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THE STRUCTURE AND SYNTHESIS OF XANTHOMICROL*

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Abstract—Xanthomicrol is shown to be 5,4'-dihydroxy-6,7,8-trimethoxyflavone by a combination of physical and degradative methods. Its synthesis from pentamethoxybenzene is described.

YERBA BUENA (*Satureia douglassii*, formerly *Micromeria chamissonis*) is a ground growing, evergreen vine of the mint family (Labiatae) which is widespread along the western coast of the United States. In 1908 Power and Salway[1] isolated from it in 0·02 per cent yield a yellow crystalline material which they named xanthomicrol. They assigned to it the formula $C_{15}H_{10}O_4$-$(OH)_2$ on the basis of its analysis and the formation of a diacetate. As this formula is that of a dihydroxydimethoxyxanthone we felt that the substance deserved further investigation as part of our continuing study of natural xanthones.

Xanthomicrol was isolated by a simplified route involving the extraction of dried, defatted yerba buena with ether. Crude xanthomicrol could be obtained directly by extraction from the ether solution with dilute sodium carbonate. Purification was effected by chromatography on acid-washed alumina.

The ultraviolet spectra of xanthomicrol (Table 1) and its derivatives suggested very strongly that they were not xanthones and the possibility was eliminated by examination of the NMR spectrum of the diacetate. This showed not only the expected two acetyl methyl peaks at $\tau = 7{\cdot}59$, 7·73, but also three peaks of similar height at $\tau = 5{\cdot}95$, 6·02, 6·17, proving that xanthomicrol is a trimethoxy rather than the anticipated dimethoxy compound. This result was supported by the NMR spectra of xanthomicrol monomethyl ether, prepared by reaction with diazomethane, and the dimethyl ether, prepared with methyl sulphate and potassium hydroxide. These spectra indicated strongly the presence of four and five methoxyl groups respectively.

These findings cast serious doubt on the molecular formula proposed by Power and Salway as the removal of nine hydrogens as methoxyl and two as hydroxyl leaves the compound embarrassingly poor in hydrogen. The elemental analyses obtained for xanthomicrol and its derivatives could be fitted best, however, by the assumption of a formula $C_{15}H_5O_2(OCH_3)_3$-$(OH)_2$, i.e. one corresponding to a dihydroxytrimethoxyflavone. The suggestion of a flavone nucleus was confirmed by the demethylation of xanthomicrol with hydriodic acid, followed by acetylation to give trisnorxanthomicrol pentaacetate, whose ultraviolet spectrum was essentially that of flavone[2] (Table 1).

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[1] F. B. Power and A. H. Salway, *J. Amer. Chem. Soc.* **30**, 251 (1908).

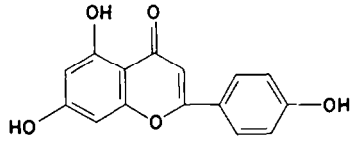
[2] T. A. Geissmann, *Modern Methods of Plant Analysis* (Edited by K. Paech and M. V. Tracey) Vol. 3, p. 487ff. Springer Verlag, Berlin (1955).

TABLE 1. ULTRAVIOLET SPECTRA OF XANTHOMICROL DERIVATIVES

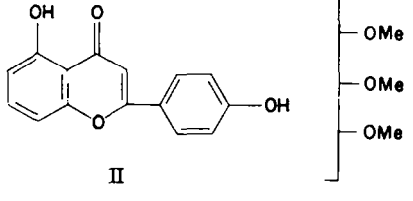
	λ_{max} (mμ)	ε	λ_{max} (mμ)	ε	λ_{max} (mμ)	ε
Xanthomicrol (VI)	282	18,900	296	18,000	336	24,700
5,4′-Dihydroxy-6,7,8-trimethoxy-flavone* (VI)	283	18,600	296	18,200	335	25,100
Trisnorxanthomicrol pentaacetate	258	16,900	301	18,800		
Flavone[2]	250	11,800	297·5	16,000		
Monomethylxanthomicrol (VII)	285	21,200	295	21,600	332	24,800
4′-Benzyloxy-5-hydroxy-6,7,8-trimethoxyflavone (X)	286	22,000	296	24,400	332	26,700
Dimethylxanthomicrol (VIII)	272	20,200			324	28,200
5,6,7,8,4′-pentamethoxy-flavone (VIII)*	272	19,900			324	28,600
4′-Benzyloxy-5,6,7,8-tetra-methoxyflavone (IX)	272	19,600			325	29,600
Xanthomicrol diacetate	270	25,800	308	21,800		

