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°. Guareschi[1] and also Randolph and Bailey,[2] give this same melting point, while Mouneyrat[3] 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.

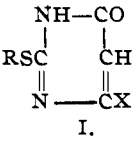
[SIXTEENTH PAPER.]

BY TREAT B. JOHNSON AND BEN H. NICOLET.

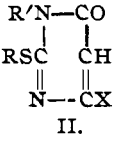
Received June 6, 1912.

In our researches[4] 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.

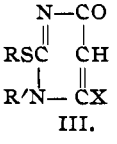
[1] *Beilstein's Handbuch*, 2, 383.
[2] *Loc. cit.*
[3] *Ber.*, 33, 2394.
[4] From Sheffield Laboratory, 1903–1910.



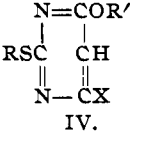
I.



II.

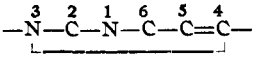


III.



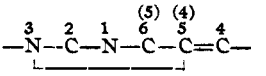
IV.

The aldehyde condensation products of hydantoin and 2-thiohydantoin (VIII) and (X) are closely related in structure to the 2,6-dioxy- and 2-thio-6-oxypyrimidines (uracil and thiouracil) (VII) and (IX). Both types of compounds contain the same carbon-nitrogen chain, —N.C.N.C.C.C—, and differ in constitution in one respect, *viz.*, in the pyrimidines (V) the nitrogen 3 is linked to carbon 4, while in the hydantoins (VI) and thiohydantoins the union is between nitrogen 3 and carbon 5. Positions 4 and 5 in the hydantoins correspond to positions 5 and 6 in the pyrimidines.



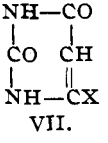
(Pyrimidine)

V.

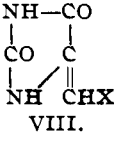


(Hydantoin)

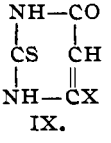
VI.



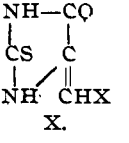
VII.



VIII.



IX.



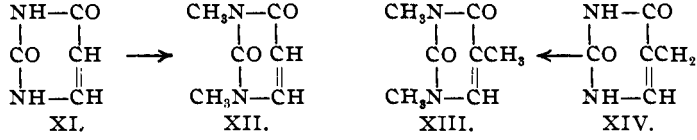
X.

Theoretically, therefore, these compounds might be expected to show some analogy in their behavior on alkylation. The results so far obtained show that the benzalhydantoins (VIII) react with alkyl halides in a similar manner to the pyrimidines (VII) while, on the other hand, the action of an alkyl halide on a benzalthiohydantoin (X) is less complicated than in the case of thiopyrimidines (IX).

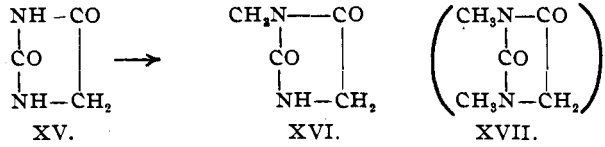
Uracil (XI) is converted easily into 1,3-dimethyluracil (XII) by alkylation with methyl iodide, in alcoholic solution, and in the presence of alkali.[1] Thymine (XIV) behaves in a similar manner. Hydantoin (XV), on the other hand, is less reactive under the same conditions and

[1] Johnson and Clapp, *J. Biol. Chem.*, 5, 49.

