Extractives from Guttiferae. Part XXVIII.† Structure and Synthesis of New Biphenyls from *Pentaphalangium Solomonse* Warb

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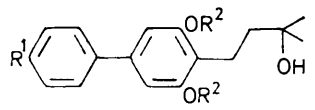
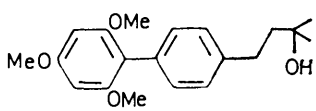
Two new natural biphenyls in *Pentaphalangium solomonse* Warb., isolated as their methyl ethers, have been identified as 3,4',5-trihydroxy- (1c) and 3,5-dihydroxy-4-(3-hydroxy-3-methylbutyl)biphenyl (1d). A synthesis of 4-(3-hydroxy-3-methylbutyl)-3,4',5-trimethoxybiphenyl is described.

We have previously reported [1] the isolation of six xanthones and a 3,8-linked biflavanone, GB-1a, from the heartwood of *Pentaphalangium solomonse* Warb. Spectral and synthetic evidence is now presented to show that the methyl ethers of two new biphenyl metabolites present in this species have structures (1a) and (1b).

Extraction of the heartwood with hot chloroform gave a mixture from which a xanthone fraction, shown by n.m.r. spectroscopy to be devoid of methoxy-groups, was methylated to facilitate separation and identification of the metabolites. In addition to the xanthones,[1] two biphenyls (as their methyl ethers) were isolated. The first (1a) gave a molecular ion at *m/e* 330 ($C_{20}H_{26}O_4$). Spectral data show that the eight double bond equivalents are accounted for by the presence of two aromatic rings. Thus the i.r. spectrum has aromatic absorptions at 1610 and 1500 cm^{-1}, and the n.m.r. spectrum shows six aromatic protons, four of which resonate as an AA'BB' system, centred at τ 2·62 (J 9 Hz) and 3·17 (J 9 Hz). The other two aromatic protons appear as a singlet at τ 3·44, and this suggests that four protons are in one aromatic system and two in another. Nine protons are accounted for in three methoxy-groups which resonate at τ 6·24 (6H) and 6·27 (3H) and the rest are assigned to a 3-hydroxy-3-methylbutyl side chain (Table 1). The signal at τ 8·32 (3H, complex) for the methylene and hydroxy-protons, was transformed, on warming the solution, to a 2H multiplet owing to the



(1) a; R^1=OMe, R^2=Me
b; R^1=H, R^2=Me
c; R^1=OH, R^2=H
d; R^1=R^2=H



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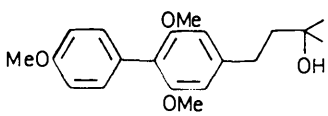


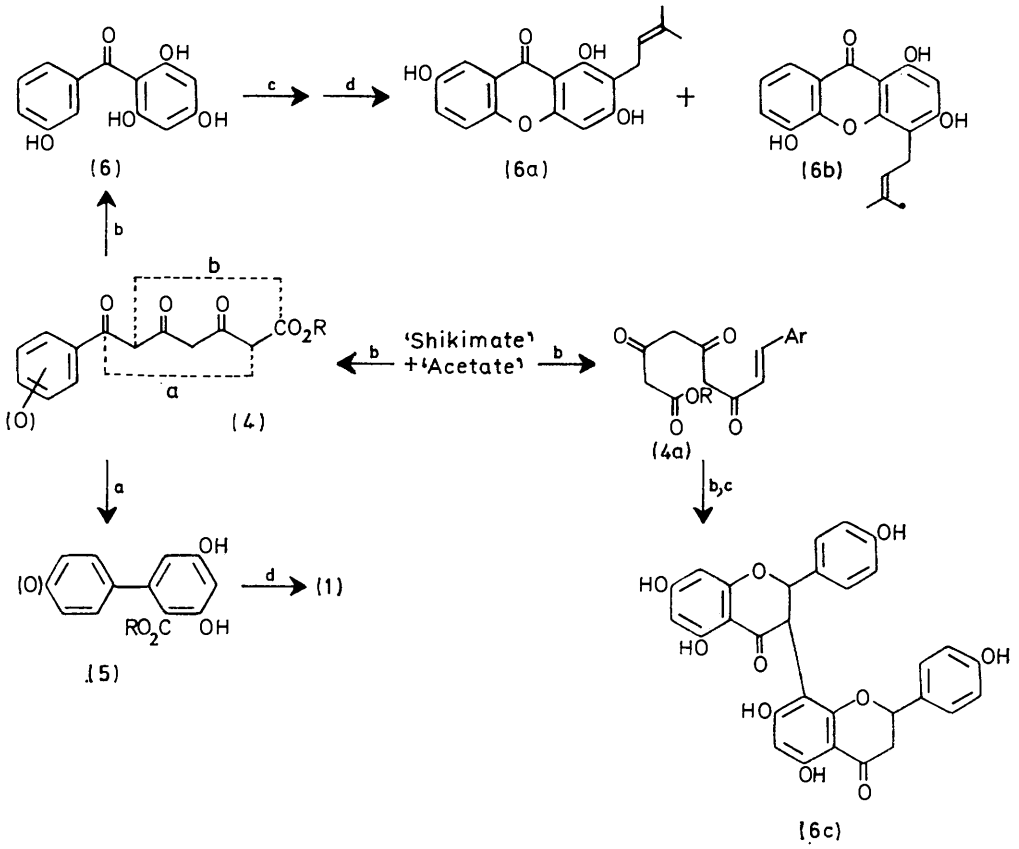
(3)

displacement of the hydroxy-signal. The presence of a hydroxy-group was also confirmed by i.r. bands at 3585 and 3520 cm^{-1}. The n.m.r. spectrum after addition of C_6D_6 to the solution showed that all the methoxy-signals are shifted up-field, indicating that each methoxy-group has at least one unsubstituted *ortho*-position. The u.v. spectrum shows an absorption at

† Part XXVII, S. Bhanu and F. Scheinmann, *Phytochemistry*, in the press.

