# SYNTHETICAL EXPERIMENTS IN THE CHROMONE GROUP

## Part XXI. Synthesis of Gentisin, the Colouring Matter of Gentian Root

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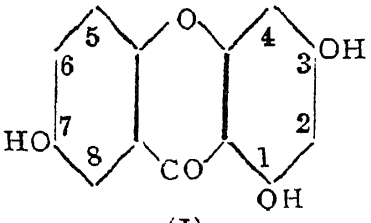
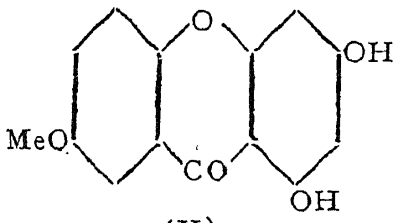
GENTISIN, the yellow colouring matter of *Gentiana lutea* (gentian root) was first isolated by Henry and Caventou,[1] and was shown by Baumert[2] to possess the formula $C_{14}H_{10}O_8$. Hlaiswetz and Habermann[3] demonstrated the presence of two hydroxyl groups and one methoxyl; but when fused with potassium hydroxide, it gave phloroglucinol and gentisic acid. Kostanecki[4] by demethylation of gentisin with hydriodic acid, showed it to be a monomethyl ether of gentisein, 1:3:7-trihydroxyxanthone (I), which was synthesised by Kostanecki and Tambor[5] by the distillation of gentisic acid and phloroglucinol in presence of acetic anhydride. Gentisein on methylation yielded gentisin, while gentisin on further methylation gave a mono-




(I)

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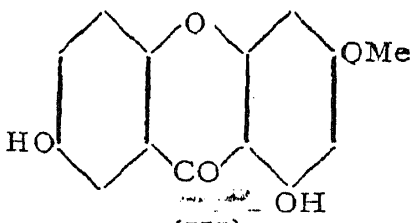


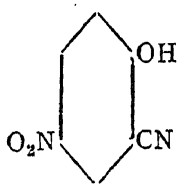

(III)

methyl ether.[5] The methylation of gentisin to a monomethyl, and not a dimethyl ether, indicated that the original methoxyl was not in the 1-position. Gentisin therefore had to be formulated as the 7-methyl ether (II) or the 3-methyl ether (III). In order to determine which of these two monomethyl ethers of gentisein was identical with gentisin, Kostanecki and Tambor[6] attempted to synthesise the 7-methyl ether by distilling a mixture of 2-hydroxy-5-methoxybenzoic acid, phloroglucinol and acetic anhydride, but they found that the product consisted of a mixture of gentisein, its dimethyl ether and a very small quantity of gentisin. This synthesis did not afford conclusive proof of the constitution of gentisin, as the possibility of its production from gentisein by methylation could not be excluded.

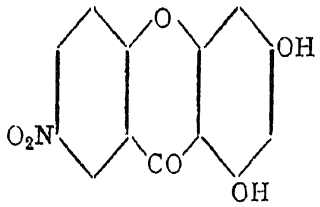
By a study of *dis*azobenzene-gentisin, which formed a diacetyl derivative, Perkin[7] suggested that gentisin should be the 3-methyl ether (III). If (II)

represented gentisin, the diazo coupling would have taken place in the 2:4-positions, and Perkin had found that such disazo resorcinol derivatives did not undergo acetylation under the usual conditions. It will be shown in a later communication that the diazo coupling of euxanthone and gentisin does not take place in the positions indicated by Perkin, but the constitution assigned by him to gentisin has now been confirmed by an unambiguous synthesis. Shinoda[8,9] synthesised the 7-methyl ether (II) by a Hoesch reaction between 5-methoxysalicylonitrile and phloroglucinol, followed by cyclicisation, and found that it was different from gentisin. We have synthesised the 3-methyl ether (III), which has proved to be identical with natural gentisin.

