LXXI.—On some Carbamido-acids and their Hydantoin.

By JOHN RICHARD SCOTT and JULIUS BEREND COHEN.

URAMIDOBENZOIC (*o*-carbamidobenzoic) acid, its nitro-derivatives, and also the hydantoin (2:4-diketo-1:2:3:4-tetrahydroquinazoline) derived from it were first prepared by Griess (*J. pr. Chem.*, 1872, [ii], 5, 371),

o-Carbamidobenzoic acid.

Diketotetrahydroquinazoline.

In the course of last year a more careful study of the hydantoin and its derivatives was begun by one of us and the results were prepared for publication, when a paper on the same subject appeared (Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, 41, 2052). As most of our results are embodied in that paper, it is only necessary to refer to the following few additional observations, before discussing the main subject of the present investigation.

Preparation of the Hydantoin from the Carbamido-compound.—6.5 Grams of the carbamido-compound were heated on the water-bath for half an hour with 40 c.c. of concentrated hydrochloric acid (Bogert and Scatchard used sodium hydroxide), yielding 5.5 grams of the hydantoin.

The sodium salt of the hydantoin was obtained by dissolving the latter (2 parts) in a solution of sodium hydroxide (1 part) in water (20 parts). On cooling, clusters of needles separated, which were recrystallised from water. The sodium salt contains 5H₂O (not recorded by Bogert and Scatchard) (Found: H₂O = 33.06; Na = 8.04. Calc. for C₈H₅O₂N₂Na, 5H₂O: H₂O = 32.8; Na = 8.4 per cent.).

The Action of Methyl Sulphate.—The dimethyl ether of the hydantoin was prepared by mixing 2 grams of the hydantoin with 3 grams of methyl sulphate, adding sodium hydroxide until alkaline, and warming on the water-bath. This method was used in preference to the action of methyl iodide on the sodium compound. After recrystallisation from boiling water or alcohol, our product melted at 164° (Bogert and Scatchard give 167—168°).

The Action of Sodium Hypochlorite.—A chloroamine derivative, not described by Bogert and Scatchard, was obtained as follows. To 30 c.c. of a 10 per cent. solution of bleaching powder, or the equivalent of sodium hypochlorite, 1 gram of the hydantoin in powder was added and the clear solution then acidified with hydrochloric or acetic acid until no further precipitate was formed. The latter was filtered and washed. The sodium salt was obtained by dissolving the substance in sodium hydroxide solution. The same substance was prepared by dissolving the hydantoin directly in warm sodium hypochlorite solution.

It was analysed by adding potassium iodide solution, acidifying with acetic acid, and titrating the free iodine with sodium thio-sulphate (Found: Cl = 18·39. $C_6H_5O_2N_2Cl$ requires Cl = 18·07 per cent.). The substance is probably represented by one of the following formulae :

It is very unstable and gradually loses its chlorine when exposed to the air. It is rapidly decomposed when warmed with alcohol, regenerating the hydantoin and at the same time emitting a smell of acetaldehyde.

o-Acetylcarbamidobenzoic acid, $NHAc \cdot CO \cdot NH \cdot C_6H_4 \cdot CO_2H$, was prepared by heating 0·5 gram of the carbamido-compound with 3 c.c. of acetic anhydride until it just dissolved. On cooling, diluting with water, and making alkaline with ammonia, the acetyl derivative was obtained; it crystallised from dilute acetic acid or alcohol in clusters of felted needles, which sintered at 220° and melted at 225° with effervescence. It dissolved in sodium hydroxide solution, from which it was precipitated by acids.

o-Benzoylcarbamidobenzoic Acid.—On heating the carbamido-compound with an excess of benzoyl chloride, the former dissolves, and after a short time the mixture becomes pasty from the separation of the unchanged hydantoin. If, however, the carbamido-compound is dissolved in dilute sodium hydroxide solution and shaken for some time with benzoyl chloride until the smell of the latter disappears, a mass of crystals of the sodium compound of

the benzoyl derivative separates. This is filtered, washed and dissolved in hot water, and, on acidifying, the benzoyl compound separates. It crystallises from boiling water, in which it is moderately soluble, in clusters of long, colourless prisms, which partly melt at about 200°, decomposing into the hydantoin and benzoic acid,

Carbamidophthalic Acid and its Hydantoin.

