[CONTRIBUTION FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

HYDANTOINS: SYNTHESIS OF 5-THIOHYDANTOINS.

[NINETEENTH PAPER.]

BY TREAT B. JOHNSON AND LEWIS H. CHERNOFF.

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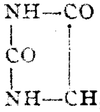
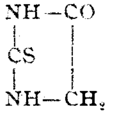
Three thio-derivatives of hydantoin (I) are possible, if one considers only the replacement of the oxygen atoms of this cycle by sulfur, *viz.*, 2-thiohydantoin (II), 5-thiohydantoin (III) and 2,5-dithiohydantoin (IV). 2-Thiohydantoin (II) is known and several of its derivatives have also been described in the literature. On the other hand, 5-thiohydantoin (III) and 2,5-dithiohydantoin (IV), so far as the writer is aware, have not been prepared and the properties of such sulfur compounds are unknown. We shall describe in this paper a general method of synthesizing 5-thiohydantoins and also give a description of the properties of the prototype of the series 5-thiohydantoin (III).


I.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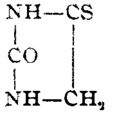
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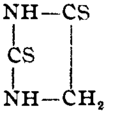
IV.

Hydantoin is formed quantitatively by the action of hydrochloric acid on the ethyl ester of hydantoic acid (V).[1] Bailey[2] effected the same condensation by the action of sodium and potassium alcoholates on the hydantoic ester. Isomeric with ethyl hydantoate is the amide of carbethoxyaminoacetic acid (VI), which Fischer and Otto[3] prepared by heating the ethyl ester of this acid with ammonia. Theoretically, this amide (VI) would be expected to undergo a condensation, in the presence of alkali, with formation of hydantoin, but Fischer observed that no such change can be effected and writes as follows regarding the properties of this amide: "Beim Stehen in wässeriger Lösung mit 1 Molekül Normal-Alkali bei Zimmertemperatur entwickelt es Ammoniak; es bildet sich wenig Carbäthoxyglycin, der Rest des Amids ist unverändert. Zum Unterschiede von dem isomeren Hydantoïnsäureester lässt sich das Amid nicht in Hydantoïn verwandeln." On the other hand, Lehmann[4] has shown that the phenyl derivative of this amide (IX) is converted smoothly into 4-phenylhydantoin (XI) by means of alkali. Recently this same reaction has been investigated by Clark and Francis,[5] who apparently were not aware of the observation of Lehmann. They applied it success-

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[1] Harries and Weiss, *Ber.*, 33, 3418.

[2] *Am. Chem. J.*, 28, 386.

[3] *Ber.*, 36, 2106.

[4] *Ber.*, 34, 366.

[5] *J. Chem. Soc.*, 99, 319.

fully in the preparation of 4-phenyl- and 4-methoxyphenylhydantoins (XI) and (XII).

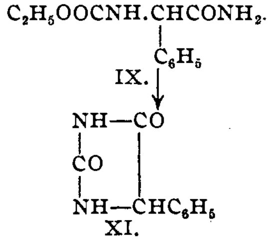
While ethyl hydantoate condenses smoothly to hydantoin with formation of alcohol, Harries and Weiss[1] have shown that the corresponding ethyl thiohydantoate (VII) does not undergo an analogous condensation with formation of 2-thiohydantoin (II). This remarkable difference in the behavior of these two esters suggested to us, that we compare the behavior towards alkali of their isomeric acid amides—carbethoxyaminoacetamide[2] (VI) and carbethoxyaminoacetthioamide (VIII), respectively. A description of the latter compound (VIII) is given in a previous paper from this laboratory.[3] It was prepared by the addition of hydrogen sulfide to carbethoxyaminoacetonitrile[4] (XIV) in alcoholic solution.

$NH_2CONHCH_2COOC_2H_5$. V.

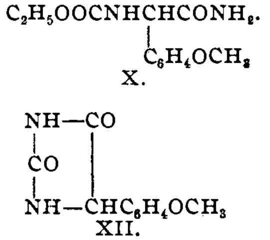
$C_2H_5OOCNHCH_2CONH_2$. VI.

$NH_2CSNHCH_2COOC_2H_5$. VII.

$C_2H_5OOCNHCH_2CSNH_2$. VIII.