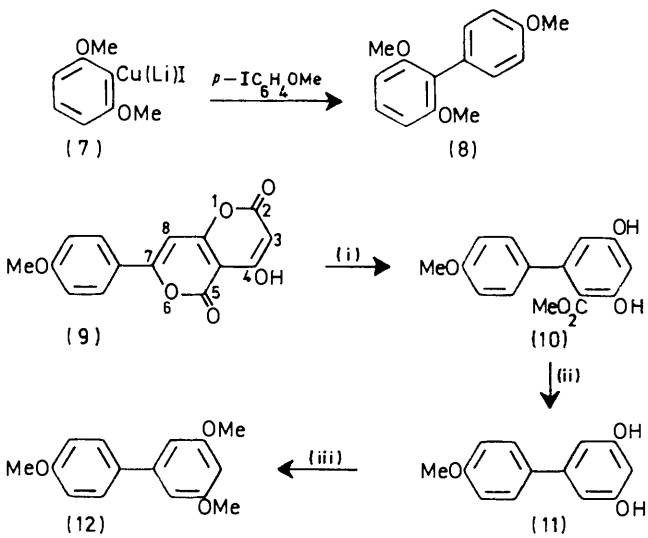
[1] (*a*) P. J. Owen and F. Scheinmann, *J.C.S. Perkin I*, 1974, 1018; (*b*) P. J. Owen, Ph.D. Thesis, University of Salford, 1972.

268 nm (log ε 4·4) suggesting a biphenyl with auxochromic groups [*cf.* biphenyl 248 nm (log ε 4·2)].[2] Although the other spectral data lead to three possible structures (1a), (2), and (3) for the biphenyl, the u.v. data (Table 2) favour structure (1a) since biphenyls with substituents *ortho* to the biphenyl link [as in (2) and (3)] show marked reductions in their extinction coefficients. Further, a biogenetic argument supports (1a), as the metabolite can be considered to be derived from a phenacylpolyacetate (4) (Scheme). An aldol condensation (route a) will lead to a biphenyl (5) similar to the natural derivatives (1), and a Claisen condensation (route b) will result in a benzophenone (6) [3] which may lead to the xanthones reported previously.[1]



Possible biogenetic relationship of the phenols in *P. solomonse* Warb. a, aldol-type cyclisation; b, Claisen condensation; c, oxidative coupling; d, isoprenylation

In order to establish the substitution pattern of the natural biphenyl, 2,4',6- and 3,4',5-trimethoxybiphenyls were synthesised for spectral comparison. 2,4',6-Tri-methoxybiphenyl (8) has been prepared by Ehrhart,[4] but we used a newer synthetic coupling method involving a lithium-cuprate complex.[5] 1,3-Dimethoxybenzene reacts readily with butyl-lithium to give the 2-lithio-derivative [6] which when treated with copper(I) iodide in pyridine gave the lithium-cuprate complex (7).



Reagents: (i) M-KOH–MeOH; (ii) 32% NaOH, 70°; (iii) Me_2SO_4–K_2CO_3–Me_2CO

[2] A. E. Gillam and E. S. Stern, in 'Introduction to Electronic Absorption Spectroscopy in Organic Chemistry,' 3rd edn., eds. E. S. Stern and C. J. Timmons, E. Arnold Ltd., London, 1970, p. 124; A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon Press, Oxford, 1964, p. 129.

[3] J. L. Douglas and T. Money, *Canad. J. Chem.*, 1967, **45**, 1990.

[4] G. Ehrhart, *Chem. Ber.*, 1963, **96**, 2042.

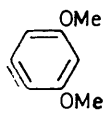
[5] M. Nilsson and C. Ullenius, *Acta Chem. Scand.*, 1971, **25**, 2428; 1970, **24**, 2377; C. Ullenius, *ibid.*, 1972, **26**, 3383.

[6] (*a*) D. A. Shirley, J. R. Johnson, and J. P. Hendrix, *J. Organometallic Chem.*, 1968, **11**, 209; (*b*) K.-H. Boltze, H.-D. Dell, and H. Jansen, *Annalen*, 1967, **709**, 63.

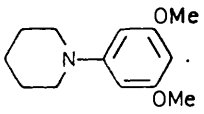
Reaction with *p*-iodoanisole then gave the biphenyl (8) in good yield. The u.v. spectrum [$\lambda_{max.}$ 252 nm (log ε 4·0)] differs appreciably from that of the natural product derivative (1a). The chemical shifts of the aromatic protons in (1a) and (8) also differ, and as expected, since the two benzene rings are not coplanar in structure (8), the 2- and 6-methoxy-signals are shielded by the other ring and appear at higher field (τ 6·38) (Table 1). These facts support the u.v. data in suggesting that the natural product does not have the 2,4',6-oxygenation pattern.

