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

FOUR-MEMBERED CYCLIC-UREAS. II. THE CONDENSATION OF ISOCYANIC ACID WITH A SCHIFF BASE.

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The investigations of Frerichs and Hartwig[1] presented the first instance of isolation of a four-membered cyclic-urea in an unsaturated form. They obtained this compound by boiling a mixture of urea and cyanoacetic ester. The transformation of urea into ammonium cyanate with the dissociation of the latter, between 150 and 190°, is well known. The isocyanic acid (in equilibrium with cyanic acid) is then considered as adding directly to the cyanogen group of the ester. The product was considered as a derivative of cyclomethine-urea (I).


(I).

In a strictly analogous manner the addition of phenyl isocyanate to methyleneaniline was shown by Senier and Shepheard[2] to yield a true four-membered cyclic-urea (II)—with the ring completely saturated.


(II).

As was to be expected, this degree of saturation rendered the molecule more susceptible to hydrolysis, and the hydrolytic products (formaldehyde and sym-diphenyl-urea) constituted the strongest evidence in favor of the cyclo-urea structure. A second example of this condensation was reported at the same time wherein α-naphthyl isocyanate replaced the phenyl isocyanate above.

The striking comparison between the isocyanates and ketenes in adding to unsaturated compounds has only recently been demonstrated by Staudinger and Endle.[3] As explained in the first paper of this series,[4] the temperatures required for their reactions involving phenyl isocyanate precluded any possibility of isolating the cyclic-ureas in question. A study, however, of the decomposition products answered all requirements as proof of the particular cyclo-urea structure in the initial stage of a condensation.

In the first paper of this series it is also stated that practically all of those compounds studied by Schiff, and others of the early investigators, in this field possess no ring structure of the four-membered heterocyclic

[1] *J. prakt. Chem.*, [3] **72**, 489 (1905); *Ibid.*, [3] **73**, 44 (1906).

[2] *J. Chem. Soc.*, **95**, 504 (1909).

[3] *Ber.*, **50**, 1042 (1917).

[4] THIS JOURNAL, **40**, 370 (1918).

type. According to Dixon[1] the so-called "methylene-urea," so often mentioned in the literature, must be assigned an entirely new structure. From an earlier publication by Dixon and Taylor,[2] it would appear that certain examples of this cyclic-urea structure were obtainable from thio-urea and formaldehyde or acetaldehyde under definite conditions. The more recent publication by Dixon casts considerable doubt on these conclusions and one is now inclined to interpret the earlier publication in terms of the later and conclude that these condensation products of thio-urea and the simple aldehydes may share with equal certainty the structures he now assigns to the so-called "methylene-urea" class. These latter, as well as the thio-urea condensation products, are non-crystalline and marked in their insolubility in all of the ordinary solvents. The four-membered cyclic-ureas, on the other hand, are crystalline and more or less soluble in several well known solvents.

In our attempts to investigate the structure of a compound which we believe to belong to the four-membered cyclic-ureas but which, through the investigations of Bailey and Moore,[3] has been reported as a new and peculiarly constituted "triazolotriazole," we were confronted on every hand with the greatest uncertainty concerning the structures of practically all compounds heretofore considered as four-membered cyclic-ureas. The one instance by Frerichs and Hartwig (*loc. cit.*) actually presents a type partially unsaturated, but in the work of Senier and Shepheard (*loc. cit.*) we are given the only instances of isolation of two compounds of the saturated type. It fell to our lot, therefore, to investigate this subject from as many points of attack as possible and thus prepare a sure footing for subsequent work. We elected first the study of the addition of isocyanic acid to an unsaturated compound containing the $=C:N-$ linking in the form of aldehyde-imines or Schiff bases. An example each of a Schiff base from an aromatic amine and one from an aliphatic amine will be discussed. Benzylidenaniline and benzylidenethylamine are the examples chosen.

