield of the orange precipitate varied from 0.3 to 0.4 gram; of the yellow clusters from 0.4 to 0.6 gram. Both were recrystallized from water. The orange precipitate gave a yellow powder which did not melt. With copper sulphate and ammonia it gave the amethyst precipitate characteristic of cyanuric acid. On recrystallization, clear crystals, mostly diamond shaped under the microscope, were obtained. They lost water rapidly on standing in the air and became opaque. The optical properties agreed with those of the dihydrate of cyanuric acid.

Optical Properties.

Habit: thin, transparent plates

Extinction: symmetrical

Interference figure: biaxial, small optic angle

Indices: $\gamma = 1.66$ $\alpha = 1.4747$ (?)

The yellow clusters gave, on recrystallization, light yellow needles, which sintered at 240° but did not melt by 290°. It also gave a purple precipitate with copper sulphate and ammonia, but its optical properties were not like those of cyanuric acid.

Optical Properties.

Habit: thick needles

Extinction: parallel, γ parallel to elongation

Indices: $\gamma = 1.69$ $\alpha < 1.459$

Birefringence: strong

Interference figure: biaxial

Filtrate (2) gave a crystalline precipitate of shining clusters. The yields varied from 0.3 to 0.6 gram. (Biltz gives 1.1 grams) It did not melt. The substance was identified as spirodihydantoin by its diammin copper salt, by converting it into allantoin by the action of barium hydroxide, and by comparing its optical properties with the spirodihydantoin obtained from uroxanic acid.

Identification of Spirodihydantoin.

The Diammin Copper Salt.[1] A few drops of conc. ammonium hydroxide were added to 0.1 gram of the substance in 2.5cc. of water. To this was added a solution of tetrammin copper sulphate, prepared by dissolving 0.5 gram of copper sulphate in 2.5cc. of water and adding ammonium hydroxide until the solution became a clear deep blue. On standing a few minutes the solution became quite thick with a mat of characteristic fine light blue needles. Ordinarily it was not necessary to use 0.1 gram. Just a little of the substance in a few drops of water and one of ammonium hydroxide gave the test on the addition of a few drops of the tetrammin copper sulphate solution.

Allantoin from Spirodihydantoin.[2] 1 gram of the substance was dissolved in 100cc. of boiling water. 3 grams of crystalline barium hydroxide was added and the solution heated 20 minutes on a boiling water bath. The barium carbonate formed was filtered off. Carbon dioxide was then passed in while the solution was kept

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[1] Biltz, Ber. 53, 1960 (1920)

[2] Biltz, Ann. 413, 39 (1917)

at water bath temperature. The solution was filtered again, and the trace of barium remaining was removed by careful addition of dilute sulphuric acid (0.1N). The solution was evaporated until crystallization began, and cooled and filtered. The crystals melted at 230° with decomposition. On recrystallization from hot water, they melted at 223° with decomposition and foaming. Mixed with allantoin (Kahlbaum - m.pt. 226°) it melted at 226°.

Spirodihydantoin from Uroxanic Acid.[1] 1.5 gram of uroxanic acid was dissolved at room temperature in about 2 hours in 30cc. of conc. hydrochloric acid. Carbon dioxide was evolved slowly. The solution was allowed to stand overnight and then evaporated on the water bath to about 5cc. On cooling a crystalline precipitate came down which gave the characteristic diammin copper salt.

Optical Properties.

Habit: hexagonal plates

Optical Orientation: 27°, α parallel to elongation

Interference figure: biaxial, small optic angle

Indices: $\gamma = 1.602$

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[1] Biltz, Ber. 53, 1957 (1920)

Optical Properties of Spirodihydantoin from alloxan and urea.

Habit: hexagonal plates

Optical Orientation: 25°-26°, α parallel to elongation

Interference figure: biaxial, small optic angle

Indices: $\alpha = 1.571$- $\gamma = 1.602$ (JACS. 45, 145)

Birefringence: weak

Filtrate (3) gave a small orange-brown precipitate, the yields varying from 0.01 to 0.06 gram. It did not melt and with the tetrammin copper sulphate it gave a bluish green solution and a flocculent yellowish precipitate on standing. Under the microscope it appeared to be a mixture.

