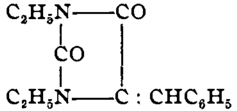


$$\begin{array}{lcl} C_2H_5N & — & CO \\ | & & | \\ CO & & | \\ | & & | \\ C_2H_5N & — & C:CHC_6H_5 \end{array}$$

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.]

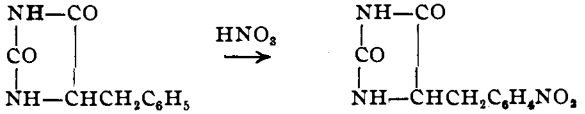
BY TREAT B. JOHNSON AND ROBERT BENGIS.

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.



$$\begin{array}{lcl} \begin{array}{lcl} NH & — & CO \\ | & & | \\ CO & & | \\ | & & | \\ NH & — & CHCH_2C_6H_5 \end{array} & \xrightarrow{HNO_3} & \begin{array}{lcl} NH & — & CO \\ | & & | \\ CO & & | \\ | & & | \\ NH & — & CHCH_2C_6H_4NO_2 \end{array} \end{array}$$

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).

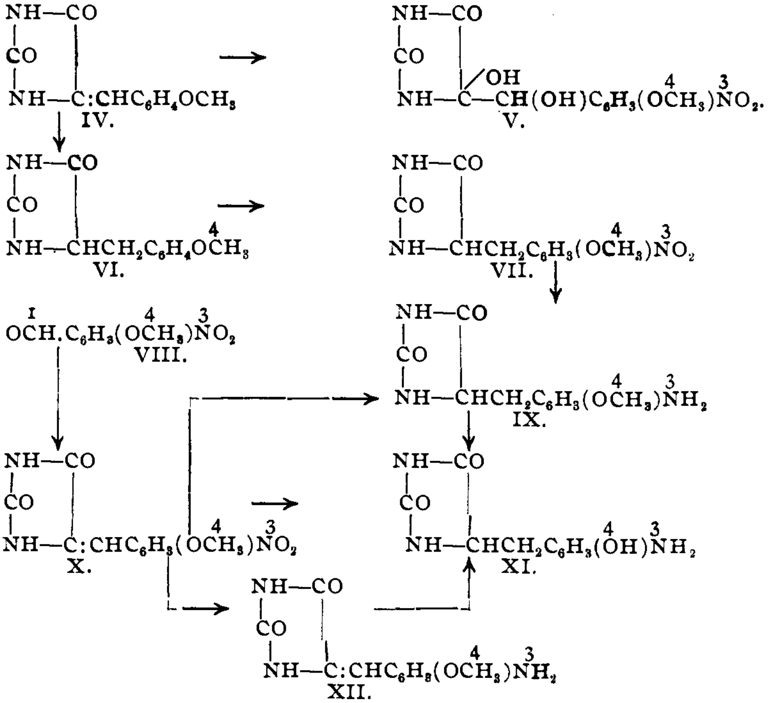
[2] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368.

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

It is very probable that the nitrotyrosine, which Strecker[1] obtained by nitration of tyrosine, is also a 3-nitro derivative:

$$\overset{3}{N}O_2(\overset{4}{O}H)C_6H_3CH_2CH(NH_2)COOH.$$

By reduction of 3-nitroanisalhydantoin (X) with ferrous sulfate and ammonia, the double bond is not affected, and 3-aminoanisalhydantoin (XII) is formed. This compound is reduced by tin and hydrochloric acid, forming the 3-aminohydantoin (IX). When 3-aminoanisalhydantoin (XII) is digested with strong hydriodic acid, methyl iodide is evolved and the hydriodide of 4-(3-amino-4-hydroxybenzyl)-hydantoin (XI) is formed. In order to prepare this interesting compound, it is not, however, necessary to isolate the intermediate products (XII) and (IX). By warming the 3-nitroanisalhydantoin (X) with hydriodic acid the nitro group and double bond are reduced and the methyl group detached in one operation with formation of the hydantoin (XI). This is then easily obtained in the form of its hydrochloride by digesting the hydriodide in aqueous solution with silver chloride. Anisalhydantoin (IV) undergoes nitration with substitution, apparently, in position 3. At the same time this compound is oxidized at the double bond giving a glycol derivative (V). These various changes are represented by the following structural formulas:



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[1] *Ann.*, 73, 70. Stäedeler, *Ibid.*, 116, 78.

