Studies in the Xanthone Series. Part 13. Structural and Synthetic Studies on Toxyloxanthone B

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A re-consideration of the ^{1}H n.m.r. data for toxyloxanthone B trimethyl ether and an unambiguous total synthesis both show that toxyloxanthone B has the 1,1-dimethylpyrano[3,2-*a*]xanthone structure (1a) and *not* the 3,3-dimethylpyrano[3,2-*a*]xanthone system (2) previously assigned. The synthesis is based on the preparation of 1,7-dihydroxy-3,5-dimethoxyxanthone (5) from cyclisation of a benzophenone precursor (3a) or (3b) and selective demethylations. A Claisen rearrangement of the 7-prop-2-ynyloxyxanthone (6) followed by cyclisation and methylation gives toxyloxanthone B trimethyl ether.

DESHPANDE *et al.*[1] isolated a new pyranoxanthone, toxyloxanthone B (1a) from the stem bark of *Toxylon pomiferum* Raffin, *Maclura pomifera* Schneid, and *M. avrantiaca* Nutt (Osage Orange), and assigned the novel dimethylpyrano[3,2-*a*]xanthone ring system (1a) the low value for H-1 is largely accounted for by the deshielding anisotropic influence of the xanthone carbonyl group. The proton resonance is consistent with the low

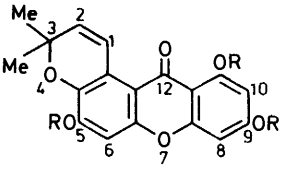
N.m.r. data of xanthone derivatives (τ values measured in $CDCl_3$; multiplicity and coupling constants in parentheses)

	Xanthone nucleus protons [a]				Pyran [b] protons			
Compound	H-2	H-4	H-5	H-8	2Me at C-3	H-2	H-1	OMe (All s)
(4)	3.70 (d, *J* 2 Hz)	3.78 (d, *J* 2 Hz)	3.37 (s)	2.49 (s)				6.05 (9 H) 6.17 (3 H)
(5)	3.49 (d, *J* 3 Hz)	3.63 (d, *J* 3 Hz)	2.91 (s)	2.55 (s)				6.01 (3 H) 6.10 (3 H)
(1b)	3.64 (s)	3.64 (s)	3.19 (s)		8.50 (s)	4.15 (d, *J* 10 Hz)	1.88 (d, *J* 10 Hz)	6.01 (3 H) 6.11 (3 H)
(1c)	3.66 (d, *J* 2 Hz)	3.75 (d, *J* 2 Hz)	3.34 (s)		8.56 (s)	4.28 (d, *J* 10 Hz)	1.90 (d, *J* 10 Hz)	6.06 (6 H) 6.14 (3 H)
(6)	3.64 (m)	3.64 (m)	3.14 (s)	1.79 (s)	8.28 (s)		7.40 (s)	6.04 (3 H) 6.17 (3 H)
(7)	3.57 (m)	3.57 (m)	3.15 (s)	1.66 (s)	8.27 (s)		7.40 (s)	6.00—6.07 (9 H)
Deshpande [1] (1c)	3.65 (d, *J* 2 Hz)	3.75 (d, *J* 2 Hz)	3.34 (s)		8.50 (s)	4.27 (d, *J* 10 Hz)	1.87 (d, *J* 10 Hz)	6.04 (3 H) 6.06 (3 H) 6.14 (3 H)

[a] Xanthone numbering as in (4) has been used. [b] Pyran numbering as in the ring system for (1) has been used. This spectrum was measured in hexadeuteriodimethyl sulphoxide.

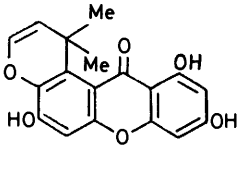
4,4-dimethylchromen ring system (2) to the metabolite. A re-examination by us [2] and an Indian group [3] of the recorded n.m.r. data (Table) suggested that the signals of the chromen ring had been incorrectly assigned. We now provide evidence to show that the structure of toxyloxanthone B must be revised to (1a) which incorporates the biogenetically acceptable 2,2-dimethylchromen ring system.