Two routes were considered for the synthesis of 3,4',5-trimethoxybiphenyl. One used a direct coupling method involving a benzyne intermediate and the other, in part, followed a possible biogenetic route. The biogenetic-type synthesis used a masked polyketide in the form of a pyranopyrandione (9).[3] The *p*-methoxyphenylpyranopyrandione (9) was prepared by treating *p*-methoxyacetophenone with diethyl malonate or bis-2,4-dichlorophenyl malonate using the methods previously reported for phenylpyranopyrandiones.[7] On reaction with methanolic potassium hydroxide, the dione (9) formed the biphenylcarboxylate (10). This was hydrolysed and decarboxylated with concentrated sodium hydroxide solution to give the dihydric phenol (11). Subsequent methylation gave 3,4',5-trimethoxybiphenyl (12). The u.v. spectrum [$\lambda_{max.}$ 264 nm (log ε 4·3)] resembles that of the natural product derivative (1a) and therefore clearly shows the 3,4',5-oxygenation pattern of the biphenyl metabolite. Thus all the experimental data support structure (1c) for the new biphenyl metabolite.

Attempts to synthesise the biphenyl (12) from 4-chlororesorcinol dimethyl ether and *p*-lithioanisole



(13)

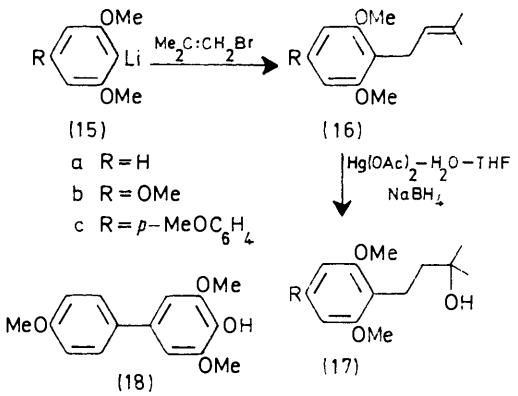


(14)

failed to give the benzyne intermediate (13), and anisole and 4,4'-dimethoxybiphenyl were the main products. The weak metallating agent *p*-lithioanisole [8] was augmented by the stronger base lithium piperidide [9] which gave the benzyne (13) but only 1,3-dimethoxy-5-piperidinobenzene was isolated, together with a small amount of 1,3-dimethoxy-4-piperidinobenzene. Thus it appears that the rate of addition of *p*-lithioanisole to the benzyne is not competitive with that of lithium piperidide or piperidine, and this route to 3,4',5-trimethoxybiphenyl (12) was abandoned.

The synthesis of (1a) was completed by first developing a method for introduction of the 3-hydroxy-3-methylbutyl group [(15) ⟶ (17)] by using 1,3-dimethoxy- and 1,3,5-trimethoxy-benzene as model compounds since the key intermediate (12) was available only in small amounts.

A methylbut-2-enyl group was introduced by allylating the lithio-derivatives (15a) and (15b) with 3-methylbut-2-enyl bromide to give the allylbenzenes (16a) and (16b).[10] Hydration of the double bond was readily achieved by using mercury(II) acetate in aqueous tetrahydrofuran followed by reduction of the complex with sodium borohydride [11] to give the 3-hydroxy-3-methylbutyl derivatives (17a) and (17b). By allylating the lithio-derivative of 3,4',5-trimethoxybiphenyl under similar conditions, in addition to the expected biphenyl (16c) a small amount of a second product (18) was isolated. A molecular ion at *m/e* 260, an increase of



16 a.m.u., suggested that an extra oxygen atom had been introduced into the biphenyl (12) to give the by-product (18). The n.m.r. spectrum (Table 1) confirmed the absence of the 3-methylbut-2-enyl side-chain and showed the AA'BB' system for protons at C-2', C-3', C-5', and C-6', and a singlet for the two protons at C-2 and C-6. This allows for introduction of oxygen only at C-4, consistent with the structure 4-hydroxy-3,4',5-trimethoxybiphenyl (18). Hydration of the biphenyl (16c) with aqueous mercury(II) acetate and sodium borohydride gave the biphenyl (17c) identical with the metabolite methyl ether (1a).

In an attempt to obtain more of the natural product derivative (1a) [1] from *P. solomonse* Warb. a mixture of two biphenyls (1a and b) was isolated. Preparative t.l.c. gave the second biphenyl (1b), having a molecular ion at *m/e* 300 ($C_{19}H_{24}O_3$). The u.v. spectrum with a single absorption maximum at 264 nm (log ε 4·3) again suggests a biphenyl metabolite. The similarity of the n.m.r. spectra of (1a) and (1b) shows that the new metabolite (1b) has the 3-hydroxy-3-methylbutyl side chain at C-4, two aromatic protons at C-2 and C-6, and two methoxy-groups at C-3 and C-5 (Table 1). However the biphenyls differ in the aromatic region since (1b) has a multiplet (5H) at τ 2·66, due to a monosubstituted aromatic ring. The chemical shifts of the methoxy and aromatic protons of (1b) are in good agreement with the

[7] (*a*) E. Ziegler and H. Junek, *Monatsh.*, 1958, **89**, 323; (*b*) C. Goetschel and C. Mentzer, *Bull. Soc. chim. France*, 1962, 365.
[8] R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes,' Academic Press, New York and London, 1967, p 10.
[9] Ref. 8, pp. 130—134.
[10] K.-H. Boltze and H.-D. Dell, *Angew. Chem. Internat. Edn.*, 1966, **5**, 415.
[11] N. Wakabayashi, *J. Medicin. Chem.*, 1969, **12**, 191.

