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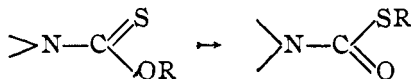
AMERICAN CHEMICAL SOCIETY

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

ON THE MOLECULAR REARRANGEMENT OF UNSYMMETRICAL ACYLAMIDINES INTO ISOMERIC SYMMETRICAL DERIVATIVES.

BY HENRY L. WHEELER, TREAT B. JOHNSON, AND DAVID F. MCFARLAND.

In papers from this laboratory, which were published several years ago,¹ it was shown that thioncarbamic esters undergo a molecular rearrangement into thiolcarbamic esters when heated with alkyl halides.



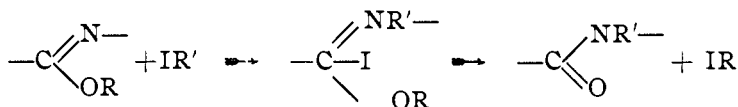
The more negative the radicals attached to nitrogen the less readily the rearrangement took place. Methyl iodide produced a rearrangement more readily than other halides. In the case of the acetylthioncarbamic esters only the methyl derivatives were found to undergo a molecular rearrangement.

It was shown that the aromatic imido esters, in general, readily undergo an analogous metastatic change,² while Dr. H. F. Mer-

¹ *Am. Chem. J.*, **22**, 140 (1899); *Ibid.*, **24**, 60, 189, 424 (1900).

² *Ibid.*, **21**, 185 (1899); *Ibid.*, **23**, 135 (1900).

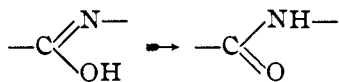
riam has found that the aliphatic members do not show a similar tendency. These molecular rearrangements were brought about catalytically with only a trace of alkyl halide, and here again methyl iodide acted the most readily. By employing a halide with a group different from R, it was shown that the change involved an addition of alkyl to nitrogen and then a separation from oxygen. This may be represented as follows:



The mechanism of the rearrangement of the thioncarbamic esters was previously shown by us to be similar.

Wislicenus and Goldschmidt¹ found that N-substituted imidoesters undergo a molecular rearrangement on simply heating alone to a high temperature, the imidoesters of Pinner being decomposed by this treatment.

We² have found that when R in the above formula is an acyl group, the rearrangement takes place by heat alone far more readily than when it is an alkyl group. In fact, some of these acyl derivatives (acyclo) undergo isomerization as readily as the parent substances, the pseudofoms of the amides.



It appears also that oxygenimidoanhydrides, $\begin{array}{c} \text{NR} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{OCOR}' \end{array}$, undergo a molecular rearrangement more readily than thioimidoanhydrides, $\begin{array}{c} \text{NR} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{SCOR}' \end{array}$, and that among these labile forms the

cyclo derivatives, in general, show the greatest stability. Before we undertook the investigation of this subject, it was known that certain cycloimidoesters undergo a molecular rearrangement on heating.

The first observation of this sort was made by Hofmann and Olshausen,³ who showed that *o*-cyanuric methyl ester gave the

¹ *Ber. d. chem. Ges.*, **33**, 1467 (1900).

² *Am. Chem. J.*, **30**, July (1903).

³ *Ber. d. chem. Ges.*, **3**, 272 (1870).

N-derivative on heating. Ponomaren¹ and Hofmann² then further investigated the subject. Haitinger and Lieben³ found that methoxy pyridine gave methylpyridon, and Knorr⁴ found that methoxylepidine gave methyllepidon, facts which led Michael⁵ to state that all compounds having the grouping ROCN would give the isomer OCNR on heating.

In the pyrimidine series, such rearrangements were afterwards observed by E. v. Meyer⁶ and by Pinner.⁷ Andreocci⁸ apparently found a similar case among the pyro- $\beta\beta'$ -diazoles. Knorr and Fertig⁹ further investigated the molecular rearrangement of alkyl-oxyquinoline derivatives by means of alkyl halides and showed that the reaction involved an addition. Wislicenus and Körber¹⁰ showed that the 8-alkyloxycaffeins also undergo a metastatic change on heating. This appears to be a complete list of these molecular rearrangements in the cyclo series.

