TABULAR SUMMARY (*continued*).

Mineral.	Literature.
Brucite,	(59).
Spinel,	(15), (27), (53), (77).
Magnetite,	(42), (73).
Calcite,	(32), (49), (75).
Magnesite,	(?80).
Dawsonite,	(?56).

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WASHINGTON. D. C.
July 21. 1913.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

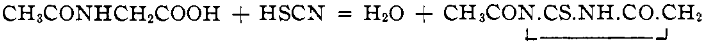
HYDANTOINS: THE SYNTHESIS OF 2-THIOHYDANTOINS FROM ACYL DERIVATIVES OF α-AMINOACIDS.

[TWENTY-THIRD PAPER.]

BY TREAT B. JOHNSON AND WALTER M. SCOTT.

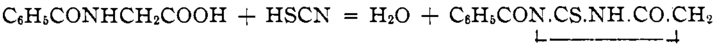
Received June 26, 1913

It has been shown by the writer and his co-workers[1] that an acyl derivative of an α-amino acid can enter into an interesting reaction with ammonium thiocyanate in acetic anhydride solution. These reagents interact in an unique manner, in this anhydrous solvent, with formation of an acylthiolhydantoin. For example, aceturic, I, and hippuric acids, III, combine with the thiocyanate forming 2-thio-3-acetylhydantoin, II, and 2-thio-3-benzoylhydantoin, IV, respectively.[2] This reaction has also been applied successfully with acetyalanine,[3] V, and with the cyclic acylamino acid, namely, pyrrolidonecarboxylic acid,[4] VII. The acyl



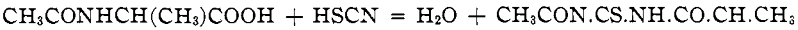
$$CH_3CONHCH_2COOH + HSCN = H_2O + CH_3CON.CS.NH.CO.CH_2$$

I. II.



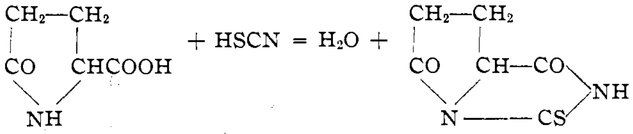
$$C_6H_5CONHCH_2COOH + HSCN = H_2O + C_6H_5CON.CS.NH.CO.CH_2$$

III. IV.



$$CH_3CONHCH(CH_3)COOH + HSCN = H_2O + CH_3CON.CS.NH.CO.CH.CH_3$$

V VI.



VII. VIII.

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[1] See Addenda to this paper.

[2] Johnson and Nicolet, THIS JOURNAL, **33**, 1975.

[3] Johnson, *J. Biol. Chem.*, **11**, 98.

[4] Johnson and Guest, *Am. Chem. J.*, **47**, 242.

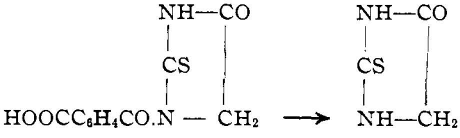
group (benzoyl, etc.) of the acylamino acid is not replaced by acetyl, by action of the acetic anhydride, but the hydantoin formed always contains, in the 3-position of the ring, the same acyl group that was present in the original acylamino acid. When a simple amino acid interacts with ammonium thiocyanate in acetic anhydride, it first undergoes acetylation and the resulting acyl derivative then reacts normally as aceturic acid, giving the corresponding 3-acetylthiohydantoin.

The primary object of the work described in this paper was to determin whether this reaction is of general application with other acyl derivatives of α-amino acids, and also to decide whether a β-amino acid would undergo an analogous change with formation of a pyrimidine derivative. It was of especial interest to determin, for reasons which will be discussed in our next paper, whether the reactivity of acylamino acids would be influenced by the positive and negative character of the acyl groups present.