* Synthetic

Xanthomicrol and its demethylation product give strongly yellow, non-fluorescent solutions when treated with boroacetic anhydride,[3] suggesting the presence of a free hydroxyl group in the 5 position, but the absence of an oxygen substituent at C-3[4]. The solubility in dilute sodium carbonate solution places the other hydroxyl group in the 4′ or 7 position.[5] The hydroxyl groups were assigned by examining the changes produced in the ultraviolet and visible spectra of xanthomicrol and monomethylxanthomicrol when their alcoholic solutions were made ca. 0·002 M in hydroxide ion. The shifts produced were effectively identical with those reported by Nordstrom *et al.*[6] for derivatives of apigenin (I) having free hydroxyl groups at the 4′ and 5 positions respectively. The ionization of xanthomicrol at the 4′ hydroxyl as well as the ready formation of a monomethyl ether is explained by the well known lack of reactivity of strongly chelated hydroxyl groups such as the one at C-5.[7] On this basis the partial structure (II) may be written for xanthomicrol.



I



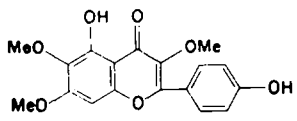
II

Micro base fusion of xanthomicrol and paper chromatography of the products gave as the major product a compound whose R_f values in two solvents and whose

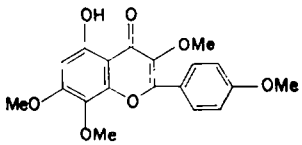
[3] O. Dimroth and T. Faust, *Ber. Dtsch. Chem. Ges.* **54**, 3020 (1921); O. Dimroth, *Leibigs Ann.* **446**, 97 (1926).
[4] E. Rodd (Editor), *The Chemistry of Carbon Compounds* Vol. IV B, p. 910. Elsevier, Amsterdam (1956).
[5] *Inter al.* L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 3136 (1951).
[6] G. H. Mansfield, T. Swain and C. G. Nordstrom, *Nature, Lond.* **172**, 23 (1953).
[7] S. Wawzonek, *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 2, p. 265. John Wiley, New York (1951).

color reactions were identical with those of *p*-hydroxybenzoic acid but different from all other phenolic acids tested, including vanillic and syringic. The same substance was formed by the micro ozonolysis of xanthomicrol diacetate followed by mild hydrolysis with aqueous alcoholic base. Thus it could be shown that the p-hydroxybenzoic acid did not arise by demethylation during the base fusion and the spectral assignment of a hydroxyl to C-4′ was confirmed.

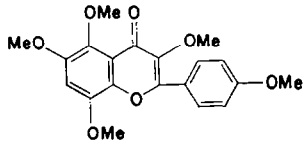
If the B ring of xanthomicrol contains no methoxyl groups, then only the four structures derived from II by addition of methoxyls to three of the positions 3, 6, 7, or 8 are possible. Three of these may be eliminated. Xanthomicrol and its diacetate differ in melting points and spectra from penduletin[8] (III); monomethylxanthomicrol in melting point and ultraviolet spectrum from flindulatin[9] (IV); and dimethylxanthomicrol in melting point from 3,5,6,8,4′-pentamethoxyflavone[10] (V). The remaining possibility (VI) is not a flavonol and is consistent with the color tests with boroacetic anhydride, the observation that xanthomicrol does not give a pink color with magnesium and hydrochloric acid in ethanol and the similarity of the melting point of xanthomicrol dimethyl ether (152·5–155°) and those recorded for the naturally occurring pentamethoxyflavone tangeretin (VIII) (153–154°).[11]