In the acyclo series Grabriel and Neumann¹¹ found that by the action of heat benzimidochlorethyl ester is transformed into β -chlorethylbenzamide, and the mechanism of this reaction was shown to involve an inner addition with the formation of an intermediate five-membered ring, by Wislicenus and Körber.¹² Recently the work on the molecular rearrangements of acycloimidoesters has been greatly extended by Lander.¹³

It is probable that the mechanism of these rearrangements by heat alone is similar to that in the case of the action of alkyl halides. A small quantity of foreign material may act catalytically, by addition and then a separation.¹⁴ Or, under the influence of heat, this effect may take place within the molecule itself, as in the case of the molecular rearrangement of N-dialkylaminoesters into betaines.¹⁵

¹ *Ber. d. chem. Ges.*, **18**, 3271 (1855).

² *Ibid.*, **19**, 2061 (1896).

³ *Monatsh. Chem.*, **6**, 323 (1885).

⁴ *Am. Chem. J.*, **236**, 104 (1886).

⁵ *J. prakt. Chem.*, **37**, 510 (1888).

⁶ *Ibid.*, **39**, 271 (1889).

⁷ *Die Imidoäther u. Ihre Derivate*, p. 215 (1892).

⁸ *Ber. d. chem. Ges.*, **24**, R. 205 (1891).

⁹ *Ibid.*, **30**, 922, 929; *Ibid.*, **30**, 937 (1897).

¹⁰ *Ibid.*, **35**, 1991 (1902).

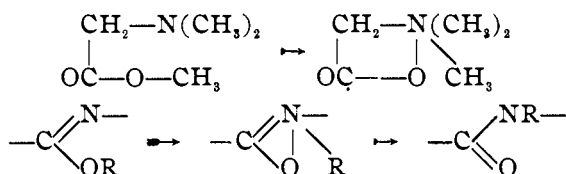
¹¹ *Ibid.*, **25**, 2383 (1892).

¹² *Ibid.*, **35**, 164 (1902).

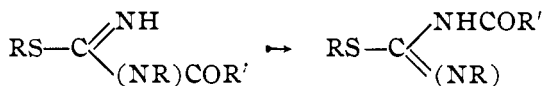
¹³ *J. Chem. Soc. (London)*, **83**, 406 (1903).

¹⁴ Compare Lander: *Loc. cit.*, p. 414.

¹⁵ Willstätter: *Ber. d. chem. Ges.*, **35**, 585 (1902).



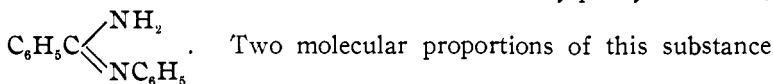
The three-membered, intermediate ring in the case of the imidoesters not being stable, the bonds shift and the stable amides are formed. In fact, this ring-formation is considered in a recent article,¹ by Kauffmann, to represent the structure of the pyridines. The molecular rearrangement of alkyloxy pyridine derivatives therefore halts at what corresponds to the intermediate stage in other cases. Closely similar to these rearrangements are those of the imido acid anhydrides. Outwardly the molecular rearrangements of unsymmetrical acylthioureas, acylpseudothioureas² and their corresponding cyclo derivatives, the arylpseudothiohydantoins, appear to be similar:



In these cases the mechanism, however, probably involves the formation of an unstable, four-membered ring as an intermediate condensation product.³

All of the unsymmetrical acylthiourea and acylpseudothiourea derivatives, which have been investigated, undergo the above represented isomerization on melting, and some so readily that they cannot be crystallized by warming with alcohol. Similar results would be expected in the true amidine series.

We first selected for examination benzenylphenyl amidine,



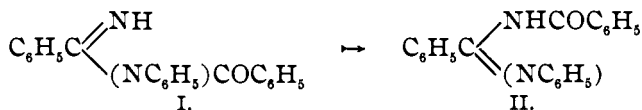
were slowly treated in cold ether with benzoyl chloride. On filtering from the precipitate of amidine hydrochloride which formed, and evaporating the ether spontaneously in a vacuum, a crystalline benzoyl derivative was obtained. This material, when carefully prepared, was homogeneous, and it had the structure represented by formula I. When allowed to stand for some time, or,

¹ *Ber. d. chem. Ges.*, **36**, 1062 (1903).

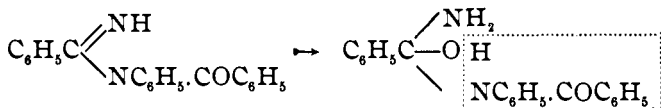
² *Am. Chem. J.*, **27**, 270 (1902).