When benzylidenaniline is dissolved in glacial acetic acid and dry potassium cyanate is stirred into the ice-cold solution one molecule of isocyanic acid slowly adds to the double linking and a crystalline precipitate separates after several hours. This product (III) is a four-membered cyclic-urea and is to be considered as 1,4-diphenyluretidone after the system of nomenclature proposed in the first paper of this series.

$$\begin{array}{c} C_6H_5.CH:N.C_6H_5 \\ + \\ HN:CO \end{array} \longrightarrow \begin{array}{c} C_6H_5.HC - N.C_6H_5 \\ \vert \qquad \vert \\ HN - CO \end{array} \quad (III).$$

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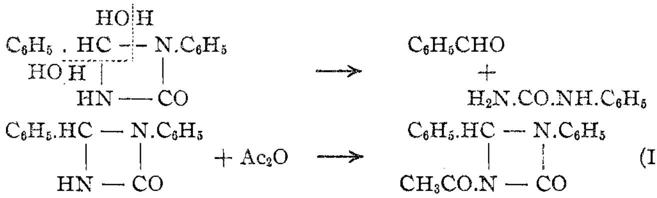
[1] *J. Chem. Soc.*, **113**, 238 (1918).

[2] *Ibid.*, **109**, 1244 (1916).

[3] THIS JOURNAL, **39**, 279 (1917).

The compound was not obtained in quantitative yield, chiefly owing to the difficulty of securing its complete separation from the acid mixture. For this reason it is necessary to operate with as small a volume of acetic acid as possible. This diphenyluretidone is hydrolyzed by boiling with water (acids and alkalies also operate to this end) and the products are benzaldehyde and phenyl-urea exactly as required by the decomposition of a four-membered cyclic-urea of the structure already indicated.



$$\begin{array}{ccc}
\begin{array}{l} \qquad \mathrm{HO\,H} \\ \mathrm{C_6H_5\,.\,HC - N.C_6H_5} \\ \quad \mathrm{HO\,H}\ |\qquad | \\ \qquad \mathrm{HN - CO} \end{array} & \longrightarrow & \begin{array}{c} \mathrm{C_6H_5CHO} \\ + \\ \mathrm{H_2N.CO.NH.C_6H_5} \end{array} \\
\begin{array}{l} \mathrm{C_6H_5.HC - N.C_6H_5} \\ \qquad |\qquad | \\ \qquad \mathrm{HN - CO} \end{array} + \mathrm{Ac_2O} & \longrightarrow & \begin{array}{l} \mathrm{C_6H_5.HC - N.C_6H_5} \\ \qquad |\qquad | \\ \mathrm{CH_3CO.N - CO} \end{array} \quad \text{(IV).}
\end{array}$$

This hydrolysis is also in agreement with the results of Senier and Shepheard (*loc. cit.*). We conclude, therefore, that the reaction between isocyanic acid and benzylidenaniline leads directly to a four-membered cyclic-urea of the atomic arrangement shown in Formula III. In order to prove the presence of the one free imino hydrogen which Formula III demands, we had only to boil the compound with acetic anhydride and fused sodium acetate when a beautifully crystalline monoacetyl derivative (IV) was secured. This acetyl derivative, upon the new system of nomenclature, will be known as 3-acetyl-1,4-diphenyl-uretidone. It is of course hydrolyzed after the manner of the diphenyluretidone itself.

From the earlier publication by Dixon and Taylor (*loc. cit.*) we were led to believe that possibly phenyl-urea and benzaldehyde, the hydrolytic products of diphenyluretidone, might be made to condense directly to this original cyclo-urea. Indeed phenyl-urea and benzaldehyde condense readily both with or without the presence of acid or solvent, and the product resulting is a benzylidene bis-phenylureide,

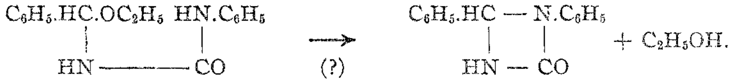
$$\mathrm{C_6H_5CH : (NH.CO.NHC_6H_5)_2}.$$

