ture of the lower melting substance. The freezing-point method was used.

Molecular weight:

Calculated for $C_{36}H_{34}O$: 484.
Found: 425.

Properties.—Yellow prisms, melting at 226°. Soluble in benzene and toluene; slightly soluble in methyl alcohol, ethyl alcohol, ether, acetone, and glacial acetic acid. The solutions show fluorescence.

Part of the expenses of this research were defrayed by a grant from the C. M. Warren Fund for Research, for which we wish to express our gratitude.

CAMBRIDGE, MASS.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

HYDANTOINS: THE SYNTHESIS OF 2-THIOHYDANTOIN.

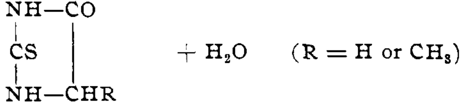
[SEVENTH PAPER.]

BY TREAT B. JOHNSON AND BEN H. NICOLET.

Received November 13, 1911.

Two methods of synthesizing 2-thiohydantoin have recently been described in the literature. Komatsu[1] has prepared this compound by the action of potassium thiocyanate on glycocoll. He states that this amino acid reacts with the thiocyanate, in the presence of acetic anhydride, giving the hitherto unknown thiohydantoic acid, $NH_2CSNHCH_2COOH$, which can be converted into the hydantoin by the action of strong hydrochloric acid. He also examined the behavior of potassium thiocyanate towards alanine and obtained 2-thio-4-methylhydantoin. The general reactions involved in these condensations are represented by him as follows:

$$NH_2.CHR\,.\,COOH + HSCN = NH_2CSNH.CHR\,.\,COOH \longrightarrow$$



$$\begin{array}{l} NH\text{—}CO \\ \mid \qquad\ \mid \\ CS \qquad\ \mid \qquad\qquad + H_2O \qquad (R = H \text{ or } CH_3) \\ \mid \qquad\ \mid \\ NH\text{—}CHR \end{array}$$

The second method of synthesis has recently been described in a publication from this laboratory.[2] We showed, for example, that ethyl acetyl- and benzoyldithiocarbamates, I, react smoothly with glycocoll or its ethyl ester, giving the corresponding acyl derivatives of thiohydantoic acid, II, with evolution of ethyl mercaptan. When these acyl derivatives, II, were digested with hydrochloric acid they were converted smoothly into 2-thiohydantoin, III. We also prepared 2-thio-4-methylhydantoin from alanine. The various transformations are represented as follows:

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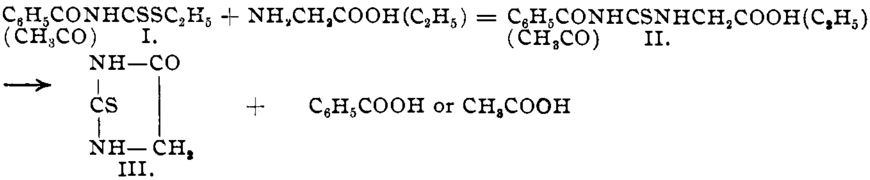
[1] *Memoirs Coll. Sci. and Eng.*, Kyoto Univ. (Japan), 3, 1 (1911).

[2] Wheeler, Nicolet and Johnson, *Am. Chem. J.*, 46, 456 (1911).



$$\underset{(CH_3CO)}{C_6H_5CONHCSSC_2H_5} + NH_2CH_2COOH(C_2H_5) = \underset{(CH_3CO)}{C_6H_5CONHCSNHCH_2COOH(C_2H_5)}$$

I. II.

$$\longrightarrow \text{III} + C_6H_5COOH \text{ or } CH_3COOH$$

III.

Since it was necessary to prepare large amounts of 2-thiohydantoin for certain investigations in progress in this laboratory, we naturally decided to employ Komatsu's method for the preparation of this compound. We find that 2-thiohydantoin can be prepared easily in this manner, but on the other hand, have made the very interesting observation that Komatsu's interpretation of the mechanism of the reactions is entirely incorrect. In this paper we shall describe a new method for preparing easily this 2-thiohydantoin, III, and also give a correct explanation of the behavior of potassium thiocyanate towards glycocoll in the presence of acetic anhydride.

