be made, that the existence of crystals in no way guarantees chemical individuality, particularly since it can be regarded as an isomorphous mixture, such as the mineral kingdom so often presents to us in the silicates. Such objections vanish with synthetic products, whose formation can be controlled by analogous reactions.

The molecular physicists would do well in the study of high molecular substances to confine themselves to the synthetic products of known structure. I will continue the experiments on the building up of giant molecules with the aid of the processes described.

Certainly it offers in other respects a great incentive to test the productiveness of our methods. As is well known, the modern physicist is endeavoring to split up matter into smaller and smaller pieces. One is long since past the atom, and how long the electrons will be for us the smallest particles of matter, cannot be predicted. It seems to me that organic synthesis is called upon to accomplish the converse, *i. e.*, to accumulate larger and larger masses in the molecule, in order to see how far the compression of matter can go, in the meaning of our present conceptions.[1]

I hope that the results to date will give an effective stimulus in this direction.

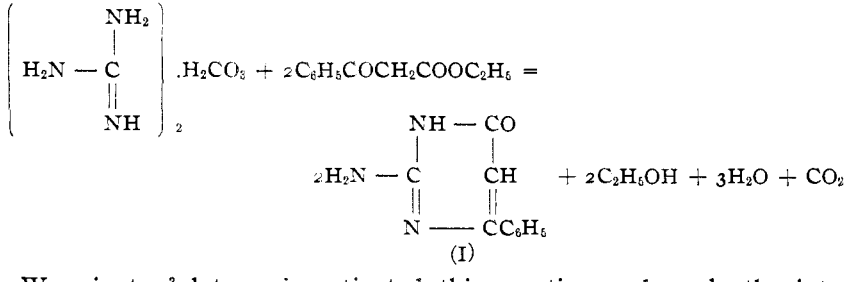
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXX. THE ISOMERISM OF 4-PHENYLISOCYTOSINE.

BY TREAT B. JOHNSON AND ARTHUR J. HILL.

Received March 23, 1914.

Jaeger[2] observed, in 1891, that guanidine carbonate and ethyl benzoylacetate interact smoothly, when heated in alcoholic solution, with formation of 2-amino-4-phenyl-6-oxypyrimidine (4-phenylisocytosine, (I) melting at 294°. The reaction may be expressed as follows:



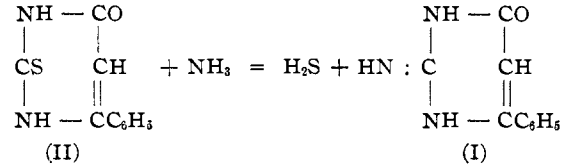
Warmington[3] later reinvestigated this reaction and made the inter-

[1] Cf. H. Crompton, *Proc. Chem. Soc.*, **28**, 193 (1912).

[2] *Ann.*, **262**, 372.

[3] *J. prakt. Chem.*, [2] **47**, 214 (1893).

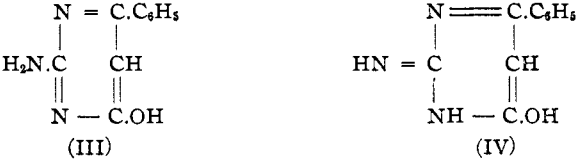
esting observation that this pyrimidine, melting at 294°, is not the only product formed, and succeeded in isolating a second isomeric modification of the pyrimidine (I), which melted at 272–274°. The conditions under which this interesting substance was obtained are discussed in the experimental part of this paper. He also prepared the pyrimidine melting at 294° by heating 2-thio-4-phenyl-6-oxypyrimidine (II) with ammonia.



(II) (I)

Warmington showed that the two bases differed decidedly in their solubility and crystalline habit, and concluded that they combined with hydrochloric acid, giving different salts, which he represented by the formulas $(C_{10}H_9ON_3)_2.HCl$ and $(C_{10}H_9ON_3)_2.HCl.H_2O$, melting at 269° and 276–277°, respectively. The two bases were recovered unaltered by decomposing their respective hydrochlorides with alkali. Both pyrimidines gave the same picrate melting at 241°, and also the same acetyl derivative melting at 248°. While the picrate underwent decomposition with alkali, with regeneration of the two isomeric pyrimidines, on the other hand, the acetyl derivative underwent hydrolysis, giving that modification which melts at 294°.

