among which hydrogen sulfide was identified. A clear solution resulted. Within two or three minutes, however, this commenced to become quite turbid, and within 15 minutes a considerable quantity of orange-colored material had deposited. Heating was discontinued at the end of 3 hours and the reaction mixture allowed to stand at room temperature for 12 hours. The orange-colored product, weighing 1.8 g., was then filtered off and the anhydride solution concentrated to a small volume and poured into cold water. After standing a short time this aqueous solution deposited 0.5 g. of material which afterwards proved to be identical with the substance which separated from the original anhydride solution. This compound was quite soluble in sodium hydroxide solution, from which it was precipitated unchanged by dilute hydrochloric acid. It was very difficultly soluble in cold water, but somewhat soluble in hot, and separated on cooling in characteristic yellow balls. It was more soluble in ethyl and amyl alcohol than in water. A cold, aqueous solution of the acid was unaffected by addition of ferric chloride solution, while the solution on warming turned brown. When heated in a capillary tube, the substance did not melt, but underwent partial decomposition when heated above 200°. Nitrogen and sulfur determinations agreed with the calculated values for the isodithiocyanic acid. For the purposes of identification this acid was synthesized in accordance with given directions.[1] The two compounds proved to be identical in every respect. We did not obtain any evidence of the formation of acetylpersulfocyanic acid or acetylthiourea.

Calc. for $C_2H_2N_2S_2$: N, 23.77; S, 54.24. Found: N, 23.88, 23.93; S, 53.86.

The above experiment was also carried out under somewhat altered conditions. The heating period was shortened to one hour and the reaction mixture then poured into cold water. A granular precipitate formed immediately. It weighed 2.4 g. and proved to be isodithiocyanic acid. The yield, therefore, was practically the same as in the first experiment.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON HYDANTOINS. XXXV. A NEW METHOD OF SYNTHESIZING GLYCOCYAMIDINE COMPOUNDS, AND THE CONVERSION OF GLYCOCYAMIDINE INTO ISOMERS OF CREATININE.

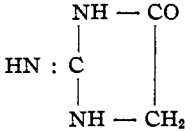
BY TREAT B. JOHNSON AND BEN H. NICOLET.

Received July 31, 1915.

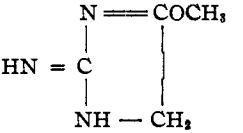
If we disregard amidine and keto-enol tautomerism, there are only five structurally isomeric monomethyl derivatives of glycocyamidine (I) theoretically possible. Three of these are nitrogen substituted com-

[1] *Ann.*, 179, 204 (1875).

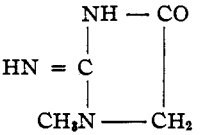
pounds represented by Formulas III (creatinine), V and VI. One is a carbon derivative or the long known alacreatinine[1] (IV), and the last an oxygen derivative corresponding to Formula II. All five isomers would be basic compounds. Previous to 1904 only two of these isomers had been described, namely, creatinine (III) and alacreatinine (IV).



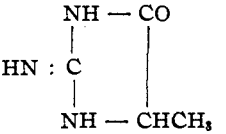
(I).



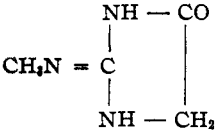
(II).



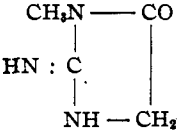
(III).



(IV).

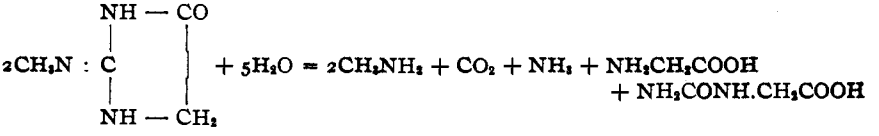


(V).



(VI).