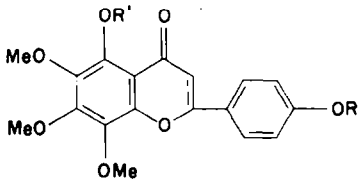
III



IV



V



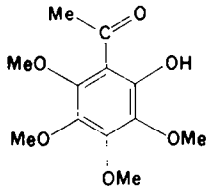
VI R = R′ = H
VII R = Me, R′ = H
VIII R = R′ = Me
IX R′ = Me, R = $CH_2\phi$
X R′ = H, R = $CH_2\phi$

Xanthomicrol has been synthesized as a confirmation of the structure (VI). Pentamethoxybenzene was prepared from pyrogallol by the method of Baker[12] and was acylated with acetyl chloride and aluminium chloride in ether. Baker reports that this reaction gives 2-hydroxy-3,4,5,6-tetramethoxyacetophenone (XI) in 27 per cent yield. We have found that when the reaction mixture is warmed, it produces a mixture of products, the major one of which is not (XI) but rather 2,6-dihydroxy-3,4,5-trimethoxyacetophenone (XII). Vapor-phase chromatography of the crude base-soluble material from the acylation showed the presence of at least two components, and chromatography on acid-washed alumina separated the mixture into (XI) and (XII) together with small amounts of other products. The pure (XI) was a yellow oil which was identified by its NMR spectrum, which showed separate peaks corresponding to one acetyl and four methoxyl groups. No aromatic hydrogen could

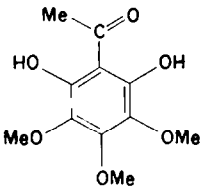
[8] S. E. Flores and J. Herran, *Tetrahedron* **2**, 308 (1958).
[9] R. F. C. Brown, P. T. Gilham, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 181 (1954).
[10] K. J. Balakrishna and T. R. Seshadri, *Proc. Indian Acad. Sci.* **27A**, 260 (1948).
[11] E. K. Nelson, *J. Amer. Chem. Soc.* **56**, 1392 (1944); L. J. Goldsworthy and R. Robinson, *Chem. & Ind.* 47 (1957).
[12] W. Baker, *J. Chem. Soc.* 662 (1941).

be found, but the hydroxyl appeared at an extremely unshielded position ($\tau = -2{\cdot}69$) characteristic of strong intramolecular hydrogen bonds.[13]

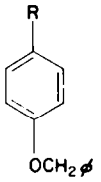
The new product (XII) crystallized as yellow needles. The structure was proved by the remarkable simplicity of its NMR spectrum and that of its acetate. Both of these compounds showed two extremely sharp methoxyl peaks in the ratio 2:1 and the acetate showed an equally sharp acetate peak also of height 2. Such a spectrum can only be explained on the basis of the symmetrical structure (XII). In addition, the hydroxyl peak was shifted upfield to $\tau = 0{\cdot}14$, as might be expected if there is a rapid averaging of the hydrogen-bonded and non-hydrogen-bonded hydroxyl protons.



XI



XII



XIII R = —CHO

XIV R = —C(=O)Cl

The formation of (XII) is an example of an unusual bisdealkylation under very mild conditions. It is normally assumed that aluminium chloride in ether will demethylate only one alkoxyl group *ortho* to an acyl group on a benzene ring. Indeed, such a reaction was used in very satisfactory yield in the syntheses leading to pentamethoxybenzene. The double demethylation leading to (XII) appears to be without precedent and may perhaps be caused by the buttressing effect of the groups in the 3 and 5 positions.[14]

p-Benzyloxybenzaldehyde (XIII) was condensed with (XI) using sodium hydride in tetrahydrofuran. The more common base for chalcone syntheses, 50 per cent sodium hydroxide in ethanol, appeared to be less satisfactory. The intermediate chalcone was oxidized with selenium dioxide[15] in amyl alcohol to give 4′–benzyloxy-5,6,7,8-tetramethoxyflavone (IX) whose ultraviolet spectrum was essentially identical with that of dimethylxanthomicrol. Simultaneous debenzylation and 5-demethylation of (IX) with aluminium chloride in ether gave xanthomicrol in 35 per cent yield from (XI).

