Synthesis of Piloquinone, a Metabolite of *Streptomyces Pilosus* Ettlinger [1]

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Synthesis of piloquinone [1,8-dihydroxy-2-methyl-3-(4-methylpentanoyl)-9,10-phenanthraquinone] (1) is described. Of the methods investigated the most successful started from 2,6-dinitrotoluene (48) which was converted into 2-bromo-6-hydroxytoluene (52). This on bromination at −70 to 20° in the presence of isopropylamine gave 3,6-dibromo-2-hydroxytoluene (53) and thence 3,6-dibromo-2-methoxytoluene (54). This was converted by an organometallic method into 4-bromo-2-methoxy-3-methylbenzaldehyde (57) which on Wittig reaction with 2-methoxybenzyltriphenylphosphonium chloride gave 4-bromo-2,2'-dimethoxy-3-methylstilbene (37). The latter was converted, *via* 4-cyano-2,2'-dimethoxy-3-methylstilbene (36), into methyl 2,2'-dimethoxy-3-methylstilbene-4-carboxylate (39), which on u.v. irradiation gave chiefly methyl 1,8-dimethoxy-2-methylphenanthrene-3-carboxylate (42). The latter on reduction and oxidation gave 1,8-dimethoxy-2-methylphenanthrene-3-carbaldehyde (44) which on reaction with isopentylmagnesium bromide followed by oxidation with Jones reagent gave 1,8-dimethoxy-2-methyl-3-(4-methylpentanoyl)phenanthrene (63). This on demethylation and acetylation gave 1,8-diacetoxy-2-methyl-3-(4-methylpentanoyl)phenanthrene (64) which on oxidation followed by treatment with base gave piloquinone (1).

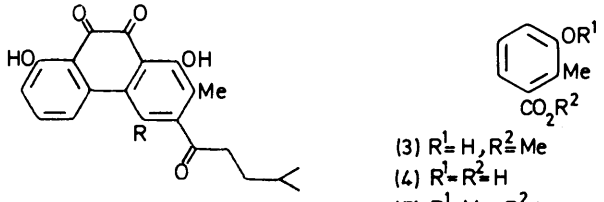
9,10-PHENANTHRAQUINONES, unlike the isomeric 9,10-anthraquinones, are extremely rare natural products. Chi *et al.*[2] reported the first natural 9,10-phenanthraquinone, claiming to have isolated a dihydroxymethyl substituted compound from *Rumex chinensis*, but we have since shown this report to be incorrect.[3] In 1963 Lederer and his co-workers isolated piloquinone (1) from the mycelium of *Streptomyces pilosus* Ettlinger, and determined its structure by a combination of classical degradative and spectroscopic methods.[4] Since then Lounasmaa and Zylber [5] have shown that 4-hydroxypiloquinone (2) co-occurs with piloquinone in *S. pilosus*.

In view of the rarity of 9,10-phenanthraquinones in nature we decided to verify the structure of piloquinone by total synthesis. The most attractive route to

[1] Preliminary communication, T. M. Cresp, R. G. F. Giles, and M. V. Sargent, *J.C.S. Chem. Comm.*, 1974, 11.
[2] J. J. Chi, S. T. Hsu, and S. Wang, *J. Chinese Chem. Soc.* (*Formosa*), 1947, **15**, 21.
[3] M. V. Sargent and D. O'N. Smith, *J. Chem. Soc.* (*C*), 1970, 329.
[4] J. Polonsky, B. C. Johnson, P. Cohen, and E. Lederer, *Bull. Soc. chim. France*, 1963, 1909; A. Gaudemar, J. Polonsky, and L. Alais, *ibid.*, p. 1918.
[5] M. Lounasmaa and J. Zylber, *Bull. Soc. chim. France*, 1970, 329.

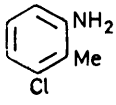
phenanthrenes involves the photocyclodehydrogenation of stilbenes,[6] but ring closure does not occur with acylstilbenes, probably because the lowest excited singlet state of the *cis*-stilbene is of the $n \longrightarrow \pi^*$, rather than the $\pi \longrightarrow \pi^*$ type.[7] We therefore decided to synthesise a stilbene which possessed a 4-substituent which could be converted into the 4-methylpentanoyl side chain after ring closure. We sought to prepare this stilbene by a Wittig reaction between 2-methoxybenzyltriphenylphosphonium chloride, readily available by reaction of triphenylphosphine and 2-methoxybenzyl chloride,[8] and a suitable 4-substituted 2-methoxy-3-methylbenzaldehyde.

We first attempted to introduce a 4-formyl group into methyl 3-hydroxy-2-methylbenzoate (3). Initially we prepared 3-hydroxy-2-methylbenzoic acid (4) by base treatment of sodium hydrogen 3-aminonaphthalene-1,5-disulphonate at high temperature and high pressure,[9,10] through the courtesy of Dr. P. Bamfield (I.C.I., Blackley), but the yield was low and we sought a more convenient alternative. 2-Amino-6-chlorotoluene (8) is readily available (Fluka) and it was converted into the phenol (9) by the method of Ullmann and Panchaud.[11] Treatment of the chlorocresol (9) with copper(I) cyanide in pyridine gave the nitrile (11) (65%) which was readily hydrolysed to the acid (4). The chloroanisole (10), available by methylation of the cresol (9), smoothly formed a Grignard reagent in tetrahydrofuran and this on carbonation gave 3-methoxy-2-methylbenzoic acid (5). During the course of our work Fringuelli *et al.*[12] described an alternative synthesis of the ester (3).



(1) R=H
(2) R=OH

(3) R^1=H, R^2=Me
(4) R^1=R^2=H
(5) R^1=Me, R^2=H
(6) R^1=CHO, R^2=Me
(7) R^1=R^2=Me



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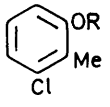
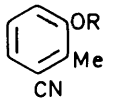
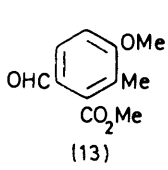


(9) R=H
(10) R=Me



(11) R=H
(12) R=$CH_2CH{=}CH_2$

Attempted formylation of the ester (3) with dichloromethyl methyl ether and titanium(IV) chloride in dichloromethane,[13] gave only the *O*-formylation product (6), a type of reaction we have observed previously with inactivated phenols.[14] Formylation under the same conditions of methyl 3-methoxy-2-methylbenzoate (7) gave chiefly methyl 6-formyl-3-methoxy-2-methylbenzoate (13) (66%) and none of the desired 4-formyl isomer. The structure of the aldehyde (13) followed from its equilibriation under acidic conditions to a mixture in which the pseudo-ester (14) predominated: methyl 2-formylbenzoate undergoes a similar equilibriation with the pseudo-ester (15) (see Experimental section).



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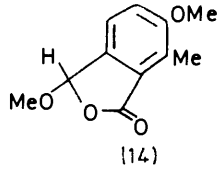

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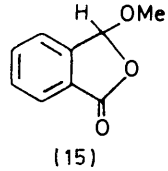

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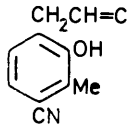

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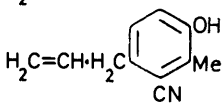

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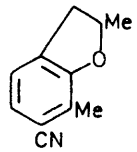

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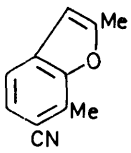

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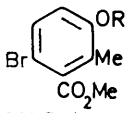
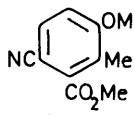


(20) R=H
(21) R=Me



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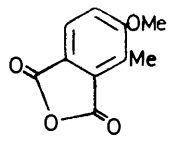


(23)

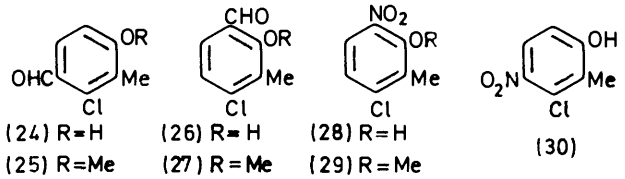
A further route to a suitable aldehyde was then investigated. Claisen rearrangement of allyl aryl ethers often gives high yields of the *o*-allylphenol.[15] The nitrile (11) was thus allylated and the ether (12) was thermally rearranged. The expected *ortho*-Claisen rearrangement product (16) was indeed the major product but was accompanied by the *para*-product (17). The *ortho*-product (16) could be separated by crystallisation in only poor yield. Its structure followed from its acid catalysed rearrangement to the coumaran (18). We had hoped that ozonolysis of the allyl compound (16) would produce a phenylacetic acid suitable for use in stilbene synthesis. As an alternative, ozonolysis of the benzofuran (19) was considered. The coumaran (18) was readily available from acid-catalysed cyclisation of the crude Claisen rearrangement product. Dehydrogenation of (18) did not occur with 2,3-dichloro-5,6-dicyanobenzoquinone in boiling benzene but readily occurred with 10% palladised charcoal in boiling diphenyl ether. However, the benzofuran (19) was difficult to separate from the reaction mixture and this route was not pursued.

