SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XXX. A New Synthesis of Hydroxy Xanthones Including Gentisein and Gentisin

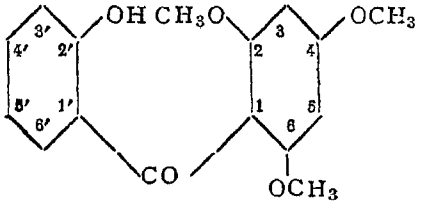
By G. Venkat Rao and T. R. Seshadri, F.A.Sc.

(From the Department of Chemistry, Delhi University)

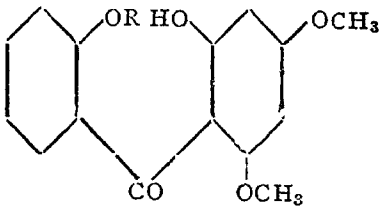
Received January 17, 1953

For the synthesis of the xanthone structure a number of methods have been used. The earliest was that employed by Kostanecki[1] in which he distilled an intimate mixture of a phenol and *o*-hydroxy benzoic acid with acetic anhydride as the condensing agent. By this method Kostanecki synthesised numerous hydroxy xanthones. However the yields were very poor and the method of working up the product was very tedious. Later Ullmann[2] developed a method in which the diphenyl ether linkage was first built and subsequent ring closure effected using various condensing agents such as concentrated sulphuric acid, anhydrous aluminium chloride and phosphorus oxychloride. A third method used by Robinson and Nishikawa[3] consists of the Hoesch condensation of *o*-hydroxy benzonitrile and a phenol in dry ether in presence of zinc chloride and hydrogen chloride. A ketimine hydrochloride is formed which on alkaline hydrolysis yields directly the xanthone. But these methods are not available easily for all cases. Consequently there was need to explore new routes to the synthesis of xanthone derivatives. The Friedel and Craft's reaction in its simple form has not so far been employed for this purpose. As a simple example of the application of this reaction salicylic acid monomethyl ether and phloroglucinol trimethyl ether are now employed. The acid chloride of the former is condensed with the latter in the presence of anhydrous aluminium chloride in cold dry ether solution. The reaction proceeds satisfactorily and a good yield of a ketone is obtained. The product gives colour with alcoholic ferric chloride solution and analysis indicates that one methoxyl group has suffered demethylation. There are two possibilities for its structure (I and II *a*). In order to settle this question the ethyl ether of salicylic acid has also been used for this condensation. This product is different from the first one and analysis shows that the ethyl group is retained. Hence it could be concluded that the ortho methoxyl which suffers demethylation belongs to the phloroglucinol part (2-position) and the structure of the products is

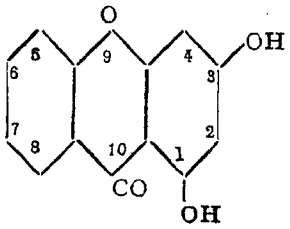
correctly represented by (II *a* and *b*). Subsequent treatment of the trimethyl ether (II *a*) with anhydrous aluminium chloride in boiling benzene gives rise to a good yield of 1 : 3-dihydroxy xanthone (III), which on methylation with excess of dimethyl sulphate in acetone solution provides the dimethyl ether.



(I)

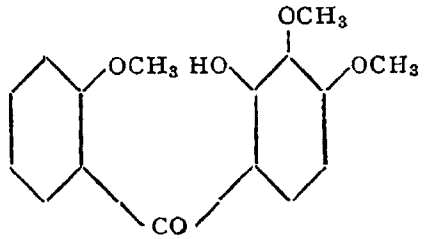


(II) *a*, R=CH_3
b, R=C_2H_5

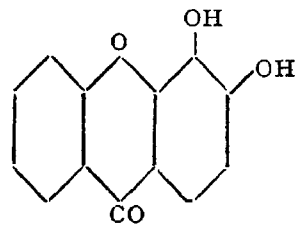


(III)

The above mentioned reaction has been carried out using *o*-methoxy benzoyl chloride and pyrogallol trimethyl ether and a good yield of 3 : 4-dihydroxy xanthone (V) has been obtained.