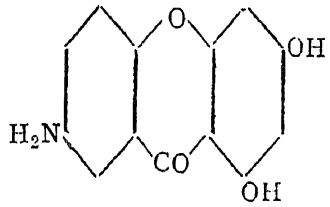
The Hoesch reaction between 5-nitrosalicylonitrile (IV) and phloroglucinol, following the method of Nishikawa and Robinson[10] for 1:3-dihydroxyxanthone, gave 7-nitro-1:3-dihydroxyxanthone (V), m.p. 295–296° (*diacetate*, m.p. 182–83°). Yumoto[11] who prepared (V) by a similar method quotes the m.p. 281–82° (*diacetate*, m.p. 162–63°). Reduction of (V) with alkaline hydrosulphite gave 7-amino-1:3-dihydroxyxanthone (VI), which on diazotisation and hydrolysis by 35% sulphuric acid yielded gentisein (I). When (V) was methylated by means of dimethyl sulphate




(IV)

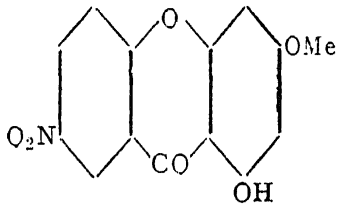



(V)

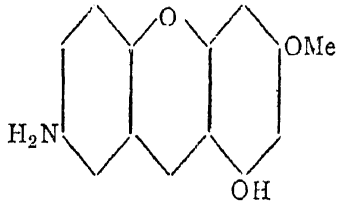



(VI)

and alkali, the ether (VII) was always contaminated with a little of the dimethyl ether, and the pure monomethyl ether was not isolable even after repeated crystallisation. It could, however, be readily obtained by methylation with diazomethane (one mol.) in ether solution. The nitro compound (VII) was then reduced to the amine (VIII) by iron and acetic acid. On




(VII)




(VIII)

diazotisation of the amine (VIII) and hydrolysis with 40% sulphuric acid, 1:7-dihydroxy-3-methoxy-xanthone, m.p. 266–67°, was obtained, identical in all its properties with natural gentisin.

## Experimental

*5-Nitrosalicylonitrile (IV)*[13; 14]

5-Nitrosalicylaldehyde (m.p. 126°) was prepared by the nitration of salicylaldehyde,[12] and the mixture of 3-nitro- and 5-nitrosalicylaldehyde thus obtained was separated by fractional crystallisation of their sodium salts from water, in which the sodium salt of the former was more soluble. 5-Nitro-2-hydroxy-benzaldoxime, prepared in the usual manner, crystallised from alcohol in stout, colourless needles, m.p. 219°-20° (Found: N, 15·1. $C_7H_6N_2O_4$ requires N, 15·2%). 5-Nitrosalicylonitrile, obtained on treatment of the oxime with boiling acetic anhydride for 2 hours and subsequent hydrolysis of the acetate (m.p. 55–56°), either by 5% warm sodium hydroxide solution or by heating with water on the water-bath for 2–3 hours, crystallised from water in straw-yellow, long silky needles, m.p. 194–96° (Walker,[13] m.p. 194–96; Bone,[14] m.p. 190°) (Found: N, 17.2. $C_7H_4N_2O_3$ requires N, 17·1%). The nitrile dissolves in sodium bicarbonate solution with effervescence, and gives a deep red colour with ferric chloride.

*7-Nitro-1 : 3-dihydroxyxanthone* (V)

Through a cooled solution of 5-nitrosalicylonitrile (3·3 g.) and phloroglucinol (2·5 g.) in dry ether (150 c.c.) containing 2 g. of freshly fused zinc chloride, a slow stream of dry hydrogen chloride gas was passed for 5 hours. The oil, which first separated in about an hour, gradually dissolved, giving a deep red solution. A deep orange oil again separated after 4 hours. The mixture was left in a refrigerator for 72 hours, the ether decanted off, the deep orange viscous oil washed twice with ether, and taken up in 10 per cent. aqueous caustic soda. On boiling for an hour, when no more ammonia was evolved, the deep brownish red solution was filtered from unreacted zinc hydroxide. The 7-nitro-1 : 3-dihydroxyxanthone, obtained by acidifying the filtrate, crystallised from alcohol in light yellow, shining, flat plates (1·7 g.), m.p. 295–96° (Found: N, 5·3. $C_{13}H_7NO_6$ requires N, 5·1%). It gives a brownish violet colour with ferric chloride, and a deep red colouration when shaken with sodium amalgam in water.