Bromination of the esters (3) and (7) was studied in the

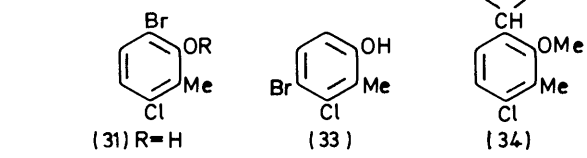
[6] C. S. Wood and F. B. Mallory, *J. Org. Chem.*, 1964, **29**, 3373; M. V. Sargent and C. J. Timmons, *J. Chem. Soc.*, 1964, 5544.
[7] F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Amer. Chem. Soc.*, 1964, **86**, 3094.
[8] R. Grice and R. L. Owen, *J. Chem. Soc.*, 1963, 1947.
[9] L. F. Fieser and W. C. Lothrop, *J. Amer. Chem. Soc.*, 1936, **58**, 749.
[10] R. E. Dean, A. Midgley, E. N. White, and D. McNeil, *J. Chem. Soc.*, 1961, 2773.
[11] F. Ullmann and P. L. Panchaud, *Annalen*, 1906, **350**, 108.
[12] F. Fringuelli, V. Mancini, and A. Taticchi, *Tetrahedron*, 1969, **25**, 4249.
[13] A. Rieche and H. Gross, *Chem. Ber.*, 1959, **92**, 83; H. Gross, A. Rieche, and G. Matthey, *ibid.*, 1963, **96**, 308.
[14] T. M. Cresp, M. V. Sargent, J. A. Elix, and D. P. H. Murphy, *J.C.S. Perkin I*, 1973, 340.
[15] A. Jefferson and F. Scheinmann, *Quart. Rev.*, 1968, **22**, 391.

hope that if the required isomer were produced the sequence ArBr ⟶ ArCN ⟶ ArCHO might be achieved. Bromination of the esters (3) and (7) gave exclusively the 6-bromo-isomers (20) and (21) respectively. Their structures followed from the conversion of (20) into (21) and thence into the nitrile (22). This on hydrolysis and dehydration yielded the phthalic anhydride (23).

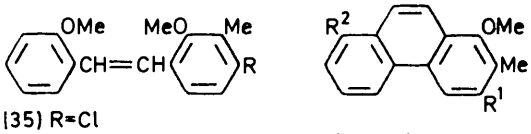
Formylation of the chlorocresol (9) was also studied. The dichloromethyl methyl ether method gave predominantly the undesired isomer (24) and only 8·5% of 4-chloro-2-hydroxy-3-methylbenzaldehyde (26), and the Duff [16] and Reimer–Tiemann methods similarly gave



(24) R=H
(25) R=Me
(26) R=H
(27) R=Me
(28) R=H
(29) R=Me
(30)



(31) R=H
(32) R=Me
(33)
(34)



(35) R=Cl
(36) R=CN
(37) R=Br
(38) R=CO_2H
(39) R=CO_2Me

(40) R^1=Cl, R^2=OMe
(41) R^1=CN, R^2=OMe
(42) R^1=CO_2Me, R^2=OMe
(43) R^1=CH_2OH, R^2=OMe
(44) R^1=CHO, R^2=OMe
(45) R^1=CO_2Me, R^2=H
(46) R^1=CN, R^2=H
(47) R^1=Cl, R^2=H

poor yields of the aldehyde (26). Formylation of the chloroanisole (10) gave only the aldehyde (25).

Other electrophilic substitutions of the chlorocresol (9) were studied. In agreement with Noelting [17] nitration of (9) gave 37% of 6-chloro-2-hydroxy-3-nitrotoluene (28) which was separated by steam-distillation from the isomer (30) (26%). Attempts to replace the chloro-substituent by a cyano-group in (28) or the derived anisole (29) failed.

Bromination of the chlorocresol (9) gave 34% of 3-bromo-6-chloro-2-hydroxytoluene (31) which was readily separated from its isomer (33) (60%) by virtue of its greater volatility and chromatographic mobility. The derived anisole (32) readily afforded a mono-Grignard reagent. This smoothly reacted with diethyl phenyl orthoformate [18] and the crude product was treated with acid to yield 4-chloro-2-methoxy-3-methylbenzaldehyde (27), identical with that obtained by methylation of the *o*-hydroxyaldehyde (26). The derived ethylene acetal (34), unlike the chloroanisole (10), could not be induced to form a Grignard reagent.

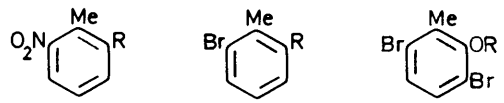
In situ Wittig reaction of 2-methoxybenzyltriphenylphosphonium chloride and the aldehyde (27) with lithium methoxide as base gave the stilbene (35) in high yield. When methanol was used as solvent the predominant product was the *trans*-isomer of (35), m.p. 55—56°; with *NN*-dimethylformamide as solvent the *cis*-isomer, m.p. 89—90°, predominated. The olefinic proton signals of these isomers were obscured by those of the aromatic protons in the n.m.r. spectra of both isomers, and the stereochemical assignments follow from the u.v. spectra of these compounds (see Table), and from the i.r. spectrum of the *trans*-isomer which showed a C–H out of plane deformation band near 970 cm^{-1}.[19] It is interesting that the *cis*-isomer has a higher m.p. than the *trans*-isomer: the isomeric bromo-compounds (37) are similar. In order to replace the chloro-substituent in stilbene (35) by cyano it was necessary to use boiling hexamethylphosphoric triamide as solvent, and the yield of the nitrile (36) was only 19%.

U.v. spectra of stilbenes

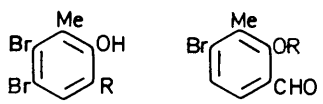
Stilbene	Conjugation band $\lambda_{max.}$/nm
cis-2,2′-Dimethoxy-	319
trans-2,2′-Dimethoxy-	332
cis-(35)	295
trans-(35)	330
cis-(37)	288
trans-(37)	333
trans-(36)	345
trans-(39)	345
trans-(59)	347

Photocyclodehydrogenation of the chlorostilbene (35) gave the chlorophenanthrene (40) and traces of the phenanthrene (47) (detected by t.l.c.). Attempts to form a Grignard reagent from this product, or to replace the chloro-substituent by cyano were fruitless.