$C_2H_5OOCNH.\underset{C_6H_5}{CH}CONH_2$. IX. XI.



$C_2H_5OOCNH\underset{C_6H_4OCH_3}{CH}CONH_2$. X. XII.

We have now made the interesting observation that this thioamide condenses smoothly, in the presence of alkali, forming the hitherto unknown 5-thiohydantoin (III). In fact, the reaction proceeds at ordinary temperature in the presence of a molecular proportion of the alkali. That we were dealing with the 5-thiohydantoin, and that the thioamide does not react in its pseudo-form giving the cycle (XIX), was established by the fact that it underwent hydrolysis with hydrochloric acid giving hydantoin with evolution of hydrogen sulfide. This method of synthesizing 5-thiohydantoins appears to be a general one. We have prepared the two thioamides—carbethoxyaminophenylacetthioamide (XV) and carbethoxyaminomethoxyphenylacetthioamide (XVI) and find that both compounds condense smoothly, in the presence of alkali, forming 4-phenyl-5-thiohydantoin (XVII) and 4-methoxyphenyl-5-thiohydantoin (XVIII), respectively.

The various changes involved in these transformations are represented by the following formulas:

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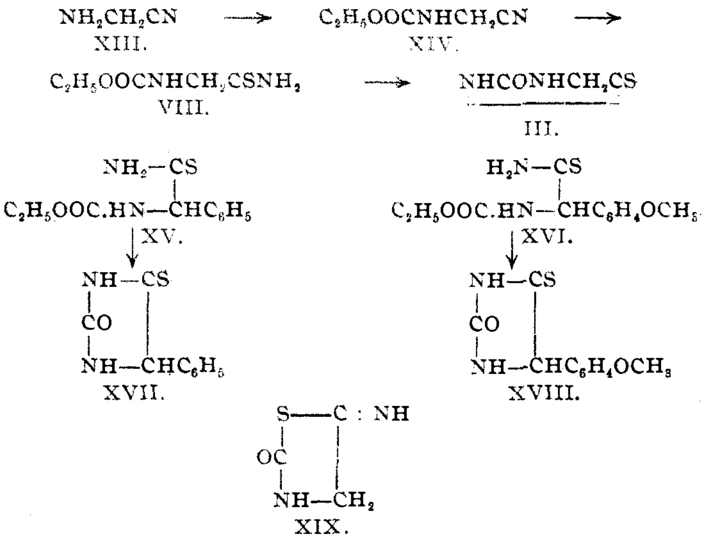
[1] *Ann.*, 327, 356.

[2] Fischer and Otto, *Loc. cit.*

[3] Johnson and Burnham, *Am. Chem. J.*, 47, 232.

[4] Johnson and McCollum, *Ibid.*, 35, 67.



A description of the properties of 5-thiohydantoin is given in the experimental part of this paper.

Experimental Part.

5-Thiohydantoin, $\underline{NH.CO.NH.CS.CH_2}$.—The starting point for the synthesis of this hydantoin was carbethoxyaminoacetonitrile.[1] This was converted into its thioamide derivative carbethoxyaminoacetthioamide $C_2H_5OOC.NHCH_2CSNH_2$ by the addition of hydrogen sulfide,[2] and the latter then condensed to the thiohydantoin by the action of alkali. The thioamide is finely pulverized and moistened with water. A 5–10% solution of sodium hydroxide, containing exactly one molecular proportion of the alkali, is then added, when the thioamide dissolves at ordinary temperature giving a light yellow solution. It is absolutely essential to use no more than the required amount of alkali or the product will be colored. The sodium salt of 5-thiohydantoin is formed in solution at once and on acidifying with cold, dilute hydrochloric acid the thiohydantoin separates in the form of prisms, slightly colored, which slowly undergo oxidation when moist. If pure thioamide is used and proper precautions are taken to avoid an alkalin solution the hydantoin can be obtained nearly colorless and the yield is excellent. The best results are obtained by working with less than 5 grams of the thioamide at a time. The thiohydantoin crystallizes from hot water in spear-shaped crystals arranged in twins. No definit melting point could be assigned, but it gradually decomposed when heated above 220° and did not effervesce

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[1] Johnson and McCollum, *Loc. cit.*

[2] Johnson and Burham, *Loc. cit.*

below 270°. Its behavior in the capillary tube was very characteristic. Analysis (Kjeldahl):