Deshpande *et al.* ruled out the presence of a 2,2-dimethylchromen moiety in toxyloxanthone B from the n.m.r. data of its trimethyl ether derivative (1c) (Table).[1] The low chemical shift (τ 1.87) for one of the olefinic protons ([H-1 in (1a)] was not in accordance with the accepted values (τ 3.3 and 4.3) for an olefinic proton of other pyranoxanthones and thus the alternative 4,4-dimethylchromen ring was favoured. However, in the values found for a proton [4] and a methylene group attached to position C-8 of the xanthone nucleus.[5]



(1)

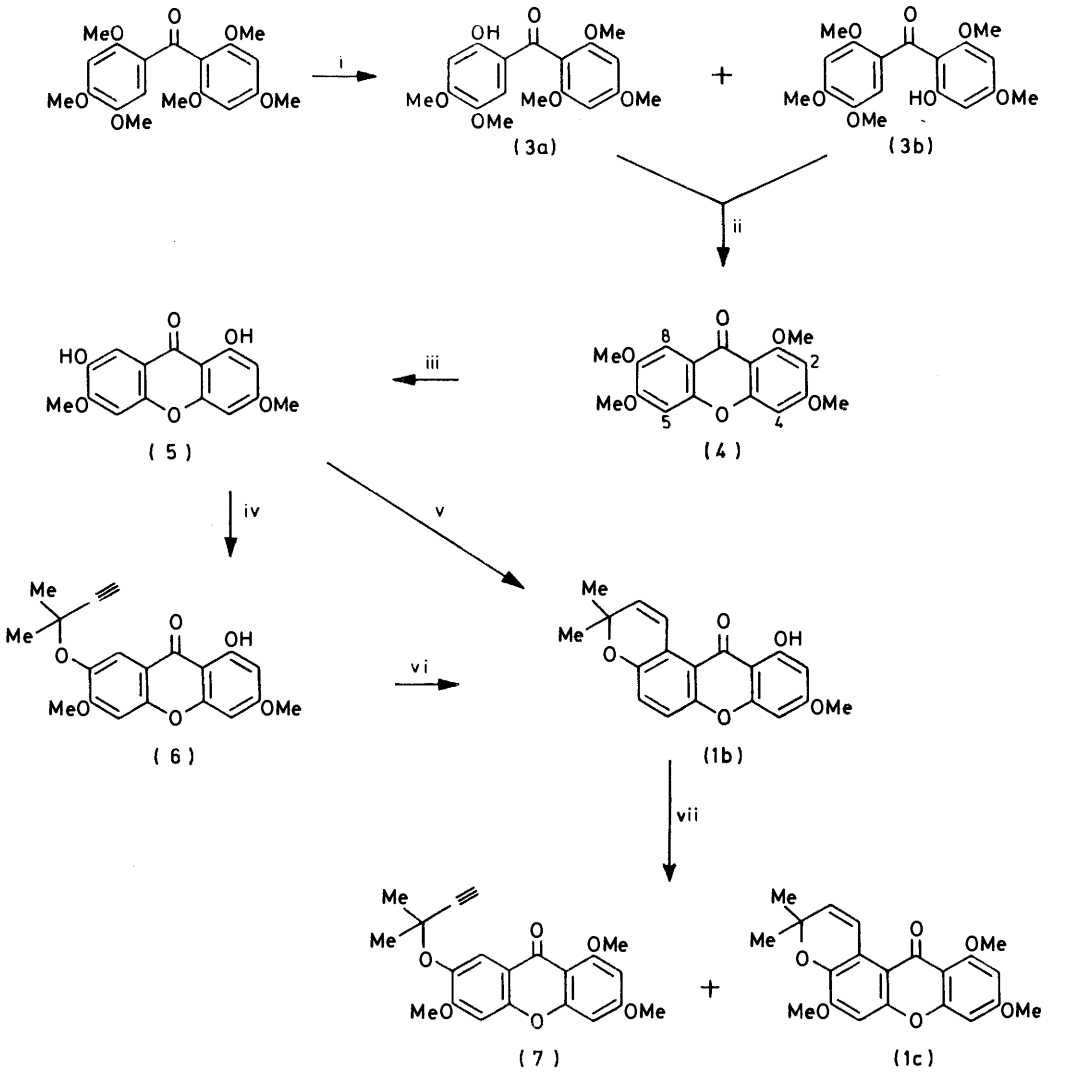
a ; R = R′ = H
b ; R = H , R′ = Me
c ; R = R′ = Me