3-Aminophthalic Acid Hydrochloride.—Thirty grams of finely powdered 3-nitrophthalic acid are added in small portions to a filtered solution of 120 grams of stannous chloride in 300 c.c. of concentrated hydrochloric acid, the mixture being kept cool and each portion being allowed to dissolve before the next is added. The hydrochloride of the amino-acid soon begins to crystallise, and after standing overnight is filtered and washed with a little concentrated hydrochloric acid. After recrystallising from hot concentrated hydrochloric acid, it is dried in a vacuum over sulphuric acid and sodium hydroxide. A little more of the hydrochloride can be obtained by cooling the united filtrates and allowing them to stand. The substance prepared in this way forms a mass of fine, colourless needles, which darken on heating, soften at 210° and melt with evolution of gas at 225°. The free amino-acid may be obtained by gradually adding the hydrochloride to water, in which it is fairly soluble, until the free amino-acid begins to separate, when it is rapidly filtered and the filtrate cooled. After a short time the amino-acid crystallises in colourless needles, which melt at 191—192° with decomposition, forming a yellow liquid.

3-Carbamidophthalic Acid.—Twenty grams of 3-aminophthalic acid hydrochloride in powder are dissolved in 200 c.c. of cold water, the solution filtered, and 8 grams of potassium isocyanate in a little water added. The mixture is kept cool by immersion in water, and after standing for half-an-hour, 20 c.c. of concentrated hydrochloric acid added. The carbamido-compound begins to separate as a crystalline precipitate, precipitation being hastened by agitation. After standing for some hours the carbamido-compound is filtered, washed with water, and dried in a vacuum. *Carbamidophthalic acid* forms a crystalline, greenish-yellow powder melting at 183—185° with decomposition. The yield is 60 per cent. of the theoretical. It is insoluble in chloroform, acetone, and light petroleum, and sparingly soluble in alcohol and ether (Found :

$\text{H}_2\text{O} = 3.56$; $\text{N} = 11.97, 12.04$. $\text{C}_9\text{H}_8\text{O}_5\text{N}_2 \cdot \frac{1}{2}\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 3.87$; $\text{N} = 12.02$ per cent.).

Acetylcarbamidophthalic Anhydride.—One gram of carbamidophthalic acid is heated with 10 c.c. of acetic anhydride; a clear solution is obtained, from which the acetyl compound soon begins to crystallise. After being dried in a vacuum, it melts at $246-247^\circ$ with decomposition. It does not dissolve in sodium carbonate solution and therefore contains no free carboxyl group.

Hydantoin of 3-Carbamidophthalic acid (Diketotetrahydroquinazolinecarboxylic Acid).—Ten grams of carbamidophthalic acid are heated on the water-bath with a mixture of 15 grams of concentrated hydrochloric acid and 10 c.c. of water. The mixture soon forms a colourless, pasty mass. The heating is continued until most of the hydrochloric acid is removed. The mass is then extracted with hot water and the insoluble hydantoincarboxylic acid filtered off, washed with warm water, and dried in a vacuum. The yield is 8.5 grams or 95 per cent. of the theoretical. Thus prepared, the hydantoin is a colourless powder, slightly soluble in alcohol and boiling water; it crystallises from the latter in minute needles, which do not melt below 320° , but sublime slowly above 280° . It dissolves readily in sodium carbonate solution and is reprecipitated by acetic acid (Found: $\text{N} = 13.28$. $\text{C}_9\text{H}_6\text{O}_4\text{N}_2$ requires $\text{N} = 13.59$ per cent.).

The *sodium* salt is obtained by dissolving the acid in just sufficient hot sodium carbonate solution to give a clear solution. On cooling, the salt crystallises in radiating masses of slender needles. It may be recrystallised from water, in which it is very soluble (Found in air-dried material: $\text{H}_2\text{O} = 19.06$; $\text{Na} = 7.99$. $\text{C}_9\text{H}_5\text{O}_4\text{N}_2\text{Na} \cdot 3\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 19.15$; $\text{Na} = 8.16$ per cent.).

Action of Sodium Hypochlorite on the Hydantoin.

The hydantoin dissolves in sodium hypochlorite solution with a brown colour, and from the solution acetic acid throws down a colourless precipitate, which is filtered, washed with water, and dried in a vacuum. The substance liberates iodine from potassium iodide, and when heated with alcohol loses chlorine, regenerating the original substance. It is therefore probably represented by one of the following formulæ or the tautomeric forms:

It is very unstable and readily decomposes in the air. On titrating

the amount of iodine liberated from potassium iodide in a known weight of substance, only 70 per cent. of the theoretical quantity of chlorine was found to be present.

The sodium salt is prepared by dissolving the chlorine compound in a little warm sodium hydroxide solution. On cooling, the salt crystallises in colourless needles, which may be recrystallised from a little water. It contains water of crystallisation, but analysis showed that this product also was not pure.

Action of Methyl Sulphate on the Hydantoin.