During this year Korndörfer,[2] who worked under the direction of E. Schmidt, published a paper entitled "Untersuchungen über das Glycocyamin und das Glycocyamidin," in which he described the behavior of glycocyamidine towards methyl iodide. He observed that the cycle underwent alkylation smoothly, forming the hydriodic acid salt of a new base to which he assigned Formula V and named it α-methylglycocyamidine. Creatinine (III) was represented by him as the β-derivative, and alacreatinine (IV) as the γ-derivative of glycocyamidine. The evidence on which Korndörfer established the constitution of this glycocyamidine derivative was the fact that it underwent hydrolysis when heated with barium hydroxide solution, with formation of ammonia, methylamine, glycocoll and hydantoic acid. The reaction may be expressed as follows:



Six years after the appearance of this work a second paper, under the same title, was published by M. Schenck,[3] in which this investigator

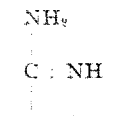
[1] *Ann.*, **167**, 83; *Ber.*, **6**, 1371 (1873).

[2] *Archiv. Pharm.*, **242**, 620 (1904).

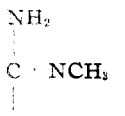
[3] *Ibid.*, **248**, 376 (1910).

refers to the previous work of Korndörfer[1] on α-methylglycocyamidine, and calls attention to the fact that Formula VI could be assigned to his alkylation products as well as V, since both compounds would give the same decomposition products on hydrolysis with alkali. Schenck, therefore, sought to determine the constitution of Korndörfer's methylglycocyamidine and distinguish between the two modifications (V) and (VI) by oxidation with potassium permanganate. He wrote as follows:

"Eine Entscheidung zwischen den beiden obigen Formeln (V and VI) konnte sich durch die Oxydation mit Kaliumpermanganat treffen lassen, indem ein Methylglykocyamidin der letzteren Art dasselbe Methylguanidin liefern müsste, wie das Kreatinin, während ein Methylglykocyamidin der Korndörfer'schen Formel hierbei das bisher unbekannte Methylguanidine (VIII) ergeben solte."



(VII).



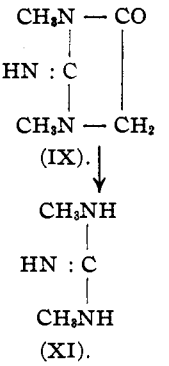
(VIII).

Schenck oxidized his methylglycocyamidine according to the method used by Neubauer[2] in his work on creatinine and obtained a *methylguanidine*, which proved to be identical, as might be expected, with that obtained by oxidation of creatinine,[3] and also that formed by addition of methylamine to cyanamide. Schenck considered this result sufficient proof of the structure of the methylglycocyamidine and concluded as folllows:

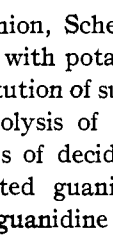
"Demnach muss man die von Korndörfer angenommene α-Formel V des Methylglykocyamidins aufgeben und die γ-Formel VI annehmen."

No further papers were contributed on this subject until that of E. Schmidt,[4] entitled "Ueber das Kreatinin," appeared during the same year. He reviewed the work of Korndörfer and Schenck, emphasizing the significance of Schenck's speculations, and stated that an investigation dealing with the synthesis of the unknown α-methylglycocyamidine was in progress. So far as we are aware, no report has been made of this work. His students, Kunze[5] and Henzerling,[6] investigated the behavior of creatinine on aklylation and obtained, by the action of methyl iodide and ethyl iodide, methyl- and ethylcreatinines to which they assigned Formulas IX and X, respectively. They state that both compounds underwent oxidation with potassium permanganate, forming symmetrical dimethylguanidinine (XI) and *sym*-methylethylguanidine (XII), respectively.

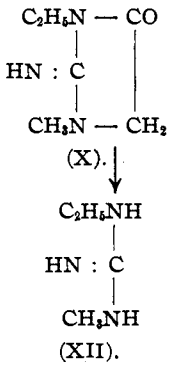
[1] *Loc. cit.*
[2] *Ann.*, **119**, 46 (1861).
[3] Neubauer, *loc. cit.*
[4] *Archiv. Pharm.*, **248**, 568 (1910).
[5] *Ibid.*, **248**, 578 (1910).
[6] *Ibid.*, **248**, 604 (1910).



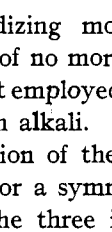
(IX).



(XI).



(X).



(XII).