In the presence of dry hydrogen chloride, phenyl-urea and benzaldehyde in absolute alcoholic solution, condensed to a viscous red mass—a hydrochloride of a base containing an ethoxyl group. When this hydrochloride is diluted with alcohol and poured into cold water a flocculent white precipitate is formed at once. This precipitate is a base which would appear to have the constitution

$$\mathrm{C_6H_5.NH.CO.NH.CH(OC_2H_5)C_6H_5}.$$

In their publication on thio-urea Dixon and Taylor (*loc. cit.*) announced the formation of a base of similar structure. They considered the α-ethoxybenzyl group as directly attached to the sulfur atom of thio-urea and regarded its transference to a nitrogen atom as a simple occurrence usually taking place upon long standing or gently heating the compound. In the product which we have prepared it would appear that the α-ethoxybenzyl group is attached to a nitrogen atom from the beginning or at least from the moment of precipitation of product as a free base. This is evidenced mainly from the comparative stability of the base upon long standing or upon gently heating, even up to its softening point (150–5°). At this point a dissociation begins and a small amount of the benzylidene-bis-phenylureide (previously mentioned) is produced. A partial transformation into this insoluble bis-phenylureide takes place even when the base is boiled with absolute alcohol; benzaldehyde, of course, is liberated at the same time in that only one molecule of benzaldehyde is required for condensation here with two molecules of the phenyl-urea simultaneously produced.

Dixon and Taylor describe the gradual transformation of their thio-urea base into an insoluble "condensation product" as one of a ring closing and consequent formation of a cyclomethylenethio-urea. In the same manner we hoped to secure a ring closing with our phenyl-urea base, by the loss of one molecule of alcohol, and thus obtain 1,4-diphenyluretidone.

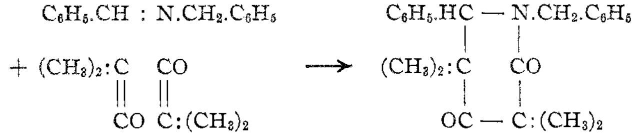


$$\begin{matrix} C_6H_5.HC.OC_2H_5 & HN.C_6H_5 \\ | & | \\ HN & \text{———}CO \end{matrix} \quad \xrightarrow[(?)]{} \quad \begin{matrix} C_6H_5.HC & - & N.C_6H_5 \\ | & & | \\ HN & - & CO \end{matrix} \quad + C_2H_5OH.$$

This change, however, could not be accomplished by the means at hand. There must be some condition whereby some of the ureas will condense with aldehydes to give four-membered cyclic-ureas. Certain it is that we have not been able to secure this ring structure when operating with phenyl-urea and benzaldehyde. It is doubtful also whether Dixon and Taylor actually had isolated a true four-membered cyclic-thiourea. The possibility still presents itself that their insoluble "condensation product" may have been formed through the loss of a molecule of alcohol from the carbon carrying the ethoxyl group and the adjoining nitrogen with a free hydrogen atom. A structure similar to that proposed by Dixon for "methylene-urea" is also within the possibilities. When our free ethoxyl base is dissolved in a very small quantity of glacial acetic acid there separates, after several hours, a semi-crystalline substance melting with decomposition at about 240°. This compound is very slightly soluble in alcohol or glacial acetic acid and is insoluble in other common solvents. Its properties might indicate that here was a compound similar to those obtained by Dixon and Taylor. As it has shown no properties distinctly characterizing it as a cyclic-urea we may assume that possibly this elimination of alcohol from the carbon-nitrogen linking, as suggested above for Dixon and Taylor's highly insoluble condensation products, may have occurred under these conditions. Tentatively we may assign to it the formula $C_6H_5.NH.CO.N:CH.C_6H_5$. Our analyses also would correspond with the requirements of this formula. Further work, however, will be required to place this formula outside the realms of speculation.

From our present investigation we are satisfied that the compound cannot come under the classification of cyclic ureas or uretidones. The uretidones as a class are crystalline substances of no extensive range of insolubilities. Under these considerations as just presented we are again forced to the conclusion that no adequate proof of the actual synthesis of the saturated four-membered cyclic-urea from an aldehyde and urea has ever been advanced. This fact alone would almost seem to discourage the chemist from any further use of this term. In a later publication, however, we shall endeavor to show under what conditions this method of synthesizing four-membered cyclic-ureas is possible. For the present we are concerned only with the synthesis of this ring by the addition of isocyanic acid upon an aryl Schiff base.

