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SYNTHESIS OF OSAJAXANTHONE

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Abstract—Prenylation of 1,3-dihydroxy-7-methoxyxanthone (**1**) with prenyl bromide and methanolic methoxide yielded a mixture of 2-*C*-prenyl derivative (**4a**), 2,4-di-*C*-prenyl derivative (**2**) and 3-*O*-prenyl derivative (**3**). 2-*C*-Prenyl derivative (**4a**) with HI gave a mixture of dihydro-osajaxanthone (**8**) and its angular isomer (**9**). The acetate of the former with excess of NBS gave a dibromo derivative which on dehydrobromination with pyridine and deacetylation with alcoholic potash formed 4'-bromo-osajaxanthone (**11**) in good yield. Refluxing with zinc and glacial acetic acid afforded osajaxanthone (**13**) identical with a natural sample.

OSAJAXANTHONE was first isolated along with two other xanthones from the root bark of Osage orange (*Maclura pomifera*; Family Moraceae)[1] and was shown to be 6',6'-dimethyl-1,7-dihydroxypyrano-(2',3',3,2) xanthone (**13**) by Wolfrom *et al.*[2] More recently, it has been found to be present also in two *Guttiferae species*, (i) Brazilian *Kielmeyera corymbosa*, by Gottlieb *et al.*[3] and (ii) Malaysian heartwood of *Calophyllum scriblitifolium* by Jackson *et al.*[4] It is possible that such a system biogenetically involves the initial formation of 1,3,7-trihydroxyxanthone followed by successive stages of prenylation in the 2-position, cyclization and dehydrogenation. Following this path, a synthesis of osajaxanthone has now been accomplished.

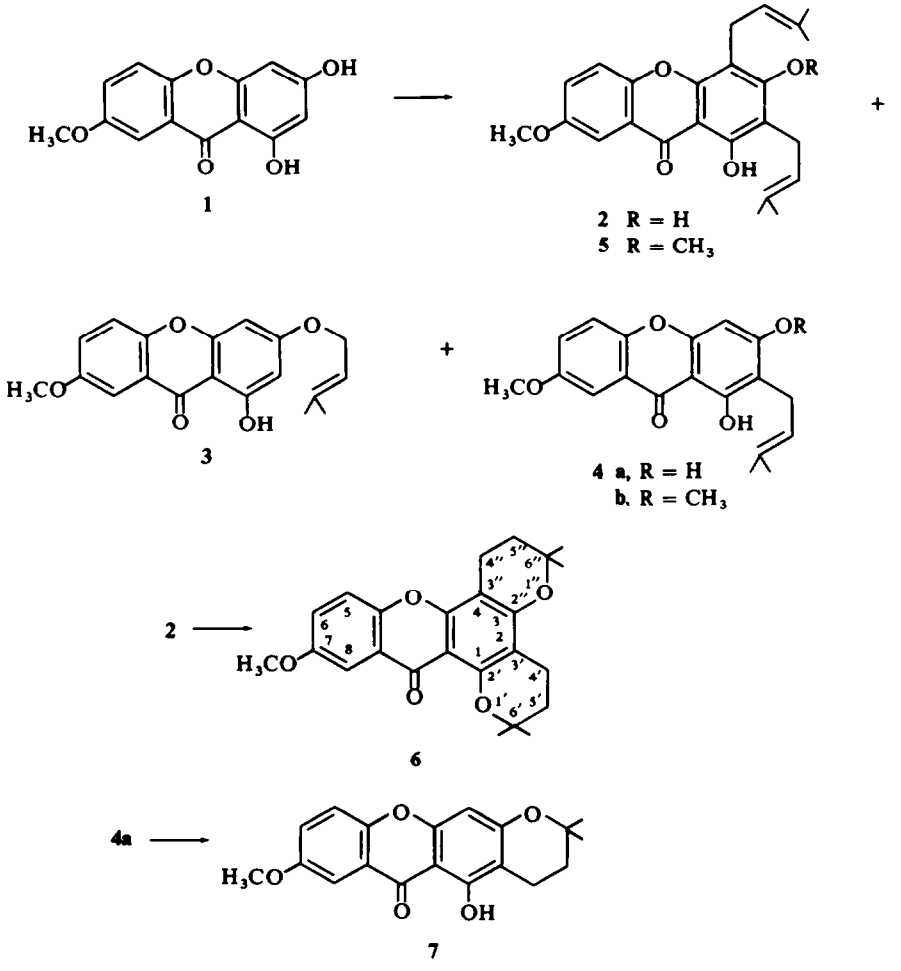
Nuclear prenylation is a facile process and occurs even with monohydric phenols and resorcinol system is not as much necessary as for *C*-methylation.[5a] Earlier monohydric phenols were *C*-prenylated by heating the sodium salt of a phenol with prenyl bromide in anhydrous aprotic solvents.[5b] More recently, this method has been used for the synthesis of 8-formyl-5,7-dimethoxy-2,2-dimethyl chroman from 2-hydroxy-4,6-dimethoxy benzaldehyde in this laboratory.[5c] A modification of the above method has recently been used in xanthones. Thus 1-hydroxy-3,5,6-trimethoxyxanthone when reacted with prenyl bromide in dioxan at room temperature in the presence of silver oxide as electrophilic catalyst, yielded as the main product 2-*C*-prenyl derivative and 1-prenyl ether and 2,4-di-*C*-prenyl derivative as the minor ones.[6] Obviously prenyl carbonium ion $Me_2C{=}CH{-}CH_2^{\oplus}$ being resonance stabilised is more readily formed and brings about facile electrophilic substitution. More recently it has been observed by Locksley *et al.*[7] that 1-prenyloxy-3,7-dimethoxy xanthone even during column chromatography over silica gel gave 2-*C*- and 4-*C*-prenyl and 2,4-di-*C*-prenyl-1-hydroxy-3,7-dimethoxyxanthones. Even silica gel seems to have promoted heterolytic fission of the parent ether giving prenyl ion which then attacked the free nuclear positions 2 and 4 of the xanthone ring. Though these reactions are facile, the yields are not good from a preparative point of view. We considered *C*-prenylation as analogous to *C*-alkylation and chose 1,3-dihydroxy-7-methoxyxanthone (**1**) for bringing about *C*-prenylation under the same conditions as *C*-