To avoid the need for selective demethylation at C-5 an alternative route was explored in which (XII) was esterified with *p*-benzyloxybenzoyl chloride (XIV) and the crude ester treated with sodium hydride in tetrahydrofuran. The β-diketone produced by this reaction[16] was not isolated but was cyclized smoothly by brief treatment with warm 98 per cent formic acid to give 4′-benzyloxy-5-hydroxy-6,7,8-trimethoxyflavone (X) which showed a U.V. spectrum markedly different from (IX) but very similar to that of methylxanthomicrol. Debenzylation now could be performed under the milder conditions of HCl in acetic acid to give xanthomicrol in 48 per cent yield.

[13] Compare *o*-hydroxyacetophenone $\tau = -2{\cdot}13$.
[14] W. J. Horton and J. T. Spence, *J. Amer. Chem. Soc.* **80**, 2453 (1958).
[15] H. S. Mahal, H. S. Rai and K. Venkataraman, *J. Chem. Soc.* 866 (1935).
[16] Ref. 7, p. 233.

The occurrence of a flavone with the structure shown for xanthomicrol in a member of the Labiatae is of some interest. Heretofore, flavones, as distinct from flavonols, totally oxygenated in ring A, have been found only in various members of the genus Citrus, e.g. tangeretin[11] nobiletin[17] and desmethylnobiletin.[18] Now there appears in xanthomicrol a new member of this group, closely related to tangeretin but produced by a totally different botanical family.

EXPERIMENTAL

All melting points were taken on a Kofler block. Infrared spectra were taken in chloroform on a Perkin–Elmer Model 21 and ultraviolet spectra on a Cary Model 11 or Model 14 in ethanol. NMR spectra were taken in carbon tetrachloride or carbon tetrachloride–chloroform on a Varian 60 mc instrument and are given as τ values[19] measured from an internal tetramethylsilane reference. Numbers in parentheses represent estimated relative intensities. Combustion analyses are by Drs. Weiler and Strauss, Oxford, and Dr. A. Bernhardt, Mulheim.

Isolation of xanthomicrol (VI)

Samples of *Micromeria chamissonis* were gathered near Seattle during the summer months. During this period the time of gathering did not appear to affect the yields. The whole plant was dried with forced air at 52°C, ground in a Wiley mill, and defatted by extraction in a Soxhlet with petroleum ether (30–60°).

Defatted, ground plant material (2050 g) was extracted in a Soxhlet with ether for 18 hr. The extracts were concentrated to ca. 500 ml, stored in the icebox overnight, and filtered. The filtrate was washed with dilute sodium bicarbonate and then extracted with 1/3 saturated Na_2CO_3 solution (6 × 60 ml). The extracts were filtered, acidified, and extracted with ether which was dried and evaporated to give 1·31 g of dark crystalline material.

This was chromatographed on 13 g of acid-washed alumina and eluted with CH_2Cl_2–ether to give 553 mg of xanthomicrol. One crystallization from methanol gave pure xanthomicrol (314 mg 0·015%). M.p. 227–230°. U.V.: λ_{max} mμ (ε): 282 (18,900), 296 (18,000), 336 (24,700); in 0·002 N NaOH/EtOH, 276 (15,100), 402 (32,500). I.R.: 3·08, 6·07, 6·26, 6·32, 6·43 μ (Nujol). (Found: C, 62·44; H, 4·77; CH_3O, 26·85. $C_{15}H_7O_4(OCH_3)_3$ requires: C, 62·79; H, 4·68; CH_3O, 27·02%).