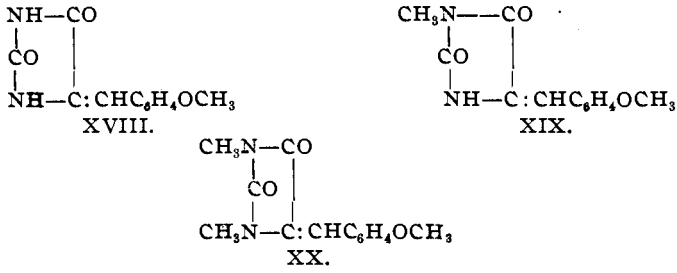
gives only a monomethyl derivative, viz., 1-methylhydantoin[1] (XVI). Harries and Weiss[2] obtained the same hydantoin by the action of methyl iodide on the silver salt of hydantoin. Siemonsen[3] later investigated the action of methyl iodide on the silver salt of 1-methylhydantoin, but he did not succeed in isolating any 1,3-dimethylhydantoin (XVII). The plain hydantoin therefore behaves abnormally. On the other hand, the aldehyde condensation products (VIII) react in a similar manner to uracil and undergo alkylation forming disubstitution products. 4-Anisalhydantoin[4] (XVIII), for example, reacts smoothly with methyl iodide, forming first 1-methyl-4-anisalhydantoin (XIX) and then 1,3-dimethyl-4-anisalhydantoin (XX) corresponding to 1,3-dimethyluracil (XII). We obtained no evidence of the formation of a 3-alkyl or a 5-alkyloxy derivative. Benzalhydantoin reacts in a perfectly similar manner. Therefore, by destroying the influence of the hydrogen atoms in position 4 of the hydantoin ring alkylation in both positions, 1 and 3, can easily be effected.



XI. XII. XIII. XIV.



XV. XVI. XVII.



XVIII. XIX.

XX.

2-Thio-4-benzalhydantoin[5] (XXI) reacts smoothly with molecular proportions of methyl iodide and ethyl bromide, forming almost quantitatively the corresponding mercaptodihydroimidazoles (XXII). These two compounds are soluble in alkali, due to the presence of the —CO.NH— grouping, and undergo a further alkylation, by the action of these halides, with replacement of their N-hydrogen atoms. They differ, however, from

[1] Franchimont and Klobbie, *Rec. trav. chim.*, 8, 289.

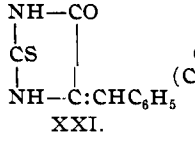
[2] *Ann.*, **327**, 375; **361**, 69.

[3] *Ann.*, **333**, 114.

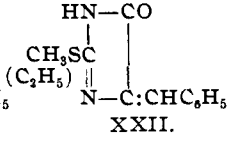
[4] Johnson and Nicolet, *Am. Chem. J.*, **47**, 459.

[5] Wheeler, Nicolet and Johnson, *Am. Chem. J.*, **46**, 456.

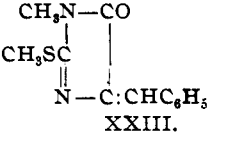
the mercaptopyrimidines in their behavior and form only a 1-alkyl derivative, *viz.*, a 1-alkyl-2-mercapto-5-ketodihydroimidazole. The following representatives of this class of compounds, which were obtained from 2-thio-4-benzalhydantoin, are described in the experimental part of this paper: 1-methyl-2-methylmercapto-4-benzalhydantoin (XXIII), 1-methyl-2-ethylmercapto-4-benzalhydantoin (XXIV) and 1-ethyl-2-ethylmercapto-4-benzalhydantoin (XXV). We obtained no evidence of the formation of 3-alkyl- or 5-alkyloxy derivatives corresponding to formulas (XXVI) and (XXVII):



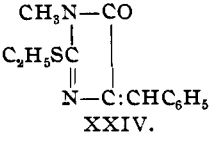
XXI.



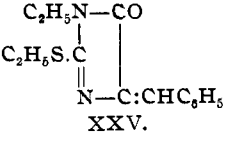
XXII.



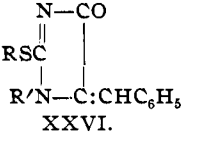
XXIII.



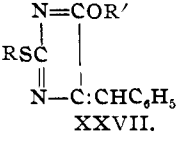
XXIV.



XXV.

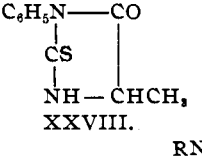


XXVI.

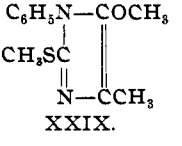


XXVII.

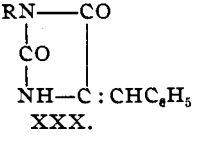
These results are of interest since Marckwald, Neumark and Stelzner[1] have shown that 2-thiohydantoins containing an aryl or alkyl group in position 1 and a free hydrogen in position 4 are transformed by alkylation into true glyoxaline derivatives. For example: 1-phenyl-2-thio-4-methylhydantoin (XXVIII) reacted with methyl iodide, in alcoholic solution, and in the presence of alkali forming 1-phenyl-2-methylmercapto-4-methyl-5-methoxyimidazole (XXIX). The mercaptobenzalimidazoles (XXIII) are decomposed quantitatively when heated with hydrochloric acid with formation of the corresponding hydantoins (XXX) and evolution of mercaptans. The study of hydantoins will be continued.



