

3. 1-Phenyl-2-thiohydantoins from some α -Aminoacids. By Charles A. Brautlecht, *J. Biol. Chem.*, 10, 139-46.
4. The Reduction of Aldehyde Condensation-Products of 1-Phenyl-2-thiohydantoin. By Treat B. Johnson and Charles A. Brautlecht, *THIS JOURNAL*, 33, 1531-38.
5. Synthesis of 3,5-Dichlorotyrosine. By Henry L. Wheeler, Charles Hoffmann and Treat B. Johnson, *J. Biol. Chem.*, 10, 147-57.
6. The Action of Acylthioncarbamates, Acyldithiocarbamates and Acylimidodithiocarbonates on α -Aminoacids. 2-Thiohydantoin. By Henry L. Wheeler, Ben H. Nicolet and Treat B. Johnson, *Am. Chem. J.*, 46, 456-74.
7. The Synthesis of 2-Thiohydantoin. By Treat B. Johnson and Ben H. Nicolet, *THIS JOURNAL*, 33, 1973-78.
8. The Action of Bromine on Tyrosine Hydantoin. By Treat B. Johnson and Charles Hoffmann, *Am. Chem. J.*, 47, 20-7.
9. The Action of Potassium Thiocyanate on Alanine. By Treat B. Johnson, *J. Biol. Chem.*, 11, 97-101.
10. The Action of Potassium Thiocyanate on Pyrrolidonecarboxylic Acid. 2-Thiohydantoin-4-Propionic Acid. By Treat B. Johnson and Herbert H. Guest, *Am. Chem. J.*, 47, 242-51.
11. A New Method of Synthesizing N-Alkyl Derivatives of α -Aminoacids. Methyl Tyrosine. By Treat B. Johnson and Ben H. Nicolet, *Am. Chem. J.*, 47, 459-75.
12. The Synthesis of Thiotyrosine. By Treat B. Johnson and Charles A. Brautlecht, *J. Biol. Chem.*, 12, 175-96.
13. A New Method for the Synthesis of Phenylalanine. By Treat B. Johnson and William B. O'Brien, *J. Biol. Chem.*, 12, 205-13.
14. The Action of Potassium Thiocyanate on Asparagine. By Treat B. Johnson and Herbert H. Guest, *Am. Chem. J.*, 48, 103-11.
15. The Desulfurization of 2-Thiohydantoins. By Treat B. Johnson, George M. Pfau and Willard W. Hodge, *THIS JOURNAL*, 34, 1041-48.
16. The Alkylation of 2-Thio-4-benzalhydantoin. By Treat B. Johnson and Ben H. Nicolet, *THIS JOURNAL*, 34, 1048-54.
17. Synthesis of the Hydantoin of 3-Aminotyrosine. By Treat B. Johnson and Robert Bengis, *THIS JOURNAL*, 34, 1054-61.
18. The Synthesis of 3-Bromotyrosine. By Treat B. Johnson and Robert Bengis, *THIS JOURNAL*, 34, 1061-66.
19. Synthesis of 5-Thiohydantoins. By Treat B. Johnson and Lewis H. Chernoff, *THIS JOURNAL*, 34, 1208-13.
20. The Action of Thiocyanates on α -Aminoacids. By Treat B. Johnson, *Am. Chem. J.*, 49, 68-9.
21. The Action of Ammonium and Potassium Thiocyanates on α -Aminoacids. By Treat B. Johnson and Ben H. Nicolet, *Am. Chem. J.*, 49, 197-204.
22. The History of 2-Thiohydantoin. By Treat B. Johnson, *THIS JOURNAL*, 35, 780-84.

NEW HAVEN, CONN.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]
**HYDANTOINS: THE ACTION OF AMMONIUM THIOCYANATE ON
 LACTONE-ANHYDRIDES OF ACYL-AMINOACIDS.**

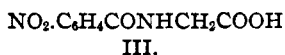
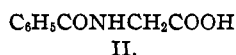
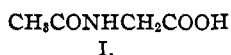
[TWENTY-FOURTH PAPER.]

BY TREAT B. JOHNSON AND WALTER M. SCOTT.

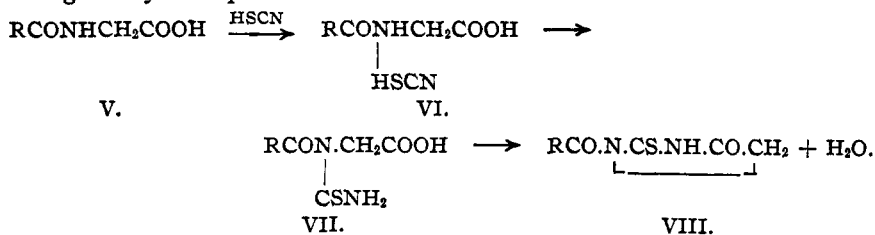
Received June 28, 1913.