Methylation of xanthomicrol with diazomethane: monomethylxanthomicrol (VII)

Xanthomicrol (94 mg) was dissolved with heating in methanol (ca. 20 ml), cooled in ice, and treated with excess diazomethane in ether. The reaction mixture was cooled in an ice bath for 2 hr and the excess diazomethane decomposed by glacial acetic acid, added dropwise. The solution was evaporated to give crude product which was chromatographed on acid-washed alumina. Benzene–dichloromethane (4:1) and dichloromethane eluted monomethylxanthomicrol (47 mg, 48%). Crystallization from ethyl acetate–hexane gave long yellow needles, m.p. 180–181°. U.V.: λ_{max} mμ (ε): 285(21,200), 295(21,600), 332(24,800); in 0·002 N NaOH/EtOH, 302(29,100), 395(6,900). NMR: 6·13(1), 6·07(2), 5·94(1)τ. (Found: C, 63·76; H, 5·01. $C_{19}H_{18}O_7$ requires: C, 63·68; H, 5·06%).

Methylation of xanthomicrol with methyl sulfate: dimethylxanthomicrol (VIII)

Xanthomicrol (85 mg) in acetone (2 ml) was treated alternately with portions of methyl sulfate (1 g) and potassium hydroxide solution (3 g of 30% aqueous base.) Acetone (1 ml) was added and the mixture heated on the steam bath for 1½ hr. The mixture was cooled and water added. The crystalline product was filtered off, washed and dried to give dimethylxanthomicrol (74 mg, 80%). Crystallization from dichloromethane–cyclohexane gave pale yellow needles, m.p. 153–156°. U.V.: λ_{max} mμ (ε): 272(20,200), 324(28,200). NMR: 6·15(1), 6·10(2), 6·03(1), 5·97(1)τ. (Found: C, 64·75; H, 5·51. $C_{20}H_{20}O_7$ requires: C, 64·51; H, 5·41%).

[17] R. Robinson and K. F. Tseng, *J. Chem. Soc.* 1004 (1938).
[18] P. S. Sarin and T. R. Seshadri, *Tetrahedron* **8**, 64 (1960).
[19] G. V. D. Tiers, *J. Phys. Chem.* **62**, 1151 (1958).

Xanthomicrol diacetate

Xanthomicrol (56 mg) was treated with acetic anhydride (0·6 ml) and pyridine (0·7 ml) at room temperature for 23 hr. Water was added and the product extracted with ether, which was washed with dilute acid, base, and water and dried over sodium sulfate. Evaporation of solvent and crystallization from cyclohexane–dichloromethane gave xanthomicrol diacetate (40 mg, 57%) as white needles, m.p. 126·5–128·5° U.V.: λ_{max} mμ (ε): 270(25,800), 308(21,800). NMR: 7·73 (1), 7·59(1), 6·17(1), 6·02(1), 5·59(1)τ. (Found: C, 61·60; H, 4·94. $C_{22}H_{20}O_9$ requires: C, 61·68; H, 4·71%).

Trisnorxanthomicrol pentaacetate

Xanthomicrol (44 mg) was refluxed with 48% HI (2 ml) for 3 min. The solid first dissolved and then crystallized again. The mixture was poured into water, $NaHSO_3$ was added, and the solution was extracted with ether, ethyl acetate, and 1-butanol. Some solid remained; the aqueous solution was decanted and the residue was dissolved in methanol and added to the combined extracts. These were washed with water and dilute sodium bicarbonate, and then evaporated to give crystalline orange-yellow product (31 mg) dec. > 300°. U.V. maxima 302 and 340 mμ. Treatment with boro-acetic anhydride gave a strongly yellow-orange, non-fluorescent solution.