Optical Properties.

1.
Habit: rectangular plates

Optical Orientation: parallel extinction, γ parallel to elongation

Indices: $\gamma = 1.7174$

2.
Habit: small hexagonal plates

Extinction: symmetrical

Indices: $\gamma > 1.8$

The three unknown substances were not investigated further. None proved to be unchanged urea for the optical properties of the latter did not agree with any of them.

Optical Properties of Urea. Habit: prisms

Extinction: parallel

Indices: α = 1.4743+ (J.A.C.S 45, 144)

γ = 1.6005-

2. Oxidation with Hydrogen Peroxide.

In 0.2 N excess alkali.

2 grams of spirodihydantoin was mixed with 128cc. of water. 3.2 grams of solid potassium hydroxide was added; the spirodihydantoin dissolved. Then 48cc. of 3% hydrogen peroxide was added and the oxidation solution left at room temperature. The solution was decidedly fluorescent. Bubbles of gas came off during the whole time. After standing one day a slight odor of ammonia developed. As the solution after six days gave no precipitate on acidifying a sample with dilute hydrochloric acid, the whole solution was made acid and evaporated at 35°. A good crystalline precipitate was obtained. Yield, 1.45 grams. It melted at 232° with foaming. On recrystallization it melted at 227°, and a mixed melting point with allantoin (226°) gave 226°. Theoretical yield, 1.7 grams. Percent yield, 85%.

Optical Properties of Allantoin.

Habit: hexagonal plates

Optical Orientation: symmetrical, extinction γ parallel to elongation

Indices: α = 1.579 γ = 1.66- (J.A.C.S 45, 145)

Optical Properties of Oxidation Product:

Habit: hexagonal plates

Optical Orientation: symmetrical, δ parallel to elongation

Indices: α = 1.579+ γ = 1.66

In 0.9 N excess alkali.

(1) 1 gram of spirodihydantoin was dissolved in a solution of 5 grams potassium hydroxide in 64cc. of water. 24cc. of 3% hydrogen peroxide was added and the solution allowed to stand at room temperature. The solution was fluorescent. After 5 days it was acidified with dilute hydrochloric acid. On standing 4 days at room temperature 0.34 gram of crystals had separated. M.pt. 234° with decomposition; mixed with allantoin, 227°-228°.

(2) 1 gram of spirodihydantoin was oxidized in the same way, with the exception that it was evaporated over sulphuric acid in a vacuum desiccator instead of acidifying. When the solution had ~~evaporated~~

~~nearly to~~ evaporated nearly to dryness a heavy white residue had formed, which was filtered - weight, 1.5 grams. The substance gave a residue on platinum foil and melted at 220° with foaming; mixed with potassium uroxanate (220°-221°) it melted at 220°-222°. Theoretical yield, 1.6 grams - 94%. The salt was dissolved in 4cc. of warm water and hydrochloric acid was added until the solution was just acid. A precipitate of large rhombic crystals formed. Part melted at 225°, leaving a black residue which melted at 270°; mixed with allantoin (227°) the melting point was lowered to 205°-206°; mixed with potassium uroxanate (221°) the melting point was 223°-224°. It was redissolved in water and acidified strongly. Star-shaped crystals of uroxanic acid separated, melting at 162° with foaming; mixed with uroxanic acid from the uric acid oxidation at 162°. Therefore the oxidation product is uroxanic acid.

Action of Alkali. 0.25 gram of spirodihydantoin was dissolved in 1.25 grams of potassium hydroxide in 30cc. of water. (0.9 N) After standing one day at room temperature the solution was evaporated in a vacuum desiccator. It had evaporated nearly to dryness after six days. 0.36 gram of potassium uroxanate was obtained. Theoretical, 0.4 grams. It melted at 228°-230° with foaming. The salt was dissolved in 1cc. of warm water, cooled, and made just acid with hydrochloric acid. Rhombic crystals separated which melted partly at 230° and the black residue at 275°. Biltz[1] gives as the melting point: that it turns gray at 220° and foams, under blackening, at about 260°. The salt was again dissolved in a little water and acidified strongly with hydrochloric acid. Characteristic crystals of uric acid separated which melted at 162° with foaming; mixed with uroxanic acid it melted at 162°.

