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No. 27

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BY

FREDERICK B. POWER, PH.D.

AND

FRANK SHEDDEN, B.SC., A.I.C.

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES

FREDERICK B. POWER, PH.D., *Director*

6, King Street, Snow Hill

LONDON, E.C.

VIII.—*Derivatives of Gallic Acid.*

By Frederick B. Power and Frank Shedden.

In a paper entitled: "The Chemical Character of so-called Iodotannin Compounds" (*Pharm. Journ.*, 1901, [iv], 13, 147), the authors have recorded the results of an investigation which was undertaken for the purpose of ascertaining the character of the compounds prepared by the direct action of iodine on tannic acid in the presence of water. It was shown that under these conditions no definite compound of either tannic or gallic acid with iodine could be formed, and it therefore seemed of interest to ascertain whether iodine could be introduced into the gallic acid molecule by indirect methods. With this object in view, the following method of procedure was adopted. The well-crystallised ethyl gallate was converted into its triacetyl derivative, which, on nitration, yielded *ethyl dinitrodiacetylgallate*. This substance, on hydrolysis with sulphuric acid, was converted into *ethyl dinitrogallate*, and from the latter, on reduction, *ethyl monoaminogallate* and *ethyl diaminogallate* were obtained in the form of hydrochlorides. These hydrochlorides were then separately diazotised, and the resulting solutions boiled with potassium iodide in accordance with the well-known reaction. Although many experiments were made, it was not possible to isolate any product containing iodine.

As most of the substances required for the original purpose of this investigation represent new derivatives of gallic acid, the method of preparation and their characters are here described.

Ethyl Dinitrodiacetylgallate, $C_6(NO_2)_2(C_2H_3O_2)_2(OH)\cdot CO_2C_2H_5$.

By the direct acetylation of ethyl gallate, the ethyl triacetylgallate was first prepared, which has been described by Schiff (Beilstein's *Handbuch*, 2, 1922) as a thick yellow oil, which very slowly deposits crystals. No difficulty was experienced, however, in obtaining it in colourless crystals from either acetic acid or alcohol. It melts at 133°. The triacetyl ester was nitrated in the following manner. One hundred grams of the triacetyl ester were added to a cold mixture of 50 c.c. each of nitric acid (sp. gr. 1·42) and sulphuric acid, and 150 c.c. of glacial acetic acid. The mixture, while being kept cool, was allowed to stand for five hours. The product was poured into a litre of water, the yellow, crystalline precipitate filtered off, and the nitro-compound separated from some unchanged ethyl triacetylgallate by treatment with sodium carbonate, in which it readily dissolved. The acid filtrate from the above-mentioned yellow precipitate was extracted several times with ether and the ethereal liquid shaken out with carbonate solution. This was mixed with the main sodium carbonate solution obtained as above and the whole acidified with hydrochloric acid. The separated yellow oil soon formed a crystalline cake, which was collected and recrystallised from chloroform. It formed lemon-yellow needles which melted at 165°.

0·1466 gave 0·2260 CO_2 and 0·0486 H_2O. C = 42·0; H = 3·7.
0·1974 „ 13·3 c.c. moist nitrogen at 11° and 744 mm. N = 7·9.
$C_{13}H_{12}O_{11}N_2$ requires C = 41·9; H = 3·2; N = 7·5 per cent.

The substance is strongly acid, dissolving in sodium carbonate with effervescence and forming an orange-red solution. It only dissolves slowly in absolute alcohol, and the solution gives a bluish-green coloration with ferric chloride.

The ethyl triacetylgallate was nitrated in another manner with somewhat different results. One hundred grams of the substance were mixed in a flask with 100 c.c. of nitric acid (sp. gr. 1·42), and, after being kept cool for five hours, the mixture was worked up in the manner already described. By this method, the product consisted of a mixture of the dinitro-ester and the dinitrodiacetyl ester.

An attempt was made to form the sodium salt of ethyl dinitrodiacetylgallate by dissolving it in alcohol and adding one atomic proportion of sodium dissolved in a little alcohol. No precipitate was produced, even after a portion of the alcohol had been evaporated off in a vacuum. On standing for several days, an odour of ethyl acetate was developed, and small, bright red crystals were deposited, which consisted of the *sodium* salt of *ethyl dinitrogallate*.

Ethyl Dinitrotriacetylgallate, $C_6(NO_2)_2(C_2H_3O_2)_3 \cdot CO_2C_2H_5$.

This was prepared by the acetylation of the dinitrodiacetyl compound, in the formation of which one acetyl group had become eliminated during the process of nitration. It was obtained in colourless needles, which gradually become yellow, and melt at 145—146°.

0·1716 gave 0·2704 CO_2 and 0·0504 H_2O. C = 43·0 ; H = 3·3.
0·2086 „ 12·4 c.c. moist nitrogen at 16° and 768 mm. N = 7·0.
$C_{15}H_{14}O_{12}N_2$ requires C = 43·5 ; H = 3·4 ; N = 6·8 per cent.

