Thiele–Winter Acetoxylation of Quinones. Part VI.[1] Methoxy- and Hydroxy-(phenyl)-1,4-benzoquinones and (4-Substituted phenyl)-1,4-benzoquinones

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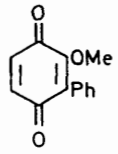
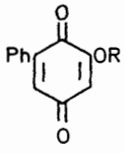
The Thiele–Winter acetoxylation of the following 1,4-benzoquinones has been studied: 2-methoxy-3-phenyl-, 2-methoxy-6-phenyl-, 2-hydroxy-5-phenyl-, 2-hydroxy-6-phenyl-, and 2-(4-substituted phenyl)- (with NO_2, Br, OMe, OH, and OAc as substituents). All these quinones undergo the reaction except (4-methoxyphenyl)-1,4-benzoquinone which gives tars. The inserted acetoxy-group always enters *ortho* or *para* to the phenyl or aryl group: it never enters *ortho* to the hydroxy- or the methoxy-group. 2-Hydroxy-5-(4-hydroxyphenyl)-1,4-benzoquinone has been prepared: its pK_a values are 4·18 and 9·27 at 20°.

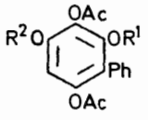
THE exact mechanism of the Thiele–Winter acetoxylation (T.W.A.) of quinones is unknown and, before discussing possible mechanisms, we thought it desirable to collect some systematic data concerning the scope of the reaction and the orientating effect of substituents. The results recorded in this and in the following paper complete our study of all the 2,3-, 2,5-, and 2,6-disubstituted 1,4-benzoquinones each containing two of the following groups; bromo-, methoxy-, and phenyl. Results obtained with some related quinones are also described. The present paper is concerned with the synthesis and T.W.A. of 2-methoxy-3-phenyl-, 2-methoxy-6-phenyl-, 2-hydroxy-5-phenyl-, and 2-hydroxy-6-phenyl-1,4-benzoquinone and also some 2-(*p*-substituted phenyl)-1,4-benzoquinones. 2-Hydroxy-5-(4-hydroxyphenyl)-1,4-benzoquinone, which may be regarded as a phenylogue of 2,5-dihydroxy-1,4-benzoquinone, has also been made and its p*K* values measured.

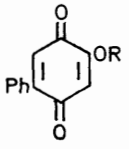
Preparation of Methoxy- and Hydroxy-(phenyl)quinones.—2-Methoxy-3-phenyl-1,4-benzoquinone (1) was made as follows. Friedel–Craft acetylation of 2,6-dimethoxybiphenyl [2] gave 3-acetyl-2,6-dimethoxybiphenyl which underwent Baeyer–Villeger oxidation with peracetic acid to give 3-acetoxy-2,6-dimethoxybiphenyl. Hydrolysis of the latter and subsequent oxidation gave the required quinone. An attempt to oxidise 2,6-dimethoxybiphenyl directly to the quinone (1) with an excess of peracetic acid was unsuccessful (*cf.* ref. 3). 2-Methoxy-6-phenyl-1,4-benzoquinone (2) was prepared by the following sequence. Benzylideneacetone was converted into 5-phenylcyclohexane-1,3-dione [4] and thence, by methylation,[5] into 3-methoxy-5-phenylcyclohex-2-enone. This was aromatised by heating it with palladised charcoal to give 3-hydroxy-5-methoxybiphenyl which was oxidised by potassium nitrosodisulphonate (Fremy's salt) [6] to the desired quinone. 2-Hydroxy-6-phenyl-1,4-benzoquinone (3) was made by hydrolysis of 2,3,5-triacetoxybiphenyl [7] followed by oxidation with silver oxide. The same quinone was also made by oxidation of 3,5-dihydroxybiphenyl with Fremy's salt.

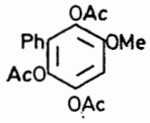
Thiele–Winter Reactions of Methoxy- and Hydroxy-(phenyl)quinones.—T.W.A. of quinone (1) proceeded readily and gave the triacetate (4) in 38—54% yield depending on the catalyst used. With perchloric acid

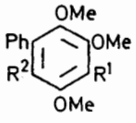

(1)


(2) R = Me
(3) R = H


(4) R^1 = Me, R^2 = Ac
(5) R^1 = Ac, R^2 = Me


(6) R = Me
(7) R = H
(8) R = Ac


(9)


(10) R^1 = H, R^2 = OMe
(11) R^1 = OMe R^2 = H

much tar was formed, which hindered purification. Previous work has shown that acetoxylation of 2-methoxy-5-phenylquinone (6) gives 2,3,6-triacetoxy-4-methoxybiphenyl (5).[8] The Thiele–Winter reaction of the 2-methoxy-6-phenylquinone (2) was sluggish and much decomposition occurred: the triacetate (9) was obtained in *ca.* 2% yield. Its structure was determined by a combined hydrolysis and methylation to give the corresponding tetramethoxybiphenyl (10) as a viscous oil. The n.m.r. spectrum of this biphenyl showed two singlets each representing two methoxy-groups. The possible alternative product, 2,3,4,5-tetramethoxybiphenyl (11) (m.p. 65—66°) was made by phenylation of 1,2,3,4-tetramethoxybenzene and its n.m.r. spectrum showed four singlets, each representing one methoxy-group. Thus the T.W.A. product must have been