(2)

Furthermore, comparison of the recorded n.m.r. data for synthetic [6] and natural [7] pyrano[3,2-*a*]xanthones

confirms that proton H-1 (τ *ca.* 2.0) is deshielded by >1.0 p.p.m. when compared with the pyran ring in other orientations.[8] Structure (2) was also unacceptable on the grounds that the olefinic protons in vinyl ether systems resonate at higher field (τ 3.7—5.5).[9] The more forcing conditions, the required 2-hydroxy-2′,4,4′,5,6′-pentamethoxybenzophenone (3a). A boron trichloride-induced demethylation of the hexamethoxybenzophenone derivative gave a mixture of the two possible 2-hydroxybenzophenones (3a) and (3b) but,



SCHEME Reagents: i, BCl_3, CH_2Cl_2; ii, NaOH; iii, HBr, HOAc; iv, $ClCMe_2C{\equiv}CH$, K_2CO_3, Me_2CO, 18 °C; v, as iv but reflux in H_2O–Me_2CO; vi, MeOH, 60 °C; vii, Me_2SO_4, K_2CO_3, Me_2CO, 54 °C

structure of toxyloxanthone B was confirmed as (1a) by the synthesis of its di- and tri-methyl ether derivatives and by direct comparison with an authentic sample.

The total synthesis of toxyloxanthone B trimethyl ether was achieved by utilizing a xanthone synthesis (see Scheme) established earlier.[6] The key intermediate, 1,3,6,7-tetramethoxyxanthone (4), was readily prepared by a facile base-catalysed cyclisation of a suitable 2-hydroxy-2′-methoxybenzophenone derivative (3a) or (3b). A Friedel-Crafts acylation of 1,3,5-trimethoxybenzene with 2,4,5-trimethoxybenzoyl chloride gave 2,2′,4,4′,5′,6-hexamethoxybenzophenone and, under interestingly, the main product (70%) was found to be the isomer of the product obtained from the Friedel-Crafts reaction, *i.e.* 2-hydroxy-2′,4,4′,5′,6-pentamethoxybenzophenone (3b). Both 2-hydroxybenzophenone derivatives (3a) and (3b) were cyclised in aqueous sodium hydroxide to give 1,3,6,7-tetramethoxyxanthone (4). Selective demethylation of the tetramethoxyxanthone was achieved by boiling with hydrogen bromide in glacial acetic acid to give 1,7-dihydroxy-3,6-dimethoxyxanthone (5).

The pyran ring was previously introduced in one step by treating 1,7-dihydroxy-3,6-dimethoxyxanthone (5) with 3-bromo-3-methylbut-1-yne and potassium car-

bonate in boiling acetone.[6] The postulated 7-(1,1-dimethylprop-2-ynyl) ether (6) intermediate was not isolated but cyclised under the conditions of the reaction. We re-examined this reaction since aryl prop-2-ynyl ethers have been previously isolated.[10] Thus 1,7-dihydroxy-3,6-dimethoxyxanthone was treated with an excess of 3-chloro-3-methylbut-1-yne as before but after one day the reaction mixture was stirred at 18 °C for a further six days with further additions of reagents daily. The reaction products were separated by preparative t.l.c. and a pale yellow band, corresponding to the reported [6] R_F value for the pyrano[2,3-*a*]xanthone (1b) was removed and the material isolated.

A molecular ion at *m/e* 354 ($C_{20}H_{18}O_6$) and a diagnostic i.r. spectrum which showed absorptions at 3 290 and 2 130 cm^{-1} indicated that the acetylenic ether (6) had been formed. This was verified by its n.m.r. spectrum (Table): the acetylenic proton resonates at τ 7.40 as a singlet, and the other spectroscopic data was also consistent with the assigned structure for the 7-propynyl ether (6).