Its diacetate prepared by refluxing with acetic anhydride and pyridine crystallised from alcohol in colourless needles, m.p. 182–83° (Found: N, 4·1. $C_{17}H_{11}NO_8$ requires N, 3·9%).

*7-Amino-1 : 3-dihydroxyxanthone (VI)*

7-Nitro-1 : 3-dihydroxyxanthone (0·2 g.) was dissolved in one per cent. sodium hydroxide (20 c.c.), heated to 70°, and sodium hydrosulphite added till the reduction was complete, at which stage there was a marked change

in the colour of the solution from orange to yellow. The amine, precipitated by acetic acid, crystallised as its hydrochloride from water containing hydrochloric acid in yellow needles (0·14 g.), m.p. 318°–20° (with charring) (Found: N, 4·9. $C_{13}H_{10}ClNO_4$ requires N, 5%).

1 : 3 : 7-*Trihydroxyxanthone* (*Gentisin*) (*I*)

The amine hydrochloride (0·1 g.) was dissolved in a mixture of water (10 c.c.), acetic acid (2 c.c.) and concentrated hydrochloric acid (0·2 c.c.), cooled, and diazotised, by sodium nitrite (0·03 g.). After keeping at 0–5° for 15 minutes, excess of nitrous acid was destroyed by urea, and the diazo solution slowly added in about five minutes to 30 c.c. of boiling 35 per cent. sulphuric acid. Boiling was continued for 5 minutes, when the diazo salt had completely decomposed, as tested by β-naphthol. On cooling the solution, the yellow product was ether-extracted, and the ether removed. The pinkish yellow residue crystallised from dilute alcohol in thin yellow needles (0·05 g.), m.p. 314–15° (Kostanecki and Tambor,[5] 315°). The substance dissolves in aqueous sodium hydroxide to form an orange sodium salt and a yellow solution; gives a brownish green colour with ferric chloride; and a blood-red colour when vigorously shaken with sodium amalgam in alkali.

1 : 3 : 7-*Triacetoxyxanthone*, obtained by refluxing (I) with acetic anhydride and a drop of pyridine, crystallised from acetic acid in long, thin needles, m.p. 225–26° (Kostanecki,[15] m.p. 226°).

7-*Nitro*-1-*hydroxy*-3-*methoxyxanthone* (*VII*)

7-Nitro-1 : 3-dihydroxyxanthone (0·27 g.) was dissolved in ether (150 c.c.) and diazomethane (0·04 g.; 1 mol.) in ether was added, and the mixture kept at the room temperature for one hour with occasional shaking, when a yellow shining mass of crystals separated. After 12 hours in the refrigerator, the product was filtered (0·23 g.). It crystallised from acetic acid—(if boiled for a long time, partial acetylation takes place)—or from benzene in light yellow, thin, rectangular plates, m.p. 249–50° (Found: N, 4·9 $C_{14}H_9NO_5$ requires N, 4·9%). The substance gives a reddish brown colour with ferric chloride. It does not dissolve in aqueous alkali, but in alcohol sodium hydroxide it gives a sparingly soluble orange sodium salt.

The *acetate* obtained by refluxing with acetic anhydride and pyridine, crystallised from acetic acid in long, thin colourless needles, m.p. 263–64° (Found: N, 4·5. $C_{16}H_{11}NO_7$ requires N, 4·2%).