TABLE 1. NMR SPECTRA OF XANTHONES IN $CDCl_3$ WITH TETRAMETHYLSILANE AS INTERNAL REFERENCE STANDARD USING VARIAN A-60 SPECTROMETER (VALUES REPRESENT δ VALUES IN PPM)

Xanthones	H-2	H-4	H-5 H-6	H-8	—O—CH₃	—O—CO—CH₃	—CH=	—CH₂—	=C(CH₃)₂
1. 2,4-Di-*C*-prenyl-1,3-dihydroxy-7-methoxy (2)	—	—	7·22–7·30 (m) (2H)	7·48 m (1H)	3·84 (s) (3H)	—	5·30 (m) (2H)	3·45 (d) (4H)	1·85 (s) 1·75 (s) (12H)	—
2. 2,4-Di-*C*-prenyl-3,7-dimethoxy-1-hydroxy (5)	—	—	7·26–7·33 (m) (2H)	7·63 (m) (1H)	3·82 (s) 3·89 (s) (6H)	—	5·25 (m) (2H)	3·45 (m) (4H)	1·84 (d) 1·70 (s) (12H)	—
3. 1-Hydroxy-3-prenyloxy-7-methoxy (3)	6·40 (s) (1H)	6·35 (s) (1H)	7·22–7·30 (m) (2H)	7·60 (m) (1H)	3·90 (s) (3H)	—	—	4·60 (d) (2H)	1·80 (s) (6H)	—
4. 2-*C*-prenyl-3,7-dimethoxy-1-hydroxy (4b)	—	6·30 (s) (1H)	7·22–7·25 (m) (2H)	7·52 (m) (1H)	3·85 (s) (3H)	—	5·23 (m) (1H)	3·32 (d) (2H)	1·73 (d) (6H)	—
5. Diacetyl-dihydro-osajaxanthone (10)	—	6·72 (s) (1H)	7·33–7·37 (m) (2H)	7·90 (t) (1H)	—	2·46 (s) 2·26 (s) (6H)	—	2·70 (t) (2H) 1·82 (t) (2H)	—	1·37 (s) (6H)
6. Diacetyl dihydro-iso-osajaxanthone	—	6·72 (s) (1H)	7·33–7·37 (m) (2H)	7·93 (t) (1H)	—	2·31 (s) 2·27 (s) (6H)	—	2·62 (t) (2H) 1·82 (t) (2H)	—	1·45 (s) (6H)
7. 1,7-Diacetoxy-6′,6′-dimethyl-4′-bromo-pyrano (2′,3′,2,3) (11)	—	6·81 (s) (1H)	7·34–7·40 (m) (2H)	7·90 (t) (1H)	—	2·52 (s) 2·30 (s) (6H)	6·21 (s) (1H)	—	—	1·47 (s) (6H)

s = singlet, d = doublet, t = triplet, m = multiplet.