The hydantoin of 3-aminotyrosine (XI) is of special interest because of its possible use for further important systheses. It is more suitable for synthetical purposes than the aminotyrosine (XIII) because of the

$$\overset{3}{N}H_2(\overset{4}{O}H)C_6H_3—CH_2CH_2(NH_2)COOH.$$

XIII.

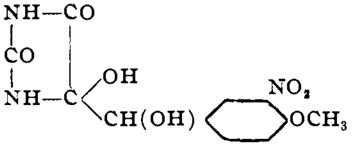
fact that the influence of one of the basic amino radicles is destroyed. The investigation of this interesting hydantoin is now in progress.

Experimental Part.

The anisalhydantoin, which was used in this investigation, was prepared by condensation of anisic aldehyde with hydantoin according to the method of Wheeler and Hoffman.[1] The following proportions were used in its preparation: 20 grams of hydantoin, 50 grams of anhydrous sodium acetate, 32 grams of anisic aldehyde and 80 cc. of glacial acetic acid. The yield of anisal hydantoin was 88% of the theoretical.

The Action of Nitric Acid on Anisalhydantoin.

4-Hydroxy-4-(α-hydroxynitroanisyl)-hydantoin,



.—Twenty-five cc. of concentrated nitric acid were placed in a small flask and cooled below 0°. Five grams of finely pulverized hydantoin were then carefully added when there was an immediate reaction and the hydantoin dissolved. The solution assumed a dark color and finally a small amount of a brown substance separated. After standing at ordinary temperature for one hour, when red fumes began to be evolved, the solution was poured into about 400 cc. of water and the solution filtered. Nothing separated on standing. The nitric acid was then neutralized with sodium hydroxide and the solution evaporated to dryness. The residue obtained was triturated with 200 cc. of cold water to remove sodium nitrate and the undissolved hydantoin recrystallized from hot water. It separated on cooling in yellow needles, which melted with decomposition at 206–207°. The hydantoin can also be purified by crystallization from 95% alcohol. Analyses (Kjeldahl):

Calculated for $C_{11}H_9O_5N_3$: N, 15.90; $C_{11}H_8O_7N_4$: N, 18.12; $C_{11}H_{11}O_7N_3$: N, 14.14.
Found: N, 13.98, 14.03, 14.10.

Reduction of Anisalhydantoin with Sodium Amalgam.—Thirty-six grams of the hydantoin were suspended in a mixture of 250 cc. of water and 15 cc. of sodium hydroxide solution (10%). Three hundred and forty grams of 3% sodium amalgam were then added in portions of about

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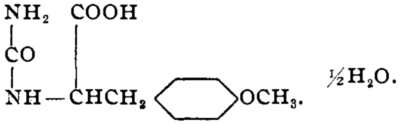
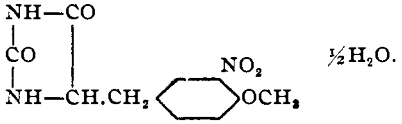
[1] *Am. Chem. J.*, **45**, 368.

50 grams and the solution heated at 70–80° during the reduction. After about 24 hours the reaction was complete and the solution had assumed a much lighter color. After filtering, it was acidified with hydrochloric acid and cooled, when anisylhydantoin separated. This was filtered off and purified by crystallization from water. It melted at 175–176°. The yield was 73% of theory. A secondary product was isolated which melted at 156° with effervescence after crystallization from water. It contained water of crystallization and a nitrogen determination agreed with the calculated value for *anisylhydantoic acid.*



Calculated for $(C_{11}H_{14}O_4N_2)_2.H_2O$: N, 11.76; H_2O, 3.64.
Found: N, 12.0 ; H_2O, 3.82.

