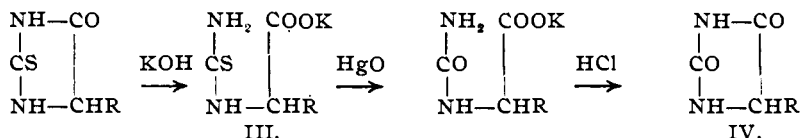


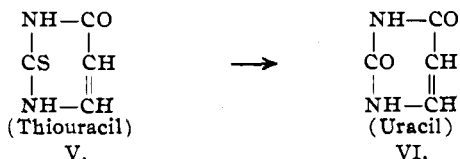
acids are transformed easily into hydantoic acids, which then condense to form quantitatively the hydantoin (IV). These changes are represented as follows:



These investigators also found that thiohydantoin can be desulfurized in alcohol solution by the action of bromine, and applied this method successfully with several 4,4-disubstituted 2-thiohydantoin.

Biltz¹ showed, a little later, that thiohydantoin can be converted into hydantoin by digestion with dilute nitric acid and also by oxidation with potassium permanganate in an alkaline solution. He writes as follows: "Diese beiden Mittel haben den Vorteil, dass die Gefahr einer weiteren Substitution, wie sie bei Verwendung von Brom gelegentlich zu befürchten ist, wegfällt. Die Ausbente waren vortrefflich." These methods of desulfurization, however, are not applicable to all types of 2-thiohydantoin. Komatsu² states that no reliable results were obtained when attempts were made to desulfurize 4-methyl-2-thiohydantoin (IX) by these methods. In this case, he obtained the hydantoin (X) by digesting the thiohydantoin in aqueous solution with mercury oxide.

We shall now describe a method of desulfurization which is an improvement over the methods proposed by Bailey and Randolph and by Biltz. It has been shown in a previous paper from this laboratory that 2-thio-6-oxypyrimidines (V) can be converted nearly quantitatively



into the corresponding oxygen derivatives (VI) by digestion with chloroacetic acid in aqueous solution.³ We now find that this same reagent can be used for the desulfurization of 2-thiohydantoin. In fact, the reaction is very smooth and we have not yet observed a case, among the thiohydantoin so far examined, where it has not been successful. The statement in a previous paper⁴ that 1-phenyl-2-thiohydantoin (XI) is not desulfurized by this reagent is wrong. The cause for failure in this experiment was the fact that the aqueous solution of chloroacetic acid used

¹ *Ber.*, 42, 1795 (1909).

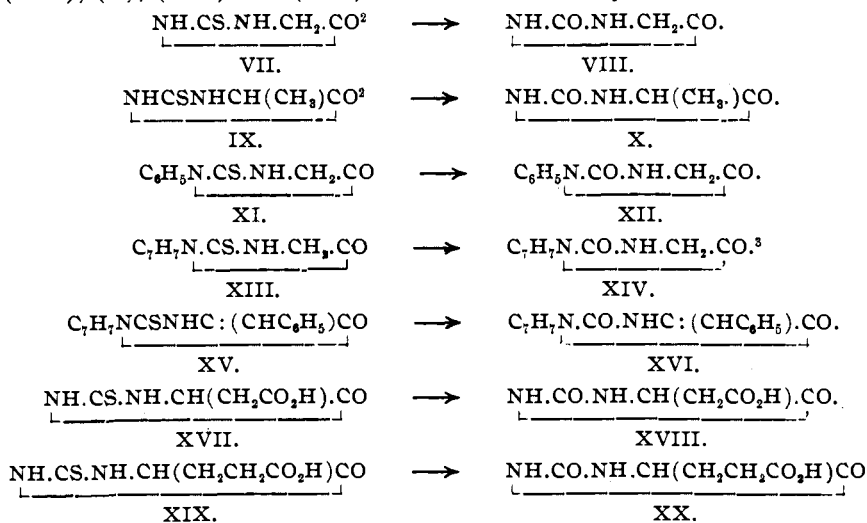
² *Mem. Coll. Sci. Eng. (Kyoto)*, Vol. 3 (1911).

³ Wheeler and Liddle, *Am. Chem. J.*, 40, 547.

