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.]

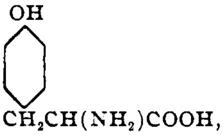
HYDANTOINS: THE SYNTHESIS OF 3-BROMOTYROSINE.

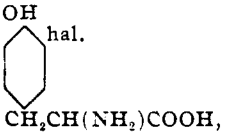
[EIGHTEENTH PAPER.]

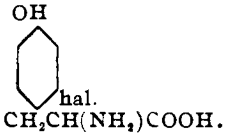
By Treat B. Johnson and Robert Bengis.

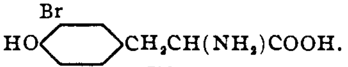
Received June 10, 1912.

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

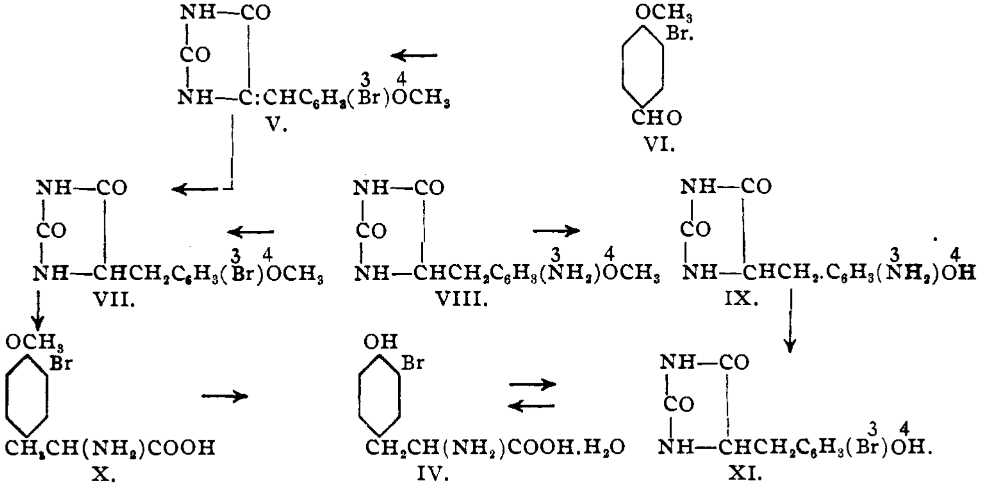
---

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

[2] Johnson and Bengis, This Journal, **34**, 1054.

cuprous bromide. The yield of the bromo-compound (VII) was nearly 90% of the calculated quantity. When 4-(3-bromo-4-methoxybenzyl) hydantoin (VII) was heated, under pressure, with barium hydroxide, the hydantoin ring was ruptured and practically a quantitative yield of α-amino-β-(3-bromo-4-methoxyphenyl)-propionic acid (X) was obtained. This amino acid was easily demethylated by heating with hydrobromic acid and 3-bromotyrosine (IV) was formed. This halogen amino acid, when crystallized from water, contains one molecule of water of crystallization. A description of its chemical properties is given in the experimental part of this paper.

The hydantoin of 3-bromotyrosine (XI) was prepared from the hydantoin of 3-aminotyrosine[1] (IX) by diazotization and finally warming with cuprous bromide (Sandmeyer's reaction). These various transformations are represented by the following structural formulas:



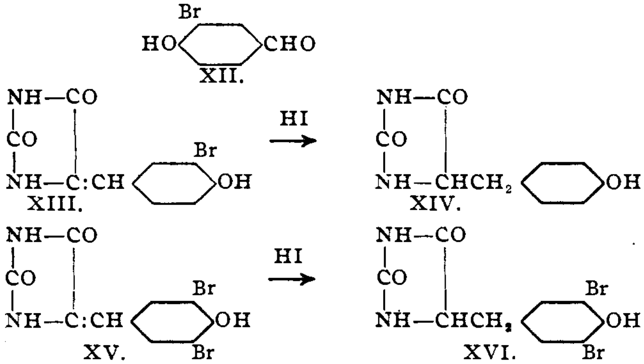
An attempt was made to develop a synthesis of 3-bromotyrosine (IV) by starting with 3-bromo-4-hydroxybenzaldehyde (XII). This aldehyde, however, does not combine smoothly with hydantoin and the yield of 4-(3-bromo-4-hydroxybenzal)-hydantoin (XIII) was poor. When this hydantoin was warmed with hydriodic acid, it not only underwent reduction at the double bond, but the bromine atom in position 3 was displaced by hydrogen and the hydantoin of tyrosine (XIV) was formed. This result is of interest since 4-(3,5-dibromo-4-hydroxybenzal)-hydantoin[3] (XV) can be reduced with hydriodic acid without removal of the bromine atoms, giving 4-(3,5-dibromo-4-hydroxybenzyl)-hydantoin (XVI).

---

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

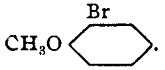
[2] Paal, *Ber.*, **28**, 2409; *Chem. Centr.*, 1, 523 (1900).

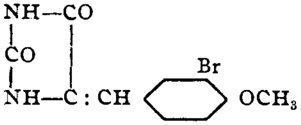
[3] Johnson and Hoffman, *Am. Chem. J.*, **47**, 20.