The Claisen rearrangement of product (6) was carried out in boiling methanol until a crystalline precipitate appeared. The 3,3-dimethylpyrano[3,2-*a*]xanthone (1b) was isolated from the reaction mixture and shown to be identical with the product obtained previously.[6] This isolation of the 7-propynyl ether (6) and formation of toxyloxanthone B dimethyl ether provides an unambiguous synthesis of the 3,3-dimethylpyrano[3,2-*a*]-xanthone ring system.

The one-step synthesis of toxyloxanthone B dimethyl ether (1b) was repeated by modifying the method of Collins *et al.*[11] whereby 1,7-dihydroxy-3,6-dimethoxyxanthone (5) was boiled in *aqueous* acetone with an excess of 3-chloro-3-methylbut-1-yne and potassium carbonate. The product (1b) was isolated by preparative t.l.c. and was shown to be identical with that prepared before. The previously recorded [6] m.p. (243 °C) for (1b) requires correction as that sample melts at 228—229 °C in agreement with the samples prepared in this work. Deshpande *et al.*[1] recorded a value of 210—212 °C for their toxyloxanthone B dimethyl ether but repeated recrystallisation raised the m.p. to 228—229 °C.[12] To complete the synthesis of toxyloxanthone B trimethyl ether (1c) the free hydroxy-group for the pyranoxanthone (1c) was methylated with dimethyl sulphate. The crude product, a pale yellow solid, was purified by recrystallisation from methanol. During recrystallisation the solution slowly changed to a darker yellow colour and the precipitated product was shown by n.m.r. to be a 55 : 45 mixture of the 7-propynyl ether (7) and the pyranoxanthone trimethyl ether (1c) respectively. Thus in boiling methanol a retro-Claisen rearrangement occurs and the pyran and acetylene ether [(1c) and (7) respectively] are in equilibrium and either can be isolated by controlling the reaction conditions. The proton resonances for each compound were well separated in the n.m.r. spectrum (Table). Thus for the ether (7) the acetylenic proton resonance was found at τ 7.40 and that of H-8 at τ 1.66. The very low value for H-8 is explained by the combined deshielding effect of the xanthone carbonyl and acetylene groups. The mixture of products was boiled for an extended time in methanol and the colour of the solution darkened to deep yellow. The pyranoxanthone trimethyl ether (1c) was isolated by preparative t.l.c. to give the pure product. The important olefinic proton (H-1) resonance was found at τ 1.90 (d, J 10 Hz) and was in close agreement with that recorded by Deshpande *et al.*[1] Furthermore, the synthetic product (1c) was shown to be identical (u.v., i.r., m.p., and mixed m.p.) with an authentic sample of toxyloxanthone B trimethyl ether kindly provided by Professor K. Venkataraman.[13]

EXPERIMENTAL

U.v. spectra (solutions in methanol) were recorded with Unicam SP 800 and SP 8000 spectrophotometers and i.r. spectra (Nujol mulls) with Perkin-Elmer 257 and 177 grating spectrometers. Mass spectra were obtained from an A.E.I. MS 12 (single focusing) spectrometer operating at 240 °C and 70 eV. ^{1}H N.m.r. spectra were recorded on Varian HA 100 and Perkin-Elmer Hitachi R-24 high-resolution spectrometers. Silica gel HF 254 (Merck) was used for preparative t.l.c.

3-Chloro-3-methylbut-1-yne.—3-Methylbut-1-yn-3-ol (22.6 g) was cooled to 5 °C and thionyl chloride (32.5 g) was added slowly during 15 min the temperature being kept below 20 °C. The reaction mixture was heated to 60 °C and stirred at this temperature for 3 h. The mixture was then distilled under reduced pressure and a fraction boiling at 33—35 °C at 100 mmHg was collected. The fraction (8.1 g) was shown by g.l.c. to contain 80% of the 3-chloro-3-methylbut-1-yne, τ(CCl_4) 4.03 (1 H, s) and 8.35 (6 H, s).