(1) Four grams of the hydantoin were dissolved in sufficient sodium hydroxide to give a clear solution, four grams of methyl sulphate added, and the mixture warmed on the water-bath for an hour. The thick, yellowish precipitate was filtered, washed with dilute hydrochloric acid, then with water, and dried in a vacuum. It crystallised from a mixture of alcohol and water in minute needles, which melted at 307—311°. It was sparingly soluble in water and alcohol, but dissolved readily in alkalis and was reprecipitated unchanged by acids even after boiling with sodium hydroxide solution.

The percentage of nitrogen shows that it contains two methyl groups (Found : N = 12·04, 12·25. $C_{11}H_{10}O_4N_2$ requires N = 11·98 per cent.). The substance is therefore the dimethyl ether of the hydantoin,

(2) Three grams of the hydantoin were dissolved in excess of sodium hydroxide solution (about twice the amount required to dissolve the acid) and 6 grams of methyl sulphate added. On shaking the mixture vigorously it became hot and the layer of methyl sulphate gradually disappeared. The reaction was completed by heating on the water-bath for an hour. A clear solution was then obtained, from which, when cold, a mass of fine, colourless needles gradually separated. They were filtered and recrystallised from hot alcohol.

The substance obtained in this way melts at 137°. It is sparingly soluble in water, very soluble in hot alcohol, and moderately soluble in cold alcohol. It is insoluble in cold solutions of sodium carbonate or hydroxide, but gradually dissolves on heating. The substance is probably the methyl ester of the dimethylated hydantoin described above. In order to confirm this, the substance was prepared in the manner described below.

1-Methyl 2-Hydrogen 3-Carbamidophthalate.

1-Methyl 2-hydrogen 3-nitrophthalate is reduced to the amino-compound with stannous chloride and hydrochloric acid as described under aminophthalic acid. The 1-methyl ester of 3-aminophthalic acid is thus obtained in colourless needles, m. p. 150°. The yield is nearly theoretical. Five grams of the amino-ester hydrochloride and 3 grams of potassium isocyanate are dissolved separately in water and the solutions mixed. Sodium carbonate solution is then added until the mixture is only slightly acid. On rubbing the side of the vessel the carbamido-compound begins to separate as a colourless, crystalline powder. After standing overnight, the precipitate is filtered, washed with water, and dried in a vacuum. The yield is 70 per cent. of the theoretical. When heated, the substance melts with decomposition at 162° and resolidifies to a yellow mass, which melts at about 185°.

Methyl Ester of the Hydantoin.

The carbamido-ester is heated on the water-bath with hydrochloric acid as described in the preparation of the free acid (see above). The hydantoin methyl ester is obtained as a colourless powder, which may be recrystallised from dilute alcohol. When heated, it turns yellow at about 180° and melts at 310—312°.

Action of Methyl Sulphate on the Hydantoin Methyl Ester.

Three grams of the ester were mixed with 2.5 grams of methyl sulphate and sufficient sodium hydroxide to give a clear solution on shaking. The mixture gradually became hot, and in order to avoid hydrolysis of the ester it was cooled in water. After a short time the liquid became semi-solid from the separation of the crystalline methyl derivative. The latter was filtered, washed with dilute hydrochloric acid, and dried in a vacuum. The substance melted at 137—140°. It dissolved readily in hot alcohol and after crystallisation melted at 144°. Repeated recrystallisation did not change the melting point. The substance, m. p. 137°, described above is probably identical with this compound, but not quite as pure (Found: N = 11.42. $C_{12}H_{12}O_4N_2$ requires N = 11.29 per cent.). The substance contains, therefore, three methyl groups, and is the *methyl* ester of the dimethylated hydantoin,

Nitration of the Hydantoin.

Three grams of the hydantoin were dissolved in 25 grams of sulphuric acid by warming gently and 5 grams of fuming nitric acid added. The mixture became hot and acquired a deep red colour; after being heated on the water-bath for an hour, during which the red colour disappeared, the mixture was cooled and poured into 40 c.c. of cold water. The solution, on cooling, deposited a yellow, crystalline precipitate, which was filtered off and dried. It melted at 298° (with decomposition) and, after repeated crystallisation from hot water, at 253° ; the melting point was not altered by further crystallisation (Found in material dried at 120° : $N = 18.10$. $C_9H_5O_6N_3$ requires $N = 16.73$; $C_9H_4O_8N_4$ requires $N = 18.92$ per cent.). The product was therefore a mixture of the mono- and di-nitrohydantoins.

