974. *Oxidative Coupling. Part VI.*[1] *Synthesis of Xanthones.**

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Model experiments have shown that xanthones can be prepared under "physiological conditions" by either solvolytic intramolecular nucleophilic substitution or intramolecular oxidative coupling. The stereochemical implications of these reactions are discussed.

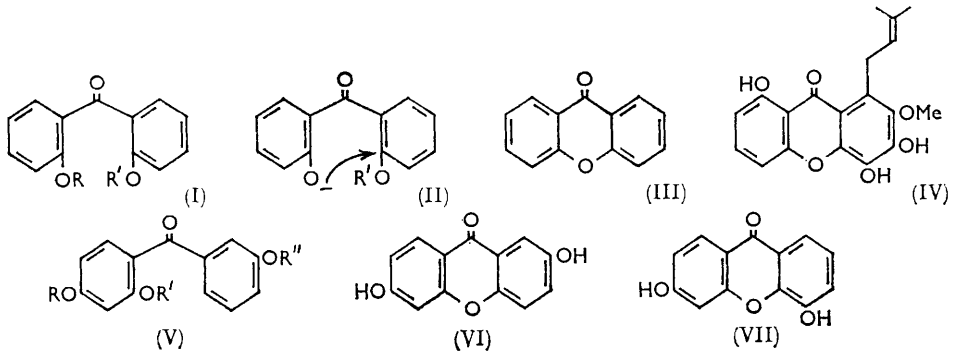
Two reviews on natural xanthones [2,3] have indicated the types of substitution pattern associated with the xanthone nucleus; these can be extended to include morellin,[4] celebixanthone,[5] 6-methoxysterigmatocystin,[6] macluraxanthone,[7] ergoflavin,[8] gambogic acid,[9] and aphloiol.[10] The biogenesis of the xanthone nucleus was suggested by Neelakantan and Seshadri [3] to involve dehydration of a 2,2′-dihydroxybenzophenone; observations by Scott,[11] Rhodes,[12] and their colleagues concerning the isolation of griseoxanthone C and the related benzophenones, griseophenones A, B, and C from cultures of *Penicillium patulum*, support it.

2,2′-Dihydroxybenzophenones can be dehydratively cyclised under a variety of conditions.[13] Barton,[14] Scott,[11] Rhodes,[12] and their collaborators showed that the xanthone nucleus can be produced from 2-hydroxy-2′-methoxybenzophenones by elimination of methanol by mild alkali at 100°. The latter type of ring closure suggested a means for cyclisation under mild solvolytic conditions by substituting the toluene-*p*-sulphonyloxy-group for the methoxy-group, since it was envisaged that the intramolecular nucleophilic displacement should be enhanced by the greater stability of the toluene-*p*-sulphonyloxy-anion. Although the monotosylate (I; R = H, R′ = $C_7H_7{\cdot}SO_2$) could not be prepared the ditosylate (I; R = R′ = $C_7H_7{\cdot}SO_2$) with sodium hydroxide (0·5N) in aqueous methanol

* A preliminary communication appeared in *Proc. Chem. Soc.*, 1963, 373.

[1] Part V, Lewis, *Chem. and Ind.*, 1964, 1672.
[2] Roberts, *Chem. Rev.*, 1961, **61**, 591.
[3] Neelakantan and Seshadri, *Current Science* (*India*), 1961, **30**, 90.
[4] Kartha, Ramachandran, Bhat, Nair, Raghavan, and Venkataraman, *Tetrahedron Letters*, 1963, 459.
[5] Stout, Stout, and Walsh, *Tetrahedron*, 1963, **19**, 667.
[6] Bullock, Kirkaldy, Roberts, and Underwood, *J.*, 1963, 829.
[7] Wolfrom, Komitsky, Fraenkel, Looker, Dickey, McWain, Thompson, Mundell, and Windrath, *Tetrahedron Letters*, 1963, 749.
[8] Robertson, *Nature*, 1963, **200**, 23.
[9] Yates, Karmarkar, Rosenthal, Stout, and Stout, *Tetrahedron Letters*, 1963, 1623.
[10] Adjanyka, Billet, and Mentzor, *Compt. rend.*, 1963, **257**, 1396.
[11] McMaster, Scott, and Trippett, *J.*, 1960, 4628.
[12] Rhodes, Boothroyd, McGonagle, and Somerfield, *Biochem. J.*, 1961, **81**, 28.
[13] Elderfield, "Heterocyclic Compounds," Vol. II, Wiley, New York, 1951, p. 428.
[14] Barton and Scott, *J.*, 1958, 1767.