³ *Ibid.*, **28**, 134 (1902).

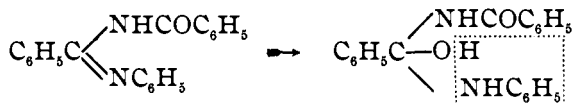
if an attempt was made to crystallize the substance from a hot solution, or if heated, it immediately underwent a molecular rearrangement into the isomeric benzoyl derivative, which is represented by formula II.



The proof of this rearrangement was obtained as follows: When the material obtained directly from the ether solution was treated with dilute hydrochloric acid it underwent hydrolysis and gave practically the calculated quantity of benzanilide and benzamide. No dibenzamide was obtained.

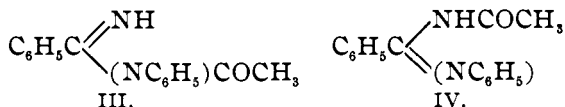


When another portion of the same preparation was warmed in a little alcohol for a few minutes on the steam-bath, and then treated with hydrochloric acid, the result obtained was precisely the reverse from the above; almost the calculated quantity of dibenzamide was obtained, while only a trace of benzanilide resulted. The hydrolysis took place in this case as follows:



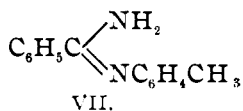
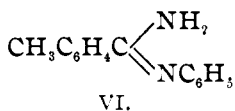
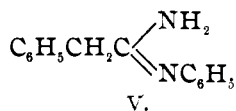
The molecular rearrangement of unsymmetrical benzoylbenzenylphenylamidine therefore took place with great ease and smoothness.

In our next experiment we employed the same benzenylphenylamidine, but used acetyl chloride instead of benzoyl chloride. In this case the product consisted of a mixture of the two following acetyl derivatives, corresponding to the above labile and stable benzoyl compounds.



The structure of these products was determined by hydrolysis as before with hydrochloric acid. The remarkable fact was then discovered that the unsymmetrical acyl derivative III was a perfectly stable substance. It showed no tendency to rearrange even at a temperature of 150°-160°. This flagrant breach of analogy, as Lachman¹ states in other cases, certainly calls for protest from the systematists.

We next examined the behavior of the three following isomeric amidines with benzoyl chloride: Phenylacetphenylamidine (V), *p*-tolenylphenylamidine (VI), and benzenylorthotolylamidine (VII).



Phenylacetphenylamidine (V) gave a mixture. This contained an unsymmetrical benzoyl derivative, which showed no tendency to undergo a molecular rearrangement. It could be repeatedly crystallized from alcohol and it could be heated above its melting-point without alteration.

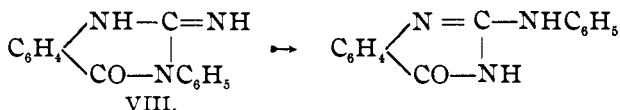
Paratolenylphenylamidine gave a mixture of the two isomeric benzoyl derivatives. That the unsymmetrical acyl derivative, contained in this mixture, readily undergoes a molecular rearrangement was shown by treating the product with dilute hydrochloric acid. Before heating, benzanilide was obtained; when the product was simply warmed on the steam-bath and then treated in the same manner with hydrochloric acid, no benzanilide resulted.

Benzenylorthotolylamidine gave the stable symmetrical amidine directly; the formation of an unsymmetrical derivative was not observed. These results show that the point of attack of acyl chlorides on the amidines differs in different cases and that both acyl derivatives may be formed together without involving a metastatic change. No conclusions as to whether a new unsymmetrical acyl amidine will or will not undergo a molecular rearrangement can be drawn from these experiments and no generalization can be made with the data at hand. The structure of the acyl amidines obtained gives no clue to the tautomeric form of the amidines beyond the probability that, in the cases where molecular rearrangements do take place,

¹ This Journal, 23, 907 (1901).

the structure of the amidine corresponds to that of the stable form of the acyl derivative. The results also emphasize how unsafe it is to predict from analogy. They suggest that perhaps similar results may be observed in other series, the closely analogous imido acid anhydrides, for example.