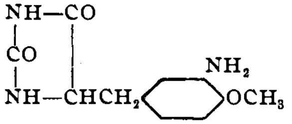
4-(3-Nitro-4-methoxybenzyl)hydantoin,



—Five cc. of fuming nitric acid were mixed with 15 cc. of concentrated nitric acid of sp. gr. 1.42 and then cooled to 10°. Five grams of the hydantoin were then added in small portions. There was an immediate reaction with evolution of heat, but the temperature was not allowed to rise above 14°. After the hydantoin had dissolved, the liquid was then poured into 200 cc. of water, when the crude nitrohydantoin separated in the form of yellow crystals. The substance was separated by filtration, washed with cold water to remove the nitric acid, and then purified by crystallization from water. The yield of crude hydantoin was 4.0 grams, or 80% of the theoretical. This hydantoin separates from water in slender prisms arranged in radiating clusters and also in cigar shaped crystals which melt at 186–188° to an oil. It contained one-half of a molecule of water of crystallization. Nitrogen determinations by Kjeldahl method:

Calculated for $(C_{11}H_{11}O_5N_3)_2.H_2O$: N, 15.85; H_2O, 3.28.
Found: N, 16.05, 16.12, 15.70, 15.84, 15.78; H_2O, 3.41.

4-(3-Amino-4-methoxybenzyl)-hydantoin,

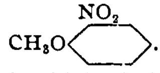


.—This hydantoin was prepared by reduction of the above nitro compound with iron sulfate and ammonia. Nine grams of the nitro compound were suspended in about 400 cc. of dilute ammonia and 85 grams of $FeSO_4.7H_2O$, dissolved in water, were then added. The flask was then placed on the steam oven and the reduction continued for about 40 hours with frequent agitation. This mixture was then evaporated to remove the excess of ammonia, diluted with water and filtered to separate the iron oxide. The filtrate was then digested with an excess of barium hydroxide to remove sulfates and ammonia, and the excess of barium finally exactly precipitated by addition of sulfuric acid. A clear solution was obtained which was then evaporated to dryness, when a crystallin residue was obtained. This product was insoluble in alcohol and extremely soluble in dilute alcohol and water. The aminohydantoin was finally obtained in the form of its hydrochloride as follows: The crude residue was dissolved in dilute hydrochloric acid, the solution decolorized by digesting with bone coal, and the solution concentrated, when the monohydrochloride separated in the form of colorless needles. This salt is very soluble in water and melts at 271–272° with decomposition. Analysis (Kjeldahl):

Calculated for $C_{11}H_{13}O_3N_3.HCl$: N, 15.47. Found: N, 15.28.

In order to obtain the free base, 2.4575 grams of this hydrochloride were dissolved in a small volume of water and the hydrochloric acid exactly neutralized by addition to this solution of the required amount of sodium hydroxide. A very slight precipitate was obtained here and was separated by filtration. On evaporating this filtrate there was apparently some oxidation and some dark colored, amorphous material separated. After concentration to a small volume and filtering the hydantoin separated, on cooling, in the form of a gray powder. This base is very soluble in absolute alcohol and water. It was purified for analysis by crystallization from alcohol and separated from this solvent in indefinit crystals, which melted at 175–177° to a dark oil. Analysis (Kjeldahl):

Calculated for $C_{11}H_{13}O_3N_3$: N, 17.87. Found: N, 17.96.

Nitroanisic Aldehyde.  —This aldehyde was prepared by nitration of anisic aldehyde.[1] One molecular proportion of nitric acid of sp. gr. 1.43 (9.64 grams) was mixed with 20 parts by weight of concentrated sulphuric acid (193 grams) and the mixture cooled to —10°. Twenty grams of anisic aldehyde were then added slowly and the temperature of the solution maintained between —12° and —7°. After standing for one hour the acid solution was then poured into one liter of cold water when the aldehyde separated immediately. It was purified by crystallization from 95% alcohol and melted at 83° to an oil. The yield of pure aldehyde was 15.3 grams or 76.5% of theory.