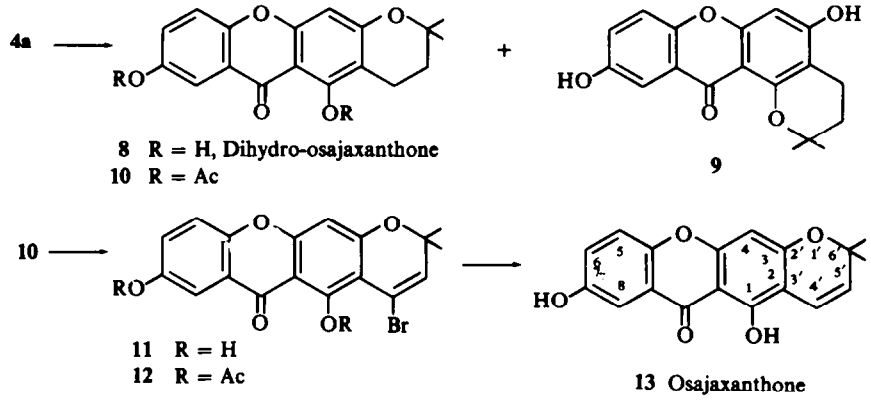
methylation,[8] and *C*-allylation.[8a] *C*-Prenylation with prenyl bromide in the presence of methanolic sodium methoxide gave a mixture of compounds which could be separated by column chromatography over silica gel. The first fraction gave a crystalline compound in about 30% yield which proved to be 2,4-di-*C*-prenyl-1,3-dihydroxy-7-methoxyxanthone (**2**). For it gave positive ferric reaction, its elemental analysis showed introduction of two prenyl units and NMR spectrum (see Table 1) had only resonance signals of H-5, H-6 and H-8 and no other aromatic proton and further the signals of prenyl protons integrated for two prenyl units. The diprenylated compound **2** on partial methylation gave the corresponding 3-methyl ether (**5**)∫ its NMR spectrum agrees with the assigned structure. Cyclization of **2** with formic acid yielded a dichroman derivative **6**.



The second fraction was only a small amount (4–5%) and it was identified as 1-hydroxy-3-prenyloxy-7-methoxyxanthone (**3**). The NMR showed all the aromatic and prenyloxy protons. The formation of prenyl ether only in small amounts indicates the instability of such compounds as was noticed even earlier.[7]

The third fraction on crystallization afforded in 20% yield a compound identified as 2-*C*-prenyl-1,3-dihydroxy-7-methoxyxanthone (4a) by its NMR spectrum and by its partial methyl ether[7] (**4b**). Further cyclization of **4a** with formic acid gave 6',6'-dimethyl-1-hydroxy-7-methoxy-4',5'-dihydropyrano (2',3',3,2) xanthone (**7**) which agrees in m.p. and spectral data with dihydro-osajaxanthone monomethyl ether prepared earlier from the natural sample of osajaxanthone as well as by synthesis[2] involving condensation of 2,2-dimethyl-5,7-dihydroxy-chroman with 2-hydroxy-5-methoxybenzoic acid in the presence of $POCl_3$ and $ZnCl_2$.

For the synthesis of osajaxanthone, the above 2-prenylated compound (**4a**) was cyclized under demethylative conditions. When hydriodic acid was used at 120°, two isomeric dihydropyran derivatives one linear (**8**) and the other angular (**9**) were formed. They were separated by column chromatography; the linear one was eluted first and constituted the major fraction (70%) and was found identical with dihydro-osajaxanthone obtained from the natural compound in its m.p., m.p. of acetate and spectral data. The minor product was the angular isomer (**9**) eluted later, and this was supported by absence of ferric reaction and by its NMR spectrum.



