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XANTHONES OF THE GENTIANACEAE—I

FRASERA CAROLINIENSIS WALT.[1]

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Abstract—The root of *Frasera caroliniensis* Walt. has been shown to contain 1-hydroxy-2,3,4,7-tetramethoxyanthone (**1**), 1-hydroxy-2,3,4,5-tetramethoxyxanthone (**6**), 1-hydroxy-2,3,7-trimethoxyxanthone (**9**), 1-hydroxy-2,3,5-trimethoxyxanthone (**11**), swerchirin (**15**), a swerchirin glycoside (**16**), 1,3-dihydroxy-4,5-dimethoxyxanthone (**18**), and a compound that yields 1,2,3,5,8-pentamethoxyxanthone (**19**) on methylation.

The new xanthones have been synthesized by a general method from suitable benzophenone precursors by elimination of a OMe group under strongly basic conditions. This method has also been used to prepare 1,2,3,4,8-pentamethoxyxanthone and 1,3,4,8-tetramethoxyxanthone.

AMONG the higher plants, the families Guttiferae and Gentianaceae represent the principal sources of xanthone derivatives.[2,3] The latter have yielded a number of simple hydroxylated and methoxylated xanthones from the genera *Gentiana*[4–7] and *Swertia*,[8–12] but the remainder of the family has been little studied. It is with the view of extending our knowledge of the chemical productivity of this family that we have undertaken a series of investigations of other genera.

Frasera is a small genus of about twelve species, found largely in the western US.[13] It is closely allied with *Swertia* and is often combined with it.[14] There are, however, a number of taxonomic differences,[13] and as will be seen below our chemical results appear to support the separation.

Frasera caroliniensis Walt., American colombo, is a large pyramidal plant found widely in the southeastern US. Because of the bitter nature of the root, characteristic of the Gentianaceae, it was formerly used in medicine as a substitute for gentian or colombo. A number of early investigations[15–19] of this plant (generally under the synonym *F. Walteri* Mich.) yielded a yellow coloring matter. This was originally believed to be identical with gentisin from *Gentiana lutea* L., but later work[20] showed that this was not true. Ultimately Trimble and Lloyd[21] reported the isolation of two yellow pigments, one, m.p. 114°, assigned the formula $C_{15}H_{15}O_6$ and the other, m.p. 178°, assigned $C_{16}H_{15}O_6$. It is not clear whether the latter corresponds to the pigment claimed by Kennedy[18] to be gentisin (m.p. reported[20] ca. 187°), especially since later studies[22] suggested that at least three compounds were present.

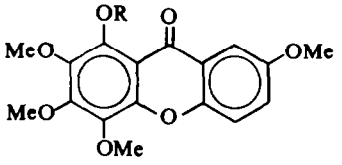
Preliminary examination of the roots of *F. caroliniensis* by TLC of extracts showed the presence of a number of different yellow pigments. Acetone extraction of a larger sample of ground root was followed by liquid–liquid extraction of the concentrated liquors with CH_2Cl_2/pentane. The residue from the pentane solution gave after crystallization a yellow crystalline mixture representing the bulk of the extract. Preparative chromatography on silica gel separated this into three chromatographically homogeneous fractions, A. B. and C.

Fraction A. Crystallization of fraction A yielded a dark yellow solid, m.p. 118°,

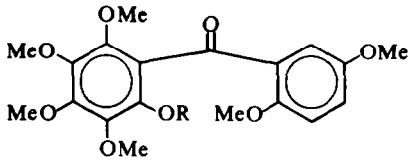
with combustion analyses indicating the formula $C_{17}H_{16}O_7$. This presumably corresponds to the product m.p. 114° isolated by Trimble and Lloyd,[21] whose analyses also agree with our formulation. The ultraviolet spectrum is consistent with the expected xanthone nucleus, as are those of all the other compounds isolated.

The NMR spectrum shows a chelated hydroxyl (τ −2·62), four methoxy groups (5·85–6·09, 12H), and three aromatic protons, all coupled. These appear in part as a quartet (~1H) at τ 2·39 with apparent J's of 1 and 3 Hz.* These small couplings suggest the presence of protons *meta* and *para* but not *ortho* to the one causing this signal. Except for 1-oxy rings, in which this signal is a widely spaced triplet from the proton at C-3,[23] it is the proton at C-1 (C-8), deshielded by the field of the adjacent CO group, that appears at lowest field. Found at τ 1·7–1·9 in unsubstituted xanthone rings, it should be shifted ca. 0·5 ppm upfield by an adjacent OMe group[24] and so should agree in both coupling and position with that observed. Comparison against model compounds confirmed these arguments.

Since the observation of a strongly deshielded proton requires that the OH group be located *ortho* to the carbonyl bridge, this product may be assigned the structure 1-hydroxy-2,3,4,7-tetramethoxyxanthone (**1**).



1: R = H
2: R = Me



3: R = Me
4: R = H

Confirmation of this proposal was obtained by synthesis. Pentamethoxybenzene was condensed with 2,5-dimethoxybenzoyl chloride using aluminum chloride in nitrobenzene. This reaction led to a mixture of the benzophenones **3** and **4**, the latter also being prepared by the selective demethylation of **3** with aluminum chloride in ether.[25] Cyclization of **4** with tetramethyl ammonium hydroxide in pyridine led in excellent yield to 1,2,3,4,7-pentamethoxyxanthone (**2**), identical with material prepared by methylation of the natural product.† Selective demethylation of synthetic **2** gave material identical in all respects with natural **1**.

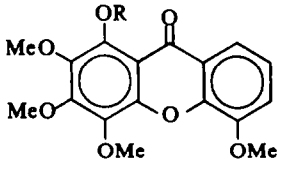
Fraction B. The broad melting range and variable NMR spectrum of fraction B indicated that it was a mixture, almost inseparable by chromatography. Following methylation, however, preparative TLC on acidified silica gel yielded two xanthones that differed significantly in their basicity. The proportions of the two components in the mixture varied depending on the history of previous purification of the sample. Fraction B from the original mixture of crystals was largely Bf, while that from the mother liquors had approximately equal amounts of the two.

The more mobile of the methyl ethers (Me Bf), m.p. 145°, has the formula $C_{18}H_{18}O_7$

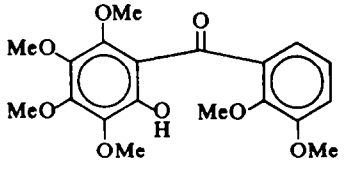
* Note that in this and the other aromatic rings involving an ABC system the measured spacings need not correspond to the true coupling constants. They are, however, useful for comparison purposes and may serve to distinguish *ortho* from *meta* or *para* coupling.

† Since the completion of this synthesis,[1] **2** has been described as a natural product (polygalaxanthone B) from *Polygala paenea* L.[26] The physical constants reported for this material and **1** derived from it are in excellent agreement with those of our materials.

and shows in its NMR spectrum five OMe groups and three aromatic protons, again all coupled. This spectrum is clearly different from that of the methyl ether **2**, and the low-field portion of the aromatic proton spectrum consists of four lines at ca. τ 2·27 with separations of 4 and 6 Hz. These values do not correspond to ideal *ortho* or *meta* coupling constants and did not permit the immediate deduction of a structure. Therefore the spectrum was compared against the series of 2,x-dimethoxybenzoic acids and a group of chromone derivatives methoxylated in all the aromatic positions. Of these 2,3-dimethoxybenzoic acid (τ 2·5, 4 and 6 Hz) and 8-methoxy-2-methylchromone (τ 2·3, 3 and 7 Hz) showed the best fit both in values and in the general appearance of the aromatic region,* suggesting that the xanthone possesses the structure **5**.