In order to obtain a higher yield of the nitrile (36), we decided to synthesise the bromo-stilbene (37). 2,6-Dinitrotoluene (48) was converted into the amine



(48) R=NO_2
(49) R=NH_2
(50) R=NO_2
(51) R=NH_2
(52) R=OH
(53) R=H
(54) R=Me



(55) R=H
(56) R=Br
(57) R=Me
(58) R=H

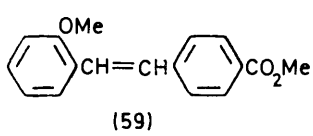
(49) and thence, *via* (50) and (51), to 2-bromo-6-hydroxytoluene (52). Janney [20] reported that bromination of

[16] J. C. Duff and V. I. Furness, *J. Chem. Soc.*, 1951, 1512; J. C. Duff, *ibid.*, 1941, 547.
[17] E. Noelting, *Ber.*, 1904, **37**, 1015.
[18] H. Stetter and E. Reske, *Chem. Ber.*, 1970, **103**, 643.
[19] L. J. Bellamy, ' The Infrared Spectra of Complex Molecules,' 2nd edn., Methuen, London, 1958, p. 45.
[20] N. W. Janney, *Annalen*, 1913, **398**, 354.

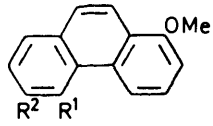
compound (52) gave solely the dibromo-compound (53) and none of its isomer (55), although his structural proof was tenuous. In our hands bromination of compound (52) gave the dibromo-compound (53) (36%) and its isomer (55) (53%). The former was more volatile in steam. Bromination of compound (52) by the method of Pearson *et al.*[21] for specific *ortho*-bromination of phenols, with 1 mol. equiv. of bromine gave the dibromo-compound (53) (43%) and the tribromo-compound (56). By using only 0·5 mol. equiv. of bromine in this method the yield of the desired dibromo-compound (53) was 97%, allowing for the recovered starting material, which was easily separated by crystallisation and chromatography. The dibromo-compound (53) was converted into the methyl ether (54). It was expected that metal–halogen interconversion with 1 mol. equiv. of phenyl-lithium would only occur at the bromo-substituent *ortho* to the methoxy-group [22] and as expected the aldehyde (57) produced (79%) on reaction of the lithio-compound with *NN*-dimethylformamide underwent smooth demethylation with boron trichloride [23] to yield the intramolecularly-hydrogen bonded *o*-hydroxy-aldehyde (58).

The aldehyde (57) and 2-methoxybenzyltriphenylphosphonium chloride on Wittig reaction gave a high yield of the bromo-stilbene (37). As with the Wittig reaction of the chloroaldehyde (27) (see above), with methanol as solvent the major product was the *trans*-isomer of (37), m.p. 53—54°, and with *NN*-dimethylformamide as solvent the major product was the *cis*-isomer, m.p. 86—88°. The peculiarity in m.p. of the two isomers should again be noted. The bromo-stilbene (37) gave the cyano-stilbene (36) (85%) on treatment with copper(I) cyanide in boiling *NN*-dimethylformamide.[24] Compound (36) was hydrolysed to the acid (38) which was methylated to give the ester (39) in good overall yield.

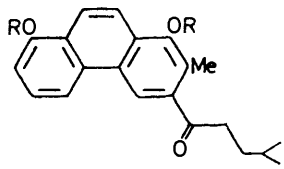
U.v. irradiation of the ester (39) gave the expected phenanthrene (42) (35%) and the phenanthrene (45) (16%). Similar irradiation of the cyano-stilbene (36) gave the expected phenanthrene (41) (31%) and the phenanthrene (46) (11%). Irradiation of methyl 2'-methoxystilbene-4-carboxylate (59), synthesised by Wittig reaction between *o*-anisaldehyde and the appropriate phosphonium salt, was also studied, since the expected product (60) was required for model reactions (see below). This stilbene (59) on u.v. irradiation gave the phenanthrene (60) (17%) and methyl phenanthrene-3-carboxylate (6%). The minor products (45), (46), and methyl phenanthrene-3-carboxylate, in the above photochemical reactions all arise by ring closure with loss of methanol.* The structures of (45) and (46) followed from their n.m.r. spectra which clearly showed the deshielded 4- and 5-protons. Had cyclisation with loss of methanol occurred in the opposite sense the products would have been (61) and (62) which possess no aromatic proton at the 5-position. The formation of the phenanthrenes (61) and (62) is presumably prevented by steric hindrance in the transition state leading to these products.



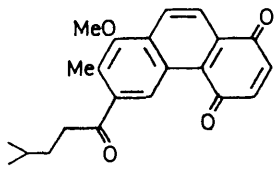
(59)



(60) R^1=H, R^2=CO_2Me
(61) R^1=Me, R^2=CO_2Me
(62) R^1=Me, R^2=CN



(63) R=Me
(64) R=Ac



(65)

With a view to the introduction of the 4-methylpentanoyl side chain the phenanthrene (60) was hydrolysed and the derived carboxylic acid treated with 2 mol. equiv. of isopentyl-lithium.[25] Only a trace of ketone was produced. We therefore treated the cyanophenanthrene (41) with isopentylmagnesium bromide. This latter phenanthrene was also synthesised from the ester (42). Reduction of (42) with lithium aluminium hydride gave the alcohol (43) (99%), which was oxidised with activated manganese dioxide [26] in boiling chloroform to the aldehyde (44) (92%), which on oximation and dehydration gave the nitrile (41). Reaction of the latter with isopentylmagnesium bromide gave the required (4-methylpentanoyl)phenanthrene (63) in only 5% yield.

Ketone (63) was best prepared (56%) by reaction of the aldehyde (44) with isopentylmagnesium bromide followed by oxidation of the crude secondary alcohol so obtained with Jones reagent in acetone. A minor unexpected product of this reaction was the quinone (65), whose structure followed from its n.m.r. spectrum, in which the 5-proton was highly deshielded.[27]

The ketone (63) was demethylated with boron tribromide [28] and the resulting crude phenol was acetylated

* For a study of the photocyclisation of *o*-methoxystilbenes with loss of methanol see the following paper.

[21] D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, 1967, **32**, 2358; see also M. Fieser and L. Fieser, 'Reagents for Organic Synthesis,' vol. 2, Wiley–Interscience, New York, 1969, p. 43.

[22] G. Wittig and U. Pockels, *Ber.*, 1939, **72**, 89; H. Gilman, W. Langham, and F. W. Moore, *J. Amer. Chem. Soc.*, 1940, **62**, 2327; G. I. Feutrill, R. N. Mirrington, and R. J. Nichols, *Austral. J. Chem.*, 1973, **26**, 345.

[23] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

[24] L. Friedman and H. Shechter, *J. Org. Chem.*, 1961, **26**, 2522.

[25] C. Tegner, *Acta Chem. Scand.*, 1952. **6**, 782.

[26] O. Mancera, G. Rosenkrantz, and F. Sondheimer, *J. Chem. Soc.*, 1953, 2189.

[27] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon. Oxford, 1969, pp. 91 and 207.

[28] J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, 1968, **24**, 2289.

to give the diacetate (64) (48%). Oxidation with chromium trioxide in aqueous acetic acid at 70° followed by hydrolysis of the crude product gave piloquinone (1) (18%). Synthetic piloquinone was identical (mixed m.p., t.l.c., n.m.r., and mass spectra) with the natural material.

EXPERIMENTAL

M.p.s were determined on a Kofler block. Silica gel was B.D.H. 60—120 mesh. Light petroleum refers to a fraction b.p. 58—65°. The phrase ' and was worked up in the usual way ' indicates that the mixture was extracted with the indicated solvent and was then washed successively with water, or acid or base followed by water as appropriate, then with saturated brine, and finally dried (Na_2SO_4). The solvent was then removed under diminished pressure. U.v. spectra were determined for ethanolic solutions using a Perkin-Elmer 137 spectrophotometer. I.r. spectra were determined using a Perkin-Elmer 337 grating spectrophotometer. N.m.r. spectra were determined for solutions in carbon tetrachloride, unless stated otherwise, using a Varian A-60-A spectrometer. Molecular weights were determined by mass spectrometry; for low resolution a Varian-MAT CH-7 instrument was used, and for high resolution an A.E.I. MS-902 instrument was used, both instruments being operated at 70 eV.