The crude product was acetylated with acetic anhydride (2 ml) and pyridine (0·5 ml) on the steam bath for 35 min. The reaction mixture was poured into water and the product crystallized. Recrystallization from hexane–dichloromethane gave 27 mg of pentaacetate (41%). For analysis this was crystallized twice from ethanol to give fine white needles with a double m.p., 220–229° and 235–246° unchanged on drying in high vacuum. U.V.: λ_{max} mμ (ε); 258(16,900), 301(18,800). (Found: C, 58·88; H, 3·93; CH_3CO, 40·0. $C_{15}H_5O_7(CH_3CO_2)_5$ requires: C, 58·60; H, 3·93; CH_3CO, 42·0%).

Base fusion of xanthomicrol

Xanthomicrol (14 mg) was heated at 260° for 15 min in a mixture of potassium and sodium hydroxide (0·4 g each) and a few drops of water. The reaction mixture was cooled, acidified with dilute sulfuric acid and extracted with ether, which was dried ($MgSO_4$) and evaporated to give a dark oil containing some crystals. Paper chromatography using BuOH:H_2O:Conc. NH_3 (4:5:1) as a solvent gave a yellow spot R_f 0·14 when sprayed with *p*-nitrobenzene diazonium fluoroborate as well as other minor spots. When i-PrOH:H_2O:Conc. NH_3 (8:1:1) was used as the solvent the same spot appeared at R_f 0·24. Parallel runs with *p*-hydroxybenzoic acid gave a spot at the same R_f's and with the same color in both solvents.

Ozonolysis of xanthomicrol diacetate

Xanthomicrol diacetate (48 mg) was dissolved in 1:1 CH_2Cl_2:EtOAc and cooled in a Dry Ice-acetone bath. A slow stream of ozone in oxygen was passed in for 1½ hr until a faint blue color developed in the solution. The reaction mixture was treated with potassium iodide in methanol and acetic acid, poured into water containing enough sodium bisulfite to reduce the iodine, and extracted with ethyl acetate. The extract was evaporated to give 38 mg of crude product which was dissolved in ethanol (5 ml) and 10% aqueous sodium hydroxide (5 ml) and allowed to stand overnight under nitrogen. Acidification and filtration gave xanthomicrol (21 mg). The filtrate was extracted with ether (2 × 5 ml), which was in turn extracted with dilute sodium bicarbonate (2 × 5 ml). Acidification and back extraction into ether gave on evaporation 4 mg of acidic material. When this was chromatographed on paper using the same systems as the base fusion products, the same yellow spot corresponding to *p*-hydroxybenzoic acid was observed on development with *p*-nitrobenzene-diazonium fluoroborate.

Pentamethoxybenzene[10]

Pentamethoxybenzene was synthesized from pyrogallol by the procedure of Baker. The overall yield was 34%.

2-Hydroxy-3,4,5,6-tetramethoxyacetophenone (XI) *and 2,6-dihydroxy-3,4,5-trimethoxyacetophenone* (XII)

Anhydrous ether (220 ml) was added to anhydrous aluminum chloride (44 g), while the system

was cooled efficiently in an ice-salt bath. Pentamethoxybenzene (44 g) was added in one portion, then acetyl chloride (44 g) dropwise over 15 min. The solution was heated to 25°; a gentle spontaneous reaction set in. The solution was stirred for 14 hr at room temperature, and heated at reflux for 2 hr. Water (310 ml) and concentrated hydrochloric acid (46 ml) were added cautiously. After evaporation of the ether on the steam bath the hot solution was stirred for 3 hr. The reaction mixture was cooled and extracted with dichloromethane (325 ml). The organic solution was extracted with 10% sodium hydroxide (650 ml). The basic solution was acidified and extracted with dichloromethane, which was washed with water, dried over anhydrous sodium sulfate and evaporated to yield crude acetophenone (19·9 g, 40·3%) as a rust-colored oil.

VPC analysis of the crude product with a silicone on firebrick column at ca. 245° showed the presence of at least two components, retention times 5 and 6·5 min.