The study of monohalogen derivatives of tyrosine will be continued.

Experimental Part.

Bromoanisic Aldehyde,[1]  $CH_3O\overset{Br}{\langle\quad\rangle}.\ CHO$.—This aldehyde was prepared by adding to 25 grams of anisic aldehyde 29.4 grams of bromine through a dropping funnel. Much heat was evolved and hydrobromic acid was generated immediately. After standing about 15 minutes a thick magma of the aldehyde was obtained. The mixture was then allowed to stand for several hours, triturated with 10–15 cc. of ether and the aldehyde then separated by suction filtration. In order to wash free from hydrobromic acid the crude product was dissolved in ether, washed with sodium hydroxide solution, and the solution then dried over anhydrous potassium carbonate. After evaporating the ether the aldehyde was obtained in the form of pale yellow prisms, which melted at 52–53° to an oil. The yield was 27 grams, or 70% of the calculated.

4-(3-Bromo-4-methoxybenzal)-hydantoin,  —

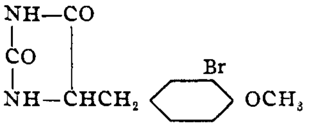
Twelve and five-tenths grams of hydantoin, 27 grams of bromoanisic aldehyde and 32 grams of anhydrous sodium acetate were dissolved in 50 cc. of glacial acetic acid and the mixture heated to boiling in an oil bath for about 6 hours. The mixture was then poured, while hot, into 800 cc. of cold water when this hydantoin separated in yellow crystals. The compound is insoluble in cold and slightly soluble in hot water, easily soluble in glacial acetic acid and difficultly soluble in alcohol. It was purified by crystallization from acetic acid and separated in yellow needles, which melted at 267–268° to a dark oil. The yield was 24 grams, or 65% of the theoretical. Analysis (Kjeldahl):

Calculated for $C_{11}H_9O_3N_2Br$: N, 9.43. Found: N, 9.33, 9.35.

---

[1] Cahours, *Loc. cit.*

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

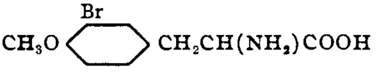


—Twenty-four and two-tenths grams of the preceding hydantoin and 40 grams of powdered tin were suspended in 250 cc. of 95% alcohol. The flask was then connected with a return condenser and hydrochloric acid gas passed into the hot solution until all the hydantoin and tin dissolved. The solution was then evaporated to dryness and the residue triturated with cold water to dissolve tin chloride. The reduced hydantoin was insoluble in water and was separated and purified by crystallization from 95% alcohol. It deposited in beautiful triclinic crystals, which melted at 210–211° to an oil. Before melting, the compound always began to shrivel at about 200°. The yield was 18.0 grams, or 75% of the calculated. Analysis (Kjeldahl):

Calculated for $C_{11}H_{11}O_3N_2Br$: N, 9.36. Found: N, 9.15.

Synthesis of 4-(3-Bromo-4-methoxybenzyl)-hydantoin from 4-(3-Amino-4-methoxybenzyl)-hydantoin.—Two and two-tenths grams of the aminohydantoin hydrochloride[1] were suspended in a mixture of 10 cc. of water and 10 cc. of dilute hydrochloric acid and cooled to 0°. One gram of finely pulverized potassium nitrite was then added slowly when the hydantoin completely dissolved and the diazonium salt was formed. The mixture was allowed to stand about 30 minutes and then added slowly to a cool solution of cuprous bromide. Nitrogen was evolved at once. After allowing to stand over night the mixture was heated to decompose the diazonium salt and cooled when this bromohydantoin separated as a brown solid. It was separated and dissolved in dilute sodium hydroxide solution to free from impurities. On acidifying the alkalin solution with hydrochloric acid the hydantoin separated in yellow crystals and the yield was 2.1 grams, or 87.5% of theory. It crystallized from alcohol in characteristic triclinic prisms, which melted at 208–210° to a yellow oil. When mixed with some of the hydantoin obtained by reduction of the benzal derivative this melting point was not altered.

α-Amino-β-(3-bromo-4-methoxyphenyl)-propionic Acid,



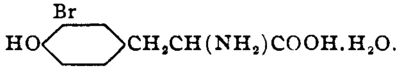
. — This amino acid was obtained by heating the above hydantoin with barium hydroxide. Three grams of the hydantoin and 9 grams of barium hydroxide were dissolved in hot water and the solution heated for 3 hours at 147°–155°. Ammonia was evolved and barium carbonate was formed. The contents of the bomb tube were transferred to a casserole and the excess of ammonia expelled by boiling. The barium was then exactly precipitated with sulphuric

---

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

acid and the solution filtered. On evaporating to dryness the amino acid was obtained as a crystallin crust. It was purified by crystallization from hot water, and separated, on cooling, in rectangular plates, which melted at 235–236° with effervescence. It does not give Millon's reaction. The yield of pure acid was 2.0 grams, or 77% of the calculated. Analysis (Kjeldahl):

Calculated for $C_{10}H_{12}O_3NBr$: N, 5.11. Found: N, 5.4.