In the conversion of spirodihydantoin to uroxanic acid the hydrogen peroxide is apparently an unnecessary factor.

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[1] Biltz, Ann. <u>413</u>, 41 (1917)

I. Oxidation of Uric Acid with Sodium Persulphate

Preliminary experiments were made on the oxidation of uric acid by sodium persulphate in alkaline solution to see what course the oxidation would take.

(1) 10 grams of uric acid was dissolved in 15 grams of sodium hydroxide and 350cc. of water (N excess alkali). 15 grams of sodium persulphate (1 atom of oxygen to 1 mol of uric acid if the salt were pure persulphate) was added and the temperature kept at 28°-30°. After 6 days much of the uric acid was regained on acidifying. No oxidation product could be found on evaporating the filtrate.

(2) 10 grams of uric acid was dissolved in 5 grams of sodium hydroxide and 350cc. of water. (0.02 N excess alkali) On the addition of 15 grams of sodium persulphate a heavy orange precipitate separated, which was found to be sodium urate. The solution was allowed to stand at room temperature. After 2 days the precipitate had not decreased. 100cc. of the solution was filtered and acidified. It was then evaporated by drawing air through. A precipitate formed after 2 days. It weighed 0.32

gram and melted at 226°. Mixed with allantoin it melted at 227°. The rest of the oxidation solution was evaporated on the steam bath. It gave a mixture of allantoin and inorganic salts. On recrystallization 0.25 gram of allantoin, metling at 227°, was obtained. The total yield of allantoin was 0.57 gram.

(3) 10 grams of uric acid was dissolved in 5 grams of sodium hydroxide and 750cc. of water. 15 grams of sodium persulphate was added, and a heavy precipitate formed as in (2). The solution was warmed at 45°-50°. After 24 hours 100cc. were filtered, acidified and evaporated by a current of air. 0.33 gram of allantoin formed. After 3 days the rest of the oxidation solution was filtered. 4 grams of sodium urate was recovered. The filtrate on evaporation gave 0.3 gram of allantoin. Total yield of the oxidation product was 0.63 gram. It melted at 226°-228°.

(4) 5 grams of uric acid was dissolved in 2.5 grams of sodium hydroxide and 175cc. of water (0.02 N excess alkali). 22 grams of sodium persulphate was added (the salt was found to be only 65% persulphate, so that less than an equivalent had been used in the other experiments). The temperature was kept at 80°-85° for 6 hours. No precipitate separated

and the solution was fluorescent. It was left at room temperature overnight. A little sodium urate separated - 0.64 gram. It was removed by filtering and the solution was acidified. On evaporating on the steam bath 0.88 gram of allantoin were obtained. It melted at 220°; mixed with allantoin (Kahlbaum) it melted at 227°. Percentage yield, 19%.

The best oxidation condition for allantoin seemed to be low excess alkali and high temperature (80°-90°). The low yields were due undoubtedly to insufficient amount of the oxidizing agent.

J. Miscellaneous Preparations.

1. Carbonyl-di-urea.

Carbonyl-di-urea was prepared according to the method of Shuttenhelm and Wiener[1]. 5 grams of uric acid were dissolved in 3.4 grams of potassium hydroxide in 400cc. of water. 130cc. of 3% hydrogen peroxide was added and the solution heated at 80°-90° on the steam bath for 5 minutes. There was a vigorous evolution of oxygen. The solution was allowed to stand overnight at room temperature. A light yellow crystalline precipitate of carbonyl-di-urea had separated. Weight, 0.62 gram; m.pt. 235°-236°.