In our opinion, Schenck's procedure of oxidizing monoalkylated glycocyamidines with potassium permanganate is of no more value for proving the constitution of such compounds than that employed by Korndörfer,[1] namely, hydrolysis of the glycocyamidine with alkali. We have available no means of deciding positively the location of the double bond in a monoalkylated guanidine (VII) or (VIII) or a symmetrically substituted dialkylguanidine (XI) or (XII). Of the three isomeric methylglycocyamidines (III), (V) and (VI), all would undergo oxidation with potassium permanganate with formation of methylguanidine (VII) or (VIII), while creatinine (III) can easily be distinguished from the isomers (V) and (VI) by hydrolysis with alkali. It is converted into sarcosine while the isomers (V) and (VI) would break down with formation of glycocoll and methylamine.

Schenck[2] later realized the weakness of his speculations and endeavored to synthesize tautomeric modifications of mono- and dialkylated guanidines. All his attempts, however, to prepare such isomers, as might be expected, were unsuccessful.

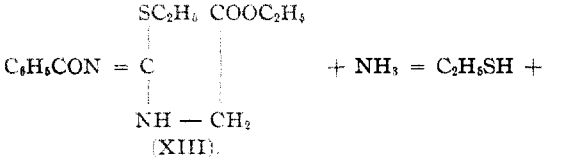
We have now developed a new method whereby glycocyamidine and its alkylated derivatives can be prepared very easily. We find that such combinations can be synthesized by the action of amines on the ethyl ester of benzoylpseudoethylthio-hydantoic acid (XIII). The latter compound has been described in a previous paper[3] from this laboratory, and is obtained by the interaction of ethyl aminoacetate with diethyl benzoylimidodithiocarbonate. When the ester is allowed to interact with an amine, mercaptan is evolved and a substituted guanidine (XIV) is formed. This then condenses to form a glycocyamidine with loss of a molecule of alcohol. Two isomeric glycocyamidines (XV) and (XVI) can theoretically be formed in such a change, depending on which nitrogen

[1] *Loc. cit.*

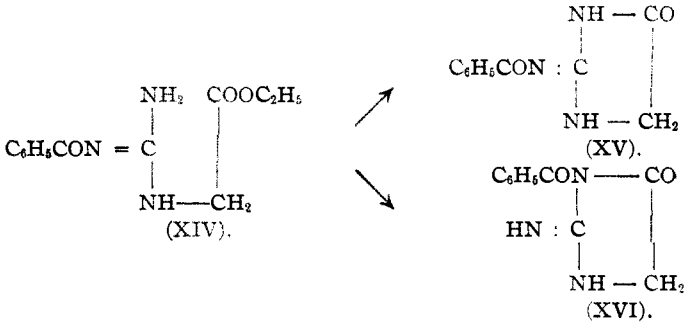
[2] *Z. physiol. Chem.*, **77**, 328 (1912); *Arch. Pharm.*, **249**, 463 (1911); *Chem. Centr.*, **2**, 1216 (1911).

[3] Wheeler, Nicolet and Johnson, *Am. Chem. J.*, **46**, 456 (1911).

of the guanidine is incorporated in the ring. Ammonia reacted according to the following expression to form 2-benzoylglycocyamidine (XV).

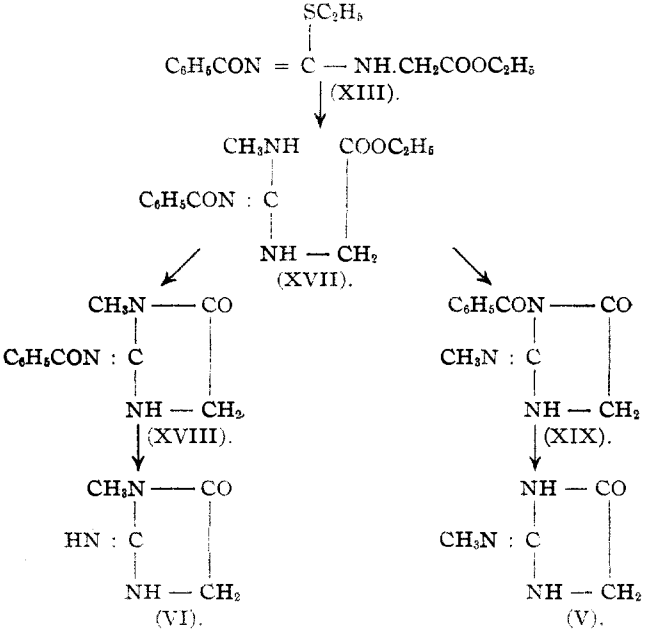


(XIII).