Warmington found that both bases were converted smoothly into 4-phenyluracil by hydrolysis with hydrochlorc acid or by interaction with nitrous acid, and also made the remarkable observation that the modification melting at 294° can be transformed into the base melting at 272° by heating with alcohol or alcoholic ammonia at 180°. In summarizing his observations he wrote as follows: "Auf Grund dieser Versuche konnte wohl kein Zweifel bestehen, dass die eben besprochenen Verbindungen tautomerer Art sind. Ihren Eigenschaften werden, wie schon erwähnt, vielliecht folgende Formeln am besten entsprechen: Da



(III) (IV)

dieselben jedoch unter dem Einfluss der Reagentien mit der grössten Leichtigkeit in einander übergehen, so ist es vorläufig unmöglich, die eine oder die andere Base mit der ihr zukommenden Formel bestimmt zu belegen."

In all our previous work on guanidine-pyrimidine condensations, we have never encountered any cases of isomerism like this described by

Warmington. It has been our experience that two such formulas as represented by (III) and (IV) represent a single, chemical individual, and consequently it was of especial interest to us to determine whether Warmington had correctly interpreted his experimental results. So far as the writer is aware, no one has hitherto attempted to confirm his work. We have now repeated that part of Warmington's investigation, which deals with the chemistry of 4-phenylisocytosine, and have obtained some very surprising and unexpected results. Not only have we found that some of Warmington's conclusions were incorrect, but we have also obtained new data, which have revealed the most remarkable case of isomerism so far recorded in the pyrimidine literature. A preliminary report of this investigation is now recorded in this paper.

We have applied Warmington's reaction according to his own directions, and have confirmed his observations by isolating his two isomeric modifications of 4-phenylisocytosine. We found, however, that they melt somewhat higher than the temperatures recorded by him. The pyrimidine, which he found to melt at 294°, melts at 303° and the isomeric modification melts at 279–280°, instead of 272°. The product melting at 303° we have designated as the γ-modification, and that form which melts at 279° as the δ-modification of 4-phenylisocytosine. Our reasons for adopting this method of distinguishing between these two isomeric bases will be disclosed below. Both pyrimidines dissolve in cold sodium hydroxide solution and are reprecipitated unaltered by addition of an amount of hydrochloric acid sufficient to neutralize the alkali. If an excess of acid is added, the bases combine immediately, giving their corresponding hydrochlorides.

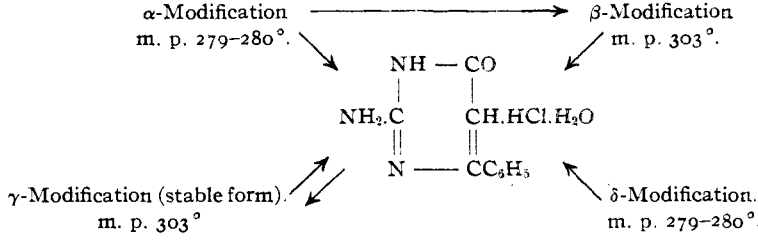
Warmington concluded that the hydrochlorides of these two bases are different substances. We find that his interpretation of their constitution was incorrect and that the two isomers combine with hydrochloric acid, giving the same salt. It is a monohydrochloride, containing one molecule of water of crystallization, $C_{10}H_{10}ON_3Cl.H_2O$, and melts at 266° with decomposition. Warmington also observed that the two bases were recovered unaltered by decomposing their hydrochlorides with alkali. We now find that the γ-modification, melting at 303°, is the stable form of the pyrimidine and is obtained by decomposing our hydrochloride with alkali. In other words, the δ-form of the pyrimidine undergoes transmutation into the γ-modification when treated with hydrochloric acid. A mixture of the two modifications melted at the same temperature as the stable γ-modification, namely, 303°. Microphotographs of these two modifications of 4-phenylisocytosine are represented in Figs. 3 and 4.