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

2-Thiohydantoin is a stable substance and undergoes no change in aqueous solution and forms perfectly stable sodium and potassium salts. On the other hand, 5-thiohydantoin slowly undergoes oxidation in aqueous solution and in the presence of alkali. In fact, its behavior in alkalin solution is its most characteristic property. The hydantoin dissolves at once in cold sodium hydoxide solution giving a pink solution, which gradually changes color and darkens on exposure to the air. The pink solution gradually changes becoming purple, changing to a deep red and finally assumes a beautiful indophenine color, which is permanent. These colors are so intense that the changes can easily be followed with very small quantities of the hydantoin. If, after the oxidation is complete, hydrochloric acid is added to the solution the color is destroyed and an amorphous, dark brown precipitate deposits and hydrogen sulfide is evolved. This amorphous substance contained sulfur, but it was insoluble in the common solvents and possessed no definit melting or decomposition point. It was not examined further.

Hydrolysis of 5-Thiohydantoin.—Two grams of 5-thiohydantoin were suspended in 20 cc. of concentrated hydrochloric acid and the mixture boiled on a sand bath for 1.5 hours. The hydantoin dissolved, hydrogen sulfide was evolved and a yellow solution was obtained. The excess of hydrochloric acid was then evaporated when a crystallin residue was obtained which was purified by crystallization from 95% alcohol. On cooling, hydantoin separated and melted at 216°. A mixture of this product of hydrolysis and some pure hydantoin melted at exactly the same temperature. Along with the hydantoin, an amorphous substance was formed which was extremely insoluble in all solvents and possessed no melting point. It was probably an oxidation product.

Anilinophenylacetthioamide, $C_6H_5CH(NHC_6H_5)CSNH_2$.—This thioamide was prepared by the addition of hydrogen sulfide to anilinophenylacetonitrile[1] $C_6H_5CH(NHC_6H_5)CN$ in alcoholic solution. The yield was excellent. The thioamide crystallizes from 95% alcohol in long, slender prisms, which melt at 130°. Analysis (Kjeldahl):

Calculated for $C_{14}H_{14}N_2S$: N, 11.57; found: 11.65.

Carbethoxyaminophenylacetthioamide, $C_6H_5CH(NHCOOC_2H_5)CSNH_2$. — From the nitrile $C_6H_5CH(NHCOOC_2H_5)CN$[2] by the action of hydrogen sulfide. Twenty-three grams of the nitrile gave 16.0 grams of the pure thioamide. It crystallized from 95% alcohol in colorless needles, which melted at 127°. Analysis (Kjeldahl):

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[1] Knonenagel, *Ber.*, 37, 4079.

[2] Lehmann, *Loc. cit.*

Calculated for $C_{11}H_{14}O_2N_2S$: N, 11.81; found: 11.83.

4-Phenyl-5-thiohydantoin, NH.CO.NH.CS.CHC_6H_5.—This hydantoin was obtained in the form of its sodium salt by dissolving the above urethane in 10% sodium hydroxide solution. After the urethane had dissolved, by gentle warming, the solution was then acidified when this hydantoin separated as a yellow powder. It was soluble in boiling alcohol, but did not separate, on cooling, in a crystallin condition. This hydantoin was apparently perfectly stable and showed no tendency to undergo oxidation. It decomposed at about 259° depending on the mode of heating. Analysis (Kjeldahl):

Calculated for $C_9H_8ON_2S$: N, 14.5; found: 14.2.

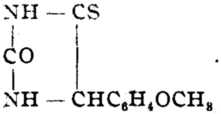
Carbethoxyamino-p-methoxyphenylacetonitrile, $CH_3O.C_6H_4CH(NHCOOC_2H_5)CN$.—This compound was prepared by heating at 100° urethane (6.6 grams) with the nitrile of *p*-methoxymandelic acid $CH_3OC_6H_4CH(OH)CN$ (12 grams) in the presence of fused zinc chloride (20 grams). After heating about 2 hours a thick syrup was obtained, which was triturated with cold water, when this urethane separated. It was purified by crystallization from dilute alcohol and separated in needles, which melted at 117°. Analysis (Kjeldahl):

Calculated for $C_{12}H_{14}O_3N_2$: N, 11.97; found: 11.94.