5: R = Me
6: R = H



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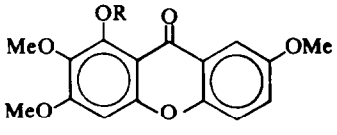
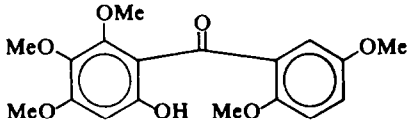
For confirmation, pentamethoxybenzene and 2,3-dimethoxybenzoyl chloride were condensed in the presence of ethereal aluminum chloride to give the benzophenone **7**. Cyclization as before with tetramethylammonium hydroxide yielded **5**, identical in all respects with material isolated as Me Bf.

The more polar material, Me Bb, m.p. 136°, has the formula $C_{17}H_{16}O_6$. The NMR spectrum shows four OMe groups, an isolated aromatic proton at τ 3·35, and three others whose coupling pattern is clearly that of **1**. This pattern locates one OMe group at C-7, but leaves the position of the isolated proton in the other ring to be determined. Comparison of the spectrum with those of the previously synthesized 1,2,3,5- and 1,3,4,8-tetramethoxyxanthones (see below) suggested C-4 for this proton in preference to C-2 and led to the proposal of structure **8**.



8: R = Me
9: R = H



10

An unambiguous synthetic approach to this compound requires 3,4,5-trimethoxyphenol, previously synthesized[28] by partial methylation of 2,6-dimethoxyhydroquinone. Attempts to repeat the earlier isolation led to much loss of product, and an improved route was devised in which the crude mixture of methylated materials was acetylated and the desired 1-acetoxy-3,4,5-trimethoxybenzene isolated by fractional crystallization. Condensation of this material with 2,5-dimethoxybenzoic acid in

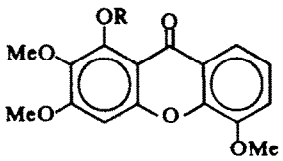
* Since the identification of these compounds a similar pattern has been reported for two 1,3,5-trioxyxanthones.[27]

trifluoroacetic anhydride (TFAA), followed by hydrolysis of the reaction mixture, gave the benzophenone **10**. This was cyclized in base in the usual way to **8**, identical with the natural methyl ether.

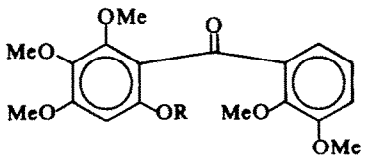
Several arguments indicate that the original fraction B is a mixture of the 1-hydroxyxanthones **6** and **9**. These compounds were prepared by selective demethylation of **5** and **8**, and both proved to have the same TLC properties as the natural mixture. The NMR spectrum of this mixture shows two chelated hydroxyl signals (τ −2·45, −2·62) as well as seven OMe peaks divisible into groups of three and four on the basis of their intensity variations in fractions containing differing concentrations of the two components. Comparison of the NMR spectrum of the mixture with those of synthetic **6** and **9** showed that every signal from the mixture could be associated with one in the pure samples. Finally a small quantity of pure **6** was ultimately obtained from one chromatographic fraction and shown to be identical with synthetic material.

The m.p. of synthetic 1-hydroxy-2,3,7-tetramethoxyxanthone (**9**) is 177°, in good agreement with the 178° obtained by Trimble and Lloyd[21] for the second of their products. Furthermore, although they proposed a different formula, the analytical results cited[21] are in excellent agreement with the formula of **9**, $C_{16}H_{14}O_6$. Thus it would appear that the early workers obtained this material, despite the fact that, in our samples at least, it was present in smaller amounts than either of the xanthones Bf (**6**) or C (**11**).

Fraction C. The final major fraction yielded a single compound, $C_{16}H_{14}O_6$, m.p. 190°. The NMR spectrum shows it to be a 1-hydroxyxanthone with three OMe groups. Three of the aromatic protons are coupled in a fashion very similar to that of **6**, while the last gives a single signal at τ 3·44 (τ 3·19 in the methyl ether). The ubiquitous appearance of phloroglucinol oxygenation made C-3 unlikely as a proton site; so a hydrogen at C-2 or C-4 was considered the probable source of this signal. The spectrum of 1,3,4,8-tetramethoxyxanthone, synthesized as an early model, shows the C-2 proton signal at τ 3·60, and the difference between this value and that given above suggested that C-4 was to be favored for the natural product. This difference is in accord with observations on the flavone series[24] and on other xanthones,[7c] which indicate that the protons at C-2 consistently appear at higher field than do those at C-4.



11: R = H
12: R = Me



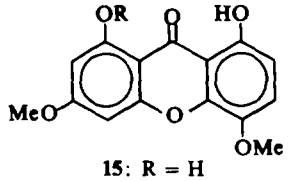
13: R = Ac
14: R = H

On this basis the structure 1-hydroxy-2,3,5-trimethoxyxanthone (**11**) was proposed. To obtain confirmation 3,4,5-trimethoxy-1-acetoxybenzene was condensed with 2,3-dimethoxybenzoic acid in TFAA to give the benzophenone **13**. This was not isolated but was hydrolyzed to the hydroxy compound **14** and cyclized as before to give 1,2,3,5-tetramethoxyxanthone (**12**), identical with the methyl ether of xanthone C. Selective demethylation yielded **11**, identical in all respects with the natural product.

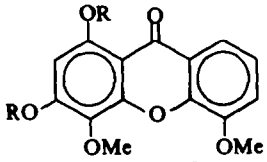
The m.p. of xanthone C is close to that reported[20] for the crystalline product obtained by Kennedy,[18] and its high yield and easy isolation suggest that the two are probably the same. The melting point of swerchirin (see below) is nearly the same, however, so it cannot be excluded as a secondary possibility.

Minor xanthones. In addition to the major products described above a number of minor xanthones were also obtained.

Chromatography of the mother liquors from the original crystallization of the crude extract gave, besides additional quantities of the compounds already discussed, two further products. Selective crystallization of fractions also containing **1** yielded material m.p. 190·5° having the formula $C_{14}H_{12}O_6$. The NMR spectrum shows two chelated hydroxyl groups, two OMe groups, and two pairs of aromatic protons, one pair *meta* coupled ($J = 2{\cdot}5$ Hz) and the other *ortho* ($J = 9$ Hz). These properties indicated the material to be the known compound swerchirin (**15**). previously isolated from several species of the Gentianaceae.[12,7,29] Direct comparison with an authentic sample obtained from *Swertia chirata*[12] confirmed the identification.



15: R = H
16: R = Sugar



17: R = Me
18: R = H

There was also obtained from fractions between those providing **6** and **11** a small amount of a very soluble compound, xanthone E. m.p. 275°, whose mass spectrum indicated the formula $C_{15}H_{12}O_6$. The NMR spectrum (DMSO) shows two OMe groups, and acetylation yielded a diacetate. This shows a signal at τ 3·28 from a single aromatic proton and a coupled pattern similar to that of **11**, i.e. 5-OR, from the others. Methylation gave a methyl ether identical in its UV properties and TLC behavior with 1,3,4,5-tetramethoxyxanthone (**17**)[29] and markedly different from **12**.

The change in the UV spectrum of this compound in base (319, 360 mμ → 347, 380 mμ) is similar to that observed[29] for other 1,3-dihydroxyxanthones, while the shifts caused by $AlCl_3$ or NaOAc[7c,*] are comparable to those produced by these reagents on model 1- and 3-hydroxyxanthones, respectively. Furthermore the NMR signal of the isolated C-2 proton in the diacetate occurs at the same position as that of 1,3-diacetoxy-4,7-dimethoxyxanthone,[29] supporting the view of a similar substitution of acetoxyl and OMe groups in that ring. Thus the structure 1,3-dihydroxy-4,5-dimethoxyxanthone (**18**) is proposed for this material.

During the liquid–liquid separation of the crude extracts a fine yellow crystalline deposit (Fraction D) appears at the interface. Filtration, sublimation, and crystallization gives a product m.p. 272° dec. Although the ultraviolet spectrum is that of a xanthone, the analysis is inconsistent with a simple xanthonic formulation. Hydrolysis with dilute acid, however, yields swerchirin (**15**), indicating that the compound is probably a glycoside.