We have now applied the reaction with seven more acylamino acids containing different acyl groups, and in every case they reacted normally, forming thiohydantoin compounds. Apparently the nature of the acyl group (positive and negative character) is not a controlling factor. The acids which we investigated were the following:

1. Aceticphthalamic acid,[1] $HOOC.C_6H_4CONHCH_2COOH$.
2. *p*-Methoxyhippuric acid,[2] $CH_3O.C_6H_4CONHCH_2COOH$.
3. Carbethoxyaminoacetic acid,[3] $C_2H_5OOC.NH.CH_2.COOH$.
4. *m*-Nitrohippuric acid,[4] $NO_2.C_6H_4CO.NH.CH_2.COOH$.
5. Acetyldibromphenylalanine,[5] $Br_2.C_6H_3.CH_2CH(NH.COCH_3)COOH$.
6. Benzoylalanine,[6] $C_6H_5CONH.CH(CH_3)COOH$.
7. Phenylsulfonaminoacetic acid,[7] $C_6H_5SO_2NHCH_2COOH$.

The acylhydantoin was isolated in every case, except in the experiment with aceticphthalamic acid (1). In this case the corresponding acylthiohydantoin, IX, was formed but was not isolated because of its instability.



IX. X.

It underwent hydrolysis when heated with acids giving phthalic acid and 2-thiohydantoin, X. The fact that 2-thiohydantoin was formed is proof

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[1] Gabriel and Kroseberg, *Ber.*, **22**, 426.

[2] Franzen, *Ibid.*, **42**, 2465.

[3] Fischer and Otto, *Ibid.*, **36**, 2107.

[4] Schwauert, *Ann.*, **112**, 69; Conrad, *J. prakt. Chem.*, [2] **15**, 254.

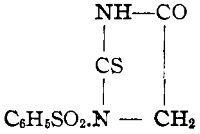
[5] Wheeler and Clapp, *Am. Chem. J.*, 40, 337.

[6] Fischer, *Ber.*, **32**, 2454.

[7] Ihrfelt, *Ber.*, **22**, Ref. 692; Knoevenagel and Lebach, *Ibid.*, **37**, 4094.

that the aceticphthalamic acid did not undergo hydrolysis before interaction with the ammonium thiocyanate. Part of the aceticphthalamic acid was transformed into phthalimidoacetic acid by action of the anhydride.

Particularly interesting is the fact that phenylsulfonaminoacetic acid (7) reacts normally to form the hydantoin, XI. In fact, the reaction was smooth and the yield of the hydantoin was good. Dr. Joseph A. Ambler has also applied the reaction successfully with another sulfonamino acid.[1] This observation, that the strongly acidic grouping $—SO_2.NH.CH_2.COOH$ can enter into reaction with a thiocyanate to form a thiohydantoin is very remarkable, and suggests that the transformation does not involve the addition of thiocyanic acid to the —NH— radicle and subsequently a rearrangement to a thiohydantoic acid, XII. Our next paper will deal with the mechanism of these interesting reactions.



XI.

$$RSO_2.\underset{\displaystyle HSCN}{N}.HCH_2.COOH \longrightarrow RSO_2.\underset{\displaystyle CS.NH_2}{N}.CH_2.COOH$$

XII.

In order to determin whether a β-amino acid would react in a manner similar to that of α-amino acids, we investigated the action of ammonium thiocyanate on anthranilic acid in acetic anhydride solution. We found that this acid does not interact with the thiocyanate to give a pyrimidine compound. The amino acid simply underwent acetylation, forming acetylanthranilic acid, $C_6H_4(NHC_2H_3O)CO_2H$, melting at 184°.

Experimental Part.