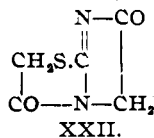
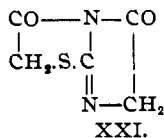
⁴ Brautlecht, *J. Biol. Chem.*, 10, 143.

was too dilute. We find that the hydantoin is desulfurized easily by digestion with 3-4 parts of chloroacetic acid in a concentrated aqueous solution.

Besides 2-thiohydantoin-4-propionic acid (XIX) and 2-thiohydantoin-4-acetic acid (XVII), whose behavior towards chloroacetic acid has already been described,¹ we have now examined the action of this halogen acid on *o*- and *p*-tolylthiohydantoin (XIII), their corresponding benzaldehyde condensation products (XV), 2-thiohydantoin (VII) and 2-thio-4-methylhydantoin (IX). In every case the corresponding hydantoin (VIII), (X), (XIV) and (XVI) was formed smoothly.



Chloroacetic acid therefore does not react with *N*-substituted 2-thiohydantoin, in a similar manner as with acyclic thioureas,⁴ forming the corresponding pseudothiohydantoin (XXI) or (XXII). This difference in behavior is of interest and suggested that di- and trisubstituted thioureas



might be desulfurized by the action of this halogen acid in aqueous solution. We therefore examined its action on phenyltolylthiourea⁵ (XXIII)

¹ Johnson and Guest, *Am. Chem. J.*, 47, 242; 48, 103.

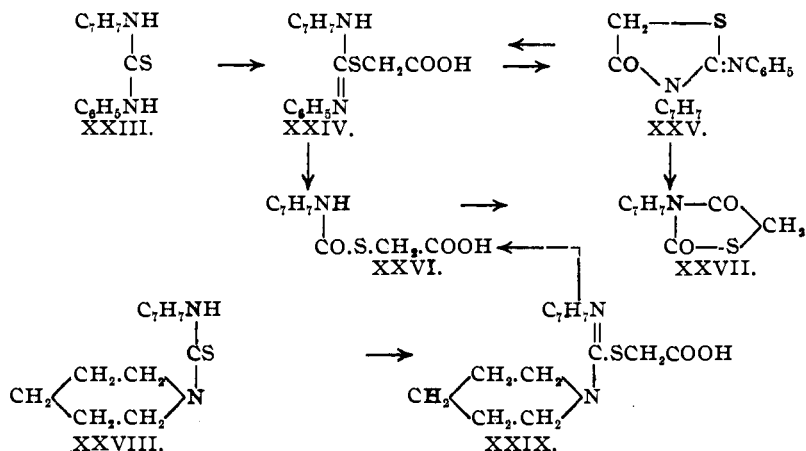
² Johnson and Nicolet, *THIS JOURNAL*, 33, 1973.

³ Beilstein's Handbuch, II, 494. Bailey and Randolph, *Loc. cit.*

⁴ Maly, *Ann.*, 168, 133. Volhard, *Ibid.*, 166, 133, *J. prakt. Chem.*, 9, 6 (1874). Claesson, *Ber.*, 10, 1352. Meyer, *Ibid.*, 10, 1965; 14, 1661.

⁵ Staats, *Ber.*, 13, 137. Gebhardt, *Ibid.*, 17, 3035. Marckwald, *Ibid.*, 25, 3099.

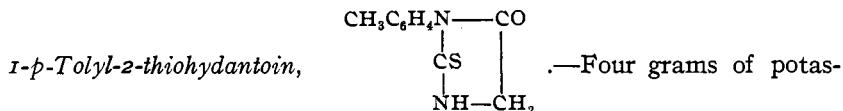
and *p*-tolylpiperidylthiourea¹ (XXVIII). In neither case did we observe the formation of the corresponding urea. On the other hand, they were both converted into the same substance—*N*-tolyl- α,μ -diketotetrahydrothiazole (XXVII).² These transformations are represented as follows:



The fact that the thiazole (XXVII) is formed from the tolylpiperidylthiourea (XXVIII) is especially significant, since it proves that in the change of the pseudothiohydantoic acid (XXIV) into the thiazole (XXVII), by hydrolysis, the pseudothiohydantoin (XXV) is not necessarily an intermediate product of the reaction. The pseudothiohydantoic acid (XXIV) very probably is converted directly into the carbaminothio-glycollic acid (XXVI), which then condenses giving the thiazole (XXVII).