TABLE 1

N.m.r. data of biphenyls and model compounds (τ values; integration and *J* in Hz given in parentheses)

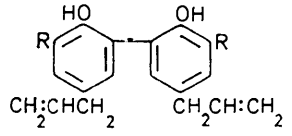
	Aromatic protons							Side-chain protons				
Compound	H-2', H-3', H-4', H-5'	H-2	H-3	H-4	H-5	H-6	Others	MeO	Me_2C	-CH=	$ArCH_2$	$-CH_2C(OH)<$	Other protons
(1a) [a]	2·62, 3·17 (4H, 9)	3·44 (1H)				3·44 (1H)		6·24, 6·27 (9H)	8·79 (6H)		7·32 (2H, 7)	8·32 (3H, 7)	
(17c) [b] [≡(1a)]	2·54, 3·09 (4H, 9)	3·35 (1H)				3·35 (1H)		6·14, 6·18 (9H)	8·72 (6H)		7·24 (2H, 7)	8·33 (3H, 7)	
(8) [a]	2·83, 3·48 (4H, 8·5)		3·20 (1H, 9, 2·5)	2·89 (1H, 9, 2·5)	3·20 (1H, 9, 2·5)			6·28, 6·38 (9H)					
(10) [c]	2·81, 3·10 (4H, 9)	3·62 (1H, 2·5)		3·71 (1H, 2·5)				6·17 (3H)					CO_2Me 6·52 (3H)
(11) [c]	2·42, 2·96 (4H, 9)	3·35 (1H, 2·5)		3·60 (1H, 2·5)		3·35 (1H, 2·5)		6·15 (3H)					OH 1·76 (2H)
(12) [c]	2·34, 2·95 (4H, 9)	3·20 (1H, 2·5)		3·49 (1H, 2·5)		3·20 (1H, 2·5)		6·15 (9H)					
(16c) [d]	2·43, 3·00 (4H, 9)	3·24 (1H)				3·24 (1H)		6·10, 6·15 (9H)	8·19, 8·31 (6H)	4·71 (1H, 7)	6·60 (2H, 7)		
(18) [b]	2·60, 3·13 (4H, 9)	3·32 (1H)				3·32 (1H)		6·08, 6·18 (9H)					OH 4·51br (1H)
(1b) [b]		3·39 (1H)				3·39 (1H)	2·66 (5H, m)	6·14 (6H)	8·72 (6H)		7·29 (2H, 7)	8·37 (3H, 7)	
(21) [e]		3·27 (1H)				3·27 (1H)	2·60 (5H, m)	6·12 (6H)					OH 4·64 (1H)
(16a) [e]				3·55 (1H, 9)	2·88, 3·01 (1H, 9)	3·55 (1H, 9)		6·25 (6H)	8·27, 8·36 (6H)	4·81 (1H, 7)	6·69 (2H, 7)		
(16b) [f]				4·09 (1H)		4·09 (1H)		6·38, 6·42 (9H)	8·29, 8·39 (6H)	4·89 (1H, 7)	6·79 (2H, 7)		
(17a) [f]				3·67 (1H, 9)	3·00, 3·13 (1H, 9)	3·67 (1H, 9)		6·19 (6H)	8·81 (6H)		7·36 (2H, 7)	8·45 (2H, 7) 8·56 (1H)	
(17b) [b]				3·96 (1H)		3·96 (1H)		6·19 (9H)	8·77 (6H)		7·37 (2H, 7)	8·41 (2H, 7) 8·15 (1H)	

[a] $CDCl_3$ at 100 MHz (HA-100) (Me_4Si). [b] $CDCl_3$ at 60 MHz (EM360) [$(Me_3Si)_2O$ (corrected to Me_4Si)]. [c] $(CD_3)_2CO$ at 60 MHz (A-60) (Me_4Si) [d] $CDCl_3$ at 60 MHz (A-60) (Me_4Si). [e] CCl_4 at 60 MHz (A-60) (Me_4Si). [f] CCl_4 at 60 MHz (EM360) [$(Me_3Si)_2O$ (corrected to Me_4Si)].

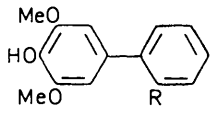
$(Me_3Si)_2O$ resonates at τ 9·93 relative to Me_4Si.

data recorded for aucuparin (21) isolated from *Sorbus aucuparia* L.[12] and *S. decora* (Sarg) Schneid[13] and *Kielmeyera* species.[14] The spectroscopic data establish the structure of the biphenyl as 4-(3-hydroxy-3-methylbutyl)-3,5-dimethoxybiphenyl (1b).

Biphenyls are rare natural products in higher plants. Those found in Magnoliales (19) and (20) are probably biosynthesised by oxidative coupling of phenolic arylpropanoids.[15] The biphenyl aucuparin (21), previously

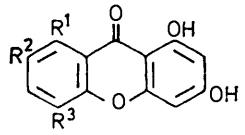


(19) R=H
(20) R=OMe

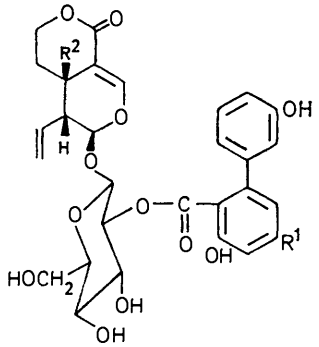


(21) R=H
(22) R=OMe

reported in Guttiferae,[14] and prior to that with methoxyaucuparin (22) in Rosaceae,[12,13] was postulated to have been formed by a 'Michael type' reaction between a phenol and 5-dehydroshikimic acid.[14] The co-occurrence of biphenyl, xanthone [*e.g.* (6a) and (6b)], and biflavanone (6c) metabolites in *P. solomonse* Warb. may have significance in suggesting an alternative mode of biphenyl biogenesis in Guttiferae (Scheme). Thus biflavanoid, xanthone, and biphenyl formation can be