In the course of the work, we found that, if pyridine was present, on treating an amidine with an acylchloride that diacyl derivatives resulted. We also examined the behavior of a cycloacylphenylguanidine on heating, *viz.*, 2-amino-3-phenyl-4-ketodihydroquinazoline (VIII). From its similarity in structure to benzoylbenzenylamidine and to the labile phenylpseudothiohydantoin, which readily undergoes a metastatic change at 100°, a molecular rearrangement might be expected to take place in this case as follows:



The material, however, proved to be quite stable and it sublimed unaltered at a high temperature.

EXPERIMENTAL PART.

Unsymmetrical Benzoylbenzylphenylamidine was prepared by slowly treating two molecular proportions of benzenylphenylamidine in ice-cold, dry ether with benzoyl chloride. The ether solution was then filtered and the filtrate evaporated in a vacuum. The crystalline mass thus produced, after washing with a little cold alcohol, melted at about 95°-97°, when carefully prepared. In a number of preparations it melted somewhat higher but then it was found to contain more or less of the isomeric symmetrical derivative. A nitrogen determination gave 9.8 per cent. nitrogen. Calculated for C₁₂H₁₆ON₂, 9.3 per cent. When an attempt was made to purify the material by crystallizing from alcohol, it underwent a molecular rearrangement into symmetrical benzoylbenzenylphenylamidine (melting-point 143°), which has already been described in a paper from this laboratory.¹

Action of Hydrochloric Acid.—The material melting at 95°-97° (0.95 gram) was treated with 2 cc. of alcohol and 2 cc. of 22 per cent. hydrochloric acid. The amidine dissolved and then a mass of crystals separated; the whole was warmed to boiling, cooled

¹ *Am. Chem. J.*, 20, 573 (1898).

and then treated with 9 cc. of 15 per cent. sodium hydroxide solution. The insoluble material was washed with 12 cc. of water; it melted at 156° - 159° and it weighed 0.60 gram. This proved to be benz-anilide, the calculated quantity of benzanilide being 0.62 gram. On acidifying the alkaline solution with acetic acid no precipitate was formed. This shows the absence of dibenzamide and of the symmetrical benzoyl derivative in the original material. On shaking the solution with ether, benzamide was extracted.

Behavior on Heating.—Another portion of the benzoyl derivative melting at 95° - 97° (0.95 gram) was warmed on the water-bath in 10 cc. of alcohol for a half hour. The alcohol was then evaporated and the varnish obtained was treated with 2 cc. of hydrochloric acid as above, except that no alcohol was used. On gently warming, the varnish solidified to a mass of colorless needles. When washed with water and dried, this weighed 0.62 gram. This all dissolved in 5 cc. of 15 per cent. alkali diluted with 5 cc. of water, except 0.03 gram of material, and was precipitated by acetic acid. It melted at 145° - 147° and had all the properties of dibenzamide, the yield being about 87 per cent. of the calculated. These results prove conclusively that a rearrangement of the unsymmetrical benzoyl derivative took place on heating.

Unsymmetrical Acetylbenzylphenylamidine.—The product, in this case, on evaporating the ether, formed a varnish which finally solidified. It then melted at about 114° and when mixed with acetanilide the melting-point was lowered to 90° - 95° . It crystallized from alcohol in the form of colorless prisms and then melted at 128° - 129° ; when this was mixed with benzamide the melting-point was lowered to 110° . A nitrogen determination gave 11.41 per cent. nitrogen. Calculated for $C_{15}H_{14}ON_2$, 11.76 per cent. The alcoholic mother-liquors from the above were allowed to stand at ordinary temperature, whereupon prisms of the symmetrical acetylbenzylphenylamidine melting at 138° - 139° were obtained. This was described in a previous article.¹

Action of Hydrochloric Acid.—The above acetyl derivative melting at 128° - 129° was warmed in alcohol with hydrochloric acid, the alcohol was evaporated, and the residue on crystallizing from water gave plates of acetanilide melting at 112° - 113° .

¹ *Am. Chem. J.*, **20**, 574 (1898).

Behavior on Heating.—The acetyl derivative, which was proved to have an unsymmetrical structure by the above experiment, was heated at various temperatures and finally for two hours at 150° - 160° . A slight decomposition took place, but on crystallizing from benzene unaltered material was obtained. When mixed with the symmetrical derivative the melting-point was lowered to 108° - 115° . There was no evidence of a rearrangement having taken place. Owing to the difficulty with which the following amidines dissolve in ether, chloroform was tried as a solvent in some of the experiments. The results were not satisfactory, as decomposition products were formed which interfered with the isolation of the acyl amidines. The best results were obtained when the amidines were simply suspended in dry ether and allowed to stand for some time with the required amount of benzoyl chloride.