(XIV). (XV). (XVI).

With methylamine we obtained the guanidine derivative represented by Formula XVII, which then underwent a molecular condensation with formation of the two possible glycocyamidines (XVIII) and (XIX). About 85% of the guanidine (XVII) condensed to form 1-methyl-2-benzoylglycocyamidine (XVIII), while the remainder was transformed

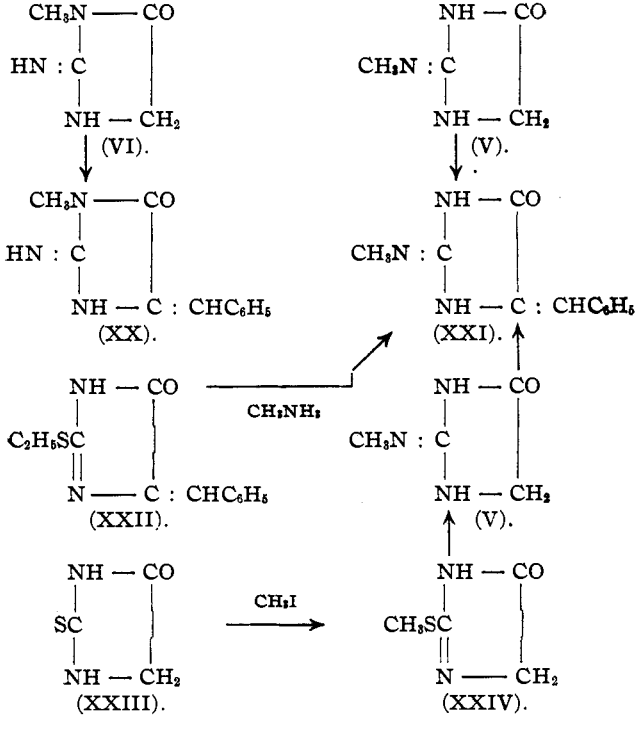


(XIII). (XVII). (XVIII). (XIX). (VI). (V).

into the 1-benzoyl-2-methylglycocyamidine (XIX). The isomers were hydrolyzed by warming with hydrochloric acid and converted into the corresponding hydrochlorides of α-methyl- and γ-methylglycocyamidines, represented by Formulas VI and V, respectively. The changes may be expressed as above.

The hydrochloride of α-methylglycocyamidine (V) was not isolated. A description of the hydrochloride of the isomeric glycocyamidine (VI), which was identical with Korndörfer's salt, is given in the experimental part of this paper.

That two isomeric methylglycocyamidines (V) and (VI) were formed in this reaction was established in the following manner: The crude glycocyamidine formed by hydrolysis was digested with benzaldehyde and sodium acetate, in acetic acid, when it interacted to form the two benzal derivatives represented by Formulas XX and XXI. These two compounds are characterized by their difference in behavior towards alkali. The glycocyamidine (XX) is insoluble in dilute alkali, while its isomer (XXI) is an acid (—CO.NH— grouping) and dissolves at once. In this manner, therefore, the isomers can be separated easily and the soluble form (XXI) obtained in a pure condition by precipitation from its alkaline solution with acid. The relative proportion of the two isomers in a mix-



ture can be determined very accurately by this method. That the benzalglycocyamidine soluble in alkali is a 2-methyl derivative (XXI) was established by its synthesis by two other methods. The same compound was obtained by heating 2-ethylmercapto-4-benzal-5-ketodihydroimidazole[1] (XXII) with methylamine, and also from 2-thiohydantoin (XXIII) in the following manner: This was first converted into its methylmercapto derivative (XXIV) by alkylation with methyl iodide and this then into the 2-methylglycocyamidine (V) by heating with methylamine. This hitherto unknown glycocyamidine was condensed with benzaldehyde when the corresponding benzal derivative (XXI) was obtained in good yield (55%).