Radenhausen[1] has shown that glycocoll and acetic anhydride react smoothly below 100°, giving acetylglycocoll,

$$NH_2.CH_2COOH + (CH_3CO)_2O = CH_3CONHCH_2COOH + CH_3COOH.$$

Komatsu has practically duplicated the conditions of Radenhausen's experiment in his directions for preparing thiohydantoic acid, and consequently it did not seem probable to the writer that the presence of potassium thiocyanate should prevent here the primary formation of this acetyl derivative. Furthermore, Curtius[2] has shown that acetylglycocoll possesses weak basic properties and combines with hydrochloric and sulfuric acids, giving the corresponding salts. These salts, however, are unstable, as might be expected, and readily undergo hydrolysis with water giving the original acid. If, now, acetylglycocoll was formed under the conditions employed by Komatsu, it might be expected that it would combine with thiocyanic acid, in the anhydrous solvent, forming a thiocyanate, V, which would then undergo a normal rearrangement, giving acetylthiohydantoic acid, VI. This could then undergo an inner condensation on further warming with anhydride and be converted into acetylthiohydantoin, VII, or 2-thiohydantoin, III, with loss of the acetyl radical.

The experimental data, which we have obtained, prove that these assumptions are correct. We find that glycocoll reacts with potassium thiocyanate, in the presence of acetic anhydride, giving an excellent yield of 3-acetyl-2-thiohydantoin, VII. We obtained no evidence of the formation of the thiohydantoic acid described by Komatsu. In fact it seems very probable that this investigator actually described an impure substance. The results of his sulfur determinations would indicate

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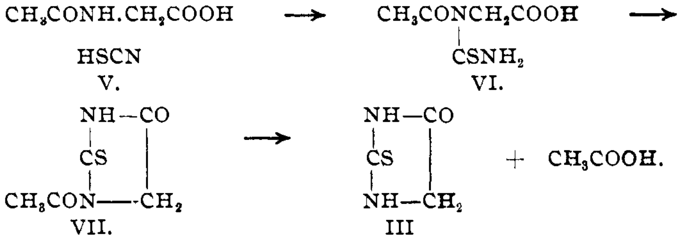
[1] *J. prakt. Chem.*, 52, 438.

[2] *Ber.*, 17, 1668 (1884).

such a possibility. When the acetylthiohydantoin, VII, was dissolved in concentrated hydrochloric acid and the solution evaporated to dryness, pure 2-thiohydantoin, III, was obtained.

Furthermore, that aceturic acid is the primary product of the reaction in this synthesis is proven by the following facts: 2-Thiohydantoin and acetic anhydride do not react at 100° giving an acetyl derivative. Secondly, acetylglycocoll reacts with potassium thiocyanate under the conditions employed by Komatsu, forming almost a quantitative yield of the same 3-acetyl-2-thiohydantoin, VII, as was obtained from glycocoll. Therefore the acetic anhydride cannot be considered as a *catalytic agent*, as stated by Komatsu, and actually takes part in the reactions involved giving primarily aceturic acid, a fact which was entirely overlooked by Komatsu. The general reactions involved in the synthesis of 2-thiohydantoin from glycocoll, acetic anhydride and potassium thiocyanate, are therefore to be represented as follows:

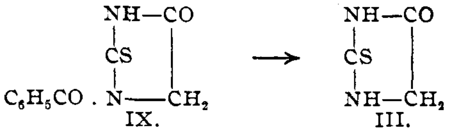
$$NH_2CH_2COOH + (CH_3CO)_2O = \underset{\text{IV.}}{CH_3CONHCH_2COOH} \longrightarrow$$



$$\underset{\text{V.}}{\overset{CH_3CONH.CH_2COOH}{HSCN}} \longrightarrow \underset{\text{VI.}}{\overset{CH_3CONCH_2COOH}{|\;CSNH_2}} \longrightarrow \underset{\text{VII.}}{\begin{array}{l} NH-CO \\ CS \quad | \\ CH_3CON-CH_2 \end{array}} \longrightarrow \underset{\text{III}}{\begin{array}{l} NH-CO \\ CS \quad | \\ NH-CH_2 \end{array}} + CH_3COOH.$$

The smooth formation of acetylthiohydantoin from acetylglycocoll by the action of potassium thiocyanate suggested that other acyl derivatives of this amino acid would likewise react with this reagent to form acylthiohydantoins. We therefore applied the reaction with hippuric acid, VIII. We now find that this acid reacts as readily as acetylglycocoll with potassium thiocyanate in acetic anhydride solution, forming 3-benzoyl-2-thiohydantoin, IX. This was then converted into 2-thiohydantoin, III, by hydrolysis with hydrochloric acid. Therefore, starting with hippuric acid, we have at hand a practical method of preparing 2-thiohydantoin, III, in any amount desired.

$$\underset{\text{VIII.}}{C_6H_5CONHCH_2COOH} + KSCN =$$

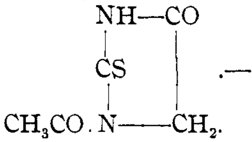


$$\underset{\text{IX.}}{\begin{array}{l} NH-CO \\ CS \quad | \\ C_6H_5CO\,.\,N-CH_2 \end{array}} \longrightarrow \underset{\text{III.}}{\begin{array}{l} NH-CO \\ CS \quad | \\ NH-CH_2 \end{array}}$$

The investigation of the action of potassium thiocyanate on amino acids and their acyl derivatives is now in progress in this laboratory.