Acetylation of xanthone D yields a crystalline peracetate whose NMR spectrum indicates the presence of 7–9 acetoxyl groups. Of these, one appears at significantly lower field (τ 7·58) than the others (τ 7·93–8·07) suggesting its assignment as an aromatic

* Analogous changes are produced by these reagents in flavanoid compounds.[30]

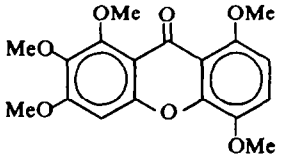
ester. The signals from the aromatic protons at C-6 and C-7 (τ 2·83, 3·16) are the same as those from the corresponding protons of swerchirin diacetate (τ 2·82, 3·18), while those from the 2 and 4 positions (τ 3·29, 2H) differ significantly from swerchirin diacetate (τ 3·46, 3·16) and 1-acetoxy-3,7-dimethoxyxanthone (τ 3·46, 3·21). On this basis it appears that the ester must bear an acetoxyl group at C-8 and thus the glycoside linkage at C-1 (**16**).

The number and kind of the sugar residues is uncertain at this time. The analyses of the natural compound and its acetate do not lead to consistent molecular formulas, but suggest, when taken with the NMR evidence, that two or three sugar units are involved. Analysis by the Glucostat method[31] of the water soluble fraction from the hydrolysis indicated that only one of these can be glucose, while paper chromatography of the hydrolyzate suggested the presence of glucose and another sugar.

A sample of the yellow aqueous liquor remaining after the liquid–liquid separation was also subjected to acidic hydrolysis and subsequent extraction. TLC of the new organic-soluble products showed the presence of the three fractions A, B, and C, indicating that these compounds are probably also present as glycosides.

A final product, methyl xanthone Z, $C_{18}H_{18}O_7$, was isolated in very small yield from chromatography of a methylated sample of natural **11**. The NMR spectrum shows five methoxyl groups, an aromatic singlet at τ 3·29, and doublets (J = 9 Hz) at τ 2·93 and 3·37. The former signal is in good agreement with those of the C-4 protons of **8** and **12** and differs from the higher field absorption shown by C-2 protons.[7c,29] The doublets are very similar in position and coupling to the 6 and 7 protons of dimethylswerchirin (τ 2·91, 3·34, J = 9 Hz) and indicate the structure to be **19**.

Owing to the small quantity of the material present and to its chromatographic similarity to **11** the unmethylated precursor of **19** has not been isolated. It is reasonable to expect, however, that it is either the 1 (or 8)-hydroxy- or the 1,8-dihydroxyxanthone.



19

The products isolated from *F. caroliniensis* represent further examples of the universal appearance of oxygen at C-5 or C-7 in xanthones from higher plants.[3] They differ, however, from those found in various *Swertia* species[8–12] in generally lacking a second oxygen atom at C-8. The only exceptions are swerchirin (previously found outside of *Swertia*[7]) and the precursor of **19**, both minor products. On this basis *Frasera* would appear to be distinguishable chemically from *Swertia*.

Consideration of the yields of the various pure compounds and apportionment of the mixed fractions by means of their NMR spectra indicate that the original 29·0 g of crude extract contained 27% **1** (A), 19% **6** (Bf), 4% **9** (Bb), and 24% **11** (C). The other components were less than 3% each. Thus the bulk of the material is concentrated in three products, and these constitute about 0·37% of the weight of the fresh plant.

Preliminary examination of two western species,[13] *F. speciosa* Dougl. *ex* Griesb.

and *F. fastigiata* (Pursh.) Heller, which resemble *F. caroliniensis* greatly in appearance and mode of growth, showed that these gave the same major fractions and products as did the eastern species. There are differences in the relative amounts of the compounds, but they are quantitative rather than qualitative, and the chromatographic patterns are very similar. *F. albicaulis* Dougl. *ex.* Griesb., on the other hand, which differs significantly in its morphology, shows a quite different pattern.[29]

The method of synthesis used here, in which the ready intramolecular displacement of methoxyl by a phenoxide ion is used to form the ether bridge of the xanthone system, has not previously been exploited systematically although the fundamental reaction has been recognized for some time.[32] It appears to have advantages in both simplicity and yield over the more conventional routes[2] for the synthesis of highly oxygenated xanthones. The ring closure often occurs in excellent yield, and the only difficulty is providing suitable conditions for the synthesis of the benzophenone precursor. We have found individual cases, depending on the exact compounds involved, in which this condensation was best performed with the acid chloride and aluminium chloride in nitrobenzene, or in ether, or with the free acid in trifluoroacetic anhydride.

One of the major advantages of this method is that conditions may be used which do not cause the demethylation sometimes encountered in other routes.[12] If selective demethylation of a totally methylated benzophenone is required, aluminum chloride in ether can be used, usually with good results,[25] and this has the advantage of cleaving preferentially the most hindered methoxy group *ortho* to the carbonyl, i.e., that one most heavily buttressed by adjacent groups.[33] Thus the direction of demethylation and so of ring closure can generally be predicted. Possible ambiguity may be avoided if desired, however, by using phenols[29] or their esters in the condensation step, providing a suitable hydroxyl group without demethylation.

In addition to the synthesis of the natural compounds described above, we have used this method to prepare the model compounds 1,2,3,4,8-pentanemethoxyxanthone and 1,3,4,8-tetramethoxyxanthone.

EXPERIMENTAL

NMR spectra were taken on a Varian A-60 or HA-60 spectrometer. The letters and numbers in parentheses refer to the multiplicity and estimated relative areas of the peaks. Combustion analyses were by Dr. A. Bernhardt, Max Planck Institute, Mulheim (Ruhr), West Germany. UV spectra were taken on a Cary 14 spectrometer in 95% EtOH. The intensities for the qualitative UV's are recorded as a decimal of the biggest peak. Melting points were taken on a Kofler micro hot stage and are corrected. TLC analyses were carried out on silica gel G, E. Merck, Darmstadt, using mixtures of hexane and ethyl acetate as solvents. Column chromatography, unless otherwise stated, used Grace–Davidson silica gel 924, 200–325 mesh.

Isolation. Fresh roots of *Frasera caroliniensis* Walt. (5500 g) from Henderson's Botanical Garden, Greensburg, Indiana, were ground into a mush with acetone (12 l.) and filtered after 3 hr. The pulp was again extracted with acetone (12 l.), filtered after 1 hr, and washed with 1·5 l. of acetone. The filtrates were combined and the acetone was distilled off until the refluxing vapors reached 85–90°. The concentrated solution (4 l.) was extracted in a liquid–liquid extractor with pentane (800 ml) and CH_2Cl_2 (200 ml). After 9 hr the solvent was replaced and a further 9 hr extraction yielded only a small amount of material. A quantity of yellow ppt formed at the liquid–liquid interface and was removed by filtration, yielding crude compound D (0·695 g, 0·0125% of root).

The pentane/CH_2Cl_2 extracts were evaporated to a thick yellow-brown oil (29·0 g, 0·527%), which showed three major spots and a brown polar streak by TLC. Crystallization from MeOH gave crystals of mixed xanthones (18·5 g, 0·337%) showing little of the brown material.

The crystals (3·0 g) were chromatographed on a silica gel column, 900 × 18 mm. The solvent system hexane/EtOAc (3:1) was used for the first 210 15 ml fractions, after which the ratio was changed to 2:1. Table 1 shows the separation obtained.

TABLE 1.

Frac.	Vol.	Comp.	Crude wt.	Sublimed wt.	% of sample
1	45	forerun	0·019		
2	375	A	0·919	0·901	30
3	45	A, B	0·050	0·047	
4	345	B	0·827	0·688	23
5	870	B, C	0·242	0·222	7
6	1170	C	1·115	1·040	35
7	900	C	0·050		
8	1275	tail	0·149		

The ground root residue was stored for 30 days in acetone (8 l.), filtered, washed, concentrated, and partitioned as above to give an additional 3·30 g of crude extract and a total yield of 32·2 g (0·56%) of crude xanthones from the fresh roots.