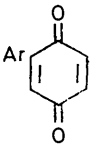
[1] Part V, J. F. W. McOmie and S. A. Saleh, *J.C.S. Perkin I*, 1974, 384.
[2] G. Ehrhart, *Chem. Ber.*, 1963, **96**, 2042.
[3] H. Davidge, A. G. Davis, J. Kenyon, and R. F. Mason, *J. Chem. Soc.*, 1958, 4569.
[4] D. Vorländer, *Ber.*, 1894, **27**, 2053.
[5] K. Arakawa and M. Irie, *Pharm. Bull.* (*Tokyo*), 1957, **5**, 524 (*Chem. Abs.*, 1958, **52**, 15,445*f*).
[6] H. Zimmer, D. C. Lankin, and S. W. Horgan, *Chem. Rev.*, 1971, **71**, 229.
[7] J. F. W. McOmie, S. A. Saleh, and J. B. Searle, following paper.
[8] J. M. Blatchly and J. F. W. McOmie, *J. Chem. Soc.*, 1963, 5311.

2,3,6-triacetoxy-5-methoxybiphenyl (9). Several attempts to prepare an authentic sample of 2,3,5,6-tetramethoxybiphenyl (10) failed (see Experimental section).

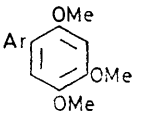
Fieser [9] reported that an *x*-hydroxy-2-phenyl-1,4-benzoquinone, now known to be the 2-hydroxy-5-phenylquinone (7),[8] reacted with acetic anhydride in the presence of boron trifluoride to give the yellow acetoxyquinone (8). We have now found that prolonged treatment of the hydroxyquinone with the same reagent yields 2,3,4,6-tetra-acetoxybiphenyl (56%). The T.W.A. of 2-hydroxy-6-phenylquinone (3), with boron trifluoride as catalyst, proceeded very slowly. After 10 days at 55° a black tar was formed, which yielded 2,3,5-triacetoxybiphenyl (6%) and a tetra-acetate (30%) which is almost certainly 2,3,5,6-tetra-acetoxybiphenyl. The orientation of the latter was deduced from its n.m.r. spectrum which shows peaks at τ 8·03 and 7·72 each corresponding to a pair of acetoxy-groups. From a study of 22 * acetoxybiphenyls of known orientation we have found that OAc groups at positions 3, 4, and 5 give signals (in $CDCl_3$) at τ 7·66—7·78 while those at positions 2 and 6 give signals at τ 7·89—8·19. These higher values are probably due to shielding of the adjacent OAc group(s) by the phenyl group. In 36 * acetoxy-benzenes and -biphenylenes the OAc groups had signals at τ 7·63—7·82. 2-Hydroxy-6-phenyl-1,4-benzoquinone could give either 2,3,4,5- or 2,3,5,6-tetra-acetoxybiphenyl but the former would be expected to show 3 OAc signals in the lower range of τ values and one in the higher range.

Thiele–Winter Reactions of (4-Substituted phenyl)-quinones.—T.W.A. of quinones containing an electronegative substituent, *e.g.* 2-cyano-1,4-benzoquinone, occurs *ortho* to the original substituent.[10] It was therefore of interest to study (4-nitrophenyl)1,4-benzoquinone (12) to see whether the effect of the nitro-group would be strongly transmitted, *via* the phenyl group, to the quinone ring. With boron trifluoride as catalyst, T.W.A. gave 2,4,5-triacetoxy-4′-nitrobiphenyl (82%). After our work had been completed, it was reported that the reaction catalysed by sulphuric acid gave the 2,4,5-triacetoxy-compound (56%), together with the 2,3,6- (18%) and 2,3,5- (19%) isomers.[11] Under similar conditions 2-phenyl-1,4-benzoquinone gave the 2,4,5- (52%) and the 2,3,6-triacetate (21%).[11] Clearly the nitro-group has only had a small effect on the orientation of the products.

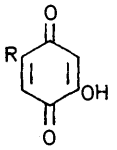
At the same time we also studied T.W.A. of (4-bromo-, (4-methoxy-, (4-hydroxy-, and (4-acetoxy-phenyl)-1,4-benzoquinone. As reported later by Wilgus and Gates [11] the attempted acetoxylation of 4′-methoxyphenylquinone (13) using boron trifluoride or sulphuric acid as catalyst gave tars. However, the other three quinones readily gave 2,4,5-triacetoxybiphenyls. The orientation was established by combined hydrolysis and methylation to give 2,4,5-trimethoxybiphenyls which showed two singlets (*J* 0Hz) in the n.m.r. spectrum. The structures of the methoxybiphenyls were also confirmed by interconversion reactions. Reduction of the nitrobiphenyl (17) gave the amine (20) which,