Experimental Part.

The Action of Potassium Thiocyanate on Glycocoll. 3-Acetyl-2-thiohydantoin,



$$\begin{array}{rcl} & \mathrm{NH} & \mathrm{—CO} \\ & | & | \\ & \mathrm{CS} & | \\ & | & | \\ \mathrm{CH_3CO.} & \mathrm{N} & \mathrm{——CH_2.} \end{array}$$

.—Two grams of pure glycocoll and 2.6 grams of potassium thiocyanate were thoroughly ground together in a mortar and suspended in 10 cc. of acetic anhydride (Kahlbaum's). This mixture was then gently heated on a steam bath when there was an immediate reaction, with evolution of heat, and within three minutes a clear orange-colored solution was obtained. In order to duplicate as closely as possible the conditions of Komatsu's[1] experiment, the solution was then heated for 30 minutes to thoroughly complete the reaction. The thick viscous liquid was then cooled and poured into about 5–6 times its volume of cold water, when this acetyl hydantoin separated in crystalline condition. The yield was 3.5 grams, corresponding to 83.3 per cent. of the theoretical. The hydantoin was purified by recrystallization from absolute alcohol and separated, on cooling, in beautiful square tables or blocks, which melted at 175–176° to a clear oil without effervescence.

Analysis (Kjeldahl): Calculated for $C_5H_6O_2N_2S$, : N, 17.71; found, 17.48.

The Action of Potassium Thiocyanate on Acetylglycocoll (Aceturic Acid).—This same 3-acetyl-2-thiohydantoin was also prepared in the following manner: Two grams of aceturic acid and 2.0 grams of dry potassium thiocyanate were suspended in a mixture of 9 cc. of acetic anhydride and 1 cc. of glacial acetic acid and the mixture then heated gently on the steam bath. There was an immediate reaction, the acid and potassium thiocyanate quickly dissolved, and within 5 minutes an orange-colored viscous liquid was obtained. After heating 30 minutes, as in the previous experiment, the liquid was cooled and then poured into cold water. The acetylhydantoin separated at once in yellow prisms. The yield was about 80.0 per cent. of the theoretical. It crystallized from alcohol in blocks and melted at 175–176° to a clear oil. A mixture of this substance with some hydantoin prepared from glycocoll melted at exactly the same temperature.

Analysis (Kjeldahl): Calculated for $C_5H_6O_2N_2S$: N, 17.71; found, 17.73, 17.76.

When this acetylthiohydantoin was heated with an excess of hydrochloric acid it was converted quantitatively into 2-thiohydantoin.[2]

The Action of Potassium Thiocyanate on Hippuric Acid. 3-Benzoyl-2-

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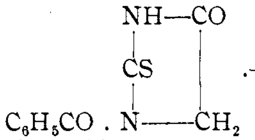
[1] *Loc. cit.*

[2] Wheeler, Nicolet and Johnson, *Loc. cit.*

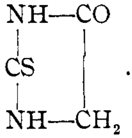
thiohydantoin, 
$$\begin{array}{l}\text{NH—CO}\\ \text{CS}\\ C_6H_5CO\,.\,\text{N—CH}_2\end{array}$$
.—Two grams of hippuric acid and 2.0 grams of potassium thiocyanate were carefully warmed with 9.0 cc. of acetic anhydride and 1 cc. of glacial acetic acid. The anhydride assumed a yellow color and within 5 minutes a perfectly clear orange-colored solution was obtained. There was no apparent loss of thiocyanic acid. After heating at 100° for 30 minutes to complete the reaction, the liquid was cooled and poured into cold water. The hydantoin separated as an oil, which soon solidified. The yield was 86 per cent. of the theoretical. The hydantoin crystallizes from alcohol in square plates, which melt at 165° to a clear oil without effervescence. A mixture of this compound and 3-acetyl-2-thiohydantoin melted at 125–150°.