Every acyl derivative of a monobasic α -amino acid, RCONHCHR'COOH , which has been examined in this laboratory, reacts smoothly with thio-

cyanic acid, in acetic anhydride solution, forming an acylthiohydantoin. The only α -amino acids which have failed to react in this manner are the dibasic amino acids—glutaminic and aspartic. If, however, the influence of one of the carboxyl groups in these compounds is destroyed by conversion of the glutaminic and aspartic acids into pyrrolidonecarboxylic acid and asparagine, respectively, then the above reaction can be applied successfully. The results, which we have obtained in our investigations, show that this unique reaction is not dependent upon the positive or negative character of the acyl group present in the acylamino acid. For example, the strongly negative *m*-nitrohippuric and phenylsulfonaminoacetic acids, III and IV, combine just as readily with thiocyanic acid as



either aceturic, I, or hippuric acids, II. The mechanism of these reactions appeared to be perfectly analogous to that involved in the transformation of amines into thioureas by interaction with thiocyanic acid, and the following provisional interpretation was given in our seventh hydantoin paper.¹ The acylamino acid first interacts with thiocyanic acid, in the anhydride solution, forming an addition product or salt, VI. The latter then undergoes a normal rhodanide rearrangement, on heating, giving a thiohydantoic acid derivative, VII, which is finally transformed into the thiohydantoin compound, VIII, by action of the acetic anhydride. These changes may be represented as follows:

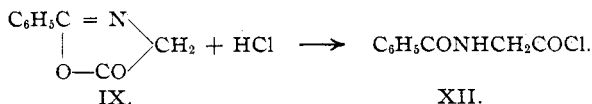
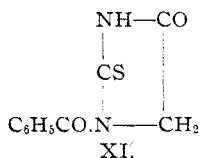
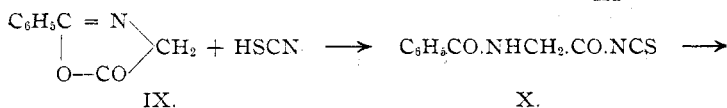
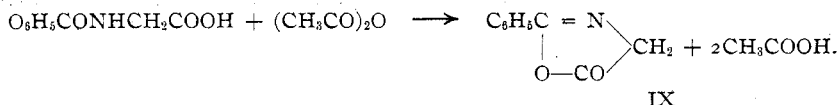


Although a thiohydantoic acid, as represented by formula VII, would be expected to condense to a thiohydantoin, if once formed, it is to be noted, however, that no experimental evidence has yet been produced, which indicates the formation of such intermediate compounds. In fact, the results, which were discussed in our last paper,² and those of new researches now in progress, suggested to the writer that our original interpretation was not the correct explanation of the action of thiocyanic acid on these acylamino acids. Our new observations now lead us to the

¹ Johnson and Nicolet, *THIS JOURNAL*, **33**, 1973.

² Johnson and Scott, *Ibid.*, **35**, 1130.

conclusion that a salt formation is not an intermediate phase, and, furthermore, that such compounds are not formed even under conditions where they would be expected to be produced. The results already published and the new data, which are now presented in a preliminary form, lead to the important conclusion that the acylamino acids do not take part directly in these transformations, but are first converted into lactone-anhydrides.¹ The latter, which are known to be formed under the conditions of our experiments, are the intermediate compounds which functionate in these reactions. The mechanism of the transformations may, therefore, be explained as follows: The acylamino acid is first transformed by the action of the acetic anhydride into its corresponding lactone-anhydride, IX. This anhydride, IX, then interacts with the thiocyanic acid, which is liberated from its ammonium salt by action of the acetic anhydride, forming the corresponding acylisothiocyanate, X. The latter, being unstable, then undergoes a molecular condensation and is converted into the isomeric acylthiohydantoin, XI. This action of thiocyanic acid is perfectly analogous to that of hydrochloric acid, which Mohr² has shown to combine quantitatively with lactone anhydrides, IX, forming the corresponding acid chlorides, XII. Isothiocyanates represented by formula X have not been prepared. The different phases of the reaction with hippuric acid may, therefore, be represented as follows:



This new interpretation of the mechanism of these reactions is supported by the following facts:

¹ Mohr and Kohler, *J. prakt. Chem.*, **80**, 521; Mohr and Gies, *Ibid.*, **81**, 49; Mohr, *Ibid.*, **81**, 473; **82**, 60, 322. Mohr and Straschein, *Ber.*, **42**, 2521; Mohr and Kohler, *Ibid.*, **40**, 997.