Warmington and Jaeger[1] condensed guanidine with ethyl benzoylacetate under one condition only, namely, by digesting the carbonate

[1] *Loc. cit.*

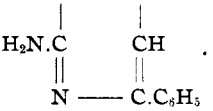
of the base with the β-ketone ester in alcoholic solution. It was, therefore, of especial interest to us to examine the behavior of the ketone ester towards guanidine, when digested in alcoholic solution in the presence of sodium ethylate. We have now effected the condensation under such conditions and have made the unexpected and most remarkable observation that an entirely different modification of 4-phenylisocytosine is a product of the reaction. We have designated this as the α-modification of 4-phenylisocytosine whose microphotograph is represented in Fig. 1. It melts at exactly the same temperature (279–280°) as the δ-modification of 4-phenylisocytosine described above, but the experimental evidence indicates that they are not identical substances. The δ-modification can be repeatedly recrystallized from alcohol without any apparent change. On the other hand, the α-modification undergoes a remarkable transformation, when subjected to the same treatment, and is converted into a fourth modification of 4-phenylisocytosine, which melts at 303°. The microphotograph of this new β-modification of the pyrimidine is represented in Fig. 2. The striking difference in the crystalline habit of the two modifications (β- and γ-) is apparent by comparison of their respective microphotographs. They also differ in their solubility in alcohol. Mixtures of the two modifications melt at 303°.

The α- and β-modifications of 4-phenylisocytosine are stable in the presence of alkali and are reprecipitated unaltered from alkaline solutions by the addition of hydrochloric acid. Both pyrimidines are converted into the same hydrochloric acid salt as is formed by dissolving the γ- and δ-modifications of 4-phenylisocytosine in this acid. In other words, they are both transformed by the action of the acid into the hydrochloride of the γ-modification. By treatment of the hydrochloride from either the α- or β-modifications with ammonia the difficultly soluble γ-modification, melting at 303°, deposited immediately. Therefore the α-, β- and δ-modifications of 4-phenylisocytosine can all be transformed into the γ-modification by conversion into their hydrochlorides and then decomposing this common salt with alkali (ammonia). These unique and interesting relationships are represented below. The melting points of the possible mixtures of the four different modifications are recorded in the experimental part of this paper.



Regarding the constitution of these four isomers, practically nothing definite can be concluded from the available data. Two general and characteristic properties, however, are very suggestive; namely, that all four modifications are stable in alkaline solutions, and that all four forms combine with hydrochloric acid to give the same salt. It is not improbable that we are dealing simply with an unique case of physical isomerism. To express the chemical differences of the four modifications by correct stereochemical formulae is indeed a difficult matter, when one takes into consideration the great number of possible tautomeric formulae, which can be assigned to 4-phenylisocytosine. It is possible that unknown chemical differences may be revealed by the application of physico-chemical methods of research which will suggest structural differences, but it is true, that our present knowledge does not justify the adoption of definite structural formulas for the four compounds. The study of these isomers and of other closely related pyrimidines will be continued.

Experimental.

The α- and β-Modifications of 2-Amino-4-phenyl-6-oxypyrimidine (*4-Phenylisocytosine*),  . — The α-modification of this pyrimidine is obtained by condensation of guanidine with ethyl benzoylacetate, in the presence of sodium ethylate. The following description of an experiment comprises the necessary information for preparing the base: Eight and nine-tenths grams of sodium were dissolved in 120 cc. of absolute alcohol, and 27 g. of guanidine thiocyanate (3 molecular proportions) and 15 g. of ethyl benzoylacetate added to the cold solution. The mixture was then digested on the steam bath for 10 hours. At the end of this time a thick magma of the sodium salt of the pyrimidine was obtained. The alcohol was then evaporated in an open dish and the residue finally dissolved in the least possible volume of cold water. This solution was then carefully acidified with cold dilute hydrochloric acid in order to precipitate the pyrimidine. Care must be taken here to avoid adding any excess of the acid, in order to prevent the formation of the hydrochloric acid salt. The pyrimidine sometimes separated as an oil, which finally solidified on cooling. At other times it separated at once in a granular condition. The yield of the base is not good, seldom exceeding 3 g. from 15 g. of the β-ketone ester. This product was purified by crystallization from absolute alcohol and deposited in tabular crystals which melted at 279–280° with effervescence (Fig. 1). The pyrimidine is soluble in hot water and sodium hydroxide solution, and is precipitated unchanged from its alkaline solutions by addition of acids.