2,2′,4,4′,5′,6-Hexamethoxybenzophenone.— 2,4,5-Trimethoxybenzoic acid (20 g) was boiled with thionyl chloride (55 ml) for 3 h and then the excess of thionyl chloride was removed under reduced pressure to give a pale-green solid residue. This residue and 1,3,5-trimethoxybenzene (16 g) were dissolved in dry ether (600 ml) and the mixture was stirred briskly as powdered, anhydrous aluminium chloride (44 g) was added in small portions to the cooled solution. Immediately an orange-red ether solution and an insoluble dark red oil were formed. The reaction mixture was stirred for 18 h during which time the oil had changed to an orange solid. The ether solution was removed and concentrated under reduced pressure to give a dark-red oil. This oil and the orange solid were combined and decomposed by the slow addition of water and concentrated HCl. The oily solution produced was extracted with toluene (4 × 300 ml) and the combined extracts, after drying ($MgSO_4$), were concentrated under reduced pressure to give a dark-brown oil. The oil was dissolved in hot methanol and then cooled to give 2,2′,4,4′,5′,6-hexamethoxybenzophenone (3.4 g) as pale yellow cubes, m.p. 120 °C; $\nu_{max.}$ 1 643, 1 602, 1 518, 1 281, 1 225, 1 163, 1 140, 1 050, 830, and 815 cm^{-1}; τ($CDCl_3$) 2.66 (1 H, s), 3.58 (1 H, s), 3.92 (2 H, s), 6.13 (3 H, s), 6.19 (6 H, s), 6.33 (6 H, s), and 6.42 (3 H, s); M^+, 362.136 4. $C_{19}H_{22}O_7$ requires M, 362.136 4.

2-Hydroxy-2′,4,4′,5′,6-pentamethoxybenzophenone and 2-Hydroxy-2′,4,4′,5,6′-pentamethoxybenzophenone.— 2,2′,4,4′,5′,6-Hexamethoxybenzophenone (1 g) was dissolved in dichloromethane (20 ml) and treated with a solution of

boron trichloride in dichloromethane (10 ml of a 10% w/v solution). The deep red solution was stirred at 18 °C for 20 min and then decomposed by pouring it into water (100 ml). The two layers were stirred briskly together for 4 h until the organic layer was pale yellow in colour. The dichloromethane layer was removed, dried ($MgSO_4$), and concentrated under reduced pressure to give a pale yellow oil. The oil was dissolved in hot methanol and allowed to crystallise slowly giving first yellow cubes of 2-hydroxy-2′,4,4′,5,6′-pentamethoxybenzophenone (0.25 g), m.p. 165—166 °C (lit.,[12] 171—173 °C), $\nu_{max.}$ 1 630, 1 600, 1 509, 1 275, 1 241, 1 220, 1 171, 1 145, 1 078, 1 050, 967, 933, 842, and 825 cm^{-1}; $\tau(CDCl_3)$ −2.56 (1 H, s), 3.39 (1 H, s), 3.60 (1 H, s), 3.91 (2 H, s), 6.13 (3 H, s), 6.19 (3 H, s), 6.31 (6 H, s), and 6.39 (3 H, s); M^+, 348, and then yellow needles of 2-hydroxy-2′,4,4′,5′,6-pentamethoxybenzophenone (0.55 g), m.p. 129—130 °C; $\nu_{max.}$ 1 612, 1 580, 1 515, 1 410, 1 348, 1 230, 1 218, 1 174, 1 123, 1 058, 1 049, 833, and 818 cm^{-1}; $\tau(CDCl_3)$ −2.96 (1 H, s), 3.16 (1 H, s), 3.57 (1 H, s), 3.94 (1 H, d, J 2.5 Hz), 4.20 (1 H, d, J 2.5 Hz), 6.09 (3 H, s), 6.17 (6 H, s), 6.33 (3 H, s), and 6.54 (3 H, s); M^+, 348.

2-Hydroxy-2′,4,4′,5,6′-pentamethoxybenzophenone.— The method used to prepare the hexamethoxybenzophenone derivative was repeated except that the acyl chloride intermediate was prepared by boiling for 6 h and the ether solution containing the aluminium chloride complex was stirred for 48 h with frequent boiling to induce demethylation. Thus 2,4,5-trimethoxybenzoic acid (10 g), thionyl chloride (30 ml), 1,3,5-trimethoxybenzene (8 g), aluminium chloride (30 g), and ether (500 ml) were allowed to react together to give 2-hydroxy-2′,4,4′,5,6′-pentamethoxybenzophenone (2.0 g) as yellow cubes from methanol, m.p. 165 °C, and was shown (m.p., mixed m.p., i.r., n.m.r.) to be identical to the derivative prepared above. From the reaction mixture 2,2′,4,4′,5,6′-hexamethoxybenzophenone (2.2 g), m.p. 120—121 °C, identical (m.p., mixed m.p., i.r., n.m.r.) with the sample prepared previously, was isolated.