² *Loc. cit.*

1. Acetic anhydride is the only solvent in which we have been able to effect the transformation. We intend to investigate the action of other acid anhydrides.

2. The lactone-anhydride formation is a normal change when acyl-amino acids are heated with acetic anhydride. Several compounds of this type have been isolated and their properties carefully investigated by Mohr¹ and his co-workers.

3. Acylthiohydantoin is not formed when acylamino acids are warmed in glacial acetic acid with ammonium thiocyanate. This observation is of especial interest, as it shows that a salt formation is not an intermediate phase. Hippuric acid and benzoylalanine² were both recovered unaltered when subjected to this treatment. On the other hand, if either of these two acids are first converted into their corresponding lactone anhydrides, and the latter are warmed with ammonium thiocyanate in glacial acetic acid, the corresponding acylthiohydantoin is formed. The lactone-anhydride of benzoylalanine has been described by Mohr and Straschein.¹ The corresponding lactone of hippuric acid has not been isolated in a state of purity.³

3. The formation of thiohydantoin is completely inhibited by substitution of the hydrogen atoms of either the —NH— or the —COOH groups of the acyl-amino acids. In other words, any change in the constitution of the acylamino acid, which prevents a lactone formation, also inhibits the formation of thiohydantoin. For example, acetylphenylglycocoll, $\text{CH}_3\text{CO}(\text{C}_6\text{H}_5)\text{N}.\text{CH}_2\text{COOH}$, and ethyl hippurate,



underwent no change when heated in acetic anhydride solution with an excess of ammonium thiocyanate.

4. There was no evidence of the formation of benzoylthiourea, $\text{C}_6\text{H}_5\text{CONHCSNH}_2$,⁴ when benzamide was heated with ammonium thiocyanate in acetic anhydride or acetic acid. In other words, the amide grouping is not sufficiently basic to combine with thiocyanic acid to form a salt in presence of the anhydride.

5. Substitution of a hydrogen in the methylene group —NHCHRCO— does not prevent the formation of thiohydantoin.

Having shown that lactone-anhydrides of acylamino acids react with thiocyanic acid to form acylthiohydantoin, it at once became of interest to investigate the action of thiocyanic acid, in acetic anhydride solution, on an anhydride of an unsaturated α -acylamino acid. We selected for this work Erlenmeyer's lactimide of β -phenyl- α -benzoylaminoacrylic

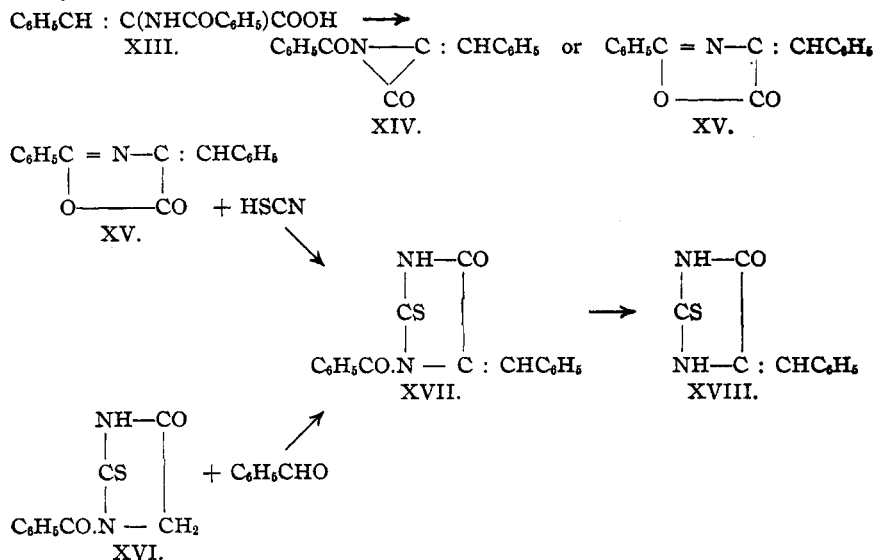
¹ *Loc. cit.*

² Fischer, *Ber.*, **32**, 2454.

³ Mohr, *J. prakt. Chem.*, **82**, 60.