(23) $R^1=R^3=H$, $R^2=OH$
(24) $R^1=R^2=OH$, $R^3=H$
(25) $R^1=R^3=OH$, $R^2=H$



(26) $R^1=OH$, $R^2=H$
(27) $R^1=R^2=OH$
(28) $R^1=R^2=H$

represented as different modes of cyclisation of acetate–shikimate derived precursors and is in accord with the

[12] H. Erdtman, G. Eriksson, and T. Norin, *Acta Chem. Scand.*, 1963, **17**, 1151.
[13] N. Narasimhachari and E. von Rudloff, *Canad. J. Chem.*, 1962, **40**, 1118.
[14] O. R. Gottlieb, *Phytochemistry*, 1968, **7**, 411.
[15] D. M. Holloway and F. Scheinmann, *Phytochemistry*, 1973, **12**, 1503; O. R. Gottlieb, *ibid.*, 1972, **11**, 1537.

suggestion that there are evolutionary similarities in the biogenesis of the phenols in Guttiferae.[16] A similar mode of biogenesis has been suggested to account for the occurrence of xanthones (23)—(25) and biphenyl-iridoids (26)—(28) in genera of the Gentianaceae family.[17] The co-occurrence of xanthones and biphenyls is in accord with the results of 'biogenetic type' synthesis reviewed by Money,[18] since it has been shown that the same masked arylpolyketide precursor can lead to either a biphenyl by an aldol condensation or a benzophenone by a Claisen reaction.[3] Although benzophenones have not been isolated from *P. solomonse* Warb. they are postulated to form the xanthones by oxidative coupling.[1,19] The biogenesis of biflavanones also probably involves a Claisen type cyclisation of a cinnamylpolyketide (4a) and oxidative dimerisation.[20] The Scheme illustrates the relationship in the formation of various phenolic metabolites and emphasises four reaction modes that are probably involved.

EXPERIMENTAL

Microanalyses were performed by Mrs. A. Bowman, Salford. U.v. spectra were measured for solutions in methanol, unless otherwise stated, with a Unicam SP 800 recording spectrophotometer, and i.r. spectra for Nujol mulls with a Perkin-Elmer 257 grating spectrophotometer; n.m.r. spectra were measured with Varian A-60, HA-100 and EM360 instruments. Mass spectra were obtained at 70 eV, with an A.E.I. MS12 (single focusing) spectrometer and accurate mass measurements were obtained with an A.E.I. MS9 (double-focusing) spectrometer. Analytical and preparative t.l.c. was carried out on silica G (Merck nach Stahl) by elution with ethyl acetate–toluene (15 : 85), and column chromatography on silica gel M.F.C. (Hopkin and Williams).

The isolation of the biphenyl (1a) was described previously.[1] For isolation of the second biphenyl (1b), the crude heartwood extract [1] was washed with hot light petroleum (b.p. 60—80°) and the oily residue methylated with dimethyl sulphate and potassium carbonate in acetone. Separation of the methylated extract by preparative t.l.c. and removal of the band corresponding to (1a) gave a mixture shown by n.m.r. to contain two biphenyl derivatives (1a and b). A second separation by t.l.c. and recrystallisation from light petroleum (b.p. 60—80°) gave a sample of the second biphenyl derivative (1b), m.p. 73°, $\lambda_{max.}$ Table 2; $\nu_{max.}$ 3300, 1595, 1575, 1415, 1230, 1160, 1120, 775, and 715 cm^{-1}; τ Table 1 (Found: M^+, 300·1736. $C_{19}H_{24}O_3$ requires M, 300·1725).

4-Hydroxy-7-p-methoxyphenylpyrano[4,3-b]*pyran-2,5-dione* (9).—(*a*) *p*-Methoxyacetophenone (15 g) and diethylmalonate (16 g) were boiled together, under nitrogen, for 18 h.[7b] The dark brown solution was diluted with ether and extracted with small portions of 10% sodium carbonate solution. The extract was acidified with concentrated hydrochloric acid and the yellow precipitate filtered, dried, and recrystallised from ethanol as a yellow amorphous powder (1·4 g, 4·9%), m.p. 226—228°. Sublimation of a portion of the solid gave the pure dione (9), m.p. 233—234°.

(*b*) *p*-Methoxyacetophenone (6·0 g) and bis-2,4-dichlorophenyl malonate (15·8 g) were heated together at 260—270° for 1 h.[7a] To the cooled reaction mixture toluene (20 ml) was added and the resulting precipitate was filtered off. Sublimation of the precipitate produced very little of the pyranopyrandione. Chromatography on silica gel of the toluene solution, and elution with toluene and then toluene–ethyl acetate (93 : 7) gave the *dione* (9) as the first yellow band eluted. Removal of the solvent gave a yellow amorphous powder (1·47 g, 13%), m.p. 235°, $\lambda_{max.}$ 268sh ($\varepsilon \times 10^{-3}$ 10·2), 281 (11·4), 320sh (8·3), and 362 nm (21·6), $\nu_{max.}$ 3350, 1740, 1695, 1570, 1535, 1285, 1220, 1200, and 1125 cm^{-1}, τ ($CDCl_3$) −0·55 (1H, s), 2·25 and 3·09 (4H, q, J 9 Hz), 3·62 (1H, s), 4·55 (1H, s), and 6·18 (3H, s) (Found: C, 63·0; H, 3·8%; M^+, 286·0485. $C_{15}H_{10}O_6$ requires C, 63·0; H, 3·5%; M, 286·0477).