produced the xanthone (III; 0·7%) together with the phenol (I; R = R′ = H; 98%) after 8 days at room temperature, hydrolysis of the ditosylate to the monotosylate being followed by an intramolecular nucleophilic substitution (I→II→III) together with predominant



hydrolysis of the second tosyl group by solvent hydroxyl anions. *In vivo* the synthesis of the xanthone nucleus could involve a similar mechanistic pathway, a phosphate group participating in the displacement.[15]

An alternative route for the biogenesis of hydroxy-xanthones could arise through oxidative coupling. For geodin, erdin, and griseofulvin, 2,4′-dihydroxybenzophenones are regarded as intermediates which, through oxidative coupling, yield dienones;[14] consequently with 2,3′-dihydroxybenzophenones oxidative coupling should enable ring closure of the ether bridge to give a xanthone with a hydroxyl group *ortho* and/or *para* to this ether bridge. The hydroxylation pattern of celebixanthone (IV),[5] derivable from a 2,2′,3,4,6′-pentahydroxybenzophenone more logically than any other arrangement, suggests that this type of synthesis may occur in Nature.

The synthesis of 2,3′,4-trihydroxybenzophenone (V; R = R′ = R″ = H) was considered suitable for study of the oxidative coupling since it contains the necessary hydroxyl groups for activation. Friedel–Crafts condensation of 3-methoxybenzoyl chloride with dimethylresorcinol gave the expected 2,3′,4-trimethoxybenzophenone (V; R = R′ = R″ = Me) which showed non-bonded carbonyl absorption at 1660 cm.$^{-1}$. Demethylation yielded 2,3′,4-trihydroxybenzophenone (V; R = R′ = R″ = H) which showed a hydrogen bonded carbonyl absorption at 1628 cm.$^{-1}$ with bonded and free hydroxyl absorption maxima at 3420 and 3530 cm.$^{-1}$, respectively.[16]

This trihydroxybenzophenone, in alkaline solution at room temperature with an excess of potassium ferricyanide, gave a dihydroxyxanthone in 83% yield after 2 hours. The identity of this and its dimethyl derivative was confirmed by comparison with authentic 2,6-dihydroxyxanthone (VI) and 2,6-dimethoxyxanthone thus indicating that oxidative coupling had taken place *para* to the 3′-hydroxyl group. The absence of the isomer 3,5-dihydroxyxanthone (VII) (corresponding to *ortho* coupling with the 3′-hydroxyl group) was established by paper chromatography in two solvent systems, with use of authentic 2,6-dihydroxyxanthone[17] and 3,5-dihydroxyxanthone (VII), obtained by demethylation of 3,5-dimethoxyxanthone.[18] The stereospecificity of the oxidation was thus confirmed. The rate of oxidation depends on pH, being slow at pH 7 and increasing as the pH approached 14.

We therefore suggest that natural xanthones may be derived by solvolytic or oxidative

[15] Gibson, *Biochem. J.*, 1964, **90**, 256.
[16] Mustafa, Sidky, Zayed, and Soliman, *Tetrahedron*, 1963, **19**, 1335.
[17] Mittal and Seshadri, *J. Sci. Ind. Res. (India)*, 1955, **14**, *B*, 76.
[18] Noyce and Weldon, *J. Amer. Chem. Soc.*, 1952, **74**, 5144.

reactions and the hydroxyl-group patterns in natural xanthones show that the necessary activation for oxidative coupling is present in euxanthone, isogentisin, swerchirin, mangiferin, jacareubin, mangostin, decussatin, celebixanthone, pinselin, gentisin, ravenelin, swertianol, macluraxanthone, ergoflavin, and aphloiol, while the remainder may be derived through the solvolysis, *e.g.*, sterigmatocystin, griseoxanthone C, lichexanthone, and 6-methoxysterigmatocystin. Definite evidence regarding the actual hydroxylation pattern of benzophenones and their transformation into hydroxyxanthones can only be obtained from radioactive tracer experiments, but a preliminary examination of the hydroxyl patterns suggest that the second group of xanthones could be derived solely from acetate, as found for griseofulvin,[19] while the first could arise from both the acetate and shikimate pathways, as found for flavones,[20] with deoxygenation [21] occurring in the appropriate cases.