These aldehyde condensation products should prove to be of general usefulness to biochemists for isolating glycocyamidine compounds and determining the constitution of alkylation products of this type. Hitherto, the characteristic derivatives, which have been of service for the isolation and identification of such compounds, have been the picrates and gold and platinum double salts. Some give characteristic precipitates with inorganic salts ($ZnCl_2$). The benzal compounds are difficultly soluble, possess high melting points and are very stable in the presence of dilute alkali. The study of glycocyamidine compounds will be continued.

Experimental Part.

2-Benzoylglycocyamidine (XV).—Ethyl benzoylpseudoethylthiohydantoate,[2] $C_6H_5CON : C(SC_2H_5)NH.CH_2COOC_2H_5$, was dissolved in alcohol and 1.5 molecular proportions of ammonia in aqueous solution added. Ethyl mercaptan was evolved slowly. The mixture was allowed to stand for 5 days and finally heated on the steam bath for one-half hour to complete the reaction. After concentration of the solution and cooling, the glycocyamidine was obtained in the form of colorless needles. The compound is moderately soluble in hot alcohol and difficultly soluble in cold. It has no definite melting point but blackens and decomposes when heated to 230°. Analysis:

Calc. for $C_{10}H_9O_2N_3$: N, 20.6. Found: N, 20.38.

The Action of Methylamine on Ethyl Benzoylpseudoethylthiohydantoate with Formation of 1-Methyl-2-benzoylglycocyamidine (XVIII) and 1-Benzoyl-2-methylglycocyamidine (XIX).—The ethylhydantoate was covered with its own weight of alcohol, and somewhat more than the calculated amount of methylamine, in 33% aqueous solution, then added. Ethyl mercaptan was evolved immediately at ordinary temperature. The mixture was allowed to stand in a tightly stoppered flask for 24 hours and then heated to boiling for one-half hour. On cooling the glycocyamidine (XVIII) separated in the form of distorted needles which melted at 214°. The compound was readily soluble in hot alcohol, mod-

[1] Johnson and Nicolet, THIS JOURNAL, 34, 1048 (1912).

[2] Wheeler, Nicolet and Johnson, *loc. cit.*

erately soluble in cold and very soluble in hot water. The yield was excellent, being about 85% of the theoretical. Analysis:

Calc. for $C_{18}H_{17}O_3N_3$: N, 15.95. Calc. for $C_{11}H_{11}O_2N_3$: N, 19.30. Found: N, 19.12.

1-Benzoyl-2-methylglycocyamidine (XIX) was also a product of this reaction, but it was not isolated. The experimental evidence, which indicates its formation, is given below.

Hydrochloride of 1-Methylglycocyamidine (VI).—The 1-methyl-2-benzoylglycocyamidine (benzoylisocreatinine) described above was dissolved in alcohol and digested for 8–10 hours on the steam bath with an excess of concentrated hydrochloric acid. The solution was then evaporated to dryness and the residue triturated with a small amount of cold water. This dissolved completely the glycocyamidine hydrochloride and left behind the benzoic acid. After filtering, this aqueous solution of the hydrochloride was evaporated to dryness and the salt dissolved in the smallest possible vloume of 95% alcohol and this solution diluted with ether. The hydrochloride of methylglycocyamidine separated at once and the yield corresponded to about 75% of the calculated amount. The salt crystallized in characteristic granular crystals. When heated in a capillary tube, the salt began to change in appearance at 200°, blackened badly above 250° and at about 283–285° decomposed with strong effervescence. It is very soluble in hot water and alcohol, and practically insoluble in ether. It is easily purified by dissolving in fresh alcohol and then reprecipitating by addition of ether.

Calc. for $C_4H_8ON_3Cl$: N, 28.0. Found: N, 27.60.