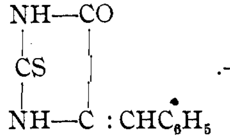
Analysis (Kjeldahl): Calculated for $C_{10}H_8O_2N_2S$: N, 12.72; found, 12.91, 12.89.

Several experiments were performed in order to determin whether the yield of this thiohydantoin was influenced by the proportions of anhydride and acetic acid used for the condensation. With pure glacial acetic acid there was no evidence of the formation of the benzoylthiohydantoin. Glycocoll likewise gave no 2-thiohydantoin when warmed with potassium thiocyanate in glacial acetic acid. With pure acetic anhydride the yield of benzoylthiohydantoin was much less than when 1 part of acid and 9 parts of anhydride were used. With equal parts of anhydride and acid the benzoylthiohydantoin was formed, but on pouring into water a red oil was always obtained, which showed no signs of crystallizing. In these experiments the yield of the benzoylthiohydantoin was determined indirectly by diluting the solution with strong hydrochloric acid and then evaporating to dryness on the steam bath. The benzoyl group was removed by this treatment and 2-thiohydantoin was formed. The latter was then extracted by alcohol and the potassium salt precipitated by the addition of alcoholic potash. This was then filtered off and weighed. The yields of benzoylthiohydantoin obtained when using different proportions of anhydride and acid are given in the table. In all cases the reaction was carried out with 2 grams of hippuric acid and potassium thiocyanate respectively in 10 grams of the solvent.

TABLE I.

	Acetic anhydride.	Acetic acid.	Yield of benzoylthiohydantoin.
1............	..	10	Hippuric acid recovered unaltered.
2............	5	5	67 per cent.
3............	5	5	52 per cent.
4............	9	1	86 per cent.
5............	10	..	38 per cent.
6............	10	..	40 per cent.

Hydrolysis of 3-Benzoyl-2-thiohydantoin with Hydrochloric Acid. 2-Thiohydantoin,  $\begin{array}{l}\mathrm{NH{-}CO}\\ \mathrm{CS}\\ \mathrm{NH{-}CH_2}\end{array}$.—This hydantoin is formed quantitatively by hydrolysis of the above benzoyl derivative with strong hydrochloric acid. After evaporating to dryness on the steambath the thiohydantoin is then purified by crystallization from alcohol. The hydantoin melted with decomposition at 227° and was identical with the thiohydantoin which was prepared by hydrolysis of benzoylthiohydantoic acid.[1]

Condensation of Benzaldehyde with 3-Benzoyl-2-thiohydantoin. 4-Benzal-2-thiohydantoin,[1]  $\begin{array}{l}\mathrm{NH{-}CO}\\ \mathrm{CS}\\ \mathrm{NH{-}C:CHC_6H_5}\end{array}$.—Two grams of 3-benzoyl-2-thiohydantoin were condensed with a molecular proportion of benzaldehyde by digestion in glacial acetic acid in the presence of anhydrous sodium acetate. On cooling and pouring into water we obtained 1.6 grams of this benzalthiohydantoin. It melted at 258° and a mixture of this substance with some benzalthiohydantoin, which was prepared by hydrolysis of 1-benzoyl-4-benzalthiohydantoin, melted at the same temperature. Benzoic acid was identified in the acetic acid filtrate.

Analysis (Kjeldahl): Calculated for $C_{10}H_8ON_2S$: N, 1373; found, 13.27.

Action of Acetic Anhydride on 2-Thiohydantoin.—Five-tenths of a gram of 2-thiohydantoin was warmed with 10 cc. of acetic anhydride for exactly 30 minutes. The mixture was then cooled and poured into cold water when a clear solution was obtained. No acetylthiohydantoin separated. The aqueous solution was then evaporated to dryness and the residue obtained crystallized from hot alcohol. Pure thiohydantoin separated on cooling.

NEW HAVEN, CONN.

[FROM THE LABORATORY OF PHYSIOLOGICAL CHEMISTRY OF THE UNIVERSITY OF ILLINOIS.]

STUDIES ON WATER DRINKING. VIII.[2] THE UTILIZATION OF INGESTED FAT UNDER THE INFLUENCE OF COPIOUS AND MODERATE WATER DRINKING WITH MEALS.

H. A. MATTILL AND P. B. HAWK.

Received August 10, 1911.

Introduction.

Current Theories.—Notwithstanding the fact that many persons are

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[1] Wheeler, Nicolet and Johnson, *Loc. cit.*

[2] Presented in abstract at the New Haven meeting of the American Society of Biological Chemists, December, 1910; Proceedings, Vol. II, p. xiv. This paper and the