(IV)

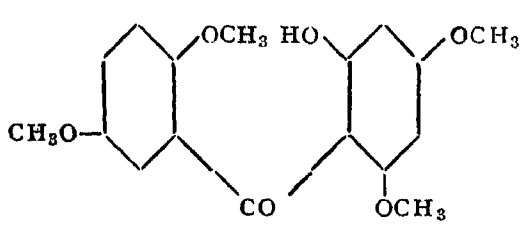


(V)

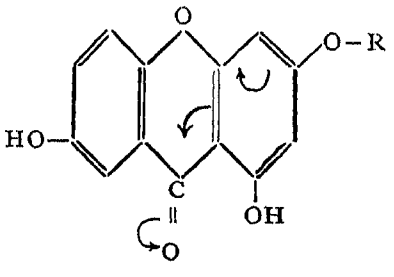
The method has next been employed for the synthesis of gentisein (VI *a*) and its naturally occurring monomethyl ether gentisin. Gentisin (VI *b*), the yellow colouring matter of *Gentiana lutea* (gentian root) was shown by Kostanecki[4] to be a monomethyl ether of gentisein, 1 : 3 : 7-trihydroxy xanthone which was synthesised by the distillation of a mixture of gentisic acid, phloroglucinol and acetic anhydride.[5] He obtained gentisin itself by the partial methylation of gentisein[5] (yield not stated). This synthesis was at that time not considered to be definite proof of its constitution. In view of recent analogies it should be taken as establishing the constitution of gentisin as the 3-methyl ether of gentisein. However, the point was unequivocally established by Shinoda's synthesis[6] of gentisein 7-methyl ether which was different from gentisin. The possibility of gentisin being the

1-methyl ether of gentisein was eliminated even earlier since methylation of gentisin with excess of methyl iodide did not yield a dimethyl ether but gave only a monomethyl ether. The constitution has been further confirmed by the recent work of Anand and Venkataraman[7] who prepared 7-nitro-1-hydroxy-3-methoxy xanthone and converted the nitro group into the hydroxyl by conventional methods.

The present synthesis consists of the condensation of 2:5-dimethoxy benzoyl chloride with phloroglucinol trimethyl ether. The 2-hydroxy-4:6:2′:5′-tetramethoxy benzophenone (VII) obtained as the intermediate undergoes easy conversion into gentisein (VI *a*), either by treatment with aluminium chloride in boiling benzene solution or with boiling hydriodic acid in acetic anhydride solution. The preparation of gentisin (VI *b*) has now been done by the partial methylation of gentisein (VI *a*) using 1 mole of dimethyl sulphate in acetone solution in the presence of anhydrous potassium carbonate. The partial methylation yields mainly gentisin (VI *b*), since the 3-hydroxyl in (VI *a*) is the most acidic and reactive. It corresponds to the 7-hydroxyl in chromones and is influenced by the C = O group in the para position,[8] whereas the 7-hydroxyl in xanthones is not so affected and the 1-hydroxyl is protected by chelation. There is however some unchanged gentisein, and the mixture is separated by using difference in solubilities in sodium carbonate and sodium hydroxide solutions. Unreacted gentisein dissolves in aqueous sodium carbonate by virtue of the 3-hydroxyl group which is markedly acidic (see formula VI *a*). The sodium hydroxide soluble portion gives a good yield of gentisin. There is no detectable amount of the dimethyl ether. Gentisin has also been obtained by the partial demethylation and simultaneous ring closure of 2-hydroxy-4:6:2′:5′-tetramethoxy benzophenone (VII) using hydriodic acid at 110°. The principle of this reaction has already been discussed in connection with isoflavone derivatives.[9,10] In this reaction the trimethoxy xanthone should be first formed and the more easily susceptible 1 and 7-methoxyl groups undergo preferential demethylation, the more stable 3-methoxyl remaining behind.



(VII)



(VI) *a*, R = H
b, R = CH_3

Experimental

1 : 3-*Dihydroxy xanthone* (*III*)

(*a*) *2-Hydroxy-4 : 6 : 2'-trimethoxy benzophenone* (*II a*).—Freshly powdered anhydrous aluminium chloride (12 g.) was dissolved in dry ether (100 c.c.) with cooling in ice, and to the solution was added phloroglucinol trimethyl ether (4·2 g.). The mixture was cooled for fifteen minutes, after which time freshly distilled *o*-methoxy benzoyl chloride (5 c.c.) was added in small quantities during half an hour with occasional shaking. Only after the addition of the acid chloride was complete a dark brown oily complex separated and the reaction mixture was allowed to stand at the temperature of the laboratory for 48 hours. It was then treated with crushed ice and concentrated hydrochloric acid (25 c.c.), and the ether distilled off on a water-bath. Benzene (50 c.c.) was then added and the mixture refluxed for half an hour on a water-bath. The benzene layer was separated while still hot and the aqueous solution extracted once again with benzene (50 c.c.). The combined benzene extract was washed with water and dilute sodium bicarbonate solution (5%) and the solvent distilled off when an oily product was obtained which solidified on cooling. It crystallised from methanol as stout rhombohedrons melting at 92–3°; yield, 4·5 g. (Found: C, 66·8; H, 6·0; $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%).