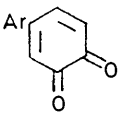
(12) Ar = *p* — $NO_2C_6H_4$
(13) Ar = *p* — $MeOC_6H_4$
(14) Ar = *p* — BrC_6H_4
(15) Ar = *p* — HOC_6H_4
(16) Ar = *p* — $AcOC_6H_4$



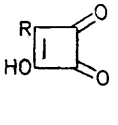
(17) Ar = *p* — $NO_2C_6H_4$
(18) Ar = *p* — $MeOC_6H_4$
(19) Ar = *p* — BrC_6H_4
(20) Ar = *p* — $NH_2C_6H_4$



(21) R = *p* — HOC_6H_4
(22) R = OH



(23) Ar = *p* — HOC_6H_4



(24) R = *p* — HOC_6H_4
(25) R = OH

on diazotisation followed by Sandmeyer reaction, gave the 4′-bromobiphenyl (19), identical with the product derived from 4′-bromophenylquinone. Debromination of this bromobiphenyl with hydrazine and palladium–charcoal gave 2,4,5-trimethoxybiphenyl. The tetramethoxybiphenyl (18) obtained from the (4-hydroxy- and 4-acetoxy-phenyl)quinones was synthesised by a crossed Ullmann reaction between 5-bromo-1,2,4-trimethoxybenzene and 4-iodoanisole. A similar crossed Ullmann reaction with 4-bromo- in place of 4-iodoanisole gave a mixture of the two symmetrical biphenyls.

The tetra-acetoxybiphenyl obtained from (4-hydroxyphenyl)-1,4-benzoquinone was hydrolysed and then oxidised to give 2-hydroxy-5-(4-hydroxyphenyl)-1,4-benzoquinone (21) which is a phenylogue of 2,5-dihydroxy-1,4-benzoquinone (22). Spectroscopic studies have shown that 4-(4-hydroxyphenyl)-1,2-benzoquinone (23) exists in solution in the form shown and not in the tautomeric 3-hydroxy-4,4′-diphenoquinone form.[12] By analogy compound (21) probably exists mainly as such in solution rather than as any of the other three possible tautomeric forms. Acetylation of the quinone (21) gives a yellow diacetate. This colour suggests that the diacetate has the *para*-benzoquinone structure corresponding to quinone (21) since *para*-quinones are generally yellow, *ortho*-quinones orange or red, and diphenoquinones purple.

As expected, compound (21) (pK_1 4·18, pK_2 9·27 at

* Compounds containing both ArMe and ArOAc were excluded owing to the difficulty of assigning signals unambigously to the two different kinds of Me group.

[9] L. F. Fieser, *J. Amer. Chem. Soc.*, 1948, **70**, 3165.

[10] J. F. W. McOmie and J. M. Blatchly, *Org. Reactions*, 1972, **19**, 199.

[11] H. S. Wilgus and J. W. Gates, *Canad. J. Chem.*, 1967, **45**, 1975.

[12] H. Musso and H. Pietsch, *Chem. Ber.*, 1967, **100**, 2854.

20°; see Experimental section) is a weaker acid than 2,5-dihydroxyquinone (22) (pK_1 2·71 and 5·18).[13] There is a rather similar difference in acid strength between that of the phenylogue (24) of squaric acid and that of squaric acid (25) itself (pK_1 1·85, pK_2 8·35 and pK_1 1·50, pK_2 2·93 respectively).[14]

Discussion of Results.—The main results of the experiments recorded in this paper, together with previous results,[8,11] may be summarised as follows: (1) acetoxylation of 2-phenyl- and 2-(4-substituted phenyl)-quinones occurs mainly or exclusively *para* to the aryl group; (2) acetoxylation of the 2-methoxy-3-phenylquinone occurs *para* to the phenyl group; (3) acetoxylation of 2-hydroxy-5-phenyl-, 2-methoxy-5-phenyl-, 2-hydroxy-6-phenyl-, and 2-methoxy-6-phenyl-1,4-benzoquinone occurs *ortho* to the phenyl group.

T.W.A. of hydroxyquinones probably proceeds *via* the corresponding acetoxyquinones since esterification of the hydroxy-group occurs very easily in hydroxyquinones and often there is no further reaction. Moreover when the preformed acetoxyquinones are used they give the same products as the original hydroxyquinones. Thus the acetoxy-, hydroxy-, and methoxy-group (OR) have the same orientating effect when present in phenyl-1,4-benzoquinone and although acetoxylation occurs *ortho* and *para* to the phenyl group it does not occur *meta* to it or *ortho* to the OR group. In a few acetoxy- and hydroxy-quinones (see review in ref. 10) acetoxylation does occur *ortho* to the OR group but, except for two *ortho*-quinones with special structural features,[15,16] it never occurs *ortho* to a methoxy-group: however this represents a difference in reactivity and not a difference in control of orientation.

EXPERIMENTAL

N.m.r. spectra were measured in $CDCl_3$ at 100 or 60 MHz, and those for compounds marked with an obelus (†) are listed in Supplementary Publication No. SUP 21196 (3 pp.).* Petroleum refers to light petroleum (b.p. 60—80°) unless stated otherwise.