The Action of Ammonium Thiocyanate on Aceticphthalamic Acid, $HOOC.C_6H_4CONHCH_2COOH$.—The phthalamic acid was prepared by saponification of ethyl phthalylaminoacetate with potassium hydroxide.[2] The phthalamic acid and one and one-quarter molecular proportions of the thiocyanate were dissolved in about 5-7 parts by weight of acetic anhydride and the solution heated on the steam bath for 20 minutes. An orange colored solution was obtained. After cooling, this was then poured into water, when only a very small amount of crystallin material deposited. The solution was then evaporated to dryness to remove all the acetic acid and the crystallin residue obtained finally purified by fractional crystallization from water. We succeeded in separating, in a pure

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[1] Unpublished work.

[2] Gabriel and Kroseberg, *loc. cit.*

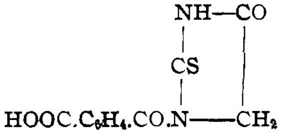
condition, three different compounds, namely, 2-thiohydantoin, phthalylaminoacetic acid and phthalic acid. The thiohydantoin deposited from water in beautiful flat prisms, melting at 225–227° with decomposition. When this was mixed with some pure thiohydantoin the melting point was not affected. The yield was small. Nitrogen determination (Kjeldahl):

Calculated for $C_3H_4ON_2S$: N, 24.14; found: N, 24.3.

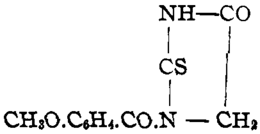
Phthalylaminoacetic acid separated in colorless, slender prisms or needles which melted at 192–193°. The product gave no test for sulfur and dissolved immediately in cold alkali:

Calculated for $C_{10}H_7O_4N$: N, 6.83; found: N, 7.1.

When the aqueous mother liquor was concentrated and cooled, phthalic acid finally separated in the form of plates. We did not succeed in isolating the thiohydantoin derivative of the phthalamic acid, XIII,

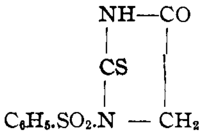


XIII.



2 - Thio - 3 - paramethoxybenzoylhydantoin, —This new hydantoin was prepared by the action of ammonium thiocyanate on *p*-methoxyhippuric acid in acetic anhydride. The hippuric acid was obtained by saponification of its ethyl ester, and the latter synthesized according to Franzen's method.[1] The hydantoin crystallizes from alcohol in beautiful, light yellow prisms, which melt at 166°. The compound is difficultly soluble in water.

Calculated for $C_{11}H_{10}O_3N_2S$: N, 11.12; found: N, 11.18.



2-Thio-3-phenylsulfonylhydantoin, — From phenylsulfonylglycocoll by the action of ammonium thiocyanate in acetic anhydride solution. On pouring the anhydride solution into water the hydantoin separated as an oil, which soon solidified. The compound was purified by crystallization from hot water and separated, on cooling, in colorless needles. The hydantoin begins to decompose at about 190° and then melts to an oil at 210–211°. The yield was good:

Calculated for $C_9H_8O_3N_2S_2$: N, 10.94; found: N, 10.93.

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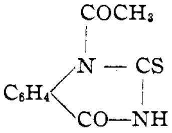
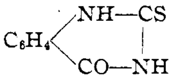
[1] *Loc. cit.*

The Action of Ammonium Thiocyanate on o-Aminobenzoic Acid.—The amino acid and one and one-quarter molecular proportions of the thiocyanate were heated, in the usual manner, with acetic anhydride for 20 minutes and the mixture then poured into cold water. A crystallin substance separated at once and was purified by crystallization from hot water. It separated, on cooling, in the form of plates, which melted at 184°. They did not respond to a test for sulfur and dissolved immediately in alkali. The compound was identified as acetylanthranilic acid, $HOOC.C_6H_4NHCOCH_3$:

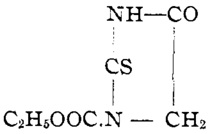
Calculated for $C_9H_9O_3N$: N, 7.82; found: N, 8.0.