Experimental Part.

BY GEORGE MORTON PFAU.



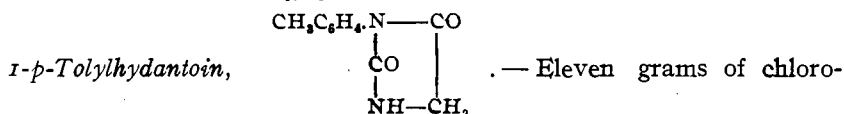
sium hydroxide and 5.5 grams of glycooll were dissolved in 10 cc. of water and 25 cc. of alcohol and 10 grams of *p*-tolylisothiocyanate added to the solution. On warming, the mustard oil dissolved. The solution was then boiled on a sand bath for one hour, when the liquid finally assumed a red color and yellow crystals began to deposit. The solution was then heated on the steam bath to expel the excess of alcohol, then diluted with dilute hydrochloric acid, and finally evaporated to dryness. A crystallin residue of the hydantoin mixed with potassium chloride was obtained. This was first triturated with cold water to remove potas-

¹ Gebhardt, *Loc. cit.*

² Voltzkow, *Ber.*, 13, 1579. Evers, *Ibid.*, 21, 976.

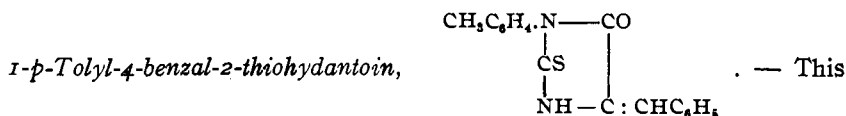
sium chloride and the hydantoin crystallized from alcohol. It melted at 228° to a clear red oil and the yield was 88% of the calculated. Aschan¹ states that this hydantoin melts at 180° , while Marckwald, Neumark and Stelzner¹ write as follows: "Nur der letztere Körper zeigte wesentlich von den Ausgaben Aschan's abweichende Eigenschaften. Der gewannte Autor beschreibt denselben als goldgelbe, sich bei 180° zersetzende Substanz, während wir ein offenbar reineres Product erhielten, welches ebenso wie die homologen Verbindungen farblos war und bei 210° schmolz." Our hydantoin was yellow, as observed by Aschan. Analysis (Kjeldahl):

Calculated for $C_{10}H_{10}ON_2S$: N, 13.49. Found: N, 13.40.



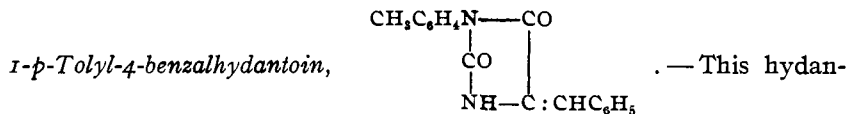
acetic acid were dissolved in 20 cc. of water and 5 grams of *1-p*-tolyl-2-thiohydantoin suspended in the solution. This mixture was then heated on a sand bath, when the thiohydantoin dissolved within one hour. On cooling, this hydantoin separated and was purified by crystallization from 95% alcohol. It separated in prismatic crystals, which melted at 206° to a clear red oil. It did not give a test for sulfur. Analysis (Kjeldahl):

Calculated for $C_{10}H_{10}O_2N_2$: N, 14.73. Found: N, 14.80.



hydantoin was formed by heating a mixture of 5 grams of *1-p*-tolyl-2-thiohydantoin, 2.7 grams of benzaldehyde, 10 grams of sodium acetate and 25 cc. of glacial acetic acid to boiling in an oil bath for 4 hours. A dark brown solution was obtained, which was poured into water. The crude condensation product separated as a gray powder. It was purified by crystallization from alcohol and separated in plates, which melted at 188° to a red oil. The yield of pure hydantoin corresponded to 75% of the calculated. Analyses (Kjeldahl):

Calculated for $C_{17}H_{14}ON_2S$: N, 9.53. Found: N, 9.86, 9.66.



can be prepared by desulfurization of the corresponding 2-thiohydantoin with chloroacetic acid. This was accomplished by boiling 4 grams of the thiohydantoin with a mixture of 10 grams of chloroacetic

¹ *Loc. cit.*

acid and 20 cc. of water for about one hour. A clear solution was obtained, from which, on cooling, this hydantoin separated. The yield was quantitative. This compound was purified by crystallization from 95% alcohol and separated in plates, which melted at 259° to a clear oil.