This salt agreed in all its properties, so far as we were able to judge, with that described by Korndörfer.[1] It combined with picric acid, giving an insoluble picrate, which separated in short prisms melting at 196° when heated slowly. Korndörfer gives 193° as the melting point. The chloraurate deposited as short, yellow prisms which melted at 166° with slight effervescence. Korndörfer gives 168° as the melting point of his salt. Our salt (HCl) gave in aqueous solution the same color reactions, described by Korndörfer, with sodium nitroprusside, picric acid and Fehling's solution.

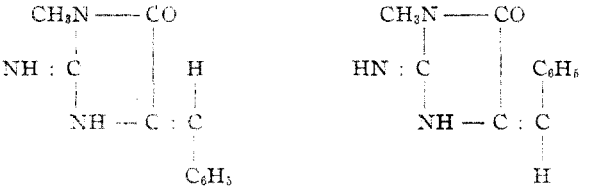
Condensation of Benzaldehyde with a Mixture of 1-Methylglycocyamidine and 2-Methylglycocyamidine.—In this experiment we used 3 g. of the crude hydrochloride of 1-methylglycocyamidine, which was prepared by hydrolysis of the corresponding benzoyl derivative (XVIII) and (XIX) described above. The crude hydrochloride, one molecular proportion of benzaldehyde, three molecular proportions of anhydrous sodium acetate and 20 cc. of glacial acetic acid were heated to boiling, in an oil bath, for one hour. After cooling and diluting with water 3.35

[1] *Loc. cit.*

g. of the condensation product were obtained. This reaction product was not a definite substance, although after crystallization from alcohol it melted quite sharply at 219–220°. When it was triturated with cold 5% sodium hydroxide solution (it is necessary that this alkali be kept cold in order to avoid all hydrolysis), the greater part remained undissolved and was identified as *1-methyl-4-benzalglycocyamidine* (XX). This new compound crystallizes from alcohol in flat, orange-colored prisms which melt at 246–247° with violent effervescence. It is slightly soluble in hot water and insoluble in cold.

Calc. for $C_{11}H_{11}ON_3$: N, 20.86. Found: N, 20.94.

Mixed with this hydantoin there was always obtained a small amount of material which crystallized from alcohol in needles melting at 237–239°. This compound also was insoluble in hot 5% potassium hydroxide solution. It contained the same percentage of nitrogen as the above benzal derivative (Found : N, 20.7). Owing, however, to the extremely small quantity obtained, its constitution could not be established, but it was very probably a stereoisomeric modification of 1-methyl-4-benzalglycocyamidine. Such a relationship would be expressed by the following formulas:



That combinations of this type (hydantoins) can exist in isomeric forms has already been shown by Johnson and Hadley[1] and also Johnson and Bates.[2]

The sodium hydroxide solution (see above) was acidified with acetic acid, when a crystalline substance separated at once. This was purified by crystallization from alcohol and separated as needle-like prisms, which melted at 223° to a clear oil. It was identified as *2-methyl-4-benzalglycocyamidine* (see below). A mixture of this compound with its isomer melting at 246–247°, melted at 210°. In other words, the original *methylglycocyamidine hydrochloride*, which was used in this condensation was a mixture of two salts, namely, *1-methylglycocyamidine* and *2-methylglycocyamidine* hydrochlorides. The chief proportion of the salt was the 1-methyl derivative.

2-Methyl-4-benzalglycocyamidine (XXI).—For the purpose of identification this glycocyamidine derivative was synthesized by two different methods. It was prepared from 2-ethylmercapto-4-benzalhydantoin

[1] THIS JOURNAL, 37, 171 (1915).
[2] *Ibid.*, 37, 383 (1915).

as follows: The hydantoin was dissolved in an alcoholic solution of methylamine and this heated in a bomb tube. After heating for six hours at 100° there was no odor of ethylmercaptan and the mercaptohydantoin was recovered unaltered. Only a trace of ethylmercaptan was noticeable after heating again for 3 hours at 155–160°. When heated at 200° mercaptan was not only evolved, but the compound had apparently undergone complete decomposition and no definite crystalline substance could be isolated. A partial change of the mercaptohydantoin into the 2-methylamino derivative was finally effected by heating for 36 hours at 100°. Under these conditions about one-fifth of the mercapto compound had undergone the desired change and the benzalglycocyamidine was obtained in the form of needles which melted at 222°. The substance was readily soluble in dilute alkali (—CO.NH— group) and was reprecipitated by acids. The yield was poor. A mixture of this material with some of the product obtained in the previous experiment (melting at 223°) melted at 221°. They were apparently identical (Found: N, 20.4%).