2-Methoxy-5-phenyl-1,4-benzoquinone.†—This is formed in low yield by phenylation of methoxy-1,4-benzoquinone. The report to the contrary was made because the wrong specimen was used for the mixed m.p.[8]

3-Acetyl-2,6-dimethoxybiphenyl.—A mixture of 2,6-dimethoxybiphenyl [2] (12·9 g), polyphosphoric acid (90 g), and acetic anhydride (4 ml) was heated to 65—70° with stirring for 4·5 h. The mixture was poured into water, and the product was collected in ether. It was crystallised from benzene by the addition of petroleum, and gave *3-acetyl-2,6-dimethoxybiphenyl* (11·4 g, 74%), m.p. 116—117° (Found: C, 74·9; H, 6·4. $C_{16}H_{16}O_4$ requires C, 75·0; H, 6·3%), $\lambda_{max.}$ (EtOH) 210, 246, and 273 nm (log ε 4·16, 4·27, and 4·06).

3-Acetoxy-2,6-dimethoxybiphenyl.†—A solution of 3-acetyl-2,6-dimethoxybiphenyl (10·2 g) and sodium acetate (0·5 g) in warm acetic acid (20 ml) was treated with a 36% solution of peracetic acid (20 ml), and the mixture was stirred for 23 h at 45—50°. A dilute solution of sodium hydrogen sulphite was added to reduce the excess of peracid, and the mixture was poured into water. The product was collected in ether and gave *crystals* (7·2 g, 66%), m.p. 92—93° (from petroleum) (Found: C, 70·1; H, 5·8. $C_{16}H_{16}O_4$ requires C, 70·5; H, 5·9%). Combined hydrolysis and methylation of the acetate gave 2,3,6-trimethoxybiphenyl (50%) as tan crystals, m.p. 89—91° (lit.,[11] 91—92°).

3-Hydroxy-2,6-dimethoxybiphenyl.—A mixture of 3-acetoxy-2,6-dimethoxybiphenyl (14 g), sodium hydroxide (8 g), water (60 ml), and ethanol (6 ml) was boiled under reflux for 3 h. The resulting solution was washed with methylene chloride, then acidified. The product was collected in ether and gave *crystals* (7·8 g, 65%), m.p. 95—97° (from petroleum) (Found: C, 73·4; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

2-Methoxy-3-phenyl-1,4-benzoquinone (1).†—3-Hydroxy-2,6-dimethoxybiphenyl (2·3 g) was suspended in water (10 ml), and a solution of sodium dichromate (3 g) in 10% sulphuric acid (20 ml) was added. The mixture was stirred vigorously for 2 h, and the product was collected in ether. Evaporation of the ether extract gave an oil which was dissolved in hot petroleum. Cooling the petroleum solution gave *orange needles* (1·8 g, 42%), m.p. 74·5—76° (sealed tube). Vacuum sublimation at 100° and 0·5 mmHg gave a sample, m.p. 78—79° (Found: C, 73·2; H, 4·6. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·7%), $\lambda_{max.}$ (ethanol) 209, 245, and 394 nm (log ε 4·08, 4·08, and 3·11).

Thiele–Winter Acetoxylation of 2-Methoxy-3-phenyl-1,4-benzoquinone.—A mixture of the quinone (0·64 g), acetic anhydride (20 ml), and 40% boron trifluoride in acetic acid (0·2 ml) was stirred for 3 h at room temperature. The mixture was poured into water, and the product was collected in ether and gave *2,4,5-triacetoxy-6-methoxybiphenyl* (5) † (0·31 g) as crystals (from benzene–petroleum), m.p. 106—107° (sealed tube). A further 0·1 g of the triacetate was obtained by thick layer chromatography of the residues from crystallisation. The total yield of *triacetate* was 38% (Found: C, 64·1; H, 5·1. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1%).

In similar experiments using concentrated sulphuric acid (0·2 ml) (for 1 h) and 72% perchloric acid (0·2 ml) (for 0·5 h) as catalysts in place of boron trifluoride the yields of product were 54 and 42% respectively. The mixed m.p.s of all three samples were 105—106·5°.

Combined hydrolysis and methylation of the triacetate gave 2,3,4,6-tetramethoxybiphenyl † (47%), m.p. and mixed m.p. 92·5—93·5° (lit.,[8] 93°) (Found: C, 70·0; H, 6·9. Calc. for $C_{16}H_{18}O_4$: C, 70·0; H, 6·6%).

3-Hydroxy-5-methoxybiphenyl.— 3-Methoxy-5-phenylcyclohex-2-enone [5] (2·2 g) and 10% palladised charcoal (2 g) were heated in diphenyl ether (25 g) until a vigorous evolution of hydrogen occurred. The mixture was boiled under reflux, and the crude phenol was obtained by extraction into a solution of sodium hydroxide. The extract was acidified, and the oily product was chromatographed in benzene on a column of silica gel. The product, which solidified, was sublimed at 85—95° and 0·4 mmHg and gave *3-hydroxy-5-methoxybiphenyl* (1·8 g, 81%), m.p. 70·5—71° (Found: C, 78·1; H, 6·2. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%).