1,3,6,7-Tetramethoxyxanthone (4).—2,2′,4,4′,5,6′-Hexamethoxybenzophenone (2.2 g) was demethylated with boron trichloride (22 ml of a 10% w/v solution) using the previously described method. The crude intermediate 2-hydroxybenzophenones were not separated but boiled for 18 h with aqueous sodium hydroxide (2M; 50 ml) containing sufficient methanol and pyridine to give a solution. Acidification (2M HCl) and extraction with chloroform gave a pale yellow amorphous powder (1.6 g) which recrystallised from methanol as cream coloured needles of 1,3,6,7-tetramethoxyxanthone (1.38 g), m.p. 194 °C (lit.,[14] 210—212 °C); $\nu_{max.}$ 1 630, 1 610, 1 510, 1 430, 1 280, 1 220, 1 173, 1 138, 1 112, 1 027, 836, and 804 cm^{-1}; $\tau(CDCl_3)$ see Table.

1,7-Dihydroxy-3,6-dimethoxyxanthone (5).—1,3,6,7-Tetramethoxyxanthone (4.9 g) was dissolved in an HBr–glacial acetic acid solution (45% w/v; 100 ml) and the mixture boiled for 4 h. A solid was isolated [15] which recrystallised from methanol to give crude 1,7-dihydroxy-3,6-dimethoxyxanthone (2.6 g), m.p. 193—198 °C. Chromatography [15] gave the pure compound (R_F 0.3), m.p. 227 °C (lit.,[6] 235—237 °C): $\lambda_{max.}$ ($\varepsilon \times 10^{-3}$) 236 (25.3), 255 (34.9), 307 (14.9), and 362 nm (9.7); $\nu_{max.}$ 3 300, 1 668, 1 612, 1 588, 1 291, 1 277, 1 218, 1 172, 1 100, 1 034, 978, and 828 cm^{-1}; for $\tau[(CD_3)_2SO]$ see Table.

The methanol-insoluble material from the above recrystallisation was shown (m.p., mixed m.p., u.v., i.r.) to be essentially 1-hydroxy-3,6,7-trimethoxyxanthone (0.5 g), m.p. 214 °C.

1-Hydroxy-3,6-dimethoxy-7-(1,1-dimethylprop-2-ynyloxy)-xanthone (6).—The crude 1,7-dihydroxy-3,6-dimethoxyxanthone (0.5 g) was dissolved in acetone and heated under reflux. To the well stirred solution was added potassium carbonate (1 g) and 3-chloro-3-methylbut-1-yne (1 g). The reaction mixture was boiled for 24 h and then further additions of the acetylene compound (1 g) and potassium carbonate (1 g) were made. The reaction mixture was stirred at 18 °C for 6 more days with daily additions of the acetylene compound (1 g) and potassium carbonate (1 g). The potassium carbonate was filtered off and the solution concentrated under reduced pressure. The resulting oil was dissolved in chloroform, the solution filtered, and the components of the mixture were separated by preparative t.l.c. A pale yellow band at R_F 0.7 (15% ethyl acetate in toluene) was removed and the material eluted from the silica with chloroform. Concentration of the solvent under reduced pressure gave a pale yellow solid (84 mg) which was recrystallised from methanol to give pale yellow needles of the 7-propynyl ether, m.p. 203—204 °C; $\lambda_{max.}$ ($\varepsilon \times 10^{-3}$) 240 (29.6), 255 (39.3), 308 (19.3), and 350 nm (10.3); $\nu_{max.}$ 3 290, 2 130, 1 660, 1 600, 1 570, 1 285, 1 220, 1 162, 1 128, 1 085, 1 041, 919, 885, 837, and 810 cm^{-1}; for $\tau(CDCl_3)$ see Table; M (mass spectrum), 354.111 2; $C_{20}H_{18}O_6$ requires M, 354.110 2.