2-*Methoxybenzyltriphenylphosphonium Chloride*.—Methyl sulphate (114 ml) was added dropwise over 0·5 h to a stirred mixture of freshly distilled salicylaldehyde (122 g), potassium carbonate (345 g), and dry *NN*-dimethylformamide (DMF) (450 ml) under dry nitrogen. The mixture was stirred at room temperature for 20 h. Water and dilute hydrochloric acid were added and the mixture was worked up in the usual way (ether). Fractionation under reduced pressure afforded 2-methoxybenzaldehyde (119·3 g, 88%), b.p. 120—122° at 18 mmHg (lit.,[29] 94—95° at 5 mmHg). Sodium borohydride (12 g) in aqueous sodium hydroxide (5%; 250 ml) was added dropwise over 15 min to an ice-cooled, stirred solution of the anisaldehyde (50 g) in methanol (200 ml). The mixture was set aside overnight and then the bulk of the methanol was removed on a rotary evaporator, water was added, and the mixture was worked up in the usual way (ethyl acetate). Removal of the solvent left 2-methoxybenzyl alcohol as an oil (48·4 g, 96%). This was converted by the method of Grice and Owen [8] into 2-methoxybenzyl chloride (82·5%), b.p. 64—65° at 0·3 mmHg (lit.,[8] 52—54° at 0·1 mmHg). The chloride (35 g) was added to a solution of triphenylphosphine (64·5 g) in dry toluene (100 ml) and the solution was heated for 15 h at 110° (bath). The mixture was cooled, and the solid was filtered off, washed with dry ether, and dried *in vacuo* to yield the *phosphonium salt* (86·5 g, 92·5%), prisms (from dichloromethane–dry ether), m.p. 242—244° (Found: C, 74·2; H, 5·7; Cl, 8·5. $C_{26}H_{24}ClOP$ requires C, 74·55; H, 5·75; Cl, 8·45%).

2-*Cyano*-6-*hydroxytoluene* (12).—2-Chloro-6-hydroxytoluene [11] (9) (5·0 g) was heated under gentle reflux with copper(I) cyanide (3·8 g) and pyridine (2·3 ml) for 6 h. The mixture was cooled and then stirred at 60—70° for 0·5 h with iron(III) chloride hexahydrate (14 g) in water (25 ml) and concentrated hydrochloric acid (5 ml). The cooled mixture was worked up in the usual way (ethyl acetate) and the crude product was crystallised from benzene (charcoal) to afford needles of the nitrile (11) (3·05 g, 65%), m.p. 200—201·5° (lit.,[17] 195°) (Found: C, 72·4; H, 5·05; N, 10·6%; M^+, 133. Calc. for C_8H_7NO: C, 72·2; H, 5·25; N, 10·55%; *M*, 133), $\nu_{max.}$ (KCl) 2215 (CN) cm^{-1}. On the larger scale it was more convenient to separate the crude nitrile by filtration, after treatment with iron(III) chloride, and to crystallise it from methanol (charcoal).

3-*Hydroxy*-2-*methylbenzoic Acid* (4).—The nitrile (11) (2·0 g) was heated under reflux for 18 h with water (4 ml), glacial acetic acid (4 ml), and concentrated sulphuric acid (4 ml). The solution was poured over ice and worked up in the usual way (ethyl acetate) to afford the acid (4) (1·83 g, 80%) which formed plates from chloroform, m.p. 145—146° (lit.,[10] 145—146°). The methyl ester (5) (methanol–sulphuric acid) formed laths from cyclohexane, m.p. 82—83° (lit.,[12] 75—76°) (Found: C, 64·95; H, 6·2%; M^+, 166. Calc. for $C_9H_{10}O_3$: C, 65·05; H, 6·05%; *M*, 166). On methylation (Me_2SO_4–K_2CO_3–Me_2CO) the acid formed methyl 3-methoxy-2-methylbenzoate (7) as an oil, b.p. 100—102° at 1 mmHg (lit.,[30] 113° at 5 mmHg).

3-*Methoxy*-2-*methylbenzoic Acid* (6).—2-Chloro-6-methoxytoluene [11] (10) (10·0 g) in dry tetrahydrofuran (35 ml) was stirred and heated under reflux with magnesium turnings (1·7 g) and a crystal of iodine under dry nitrogen. After 24 h a stream of carbon dioxide was passed over the stirred, cooled solution for several h. The mixture was diluted with benzene and the product (6) (7·5 g, 70%) was obtained in the usual way. It crystallised from cyclohexane as plates, m.p. 148—149° (lit.,[10] 152°). On esterification (methanol–sulphuric acid) it gave the methyl ester (7) identical with that already described.

Formylation of Methyl 3-*Hydroxy*-2-*methylbenzoate* (3).—The phenol (4) (500 mg) in dichloromethane (2 ml) was stirred and cooled to 0° and powdered aluminium chloride (820 mg) was added followed dropwise by dichloromethyl methyl ether (0·53 ml). The mixture was stirred at room temperature for 20 min and iced water was then added. The mixture was worked up in the usual way (ether) to give an almost quantitative yield of crude methyl 3-formyloxy-2-methylbenzoate (6). A sample was distilled, b.p. 105—117° (bath) at 2 mmHg, and the distillate chromatographed over a silica gel layer plate (20 × 20 × 0·1 cm) with 20% ether–pentane as eluant. The major band was separated and redistilled, b.p. 90—95° (bath) at 0·1 mmHg, to yield the ester (6) as an *oil* (Found: M^+, 194·0600. $^{12}C_{10}{}^1H_{10}{}^{16}O_4$ requires *M*, 194·0579), τ 1·78 (1H, s, O·CHO), 2·17—2·89 (3H, m, ArH), 6·19 (3H, s, OMe), and 7·62 (3H, s, Me), $\nu_{max.}$ (CCl_4) 1755 (O–CHO) and 1730 (CO_2Me) cm^{-1}. Similar results were obtained when titanium(IV) chloride was used as catalyst.

Formylation of Methyl 3-*Methoxy*-2-*methylbenzoate* (7).—A solution of the ester (7) (2·15 g) and titanium(IV) chloride (2·6 ml) in dichloromethane (40 ml) was stirred at 0° during the addition of dichloromethyl methyl ether (8·4 ml) in dichloromethane (8 ml) over 15 min. The cooling bath was removed and the mixture was stirred at room temperature for 5 h and then poured into ice–dilute hydrochloric acid. The mixture was worked up in the usual way (dichloromethane) and the crude product was preadsorbed on silica gel and chromatographed over a column of silica gel with 10—20% ethyl acetate–light petroleum as eluant. Early fractions gave 3-*ethoxy*-6-*methoxy*-7-*methylphthalide* (191 mg), blades (from dichloromethane–light petroleum), m.p.

[29] B. C. Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 1835.
[30] M. S. Carpenter and W. M. Easter, *J. Org. Chem.*, 1955, **20**, 401.

98—100° (Found: C, 64·95; H, 6·4%; M^+, 222. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%; M, 222), τ ($CDCl_3$) 2·66 and 2·90 (2H, ABq, J 8·0 Hz, 4- and 5-H), 3·80 (1H, s, 3-H), 6·10 (3H, s, OMe), 6·18 (2H, q, OCH_2CH_3), 7·44 (3H, s, Me), and 8·68 (3H, t, OCH_2CH_3). Further elution gave *methyl 6-formyl-3-methoxy-2-methylbenzoate* (13) (1·64 g, 66%), prisms (from light petroleum), m.p. 63—64·5° (Found: C, 63·2; H, 5·85%; M^+, 208. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%; M, 208), τ 0·33 (1H, s, CHO), 2·47 and 3·13 (2H, ABq, J 8·0 Hz, 5- and 4-H), 6·13 and 6·17 (each 3H, s, OMe), and 7·92 (3H, s, Me), $\nu_{max.}$ ($CHCl_3$) 1730 (CO_2Me) and 1690 (CHO) cm^{-1}. Further elution gave *3-hydroxy-6-methoxy-7-methylphthalide* (364 mg), needles (from aqueous acetone), m.p. 172—173° (Found: C, 61·95; H, 5·15%; M^+, 178. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%; M, 178), τ [$(CD_3)_2CO$] 2·53 and 2·76 (2H, ABq, J 8·5 Hz, 4- and 5-H), 3·49br (1H, s, 3-H), 6·09 (3H, s, OMe), and 7·53 (3H, s, Me).