TABLE 2

U.v. data for biphenyls in methanol

Compound	$\lambda_{max.}$/nm (log ε)		
(1a)	268 (4·4)		
(17c)[≡(1a)]	268 (4·5)		
(12)	264 (4·3)		
(8)	253 (4·0)	275 [a] (3·8)	
(1b)	264 (4·3)		
(21) [b]	273 (4·15)		
(10)	244 (4·2)	272 [a] (4·0)	299 [a] (3·8)
(11)	263 (4·2)		
(16c)	269 (4·4)		
(18)	272 (4·2)		

[a] Shoulder. [b] Spectrum run in 95% EtOH (ref. 12).

Methyl 3,5-Dihydroxy-4'-methoxybiphenyl-2-carboxylate (10).—A suspension of the dione (9) (3·72 g) was stirred, under nitrogen, in methanolic potassium hydroxide solution (1N; 150 ml) for 7 days. The pale brown solution was evaporated to 50 ml, acidified to pH 3 with hydrochloric acid (2M), and extracted with ethyl acetate. Removal of the solvent gave a brown oil (3·5 g) which was adsorbed onto a minimum amount of silica gel and placed on a preparative column [silica gel (150 g)]. The product (10) indicated by t.l.c. was eluted from the column with light petroleum (b.p. 60—80°)–toluene (1 : 1). Recrystallisation from benzene–cyclohexane (1 : 2) gave prisms of the *ester* (10) (1·163 g, 32·7%), m.p. 149—150°, $\lambda_{max.}$ Table 2, $\nu_{max.}$ 3360, 1660, 1625, 1590, 1435, 1330, 1260, 1250, 1215, 1180, and 835 cm^{-1}, τ Table 1 (Found: C, 65·8; H, 5·0%; M^+, 274·0853. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%; M, 274·0841).

3,5-Dihydroxy-4'-methoxybiphenyl (11).—The ester (10) (1·33 g) was dissolved in sodium hydroxide solution (25 ml; 32% w/v) and heated on a steam-bath until t.l.c. indicated the complete disappearance of starting material (5 h). The mixture was acidified with hydrochloric acid (2M) and extracted with ether. Evaporation of the dried ($MgSO_4$) extract gave a solid which on recrystallisation from benzene gave prisms of the *biphenyl* (11) (0·894 g, 85·1%), m.p. 158—159°, $\lambda_{max.}$ Table 2, $\nu_{max.}$ 3390, 1630, 1605, 1500, 1350, 1250, 1205, 1160, 1040, 830, and 825 cm^{-1}, τ Table 1

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(Found: C, 72·0; H, 5·2%; M^+, 216·0793. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%; M, 216·0786).

3,4′,5-Trimethoxybiphenyl (12).—3,5-Dihydroxy-4′-methoxybiphenyl (0·85 g) was methylated with an excess of dimethyl sulphate and potassium carbonate in acetone. The product was recrystallised from methanol to give white lustrous plates of *3,4′,5-trimethoxybiphenyl* (0·841 g, 88·5%), m.p. 61—62°, $\lambda_{max.}$ Table 2, $\nu_{max.}$ 1600, 1580, 1435, 1410, 1210, 1200, 1160, 1070, and 815 cm^{-1}, τ Table 1 (Found: C, 73·6; H, 6·6%; M^+, 244·1102. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%; M, 244·1099).

2,4′,6-Trimethoxybiphenyl (8).—1,3-Dimethoxybenzene (5·52 g, 40 mmol) was dissolved in dry ether (50 ml) and butyl-lithium (20 ml; 40 mmol) was added at −30° under dry nitrogen. The mixture was boiled for 2 h and the lithium salt soon (10 min) precipitated. Copper(I) iodide (4·76 g, 25 mmol; dried at 120° for 2 h) was suspended in ether (50 ml) and to this was added the suspension of 2-lithio-1,3-dimethoxybenzene at −30°. There was an immediate brown colouration which persisted until all the lithium salt had been added. The mixture was stirred for 1 h at −5° and maintained at this temperature for 18 h. Dry pyridine (80 ml) was added and the temperature was raised very slowly to reflux the mixture, through which dry nitrogen was passed to remove all the ether. To the boiling mixture *p*-iodoanisole (3·74 g, 16 mmol) in dry pyridine (20 ml) was added and heating was continued for 2 h. The mixture was cooled, diluted with ether (300 ml), and extracted with hydrochloric acid (2M) until the acid extract was no longer green. The ether layer was dried ($MgSO_4$) and the solvent removed under vacuum to give a dark oily residue. This was extracted with hot portions of light petroleum (b.p. 60—80°) and on cooling the biphenyl (8) precipitated as buff needles. Recrystallisation from light petroleum (b.p. 60—80°) gave 2,4′,6-trimethoxybiphenyl as white lustrous needles (3·0 g, 77%), m.p. 119° (lit.,[4] 112°), $\lambda_{max.}$ Table 2, $\nu_{max.}$ 1595, 1250, 1180, 1115, 1100, 1035, 820, 780, and 730 cm^{-1}, τ Table 1 (Found: C, 74·1; H, 6·5%; M^+, 244·1102. Calc. for $C_{15}H_{16}O_3$: C, 73·8; H, 6·6%; M, 244·1099).

Lithiation of p-*Iodoanisole.*—*p*-Iodoanisole (4·68 g) was dissolved in ether (90 ml) and butyl-lithium (10 ml; 0·002 mol ml^{-1}) was added at −70°. The mixture was examined after (*a*) stirring at −70° for 2 h, (*b*) after warming to 18° and stirring for a further 2 h, (*c*) after stirring at 18° for a further 18 h, and (*d*) after finally boiling for 24 h. In each case an aliquot portion (25 ml) was treated with carbon dioxide. Lithiation conditions (*a*) and (*b*) led largely to *p*-anisic acid, identical with an authentic sample, whereas with (*c*) and (*d*) no anisic acid was formed, but 4,4′-dimethoxybiphenyl was the only identifiable product.