11-Hydroxy-5,9-dimethoxy-3,3-dimethylpyrano[3,2-a]xanthone (1b).—(*a*) Crude 1,7-dihydroxy-3,6-dimethoxyxanthone (1 g) dissolved in aqueous acetone (25 ml water + 75 ml acetone) was heated to reflux as potassium carbonate (2 g) and 3-chloro-3-methylbut-1-yne (2 g) were added. The reaction mixture was boiled for 7 days during which time daily additions of potassium carbonate (2 g) and the acetylene compound (2 g) were made. The cooled mixture was poured into water (100 ml) acidified with hydrochloric acid (2M) and then extracted with ethyl acetate (4 × 50 ml). The combined, dried extracts were concentrated under reduced pressure to give a dark brown oil. The oil was dissolved in chloroform and the components of the mixture were separated by preparative t.l.c.. A deep-yellow band at R_F 0.7 (15% ethyl acetate in toluene) was removed from the plates and the material was eluted from the silica with acetone. Concentration of the solvent gave a yellow solid which was recrystallised from hot methanol to give the chromen (1b) as fine yellow needles (242 mg), m.p. 227—228 °C (lit.,[6] 243 °C), $\lambda_{max.}$ ($\varepsilon \times 10^{-3}$) 242 (29.7), 264 (32.4), 319 (22.3), and 376 nm (6.5); $\nu_{max.}$ 1 648, 1 630, 1 590, 1 573, 1 283, 1 218, 1 167, 1 130, 981, and 830 cm^{-1}; for $\tau(CDCl_3)$. See Table; M, (mass spectrum) 354.111 6. Calc. for $C_{20}H_{18}O_6$, M, 354.110 2.

(*b*) A sample of the 7-propynyl ether (35 mg) was heated under reflux in methanol (15 ml) for 48 h. The solution had turned a darker shade of yellow by the end of the reflux and a suspension of fine yellow needles was observed. On cooling, the chromen (1b) crystallised as yellow needles (24 mg), m.p. 227—228 °C, identical (u.v., i.r., m.p., mixed m.p.) with the material isolated above.

5,9,11-Trimethoxy-3,3-dimethylpyrano[3,2-a]xanthone (1c).—The pyranoxanthone (1b) (100 mg) was dissolved in boiling acetone (20 ml) and treated with an excess of dimethyl sulphate and potassium carbonate. The mixture was heated under reflux for 20 h and then cooled and filtered. The solution was concentrated under reduced pressure to give a pale yellow solid which recrystallised from methanol as yellow needles, (66 mg). The product was shown by n.m.r. to be a 55 : 45 mixture of the 7-propynyl trimethyl

ether and the chromen trimethyl ether respectively. The physical data found for the 7-propynyl trimethyl ether were: R_F 0.3 (30% ethyl acetate in toluene); $\nu_{max.}$ (on mixture), 3 185 and 2 100 cm^{-1}; for $\tau(CDCl_3)$ (on mixture), see Table.

The mixture of ethers (66 mg) was heated under reflux in methanol (10 ml) for 4 h. The solution was concentrated under reduced pressure, dissolved in small volume of chloroform, and then separated into its components by preparative t.l.c. A blue-white fluorescent band at R_F 0.3 (30% ethyl acetate in toluene) was removed from the plate and the product was eluted from the silica with chloroform. The solvent was removed under reduced pressure to give a pale yellow solid which was recrystallised from diethyl ether to give the pure chromen trimethyl ether, as pale yellow prisms (32 mg); m.p. 192—193 °C (lit.,[1] m.p. 192—193 °C); $\lambda_{max.}$ ($\varepsilon \times 10^{-3}$) 242.5, (34.1), 260 (31.5), 314 (24.8), and 366 nm (6.7); $\nu_{max.}$ 1 642, 1 614, 1 590, 1 580, 1 285, 1 270, 1 208, 1 162, 1 142, 1 128, 1 105, 1 060, 910, 820, 813, 768, and 721 cm^{-1}; for $\tau(CDCl_3)$ see Table.

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