The benzophenone is insoluble in cold alkali but dissolves in hot alkali giving rise to an yellow solution which on cooling deposits a pale yellow solid. It gives a deep red colour with alcoholic ferric chloride. With concentrated nitric acid it gives a deep blue colour which changes on standing to dirty green and finally purple. It dissolves in concentrated sulphuric acid to an yellow solution which develops a bluish green fluorescence on standing.

(*b*) *Demethylation and ring closure.*—The above benzophenone (1·25 g.) was dissolved in dry benzene (50 c.c.), freshly powdered anhydrous aluminium chloride (8 g.) was added and the mixture shaken for a few minutes when a dark reddish brown complex separated. The mixture was refluxed on a water-bath for 2 hours and the solvent distilled off. The oily residue was cooled and the complex decomposed by treatment with crushed ice and concentrated hydrochloric acid (15 c.c.), and warming in a water-bath for 10 minutes. The mixture was extracted with ether thrice (50 c.c. each time). The combined ether extract was then washed with sodium carbonate solution thrice (10% solution; 20 c.c. each time). On acidifying the alkaline extract with concentrated hydrochloric acid a gelatinous mass was obtained which coagulated on heating. This was filtered, dried and crystallised from dilute alcohol when 1 : 3-dihydroxy xanthone was obtained as aggregates of colourless rectangular prisms and needles melting at 256–8°[3] yield, 0·3 g. The

substance answers all the colour reactions recorded in the literature[3] for 1 : 3-dihydroxy xanthone. It dissolved in sodium carbonate solution giving a deep yellow colour.

The diacetate of the xanthone was obtained by boiling with acetic anhydride and freshly fused sodium acetate. It crystallised from alcohol as colourless elongated rectangular prisms melting at 145°.[1]

1 : 3-*Dimethoxy xanthone*

The dihydroxy xanthone (0·25 g.) was dissolved in dry acetone (50 c.c.), redistilled dimethyl sulphate (1 c.c.) and ignited potassium carbonate (2 g.) added and the mixture refluxed on a water-bath for 48 hours. The acetone solution was filtered hot and the potassium salts washed with hot acetone. The solvent was distilled off and the residue dissolved in ether. The ether solution was washed with dilute alkali (in order to remove any partial methyl ether). The solvent was distilled off and the residue crystallised from dilute alcohol when it came out as long silky needles melting at 167–9° (Found: C, 61·7; H, 5·7; $C_{15}H_{12}O_4$ $2H_2O$ requires C, 61·5; H, 5·7%). It dissolved in concentrated sulphuric acid to give an yellow solution which developed a greenish blue fluorescence on standing.

2-*Hydroxy*-4 : 6-*dimethoxy*-2′-*ethoxy benzophenone* (*II b*)

o-Ethoxy benzoyl chloride (5 c.c.) and phloroglucinol trimethyl ether (4·2 g.) were condensed in the presence of anhydrous aluminium chloride (12 g.) in dry ether solution (100 c.c.). The reaction was carried out as mentioned earlier. The benzophenone crystallised from alcohol as straw yellow rectangular prisms melting at 160–1°; yield, 4 g. (Found: C, 67·9; H, 6·0; $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%). This benzophenone gives the same colour reactions as given by 2-hydroxy-4 : 6 : 2′-trimethoxy benzophenone (II *a*). It undergoes demethylation and de-ethylation and ring closure to 1 : 3-dihydroxy xanthone in boiling benzene solution in the presence of anhydrous aluminium chloride.