A portion of the crude oil (4·99 g) was chromatographed on Merck acid-washed alumina (100 g). Carbon tetrachloride and benzene eluted a yellow oil [0·71 g; 14%; retention time (246°), 5 min], which was considered to be 2-hydroxy-3,4,5,6-tetramethoxyacetophenone (XI). I.R.: 6·15 (*s*), 6·30 (*m*), 6·78, 6·88, 6·93 μ. U.V.: λ_{max} mμ (ε): 282(10,450), 347(2600). NMR: 7·42(3), 6·30(3), 6·27(3), 6·13(3), 6·05(3), and −2·69(1)τ. Continued elution with dichloromethane–ether gave a partially crystalline fraction which on crystallization from petroleum ether gave a bright yellow crystalline substance m.p. 86–88° [0·83 g; 17%; retention time (242°), 6·7 min]. This was assigned the structure 2,6-dihydroxy-3,4,5-trimethoxyacetophenone (XII). I.R.: 2·90, 6·17, 6·71, 6·88 μ. U.V.: λ_{max} mμ 283(14,300), 356(2850). NMR: 7·37(3), 6·22(6), 5·99(3), 0·14(2)τ. (Found: C, 54·97; H, 6·09. $C_{11}H_{14}O_6$ requires: C, 54·54; H, 5·83%).

Acetylation with excess acetic anhydride and pyridine on the steam bath gave the diacetate as a colorless oil which could not be crystallized. NMR: 7·80(2), 7·70(1), 6·20(2), 6·10(1)τ.

Investigation of other fractions by VPC indicated considerable additional amounts of XII, but still mixed with XI from which it could not be crystallized.

For the separation of larger amounts of material, the procedure given below was found to be convenient.

The crude acetophenone mixture (8·2 g) was dissolved in ether (75 ml), washed with dilute sodium bicarbonate, and extracted with 10% sodium carbonate (Frac. I, 1 × 100 ml; Frac. II, 2 × 60 ml). The extracts were acidified, extracted with ether, the ethereal solutions evaporated, and the residue taken up in hot petroleum ether to leave behind a small amount of dark residue. From Fraction I (3·40 g), 2,6-dihydroxy-3,4,6-trimethoxyacetophenone (1·64 g; 20%) was isolated by crystallization from ligroin. VPC showed Fraction II (1·59 g) to be a 1:1 mixture of the two acetophenones. The carbonate insoluble fraction (2·31 g) was chromatographed on acid-washed alumina. Elution with petroleum ether gave nearly pure (by VPC) 2-hydroxy-3,4,5,6-tetramethoxyacetophenone [1·9 g; 22%: retention time (240°), 5·5 min].

4′-Benzyloxy-5,6,7,8-tetramethoxyflavone (IX)

2-Hydroxy-3,4,5,6-tetramethoxyacetophenone (701 mg), *p*-benzyloxybenzaldehyde (638 mg), sodium hydride (263 mg.), and tetrahydrofuran (8 ml) were flushed with oxygen-free nitrogen and refluxed for 4 hr in a nitrogen atmosphere. The mixture was poured onto ice and extracted with ether (5 × 30 ml), which was freed of base, dried over anhydrous sodium sulfate and evaporated to give crude 2′-hydroxy-3′,4′,5′,6′,-tetramethoxy-4-benzyloxychalcone as an orange oil (1·11 g). U.V.: 292 mμ (shoulder), 360 mμ. I.R.: 6·13, 6·22, 6·40μ.

The chalcone (1·11 g) and fresh selenium dioxide (1·43 g) were refluxed in n-amyl alcohol (16·5 ml) for 19½ hr. The hot solution was filtered from the free selenium and steam distilled to remove the n-amyl alcohol. The residue was extracted with dichloromethane, which was washed with 5% sodium hydroxide (2 × 25 ml). The organic layer was freed of base, dried and evaporated to give 1·24 g brown tar. Chromatography on Merck alumina gave on elution with ether 4′-benzyloxy-5,6,7,8-tetramethoxyflavone (388 mg, 35%) which was recrystallized from dichloromethane–cyclohexane, m.p. 144–145°. U.V.: λ_{max} mμ (ε): 272(19,600), 325(29,600). (Found: C, 69·58; H, 5·57. $C_{26}H_{24}O_7$ requires: C, 69·63; H, 5·39%).