Acid-catalysed Cyclisation of Methyl 6-Formyl-3-methoxy-2-methylbenzoate (13).—The ester (14) (410 mg) and concentrated sulphuric acid (0·5 ml) in absolute methanol (40 ml) were heated under reflux for 23 h. Most of the methanol was removed under reduced pressure and the residue was diluted with water and worked up in the usual way (ether). The crude product was analysed by n.m.r. spectroscopy. It contained the pseudo-ester (14) (86%) and the normal ester (13) (14%). On crystallisation from dichloromethane–light petroleum it yielded *3,6-dimethoxy-7-methylphthalide* (14) as needles, m.p. 134—135° (Found: C, 62·85; H, 5·7. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%), τ ($CDCl_3$) 2·67 and 2·90 (2H, ABq, J 8·5 Hz, 4- and 5-H), 3·82 (1H, s, 3-H), 6·09 (3H, s, 6-OMe), 6·41 (3H, s, 3-OMe), and 7·43 (3H, s, Me).

Acid-catalysed Rearrangement of 3-Methoxyphthalide (15).—3-Methoxyphthalide was prepared by heating *o*-formylbenzoic acid under reflux in dry methanol. It formed plates from cyclohexane, m.p. 43—44° (lit.,[31] 46—47°), τ 2·10—2·55 (4H, m, ArH), 3·79 (1H, s, 3-H), and 6·46 (3H, s, OMe), $\nu_{max.}$ (CH_2Br_2) 1745 (CO) cm^{-1}. The pseudo-ester (15) (750 mg) was heated under reflux for 18 h with 10% w/v dry methanolic hydrogen chloride solution (75 ml) and the solvent was then removed under reduced pressure. The residue was worked up in the usual way (ether). N.m.r. spectroscopy indicated that the residue contained the pseudo-ester (15) (71%) and *o*-formylbenzoate (29%).

Acid-catalysed Cyclisation of Methyl o-Formylbenzoate.—Methyl *o*-formylbenzoate[32] on treatment as above gave the pseudo-ester (15) (67%) and the normal ester (33%).

2-Allyloxy-6-cyanotoluene (12).—2-Cyano-6-hydroxytoluene (11) (12·6 g), allyl bromide (13·8 g), and potassium carbonate (26 g) were stirred at room temperature for 18 h in dry DMF (50 ml). The mixture was poured into dilute hydrochloric acid and worked up in the usual way (ether). The crude product gave the ether (12) as *needles* (from light petroleum) (14·5 g, 89%), m.p. 44—45° (Found: C, 76·3; H, 6·7; N, 8·0. $C_{11}H_{11}NO$ requires C, 76·25; H, 6·4; N, 8·1%), τ 2·79—3·21 (3H, m, ArH), 3·69—4·28 (1H, m, $CH_2CH{=}CH_2$), 4·67 (2H, m, $CH_2CH{=}CH_2$), 5·48 (2H, m, $CH_2CH{=}CH_2$), and 7·59 (3H, s, Me).

Claisen Rearrangement of 2-Allyloxy-6-cyanotoluene (12).—The allyl ether (12) (5·0 g) was sealed in a tube and heated for 5 h in the vapour of boiling tetralin. The crude product was dissolved in ether and extracted with dilute sodium hydroxide solution. The extract was acidified and the crude phenols (2·84 g) were isolated with ether in the usual way. Repeated crystallisation of this material from light petroleum gave a small sample of *3-allyl-6-cyano-2-hydroxytoluene* (16) as needles, m.p. 68—69° (Found: C, 75·85; H, 6·6; N, 8·0%; M^+, 173. $C_{11}H_{11}NO$ requires C, 76·25; H, 6·4; N, 8·1%; M, 173), τ ($CDCl_3$) 2·75 and 2·91 (2H, ABq, J 8·5 Hz, 5- and 4-H), 2·7—3·0 (3H, m, $CH_2CH{=}CH_2$), 4·52 (1H, s, D_2O exchangeable, OH), 6·51 (2H, m, $CH_2CH{=}CH_2$), and 7·52 (3H, s, Me). This material was homogeneous on g.l.c. [Varian Aerograph model 1400; 3% OV-17 on Chromosorb W (acid washed-DMCS) column (⅛ in × 5 ft); injection temp. 200°; column temp. 150°; detector temp. 180°; nitrogen flow rate 9·7 ml min^{-1}], t_R 4·15 min. The crude mixture of phenols migrated as one spot on t.l.c. in a variety of solvent systems, and had M^+ at *m/e* 173 in the mass spectrum. Analysis by g.l.c. as above indicated that it contained the phenol (16) (79%), and presumably 3-allyl-2-cyano-6-hydroxytoluene (17) (21%), t_R 5·15 min, under the above conditions.

Acid Treatment of the Claisen Product.—The foregoing mixture of phenols (297 mg) was heated with hydrogen bromide (45% w/v) in glacial acetic acid (1·5 ml) and glacial acetic acid (5 ml) on a steam-bath for 2·25 h. The mixture was poured into water and worked up in the usual way (ether) to give *6-cyano-2,3-dihydro-2,7-dimethylbenzofuran* (18) (193 mg), needles (from pentane), m.p. 67—68° (Found: C, 76·15; H, 6·5; N, 8·35. $C_{11}H_{11}NO$ requires C, 76·25; H, 6·4; N, 8·1%), τ 2·98 (2H, apparent s, 4- and 5-H), 5·02 (1H, m, 2-H), 6·39—7·37 (2H, m, 3-H), 7·69 (3H, s, 7-Me), and 8·52 (3H, d, 2-Me). Similar treatment of the pure phenol (16) gave the coumaran (18) (79%), identical with that described above.

6-Cyano-2,7-dimethylbenzofuran (19).—The foregoing coumaran (18) (1·65 g) and 10% palladised charcoal (1·0 g) in diphenyl ether (10 g) were heated under reflux under nitrogen for 5 h. The mixture was cooled and diluted with dichloromethane and the catalyst separated by filtration. The residue left on removal of the solvent was steam-distilled. The diphenyl ether mixed with some of the benzofuran passed over first, and this was followed by the pure *benzofuran* (19) (429 mg, 26%), which after isolation with ether gave laths (from dichloromethane–light petroleum), m.p. 125·5—126° (Found: C, 76·9; H, 5·45; N, 8·2. $C_{11}H_9NO$ requires C, 77·15; H, 5·3; N, 8·2%), τ ($CDCl_3$) 2·92 (2H, s, 4- and 5-H), 3·80br (1H, s, 3-H), and 7·43 and 7·58 (each 3H, s, Me).

Bromination of Methyl 3-Hydroxy-2-methylbenzoate (3).—Bromine (3·92 g) in dichloromethane (10 ml) was added rapidly to a stirred solution of the phenol (3) (4·07 g) in dichloromethane (10 ml). The mixture was stirred for a further 10 min and then poured into water and worked up in the usual way (ether). The crude product was crystallised from dichloromethane–light petroleum and gave *methyl 6-bromo-3-hydroxy-2-methylbenzoate* (20) (5·34 g, 92%) as prisms, m.p. 88—90° (Found: C, 44·2; H, 3·75. $C_9H_9BrO_3$ requires C, 44·1; H, 3·7%), τ 2·92 and 3·42 (2H, ABq. J 8·5 Hz, 5- and 4-H), 6·09 (3H, s, OMe), and 7·90 (3H, s, Me). On methylation (Me_2SO_4–K_2CO_3–Me_2CO) this afforded *methyl 6-bromo-3-methoxy-2-methylbenzoate* (21) as an oil, b.p. 136—140° at 2 mmHg (Found: C, 46·05; H, 4·25. $C_{10}H_{11}BrO_3$ requires C, 46·35; H, 4·3%), τ 2·76 and 3·37 (2H, ABq, J 8·5 Hz, 5- and 4-H), 6·16 and 6·23 (each 3H, s, OMe), and 7·90 (3H, s, Me). On hydrolysis with aqueous methanolic sodium hydroxide this gave the corresponding *acid* as laths (from dichloromethane–light

[31] K. von Auwers and A. Heinze, *Ber.*, 1919, **52**, 584.