In the condensation of ketenes with an alkyl Schiff base Staudinger[1] noted a different course of action from that with an aryl Schiff base. With the alkyl bases it was found that two molecules of a ketene condensed with one molecule of base and the principal product consisted of a derivative of piperidine. Thus with benzylidene-benzylamine and dimethyl ketene the reaction proceeded in a manner exactly analogous to the condensation of cyanic acid to cyanuric acid. The product was 1-benzyl-3,3,5,5-tetramethyl-6-phenyl-2,4-diketo-piperidine.



$$\begin{array}{l} C_6H_5.CH : N.CH_2.C_6H_5 \\ + \begin{array}{cc}(CH_3)_2:C & CO \\ \| & \| \\ CO & C:(CH_3)_2\end{array}\end{array} \longrightarrow \begin{array}{ccc} C_6H_5.HC & - & N.CH_2.C_6H_5 \\ | & & | \\ (CH_3)_2:C & & CO \\ | & & | \\ OC & - & C:(CH_3)_2 \end{array}$$

When benzylidene-ethylamine in glacial acetic acid solution is treated with potassium cyanate we found no separation of product from the reaction mixture. The solution, however, when rid of acetic acid by steam distillation and somewhat concentrated, gave a crystalline product which by analysis accorded with a derivative of cyanidine or sym.-triazine (V).

$$\begin{array}{l} C_6H_5.HC:N.C_2H_5 \\ + \begin{array}{cc} HN & CO \\ \| & \| \\ OC & NH \end{array}\end{array} \longrightarrow \begin{array}{ccc} C_6H_5.HC & - & N.C_2H_5 \\ | & & | \\ HN & & CO \\ | & & | \\ OC & - & NH \end{array} \quad (V).$$

The properties of this 1-ethyl-6-phenyl-2,4-diketohexahydrocyanidine are in accord with the properties of a similar compound, a dimethyl-diketocyanidine, prepared by Ostrogovich[2] and known heretofore under the name of acetoguanamide.

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[1] *Ann.*, 374, 11 (1911).

[2] *Ibid.*, 288, 318 (1895).

Our experiments therefore confirm the theoretical considerations of Staudinger and Endle (*loc. cit.*) regarding the addition of one molecule of isocyanic acid to one molecule of an aryl Schiff base, and further show that the compound as such can be isolated. They also carry the analogy between isocyanic acid and a ketene one step further and prove that with an alkyl Schiff base the addition of two molecules of a ketene to form a diketopiperidine is now strictly in accord with the addition of two molecules of isocyanic acid to a similar alkyl Schiff base to give in turn a diketocyanidine.

Experimental Part.

Preparation of Potassium Cyanate.—The method employed was that of Bell,[1] in which absolute methyl alcohol is used for the extraction of the mass left upon fusion of potassium dichromate and potassium ferrocyanide. In our work a Soxhlet extractor was used for removal of the potassium cyanate. Cotton plugs were placed in the outlet tube and in the top of the extraction thimble in order to hold back any of the finely divided ferric oxide from leaving the extraction chamber. The cyanate separating out of the alcohol solution was again extracted as before and thus a very pure product finally obtained.

Condensation of Isocyanic Acid and Benzylidenaniline. 1,4-Diphenyluretidone, $C_2H_2ON_2(C_6H_5)_2$.—Into a solution of 5 g. of benzylideneaniline in 20 cc. of glacial acetic acid, cooled by ice, an equal weigh of finely pulverized potassium cyanate (over 2 mol.) was added in small portions at a time, and during constant stirring. The reaction mixture, which had become viscous during the operation, is then placed in a vacuum desiccator over soda-lime and the vessel set aside in an icebox. If a white amorphous product separates in a short time it should be removed by filtration and the mother liquor again set aside. This amorphous product often appears if the acetic acid is not kept ice-cold; it is due to a slight dissociation of the benzylidenaniline into its constituent parts with the consequent condensation of the aniline with isocyanic acid to give phenyl-urea and the subsequent condensation of this latter with benzaldehyde to yield the amorphous product—benzylidene-bis-phenylureide as described under another heading. After a day or more a crystalline product will have separated out of the cold concentrated acetic acid solution. In order to make this precipitation as nearly complete as possible it is well to use the smallest quantity of acetic acid. The product is purified by crystallization from 50% alcohol. 1,4-Diphenyluretidone is fairly soluble in alcohol, acetone or glacial acetic acid; slightly soluble in ethylacetate and insoluble in ether, chloroform, benzene, ligroin or water. The fine, colorless needles melt with decomposition at 224–5°.