Experimental

Melting points, uncorrected, were recorded on a Kofler hot stage apparatus. Infrared spectra were measured in chloroform or in KBr discs on a Unicam S.P. 200 spectrophotometer. Ultraviolet spectra were measured on a Unicam S.P. 600 spectrometer in ethanol. Whatman's No. 1 filter paper was used for paper chromatography, detection being by ultraviolet fluorescence.

2,2′-*Dihydroxybenzophenone* (I; R = R′ = H).—Xanthone (10 g.) and potassium hydroxide (30 g.) were intimately mixed and heated on an oil bath to 200°, the mixture was separated into a neutral fraction, xanthone (2·3 g.) and a phenolic fraction (6·2 g.). Distillation of the latter gave 2,2′-dihydroxybenzophenone, b. p. 128—132°/0·015 mm., which crystallised from light petroleum as a yellow solid, m. p. 55—57° (4·9 g.), $\lambda_{max.}$ 258—259, 335—336 mμ (ε 11,000, 5300), 1630 cm.$^{-1}$ (carbonyl C=O, hydrogen bonded).

2,2′-*Ditoluene*-p-*sulphonyloxybenzophenone* (I; R = R′ = $C_7H_7{\cdot}SO_2$).—The dihydroxybenzophenone (I; R = R′ = H) (1·4 g.) was dissolved in methanol (20 ml.) containing potassium (0·28 g.) and the solution evaporated to dryness. Addition of toluene-*p*-sulphonyl chloride (1·4 g.) in dimethylformamide (10 ml.) rapidly decolourised the red potassium salt. After 2 hr. at room temperature the mixture was poured into water and extracted with ether. The ether layer, washed with water, dilute alkali, water and dried (Na_2SO_4), filtered, and evaporated to dryness left a solid (2·3 g.). Crystallisation from acetone gave the *ditosylate* as plates, m. p. 147—150° (Found: C, 62·3; H, 4·3. $C_{27}H_{22}O_7S_2$ requires C, 62·1; H, 4·25 %), $\lambda_{max.}$ 227—228, 254—255, 282—284, 315—330 mμ (ε 21,100, 8050, 5100, 336), 1669 cm.$^{-1}$ (non bonded carbonyl C=O), 1393, 1195, 1180 cm.$^{-1}$ (sulphonyloxy S=O [22]). When the reaction was carried out with ½ molar quantities of potassium and toluene-*p*-sulphonyl chloride only lower yields of the ditosylate were obtained together with dihydroxybenzophenone. No monotosylate was detected.

Solvolysis.—The ditosylate (I; R = R′ = $C_7H_7{\cdot}SO_2$; 1 g.) was dissolved in aqueous methanol (60 ml., 66%) and sodium hydroxide added to give the required concentration. In each case the neutral fraction was crystallised from ethanol to give needles, m. p. 145—165° (sublimation), which was purified further by sublimation to give material of m. p. 160—172° (sublim.). The infrared spectrum (KBr) was identical with authentic xanthone (III), $\lambda_{max.}$ 1662 cm.$^{-1}$ (aromatic carbonyl C=O).

Ditosylate (g.)	[NaOH]	Temp.	Time (days)	Dihydroxybenzophenone	Xanthone
1	0·5N	17°	8	983 mg.	7 mg.
0·5	1·0N	60	3	425 mg.	35 mg.
1·0	1·0N	35	8	950 mg.	10 mg.

1,2′,3-*Trimethoxybenzophenone* (V; R = R′ = R″ = Me).—3-Methoxybenzoyl chloride (1·6 g.) was dissolved in dry nitrobenzene (5 ml.), dimethylresorcinol (1·4 g.) added followed by anhydrous aluminium chloride (1·4 g.) and the mixture stirred at room temperature for 18 hr.

[19] Birch, Massy-Westropp, Rickards, and Smith, *J.*, 1958, 360.
[20] Whalley, " Recent Developments in the Chemistry of Natural Phenolic Compounds," ed. W. D. Ollis, Pergamon Press, London, 1961, p. 20.
[21] Rickards, ref. 20, p. 1.
[22] Corey, Mitra, and Uda, *J. Amer. Chem. Soc.*, 1964, **86**, 485.

The mixture was poured into ice-cold dilute HCl and extracted with ether, and isolation of a neutral fraction gave the *benzophenone* (2·2 g.), b. p. 167—169°/0·5 mm. (Found: C, 70·8; H, 6·15. $C_{16}H_{16}O_4$ requires C, 70·55; H, 5·9%), $\lambda_{max.}$ 250 (shoulder), 307—308 mμ (ε 900, 10,100), 1662 cm.$^{-1}$ (non-bonded aromatic carbonyl C=O).