Calc. for $C_{10}H_9ON_3$: N, 22.46; found (Kjeldahl): N, 22.34, 22.31.

The β-Modification.—Especially characteristic was the behavior of the above α-modification when heated in alcoholic solution. After long boiling and subsequent cooling of the solution, it was observed that the α-form underwent a quantitative transmutation into a modification melting sharply at 303° with effervescence. This is designated as the β-modifications of the pyrimidine and its crystalline habit is represented in Fig. 2. That this raise of the melting point, by this treatment, is not to be explained by removal of impurities, is established by the facts that the 279–280° and 303° products contain absolutely the same amount of nitrogen. A mixture of the two modifications melts sharply at 303°. The lower melting α-modification therefore apparently undergoes a rearrangement when heated with the β-modification. It was also observed that the α-modification slowly undergoes transformation into the higher melting form on long standing at ordinary temperature. The β-form possesses properties much in common with those of the α-modification. A microphotograph of the β-modification is shown in Fig. 2:

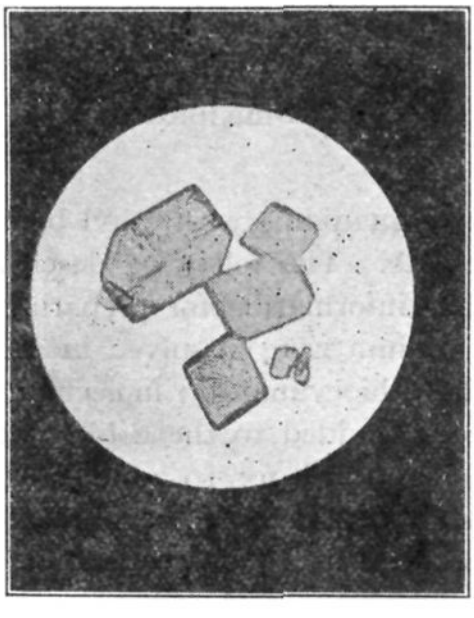


Fig. 1.—α-Modification of 4-phenylisocytosine crystallized, from alcohol. Magnified.

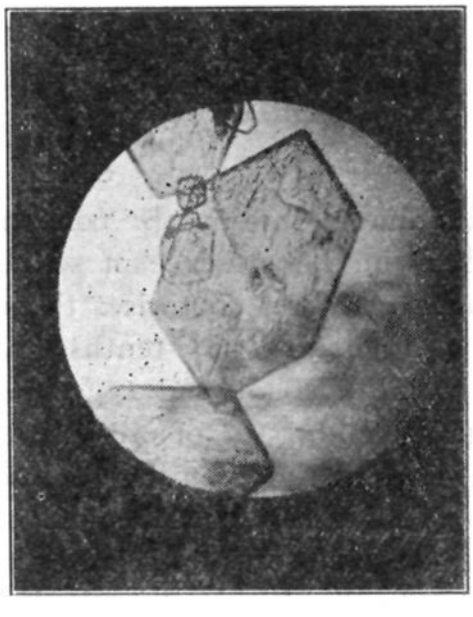


Fig. 2.—β-Modification of 4-phenylisocytosine, crystallized from alcohol. Magnified.

Calc. for $C_{10}H_9ON_3$: N, 22.46; found (Kjeldahl): N, 22.34, 22.39.