The substance was insoluble in sodium carbonate. Its cold alcoholic solution gave no reaction with ferric chloride, but on boiling, a bluish-green colour was produced.

Ethyl Dinitrogallate, $C_6(NO_2)_2(OH)_3 \cdot CO_2C_2H_5$.

This was prepared by boiling the dinitrodiacetyl compound with 50 per cent. sulphuric acid, when it crystallised out on cooling. The ethyl radicle was not eliminated by this procedure.

It was obtained in the form of small, yellow scales, of a somewhat deeper colour than the dinitrodiacetyl compound. When placed in the melting point apparatus at 80—85° it melted, but after drying at a gentle heat it fused at 153°.

0·8040 air-dried substance lost 0·0486 H_2O at 100°. H_2O = 6·0.
$C_6(NO_2)_2(OH)_3 \cdot CO_2C_2H_5, H_2O$ requires H_2O = 5·9 per cent.

It was recrystallised by dissolving the dried substance in absolute ether and adding an equal volume of light petroleum. The crystals, after drying for a few minutes in a water-oven, softened at 151° and melted to a clear liquid at 153—154°.

0·1432 gave 0·1990 CO_2 and 0·0382 H_2O. C = 37·9 ; H = 3·0.
0·1662 „ 14·4 c.c. moist nitrogen at 20° and 759 mm. N = 9·9.
$C_9H_8O_9N_2$ requires C = 37·5 ; H = 2·7 ; N = 9·7 per cent.

The substance dissolves readily in absolute alcohol, and the solution gives an olive-green colour with ferric chloride. It could not be hydrolysed by heating in a sealed tube with hydrochloric acid at 125° for six hours. It was also heated in a sealed tube with 50 per cent. sulphuric acid at 155° for five hours without altering the melting point or other properties. Ethyl gallate, on the other hand, when heated in a sealed tube with 30 per cent. sulphuric acid at 150°, is completely hydrolysed. On boiling with an excess of alcoholic sodium hydroxide, the substance was destroyed. It was treated with strong ammonia in the hope of forming the amide, but only tarry products were obtained.

Reduction of Ethyl Dinitrogallate.—The crude nitro-compound was reduced by warming with tin and hydrochloric acid. After the reaction was over, the liquid was diluted with water and the tin completely removed by hydrogen sulphide. The clear liquid was distilled in a vacuum, and, when it had become concentrated to a small bulk, white, needle-shaped crystals began to separate out. The distillation was then stopped and the crystalline precipitate filtered off and washed with dilute hydrochloric acid. This substance proved to be the *hydrochloride* of *ethyl monoaminogallate.* The yield was about 12 per cent. of the original substance.

The filtrate and washings were evaporated to complete dryness in a vacuum. The residue was a crystalline mass, which was purified by dissolving it in hot methyl alcohol and diluting the solution with hot chloroform. A light brown or nearly white, crystalline powder was thus obtained, which consisted of the *hydrochloride* of *ethyl diaminogallate.* The yield of the latter was very variable, ranging from about 10 to 25 per cent. of the original substance.

The formation of the above monoamino-derivative by reduction was at first thought to be due to the presence of a mononitro-ester in the material used. This, however, was not the case, inasmuch as a pure ethyl dinitrodiacetylgallate afforded the same yield of the monoamino-hydrochloride. The conclusion may thus be drawn that the formation of the monoamino-derivative is due to some change in the process of reduction.

Hydrochloride of Ethyl Monoaminogallate,
$C_6H(NH_2)(OH)_3 \cdot CO_2C_2H_5,HCl,H_2O$.

This substance has the following characters. It is readily soluble in water and the solution remains colourless. Its alcoholic solution gives a dark green colour with ferric chloride. It melts at 210° with blackening and frothing. When recrystallised by dissolving it in hot absolute alcohol and adding chloroform to the solution, it still melted at 210°, and was quite white, showing no tendency to change on keeping. When dissolved in a little water, it could be precipitated by the addition of strong hydrochloric acid, and this reaction, besides the other characters of the substance, distinguishes it from the diaminogallate. It may be heated in a water-oven without any change in weight.

0·1186 gave 0·1760 CO_2 and 0·0540 H_2O. C = 40·5; H = 5·05.
0·1290 „ 0·1908 CO_2 „ 0·0586 H_2O. C = 40·3; H = 5·05.
0·1724 „ 8·8 c.c. moist nitrogen at 24° and 753 mm. N = 5·65.
0·1950 „ 0·1058 gram AgCl. Cl = 13·4.
0·5504 at 105° lost 0·0392 H_2O. H_2O = 7·1.

$C_9H_{11}O_5N,HCl,H_2O$ requires C = 40·4; H = 5·2; N = 5·2; Cl = 13·3; H_2O = 6·7 per cent.

Ethyl Diazogallate, $\begin{array}{l} C_6H(OH)_2(CO_2C_2H_5)\cdot N \\ | \qquad\qquad\qquad\qquad\quad \| \\ O\text{------------------------}N \end{array}$

The ethyl monoaminogallate was dissolved in an excess of dilute hydrochloric acid, and to the ice-cold solution a dilute solution of sodium nitrite was slowly added until there was a permanent excess. The liquid was heated on a water-bath for 20 minutes, and, after cooling, the brown crystals were filtered off.