Attempted dehydrogenation either of dihydroosajaxanthone (**8**) or its acetate (**10**) with DDQ which is recently reported to be very efficient for making chromenes[9] has not been successful. Next dehydrogenation of di-*O*-acetyl derivative was carried out by refluxing with *N*-bromosuccinimide in CCl_4 medium in the presence of benzoyl peroxide followed by dehydrobromination with pyridine and deacetylation with alcoholic potash as was successfully claimed for the synthesis of jacareubin from its dihydro derivative.[6] Although the product melted very close to the m.p. of natural osajaxanthone (**13**), the mixed m.p. with the natural sample kindly supplied by Professor Gottlieb was depressed and the diacetate differed from di-*O*-acetyl osajaxanthone. On elemental analysis, these were found to possess a bromine atom. The NMR spectrum of the diacetate showed a resonance signal of only one olefinic proton at δ 6·21 ppm. Obviously two bromine atoms had entered the dihydropyran ring at the benzylic carbon atom when refluxed with NBS, and the product on successive dehydrobromination and deacetylation afforded 4'-bromo-osajaxanthone (**11**). In the experiment when two mole equivalents of NBS were used, the 4'-bromo-osajaxanthone (**11**) was obtained as the sole product. But when exactly one mole of the

reagent was employed, the product was a mixture of this bromo compound and dihydro-osajaxanthone (**8**). It appears, therefore, that there is a tendency for gem-dibromination in the reaction with NBS. The debromination of **11** with zinc dust and acetic acid yielded osajaxanthone which was found identical with the natural sample in TLC, m.m.p. and IR spectrum.

EXPERIMENTAL

All m.ps are uncorrected. Unless otherwise stated, UV spectra were taken in methanol solution and IR spectra in KBr disc. The figures in brackets in UV spectra represent log ε values. Light petroleum had boiling range 60–80°, silica gel was used for column chromatography and TLC was carried out on silica gel G chromoplates using solvent systems (A) Benzene–light petroleum, 80:20; (B) chloroform; (C) chloroform–methanol, 95:5: (D) chloroform–methanol, 98:2; R_f values are those taken on TLC.

Nuclear prenylation of 1,3-*dihydroxy*-7-*methoxyxanthone* (1)

To a solution of 1,3-dihydroxy-7-methoxyxanthone[10] (10 g) in anhydrous methanol (500 ml) was added methanolic solution of sodium methoxide (15 g Na/150 ml MeOH). The mixture was cooled, treated with prenyl bromide (20 ml) in one lot and refluxed for 3 hr. After removal of the solvent, the reaction mixture was treated with water and acidified with HCl. The solid was collected and examined on TLC using solvent B which showed the presence of number of compounds. It was, therefore, subjected to column chromatography and the column was eluted successively with (i) benzene–light petroleum, 30:70 (ii) benzene–light petroleum, 50:50 (iii) benzene–light petroleum, 60:40 and (iv) benzene alone, giving the following three main fractions.

Fraction A: It was crystallized from benzene when 2,4-di-*C*-prenyl-1,3-dihydroxy-7-methoxyxanthone (**2**) was obtained as pale yellow needles (3 g), m.p. 152–153°; green ferric reaction; R_f 0·85 (solvent A); ν_{max} 1650 cm^{-1} (xanthone —C═O); λ_{max} 235, 269, 317, 380 nm (4·49, 4·49, 4·13, 3·66 resp.) (Found: C, 73·3; H, 6·6. $C_{24}H_{26}O_5$ requires C, 73·1; H, 6·6%).

Fraction B was crystallized from benzene–light petroleum mixture when 1-hydroxy-3-prenyloxy-7-methoxyxanthone (**3**) was obtained as light yellow needles (0·4 g), m.p. 180–182°; green ferric reaction; R_f 0·80 (solvent A); ν_{max} 1655 cm^{-1} (xanthone —C═O); λ_{max} 235, 260, 309, 370 nm (4·00, 4·18, 3·75, 3·33 resp.). Mixed m.p. with an authentic sample described later was undepressed.

Fraction C crystallized from chloroform–methanol mixture yielding 2-*C*-prenyl-1,3-dihydroxy-7-methoxyxanthone (**4a**) as light yellow needles (2 g), m.p. 225–227°; R_f 0·5 (solvent B); ν_{max} 1645 cm^{-1} (xanthone —C═O); λ_{max} 238, 262, 314, 370 nm (4·39, 4·36, 4·06, 3·65 respectively). (Found: C, 69·5; H, 6·0. $C_{19}H_{16}O_5$ requires: C, 69·9; H, 5·6%).