Xanthone A (**1**). Fraction 2 was a deep yellow solid. Sublimation gave 901 mg of material which was crystallized twice from CH_2Cl_2/hexane and twice from MeOH to give pure xanthone A, m.p. 117·8–118·8°, m.m.p. with synthetic 1-hydroxy-2,3,4,7-tetramethoxyxanthone 116·7–117·7°, identity confirmed by NMR, TLC, and UV. NMR (CH_2Cl_2) τ −2·62 (s, 1), 2·39 (q, 1), 2·55 (m, 2), 5·86 (s, 3), 6·04 (s, 3), 6·09 (d, 6); UV max 234 (0·84), 270 (1·0), 301 (0·31), 317 sh (0·29), 387 (0·16) mμ. (Found: C, 61·53; H, 4·98. $C_{17}H_{16}O_7$ requires: C, 61·44; H, 4·85%).

Xanthone A *methyl ether* (**2**). Xanthone A (150 mg), NaH (0·2 g), Me_2SO_4 (2 ml), and water (2 drops) were dissolved in THF (19 ml). The reaction was refluxed 0·5 hr, hydrolyzed, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with Claisen's alkali, dried, and evaporated (135 mg). The residue was purified by preparative TLC and the isolated material (110 mg) was crystallized from CH_2Cl_2/hexane and MeOH, giving product m.p. 122·0–122·7°, m.m.p. with synthetic 1,2,3,4,7-pentamethoxyxanthone 122·0–122·5°; NMR (CH_2Cl_2) τ 2·42 (q, 1), 2·74 (m, 2), 5·93 (s, 3), 6·06 (s, 3), 6·10 (d, 6), 6·14 (s, 3); UV max 240 (33,400), 262 (43,400), 287 (10,700), 309 sh (6,800), 367 (6,600) mμ. (Found: C, 62·50; H, 5·38. $C_{18}H_{18}O_7$ requires: C, 62·42; H, 5·24%).

Xanthone B *mixture*. Fraction 4 gave after sublimation 688 mg of xanthone B mixture, a yellow solid with a melting range of 148–156° even after repeated crystallization from CH_2Cl_2/hexane and/or MeOH. The NMR spectrum shows this sample to be approximately 90–95% compound Bf.

Xanthone C (**11**). Fraction 6 yielded upon sublimation 1·04 g of a light yellow solid, xanthone C. Crystallization from CH_2Cl_2/hexane and MeOH gave material m.p. 189·0–190·0°, m.m.p. with synthetic 1-hydroxy-2,3,5-trimethoxyxanthone 189·0–189·8°; NMR (CH_2Cl_2) τ −2·65 (s, 1), 2·22 (q, 1), 2·74 (m, 2), 3·44 (s, 1), 6·02 (s, 3), 6·06 (s, 3), 6·16 (s, 3); UV max 243 (1·00), 253 (0·95), 263 sh (0·62), 272 sh 0·50, 304 (0·50), 370 (0·11) mμ. (Found: C, 63·63; H, 4·58. $C_{16}H_{14}O_6$ requires: C, 63·57; H, 4·67%).

Xanthone C *methyl ether* (**12**). Xanthone C was methylated by the procedure given for xanthone A to give the methyl ether, m.p. 146·5–148·0°, m.m.p. with synthetic 1,2,3,5-tetramethoxyxanthone 147·0–147·8°. The NMR and UV spectra and the TLC behavior were identical with those of the synthetic compound. (Found: C, 64·78; H, 5·21. $C_{17}H_{16}O_6$ requires: C, 64·55; H, 5·10%).

Column chromatography of crystal residue. The mother liquor residue (3·0 g) from the crystallization of the crude xanthone extract was dissolved in CH_2Cl_2, Super Cel (5 g) added as a support, and the mixture evaporated. The resulting dry powder was placed on top of a silica gel column (900 × 18 mm) and eluted with 3:1 hexane/EtOAc. An automatic fraction collector was used to collect the 15 ml fractions.

Swerchirin (**15**). The first xanthone material, fractions 93–124 from this column, appeared homogeneous by TLC, but the NMR spectrum showed it to be a mixture. Upon sublimation and crystallization from CH_2Cl_2/hexane the first crystals (48 mg) consisted almost entirely of a new light yellow compound, m.p. 190·2–190·8°, m.m.p. with 1,8-dihydroxy-3,5-dimethoxyxanthone (swerchirin[12]) 189·5–190·5°; NMR

(CH_2Cl_2) τ −1·99 (s, 1), −1·13 (s, 1), 2·74 (d, 1), 3·32 (d, 1), 3·49 (d, 1), 3·66 (d, 1), 6·08 (s, 3), 6·10 (s 3), (Found: C, 62·71, H, 4·22. $C_{15}H_{12}O_6$ requires: C, 62·50; H, 4·20%).

The crystallizatlon residue was found to be rich in xanthone A, and the second crop of crystals was about 95% A and 5% swerchirin (by NMR).

Acetylation gave a diacetate; NMR (CH_2Cl_2) τ 2·83 (d, 1), 3·16 (d, 1), 3·18 (d, 1), 3·47 (d, 1), 6·07 (s. 3), 6·12 (s, 3), 7·62 (s, 3), 7·64 (s, 3).

Methylation gave the dimethyl ether;[12] NMR (CH_2Cl_2) τ 2·91 (d, 1), 3·35 (d, 1), 3·50 (d, 1), 3·70 (d, 1), 6·11 (s, 6), 6·15 (s, 6).

Xanthone A (**1**). Fractions 93–168 yielded xanthone A in various proportions to swerchirin. The total yield of xanthone A from both columns was 1·60 g, corresponding to approximately 8·0 g (27%) in the 29·0 g of crude extract.

Xanthone Bf (**5**). Fractlons 169–173 gave after crystallization a product (12 mg) that proved to be almost pure xanthone Bf; NMR (CH_2Cl_2) τ −2·55 (s, 1), 2·20 (q, 1), 2·68 (m, 2), 5·86 (s, 3), 5·96 (s, 3), 6·00 (s, 3), 6·09 (s, 3); UV max 240 (0·92), 261 (1·00), 275 sh (0·65), 312 (0·37), 375 (0·14) mμ.

Xanthone B *mixture*. Fractions 174–272 yielded a medium-yellow solid with a broad m.p. (148–155°). NMR (CH_2Cl_2—sample contained the two xanthones in ca. 5:4 ratio) τ −2·62 (s, 0·8), −2·45 (s, 1), 2·28 (q, 1), 2·48 (q, 0·8), 2·78 (m, 3·6), 3·61 (s, 0·8), 5·90 (s, 3), 6·00 (s, 3), 6·03 (s, 3), 6·09 (s, 2·4), 6·11 (s, 3), 6·15 (s. 2·4), 6·18 (s, 2·4).

The compounds could not be separated cleanly by preparative TLC on normal or basic plates or by fractional crystallization from various solvent systems. The total yield of xanthone B mixture from both columns was 1·31 g, corresponding to 6·5 g (22%) in 29·0 g of crude xanthone.

Separation of methylated xanthone B *mixture*. Xanthone B mixture was methylated in THF with excess $MeSO_4$ and NaH for 2 days at room temp. Water was added and the mixture was extracted with CH_2Cl_2 which was washed with Claisen's alkali and evaporated.