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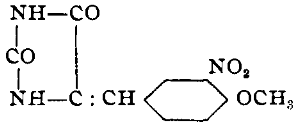
[1] Einhorn and Grabfield, *Loc. cit.*

Condensation of Nitroanisic Aldehyde with Hydantoin.

Nitroanisalhydantoin,



.—Six and six-tenths grams of hydantoin, 12 grams of the aldehyde, 16.5 grams of fused sodium acetate, and 27 cc. of glacial acetic acid were placed in a Kjeldahl flask and heated in an oil bath at 165° for 5.5 hours. The acid solution assumed a dark color and some of the condensation product separated from the hot mixture. After cooling, water was added and the material disintegrated by heating on the steam bath. The hydantoin was then separated and washed with water. This hydantoin is insoluble in boiling water and alcohol. It was purified by crystallization from glacial acetic acid and separated in the form of flat prisms, which melted at 276–277° with decomposition. The yield was 14.5 grams, or 85%, of the theoretical. The hydantoin crystallizes from glacial acetic acid with one molecule of acid of crystallization. This was determined by heating at 130°.

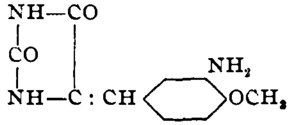
Calculated for $C_{11}H_9O_5N_3.HC_2H_3O_2$: Acetic acid, 18.57. Found: Acetic acid, 18.38

Nitrogen determination in the free hydantoin (Kjeldahl):

Calculated for $C_{11}H_9O_5N_3$: N, 15.97. Found: N, 15.95, 16.08.

Reduction of Nitroanisalhydantoin with Iron Sulfate and Ammonia.

Aminoanisalhydantoin,



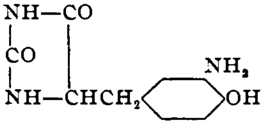
. — This hydantoin was obtained in the form of its hydrochloride as follows: The nitrohydantoin was first reduced under practically the same conditions as were employed in the reduction of the corresponding anisyl derivative above. After separation of the iron hydroxide the solution was digested with barium hydroxide to remove ammonia and sulfuric acid and the excess of barium removed by addition of the required amount of sulfuric acid. The solution was then evaporated to dryness, when the crude aminohydantoin was obtained. This was insoluble in water and 95% alcohol and was therefore dissolved in dilute hydrochloric acid, decolorized with bone coal and the solution then concentrated. On cooling, the hydrochloride separated in radiating needles, which melted at 285–286° with effervescence. More of the hydantoin was obtained by digesting the iron hydroxide residues with sodium hydroxide solution. A mixture of this hydrochloride with the hydrochloride of aminoanisylhydantoin melted below 270°. Nitrogen (Kjeldahl):

Calculated for $C_{11}H_{11}O_3N_3.HCl$: N, 15.58. Found: N, 15.7.

Reduction of Aminoanisalhydantoin with Tin and Hydrochloric Acid.— Three grams of this hydantoin were dissolved in a boiling mixture of 50 cc. of concentrated hydrochloric acid and 400 cc. of water. Two grams of tin were then added and the mixture heated on the steam bath for 3.5 hours. The tin had not all dissolved and the hot solution was then saturated with hydrochloric acid gas until a clear solution was obtained. This was then transferred to a large evaporating dish and the solution evaporated to dryness to remove the excess of hydrochloric acid. The double tin salt was then dissolved in water and the undissolved portion saved. This was identified as unaltered hydantoin and melted at 284–286°. The tin was precipitated by hydrogen sulfide and the acid solution concentrated on the steam bath. On cooling, the hydrochloride separated and melted at 271–272° with decomposition. A mixture of this product with some of the hydrochloride obtained by reduction of aminoanisylhydantoin (m. 271–272°) melted at the same temperature. Analysis (Kjeldahl):

Calculated for $C_{11}H_{13}O_3N_3.HCl$: N, 15.47. Found: N, 15.20.

This same salt was also obtained when the nitrohydantoin was reduced with sodium amalgam and the reduction product dissolved in hydrochloric acid.