2,4-*Di*-*C*-*prenyl*-3,7-*dimethoxy*-1-*hydroxyxanthone* (**5**). 2,4-Di-*C*-prenyl-1,3-dihydroxy-7-methoxyxanthone (**2**) (200 mg) was partially *O*-methylated with one mole of dimethyl sulphate (0·06 ml) by the potassium carbonate acetone method when 2,4-di-*C*-prenyl-3,7-dimethoxy-1-hydroxyxanthone (**5**) was obtained. It crystallized from benzene as light yellow needles (200 mg), m.p. 112–114° (Lit.[7] m.p. 91°); green ferric reaction; ν_{max} 1650 cm^{-1} (xanthone —C═O); λ_{max} 238, 269, 301, 386 nm (4·49, 4·58, 4·02, 3·68 respectively). (Found: C, 73·6; H, 7·2; $C_{25}H_{28}O_5$ requires: C, 73·5; H, 6·9%).

7-*Methoxy*-6′,6′-*dimethyl*-5′,6′-*dihydropyrano* (2′,3′,1,2)-6″,6″- *dimethyl*-5″,6″-*dihydropyrano* (2″,3″,3,4) xanthone (**6**). The 2,4-di-*C*-prenyl derivative (**2**) (200 mg) was heated on a steam bath with formic acid (20 ml) for 2 hr. The solution was poured over ice and the solid collected. It was chromatographed and the fraction which was eluted with benzene–ethyl acetate (95:5) crystallized from methanol yielding dichroman derivative (**6**) as colourless needles (100 mg), m.p. 226–227°; no ferric reaction; ν_{max} 1660 cm^{-1} (xanthone —C═O); λ_{max} 230, 265, 313, 367 nm (4·44, 4·53, 4·19, 3·83 respectively). (Found: C, 73·3; H, 6·8. $C_{24}H_{26}O_5$ requires: C, 73·1; H, 6·6%).

1-*Hydroxy*-3-*prenyloxy*-7-*methoxyxanthone* (**3**). To an acetone solution of 1,3-dihydroxy-7-methoxyxanthone (**1**) (250 mg) was added prenyl bromide (0·2 ml) and potassium carbonate (1 g) and the mixture refluxed for 4 hr. Acetone was removed and water added. The solid crystallized from benzene–light petroleum mixture as light yellow needles (250 mg), m.p. 182–183°; green ferric reaction (Found: C, 69·7; H, 5·6. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·6%).

2-*C*-*Prenyl*-3,7-*dimethoxy*-1-*hydroxyxanthone* (**4b**). 2-*C*-Prenyl-1,3-dihydroxy-7-methoxyxanthone (**4a**, 300 mg) was partially methylated with one mole of dimethyl sulphate (0·1 ml) by the potassium carbonate acetone method when 2-*C*-prenyl-3,7-dimethoxy-1-hydroxyxanthone (**4b**) was obtained. It crystallized from methanol as light yellow needles (300 mg), m.p. 145° (Lit.[7] 140–145°); green ferric reaction; ν_{max}

1660 cm^{-1} (xanthone —C=O); λ_{max} 235, 264, 305, 372 nm. (4·47, 4·51, 4·16, 3·74 respectively). (Found: C, 70·8; H, 6·4. $C_{20}H_{20}O_5$ requires: C, 70·5; H, 5·9%).

Dihydroosajaxanthone monomethyl ether (7). 2-*C*-Prenyl-1,3-dihydroxy-7-methoxyxanthone (**4a**, 200 mg) was heated on steam bath for one hour with formic acid (10 ml). The product was chromatographed and the fraction which eluted with chloroform was crystallized from methanol when dihydroosajaxanthone monomethyl ether (7) was obtained as light yellow needles (150 mg), m.p. 172–173° (Lit.[2] 173–174°); green ferric reaction; ν_{max} 1650 cm^{-1} (xanthone —C=O); λ_{max} 235, 262, 316, 377 nm (4.50, 4·53, 4·21, 3·79 respectively. (Found: C, 70·4; H, 5·9. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·6%).