3-Bromotyrosine, 
$\overset{Br}{HO\langle\quad\rangle}CH_2CH(NH_2)COOH.H_2O$. — This new amino acid was obtained in the form of its hydrobromide by boiling α-amino-β-(3-bromo-4-methoxyphenyl)-propionic acid with hydrobromic acid. Methyl bromide was evolved and a clear solution was obtained. After the reaction was complete the excess of acid was removed by evaporation on the steam bath and the saturated solution allowed to stand in a desiccator. The hydrobromide of bromotyrosine finally separated and melted at 190–191° with effervescence. Analysis (Kjeldahl):

Calculated for $C_9H_{10}O_3NBr.HBr$: N, 4.1. Found: N, 3.97, 4.2.

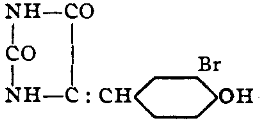
In order to obtain the bromotyrosine 3.4 grams of its hydrobromide were dissolved in 150 cc. of water and the hydrobromic acid neutralized by digesting with 2.8 grams of silver carbonate. The silver bromide was filtered off and the filtrate then saturated with hydrogen sulfide to precipitate any dissolved silver. The clear solution was then concentrated to a volume of 50 cc. and cooled when bromotyrosine separated in almost perfect tetrahedral crystals. It melts at 247–248° with effervescence. It gives a strong Millon reaction and crystallizes from water with one molecule of water of crystallization. Analysis:

Calculated for $C_9H_{10}O_3NBr.H_2O$: H_2O, 6.47. Found: H_2O, 6.57.

Nitrogen and bromine determinations in the anhydrous acid:

Calculated for $C_9H_{10}O_3NBr$: N, 5.38; Br, 30.77. Found: N, 5.33; Br, 30.45.

No precipitate of silver bromide is obtained by adding silver nitrate to a cold solution of bromtyrosine in nitric acid. When the solution, however, is warmed it becomes turbid and silver bromide separates. The amino acid is not precipitated from a dilute sulfuric acid solution by addition of phosphotungstic acid. It gives no precipitate with mercury chloride solution and the picrate and chloroplatinate are extremely soluble in water. While tyrosine has no taste, this bromo acid is intensely sweet.

4-(3-Bromo-4-hydroxybenzal)-hydantoin, 
$\begin{array}{l} NH{-}CO \\ CO \\ NH{-}C:CH\overset{Br}{\langle\quad\rangle}OH \end{array}$. — This was formed by condensation of 9.1 grams of hydantoin with 20

grams of bromohydroxybenzaldehyde in the presence of 30 grams of sodium acetate and 40 cc. of glacial acetic acid. It was purified by recrystallization from glacial acetic acid and separated in yellow needles, which decomposed at 295° with effervescence. It gave a strong Millon reaction. The yield was poor. Analysis (Kjeldahl):

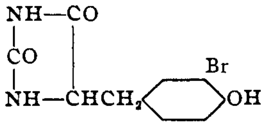
Calculated for $C_{10}H_7O_3N_2Br$: N, 9.89. Found: N, 9.85.

The Action of Hydriodic Acid on 4-(3-Bromo-4-hydroxybenzal)-hydantoin.—Two grams of the hydantoin were dissolved in a mixture of 15 cc. of hydriodic acid (sp. gr. 1.7) and 15 cc. of glacial acetic acid and the solution boiled for about 2.5 hours. The solution was then evaporated to remove the excess of hydriodic acid and the product obtained purified by recrystallization from hot water. On cooling, prisms separated which melted at 256–257° with effervescence. The compound did not contain bromine and it was identified as tyrosine hydantoin. Analysis (Kjeldahl):

Calculated for $C_{10}H_{10}O_3N_2$: N, 13.5. Found: N, 13.2.

An attempt to reduce the benzalhydantoin with tin and hydrochloric acid was unsuccessful. One gram of the hydantoin and 1.5 grams of tin were suspended in 50 cc. of strong hydrochloric acid and sufficient alcohol added to help dissolve the hydantoin on warming. The mixture was then heated on the steam bath for 4 days and cooled. We recovered 0.8 gram of the original hydantoin, which melted at 295° with decomposition.

Hydantoin of 3-Bromotyrosine,



. — This was prepared from the hydantoin of 3-aminotyrosine.[1] The aminotyrosine hydantoin was diazotized in hydrochloric acid solution in the usual manner and the diazonium solution poured into a freshly prepared solution of cuprous bromide. After allowing to stand several hours this mixture was heated to boiling and filtered. The filtrate was then saturated with hydrogen sulfide to precipitate copper and filtered. An excess of barium hydroxide was then added to remove sulfates and the excess of barium removed by addition of the required amount of sulfuric acid. After filtering, the solution was then concentrated and cooled when this hydantoin deposited as a brown solid. The yield was small. It separated from hot alcohol in small prisms, which melted at 284–285° with decomposition. It was dried for analysis at 110° (Kjeldahl):

Calculated for $C_{10}H_9O_3N_2Br$: N, 9.82. Found: N, 9.73.

NEW HAVEN, CONN.
June 8, 1912.

---

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