⁴ Miquel, *Ann. chim. phys.*, [5] **11**, 313.

acid, XV.¹ Theoretically this lactone might be expected to interact with thiocyanic acid with formation of the same hydantoin which is obtained by condensation of 2-thio-3-benzoylhydantoin (XVI) with benzaldehyde, namely, 2-thio-3-benzoyl-4-benzalhydantoin, XVII. We found, however, that this compound was not changed by warming with thiocyanic acid and acetic anhydride. There was no evidence of the formation of the thiohydantoin,² XVII. Furthermore, the β -phenyl- α -benzoylamino-acrylic acid, XIII, failed to interact with thiocyanic acid, but was converted quantitatively into the lactimide, XV, by action of the acetic anhydride. Whether these results are to be explained by the fact that these unsaturated lactone-anhydrides possess a different constitution (lactone, XIV) than that assigned to the anhydrides formed from saturated α -acylamino acids must be determined by further work.



This investigation of the action of thiocyanic acid on lactone-anhydrides of acylamino acids will be continued. We are also investigating the action of thiocyanic on polypeptides and related compounds.

Experimental Part.

The Action of Ammonium Thiocyanate on Hippuric Acid.

Experiment 1.—Two grams of hippuric acid and 1 gram of dry, finely pulverized ammonium thiocyanate were suspended in 10 cc. of glacial acetic acid and the acid heated on the steam bath until complete solution was effected (2 hours). The acid solution was then cooled and diluted

¹ *Ann.*, 275, 3.

² We have recently obtained evidence that this hydantoin may be formed by application of this reaction (T. B. Johnson).

with cold water. After standing for one hour the hippuric acid had deposited in beautiful needles and melted at 187–188°. More of the same substance was obtained on concentrating the solution. We obtained no evidence of the formation of 2-thio-3-benzoylhydantoin or 2-thiohydantoin.

Experiment 2.—Two grams of finely pulverized hippuric acid were dissolved in 10 cc. of freshly distilled acetic anhydride and the solution heated on the steam bath (protected from moisture) for exactly 30 minutes. The excess of acetic anhydride was then removed by heating at 100° under diminished pressure. A thick syrup was obtained, which showed no signs of crystallizing on cooling. No attempt was made to purify this,¹ but it was immediately dissolved, together with 1 gram of dry ammonium thiocyanate, in 10 cc. of glacial acetic acid, and the resulting solution then heated on the steam bath for 30 minutes. An orange-colored solution was obtained. This was then diluted with cold water and finally cooled. No crystallin material separated. The solution was then acidified with hydrochloric acid and evaporated to dryness at 100°, and the residue purified by recrystallization from hot water. Two definite products were separated in a pure condition, namely, 2-thiohydantoin and unaltered hippuric acid. The hydantoin melted at 227–228° with decomposition. When mixed with pure thiohydantoin from another preparation, this melting point was not lowered. The hippuric acid separated in slender prisms and melted at 188°. The yield of thiohydantoin was small.

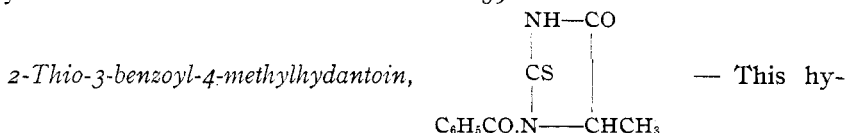
Experiment 3.—Two grams of hippuric acid were heated with 10 cc. of acetic anhydride as described in Experiment 2. The excess of anhydride was then expelled by heating at 100° under diminished pressure. We obtained a thick syrup as in Experiment 2. This was then dissolved, together with one gram of ammonium thiocyanate, in 10 cc. of acetic anhydride and the mixture heated for 20 minutes. After cooling, the anhydride solution was then poured into water, when 2-thio-3-benzoylhydantoin separated immediately in a crystallin condition. It was purified by crystallization from alcohol and melted at 166°. The yield was good.

Experiment 4.—Two grams of hippuric acid were dissolved in 10 cc. of acetic anhydride and the solution heated on the steam bath for one hour. It had assumed a light red color. One gram of dry, finely pulverized ammonium thiocyanate was then added and the mixture heated again, at 100°, for 20 minutes. It was then cooled and diluted with water, when 2-thio-3-benzoylhydantoin separated in a crystallin condition. It was purified by crystallization from 95% alcohol and melted at 166°.

The Action of Ammonium Thiocyanate on Ethyl Hippurate.—Two grams of ethyl hippurate and 0.9 gram of dry ammonium thiocyanate were dissolved in a mixture of 9 cc. of acetic anhydride and 1 cc. of glacial acetic

¹ Mohr, *loc. cit.*

acid. The solution was then heated on the steam bath for 25 minutes and finally cooled and poured into cold water. An oil separated at once and finally completely solidified. This substance gave no test for sulfur and was identified as unaltered ethyl hippurate. It was purified by recrystallization from water and melted at 59-60°.



dantoin is formed when benzoylalanine is warmed in acetic anhydride solution with ammonium thiocyanate and has been described in our previous paper.¹ It melts at 158°.