Benzoylphenylacetamide, $C_6H_5CONHCOCH_2C_6H_5$.—This was formed along with benzanilide and other products when phenylacetphenylamidine was treated with benzoyl chloride in chloroform. The hydrochloric acid salt of the amidine did not separate in this case but was removed in the subsequent treatment with water. The product was a semi-solid mass which, when dissolved in benzene, gave benzanilide and then colorless prisms which, after several recrystallizations, melted at 129° - 130° . A nitrogen determination agreed with the calculated for benzoylphenylacetamide. Calculated for $C_{15}H_{13}O_2N$, 5.8 per cent. Found, 6.1 per cent. The material was soluble in cold alkali.

Unsymmetrical Benzoylphenylacetphenylamidine.—Ten grams of phenylacetphenylamidine were suspended in 100 cc. of dry ether, and after 3.3 grams of benzoyl chloride had been added the mixture was allowed to stand four hours. The solid material then removed by filtration was found to dissolve completely in water and was therefore the hydrochloric acid salt of the amidine. After the ether solution was evaporated, a gum remained which did not crystallize on standing. When dissolved in alcohol, it gave colorless plates which, after three recrystallizations from alcohol, melted at 110° - 111° . The liquid was slightly cloudy up to 118° . A nitrogen determination gave results agreeing with the calculated for a monobenzoylphenylacetphenylamidine. Calculated for $C_{21}H_{18}ON_2$, 8.9 per cent. Found, 8.6 per cent.

Action of Hydrochloric Acid.—One-half a gram of the material melting at 110° - 111° was treated with hydrochloric acid, as in the previous cases, whereupon the leaf-like crystals of benzanilide were obtained, melting at 157° - 158° . When this benzoyl derivative was heated above its melting-point (140°) and then crystallized from alcohol, the melting-point rose to 122° - 123° , but, on treating this material with hydrochloric acid, little or nobenzoylphenylacetamide was obtained.

Dibenzoylphenylacetphenylamidine was prepared by mixing in chloroform, 4.4 grams of the amidine, 1.6 grams of pyridine and 2.9 grams of benzoyl chloride, the latter diluted with ether. The precipitate which formed consisted of the hydrochloride of the amidine. The chloroform contained material which, on crystallizing from alcohol, formed colorless prisms and melted at 175° . A nitrogen determination gave 7.2 per cent. nitrogen. Calculated 6.7 per cent. When treated with hydrochloric acid, benzanilide, phenylacetamide and benzoic acid were obtained.

Symmetrical Benzoylparatolenylphenylamidine.—Paratolenylphenylamidine (6.1 grams) suspended in 100 cc. of dry ether was treated with 2 grams of benzoyl chloride in 25 cc. of ether. The mixture was allowed to stand for three hours. On filtering and evaporating the ether, a gummy mass was obtained which, on crystallizing from alcohol, gave clusters of colorless prisms melting at 126° . A nitrogen determination showed that this substance was a monobenzoylparatolenylphenylamidine. Calculated for $C_{21}H_{18}ON_2$, 8.91 per cent. Found, 8.82 per cent.

Action of Hydrochloric Acid.—One gram of the material was suspended in alcohol and warmed with a few drops of hydrochloric acid. On standing, colorless needles separated which, on crystallizing from alcohol melted sharply at 112° - 113° . A nitrogen determination indicated that this substance was *paratoluylbenzamide*, $CH_3C_6H_4CONHCOC_6H_5$. Calculated for $C_{13}H_{13}O_2N$, 5.85 per cent. Found, 6.34 per cent. That this was the diacyl amide was further shown by the fact that the material dissolved in alkali and was decomposed into paratoluic amide melting at 151° - 157° . The unsymmetrical benzoyl derivative in this case was not isolated in a state of purity. That it was present in the gummy mass described above was shown by the fact that benzanilide was obtained when the product was treated with dilute hydrochloric

acid. A portion of the crude reaction product was warmed on the steam-bath and then treated with hydrochloric acid, whereupon no benzanilide was obtained.