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

[13] G. Schwarzenbach and H. Suter, *Helv. chim. Acta*, 1941, **24**, 617.

[14] W. Broser and M. Seekamp, *Tetrahedron Letters*, 1966, 6337.

[15] W. Steglich, W. Lösel, and V. Austel, *Chem. Ber.*, 1969, **102**, 4104.

[16] C. P. Falshaw, S. A. Lane, and W. D. Ollis, *J.C.S. Chem. Comm.*, 1973, 491.

2-Methoxy-6-phenyl-1,4-benzoquinone (2).†—A solution of 3-hydroxy-5-methoxybiphenyl (9 g) in methanol (200 ml) was added to a mixture of an ice-cold solution of Fremy's salt [6] (26·8 g) in water (2 l) and a solution of potassium dihydrogen phosphate (400 ml; 0·17M). The mixture was stirred at 10°. Unchanged 3-hydroxy-5-methoxybiphenyl (70%) and 2-methoxy-6-phenyl-1,4-benzoquinone (29%) were isolated from the mixture and separated by chromatography on silica gel with benzene as eluant. The yield of the quinone was improved to 37% when the oxidation was performed at 25°. *2-Methoxy-6-phenyl-1,4-benzoquinone* formed orange plates (from methanol), m.p. 107·5—108° (Found: C, 73·3; H, 4·7. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·7%). Reduction of the quinone with sodium dithionite followed by acetylation gave *2,5-diacetoxy-3-methoxybiphenyl* † as needles (from methanol), m.p. 123—124° (Found: C, 67·5; H, 5·95. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%).

Thiele–Winter Acetoxylation of 2-Methoxy-6-phenyl-1,4-benzoquinone.—A mixture of 2-methoxy-6-phenyl-1,4-benzoquinone (0·25 g), acetic anhydride (5 ml), and concentrated sulphuric acid (3 drops) was stirred at 65° for 10 h. The mixture was poured into iced water, and the product was collected in methylene chloride. Column chromatography on silica gel with methylene chloride gave an impure product (0·13 g) as a viscous oil.

Similar experiments on a smaller scale were performed with boron trifluoride as catalyst. The quinone (43 mg), acetic anhydride (9 ml), and 40% solution of boron trifluoride in acetic acid (4 drops) were stirred for 200 h at 40—50°, and gave the crude triacetate (26 mg). The quinone (163 mg), acetic anhydride (12 ml), and 72% perchloric acid (3 drops) were stirred at room temperature for 50 min. Unchanged quinone (27 mg) was recovered and the crude product was similar to those obtained with BF_3 and with H_2SO_4.

The products from these three experiments were united and the viscous liquid was distilled. The fraction, b.p. 95—160° at 0·01 mmHg, gave *2,3,6-triacetoxy-5-methoxybiphenyl* † (12 mg, *ca.* 2%) as a viscous oil (Found: M^+, 358; *m/e*, 316·095, 274, and 232. $C_{19}H_{18}O_7$ requires *M*, 358. $M - CH_2{=}CO$ requires *m/e*, 316·094; $M - 2 \times CH_2{=}CO$ requires *m/e*, 274; $M - 3 \times CH_2{=}CO$ requires *m/e*, 232).

The triacetate (9) (12 mg) in methanol was hydrolysed and methylated with potassium hydroxide and dimethyl sulphate, and gave *2,3,5,6-tetramethoxybiphenyl* (10) † (6 mg, 67%) as a thick oil (Found: C, 69·9; H, 6·4%; M^+, 274·120. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%; *M*, 274·120).

2,3,4,5-Tetramethoxybiphenyl (11).†—Finely divided sodium (0·28 g) in dry benzene (6 ml) was stirred under an atmosphere of nitrogen. A solution of 1,2,3,4-tetramethoxybenzene [17] (1·2 g) and chlorobenzene (1·36 g) in benzene (4 ml) was added slowly with stirring at 35—40° (external cooling). The mixture was stirred overnight, then poured into water and the product collected in ether. Chromatography on silica gel with benzene as eluant gave 1,2,3,4-tetramethoxybenzene (34%) and *2,3,4,5-tetramethoxybiphenyl* (0·1 g, 6%) as crystals (from petroleum–benzene), m.p. 64·5—66° (Found: C, 69·8; H, 6·4%; M^+, 274·122. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%; *M*, 274·120).

[17] F. Bennington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, 1955, **20**, 102.

Phenylation of 1,2,4,5-tetramethoxybenzene.—Finely powdered sodium (1·0 g) in dry benzene (10 ml) at 40° was treated with a mixture of 1,2,4,5-tetramethoxybenzene [17] (3·96 g) and chlorobenzene (4·6 g) in benzene (20 ml) as for the preparation of 2,3,4,5-tetramethoxybiphenyl above. The crude product was chromatographed on silica gel in benzene, and gave 1,2,4,5-tetramethoxybenzene (43%) and *2′,3′,5′,6′-tetramethoxy-p-terphenyl* (0·18 g, 3%) as crystals (from benzene–petroleum), m.p. 216—218° (Found: C, 75·9; H, 6·2. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%). The attempted phenylation of 1,2,4,5-tetramethoxybenzene using dibenzoyl peroxide was unsuccessful.