*The Action of Ammonium Thiocyanate on the Lactone of Benzoylalanine,*²
 $\text{C}_6\text{H}_5\text{C} = \text{N-CHCH}_3$

$\begin{array}{c} | \\ \text{O} \text{—} \text{CO} \end{array}$
. — Seven and four-tenths grams of benzoylalanine were dissolved in 35 cc. of acetic anhydride and the solution heated for 20 minutes in a boiling water bath. The excess of acetic anhydride was then removed by heating at 100° under diminished pressure. The lactone was obtained as a transparent oil and the yield was practically quantitative. This lactone was dissolved in a mixture of 25 cc. of acetic anhydride and 2 cc. of acetic acid, 3.2 grams of dry ammonium thiocyanate added to the solution and the mixture finally heated on the steam bath for 20 minutes. After cooling and pouring into cold water, we obtained 8.6 grams of 2-thio-3-benzoyl-4-methylhydantoin. It melted at 157° after the first crystallization from 95% alcohol. The same hydantoin is also formed when the lactone is warmed (in glacial acetic acid) with ammonium thiocyanate. The yield, however, is smaller.

Action of Ammonium Thiocyanate on Benzamide.—The acid amide was recovered unaltered after heating with the thiocyanate, in acetic anhydride solution, for 30 minutes. It separated from water in plates melting at 128°. There was no evidence of the formation of any benzoylthiourea, $\text{C}_6\text{H}_5\text{CONHCSNH}_2$.

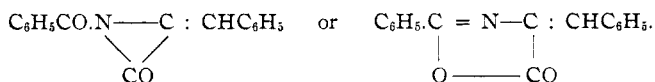
Action of Ammonium Thiocyanate on Phenylglycocoll, $\text{C}_6\text{H}_5\text{NHCH}_2\text{COOH}$. —Two grams of the amino acid and 1.5 grams of the thiocyanate were digested with a mixture of 9 cc. of acetic anhydride and 1 cc. of glacial acetic acid for 30 minutes. The mixture was then poured into water, when an oil separated. A little hydrochloric acid was then added and the mixture evaporated to dryness. We recovered the phenylglycocoll unaltered. This melted at 126-127° and gave no test for sulfur.

*Experiments with Erlenmeyer's Lactimide,*³

¹ Johnson and Scott, *loc. cit.*

² Mohr and Straschein, *loc. cit.*

³ *Ann.*, 275, 8.



—This lactimide was prepared according to Erlenmeyer's directions by condensing benzaldehyde with hippuric acid. It melted at 164–165°.

Experiment 1.—The lactimide was heated with ammonium thiocyanate in acetic anhydride solution as described in the previous experiments. The lactimide dissolved completely on warming, but there was no evidence of any reaction. On cooling, the lactimide separated and was purified by crystallization from benzene. It deposited in yellow crystals and melted at 165°.

Experiment 2.—The lactimide was converted into β -phenyl- α -benzoyl-aminoacrylic acid, XIII, by hydrolysis with



alkali and the latter, XIII, then warmed with acetic anhydride and ammonium thiocyanate. After heating for 30 minutes the solution was then cooled when the lactimide immediately deposited and melted at 165°. There was no evidence of the formation of a thiohydantoin compound.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO.]

THE THERMAL DECOMPOSITION OF SYMMETRICAL DIARYL-HYDRAZINES—A REACTION OF THE FIRST ORDER.¹

BY GEO. O. CURME, JR.

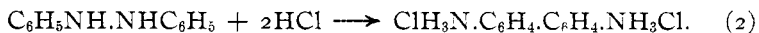
Received July 3, 1913.

Many hydrazines, as is well known, show a tendency to undergo, with great facility, a variety of molecular changes, involving a redistribution of the atoms composing their molecules. The two chief types of such reactions are the following:

(1) Many hydrazines, when heated, decompose into compounds of a lower and a higher state of oxidation. Thus hydrazobenzene decomposes into aniline and azobenzene:



(2) Symmetrical arylhydrazines and their derivatives undergo the benzidine and related rearrangements, under the influence of acids. Thus hydrazobenzene changes into benzidine and diphenylene:²



¹ The work presented in this article formed the basis of a dissertation submitted to the University of Chicago in part fulfilment of the requirements for the degree of Doctor of Philosophy.

² Other products are theoretically possible, but have never been described as occurring as a result of this rearrangement.