Carbethoxyamino-p-methoxyphenylacetthioamide, $CH_3OC_6H_4CH(NHCOOC_2H_5)CSNH_2$.—This was prepared from the preceding nitrile by the addition of hydrogen sulfide. It crystallized from 95% alcohol in prismatic crystals, which melted at 146°. Analysis (Kjeldahl):

Calculated for $C_{12}H_{16}O_3N_2S$: N, 10.45; found: 10.51.

4-p-Methoxyphenyl-5-thiohydantoin,



$$\begin{array}{ll} \text{NH} - & \text{CS} \\ | & | \\ \text{CO} & | \\ | & | \\ \text{NH} - & \text{CHC}_6\text{H}_4\text{OCH}_3 \end{array}$$

.—Three and five-tenths grams of the above thioamide were dissolved in 10% sodium hydroxide solution by gentle warming. A greenish solution was obtained, which was then acidified with dilute hydrochloric acid. This thiohydantoin separated at once as a yellow solid. It was slightly soluble in boiling alcohol and water and insoluble in ether. It partially dissolved in glacial acetic acid and separated again in an amorphous condition. It decomposed at about 263° with effervescence. Analysis (Kjeldahl):

Calculated for $C_{10}H_{10}O_2N_2S$: N, 12.6; found: 12.3.

Condensation of 5-Thiohydantoin with Benzaldehyde.—Two and five-tenths grams of the thiohydantoin, 2.6 grams of benzaldehyde and 5.5 grams of anhydrous sodium acetate were heated with 10 cc. of glacial acetic acid for 5 hours at 160–170°. The solution assumed a dark color and on pouring into cold water a brownish yellow substance separated in good quantity. This was apparently a normal condensation product or 5-thio-4-benzalhydantoin, but it could not be purified because of its insolubility. After trituration with boiling water and alcohol it was dried and analyzed. A nitrogen determination gave 14.4% of nitrogen, while the calculated for the benzalthiohydantoin is 13.73%. The product had no definit melting point and was decomposed by digestion with acids and alkali forming hydrogen sulfide and alkali sulfide, respectively.

NEW HAVEN, CONN., July 8, 1912.

[FROM THE RUDOLPH SPRECKELS PHYSIOLOGICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA.]

ON A NEW GLUCOLYTIC FERMENT OF YEAST.

BY VICTOR BIRCKNER.

Received May 14, 1912.

1. The Ferment as First Observed and Recognized.

In the early part of 1911, following a suggestion of Dr. T. Brailsford Robertson, I found it necessary for a certain purpose to prepare the ferment maltase. I tried to obtain it from yeast by the well known method of Croft Hill[1] or with a slight modification according to O. Emmerling.[2] The material chosen was the yeast of the so called California "steam beer," a local brew, which although a bottom fermentation beer, differs a good deal from the common lager beers.

The differences between lager beer and steam beer depend in the first place on the difference in temperature at which the fermentation of the wort is being carried on, and they are therefore a direct function of the respective metabolic activity of the yeast. The following table will serve to illustrate these relations:

	Temp. at start.	Temp. maximum which is allowed.	Time required for the whole ferm. process.
Lager beer..........	5°	10–11°	8 to 10 days
Calif. "steam".......	13°	18°	3 days

Besides the temperature it is probably the more extensive aeration of the steam beer yeast which in part causes its high activity. After having reached the temperature of 18°, instead of being cooled down by artificial means in the fermenting vat itself, the whole brew is transferred to large wooden pans, the so-called "clarifiers," where in a layer about one foot deep the fermentation process is carried to the end. Although in this way, by giving the mixture a large surface, the rise of temperature is checked, the fermentation process still proceeds with considerable speed on account of the ample aeration. The use of these clarifiers is a typical feature in the manufacture of the California steam beer.

The yeast of the steam beer has accommodated itself to these conditions to such an extent, that it can no longer be employed for the preparation of lager beer, while lager beer yeast may without difficulty be used for the manufacture of steam beer. The cells of the typical steam beer yeast are somewhat smaller than those of lager beer yeast.

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[1] A. Croft Hill, *J. Chem. Soc.*, 73, 634 (1898).

[2] O. Emmerling, *Ber.*, 34, 602 (1901).