This same hydantoin was also formed by condensation of benzaldehyde with 1-*p*-tolylhydantoin in the presence of fused sodium acetate and glacial acetic acid. The yield by this method was about 73% of the theoretical. Analyses (Kjeldahl):

Calculated for $C_{17}H_{14}O_2N_2$: N, 10.05. Found: N, 10.02, 9.89.

An attempt to reduce this hydantoin with stannous chloride was unsuccessful.

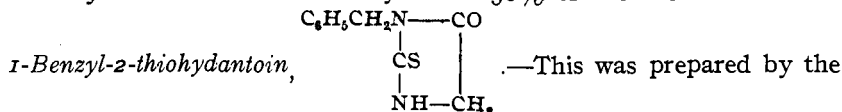
The Action of Chloroacetic Acid, in Aqueous Solution, on Symmetrical Phenyl-p-tolylthiourea, $CH_3C_6H_4NHCSNHC_6H_5$.—Two grams of the thiourea were suspended in 100 cc. of water containing 5 grams of chloroacetic acid. This mixture was then boiled for one hour, when a clear solution was obtained. On cooling, a colorless, crystalline substance separated. This was purified by crystallization from 95% alcohol and separated in needles, which melted at 161° to a clear oil. The substance contained sulfur and was identified as *N-p*-tolyl- α,μ -diketo-tetrahydrothiazole,



The yield was about 60% of the calculated. When the compound was warmed with alkali *p*-toluidine was formed. Analysis (Kjeldahl):

Calculated for $C_{10}H_9O_2NS$: N, 6.76. Found: N, 6.90.

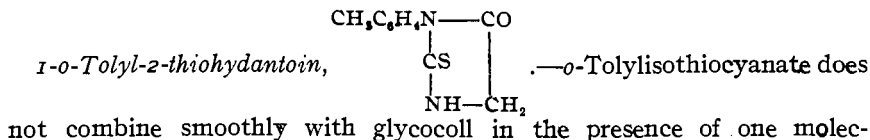
This same thiazole derivative was also obtained when *p*-tolylthiourea and *p*-tolylpiperidylthiourea were digested with chloroacetic acid in aqueous solution. In the case of the former the yield of thiazole was 80% of the calculated, while the piperidine derivative reacted less smoothly and the yield of thiazole was only about 50% of the theoretical.



action of benzyl isothiocyanate on glycocoll. It was purified by crystallization from alcohol and melted at 128° to a clear oil. The yield was poor. Analysis (Kjeldahl):

Calculated for $C_{10}H_{10}ON_2S$: N, 13.59. Found: N, 13.42.

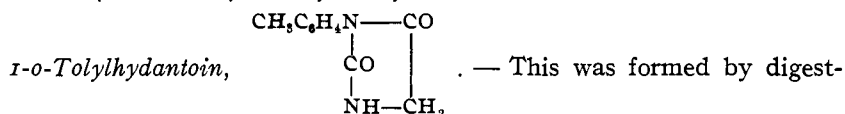
BY WILLARD WELLINGTON HODGE.



ular proportion of potassium hydroxide. If, however, 2 molecular proportions of alkali are used they combine smoothly. Eight grams of potassium hydroxide and 5.4 grams of glycocoll were dissolved in 10 cc. of water, 10 grams of the isothiocyanate added, and finally enough warm 95% alcohol to obtain a clear solution. The mixture was then heated at 100° for 3 hours, concentrated to one-half its original volume and then diluted with hydrochloric acid. On evaporating the acid solution to dryness the pure hydantoin was obtained mixed with potassium chloride. It was purified by crystallization from alcohol and separated in yellow plates, which melted at 149–150° to a turbid oil. The yield was 7.75 grams. Marckwald, Neumark and Stelzner¹ give 136° as the melting point. Analysis (Kjeldahl):

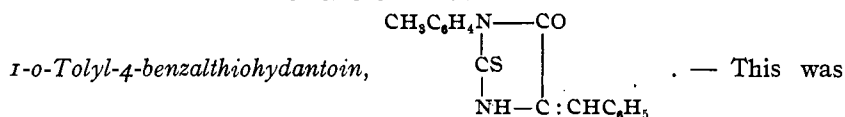
Calculated for $C_{10}H_{10}ON_2S$: N, 13.59. Found: N, 13.27.