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[1] *Chem. News*, 32, 99 (1875).

Calc. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.39; N, 12.50. Found: C, 74.81; H, 5.54; N, 12.71.

1,4-Diphenyluretidone is without basic properties. Acids and alkalies as well as hot water slowly effect its hydrolysis into benzaldehyde and phenyl-urea. Thus when subjected to distillation with steam and the benzaldehyde thus removed the phenyl-urea in residuum in flask could be determined directly by applying the method of Liebig for urea. The solution in the flask was cooled and titrated against a mercuric nitrate solution previously standardized against pure phenyl-urea using sodium carbonate as an external indicator. (1 cc. of the $Hg(NO_3)_2$ sol. here equivalent to 0.0116 g. phenyl-urea.)

Subst., 0.1605 g.; 8.5 cc. $Hg(NO_3)_2$ sol.

Calc. for $C_{14}H_{12}ON_2$: 1($NH_2.CO.NHC_6H_5$), 60.73. Found: 61.44.

The uretidone molecule is thus seen to include one molecule each of phenyl-urea and benzaldehyde. The presence of one replaceable hydrogen atom in the ring proper is proved by the formation of a monoacetyl derivative.

3-Acetyl-1,4-diphenyluretidone, $C_2HON_2(C_2H_3O)(C_6H_5)_2$ (IV).—An equal weight of 1,4-diphenyluretidone and fused sodium acetate (about 1 g. each) together with a few cc. of acetic anhydride were heated for only a few minutes over a free flame. The solution was then poured upon ice when, during the slow decomposition of excess of acetic anhydride, the acetyl derivative separated out in excellent yield. The product, purified by crystallization from diluted acetic acid, melts at 237°. Acetyldiphenyluretidone is readily soluble in acetone, fairly soluble in alcohol, ethyl acetate or glacial acetic acid and insoluble in chloroform, benzene, ether, ligroin or water. It is much more stable than the free diphenyluretidone itself.

Calc. for $C_{16}H_{14}O_2N_2$: C, 72.14; H, 5.30; N, 10.53. Found: C, 72.01; H, 5.51; N, 10.71.

Condensation of Benzaldehyde and Phenyl-urea. Benzylidene-bis-phenylureide, $C_6H_5.CH : (NH.CO.NHC_6H_5)_2$.—Phenyl-urea and benzaldehyde were brought into solution by gentle warming over a free flame. Condensation took place immediately with the production of a white, gelatinous mass. Variation in the quantity of either component in the original mixture did not appear to produce any appreciable change in the composition of the final product. The compound was thoroughly washed with cold water, then with alcohol and finally with ether and dried *in vacuo*. It melted with decomposition at 198–9°. This benzylidene-bis-phenylureide is only only slightly soluble in alcohol, acetone or ethylacetate and practically insoluble in chloroform, ether, benzene, ligroin or water. It is fairly soluble in glacial acetic acid but with dissociation.

Calc. for $C_{21}H_{20}O_2N_4$: C, 69.69; H, 5.60; N, 15.56. Found: C, 69.40; H, 5.88; N, 15.23.

This same product may also be prepared by dissolving phenyl-urea and benzaldehyde in a small quantity of alcohol and adding a few drops of conc. sulfuric acid which effects immediate condensation. The final product is identical with that prepared above.

Calc. for $C_{21}H_{20}O_2N_4$: N, 15.56. Found: N, 15.71.

Water itself does not work disadvantageously toward this condensation as evidenced in the production of this same bisphenylureide when phenyl-urea and benzaldehyde are mixed with water and a few drops of conc. hydrochloric acid added. The final product is again identical with those just described.