XXVIII.



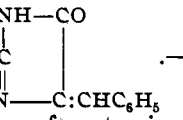
XXIX.



XXX.

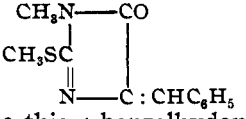
[1] *Ber.*, 24, 3278.

Experimental Part.

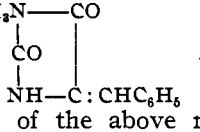
2-Methylmercapto-4-benzal-5-ketodihydroimidazole,  .—2-Thio-4-benzalhydantoin[1] and one molecular proportion of potassium hydroxide were dissolved in about 40 parts of 50% alcohol and the solution digested, on the steam bath, with an excess of methyl iodide for 3 hours. The neutral solution was then concentrated, cooled and finally diluted with water. This imidazole separated as an oil, which solidified almost immediately. The yield of crude material was about 92% of the calculated. The imidazole is very soluble in alcohol and insoluble in water. It crystallizes from dilute alcohol in cream colored needles, which melt at 202°. Analysis (Kjeldahl):

Calculated for $C_{11}H_{10}ON_2S$: N, 12.83. Found: N, 13.3, 12.76.

Behavior on Hydrolysis.—The methylmercaptoimidazole was digested on the steam bath with concentrated hydrochloric acid. Methyl mercaptan was evolved at once and a clear solution was obtained. On evaporating to dryness 4-benzalhydantoin was obtained and crystallized from alcohol in needles, which melted at 213-214°. A mixture of this product and some pure benzalhydantoin[2] melted at the same temperature.

1-Methyl-2-methylmercapto-4-benzal-5-ketodihydroimidazole,  . — This imidazole was formed by alkylation of 2-thio-4-benzalhydantoin with an excess of methyl iodide in an alcoholic solution and in the presence of two molecular proportions of sodium ethylate. The compound is very soluble in boiling alcohol and very insoluble in water. It crystallizes from alcohol in yellow prisms, which melt at 105° to an oil. The imidazole is insoluble in 5% sodium hydroxide solution. Analysis (Kjeldahl):

Calculated for $C_{12}H_{12}ON_2S$: N, 12.06. Found: N, 11.82.

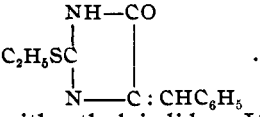
1-Methyl-4-benzalhydantoin,  .—This hydantoin was formed smoothly by hydrolysis of the above mercaptoimidazole with strong hydrochloric acid. It was purified by crystallization from alcohol and separated in flat, colorless prisms, which melted at 221°. The hydantoin is slightly soluble in hot water and practically insoluble in cold. It dissolves in cold 5% sodium hydroxide solution. Analysis (Kjeldahl):

Calculated for $C_{11}H_{10}O_2N_2$: N, 13.85. Found: N, 13.74.

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

[2] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368.

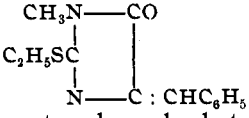
2-Ethylmercapto-4-benzal-5-ketodihydroimidazole,



. — From 2-thio-4-benzalhydantoin by alkylation with ethyl iodide. It crystallizes from alcohol in light yellow needles, which melt at 165–166°. Analysis (Kjeldahl):

Calculated for $C_{12}H_{12}ON_2S$: N, 12.06. Found: N, 11.85.

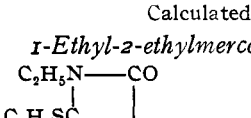
1-Methyl-2-ethylmercapto-4-benzal-5-ketodihydroimidazole,



.—This was formed by alkylation of 2-ethylmercapto-4-benzal-5-ketodihydroimidazole with methyl iodide. It is very soluble in alcohol and insoluble in water and dilute alkali. It crystallizes from dilute alcohol in yellow, prismatic crystals, which melt at 94–95°. Analysis (Kjeldahl):

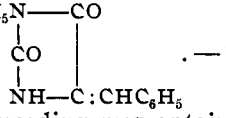
Calculated for $C_{13}H_{14}ON_2S$: N, 11.38. Found: N, 11.20.