2. Sodium Allantoxanate.

The acid sodium salt of allantoxanic acid was prepared according to Venable's directions.[2] 10 grams of uric acid was suspended in 300cc. of water. 24 grams of sodium hydroxide was slowly added while shaking constantly. It was necessary to warm slightly before all the uric acid would go into solution. 150cc. of 3% hydrogen peroxide was added and the solution was allowed to stand 48 hours. Powdered manganese dioxide was then added to decompose the excess peroxide. The solution was filtered, cooled and acidified with acetic

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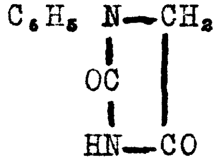
[1] Shuttenhelm and Wiener, Z.Physiol.Chem. 62, 103 (1909)

[2] Venable, J.A.C.S. 40, 1117 (1918)

acid. On standing a white precipitate of acid sodium allantoxanate was obtained - 5.7 grams.

3. Phenyl Hydantoin.[1]

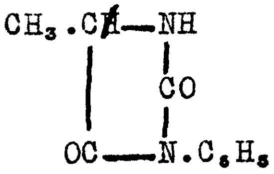


Phenyl hydantoin - was prepared by mixing equivalent weights of phenyl glycine, ammonium sulphate and potassium cyanate with water and warming at 40° for several days.

5 grams of phenyl glycine, 4.4 grams of ammonium sulphate and 2.7 grams of potassium cyanate were added to 100cc. of water and warmed at 40°. All dissolved. After 4 days alcohol was added and the potassium sulphate precipitated was filtered off. The filtrate on evaporation gave a thick brown mass which on boiling with water and cooling with ice gave crystals of phenyl hydantoin, melting at 190°-191°.

4. Phenyl Ureïdo Propionic Acid and Methyl Phenyl Hydantoin.

Phenyl Ureido propionic acid - $C_6H_5NHCONHCH(CH_3)-COOH$ was prepared according to the directions of Paal.[2] It was converted into methyl phenyl hydantoin[3] by boiling with hydrochloric acid.



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[1] Beilstein, Handbuch, Vol. II, p. 383.

[2] Paal, Ber. 27, 976.

5 grams of alanine was added in small portions to a solution of 2.3 grams of sodium hydroxide in 50cc. of water. The solution was cooled and 6.7 grams of phenyl isocyanate added. It was shaken until there was no odor of the isocyanate. On acidifying with dilute sulphuric acid a heavy white precipitate formed. It was recrystallized. Shining leaves were obtained, which melted at 172°-173°.

2 grams of phenyl ureïdo propionic acid was boiled with 160cc. of 25% hydrochloric acid over a free flame to $\frac{1}{4}$ its volume. On slow cooling fine crystalline needles separated which melted at 170.5°-171.5°.

5. Oxalyl Chloride and Phenyl Parabanic Acid.

Oxalyl chloride was prepared according to the method of Staudinger[1] from anhydrous oxalic acid and phosphorous pentachloride.

9 grams of anhydrous oxalic acid was powdered in a cooled mortar and mixed with 40 grams of phosphorous pentachloride. The mixture was put into a distilling flask, closed by a calcium chloride tube, and allowed to stand in ice water until a clear solution resulted. It was then distilled and the portion boiling at 60-100° was collected. It weighed 6 grams. When larger

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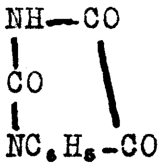
[1] Staudinger, Ber. 41, 3563 (1908)

amounts were used the results were not as good, probably because of moisture absorbed in mixing. 40 grams of oxalic acid gave 11 grams distilling below 100°.

Attempts were made to prepare phenyl parabanic acid  by the method of Biltz[1], which consisted in boiling an ether solution of phenyl urea and oxalyl chloride for 3 hours, but with no success. A red sticky mass was obtained from which only a little unchanged phenyl urea could be obtained. On recrystallizing. The fact that the oxalyl chloride was not pure might account for the failure of the preparation.

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[1] Biltz, Ber. 46, 1399 (1914)