Calc. for $C_{21}H_{20}O_2N_4$: N, 15.56. Found: N, 15.41.

Benzylidene-bis-phenylureide is hydrolyzed by warm water; acids or alkalies accomplish this results more readily. In order to determine the relative amount of phenyl-urea to benzaldehyde entering into the condensation, resort was again made to distillation with steam and titration of residuum in flask against the mercuric nitrate solution previously standardized against pure phenyl-urea (1 cc. standard sol. = 0.0116 g. phenyl-urea). Samples of the product prepared by either of the three methods gave identical values according with the constitution of a diphenylureide. The analysis reported below was made with a sample prepared without the use of a solvent.

Subst., 0.2348 g.; 15.5 cc. $Hg(NO_3)_2$ sol.
Calc. for $C_{21}H_{20}O_2N_4$: $2(NH_2.CO.NHC_6H_5)$, 75.57. Found: 76.60.

Condensation of Benzaldehyde and Phenyl-urea in the Presence of Absolute Alcohol and Hydrogen Chloride.

(*a*) **α-Ethoxybenzyl-phenyl-urea Hydrochloride,** $(C_6H_5NH.CO.NH.CH(OC_2H_5)C_6H_5)HCl$.—Two g. of phenyl-urea (1 mol.) and 2 g. of benzaldehyde (1.3 mol.) were mixed with 6–7 cc. of absolute alcohol and the mixture, thoroughly cooled, then saturated with dry hydrogen chloride. The final yellow solution was placed in a vacuum desiccator over sulfuric acid for one day and on the following day in a similar desiccator over soda-lime. The next day it was again transferred to the acid-filled desiccator and this alternation continued for a week, or more, when the mass became viscous and gave no odor of hydrogen chloride or benzaldehyde. A portion of this product was then dissolved in 95% alcohol and slightly diluted with freshly distilled water. The mixture (containing the free base as a precipitate) was at once titrated against *N*/10 alkali (using phenolphthalein as indicator). The result indicates distinctly a monohydrochloride of the free base.

Subst., 1.461 g.; cc. *N*/10 NaOH, 46.2.
Calc. for $C_{16}H_{18}O_2N_2.HCl$: 1(HCl), 11.90. Found: HCl, 11.53.

(*b*) **α-Ethoxybenzyl-phenyl-urea,** $C_6H_5NH.CO.NH.CH(OC_2H_5)C_6H_5$.—A portion of the hydrochloride of the condensation product, as just described, was dissolved in an equal volume of alcohol and then slowly poured into cold water. The precipitated free base, dried on a porous plate, was again taken up in alcohol and again precipitated by pouring the solution into water. This non-crystalline substance, thus purified, softens upon heating to 150–5°. The compound is readily soluble in glacial acetic acid, alcohol, or acetone; it is very slightly soluble in ethyl acetate or chloroform and practically insoluble in ether, benzene, ligroin or water.

Calc. for $C_{16}H_{18}O_2N_2$: C, 71.06; H, 6.71; N, 10.37. Found: C, 71.81; H, 6.59; N, 10.97.

When subjected to distillation with steam, hydrolysis was easily effected and the phenyl-urea left in flask was titrated against the same mercuric nitrate solution previously standardized against pure phenyl-urea (1 cc. sol. = 0.0116 g. phenyl-urea).

Subst., 0.1252; 5.5 cc. $Hg(NO_3)_2$ sol.
Calc. for $C_{16}H_{18}O_2N_2$: 1($NH_2.CO.NHC_6H_5$), 50.35. Found: C, 50.95.