The Hydrochlorides of the α- and β-Modifications of 2-Amino-4-phenyl-6-oxypyrimidine.—Both of these modifications dissolved in warm hydrochloric acid and were converted into the same hydrochloride. This crystallized from hydrochloric acid in hair-like crystals which melted at 266° with effervescence. A mixture of the two salts melted at the same temperature. This salt contained one molecule of water of crystallization. Attempts, however, to correctly determine the water by heating at 100°

were unsuccessful. The salt underwent partial dissociation at this temperature with loss of hydrochloric acid and consequently the analytical results were always too high. Analyses of the dehydrated salts showed that the nitrogen content varied between that of the free base and its anhydrous hydrochloride, as would be expected.

ANALYSES.

	N.		H_2O (at 104°).		Cl.	
	Calc.	Found.	Calc.	Found.	Calc.	Found.
Hydrous α-hyd. chl.	17.39	17.27	7.45	7.72	...	...
$C_{10}H_{10}ON_3Cl.H_2O$		17.56	..	10.42	...	...
After heating to 104°.	18.79	19.73	..	...	...	...
$C_{10}H_{10}ON_3Cl$						
Hydrous β-hyd. chl.	17.39	17.34[1]				
$C_{10}H_{10}ON_3Cl.H_2O$		17.47[1]	..	...	14.70	14.89

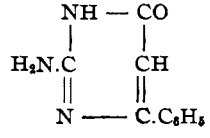
The β-modification showed the same behavior on heating at 100° as that observed in the case of the α-modification.

The Action of Alkali on the Hydrochlorides of the α- and β-Modifications.—When the hydrochloride, which is formed from either of these two bases, is treated with the required amount of alkali (NH_4OH) to neutralize the hydrochloric acid, neither the α- nor the β-modification is precipitated. A third modification of the aminopyrimidine is obtained, which melts at 303° with effervescence. This base is far less soluble in alcohol than either the α- or β-modification, and crystallizes in characteristic, slender prisms. We have designated this as the γ-modification of 2-amino-4-phenyl-6-oxypyrimidine and its crystalline habit is shown in the microphotograph represented by Fig. 3.

Calc. for $C_{10}H_9ON_3$: N, 22.46; found (Kjeldahl): N, 22.50, 32.21.

Behavior of the α- and β-Modifications of the Pyrimidine towards Alkali.—While these two modifications are transformed into the hydrochloride of the γ-modification by solution in hydrochloric acid, they are absolutely stable in alkaline solution. Both forms dissolve in cold, dilute sodium hydroxide solution. On acidifying these solutions with hydrochloric acid the α- and β-forms are regenerated unaltered and melt at 279–280° and 303°, respectively. This stability in alkaline solutions is very remarkable.

The γ- and δ-Modifications of 2-Amino-4-phenyl-6-oxypyrimidine,



The Formation of the γ-Modification by Digestion of Guanidine Carbonate with Ethyl Benzoylacetate in Alcohol Solution.—Ten grams of

[1] Nitrogen by Kjeldahl method.

ethyl benzoylacetate and 5.3 g. of guanidine carbonate were dissolved in 33 cc. of absolute alcohol and the solution digested on the steam bath for seven hours. A thick magma of the pyrimidine was obtained. This compound is practically insoluble in all the common organic solvents, but crystallized from hot dilute alcohol in slender prisms. These melted at 303° with effervescence. Mixtures of the α-modification and the β-modification with this γ-modification also melted at 303°. In other words, both forms underwent transformation to the γ-form on heating with this substance. This γ-modification dissolved immediately in dilute sodium hydroxide solution and was reprecipitated unaltered by addition of the required amount of hydrochloric acid.

Calc. for $C_{10}H_9ON_3$: N, 22.46; found (Kjeldahl): N, 22.42, 22.48.

This γ-modification dissolves in hydrochloric acid, giving the same salt as the α- and β-modifications. It contained one molecule of water of crystallization and crystallized in the same characteristic manner.

Calc. for $C_{10}H_{10}ON_3Cl.H_2O$: N, 17.39; Cl, 14.70; found N (Kjeldahl): 17.27; Cl, 14.89.

Nitrogen determination in the free base, which was obtained by decomposing its hydrochloride with the required amount of alkali.

Calc. for $C_{10}H_9ON_3$: N, 22.46; found (Kjeldahl): N, 22.43.