The product was almost insoluble in cold water, but dissolved in boiling water, and on cooling the solution long, orange-yellow needles were deposited. The solution was yellow, and gave a deep purplish-brown colour with ferric chloride. The substance melted with sudden decomposition at 182°. When recrystallised from dilute acetic acid, it formed fine, reddish-brown needles melting as before at 182°.

0·2350 at 100° lost 0·0178 H_2O. $H_2O = 7·6$.

$C_9H_8O_5N_2,H_2O$ requires $H_2O = 7·4$ per cent.

The dried substance was analysed with the following result:

0·1108 gave 0·1938 CO_2 and 0·0432 H_2O. C = 47·7; H = 4·3.

0 0924 „ 10 c.c. moist nitrogen at 24° and 769 mm. N = 12·3.

$C_9H_8O_5N_2$ requires C = 48·2; H = 3·5; N = 12·5 per cent.

0·1114 gram dissolved in 15·59 grams of pure phenol depressed the freezing point by 0·263°. This corresponds to a molecular weight of 201. Mol. wt. of $C_9H_8O_5N_2 = 224$.

One gram of the substance was heated with three times its weight of water in a sealed tube at 220° for four hours, when complete solution was effected. The dark brown liquid was filtered from a small amount of a black residue, saturated with ammonium sulphate, and extracted with ether. The ethereal solution, when washed with water, dried with sodium acetate, and evaporated, left a yellowish, oily liquid which became crystalline. The crystals, after washing with a little light petroleum, melted at 139°, and were free from nitrogen. Their aqueous solution gave a brown colour with alkalis and a bluish-black one with ferric chloride. After recrystallising this from toluene, about 0·2 gram of the substance was obtained, and it then melted at 140° without decomposition. It was dried in a water-oven and then analysed:

0·1084 gave 0·2174 CO_2 and 0·0504 H_2O. C = 54·7; H = 5·2.

$C_9H_{10}O_5$ requires C = 54·5; H = 5·1 per cent.

The substance thus produced was therefore undoubtedly ethyl gallate, the nitrogen having been completely eliminated by heating the diazogallate with water.

On treating the diazo-compound with stannous chloride in cold hydrochloric acid, considerable effervescence was produced and it became completely dissolved. After removing the tin by hydrogen sulphide, the products of the reaction were found to be ammonium chloride and ethyl gallate. The production of ethyl gallate from this diazo-compound will serve to explain the formation of the monoamino-ester by the reduction of ethyl dinitrogallate (p. 76).

Hydrochloride of Ethyl Diaminogallate,
$C_6(NH_2)_2(OH)_3 \cdot CO_2C_2H_5, 2HCl$.

This substance, as obtained in the manner already described, forms a fine, crystalline powder of a light brown colour. By redissolving it in hot absolute alcohol (in which it is somewhat sparingly soluble) and adding ethyl acetate it becomes much lighter in colour, but when kept shows a tendency to darken. The alcoholic solution rapidly assumes a pink hue. It is very easily oxidised. It dissolves readily in water, but the solution almost immediately becomes blue, and, on standing, blue flakes are deposited. The blue colour is intensified by the cautious addition of ferric chloride, but is destroyed by adding an excess. If the solution in water be acidified with hydrochloric acid, the blue colour changes to pink (compare *Ber.*, 1887, **20**, 335; 1893, **26**, 2184). Unlike ethyl monoaminogallate, it cannot be precipitated from its aqueous solution by hydrochloric acid. It melts with decomposition at 197°. After drying in a vacuum, it was analysed.

0·1318 gave 0·1738 CO_2 and 0·0570 H_2O. C = 35·9; H = 4·8.
0·1330 „ 0·1746 CO_2 „ 0·0538 H_2O. C = 35·7; H = 4·5.
0·2129 „ 19·6 c.c. moist nitrogen at 23° and 764 mm. N = 10·4.
0·1588 „ by Carius' method, 0·1520 AgCl. Cl = 23·7.

$C_9H_{12}O_5N_2, 2HCl$ requires C = 35·9; H = 4·6; N = 9·3; Cl = 23·6 per cent.

In order to ascertain the action of nitrous acid on this diamino-ester, 6·6 grams of the substance were mixed with an excess of dilute hydrochloric acid. The resulting dark coloured solution was cooled with water and a dilute solution of sodium nitrite gradually added, which caused considerable effervescence and the evolution of some nitrous fumes. This liquid was extracted with ether, but on distillation the latter left only a very slight residue. The remaining liquid was heated on a water-bath, when there was considerable effervescence, and, after this had ceased, a small portion of the liquid, when boiled with potassium hydroxide, evolved ammonia. The remainder was extracted with chloroform, then made alkaline with sodium carbonate and again extracted with chloroform, but in neither case was any definite product obtained.

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