Attempted Preparation of 3,4′,5-Trimethoxybiphenyl by using a Benzyne Intermediate.—(a) *Preparation of benzyne intermediate.* Piperidine (2·55 g) was dissolved in ether, and butyl-lithium (10 ml; 0·002 mol ml^{-1}) was added at −70°. After stirring for 0·5 h 4-chloro-1,3-dimethoxybenzene (1·73 g) was added. The temperature was allowed to reach 18° and the mixture was stirred for a further 22 h and then boiled for a final 2 h before pouring onto crushed, solid carbon dioxide. The residue so formed was extracted with water and ether. The organic layer was washed with acid (2M-HCl) and shown by t.l.c. to contain 4-chloro-1,3-dimethoxybenzene and resorcinol dimethyl ether. The acid layer after basification (2M-NaOH) was extracted with ether. Removal of the solvent gave a pale yellow oil (1·6 g) which was shown by t.l.c. to consist mainly of two components. Preparative t.l.c. gave a pure fraction and a mixture of two components. The pure fraction and the major component of the mixture were *1,3-dimethoxy-5-piperidinobenzene* (14) (0·94 g), $\lambda_{max.}$ ($CHCl_3$) 257 nm ($\varepsilon \times 10^{-3}$ 8·92), $\nu_{max.}$ 2940, 1595, 1460, 1205, 1180, 1155, 1130, 1070, 815, and 685 cm^{-1}, τ (CCl_4) 4·05 (2H, d, J 2 Hz), 4·13 (1H, t, J 2 Hz), 6·32 (6H, s), 6·90 (4H, m), and 8·40 (6H, m) [Found: M^+, 221·1413. $C_{13}H_{19}NO_2$ requires M, 221·1413], and the other component was 1,3-dimethoxy-4-piperidinobenzene (0·11 g), τ (CCl_4) (on mixture) 3·22 (1H, d, J 9 Hz), 3·60br and 3·75 (d, J 2·5 Hz) (2H), 6·18 (6H, s), 7·12 (4H, m), and 8·38 (6H, m).

(b) *Attempted preparation of 3,4′,5-trimethoxybiphenyl.* Piperidine (0·85 g) was dissolved in ether (50 ml) at −70° and butyl-lithium (5 ml; 0·002 mol ml^{-1}) was added. After stirring for 0·5 h, 4-chloro-1,3-dimethoxybenzene (1·73 g) was added, followed by a solution of *p*-lithioanisole [from *p*-iodoanisole (2·34 g), butyl-lithium (5 ml; 0·002 mol ml^{-1}) and ether (50 ml)] and the mixture was stirred as the temperature slowly rose to 18°. After 24 h at 18° water was added and the ether layer was extracted with HCl (2M). The acid portion was basified and extracted with ether. Both ether layers were inspected by t.l.c. for the presence of the biphenyl (12) but the main constituents were 1,3-dimethoxy-5-(and 4-)piperidinobenzene, 4-chloro-1,3-dimethoxybenzene, and 1,3-dimethoxybenzene. The same products were obtained by using boiling ether or tetrahydrofuran as solvents. We attempted to form the benzyne (13) in the presence of *p*-lithioanisole by using various bases and solvents: (*a*) in the presence or absence of 50% hexamethylphosphoric triamide, (*b*) in the presence of a catalytic amount of piperidine,[9] (*c*) in the presence of lithium di-isopropylamide, but the only identified products were 4,4′-dimethoxybiphenyl, anisole, and 1,3-dimethoxybenzene.

1,3-Dimethoxy-2-(3-methylbut-2-enyl)benzene (16a).—1,3-Dimethoxybenzene (11 g) was dissolved in dry ether (100 ml) at 18° and butyl-lithium (38 ml; 0·0027 mol ml^{-1}) was added. The mixture was boiled for 3 h to ensure complete conversion into the 2-lithio salt. After cooling to −70° the slurry was treated with 3-methylbut-2-enyl bromide (12 g), then boiled for 6 h, and stirred at 18° for a further 18 h. The mixture was hydrolysed with water and extracted with ether. Evaporation of the dried extract gave a brown oil which on distillation gave the product (16a) (15·1 g, 73·3%) as an oil, b.p. 132—134° at 2·5 mmHg (lit.,[10] 101° at 0·55 mmHg), $\lambda_{max.}$ 270 ($\varepsilon \times 10^{-3}$ 1·08), 273sh (1·06), and 278 nm (1·01), $\nu_{max.}$ (liquid film) 3010, 2975, 2945, 2850, 1600, 1480, 1270, 1120, 1055, 885, 800, 780, and 740 cm^{-1}, τ Table 1 (Found: M^+, 206·1310. Calc. for $C_{13}H_{18}O_2$: M, 206·1307).