Hydantoin of Aminotyrosine,  . — This new hydantoin was obtained in the form of its hydriodide by digestion of nitroanisalhydantoin with hydriodic acid. This was then changed into the hydrochloride by digestion with silver chloride. Five grams of the hydantoin were warmed with 25 cc. of hydriodic acid of sp. gr. 1.7 and a little red phosphorus for 2 hours. Methyl iodide was evolved and a clear, colorless solution was obtained. This was then evaporated on the steam bath to remove the excess of hydriodic acid, the residue triturated with water to remove red phosphorus and the solution filtered. This water solution of the hydriodide of the aminohydantoin was then digested with an excess of freshly precipitated silver chloride when we obtained a light colored liquid with silver iodide in suspension. After filtering off the silver iodide and excess of silver chloride the solution was concentrated on the steam bath. It assumed a dark color by this treatment and on cooling the salt did not separate because of its solubility. The solution was finally decolorized by digestion with bone coal and then evaporated in a vacuum over sulfuric acid. In this manner we finally succeeded in obtaining the pure salt. It separated in small prismatic crystals, which melted at 253–254° with effervescence. It contained chlorine and a mixture of the salt with the hydantoin of tyrosine melted below 241°. This salt contained one molecule of water of crystallization, which was determined by heating at 110–120°.

Calculated for $C_{10}H_{12}O_3N_3Cl.H_2O$: H_2O, 6.53. Found: H_2O, 6.9.

Nitrogen determination in the anhydrous salt (Kjeldahl):

Calculated for $C_{10}H_{12}O_3N_3Cl$: N, 16.3. Found: N, 15.9, 15.83.

The study of this hydantoin will be continued.

NEW HAVEN, CONN.
June 6, 1912.

[CONTRIBUTION FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

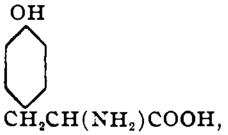
HYDANTOINS: THE SYNTHESIS OF 3-BROMOTYROSINE.

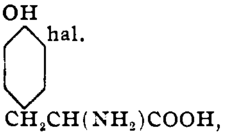
[EIGHTEENTH PAPER.]

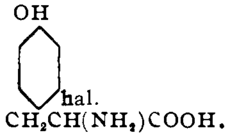
BY TREAT B. JOHNSON AND ROBERT BENGIS.

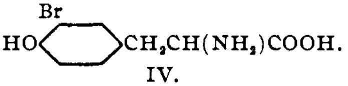
Received June 10, 1912.

This paper is a contribution to our knowledge of the chemistry of halogen derivatives of tyrosine (I). If one considers only substitution in the benzene nucleus of this amino acid, only two types of monohalogenated derivatives are theoretically possible, *viz.*, 2- and 3-substituted amino acids corresponding to formulas (II) and (III). No representative of either of these two types, so far as the writer is aware, has hitherto been described in the literature. In this paper, a description of the synthesis and properties of 3-bromotyrosine (IV) is given. We shall also describe several derivatives of this interesting amino acid.


I.


II.


III.


IV.

3-Bromotyrosine (IV) has been synthesized by two different methods. Starting with 3-bromoanisic aldehyde[1] (VI), this was condensed with hydantoin, in the presence of anhydrous sodium acetate and acetic acid, when 4-(3-brom-4-methoxybenzal)-hydantoin (V) was obtained. This compound was then converted into 4-(3-bromo-4-methoxybenzyl)-hydantoin (VII) by reduction with tin and hydrochloric acid. This same hydantoin (VII) can also be prepared from the hydantoin of 4-(3-amino-4-methoxybenzyl)-hydantoin (VIII), which the writers have described in the preceding paper.[2] This was accomplished by first diazotizing the aminohydantoin (VIII) and then warming the resulting diazonium salt with

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[1] Cahours, *Ann.*, 56, 308. Walther and Wetzlich, *J. prakt. Chem.*, [2] 61, 198.

[2] Johnson and Bengis, THIS JOURNAL, 34, 1054.