[32] C. Brown and M. V. Sargent, *J. Chem. Soc.* (*C*), 1969, 1818.

petroleum), m.p. 90—91° (Found: C, 44·95; H, 3·65. $C_9H_9BrO_3$ requires C, 44·1; H, 3·7%).

Bromination of Methyl 3-Methoxy-2-methylbenzoate (7).—On bromination as before this gave methyl 6-bromo-3-methoxy-2-methylbenzoate (21) (92·5%), identical with that already described. Hydrolysis gave the corresponding acid, identical with that already described.

Reaction of Methyl 6-Bromo-3-methoxy-2-methylbenzoate (21) *with Copper*(I) *Cyanide*.—The bromo-compound (21) (4·72 g) and copper(I) cyanide (2·5 g) were heated under gentle reflux in DMF (10 ml) for 16 h. The mixture was cooled and water (25 ml), concentrated hydrochloric acid (10 ml), and iron(III) chloride hexahydrate (20 g) were added, and the resulting mixture was maintained at 70° for 0·5 h. Work-up in the usual way (ethyl acetate) gave the crude product which was boiled with two successive portions of light petroleum (each 200 ml), and filtered. Concentration of the extract gave *methyl 6-cyano-3-methoxy-2-methylbenzoate* (22) (2·66 g, 71%), as fine needles (from light petroleum), m.p. 71—72° (Found: C, 64·5; H, 5·55; N, 6·9. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N, 6·85%), τ 2·53 and 3·11 (2H, ABq, *J* 9·0 Hz, 5- and 4-H), 6·02 and 6·08 (each 3H, s, OMe), and 7·78 (3H, s, Me). The residue (0·4 g) insoluble in light petroleum was crystallised from methanol (charcoal) and formed needles of *4-methoxy-3-methylphthalimide*, m.p. 269—270° (subl. from 255°) (Found: C, 62·9; H, 4·8; N, 7·3%; M^+, 191. $C_{10}H_9NO_3$ requires C, 62·8; H, 4·75; N, 7·35%; *M*, 191), $\nu_{max.}$ (Nujol) 1760 (CO) and 1745 (CO) cm^{-1}. On methylation (Me_2SO_4–K_2CO_3–Me_2CO) this afforded *4-methoxy-3-methyl-N-methylphthalimide*, fine needles, m.p. 184—185° (from dichloromethane–light petroleum) (Found: C, 64·7; H, 5·1; N, 7·1%; M^+, 205. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N. 6·85%; *M*, 205), τ ($CDCl_3$) 2·35 and 3·02 (2H, ABq, *J* 9·0 Hz, 6- and 5-H), 6·09 (3H, s, OMe), 6·90 (3H, s, NMe), and 7·47 (3H, s, Me), $\nu_{max.}$ (Nujol) 1760 (CO) and 1710 (CO) cm^{-1}.

Hydrolysis of the Cyanobenzoate (22).—Hydrolysis of the nitrile (22) with aqueous ethanolic sodium hydroxide gave *4-methoxy-3-methylphthalic acid*, small laths (from chloroform–acetone), m.p. 175—178° (decomp.) (Found: C, 56·6; H, 5·15. $C_{10}H_{10}O_5$ requires C, 57·15; H, 4·80%). This was dehydrated by heating under reflux in acetic anhydride and formed the corresponding *anhydride* (23), felted needles, m.p. 136—136·5° [from dichloromethane–light petroleum (charcoal)] (Found: C, 62·2; H, 4 15. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%), τ ($CDCl_3$) 2·17 and 2·78 (2H, ABq, *J* 8·0 Hz, 6- and 5-H), 5·98 (3H, s, OMe), and 7·43 (3H, s, Me), $\nu_{max.}$ (Nujol) 1830 (CO) and 1770 (CO) cm^{-1}.

Formylation of 2-Chloro-6-hydroxytoluene (9).—(a) *Dichloromethyl methyl ether method*. Titanium(IV) chloride (5·8 ml) was added to a stirred solution of the phenol (9) (5·0 g) in dichloromethane (25 ml) at 0°. A solution of dichloromethyl methyl ether (6·05 g) in dichloromethane (10 ml) was then added with stirring over 0·5 h at 0°. The cooling bath was removed and the mixture was stirred for a further 1 h then poured into ice–dilute hydrochloric acid. Work-up in the usual way (dichloromethane) gave the crude product which was preadsorbed from dichloromethane onto silica gel and chromatographed over a column of silica gel with 5% ethyl acetate–light petroleum as eluant. Early fractions gave 4-chloro-2-hydroxy-3-methylbenzaldehyde (26) admixed with 2-chloro-6-formyloxytoluene. This mixture in ether was extracted exhaustively with 5% aqueous sodium hydroxide. Acidification of the extract and isolation with ether in the usual way gave *4-chloro-2-hydroxy-3-methylbenzaldehyde* (26) (494 mg, 8·5%), as needles (from light petroleum), m.p. 61—62° (Found: C, 56·45; H, 4·5%; M^+, 172/170. $C_8H_7ClO_2$ requires C, 56·3; H, 4·1%; *M*, 172/170), τ −1·29 (1H, s, OH), 0·19 (1H, s, CHO), 2·72 and 3·08 (2H, ABq, *J* 8·0 Hz, 6- and 5-H), and 7·74 (3H, s, Me), $\nu_{max.}$ (CCl_4) 3100 (OH) and 1660 (CO) cm^{-1}. This was methylated with Me_2SO_4–K_2CO_3–DMF and afforded *4-chloro-2-methoxy-3-methylbenzaldehyde* (27) as needles, m.p. 69—70° (from light petroleum) (Found: C, 58·5; H, 4·55%; M^+, 186/184. $C_9H_9ClO_2$ requires C, 58·55; H, 4·9%; *M*. 186/184), τ −0·23 (1H, s, CHO), 2·42 and 2·81 (2H, ABq, *J* 8·5 Hz, 6- and 5-H), 6·14 (3H, s, OMe), and 7·65 (3H, s, Me), $\nu_{max.}$ (CCl_4) 1690 (CO) cm^{-1}. The neutral material gave 2-chloro-6-formyloxytoluene (600 mg, 10%) as an oil, b.p. 105—110° (bath) at 0·2 mmHg, τ 1·80 (1H, s, O·CHO), 2·6—3·3 (3H, m, ArH), and 7·78 (3H, s, Me), $\nu_{max.}$ (film) 1740 (O·CHO) cm^{-1}, *m/e* 172/170 (M^+). The column was extruded and extracted with hot ethyl acetate. The extract was evaporated and the residue crystallised from chloroform–methanol to afford needles (2·32 g, 39%) of *2-chloro-4-hydroxy-3-methylbenzaldehyde* (24), m.p. 189—190° (Found: C, 56·05; H, 4·5. $C_8H_7ClO_2$ requires C, 56·3; H, 4·1%), τ (Me_2CO) −0·27 (1H, s, CHO) and 2·38 and 3·08 (2H, ABq, *J* 8·5 Hz, 6- and 5-H). This on methylation as before gave *2-chloro-4-methoxy-3-methylbenzaldehyde* (25) as needles, m.p. 63—64° (from light petroleum) (Found: C, 58·7; H, 4·85%; M^+, 186/184. $C_9H_9ClO_2$ requires C, 58·55; H, 4·9%; *M*, 186/184), τ −0·26 (1H, s, CHO), 2·38 and 3·28 (2H, ABq, *J* 8·5 Hz, 6- and 5-H), 6·12 (3H, s, OMe), and 7·78 (3H, s, Me).