Dihydroosajaxanthone (**8**) *and dihydro-iso-osajaxanthone* (**9**). 2-*C*-Prenyl-1,3-dihydroxy-7-methoxyxanthone ( ) (1·6 g), hydriodic acid (iodine free, 55%, 40 ml) and acetic acid (40 ml) were heated at 120° for 3 hr. The product was poured over ice and sodium hydrogen sulphite. The solid was collected and examined on TLC using solvent C which showed the presence of two compounds having R_{f1} 0·9 and R_{f2} 0·5. The mixture was therefore subjected to column chromatography. The fraction eluted with chloroform–methanol (99:1) was crystallized from chloroform–methanol mixture when dihydro-osajaxanthone (**8**) was obtained as light yellow needles (1·1 g), m.p. 299° (d) (Lit.[2] 298–300°); green ferric reaction; R_f 0·9 (solvent C); ν_{max} 1650 cm^{-1} (xanthone —C=O); λ_{max} 234, 262, 317, 381 nm (4·34, 4·39, 4·08, 3·64 respectively) (Found: C, 69·2; H, 5·4. $C_{18}H_{16}O_5$ requires: C, 69·2; H, 5·2%). The acetate prepared by the acetic anhydride sodium acetate method crystallized from methanol yielding diacetyl dihydroosajaxanthone (**10**) as colourless needles, m.p. 200°; R_f 0·6 (solvent B); ν_{max} 1755 (ester —C=O), 1660 cm^{-1} (xanthone —C=O). (Found: C, 67·0; H, 5·6. $C_{22}H_{20}O_7$ requires: C, 66·7; H, 5·1%).

The second fraction eluted with chloroform–methanol (95:5) was crystallized from chloroform–methanol mixture yielding dihydro iso-osajaxanthone (**9**) as light yellow needles (0·3 g), m.p. 309°; negative ferric reaction; R_f 0·5 (solvent C); ν_{max} 1615 cm^{-1} (xanthone —C=O); λ_{max} 239, 259, 310, 369 nm (4·41; 4·46, 4·11, 3·80 respectively). (Found: C, 68·7; H, 4·9. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). The diacetate prepared by the acetic anhydride–sodium acetate method crystallized from methanol as colourless needles m.p. 216°; R_f 0·5 (solvent B); ν_{max} 1755 (ester —C=O), 1660 cm^{-1} (xanthone —C=O) (Found: C, 67·0; H, 5·3. $C_{22}H_{20}O_7$ requires: C, 66·7; H, 5·1%).

4′-*Bromo-osajaxanthone* (**11**). Di-*O*-acetyl dihydro-osajaxanthone (**10**) (400 mg), *N*-bromo succinimide (400 mg), potassium carbonate (100 mg) and a few crystals of benzoyl peroxide in carbon tetrachloride (100 ml) were heated under reflux for 8 hr and succinimide that separated was filtered off and the solvent removed. The colourless residue was dissolved in pyridine and heated on a boiling water bath for 1 hr under nitrogen. The pyridine was removed under reduced pressure and the brown oily residue was heated with N-ethanolic potassium hydroxide (20 ml) for 1 hr. Ethanol was removed and water added. The solution was acidified with hydrochloric acid and the yellow solid thus obtained was subjected to column chromatography and the fractions eluted with benzene crystallized from methanol yielding 4′-bromo-osajaxanthone (11) as pale yellow needles (150 mg), m.p. 245–247° (d); green ferric reaction; R_f 0·5 (solvent D); ν_{max} 1650 cm^{-1} (xanthone —C=O); λ_{max} 230, 289, 381 nm (4·14, 4·58, 3·59 respectively). (Found: C, 55·9; H, 3·6. $C_{18}H_{13}O_5Br$ requires: C, 55·5; H, 3·3%).

The acetate prepared by the acetic anhydride–pyridine method crystallized from methanol as colourless needles, m.p. 190°; negative ferric reaction. (Found: C, 55·3; H, 3·6; $C_{22}H_{17}O_7Br$ requires C, 55·8; H, 3·6%).

Osajaxanthone (**13**). To a magnetically stirred solution of 4′-bromo osajaxanthone (**11**, 50 mg) in glacial acetic acid (15 ml) was added zinc dust (200 mg) and the mixture refluxed for 4 hr. The mixture was filtered and the filtrate poured into water (100 ml). The solid thus obtained crystallized from methanol yielding osajaxanthone (**13**) as light yellow needles (30 mg), m.p. 248–250°; green ferric reaction; R_f 0·48 (solvent D); ν_{max} 1655 cm^{-1} (xanthone —C=O); λ_{max} 235, 285, 339, 380 nm (4·28, 4·61, 3·87, 3·68 respectively). (Found: C, 69·5; H, 4·8. $C_{18}H_{14}O_5$ requires: C, 69·7; H, 4·5%). Mixed melting point with the natural sample was undepressed and its IR spectrum was superimposable.

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