3 : 4-*Dihydroxy xanthone* (*V*)

(*a*) 2-*Hydroxy*-3 : 4 : 2′-*trimethoxy benzophenone* (*IV*).—This was obtained by the condensation of *o*-methoxy benzoyl chloride (5 c.c.), pyrogallol trimethyl ether (4·2 g.) and anhydrous aluminium chloride (12 g.) in dry ether solution (100 c.c.), the conditions being the same as mentioned earlier. 2-Hydroxy-3 : 4 : 2′-trimethoxy benzophenone crystallised from benzene-petroleum ether mixture as colourless rectangular tablets melting at 110–1° (Found: C, 66·8; H, 5·9; $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). It dissolves in hot alkali forming an orange yellow solution which deposits a

solid on cooling. It gives a deep red colour with alcoholic ferric chloride solution and forms a deep red solution with concentrated nitric acid which changes yellow on standing. The substance dissolves in concentrated sulphuric acid to an yellow solution exhibiting a bluish green fluorescence.

(*b*) *Demethylation and ring closure.*—The above benzophenone (1·25 g.) was dissolved in dry benzene (50 c.c.), anhydrous aluminium chloride (8 g.) added, the mixture refluxed on a water-bath for 2 hours and the product worked up as in an earlier case. 3 : 4-Dihydroxy xanthone crystallised from dilute alcohol as pale yellow rectangular plates melting at 240–1°.[11] It dissolved in concentrated sulphuric acid to an yellow solution exhibiting a bluish green fluorescence and in aqueous sodium carbonate to give a bright yellow solution. With alcoholic ferric chloride a green colour was obtained.

The diacetate of the xanthone was obtained by boiling with acetic anhydride and freshly fused sodium acetate. It crystallised from alcohol as colourless stout prisms melting at 161–2°.[11]

The dimethyl ether was obtained by methylation of the xanthone with dimethyl sulphate in acetone solution in the presence of anhydrous potassium carbonate. It crystallised from dilute methanol as colourless long needles melting at 156–8°.[12] It dissolved in concentrated sulphuric acid to an yellow solution which developed a bluish green fluorescence on standing.

Gentisin (*VI b*)

(*a*) *2-Hydroxy-4 : 6 : 2′ : 5′-tetramethoxy benzophenone* (*VII*).—2 : 5-Dimethoxy benzoyl chloride (8·3 g.) and phloroglucinol trimethyl ether (6·3 g.), were condensed in the presence of anhydrous aluminium chloride (12 g.) in dry ether solution (100 c.c.). The reaction was carried out as mentioned earlier. The benzophenone crystallised from benzene-petroleum ether mixture as colourless elongated rhombohedral plates melting at 174–5°; yield, 6 g. (Found: C, 64·4; H, 5·9; $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7%). The substance was slightly soluble in sodium hydroxide in the hot giving an orange yellow solution which deposited a pale yellow solid on cooling. With alcoholic ferric chloride a deep red colour was produced. With concentrated nitric acid a deep red colour changing to deep yellow on standing was obtained. It dissolved in concentrated sulphuric acid to an yellow solution which developed a greenish blue fluorescence on standing.

(*b*) *Demethylation and ring closure to gentisein* (*VI a*).—The benzophenone (1·25 g.) in benzene solution (50 c.c.) was treated with anhydrous aluminium chloride (8 g.) on a boiling water-bath for 2 hours. The rest of the reaction was carried out as mentioned earlier. Gentisein crystallised from dilute alcohol as tiny needles melting at 316–8°.[5] It gave an olive brown colour with

alcoholic ferric chloride, dissolved in sodium hydroxide and sodium carbonate solutions giving an orange yellow colour and in concentrated sulphuric acid to form a deep yellow solution exhibiting a greenish blue fluorescence.

The triacetate of gentisein[13] was obtained by boiling with acetic anhydride and freshly fused sodium acetate. It crystallised from glacial acetic acid in the form of fine silky needles melting at 226°.

(*c*) *Partial methylation of gentisein.*—Gentisein (0·75 g.) was dissolved in dry acetone (50 c.c.), and redistilled dimethyl sulphate (0·3 c.c., 1 mole) and ignited potassium carbonate (1 g.) were then added. The mixture was refluxed on a water-bath for 8 hours, after which time the solution was filtered hot and the potassium salts washed with hot acetone. The solvent was distilled off from the filtrate and the residue dissolved in large volume of ether (200 c.c.). The ether solution was thrice extracted with dilute sodium carbonate solution (10%; 20 c.c. each time) in order to remove any unchanged gentisein. The gentisin in the ether solution was then extracted with sodium hydroxide solution (5%). The alkaline solution was allowed to stand for some time (there was no detectable amount of the sparingly soluble sodium salt of the dimethyl ether) and neutralised with concentrated hydrochloric acid. A gelatinous mass was obtained. It crystallised from alcohol as fine needles melting at 266–7°; yield, 0·5 g. The substance gave an olive green colour with alcoholic ferric chloride and dissolved in concentrated sulphuric acid to an yellow solution which on standing developed a bright green fluorescence. When heated and shaken with sodium amalgam in water it gave a deep green solution which on acidification have a cherry red colour. All these reactions agreed with the reactions recorded for gentisin in the literature. The diacetate of gentisin was obtained by boiling with acetic anhydride and freshly fused sodium acetate. It crystallised from alcohol as thin long woolly needles melting at 196–7°.