The δ-Modification of 2-Amino-4-phenyl-6-oxypyrimidine.—In the preceding preparation of the γ-modification, the mother liquor obtained after filtration was heated in a pressure tube at 160–165° with 5 g. of guanidine carbonate (Warmington's method). Heating was continued for 6 hours. The solution was then evaporated to dryness and the residue warmed with a dilute solution of hydrochloric acid. On cooling a colorless salt separated. This was dissolved in water and alkali added, when a crystalline substance separated at once. This crystallized from alcohol in tables or plates, which melted at 279–280° with effervescence. It was soluble in water. A mixture of this product with the α-modification (m. p. 279–280°) melted at the same temperature. On the other hand, mixtures with the β- and γ-modifications melted at 303°. Notwithstanding the fact that this substance and the α-modification both melt at the same temperature, we have, however, obtained evidence that they are not identical. Consequently we have designated this substance as the δ-modification of 2-amino-4-phenyl-6-oxypyrimidine. The α-modification is characterized by the interesting fact that it can be transformed into the β-modification by boiling with alcohol. We have never observed such a transformation to take place in the case of this δ-modification. It was recovered unaltered after digestion in alcohol for 3 hours. In another experiment 1 g. of the pyrimidine was dissolved in about 100 cc. of absolute alcohol and the solution boiled for 7 hours. On cool-

ing, the unaltered pyrimidine was obtained and melted at 279–280° with effervescence. A microphotograph of this δ-modification is represented by Fig. 4.

Calc. for $C_{10}H_9ON_3$: N, 22.46; found (Kjeldahl): N, 22.53, 22.53.

This modification dissolves immediately in dilute sodium hydroxide solution and is reprecipitated unaltered by addition of acids. Analysis:

Calc. for $C_{10}H_9ON_3$: N, 22.46; found: N, 22.60.

When dissolved in hydrochloric acid it is transformed into the same salt as is obtained from the α-, β- and γ-modifications. This melts at 266° with effervescence and contains one molecule of water of crystallization. On decomposing the salt, by treatment in aqueous solution with the required amount of alkali, the γ-modification of the pyrimidine melting at 303° was obtained. This result was entirely unexpected, since the original base was obtained by decomposing its hydrochloride with alkali. Whether the presence of certain impurities retards the rearrangement, or whether the change is controlled by other conditions, such as temperature, and concentration of solution must be decided by further work. Analysis of hydrochloric acid salt:

Calc. for $C_{10}H_{10}ON_3Cl.H_2O$: N, 17.39; found: N, 17.59.

Fig. 3.—γ-Modification of phenylisocytosine, crystallized from alcohol. Magnified.

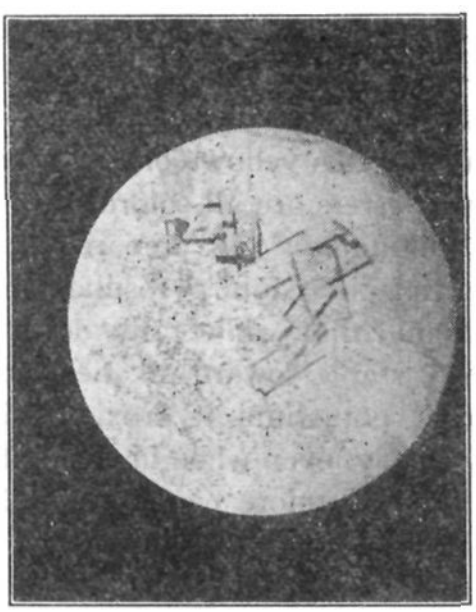


Fig. 4.—δ-Modification of 4-phenylisocytosine, crystallized from alcohol. Magnified.

MELTING POINTS OF THE MIXTURES OF THE FOUR MODIFICATIONS OF THE PYRIMIDINES.

279–280°..... α; δ; α + δ;

303°..... β; γ; α + β; α + γ; β + γ; β + δ; γ + δ.

All samples melt with effervescence.

NEW HAVEN, CONN.