The methylated mixture did not separate on normal silica gel G, but it did separate on acidified plates. Silica gel G (24 g) was mixed with 5% H_2SO_4 (60 ml) and the resulting slurry was spread on a glass plate (6″ × 9″) as rapidly as possible. This was dried at 90° for 2 to 4 hr and separated methylated xanthone B (110 mg) into two bands, the front one orange and the back yellow, using 1:1 EtOAc/hexane as the developing solvent. The solvent was allowed to run to the top of the plate, which was then removed from the tank, air dried, and replaced in the solvent. Three passes in this manner separated the bands completely. The components were eluted from the silica gel with MeOH and CH_1Cl_2, washed with $NaHCO_3$, and sublimed at 140°/10^{-5} Torr.

Methyl xanthone Bf (**5**). The forward material, methyl Bf (48 mg), after sublimation and crystallization from CH_2Cl_2/hexane had m.p. 144·2–145·2°, m.m.p. with synthetic 1,2,3,4,5-pentamethoxyxanthone 144·0–145·0; NMR, UV, and TLC confirmed the identity; NMR (CH_2Cl_2) τ 2·27 (q, 1), 2·72 (m, 2), 5·91 (s, 3), 5·98 (s, 3), 6·00 (s, 3), 6·09 (d, 6). (Found: C, 62·55; H, 5·35. $C_{18}H_{18}O_7$ requires: C, 62·42; H, 5·24%).

Methyl xanthone Bb (**8**). The more polar material, methyl Bb (32 mg), after sublimation and crystallization from CH_2Cl_2/hexane and MeOH had m.p. 135·0–136·0°, m.m.p. with synthetic 1,2,3,7-tetramethoxyxanthone 135·0–136·5°; NMR (CH_2Cl_2) τ 2·42 (q, 1), 2·79 (m, 2), 3·35 (s, 1), 6·06 (s, 3), 6·09 (s, 3), 6·15 (s, 3), 6·18 (s, 3). (Found: C, 64·69; H, 5·24. $C_{17}H_{16}O_6$ requires: C, 64·55; H, 5·10%).

Xanthone E (**18**). Fractions 273–388 yielded a light yellow compound, almost insoluble in CH_2Cl_2, $CHCl_3$, acetone, THF, and only slightly soluble in MeOH. Crystallization from MeOH gave material with m.p. 274·0–275·0°; NMR (DMSO) τ 2·32 (q, 1), 2·56 (m, 2), 3·70 (s, 1), 6·00 (s, 3), 6·12 (s, 3); UV max 243 (31,000), 260 (23,000), 290 sh (18,400), 318 (13,800), 366 (4,100); UV max (EtOH/OH^-) 238 (0·96), 242 (1·00), 260 (0·42), 282 (0·70) 347 (0·53), 380 (0·36); UV max (EtOH/OAc^-) 239 sh (26,000), 244 (28,000), 260 (15,100), 272 (14,800), 288 sh (14,300), 325 (9800), 349 (11,000), 390 sh (7300); UV max (EtOH/$AlCl_3$) 230 (22,000), 280 (25,000), 336 (14,300), 425 (4200) mμ. (Mol wt Found: 288·063. $C_{15}H_{12}O_6$ requires: 288·063).

Acetylation of xanthone E with Ac_2O and pyridine gave the diacetate, needles from MeOH/H_2O, m.p. 172–174°; NMR (CH_2Cl_2) τ 2·38 (q, 1), 2·78 (m, 2), 3·28 (s, 1), 5·95 (s, 3), 6·02 (s, 3), 7·62 (s, 3), 7·67 (s, 3). (Mol wt Found: 372·086. $C_{19}H_{16}O_8$ requires: 372·084).

Methylation of a very small sample (2 mg) of xanthone E with Me_2SO_4 and NaH in THF gave a product whose behaviour on TLC and UV spectrum were identical with those of an authentic sample of 1,3,4,5-tetramethoxyxanthone.[26]

Xanthone C (**11**). Fractions 389–440 yielded xanthone C as their main compound. The total yield from both columns was 1·392 g, corresponding to ca. 7·0 g (24%) in the 29·0 g of crude.

Methyl xanthone Z (**19**). Xanthone C (106 mg) was methylated in the usual fashion with Me_2SO_4 and NaH in THF. The methylated material was chromatographed on silica gel with a 500 × 17 mm column and 1:1 EtOAc/hexane as the eluant. The first fraction was methyl xanthone C (92 mg). The second, a very polar fraction, was methyl xanthone Z. Crystallization from CH_2Cl_2/hexane gave product m.p. 151–154°. NMR (CH_2Cl_2) τ 2·93 (d, 1), 3·29 (s, 1), 3·37 (d, 1), 6·10 (s, 3), 6·12 (s, 3), 6·15 (s, 3), 6·18 (s, 3), 6·21 (s, 3); UV max 237 (1·00), 242 (0·99), 260 sh (0·76), 273 (0·67), 292 sh (0·41), 360 (0·23) mμ. (Mol wt Found: 346·110. $C_{18}H_{18}O_7$ requires: 346·105).

Swercherin glycoside (**16**). The ppt isolated from the interface of the liquid–liquid extraction was crystallized from pyridine/MeOH, m.p. 272° dec. The product is only slightly soluble in CH_2Cl_2, MeOH, or acetone. UV max 242 (1·00), 260 (0·78), 316 (0·43), 367 (0·14) mμ. (Found: C, 51·77; H, 5·45%).

Swercherin glycoside acetate. The glycoside was acetylated with 1:1 Ac_2O/pyridine for 20 min on the steam bath. Work-up and crystallization from CH_2Cl_2/hexane and MeOH gave product m.p. 206·5–209·5°; NMR (CH_2Cl_2) τ 2·82 (d, 1), 3·16 (d, 1), 3·29 (s, 2), 6·02 (s, 3), 6·06 (s, 3), 7·58 (s, 3), 7·93–7·98 (m, ca. 18), 8·07 (s, 3); UV max 240 (1·00), 266 (0·39), 291 (0·44), 332 (0·16) mμ. (Found: C, 54·92; H, 5·16%).

Hydrolysis of swercherin glycoside. The glycoside (100 mg) was hydrolyzed with dilute HCl (10 ml) 0·5 hr on a steam bath. Extraction, evaporation, and crystallization of the residue gave 45 mg of 1,8-dihydroxy-3,5-dimethoxyxanthone, m.p. 187–189°, m.m.p. with authentic swerchirin[12] 187·5–189·8°.

Hydrolysis of 14·4 mg of glycoside in 2N HCl for 7·9 hr at 81°, and analysis of the aqueous soln by the Glucostat method[31] showed the presence of 2·08 mg (14·4%) of glucose.

2,5-Dimethoxybenzoyl chloride. 2,5-Dimethoxybenzoic acid (2·04 g, 0·012 moles), benzene (50 ml), and oxalyl chloride (10 ml, 14·8 g, 0·117 moles) were placed in a 100 ml flask fitted with a magnetic stirring bar and drying tube. The reaction was stirred at room temp for 24 hr and the solvents removed *in vacuo*. The remaining oil, which crystallized on standing, was used without further purification.

2,2',3,4,5,5',6-Heptamethoxybenzophenone (**3**). To the flask containing the 2,5-dimethoxybenzoyl chloride (0·012 moles) were added pentamethoxybenzene[25] (2·28 g, 0·010 moles), dry nitrobenzene(20 ml), and anhyd $AlCl_3$ (1·6 g), 0·012 moles). After 6 hr at room temp the reaction was hydrolyzed with dil HCl and steam distilled to remove the nitrobenzene. The residue (3·46 g) was washed with sat $NaHCO_3$ aq, leaving 2·70 g of ether soluble oil. This was washed with 10% NaOH aq, giving 0·563 g hydroxide soluble material, and with Claisen's alkali, yielding 0·93 g of soluble product and 1·16 g of neutral material.