We obtained no evidence of the formation of the ketothiotetrahydroquinazoline,[1] XV, or its acetyl derivative, XIV. Rupe prepared the cycle

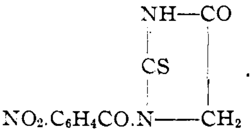

XIV.


XV.

XV by action of potassium thiocyanate on the ethyl ester of anthranilic acid.

2-Thio-3-carbethoxyhydantoin,  — The carbethoxyaminoacetic acid used in this experiment was prepared according to the method of Fischer and Otto.[2] After digesting with ammonium thiocyanate for 20 minutes the anhydride solution was then poured into water as usual. No hydantoin separated and consequently the solution was evaporated to dryness and the residue dissolved in a small volume of warm water. On cooling, this hydantoin separated in plates, which melted at 168°. The substance gave a strong test for sulfur:

Calculated for $C_6H_8O_3N_2S$: N, 14.89; found: N, 14.92.

2-Thio-3-metanitrobenzoylhydantoin,  . — From *m*-nitrohippuric acid and ammonium thiocyanate. The hydantoin separated immediately when the anhydride solution was poured into water and was purified by recrystallization from alcohol. It melted at 198–199° and gave a strong test for sulfur:

Calculated for $C_{10}H_7O_4N_3S$: N, 15.85; found: N, 16.00.

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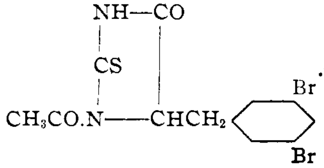
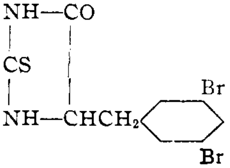
[1] Rupe, *Ber.*, **30**, 1098.

[2] *Loc. cit.*



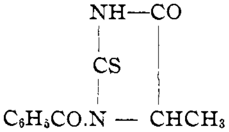
2-Thio-3-acetyl-4-dibrombenzylhydantoin, .—From dibromphenylalanine[1] and ammonium thiocyanate in acetic anhydride solution. The hydantoin separated at once when the anhydride solution was poured into water. The yield was excellent. It was purified for analysis by recrystallization from 95% alcohol and separated, on cooling, in plates which melted at 171°. The substance gave a strong test for sulfur:

Calculated for $C_{12}H_{10}O_2N_2Br_2S$: N. 6.90; found: N. 6.86.



2-Thio-4-dibrombenzylhydantoin, .— A quantitative yield of this hydantoin was obtained by hydrolysis of the above acetyl compound with hydrochloric acid. It was purified for analysis by crystallization from 95% alcohol and separated, on cooling, in colorless needles, which melted at 243°. The sulfur was not removed by the acid treatment:

Calculated for $C_{10}H_8ON_2Br_2S$: N, 7.69; found: N, 7.53.



2-Thio-3-benzoyl-4-methylhydantoin, — From benzoylalanine[2] and ammonium thiocyanate. On pouring the anhydride solution into cold water this hydantoin separated as an oil, which solidified on standing. It was purified by recrystallization from alcohol and melted at 158°. The yield was good:

Calculated for $C_{11}H_{10}O_2N_2S$: N, 11.97; found: N, 11.89.

Addenda.

For the sake of reference, a complete list of the papers on Hydantoins, which have been published from this laboratory, is given below. These papers are arranged in the order in which they appeared.

HYDANTOINS.

1. A Synthesis of Phenylalanine and of Tyrosine. By Henry L. Wheeler and Charles Hoffmann, *Am. Chem. J.*, **45**, 368–83.
2. Aldehyde Condensation—Products of Phenylthiohydantoins. By Henry L. Wheeler and Charles A. Brautlecht, *Am. Chem. J.*, **45**, 446–58.

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[1] Wheeler and Clapp, *loc. cit.*

[2] Fischer, *loc. cit.*

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-Dichlortyrosine. 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, RCONHCHRCOOH, which has been examined in this laboratory, reacts smoothly with thio-