Desulfurization of 1-o-tolylthiohydantoin with Chloroacetic Acid.



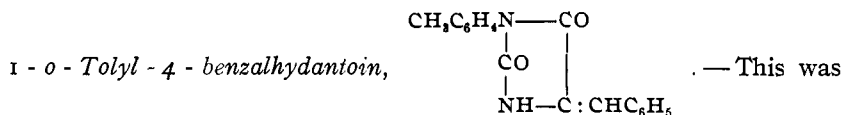
ing 1.5 grams of the thiohydantoin with 3.3 grams of chloroacetic acid in 6 cc. of water. On evaporating the solution and cooling it was obtained as a viscous oil, which soon crystallized. The hydantoin crystallized from boiling water in colorless prismatic crystals, which melted at 148° to a clear oil. Analysis (Kjeldahl):

Calculated for $C_{10}H_{10}O_2N_2$: N, 14.73. Found: N, 14.52.



formed almost quantitatively by condensation of benzaldehyde with *o*-tolyl thiohydantoin. It was purified by crystallization from alcohol and separated in prisms melting at 165° to a light red oil. Analysis (Kjeldahl):

Calculated for $C_{17}H_{11}ON_2S$: N, 9.52. Found: N, 9.49.



formed by condensation of benzaldehyde with tolylhydantoin. It crystallized from alcohol in prismatic crystals which melted at 193–194° to an oil. Analysis (Kjeldahl):

Calculated for $C_{17}H_{14}O_2N_2$: N, 10.1. Found: N, 9.91.

This same hydantoin can also be prepared from 1-*o*-tolyl-4-benzal-

¹ *Loc. cit.*

thiohydantoin by digestion in aqueous solution with chloroacetic acid. For example, 1.75 grams of the benzalthiohydantoin were digested for four hours with 5 grams of chloroacetic acid in 10 cc. of water. The resulting solution was then diluted with about 50 cc. of hydrochloric acid and evaporated nearly to dryness and cooled. The hydantoin separated and was purified by crystallization from alcohol. It separated in colorless prisms, which melted at 193-4°. Analysis (Kjeldahl):

Calculated for $C_{17}H_{14}O_2N_2$: N, 10.11. Found: N, 10.07.

Desulfurization of 1-Phenylthiohydantoin.—This hydantoin was converted smoothly into phenylhydantoin by digestion with chloroacetic acid. The hydantoin was purified by crystallization from water and melted at 154-155°. Guareschi¹ and also Randolph and Bailey,² give this same melting point, while Mouneyrat³ states that it melts at 159-160°. Analysis (Kjeldahl):

Calculated for $C_9H_8O_2N_2$: N, 15.90. Found: N, 15.80.

NEW HAVEN, CONN.,
June 1, 1912.

[CONTRIBUTION FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

HYDANTOINS: THE ALKYLATION OF 2-THIO-4-BENZALHYDANTOIN.

[SIXTEENTH PAPER.]

BY TREAT B. JOHNSON AND BEN H. NICOLET.

Received June 6, 1912.

In our researches⁴ on pyrimidines much attention has been devoted to the alkylation of 2-mercaptopyrimidines corresponding to the general formula (I). It has been shown that these compounds undergo alkylation generally with the formation of two isomeric products. The alkyl group substitutes sometimes, chiefly in the 1 or 3 position, (II) and (III), and again equally in both positions, depending upon the constitution of the pyrimidine and the nature of the halide used. In some cases, however, it has been observed that no 3-alkyl derivative (III) is formed, but that the substitution takes place in position 1 (II) and on the oxygen in position 6 (IV). In fact, there is no uniformity in behavior and it is impossible to predict, when working with a new mercatopyrimidine, which of these three positions in the molecule a certain radicle will select during the process of alkylation. The structure of each new alkyl derivative must be determined separately.

¹ *Beilstein's Handbuch*, 2, 383.

² *Loc. cit.*

³ *Ber.*, '33, 2394.

⁴ From Sheffield Laboratory, 1903-1910.