1-Iodo-2,3,5,6-tetramethoxybenzene.—A solution of 1,2,4,5-tetramethoxybenzene [17] (3·4 g, 0·017 mol) in absolute tetrahydrofuran (50 ml) was stirred for 10 min with a solution of n-butyl-lithium (0·018 mol) in ether under an atmosphere of nitrogen. The mixture was added to a stirred solution of iodine (6 g) in ether (80 ml) and, after 0·5 h, poured into a dilute solution of sodium hydrogensulphite to destroy the excess of iodine. The product was collected in ether and gave *1-iodo-2,3,5,6-tetramethoxybenzene* (2·3 g, 41%) as crystals [from petroleum (b.p. 40—60°)], m.p. 86—87° (Found: C, 37·2; H, 3·7. $C_{10}H_{13}IO_4$ requires C, 37·1; H, 4·0%).

Attempts to convert this iodo-compound into 2,3,5,6-tetramethoxybiphenyl by a crossed Ullmann reaction, by treatment with phenylcopper,[18] or by photolysis in benzene [19] failed.

1,4-Bis(cyclohex-1-enyl)-2,3,5,6-tetramethoxybenzene.— A solution of 1,2,4,5-tetramethoxybenzene [17] (1·5 g, 0·008 mol) in absolute tetrahydrofuran (30 ml) was stirred for 10 min with a solution of n-butyl-lithium (0·010 mol) in ether under an atmosphere of nitrogen. The mixture was added to a solution of cyclohexanone (8 ml) in ether (20 ml), stirred for 68 h, and then acidified with hydrochloric acid. The mixture was extracted with ether, and the residue from the ether extract was heated with 98% formic acid under reflux for 1 h. The cooled mixture was neutralised and the products extracted into ether. Chromatography on silica gel in benzene gave 1,2,4,5-tetramethoxybenzene (71%) and *1,4-bis(cyclohex-1-enyl)-2,3,5,6-tetramethoxybenzene* (0·007 g, 2%) as crystals [from ether petroleum (b.p. 30—40°)], m.p. 174—176·5° (Found: M^+, 358·213. $C_{22}H_{30}O_4$ requires *M*, 358·214).

Thiele–Winter Acetoxylation of 2-Hydroxy-5-phenyl-1,4-benzoquinone.—A solution of the quinone (2·8 g) in acetic anhydride (20 ml) and boron trifluoride–acetic acid complex (2 ml) was kept for 24 h at 35°. The mixture was poured into water and, after allowing the acetic anhydride to be hydrolysed, the precipitated solid was collected. Recrystallisation from aqueous ethanol gave *2,3,4,6-tetraacetoxybiphenyl* † as needles (3·0 g, 56%), m.p. 141—143° (Found: C, 62·0; H, 4·4. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%).

Combined hydrolysis and methylation of this tetraacetate gave 2,3,4,6-tetramethoxybiphenyl. The crude product (42% yield) was sublimed under reduced pressure and recrystallised from petroleum (b.p. 40—60°). It had m.p. 92°, and mixed m.p. 92—93° with an authentic sample.[8]

2-Hydroxy-6-phenyl-1,4-benzoquinone (3).†—(*a*) 2,3,5-Triacetoxybiphenyl [7],† (2·15 g) in methanol (16 ml) and con-

[18] M. Nilsson and O. Wennerstrom, *Acta Chem. Scand.*, 1970, **24**, 482.

[19] W. Wolf and N. Kharasch, *J. Org. Chem.*, 1965, **30**, 2493.

centrated sulphuric acid (0·6 ml) was refluxed under nitrogen for 30 min. The mixture was cooled, diluted with water, and the methanol removed by evaporation. Ether extraction of the aqueous solution gave 2,3,5-trihydroxybiphenyl (0·97 g, 91%). Freshly prepared silver oxide (2·55 g) was added to a suspension of the trihydroxybiphenyl (0·97 g) in ether (25 ml) containing anhydrous sodium sulphate (3·1 g), and the mixture was stirred for 15 min at 20°. The mixture was filtered and the filtrate was evaporated under reduced pressure to give *2-hydroxy-6-phenyl-1,4-benzoquinone* (0·88 g, 92%) as an orange-brown powder, m.p. 115—116° (decomp.) (Found: C, 71·8; H, 4·3. $C_{12}H_8O_3$ requires C, 72·0; H, 4·0%).

(*b*) 3,5-Dihydroxybiphenyl (1·5 g) in tetrahydrofuran (25 ml) was oxidised with potassium nitrosodisulphonate (8 g) at 40° during 2 h. The crude product was sublimed at 60° and 0·001 mmHg and gave the quinone as granules (1·5 g, 94%), m.p. 113—115° (decomp.). Its i.r. spectrum was identical with that of the quinone made in (*a*) above.