The neutral fraction was crystallized from CH_2Cl_2/hexane to give white crystals of benzophenone (960 mg, 25%), m.p. 93–94°. Recrystallization gave material suitable for analysis, m.p. 94·0–95·0°; NMR (CH_2Cl_2) τ 2·81 (q, 1), 3·01–3·12 (m, 4), 6·09 (s, 3), 6·19 (s, 6), 6·25 (s, 3), 6·40 (s, 6), 6·43 (s· 3); UV max <240 (>1·0), 256 (0·43), 343 (0·24) mμ. (Found: C, 61·30; H, 6·06. $C_{20}H_{24}O_8$ requires: C, 61·22; H, 6·16%).

The hydroxide soluble material was rewashed with $NaHCO_3$ and molecularly distilled (140°/10^{-4} Torr) giving crude 2-hydroxy-2',3,4,5,5',6-hexamethoxybenzophenone (0·525 g, 13%).

2-Hydroxy-2',3,4,5,5',6-hexamethoxybenzophenone (**4**). The above benzophenone (0·298 g) was dissolved in anhyd ether (20 ml) and a soln of $AlCl_3$ (1·32 g) in dry ether was added. After 1·5 hr at room temp water (15 ml) and conc HCl (1 ml) were added, and the ether layer was extracted with 10% NaOH aq. Unreacted starting material (0·138 g) was recovered from the ether, and acidification of the basic extract yielded 0·12 g (42% overall, ca. 100% based on recovered starting material) of product as a viscous yellow oil. Chromatography and molecular distillation gave analytically pure material; NMR (CH_2Cl_2) τ −1·90 (s, 1), 3·10–3·26 (m, 3), 5·96 (s, 3), 6·15 (s, 3), 6·25 (s, 3), 6·32 (d, 6), 6·70 (s, 3); UV max 240 (1·0), 258 (0·24), 294 (0·40), 345 (0·16) mμ. (Found: C, 60·16; H, 5·82. $C_{19}H_{22}O_8$ requires: C, 60·31; H, 5·86%).

1,2,3,4,7-Pentamethoxyxanthone (**2**). 2-Hydroxy-2',3,4,5,5',6-hexamethoxybenzophenone (60 mg) was refluxed for 2 hr in pyridine (5 ml) and tetramethylammonium hydroxide (10% aq soln, 5 ml). The reaction was poured into water, acidified, and extracted with ether. The etheral soln was washed with 10% NaOH and Claisen's alkali, dried, and evaporated. Sublimation of the residue at 150°/10^{-4} Torr gave 1,2,3,4,7-pentamethoxyxanthone as a white solid (50 mg, 91%). Crystallization from CH_2Cl_2/hexane gave analytical material, m.p. 122·6–122·8°; NMR (CH_2Cl_2) τ 2·42 (q, 1), 2·65–2·76 (m, 2), 5·95 (s, 3), 6·07 (s, 3), 6·10–6·14 (t, 9); UV max 240 (0·78) 262 (1·00), 288 (0·24), 310 sh (0·15), 366 (0·15) mμ. (Found: C, 62·45; H, 5·36. $C_{18}H_{18}O_7$ requires: C, 62·42; H, 5·24%).

1-Hydroxy-2,3,4,7-tetramethoxyxanthone (**1**). 1,2,3,4,7-pentamethoxyxanthone (65 mg) in anhyd ether (25 ml) was treated with $AlCl_3$ at room temp for 3 hr. Dil HCl was added and the aqueous soln was extracted with ether, which was washed with 10% NaOH and Claisen's alkali, dried, and evaporated. The ether layer gave recovered starting material (29 mg, 44%).

The combined base washings were acidified and extracted with ether, which was dried and evaporated,

yielding yellow 1-hydroxy-2,3,4,7-tetramethoxyxanthone (35 mg, 56%) Sublimation at 140°/10^{-4} Torr followed by crystallization from CH_2Cl_2/hexane gave pure product, m.p. 116·7–117·7°; NMR (CH_2Cl_2) τ −2·5 (s, 1), 2·45 (q, 1), 2·60–2·72 (m, 2), 5·93 (s, 3), 6·12 (s, 3), 6·16 (s, 6); UV max 234 (0·90), 270 (1·00), 301 (0·34), 387 (0·16) mμ. (Found: C, 61·15; H, 5·02. $C_{17}H_{16}O_7$ requires: C, 61·44; H, 4·85%).

2,3-*Dimethoxybenzoyl chloride.* 2,3-Dimethoxybenzoic acid (1·0 g, 5·5 mmoles), benzene (20 ml), and oxalyl chloride (5 ml, 7·4 g, 0·058 moles) were refluxed for 0·5 hr. The excess oxalyl chloride and benzene were removed *in vacuo* and the remaining light-colored solid was used without further purification.

2-*Hydroxy*-2',3,3',4,5,6-*hexamethoxybenzophenone* (7). The acid chloride prepared above was treated with pentamethoxybenzene (1·0 g, 4·3 mmoles) and $AlCl_3$ (1·5 g, 11 mmoles) in anhyd ether (40 ml). The reaction was refluxed for 1 hr and left overnight at room temp before being hydrolyzed with water (150 ml) and conc HCl (3 ml) and extracted with ether (3 × 50 ml). The ether layer was washed with sat $NaHCO_3$ aq (4 × 75 ml), 10% NaOH (2 × 50 ml), and Claisen's alkali (3 × 50 ml). The Claisen's alkali soln yielded crude product (0·857 g) after acidification. Column chromatography gave yellow crystals of 2-hydroxy-2',3,3',4,5,6-hexamethoxybenzophenone (0·306 g, 19%), m.p. 116·5–117·5°; NMR (CH_2Cl_2) τ −2·01 (s, 1), 2·92 (q, 1), 3·02–3·40 (m, 2), 6·03 (s, 3), 6·12 (s, 3), 6·14 (s, 6), 6·30 (s, 6); UV max <235 (>1·0), 270 (0·11), 352 (0·16) mμ. (Found: C, 60·35; H, 5·97. $C_{19}H_{22}O_8$ requires: C, 60·31; H, 5·86%).

1,2,3,4,5-*Pentamethoxyxanthone* (5). The above benzophenone (0·215 g), pyridine (10 ml), and tetramethylammonium hydroxide (10% aq soln 5 ml) were refluxed 54 hr. Acidification with dil HCl, extraction with CH_2Cl_2 (4 × 25 ml), and washing with Claisen's alkali (4 × 25 ml) gave 1,2,3,4,5-pentamethoxyxanthone (113 mg, 57%). Sublimation at 140°/10^{-4} Torr and crystallization from CH_2Cl_2/hexane and MeOH provided analytical material m.p. 144·0–145·0°; NMR (CH_2Cl_2) τ 2·21 (q, 1), 2·75 (m, 2), 5·89 (s, 3), 5·95 (s, 3), 5·98 (s, 3), 6·09 (d, 6); UV max 246 (0·87), 252 (1·0), 295 (0·26), 355 (0·13) mμ. (Found: C, 62·60; H, 5·39. $C_{18}H_{18}O_7$ requires: C, 62·42; H, 5·24%).

1-*Hydroxy*-2,3,4,5-*tetramethoxyxanthone* (6). The above xanthone (82 mg), anhyd $AlCl_3$ (1·0 g), and dry ether were refluxed for 8 hr. The mixture was hydrolyzed 15 min on a steam bath with water (50 ml) and conc HCl (5 ml). Extraction with CH_2Cl_2 (3 × 20 ml), filtration of the extract through silica gel, and sublimation at 160°/10^{-4} Torr gave 1-hydroxy-2,3,4,5-tetramethoxyxanthone (62 mg, 79%). Two crystallizations from MeOH gave pure product, m.p. 155·0–156·0°; NMR (CH_2Cl_2) τ −2·40 (s, 1), 2·23 (q, 1), 2·73 (m, 2), 5·89 (s, 3), 5·98 (s, 3), 6·02 (s, 3), 6·10 (s, 3); UV max 243 (25,000), 260 (27,000), 275 (17,200), 312 (10,600), 380 (3700). (Found: C, 61·55; H, 5·03. $C_{17}H_{16}O_7$ requires: C, 61·44; H, 4·85%).