A portion of the crude product (m. p. 298°) was converted into the sodium salt by dissolution in hot sodium carbonate solution. On cooling, the salt crystallised out in glistening yellow plates, which were recrystallised from hot water, and dried at 150° (Found: $N = 16.75$. $C_9H_4O_6N_3Na$ requires $N = 15.38$; $C_9H_3O_8N_4Na$ requires $N = 17.61$ per cent.). Here again the product was a mixture of the mono- and di-nitro-derivatives.

Preliminary Note on 4-p-Hydroxybenzylhydantoin and its Derivatives.

4-p-Hydroxybenzylhydantoin was prepared by Dakin's method (*J. Biol. Chem.*, 1910, **8**, 30). To 6 grams of tyrosine in 30 c.c. of boiling water about 3 grams of potassium isocyanate were added and the liquid boiled until a clear solution was obtained. Twenty c.c. of concentrated hydrochloric acid diluted with 40 c.c. of water were then added and the solution boiled for a quarter of an hour. The hydantoin separated in colourless crystals, which, after cooling, were filtered and washed. The yield was equal to the weight of the original tyrosine.

4-p-Acetoxybenzylhydantoin.—Two grams of the hydantoin were mixed with 8 grams of acetic anhydride. No apparent action took place, and the hydantoin remained undissolved until a minute quantity (0.2 gram) of anhydrous sodium acetate was added, when the hydantoin at once passed into solution.* The product was evaporated and water added, when the acetyl derivative separated as a viscous mass, which soon solidified. It was crystallised from

* It is evident that the sodium acetate acts as a catalyst, and it is our intention to study this effect in other cases of acetylation.

dilute alcohol and formed clusters of colourless needles, m. p. 117—118°.

4-p-Acetoxybenzylhydantoin OO-Dimethyl Ether,

—To a mixture of 0.9 gram of the acetyl derivative and 1.5 grams of methyl sulphate a 10 per cent. solution of sodium hydroxide was added drop by drop with gentle warming until the reaction was permanently alkaline. After standing, the oily liquid solidified, and the crystalline mass was filtered, washed, and crystallised from alcohol, when it formed glistening needles, m. p. 144—145° (Found : N = 9.65. $\text{C}_{14}\text{H}_{16}\text{O}_{11}\text{N}_2$ requires N = 10.1 per cent.).

4-p-Hydroxybenzylhydantoin OO-Dimethyl Ether,

—On boiling the preceding compound with a little concentrated hydrochloric acid it gradually dissolved and glistening foliated crystals were obtained on cooling, which melted at 180—182° after crystallisation from alcohol.

Methyl Ether of the Dimethylated Hydantoin.—One gram of methyl sulphate was added to 0.5 gram of the hydantoin and the mixture made gradually alkaline with sodium hydroxide and warmed until the excess of methyl sulphate was removed. A colourless solid separated, which was filtered, washed with water, and extracted from the unchanged hydantoin with alcohol. After the alcohol had been evaporated and the residue crystallised from toluene, the substance melted at 134° (Found : N = 11.23. $\text{C}_{13}\text{H}_{16}\text{O}_3\text{N}_2$ requires N = 11.3 per cent.).

Action of Benzenediazonium Chloride on the Hydantoin.

0.3 Gram of the hydantoin was dissolved in the least quantity of 10 per cent. sodium hydroxide solution. To this solution, diluted to 10 c.c., were added 6 c.c. of a solution containing in 10 c.c. 1 gram of aniline dissolved in 3 c.c. of concentrated hydrochloric acid and 3 c.c. of water and diazotised with 0.8 gram of sodium nitrite. The solution turned deep red, a brown precipitate formed, and finally a thick, orange, crystalline precipitate separated, which was filtered and washed with cold water. It crystallised from absolute alcohol in clusters of orange needles, which softened at 205°, darkened, owing probably to decomposition, and melted completely at 220° (Found : N = 18.5. $\text{C}_{16}\text{H}_{13}\text{O}_3\text{N}_4$ requires N = 18.1 per cent.).

The compound has probably the following formula :

Sodium Salt.—4-*p*-Hydroxybenzylhydantoin dissolves in sodium hydroxide solution, and the sodium salt slowly separates on evaporation or, more rapidly, by addition of alcohol, in colourless, flat, prismatic crystals (Found : Na = 13·6, 13·2, 13·4; H₂O = 26·0. C₁₀H₈O₃N₂Na₂·5H₂O requires Na = 13·5; H₂O = 26·4 per cent.).

For the tyrosine, which served for the above experiments, we are indebted to Dr. H. Raistrick.

THE ORGANIC CHEMICAL LABORATORIES,
THE UNIVERSITY, LEEDS.

[Received, March 18th, 1921.]