(b) *Duff method*. This reaction was based on the method of Berres.[33] A melt of the phenol (9) (14·25 g), hexamethylenetetramine (7·5 g), and paraformaldehyde (12·5 g) at 110° (bath) was treated dropwise with stirring over 1 h with acetic acid (30 ml). Stirring and heating were continued during the addition of concentrated hydrochloric acid (34 ml) over 1 h and after an additional 0·5 h the mixture was steam-distilled. Ether extraction of the distillate gave 4-chloro-2-hydroxy-6-methylbenzaldehyde (26) (864 mg, 5%) identical with that already described.

(c) *Reimer–Tiemann method*. This reaction was based on the method of Hodgson and Jenkinson.[34] A stirred mixture of the phenol (9) (23·6 g), calcium hydroxide (70 g), and sodium carbonate (80 g) in water was maintained at 60—65° during the dropwise addition of chloroform (52 g) over 20 min. The mixture was then stirred and heated on a steam-bath for 1 h. After acidification, the mixture was steam-distilled, and the product (4·6 g) isolated from the distillate with ether. It consisted of the starting phenol (9) and 4-chloro-2-hydroxy-6-methylbenzaldehyde (26) (30%) (as judged by n.m.r. spectroscopy).

Formylation of 2-Chloro-6-methoxytoluene (10).—Titanium(IV) chloride (3·2 ml) was added to a solution of the anisole (10) (3·05 g) in dichloromethane (15 ml) at 0°. Dichloromethyl methyl ether (3·4 g) in dichloromethane (5 ml) was then added with stirring over 5 min, and the mixture was stirred for 1 h at room temperature. Work-up in the usual way (dichloromethane) gave 2-chloro-4-methoxy-3-methylbenzaldehyde (25) (2·42 g, 67·5%) as needles, m.p. 63—64°, identical with that already described.

Nitration of 2-Chloro-6-hydroxytoluene (9).—(*a*) To a

[33] C. Berres, G.P. 952,629/1956.

[34] H. H. Hodgson and T. A. Jenkinson, *J. Chem. Soc.*, 1927 1740.

mixture of sodium nitrate (2·11 g), water (5·6 ml), and concentrated sulphuric acid (1·95 ml) was added dropwise a solution of the phenol (9) (2·0 g) in glacial acetic acid (5 ml). After stirring for 12 h the mixture was diluted with water and worked up in the usual way (ether). The crude product was steam-distilled and the distillate further purified by chromatography over a column of silica gel with light petroleum as eluant. This gave 6-chloro-2-hydroxy-3-nitrotoluene (28) (0·92 g, 35%), as yellow needles (from cyclohexane), m.p. 62—63° (lit.,[17] 64·5°), τ −1·17 (1H, s, OH), 2·09 and 3·01 (2H, ABq, J 9·0 Hz, 4- and 5-H), and 7·63 (3H, s, Me), $\nu_{max.}$ (CCl_4) 3115br (OH), 1525 (NO_2), and 1340 (NO_2) cm^{-1}. On methylation (Me_2SO_4–K_2CO_3–Me_2CO) it yielded *6-chloro-2-methoxy-3-nitrotoluene* (29), needles (from pentane), m.p. 41—42° (Found: C, 47·8; H, 4·15; N, 6·95. $C_8H_8ClNO_3$ requires C, 47·65; H, 4·0; N, 6·95%), τ 2·48 and 2·80 (2H, ABq, J 8·5 Hz, 4- and 5-H), 6·10 (3H, s, OMe), and 7·60 (3H, s, Me). The involatile residue was chromatographed over silica gel with 5% ether–pentane as eluant and afforded *2-chloro-6-hydroxy-3,5-dinitrotoluene* (0·62 g, 19%) as pale yellow needles (from cyclohexane), m.p. 79—80° (Found: C, 35·95; H, 2·2; N, 11·5. $C_7H_5ClN_2O_5$ requires C, 36·15; H, 2·2; N, 12·05%), τ −1·20 (1H, s, OH), 1·46 (1H, s, ArH), and 7·52 (3H, s, Me), $\nu_{max.}$ (CCl_4) 3115br (OH), 1530 (NO_2), and 1340 (NO_2) cm^{-1}.

(*b*) This method was adapted from that of Noelting.[17] A solution of the phenol (5 g) in glacial acetic acid (10 ml) was stirred at 0° and concentrated nitric acid (3·16 g) in acetic acid (10 ml) was added over 10 min. After the addition the mixture was stirred for a further 0·5 h at room temperature and poured onto ice. The product was separated by filtration and steam-distilled. The phenol (28) (2·46 g, 37%) was isolated from the distillate with ether, and crystallised from light petroleum as needles, m.p. 62—63°, identical with that prepared earlier. The involatile residue was crystallised from water and then from chloroform–methanol as yellow prisms of 2-chloro-6-hydroxy-3-nitrotoluene (30) (1·69 g, 26%), m.p. 135—136° (lit.,[17] 135°), τ (Me_2CO) 2·30 and 3·12 (2H, ABq, J 9·0 Hz, 4- and 5-H).

Bromination of 2-Chloro-6-hydroxytoluene (9).—Bromine (146·5 g) in dichloromethane (250 ml) was added over 50 min to a stirred solution of the phenol (130·4 g) in dichloromethane (750 ml). Stirring was continued for 5 min longer and the solution was worked up in the usual way. The crude product was distilled under reduced pressure and the fraction b.p. 90—108° at 2·8 mmHg (101·8 g) contained the *o*-bromo-isomer (31) and the *p*-bromo-isomer (33) (23%) (as indicated by n.m.r. spectroscopy). This material was applied to a column of silica gel which was eluted with light petroleum. Early fractions afforded *3-bromo-6-chloro-2-hydroxytoluene* (31) (69·4 g, 34%), needles (from cold pentane), m.p. 27—27·5° (Found: C, 38·2; H, 3·0. C_7H_6BrClO requires C, 37·95; H, 2·9%), τ 2·81 and 3·20 (2H, ABq, J 9·0 Hz, 4- and 5-H), 4·47 (1H, s, OH), and 7·67 (1H, s, Me), $\nu_{max.}$ (CCl_4) 3520 (bonded OH) cm^{-1}. On methylation (Me_2SO_4–K_2CO_3–Me_2CO) at room temperature this afforded *3-bromo-6-chloro-2-methoxytoluene* (32) (96%) as an oil, b.p. 73° at 0·05 mmHg (Found: C, 40·65; H, 3·45. C_8H_8BrClO requires C, 40·8; H, 3·4%), τ 2·72 and 3·03 (2H, ABq, J 8·5 Hz, 4- and 5-H), 6·23 (3H, s, OMe), and 7·64 (3H, s, Me). The column was extruded and washed with ethyl acetate. The washings were evaporated and the residue combined with the pot residue from the above distillation to afford crude 3-bromo-2-chloro-6-hydroxytoluene (33) (121·6 g, 60%) which was crystallised from light petroleum (charcoal) as *needles* (94·7 g), m.p. 67·5—68·5° (Found: C, 38·2; H, 2·9. C_7H_6BrClO requires C, 37·95; H, 2·9%), τ 2·72 and 3·49 (2H, ABq, J 9 Hz, 4- and 5-H), 5·23 (1H, s, OH), and 7·66 (3H, s, Me), $\nu_{max.}$ (CCl_4) 3600 (free OH) cm^{-1}.