3,4,5-*Trimethoxyphenol.*[27] 2,6-Dimethoxyhydroquinone[25] (20 g, 0·118 moles) was dissolved in water (82 ml) and NaOH (11·8 g, 0·30 moles) under N_2. Me_2SO_4 (19 g, 0·15 moles) was added in one portion and the reaction was stirred 1hr. Me_2SO_4 (6·0 g, 0·048 moles) and NaOH (3·0 g, 0·075 moles) were added, and after further stirring the reaction was acidified with conc HCl and extracted with CH_2Cl_2. The extract was condensed and fractionally crystallized in five steps from CH_2Cl_2/hexane/acetone to yield three main fractions. 1,2,3,5-Tetramethoxybenzene and another compound, possibly 2,4,6-trimethoxyphenol, were concentrated in the mother liquors. The middle fractions yielded 3,4,5-trimethoxyphenol (6·2 g, 28%; m.p. 144–145°, lit.[28] 146°), and the least soluble crystals were the starting hydroquinone (0·5 g).

1-*Acetoxy*-3,4,5-*trimethoxybenzene—Method A.* 3,4,5-Trimethoxyphenol (6·2 g) was heated on a steam bath with pyridine (19 ml) and Ac_2O (10 ml) for 0·5 hr. Addition of water and extraction with CH_2Cl_2, followed by crystallization from H_2O/EtOH gave crystals of 1-acetoxy-3,4,5-trimethoxybenzene m.p. 70–72° (lit.[28] 74°).

Method B. 2,6-Dimethoxyhydroquinone (2·0 g, 0·012 moles) was dissolved in water (8·3 ml) and NaOH (1·2 g, 0·03 mole) under N_2. Me_2SO_4 (1·9 g, 0·015 mole) was added. After 1 hr the reaction was brought to pH 5 with dil HCl and extracted with CH_2Cl_2. The extracts were evaporated and the residue treated with Ac_2O (5 ml) and pyridine (5 ml) on the steam bath for 0·5 hr. After the usual work-up a four step fractional crystallization from CH_2/Cl_2/hexane/acetone yielded 1-acetoxy-3,4,5-trimethoxybenzene (1·2 g, 42%) from the two middle fractions.

6-*Hydroxy*-2,2',3,4,5'-*pentamethoxybenzophenone* (10). 1-Acetoxy-3,4,5-trimethoxybenzene (2·0 g, 8·9 mmoles), 2,5-dimethoxybenzoic acid (2·0 g, 11 mmoles), and trifluoroacetic anhydride (10 ml) were placed in a stoppered flask. After 2 weeks at room temp the mixture was hydrolyzed and extracted with CH_2Cl_2. The extract was evaporated and the residue was heated with 10% NaOH (25 ml) on the steam bath for 10 min. This reaction mixture was diluted with water (50 ml) and extracted with CH_2Cl_2 (3 × 25 ml). Hexane (50 ml) was added to the extract, which was washed with Claisen's alkali (6 × 50 ml). The washings were acidified with conc HCl, diluted with water (200 ml), and extracted with CH_2Cl_2 (5 × 50 ml). The extract

was dried and evaporated, yielding 1·89 g of crude benzophenone containing some 1-hydroxy-3,4,5-trimethoxybenzene (TLC).

The crude product in CH_2Cl_2 (50 ml) was filtered through silica gel G (3·0 g) and washed with 5% NaOH (3 × 25 ml). Column chromatography followed by molecular distillation at 130–150°/10^{-4} Torr gave pure 6-hydroxy-2,2',3,4.5-pentamethoxybenzophenone as a yellow oil (1·60 g, 52%); NMR (CH_2Cl_2) τ −2·75 (s, 1), 3·14–3·23 (m, 3), 3·75 (s, 1), 6·15 (s, 3), 6·28 (s, 3), 6·36 (d, 6), 6·65 (s, 3); UV max <235 (>1·0), 273 (0·90), 348 (0·39) mμ. (Found: C, 62·21; H, 5·81. $C_{18}H_{20}O_7$ requires: C, 62·06; H, 5·79%).

1,2,3,7-*Tetramethoxyxanthone* (**8**). The above benzophenone (0·50 g), pyridine (10 ml), and tetramethylammonium hydroxide (10% aq soln, 4 ml) were heated on a steam bath for 12 hr. The reaction was added to conc HCl (10 ml) and water (150 ml) and extracted with CH_2Cl_2 (4 × 50 ml). The extract was passed through basic alumina (2 g), yielding xanthone (0·430 g, 95%). Crystallization from CH_2Cl_2/hexane and MeOH gave pure product, m.p. 135·0–136·0°; NMR (CH_2Cl_2) τ 2·40 (q, 1), 2·77 (m, 2), 3·33 (s, 1), 6·05 (s, 3), 6·08 (s, 3), 6·15 (s, 3), 6·18 (s, 3); UV max 243 (0·98), 258 (1·00), 280 (0·36), 312 (0·36), 356 (0·20) mμ. (Found: C, 64·73; H, 5·25. $C_{17}H_{16}O_6$ requires: C, 64·55; H, 5·10%).

1-*Hydroxy*-2,3,7-*trimethoxyxanthone* (**9**). 1,2,3,7-Tetramethoxyxanthone (180 mg), $AlCl_3$ (1·0 g), and anhyd ether (30 ml) were refluxed 1·5 hr. A ppt formed but dissolved with the addition of dry THF (10 ml). The reaction was refluxed an additional hr, then added to water (200 ml) and conc HCl (3 ml). After standing overnight it was extracted with CH_2Cl_2 (5 × 50 ml). The extract was evaporated and the residue was sublimed at 150°/10^{-5} Torr, dissolved in CH_2Cl_2 and passed through silica gel G, and crystallized from MeOH to give pure **9** (160 mg, 93%), m.p. 177·0–177·5°. NMR (CH_2Cl_2) τ −2·65 (s, 1), 2·45 (q, 1), 2·73 (m, 2), 3·59 (s, 1), 6·07 (s, 3), 6·12 (s, 3), 6·16 (s, 3); UV max 238 (27,600), 262 (28,600), 300 (11,700), 320 sh (10,600), 363 (5,100) mμ. (Found: C, 63·80; H, 4·73. $C_{16}H_{14}O_6$ requires: C, 63·57; H, 4·67%).

6-*Hydroxy*-2,2',3,3',4-*pentamethoxybenzophenone* (**14**). 1-Acetoxy-3,4,5-trimethoxybenzene (2·0 g), excess 2,3-dimethoxybenzoic acid, and trifluoroacetic anhydride (10 ml) were placed in a stoppered flask. After 6 days at room temp the mixture was hydrolyzed with water (200 ml) and conc HCl (2 ml), then extracted with CH_2Cl_2 (3 × 50 ml). The extract was washed with $NaHCO_3$ (2 × 50 ml), evaporated, and the residue hydrolyzed on the steam bath for 0·5 hr with 10% NaOH (50 ml). The basic soln was extracted with CH_2Cl_2 (3 × 50 ml) and the organic layer was washed with Claisen's alkali (6 × 25 ml). The base washings were acidified with dil HCl, extracted with CH_2Cl_2 (4 × 25 ml), and the extracts passed through silica gel G (2 g). After evaporation the product was crystallized from CH_2Cl_2/hexane to yield 800 mg (26%) of pure **14**, m.p. 110·8–111·2°; NMR (CH_2Cl_2) τ −2·75 (s, 1), 2·90–3·32 (m, 3), 3·72 (s, 1), 6·12 (s, 6), 6·27 (s, 3), 6·37 (s, 3), 6·68 (s, 3); UV max <230 (>1·0), 293 (0·95), 340 (0·36) mμ. (Found: C, 62·24; H, 5·83. $C_{18}H_{20}O_7$ requires: C, 62·06; H, 5·79%).