1,2′,3-*Trihydroxybenzophenone* (V; R = R′ = R″ = H).—The trimethoxybenzophenone (8 g.) in glacial acetic acid (100 ml.) containing hydrobromic acid (40 ml., 60%) was refluxed for 6 hr.; isolation of a phenolic fraction gave a brown oil which solidified (5·9 g.). Purification by elution with benzene from alumina give 1,2′,3-*trihydroxybenzophenone* (V; R = R′ = R″ = H) which crystallised from benzene as pale yellow plates, m. p. 178—182° (Found: C, 68·1; H, 4·6. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·4%), $\lambda_{max.}$ 238—242, 289, 330 mμ (ε 10,400, 1300, 7000), 1628 cm.$^{-1}$ (hydrogen bonded carbonyl C=O), 3530 (free OH group), 3420 cm.$^{-1}$ (bonded OH group). Demethylation with aluminium chloride in boiling chloroform for 2½ hr. also gave the trihydroxybenzophenone, R_F 0·62 (n-butanol saturated with ammonia); 0·86 (60% acetic acid).

Oxidations.—The phenol (V; R = R′ = R″ = H) (460 mg.) was dissolved in water (10 ml.) containing sodium hydroxide (350 mg.) and potassium ferricyanide (1·4 g.) in water (10 ml.) slowly added with stirring. After 2 hr. the dark brown solution was acidified and extracted with ethyl acetate, the organic layer was separated, washed thrice with water, dried and evaporated to yield a yellow solid (408 mg.). Crystallisation from ethanol gave 2,6-dihydroxyxanthone (VI), m. p. 335—345° (sublim.) (Found: C, 68·5; H, 3·7; $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%); $\lambda_{max.}$ 238, 315—316 mμ (ε 50,000, 16,100), 1638 cm.$^{-1}$ (non-bonded carbonyl C=O), identical with authentic 2,6-dihydroxyxanthone [17] (VI), R_F 0·73 (60% acetic acid) and 0·29 (n-butanol saturated with ammonia).

At different pH, aqueous and aqueous methanolic solutions of the trihydroxybenzophenone and potassium ferricyanide solution being used, the amount of 2,6-dihydroxyxanthone decreased with decrease in pH. At pH 7 very little xanthone was produced and none at pH 2. Potassium permanganate produced only small amounts of xanthone at pH 2 and extensively destroyed organic material.

Use of manganese dioxide or lead dioxide as oxidising agent with various solvents and temperatures gave no xanthone.

2,6-*Dimethoxyxanthone.*—The dihydroxyxanthone from the oxidations was methylated in alkaline solution with excess of dimethyl sulphate and the neutral fraction extracted with ethyl acetate. Evaporation and crystallisation of the residue from ethanol gave plates, m. p. 160—164°, $\lambda_{max.}$ 240, 309—311 mμ (ε 32,400, 25,600), 1648 cm.$^{-1}$ (non-bonded carbonyl C=O), identical with 2,6-dimethoxyxanthone prepared by the method of Mittal and Seshadri,[17] R_F 0·92 (n-butanol saturated with ammonia); 0·89 (60% acetic acid).

3,5-*Dimethoxyxanthone.*—3,5-Dimethoxyxanthone, prepared as described by Noyce and Weldon,[18] crystallised from methanol as needles, m. p. 170—172°, $\lambda_{max.}$ 236—237, 267—268, 303—304 mμ (ε 34,300, 17,400, 11,200), 1642 cm.$^{-1}$ (non-bonded carbonyl C=O), R_F 0·87 (n-butanol saturated with ammonia); 0·83 (60% acetic acid).

3,5-*Dihydroxyxanthone* (VII).—3,5-Dimethoxyxanthone (100 mg.) was dissolved in glacial acetic acid (10 ml.) and hydrobromic acid (2 ml., 50%) added and the mixture refluxed for 1½ hr. Isolation of a phenolic fraction *via* ethyl acetate extraction, gave a solid (86 mg.) which was further purified by sublimation at 170—190°/0·01 mm. 3,5-*Dihydroxyxanthone* (VII) crystallised from methanol as pale yellow needles, m. p. 217—220° (Found: C, 68·2; H, 4·0; $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%), $\lambda_{max.}$ 236—238, 268, 330—335 mμ (ε 36,100, 21,500, 6300), 1638 cm.$^{-1}$ (non-bonded carbonyl C=O), R_F 0·83 (60% acetic acid); 0·61 (n-butanol saturated with ammonia).

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