(*d*) *Partial demethylation of* 2-*hydroxy*-4:6:2′:5′-*tetramethoxy benzophenone* (*VII*) *to gentisin* (*VI b*).—The above benzophenone (1 g.) was dissolved in acetic anhydride (10 c.c.) and hydriodic acid (10 c.c., 1·7 d.) was then added. The mixture was maintained at a temperature of 110° for a period of half an hour. The free iodine was removed by the addition of sodium bisulphite. The mixture of gentisein and gentisin were separated as in the previous case; yield of gentisein, 0·15 g.; gentisin, 0·1 g.

1:3:7-*Trimethoxy xanthone* (*gentisin dimethyl ether*)

Previous investigators did not prepare gentisein trimethyl ether (gentisin dimethyl ether) and record its properties. This has now been done. The

hydroxyl group in 1-position is highly resistant and requires long boiling with excess of dimethyl sulphate to complete the methylation.

Gentisein (0·25 g.) was dissolved in dry acetone (50 c.c.), redistilled dimethyl sulphate (1 c.c.) and ignited potassium carbonate (2 g.) added and the mixture refluxed on a water-bath for a period of 80 hours. The acetone solution was filtered hot and the potassium salts washed with hot acetone. The solvent was distilled off and residue dissolved in ether. The ether solution was washed with dilute alkali in order to remove any partial methyl ether and subsequently with water. The ether was then distilled off and the residue crystallised from dilute methanol when it came out in the form of colourless rectangular plates with a marked tendency to taper at the ends and melted at 171–3°; yield, 0·2 g. (Found: C, 67·6; H, 5·2; $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). It dissolved in concentrated sulphuric acid to an yellow solution which developed a greenish blue fluorescence on standing.

Summary

A new synthesis of hydroxy xanthones and their derivatives is described. It employs the Friedel and Craft's reaction for the condensation of an ortho methoxy benzoyl chloride with a fully methylated polyhydric phenol. The resulting benzophenone has an ortho hydroxyl group which in a test case has been shown to belong to the phenol part. By subsequent treatment with aluminium chloride or hydriodic acid demethylation and xanthone ring closure are effected. As examples the synthesis of 1 : 3-dihydroxy xanthone, 3 : 4-dihydroxy xanthone and gentisein is given. The naturally occurring xanthone, gentisin is conveniently obtained by the partial methylation of gentisein or by the partial demethylation and ring closure of 2-hydroxy-4 : 6 : 2′ : 5′-tetramethoxy benzophenone.

References

1. Kostanecki and Nessler .. *Ber.*, 1891, **24**, 3981.
2. Ullmann aud Zloakstoff .. *Ibid.*, 1905, **38**, 2111.
3. Robinson and Nishikawa .. *J. Chem. Soc.*, 1922, **121**, 839.
4. Kostanecki .. *Chem. Zentr.*, 1891, **1**, 587.
5. ———— and Tambor .. *Monatsh.*, 1894, **15**, 1.
6. Shinoda .. *J. Chem. Soc.*, 1927, 1983.
7. Anand and Venkataraman .. *Proc. Ind. Acad. Sci.*, 1947, **25A**, 438.
8. Narasimhachari and Seshadri .. *Ibid.*, 1950, **32A**, 256 and 342.
9. Aghoramurthi *et al.* .. *Ibid.*, 1951, **33A**, 257.
10. Narasimhachari *et al.* .. *Ibid.*, 1952, **36A**, 194.
11. Grabe and Eichengrun .. *Ber.*, 1891, **24**, 967.
12. Ullmann and Denzler .. *Ibid.*, 1906, **39**, 4337.
13. Kostanecki .. *Monatsh.*, 1891, **12**, 209.