1-Ethyl-2-ethylmercapto-4-benzal-5-ketodihydroimidazole,



. — This imidazole was prepared by alkylation of 2-thio-4-benzalhydantoin with ethyl bromide in the presence of sodium ethylate. It was obtained as an oil, which showed no signs of solidifying.

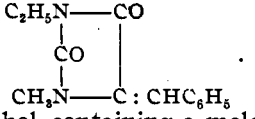
1-Ethyl-4-benzalhydantoin,



. — This hydantoin was obtained by hydrolysis of the preceding mercaptoimidazole with hydrochloric acid. It was purified by crystallization from alcohol and separated in colorless prisms melting at 160°. It is soluble in dilute alkali. This same hydantoin is also formed by the action of one molecular proportion of ethyl bromide on 4-benzalhydantoin in the presence of alkali.

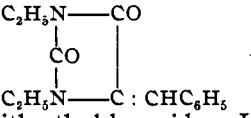
Calculated for $C_{12}H_{12}O_2N_2$: N, 12.96. Found: N, 13.1.

1-Ethyl-3-methyl-4-benzalhydantoin,



. — 1-Ethyl-4-benzalhydantoin was dissolved in alcohol containing a molecular proportion of sodium ethylate and then digested with an excess of methyl iodide until the solution was neutral. After evaporating the solution the hydantoin was obtained as a solid, which was readily soluble in cold alcohol and insoluble in alkali. It crystallizes in yellow flakes, which melted at 94° to an oil. Analysis (Kjeldahl):

Calculated for $C_{13}H_{14}O_2N_2$: N, 12.1. Found: N, 11.75.

1,3-Diethyl-4-benzalhydantoin,  —From 1-ethyl-4-benzalhydantoin by alkylation with ethyl bromide. It melted at 91–92°. Analysis (Kjeldahl):

Calculated for $C_{14}H_{16}O_2N_2$: N, 11.47. Found: N, 11.07.

NEW HAVEN, CONN.,
June 5, 1912.

[CONTRIBUTION FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

HYDANTOINS: SYNTHESIS OF THE HYDANTOIN OF 3-AMINO-TYROSINE.

[SEVENTEENTH PAPER.]

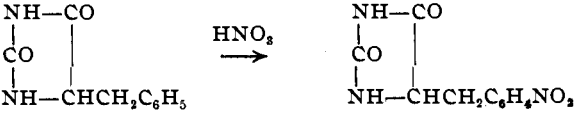
BY TREAT B. JOHNSON AND ROBERT BENGIS.

Received June 8, 1912.

In a previous paper from this laboratory entitled "The Synthesis of Thiotyrosine"[1] (I), Johnson and Brautlecht have described the action of nitric acid on the hydantoin of phenylalanine (II). They observed that this compound is attacked by nitric acid in the *para* position of the benzene ring with formation of 4-paranitrobenzylhydantoin (III). In this paper we shall describe the behavior of nitric acid towards anisylhydantoin (VI) and anisalhydantoin[2] (IV).

$HS.C_6H_4.CH_2.CH(NH_2)COOH.$

I.



II. III.

4-Anisylhydantoin (VI), which was prepared by the reduction of anisalhydantoin (IV) with sodium amalgam, reacts smoothly with concentrated nitric acid, forming a mononitro derivative. We find that the nitro group substitutes in the 3 position of the benzene ring forming 4-(3-nitro-4-methoxybenzyl)hydantoin (VII), which, on reduction, is converted quantitatively into the corresponding 4-(3-amino-4-methoxybenzyl)-hydantoin (IX). The constitution of this aminohydantoin (IX), and also that of the nitro derivative (VII), was established by the fact that the same aminohydantoin (IX) was also formed by reduction of 4-(3-nitro-4-methoxybenzal)-hydantoin (X) with tin and hydrochloric acid. The nitrobenzalhydantoin (X) was obtained easily by condensation of 3-nitro anisic aldehyde[3] (VIII) with hydantoin in the presence of sodium acetate.

[1] *J. Biol. Chem.*, August Number (1912).

[2] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368.

[3] Einhorn and Grabfield, *Ann.*, **243**, 370.