3,5-Dihydroxybiphenyl.— 3-Hydroxy-5-methoxybiphenyl (6·5 g) in 48% hydrobromic acid (70 ml) and acetic acid (70 ml) was refluxed for 6 h. Chromatography of the product with 4% methanol in methylene dichloride gave starting material (0·4 g) and 3,5-dihydroxybiphenyl (5·6 g, 93%), m.p. 159—160° (lit.,[20] 160—161°).

Thiele–Winter Acetoxylation of 2-Hydroxy-6-phenyl-1,4-benzoquinone.—A mixture of the quinone (0·65 g), acetic anhydride (10 ml), and boron trifluoride–acetic acid complex (1 ml) was kept at 55° for 10 days. The mixture was added to water and, after 12 h, the black solid was collected. A benzene solution of the solid was applied to a column of silica gel (50 g), and elution with chloroform–benzene (1 : 9 v/v) gave 2,3,5-triacetoxybiphenyl (0·065 g, 6%); elution with chloroform–benzene (2 : 8 v/v) gave *2,3,5,6-tetra-acetoxybiphenyl* † (0·37 g, 30%) as needles (from ethanol), m.p. 214—218° (Found: C, 62·3; H, 4·5. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%).

Thiele–Winter Acetoxylation of (4-Substituted phenyl)-1,4-benzoquinones.—The reaction mixtures were tested at intervals by t.l.c. until all the quinone had reacted. The yields were recorded after two recrystallisations of the products from ethanol and are therefore largely dependent on the solubilities of the products in this solvent.

(a) *(4-Nitrophenyl)-1,4-benzoquinone* (12). A mixture of the quinone[21] (1·5 g), acetic anhydride (8 ml), and boron trifluoride–acetic acid complex (0·4 ml) was kept at 45° for 105 min. The product was recrystallised twice from ethanol and gave 2,4,5-triacetoxy-4′-nitrobiphenyl (2·0 g, 82%), m.p. 116—120° (lit.,[11] 115—117°) (Found: C, 57·8; H, 4·3. Calc. for $C_{18}H_{15}NO_8$: C, 57·9; H, 4·1%). Combined hydrolysis and methylation gave *2,4,5-trimethoxy-4′-nitrobiphenyl* (17) (95%) as yellow-brown plates (from methanol), m.p. 105—106° (Found: C, 62·4; H, 5·4. $C_{15}H_{15}NO_5$ requires C, 62·4; H, 5·2%).

(b) *(4-Bromophenyl)-1,4-benzoquinone* (14). A mixture of the quinone[21] (1·65 g), acetic anhydride (8 ml), and boron trifluoride–acetic acid complex (0·4 ml) was kept at 45° for 90 min and, after work-up, gave *2,4,5-triacetoxy-4′-bromobiphenyl* (2·1 g, 86%) (from ethanol), m.p. 141—142° (Found: C, 53·1; H, 3·7. $C_{18}H_{15}BrO_6$ requires C, 53·1; H, 3·7%). Combined hydrolysis and methylation gave *4′-bromo-2,4,5-trimethoxybiphenyl* (19) (72%) (from petroleum), m.p. 107—108° (Found: C, 55·8; H, 4·6. $C_{15}H_{15}BrO_3$ requires C, 55·75; H, 4·7%).

(c) *(4-Hydroxyphenyl)-1,4-benzoquinone* (15). Boron trifluoride–acetic acid complex (0·4 ml) was added to a solution of the quinone[21] (1·25 g) in acetic anhydride (16 ml). The mono-acetate crystallised out but redissolved on warming to 45°. The mixture was kept at this temperature for 1 h then worked up to give *2,4,4′,5-tetra-acetoxybiphenyl* (1·15 g, 48%) as needles (from methanol), m.p. 137—137·5° (Found: C, 62·4; H, 4·7. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%). Combined hydrolysis and methylation gave *2,4,4′,5-tetramethoxybiphenyl* (18) (75%) as crystals (from petroleum), m.p. 76—77° (Found: C, 70·3; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·0; H, 6·6%).

(d) *(4-Acetoxyphenyl)-1,4-benzoquinone* (16).—The quinone was made from (4-hydroxyphenyl)-1,4-benzoquinone by treatment with acetic anhydride containing sodium acetate. *(4-Acetoxyphenyl)-1,4-benzoquinone* formed yellow crystals (from petroleum), m.p. 156—157° (Found: C, 69·1; H, 4·4. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%). The quinone (1·52 g) was treated as in (c) above and gave the same tetra-acetoxybiphenyl (0·91 g, 45%), m.p. and mixed m.p. 137—137·5°.

4′-Amino-2,4,5-trimethoxybiphenyl (20).—2,4,5-Trimethoxy-4′-nitrobiphenyl (3 g) in ethanol (765 ml) was heated under reflux with 5% palladium–charcoal (0·77 g) and hydrazine hydrate (28·7 ml) for 1 h. The product was crystallised from ethanol–petroleum to give the *amine* (1·53 g, 58%), m.p. 121—126° (Found: C, 68·9; H, 6·5; N, 5·6. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%).