4′,5-Dihydroxy-6,7,8-trimethoxyflavone (VI)

4′-Benzyloxy-5,6,7,8-tetramethoxyflavone (55 mg) was dissolved in a solution of anhydrous

aluminium chloride (335 mg) in anhydrous ether (1·4 ml) and refluxed for 10 hr. Water (10 ml), ether (5 ml) and concentrated hydrochloric acid (0·5 ml) were added and refluxing was continued for ¾ hr. The organic layer was separated and the aqueous layer extracted thoroughly with ether. The ether solutions were washed with dilute hydrochloric acid, sodium carbonate and 5% sodium hydroxide. The sodium carbonate solution was acidified and extracted with ether to give 42 mg 5,4′-dihydroxy-6,7,8-trimethoxyflavone (99%). Crystallization from EtOAc gave material (m.p. 224–229°) identical with natural xanthomicrol in all respects: I.R. and U.V. curves were superimposable; mixed m.p. was not depressed.

p-*Benzyloxybenzoyl chloride* (XIV)

p-Benzyloxybenzoylchloride was prepared fresh for every reaction by treating *p*-benzyloxybenzoic acid[20] with about five times its weight of thionyl chloride, refluxing for 15 min, and removing the excess thionyl chloride *in vacuo*. The whole crude acid chloride was then used for esterification.

4′-*Benzyloxy*-5-*hydroxy*-6,7,8-*trimethoxyflavone* (X)

The acid chloride was prepared from 1·5 g of *p*-benzyloxybenzoic acid and added to 2,6-dihydroxy-3,4,5-trimethoxyacetophenone (660 mg) in 5 ml of benzene and 1 ml of pyridine. After refluxing 25 min the mixture was poured into water and worked up by extraction with ether and washing with dil H_2SO_4 and dil $NaHCO_3$ to give 1·811 g of crude ester as a dark yellow oil. This was refluxed 7 hr in dry tetrahydrofuran (15 ml) with 370 mg of sodium hydride and then added to dilute sulfuric acid. The product was extracted with ether, the ether evaporated, and the residue cyclized with 98% formic acid on the stream bath for 5 min. The addition of water gave a copious crystalline precipitate which was crystallized from ethanol-dichloromethane to give 596 mg of 4′-benzyloxy-5-hydroxy-6,7,8-trimethoxyflavone (56%) m.p. 155–158°. An analytical sample melted 158–159·5°. U.V.: λ_{max} (ε), 286(22,000), 296(22,400), 332(26,700). (Found: C, 69·35; H, 5·32. $C_{25}H_{22}O_7$ requires: C, 69·12; H, 5·07%).

Debenzylation of 4′-*benzyloxy*-5-*hydroxy*-6,7,8-*trimethoxyflavone*

4′-Benzyloxy-5-hydroxy-6,7,8-trimethoxyflavone (100 mg), glacial acetic acid (5 ml) and concentrated hydrochloric acid (1 ml) were heated on a steam bath for 2½ hr. The solution was allowed to cool to room temperature, and water (35 ml) was added. Filtration gave a yellow crystalline product (82 mg, m.p. 177–217°), which was dissolved in ether and extracted exhaustively with half-saturated sodium carbonate solution. Acidification of the basic solution, extraction with ether and evaporation of the solvent gave 5,4′-dihydroxy-6,7,8-trimethoxyflavone (67 mg, 85%). The material, recrystallized from benzene, melted at 222–224°; mixed m.p. with xanthomicrol undepressed. U.V.: λ_{max} mμ (ε): 283(18,600), 296(18,200), 335(25,100). I.R.: identical with natural xanthomicrol.

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[20] J. B. Cohen and H. W. Dudley, *J. Chem. Soc.* **97**, 1746 (1910).