7-*Amino*-1-*hydroxy*-3-*methoxyxanthone* (*VIII*)

The nitro-compound (VII; 0·2 g.) was suspended in 30 c.c. of boiling alcohol containing acetic acid (3 c.c.), and iron powder (0·2 g.) was added

to it in the course of an hour, when the nitro-compound gradually dissolved, giving a brown solution. It was refluxed for a further 30 minutes, filtered from the unreacted iron, most of the alcohol boiled off, and 2 c.c. of concentrated hydrochloric acid added, when the amine hydrochloride was precipitated. The amine crystallised as its hydrochloride from 150 c.c. of water containing hydrochloric acid, in bunches of short, thin, flat colourless needles (0·15 g.), which shrank at 270° and melted at 273–75° (with charring) (Found: N, 4·8. $C_{14}H_{12}ClNO_4$ requires N, 4·7%). The amine, liberated by neutralising the aqueous solution of the hydrochloride with sodium carbonate, crystallised from alcohol in long, thin, greenish yellow needles, m.p. 215–16° (Found: N, 5·2. $C_{14}H_{11}NO_4$ requires N, 5·4%). The alcoholic solution gives a brown colour with ferric chloride.

1 : 7-*Dihydroxy*-3-*methoxyxanthone* (*Gentisin*) (*III*)

A cooled suspension of the hydrochloride (0·15 g.) in acetic acid (4 c.c.), water (2 c.c.), and hydrochloric acid (0·2 c.c.) was diazotised by means of sodium nitrite (50 mg.). The amine hydrochloride dissolved slowly, and after keeping for 15 minutes, excess of nitrous acid was destroyed by urea, and the diazo solution added slowly to boiling 40 per cent. sulphuric acid (30 c.c.), and boiling continued for 10 minutes, when the solution gave no test for a diazo salt. On cooling and dilution, a yellow product separated which was collected, and crystallised from alcohol. The long, light yellow, shining needles (0·09 g.), softened slightly at 258–59° and melted at 266–67°, being identical in behaviour with a sample of natural gentisin. A mixture of the synthetic substance and gentisin gave the same melting point (Found: C, 65·1,; H, 3·6. $C_{14}H_{10}O_5$ requires C, 65·1, H, 3·9%). The substance exhibits all the properties described for natural gentisin. It dissolves readily in alkali with a golden yellow colour, and gives an olive-green colour with ferric chloride. When heated and shaken with sodium amalgam in water, it gives a deep green solution, which on acidification gives a cherry red precipitate. In concentrated sulphuric acid it gives a yellow solution, which on standing develops a bright green fluorescence, which earlier workers have not recorded. We have found, however, that natural gentisin behaves similarly.

The *diacetate*, obtained in the usual manner by treatment with acetic anhydride and pyridine, crystallised from alcohol in long thin needles, m.p. 195–96°, not depressed when mixed with the diacetate prepared from natural gentisin (Hlaiswetz and Habermann,[3] m.p. 195–6°).

The *dibenzoate* obtained by shaking a solution of the compound in 10 per cent. sodium hydroxide with 6–8 mols. of benzoyl chloride,

crystallised from alcohol in bunches of short thick needles, m.p. 192° (Kostanecki and Tambor,[4] m.p. 192°).


## Summary

1 : 7-Dihydroxy-3-methoxyxanthone has been synthesised and shown to be identical with natural gentisin. 7-Nitro-1 : 3-dihydroxyxanthone, obtained by a Hoesch reaction between 5-nitrosalicylonitrile and phloroglucinol, followed by hydrolysis and cyclicisation, was methylated by diazomethane to its 3-methyl ether. This, on reduction, diazotisation, and hydrolysis with sulphuric acid, gave 3-methoxy-1 : 7-dihydroxyxanthone, identical in all its properties with natural gentisin.


We are greatly indebted to Dr. A. T. Peters of the University of Leeds for a sample of natural gentisin isolated by Professor A. G. Perkin.

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