4′-Bromo-2,4,5-trimethoxybiphenyl (19).—(*a*) The foregoing amine (0·8 g) in concentrated hydrochloric acid (0·8 ml) and water (3·5 ml) was diazotised at 0° by dropwise addition of sodium nitrite (0·24 g) in water (1 ml). After 15 min at 0°, the mixture was added to copper(I) bromide (0·75 g) in 48% hydrobromic acid (3·5 ml), and the mixture was stirred for 30 min, then heated for 5 min at 100°. The tarry product was extracted with petroleum and gave the bromobiphenyl (0·4 g, 40%), m.p. and mixed m.p. 107—108°.

(*b*) Bromine (0·72 g) in acetic acid (5 ml) was added dropwise during 1 h to a stirred solution of 2,4,5-trimethoxybiphenyl[8] (1 g) in acetic acid (5 ml). After 12 h at 0°, the product (1 g) was collected and gave the bromobiphenyl (0·6 g, 45%), m.p. and mixed m.p. 107—108° (from petroleum) (Found: C, 55·7; H, 4·6. Calc. for $C_{15}H_{15}BrO_3$: C, 55·75; H, 4·7%).

Debromination of 4′-Bromo-2,4,5-trimethoxybiphenyl.—(*a*) A mixture of the 4′-bromobiphenyl (19) (0·2 g), anhydrous sodium acetate (0·2 g), and palladium black (40 mg) in ethanol (10 ml) was hydrogenated at 50° (3 atm) for 24 h. The product, purified by chromatography on a column of silica gel followed by crystallisation from petroleum, gave 2,4,5-trimethoxybiphenyl (0·12 g, 80%), m.p. and mixed m.p. 88—89°.

(*b*) Debromination of the bromobiphenyl (19) by hydrazine hydrate in the presence of 5% palladium–charcoal gave 2,4,5-trimethoxybiphenyl (61%), m.p. and mixed m.p. 88—89°.

2,4,4′,5-Tetramethoxybiphenyl (18).—A finely ground mixture of 5-bromo-1,2,4-trimethoxybenzene (1·23 g), 4-iodoanisole (1·17 g), and copper bronze (1 g) was heated in a Pyrex tube to 200°, and copper bronze (3 g) was added in portions during 30 min with continuous manual stirring. The temperature was raised to 270° and kept at 270—280° for 2 h. The hot reaction mixture was poured onto

[20] M. Nilsson and T. Norin, *Acta Chem. Scand.*, 1963, **17**, 1157.
[21] P. Brassard and P. L. Écuyer, *Canad. J. Chem.*, 1958, **36**, 700.

sand and, when cool, was extracted with acetone. The extract was chromatographed on a column of silica gel (50 g) and was eluted with increasing concentrations of benzene in petroleum. Fraction (i) consisted of 4-iodoanisole (0·1 g), fraction (ii) 5-bromo-1,2,4-trimethoxybenzene, fraction (iii) 4,4′-dimethoxybiphenyl (0·05 g) as leaflets (from petroleum), m.p. 176—177° (lit.,[22] 175°), fraction (iv) 2,4,4′,5-tetramethoxybiphenyl (0·22 g, 16%), m.p. and mixed m.p. 72—75°, and fraction (v) 2,2′,4,5,5′-hexamethoxybiphenyl (0·18 g, 22%) as needles from benzene–petroleum, m.p. 179—181° (lit.,[23] 180°).

2-*Hydroxy*-5-(4-*hydroxyphenyl*)-1,4-*benzoquinone* (21).—Sodium hydroxide (0·55 g) in water (3 ml) was added to a solution of 2,4,4′,5-tetra-acetoxybiphenyl (1·2 g) in ethanol (7 ml) under nitrogen. After 30 min, addition of concentrated hydrochloric acid (2 ml) and water (5 ml) gave a deep red solution. This was warmed to 85° and a hot solution of hydrated iron(III) chloride (2 g) in water (4 ml) was added. The mixture was cooled and the solid (0·6 g, 89%) collected. The *quinone* (21) formed a brown-black powder (from acetone), m.p. 210° (decomp.) (Found: C, 66·5; H, 3·5. $C_{12}H_8O_4$ requires C, 66·8; H, 3·7%).

Treatment of the above quinone with acetic anhydride and one drop of boron trifluoride–acetic acid complex gave 2-*acetoxy*-5-(4-*acetoxyphenyl*)-1,4-*benzoquinone* as orange-yellow needles (from methanol), m.p. 154—155° (Found: C, 64·4; H, 4·0. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%).

The pK values of the dihydroxyquinone (21) were determined by measuring the u.v. spectra of very dilute solutions of the quinone in buffers of ionic strength 0·01 at known pH values at 20°.

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[22] M. Busch and W. Schmidt, *Ber.*, 1929, **62**, 2618.
[23] R. Fabinyi and T. Szeki, *Ber.*, 1910, **43**, 2676