The free base is comparatively stable under ordinary conditions. Warming its absolute alcoholic solution always gave a small amount of flocculent precipitate which proved to be benzylidene-bis-phenylureide. Upon heating the compound to the point where softening just begins and then taking up the mass in absolute alcohol a considerable amount of benzylidene-bis-phenylureide remained undissolved. This free base did not show any great tendency to go over into an insoluble product which might be compared with the insoluble products described by Dixon and Taylor (*loc. cit.*) as resulting from their ethoxyl thio-urea bases. The only condition by which our free base was transformed into a semi-crystalline high melting (235–240°) substance was found to arise when its conc. solution in glacial acetic acid was allowed to stand several hours. There separated from this medium a substance very slightly soluble in alcohol or acetic acid and practically insoluble in the other organic solvents. Though the product analyzed for a compound of the same empirical formula as 1,4-diphenyluretidone, it did not possess any of the properties of this true cyclic-urea which nevertheless we had hoped to prepare from this free base. Our ring closing therefore had not proceeded in the manner outlined by Dixon and Taylor (*loc. cit.*) and the insoluble product was not further investigated.

Calc. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.39; N, 12.50. Found: C, 74.41; H, 5.53; N, 12.60.

Condensation of Isocyanic Acid and Benzylidene Ethylamine.

1 - Ethyl-6-phenyl - 2,4 - diketohexohydrocyanidine, $C_3H_3O_2N_3(C_2H_5)(C_6H_5)$ (V).—To an ice-cooled solution of 2.5 g. of benzylidene ethylamine (1 mol.) in 10 cc. of glacial acetic acid, 3.5 g. (2.3 mol.) of pulverized potassium cyanate were slowly added during constant stirring. After several days' standing the cooled reaction mixture failed to show any separation of product. A few drops of hydrochloric acid were then added to secure the decomposition of all cyanate and the solution subjected to distillation with steam to remove the acetic acid. Upon evaporation of the residuum in flask to small volume there soon appeared a considerable quantity of fine, colorless needles in clusters. Recrystallization of this substance from alcohol gave a pure product melting at 226°. This ethyl-phenyldiketocyanidine is readily soluble in glacial acetic acid, fairly soluble in alcohol, acetone, chloroform, benzene, ethyl acetate or water, crystallizing from each; it is slightly soluble in ether and insoluble in ligroin.

Calc. for $C_{11}H_{13}O_2N_3$: C, 60.27; H, 5.98; N, 19.18. Found: C, 60.21; H, 6.19; N, 19.27.

This diketo-sym-triazine gives a flocculent precipitate with silver nitrate. As previously stated, this substance corresponds closely in its properties to those of the methyl keto-triazine of Ostrogovich—a compound prepared by condensing urea with acetylurethane. The compounds are closely similar but in the one only a tetrahydro ring is present, whereas in the case we describe the completely reduced or hexahydro ring is at hand.

Ann Arbor, Mich.

[Contribution from the Division of Agricultural Biochemistry, University of Minnesota.]

THE FORMS OF NITROGEN IN PROTEIN-FREE MILK.[1]

By Cornelia Kennedy.

Received November 30, 1918.

Since the use of so-called protein-free milk as an adjuvant to isolated proteins to furnish the inorganic elements of the diet[2] has been questioned[3] because of the unknown nature of its nitrogen content, it seemed advisa-

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[1] Published with the approval of the Director as Paper No. 148, Journal Series, Minnesota Agricultural Experiment Station. Presented before the Division of Biological Chemistry of the American Chemical Society, at the Cleveland meeting, September, 1918.

[2] T. B. Osborne, and L. B. Mendel, "Feeding Experiments with Isolated Food-Substances," *Carnegie Inst. Publication* 156, 2, 82 (1911); "Relation of Growth to Diet," *J. Biol. Chem.*, **15**, 318 (1913); "Influence of Butter-Fat on Growth," *Ibid.*, **16**, 426 (1913); "Influence of Fats on Growth," *Ibid.*, **17**, 404 (1914); "Protein Minima for Maintenance," *Ibid.*, **22**, 256 (1915).

[3] E. V. McCollum, N. Simmonds and W. Pitz, "Is Lysine the Limiting Amino Acid in the Proteins of Wheat Maize or Oats?" *Ibid.*, **28**, 485 (1916); J. C. Drummond, "The Growth of Rats upon Artificial Diets Containing Lactose," *Biochem. J.*, **10**, 91 (1916); H. H. Mitchell and R. A. Nelson, "Preparation of Protein-Free Milk," *J. Biol. Chem.*, **23**, 461 (1915).