2-(3-Hydroxy-3-methylbutyl)-1,3-dimethoxybenzene (17a).—1,3-Dimethoxy-2-(3-methylbut-2-enyl)benzene (0·5 g, 2·5 mmol) was dissolved in aqueous tetrahydrofuran (20 ml; 1 : 3). Aqueous mercury(II) acetate (0·8 g, 2·5 mmol; in 10 ml) was slowly added over 0·25 h at 18°. The yellow precipitate which formed, slowly dissolved during 1 h to give a colourless solution. The mixture was stirred at 18° for a further 18 h, and then treated with aqueous potassium hydroxide (1·0 g, 17·5 mmol; in 5 ml). After reduction with sodium borohydride (0·1 g, 2·5 mmol; 1 h), added slowly over 15 min, the solution was decanted from the precipitated mercury and extracted with ether (3 × 20 ml). Evaporation of the dried extract gave the

crude hydroxy-compound (17a) as an oil. Recrystallisation from light petroleum (b.p. 60—80°) gave white needles of the *product* (17a) (0·43 g, 79%), m.p. 45—46°, $\lambda_{max.}$ 269 (ε × 10^{-3} 1·05), 272sh (1·02), and 277 nm (0·99), $\nu_{max.}$ 3370, 1600, 1270, 1150, 1100, 915, 785, and 725 cm^{-1}, τ Table 1 (Found: C, 69·6; H, 9·0%; M^+, 224·1416. $C_{13}H_{20}O_3$ requires C, 69·6; H, 8·9%; *M*, 224·1412).

1,3,5-*Trimethoxy*-2-(3-*methylbut*-2-*enyl*)*benzene* (16b).—The foregoing method was used to give the *trimethoxy-compound* (16b) (3·3 g, 47%) as an oil, b.p. 160° at 4 mmHg, $\lambda_{max.}$ 270 (ε × 10^{-3} 0·91), 274sh (0·89), and 277 nm (0·82), $\nu_{max.}$ (liquid film) 3010, 2950, 2860, 1610, 1500, 1215, 1160, 1130, 965, and 825 cm^{-1}, τ Table 1 (Found: M^+, 236·1407. $C_{14}H_{20}O_3$ requires *M*, 236·1412).

2-(3-*Hydroxy*-3-*methylbutyl*)-1,3,5-*trimethoxybenzene* (17b).—The foregoing method was repeated except that the weight of sodium borohydride was halved. Thus 1,3,5-trimethoxy-2-(3-methylbut-2-enyl)benzene (0·1 g, 0·42 mmol), mercury(II) acetate (0·13 g, 0·42 mmol), potassium hydroxide (0·17 g, 2·94 mmol), and sodium borohydride (8 mg, 0·21 mmol) in aqueous tetrahydrofuran (14 ml; 4 : 3) gave, after preparative t.l.c. and recrystallisation from light petroleum (b.p. 60—80°) white needles of the *product* (17b), m.p. 59—60° (65 mg, 60·2%), $\lambda_{max.}$ 270 (ε × 10^{-3} 0·87), 273sh (0·84), and 276sh nm (0·78), $\nu_{max.}$ 3580, 3300br, 1615, 1600, 1505, 1215, 1160, 1105, 1070, 960, and 815 cm^{-1}, τ Table 1 (Found: C, 66·4; H, 8·6%; M^+, 254·1512. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%; *M*, 254·1518).

3,4′,5-*Trimethoxy*-4-(3-*methylbut*-2-*enyl*)*biphenyl* (16c).—3,4′,5-Trimethoxybiphenyl (0·340 g) was treated with butyl-lithium (0·94 ml; 30% excess at 0·0025 mol ml^{-1}) and then with 3-methylbut-2-enyl bromide (0·5 g; 100% excess) as described for 1,3-dimethoxy- and 1,3,5-trimethoxy-benzene. This gave, after preparative t.l.c., the trimethoxy product (0·171 g, 39·3%) as a white powder. Recrystallisation from light petroleum (b.p. 60—80°) gave the pure *product* (13) as white plates, m.p. 98—99°, $\lambda_{max.}$ Table 2, $\nu_{max.}$ 1610, 1595, 1580, 1530, 1300, 1270, 1180, 1130, 1045, 830, and 820 cm^{-1}, τ Table 1 (Found: C, 76·8; H, 7·9%; M^+, 312·1725. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7%; *M*, 312·1725). A by-product was also obtained from the mixture by preparative t.l.c. and was identified as 4-*hydroxy*-3,4′,5-*trimethoxybiphenyl* (18) (23 mg, 6·4%), m.p. 99°, $\lambda_{max.}$ Table 2, $\nu_{max.}$ 3450, 1615, 1510, 1350, 1300, 1250, 1235, 1125, 1050, 830, and 820 cm^{-1}, τ Table 1 (Found: M^+, 260·1062. $C_{15}H_{16}O_4$ requires *M*, 260·1049).

4-(3-*Hydroxy*-3-*methylbutyl*)-3,4′,5-*trimethoxybiphenyl* (17c) [≡(1a)].—3,4′,5-Trimethoxy-4-(3-methylbut-2-enyl)-biphenyl (0·131 g) was hydrated with mercury(II) acetate (0·134 g), potassium hydroxide (0·165 g), and sodium borohydride (8 mg) using the method described for the hydration of (16a), except that more tetrahydrofuran (6 ml) was needed to obtain complete solution. Preparative t.l.c. of the reaction mixture gave 4-(3-hydroxy-3-methylbutyl)-3,4′,5-trimethoxybiphenyl (93 mg, 65·5%) as a white powder. Recrystallisation from light petroleum (b.p. 60—80°) gave white lustrous needles of the product (17c), m.p. 116—117° (lit.,[1b] 117°), $\lambda_{max.}$ Table 2, $\nu_{max.}$ 3580, 3520br, 1615, 1595, 1575, 1500, 1410, 1300, 1260, 1230, 1190, 1155, 1110, 1050, 825, and 835 cm^{-1}, τ Table 1 (Found: C, 72·8; H, 7·7%; M^+, 330. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%; *M*, 330).

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