Dibenzoylbenzenylorthotolylamidine.—Ten grams of benzenyl-orthotolylamidine were suspended in 100 cc. of dry ether and treated with 3.3 grams of benzoyl chloride in 20 cc. of ether. The mixture was then allowed to stand over night. The amidine hydrochloride which separated was mixed with some material which did not dissolve when the mixture was treated with water. When this material was crystallized from alcohol, colorless, beautiful, diamond-shaped plates were obtained, melting sharply at 167°. A nitrogen determination showed that this material was a dibenzoyl derivative: Calculated for $C_{28}H_{22}O_2N_2$, 6.7 per cent. Found, 7.0 per cent. When this substance was treated with dilute hydrochloric acid in alcohol, crystals of benzorthotoluide separated melting at 142°.

Symmetrical Benzoylbenzenylorthotolylamidine.—On evaporating the ether solution from the above dibenzoyl derivative, a varnish was obtained. From this, on crystallizing from alcohol, colorless prisms were obtained melting at 111°-113°. A nitrogen determination gave 8.9 per cent. Calculated for $C_{21}H_{18}ON_2$, 8.9 per cent.

Action of Hydrochloric Acid.—A gram of the substance was treated with dilute hydrochloric acid (2 cc.) and 2 cc. of alcohol. From this solution long, colorless needles of dibenzamide separated, melting at 148°. When these needles were mixed with dibenzamide the melting-point was not lowered.

Orthophenylguanidinebenzoic Acid,

$C_6H_5 \begin{cases} NH.C(NH)-NHC_6H_5 \\ COOH \end{cases}$.—In the course of some experi-

ments with pseudothioureas we heated orthoaminobenzoic acid with phenylpseudomethylthiourea and obtained a product which crystallized from alcohol in colorless prisms, melting at 248°. This material was not dissolved at first by sodium hydroxide or hydrochloric acid, but on standing in these solvents it underwent a change, being converted into a substance, crystallizing in hair-like needles from alcohol, melting at 256°. This latter material was readily soluble in alkali, and a nitrogen determination gave

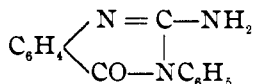
results agreeing with the calculated for 2-anilino-4-ketodihydroquinazoline, $C_6H_4 \left\langle \begin{array}{l} N = C.NHC_6H_5 \\ | \\ CO-NH \end{array} \right.$ Found, 17.67 per cent.

Calculated for $C_{14}H_{11}ON_3$, 17.72 per cent.

At this point we were unable to decide whether the above product first obtained, melting at 248° , underwent a direct condensation into the above quinazoline derivative soluble in alkali, or whether it first condensed to give the isomeric 2-amino-3-phenyl-4-ketodihydroquinazoline, which would be insoluble in alkali, this then undergoing a molecular rearrangement into the above quinazoline, melting at 256° . To decide this question we prepared 2-amino-3-phenyl-4-ketodihydroquinazoline from 2-Chlor-3-phenyl-4-ketodihydroquinazoline.—This chloride was prepared from 2-thio-3-phenyl-4-ketotetrahydroquinazoline by following the directions of McCoy.¹

McCoy obtained this chloride, but did not purify the substance. We found that the oil first obtained solidified and could be crystallized from alcohol. It then formed colorless prisms and melted at 132° . It was analyzed with the following results: Calculated for $C_{14}H_9ON_2Cl$, 10.9 per cent. nitrogen. Found, 10.7 and 11.1 per cent.

2-Amino-3-phenyl-4-ketodihydroquinazoline,



The above chloride was heated in a closed tube at 120° - 130° with an excess of alcoholic ammonia. The product crystallized from alcohol in colorless prisms and melted at 237° - 238° . It was insoluble in sodium hydroxide, as was expected, and a nitrogen determination gave: 17.50 per cent. nitrogen. Calculated for $C_{14}H_{11}ON_3$, 17.72 per cent. When this material was boiled with dilute hydrochloric acid, complete solution finally took place and, on cooling, 3-phenyl-2,4-diketotetrahydroquinazoline² separated. When the above cyclocacylguanidine was heated above its melting-point (in a bath at 250°), it simply sublimed unaltered without undergoing any molecular rearrangement.

¹ *Ber. d. chem. Ges.*, **30**, 1691 (1897).

² Busch: *J. prakt. Chem.*, **51**, 265 (1895); Paul: *Ber. d. chem. Ges.*, **27**, 978 (1894).

NEW HAVEN, CONN., May 26, 1903.