This same glycocyamidine compound was also obtained in the following manner: Three grams of 2-thiohydantoin[1] were alkylated with methyl-iodide in dilute alcohol solution and in the presence of alkali and converted into the corresponding methyl-mercapto derivative[2] (XXIV). The resulting solution was then concentrated to a volume of about 20 cc. and heated for 6 hours at 100° with an excess of methylamine. Ethylmercaptan was evolved and the corresponding *2-methylglycocyamidine* was formed. The reaction, however, is not a smooth one and we always obtained here a purple, tarry product on evaporating, from which it was practically impossible to isolate the glycocyamidine. Therefore, in order to establish its presence the reaction mixture was concentrated as much as possible by heating on the steam bath and the residue dissolved in glacial acetic acid. Approximately the required amount of benzaldehyde and an excess of anhydrous sodium acetate were then added and the mixture boiled for 3 hours. On pouring this mixture into water, 2-methyl-4-benzalglycocyamidine separated at once. The yield was about 55% of the theoretical. The glycocyamidine dissolved completely in alkaline solutions and crystallized from alcohol in prismatic crystals which melted at 223°. This melting point was not lowered by mixing with this product some of the glycocyamidine obtained by the action of methylamine on 2-ethylmercapto-4-benzalhydantoin.

4-Benzalglycocyamidine.—This compound has previously been described by Ruhemann and Stapleton.[3] We obtained the same compound

[1] Johnson and Nicolet, *loc. cit.*

[2] Komatsu, *Memoirs Coll. Sci. and Eng. Kyoto Univ.*, 3, 7 (1911).

[3] *J. Chem. Soc.*, 77, 239 (1900).

by condensing glycocyamidine with benzaldehyde in glacial acetic acid and in the presence of sodium acetate. It was purified by crystallization from alcohol and separated as a crystalline powder which melted at 297°. Ruhemann and Stapleton assigned to their compound a melting point of 295°. This compound undergoes alkylation with substitution in the 1-position of the ring. It reacted with methyl iodide in the presence of potassium hydroxide forming 1-methyl-4-benzalglycocyamidine. This was insoluble in dilute alkali and melted at 246°. We obtained no evidence of the formation of 2-methyl-4-benzalglycocyamidine melting at 223°.

The Molecular Rearrangement of 2-Methylglycocyamidine into 1-Methylglycocyamidine.—Two grams of 2-thiohydantoin were alkylated

with methyl iodide and converted into the corresponding 2-methyl-mercapto derivative (XXIV) as described above. The mercapto group was then removed by heating with methylamine as already described. After the reaction was complete the solution of methylglycocyamidine was then concentrated to a small volume, diluted with 20 cc. of 5% potassium hydroxide solution, and the mixture then warmed on the steam bath for 10 minutes. The solution was then made strongly acid with an excess of hydrochloric acid and finally digested on the steam bath for 8 hours. After this treatment, the solution was concentrated, as far as possible, by heating at 100° and the residue then condensed with benzaldehyde by heating in glacial acetic acid solution in the presence of sodium acetate. On pouring into water, we obtained, as usual, the condensation product. This was triturated with 5% potassium hydroxide solution when only about 30% of it dissolved, leaving behind a crystalline residue which was identified as 1-methyl-4-benzalglycocyamidine. It melted at 246°. When the alkaline solution was acidified with hydrochloric acid the isomeric 2-methyl-4-benzalglycocyamidine melting at 222° was obtained. In other words, 2-methylglycocyamidine undergoes hydrolysis with alkali and is transformed into its corresponding glycocyamine. This is closed by action of acid forming the original 1-methylglycocyamidine and also some 2-methylglycocyamidine. It is apparent from these results that, in the alkylation of glycocyamidines in the presence of alkali, different alkylation products can be formed, depending on the conditions employed.

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