1,2,3,5-*Tetramethoxyxanthone* (**12**). The above benzophenone (508 mg), pyridine (10 ml), and tetramethylammonium hydroxide (10% aq soln, 4 ml) were heated on a steam bath for 16 hr. The reaction was poured into dil HCl and extracted with CH_2Cl_2. The extract was passed through alumina, evaporated, and the residue sublimed at 130°/10^{-4} Torr. Crystallization of the sublimate from CH_2Cl_2/hexane gave pure 1,2,3,5- tetramethoxyxanthone (406 mg, 87%), m.p. 148·5–149·5°, NMR (CH_2Cl_2) τ 2·22 (q, 1), 2·70 (m, 2), 3·19 (s, 1), 6·02 (t, 9), 6·12 (s, 6); UV max 243 sh (33,600), 249 (40,000), 268 sh (16,600), 283 (13,700), 300 sh (10,000), 343 (6,300) mμ. (Found: C, 64·71; H, 5·19. $C_{17}H_{16}O_6$ requires: C, 64·55; H, 5·10%).

1-*Hydroxy*-2,3,5-*trimethoxyxanthone* (**11**). 1,2,3,5-Tetramethoxyxanthone (265 mg), $AlCl_3$ (1·0 g), and dry ether (30 ml) were refluxed 1·5 hr. The reaction was hydrolyzed overnight in water (200 ml) and conc HCl (10 ml), then extracted with CH_2Cl_2. Evaporation of the extract and sublimation of the residue at 160°/10^{-4} Torr yielded **11** (205 mg, 81%). Crystallization from CH_2Cl_2/hexane and MeOH gave pure xanthone, m.p. 189·0–190·0°; NMR (CH_2Cl_2) τ −2·60 (s, 1), 2·29 (q, 1), 2·78 (m, 2), 3·49 (s, 1), 6·05 (s, 3), 6·08 (s, 3), 6·17 (s, 3); UVmax 220 (0·68), 242 (1·00), 253 sh (0·93), 258 sh (0·63), 302 (0·50), 370 (0·12) mμ. (Found: C, 63·34; H, 4·82. $C_{16}H_{14}O_6$ requires: C, 63·57; H, 4·67%).

2,6-*Dimethoxybenzoyl chloride*. 2,6-Dimethoxybenzoic acid (3·60 g, 20 mmoles) was dissolved in benzene (200 ml) and oxalyl chloride (20 ml). After 28 hr at room temp the reaction was evaporated to dryness under vacuum and the resulting acid chloride used without purification.

2,2',3,4,6,6'-*Hexamethoxybenzophenone*. The previously prepared acid chloride (20 mmoles), 1,2,3,5-tetramethoxybenzene[25] (4·0 g, 20 mmoles), and anhyd $AlCl_3$ were dissolved in nitrobenzene (400 ml). After 2 days at room temp the reaction was acidified with dil HCl, and the nitrobenzene layer was separated, washed with 10% NaOH (4 × 100 ml), and steam distilled. The residue after steam distillation was extracted with ether and CH_2Cl_2, and the extract was dried and evaporated. The residue was crystallized from ether and EtOH, giving 2,2',3,4,6,6'-hexamethoxybenzophenone (2·05 g, 27%). Sublimation and recrystal-

lization from EtOH gave pure product, m.p. 136·0–136·5°; NMR (CH_2Cl_2) τ 2·57 (q, 1), 3·30 (m, 2), 3·57 (s, 1), 6·60 (s, 3), 6·18 (s, 3), 6·27 (d, 9), 6·37 (s, 3); UV max <235 (>1·0), 278 (0·56), 305 sh (0·33) mμ. (Found: C, 63·25; H, 6·09. $C_{19}H_{12}O_7$ requires: C, 62·98; H, 6·12%).

2-Hydroxy-2',3,4,6,6'-pentamethoxybenzophenone. The above benzophenone (0·50 g) was refluxed 2 hr in anhyd ether (15 ml) containing excess $AlCl_3$. The reaction was acidified and extracted with ether, which was washed with Claisen's alkali. The Claisen extract was acidified and extracted with CH_2Cl_2, which was dried and evaporated to yield 2-hydroxy-2',3,4,6,6'-pentamethoxybenzophenone (0·30 g, 60%). Crystallization from MeOH gave pure material, m.p. 167·0–168·0°. NMR (CH_2Cl_2) τ −3·75 (s, 1), 2·53 (q, 1), 3·25 (m, 2), 3·95 (s, 1), 6·03 (s, 3), 6·13 (s, 3), 6·22 (s, 6), 6·57 (s, 3); UV max 290 (1·00), 330 sh (0·23) mμ. (Found: C, 62·21; H, 5·82. $C_{18}H_{20}O_7$ requires: C, 62·06; H, 5·79%).

1,3,4,8-Tetramethoxyxanthone. The above benzophenone (110 mg), pyridine (25 ml), and tetramethylammonium hydroxide (10% aq soln, 10 ml) were heated on the steam bath for 2 hr. After standing overnight at room temp the reaction was acidified, extracted with CH_2Cl_2, and the extract dried and evaporated. The product was chromatographed on alumina to yield 1,3,4,8-tetramethoxyxanthone (75 mg, 78%). Crystallization from MeOH gave material m.p. 191·2–191·8°; NMR (CH_2Cl_2) τ 2·48 (t, 1), 2·98 (q, 1), 3·23 (q, 1), 3·60 (s, 1), 6·05 (d, 9), 6·12 (s, 3); UV max 236 (36,200), 242 sh (31,000), 313 (15,200), 340 sh (5500) mμ. (Mol wt Found: 316·095. $C_{17}H_{16}O_6$ requires: 316·095).

2-Hydroxy-2',3,4,5,6,6'-hexamethoxybenzophenone. The acid chloride from 2,6-dimethoxybenzoic acid (3·57 g, 18 mmoles), pentamethoxybenzene (2·80 g, 13 mmoles), and $AlCl_3$ (2·5 g, 19 mmoles) were dissolved in nitrobenzene (30 ml). After 4 hr at room temp the reaction was hydrolyzed with dil HCl and extracted with CH_2Cl_2. The extract was steam distilled and the residue was extracted with CH_2Cl_2. This was washed with $NaHCO_3$ (3 × 50 ml), 10% NaOH (5 × 50 ml), and Claisen's alkali (5 × 30 ml). The Claisen's soln was acidified and extracted with CH_2Cl_2, which was dried and evaporated to give 426 mg of dark oil. Molecular distillation (140°/10^{-4} Torr) yielded a lighter oil. Purification of a sample (61 mg) of this by preparative TLC gave 2-hydroxy-2',3,4,5,6,6'-hexamethoxybenzophenone (37 mg); NMR (CH_2Cl_2) τ −2·90 (s, 1), 2·67 (q, 1), 3·37 (m, 2), 5·94 (s, 3), 6·12 (s, 3), 6·25 (s, 6), 6·30 (s, 3), 6·72 (s, 3); UV max <235 (>1·0), 270 (1·00), 356 (0·25) mμ.

1,2,3,4,8-Pentamethoxyxanthone. The above benzophenone (37 mg) was refluxed in pyridine (1·0 ml) and tetramethylammonium hydroxide (10% aq soln, 0·5 ml) for 10 hr. The reaction was acidified, extracted with CH_2Cl_2, dried, and purified by column chromatography on basic alumina to give 27 mg (87%) of white crystals of 1,2,3,4,8-pentamethoxyxanthone, m.p. 112·0–113·0°; NMR (CH_2Cl_2) τ 2·42 (t, 1), 2·96 (q, 1), 3·20 (q, 1), 5·93 (s, 3), 6·03 (s, 6), 6·08 (s, 3), 6·10 (s, 3); UV max 240 sh (34,600), 248 (36,400), 290 sh (10,500), 305 (12,800), 350 (6200) m. (Mol wt Found: 346·107. $C_{18}H_{18}O_7$ requires: 346·105).

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