Reaction of the Grignard Reagent of 3-Bromo-6-chloro-2-methoxytoluene (32) *with Diethyl Phenyl Orthoformate.*—The anisole (32) (70·3 g) and 1,2-dibromoethane (56 g) were added over 1·25 h to a stirred suspension of magnesium turnings (14·6 g) in dry ether under dry nitrogen. The mixture was then stirred under reflux for 0·25 h. Diethyl phenyl orthoformate [18] (58·5 g) in dry ether (100 ml) was added with stirring to the cooled solution at such a rate that gentle reflux was maintained. After the addition the mixture was heated under gentle reflux for 0·5 h, and then cooled in ice and treated with an excess of saturated aqueous ammonium chloride. The ether layer was separated and washed exhaustively with dilute sodium hydroxide solution and with saturated brine, and dried (Na_2SO_4). The residue left on removal of the solvent was stirred at room temperature for 1 h with concentrated hydrochloric acid (10 ml), water (100 ml), and sufficient acetone to render the mixture homogeneous. The mixture was poured into water and worked up in the usual way (ether). The crude product was crystallised twice from light petroleum to afford 4-chloro-2-methoxy-3-methylbenzaldehyde (27) (38·2 g, 60%), m.p. 69—70°, identical with that prepared earlier.

4-Chloro-2-methoxy-3-methylbenzaldehyde Ethylene Acetal (34).—The aldehyde (27) (5·4 g) and ethylene glycol (60 ml) in benzene (600 ml) were heated under reflux with a few crystals of toluene-*p*-sulphonic acid in a Dean–Stark apparatus for 3 days. Work-up in the usual way gave the crude product which on distillation under reduced pressure gave the *acetal* (4·12 g, 61%) as an oil, b.p. 122—130° at 1 mmHg. An analytical sample was obtained by re-distillation, b.p. 115—125° (bath) at 0·4 mmHg (Found: C, 57·3; H, 5·75%; M^+, 228·0547. $C_{11}H_{13}ClO_3$ requires C, 57·75; H, 5·7%. $^{12}C_{11}{}^{1}H_{13}{}^{35}Cl^{16}O_3$ requires M, 228·0553), τ 2·73 and 2·94 (2H, ABq, J 9·0 Hz, 5- and 6-H), 4·06 (1H, s, CH), 6·11 (4H, m, CH_2), 6·30 (3H, s, OMe), and 7·74 (3H, s, Me).

Wittig Reaction between 2-Methoxybenzyltriphenylphosphonium Chloride and 4-Chloro-2-methoxy-3-methylbenzaldehyde (27).—(*a*) Lithium methoxide [from lithium (0·1388 g)] in absolute methanol (33·5 ml) was added dropwise over 1 h to a stirred solution of the phosphonium salt (8·4 g) and the aldehyde (27) (3·68 g) in absolute methanol (100 ml) under dry nitrogen. The mixture was stirred at room temperature for 0·75 h and then heated under reflux for 5 h. T.l.c. (10% ethyl acetate–light petroleum) indicated that some aldehyde was still present. The solution was cooled to room temperature and more phosphonium salt (4·2 g) was added followed dropwise over 15 min by lithium methoxide (16·8 ml) of the same concentration as that used before. The mixture was heated under reflux for 1 h and most of the methanol was removed by distillation under reduced pressure. The residue was diluted with water and worked up in the usual way (ether). The crude product was preadsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel (3·5 × 46 cm) with 10% ethyl acetate–light petroleum as eluant. The stilbene (35) (4·52 g, 79%) was obtained as

an oily mixture of isomers, in which the *trans*-isomer predominated, which crystallised after 3 days. Repeated crystallisation of this material from pentane afforded plates of trans-4-*chloro*-2,2′-*dimethoxy*-3-*methylstilbene*, m.p. 55—56° (Found: C, 70·8; H, 5·95. $C_{17}H_{17}ClO_2$ requires C, 70·7; H, 5·95%), τ 2·33—3·34 (8H, m, Ar and olefinic H), 6·13 and 6·30 (each 3H, s, OMe), and 7·69 (3H, s, Me), $\lambda_{max.}$ 237 and 330 nm (ε 13,000 and 19,500), and $\lambda_{infl.}$ 303 nm (ε 16,300), $\nu_{max.}$ (Nujol) 973 (*trans*-CH=CH) cm^{-1}.

(*b*) Lithium methoxide [from lithium (1·175 g)] in methanol (220 ml) was added over 2·75 h to a stirred mixture of the phosphonium salt (71 g) and the aldehyde (27) (27·4 g) in dry DMF (250 ml) at 90° (bath) under dry nitrogen. The mixture was stirred at 90° for a further 1 h and then poured into water and worked up in the usual way (ether). The crude product was washed well with light petroleum and the triphenylphosphine oxide separated by filtration. The filtrate was evaporated and the residue was preadsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel (total 3·6 × 60 cm) with 3% ethyl acetate–light petroleum as eluant. The stilbene (35) (41·2 g, 96%), obtained as a crystalline solid in which the *cis*-isomer predominated, after several crystallisations from light petroleum afforded cis-4-*chloro*-2,2′-*dimethoxy*-3-*methylstilbene*, m.p. 89—90° (Found: C, 70·75; H, 5·9. $C_{17}H_{17}ClO_2$ requires C, 70·7; H, 5·95%), τ 2·73—3·59 (8H, m, Ar and olefinic H), 6·23 (6H, s, OMe), and 7·71 (3H, s, Me), $\lambda_{max.}$ 225 and 295 nm (ε 18,100 and 9900).

3-*Chloro*-1,8-*dimethoxy*-2-*methylphenanthrene* (40).—The mixture of stilbenes (35) (5·0 g) in cyclohexane (1 l) containing iodine (110 mg) was irradiated, with stirring, with a Hanovia medium pressure mercury lamp (500 W) through a Pyrex jacket. The residue left on removal of the solvent afforded the *phenanthrene* (40) (0·97 g, 20%) as needles (from methanol), m.p. 141—142° (Found: C, 71·1; H, 5·25%; M^+, 288/286. $C_{17}H_{15}ClO_2$ requires C, 71·2; H, 5·25%; *M*, 288/286), τ ($CDCl_3$) 1·56 (1H, s, 4-H), 1·76 and 2·04 (2H, ABq, $J_{9,10}$ 9·0 Hz, 9- and 10-H), 1·89 (1H, d, $J_{5,6}$ 8·0 Hz, 5-H), 2·47 (1H, dd, $J_{5,6} = J_{6,7}$ 8·0 Hz, 6-H), 3·03 (1H, d, $J_{6,7}$ 8·0 Hz, 7-H), 6·00 and 6·10 (each 3H, s, OMe), and 7·47 (3H, s, Me), $\lambda_{max.}$ (MeOH) 221, 258, 301, 314, 340·5, and 357·5 nm (ε 45,700, 49,300, 15,700, 17,700, 2700, and 2700), and $\lambda_{infl.}$ 233, 253, 275·5, and 325 nm (ε 34,300, 47,700, 19,700, and 3400).

2-*Bromo*-6-*nitrotoluene* (50).—The method of Gibson and Johnson [35] was adapted. The toluidine (49) [36] (25·0 g) was suspended in water (200 ml) and heated under reflux with stirring whilst hydrobromic acid (80 ml; 48% w/v) was added. The solution was stirred rapidly and cooled to 4—5° and sodium nitrite (11·5 g) in water (60 ml) was added dropwise at such a rate that the temperature did not exceed 5°. The diazonium solution was stirred for a further 15 min at 3—5° and then added in a thin stream to a stirred mixture of copper(I) bromide (27 g) in hydrobromic acid (55 ml; 48% w/v) and water (133 ml) at room temperature. The mixture was stirred at room temperature for a further 10 min and then on a steam-bath for 30 min. The mixture was steam-distilled and the bromo-compound (50) was extracted from the distillate with ether. It formed blades (32·7 g, 92%) from dichloromethane–light petroleum, m.p. 37·5—38·5° (lit.,[35] 42°).

2-*Amino*-6-*bromotoluene* (51).—The following method was adapted from that of Noelting.[17] The nitro-compound (50) (183·7 g) was added in small portions over 30 min to a mixture of tin(II) chloride (625 g) and concentrated hydrochloric acid (750 ml) which was stirred and heated on a steam-bath. The mixture was then stirred and heated for a further 3 h, then cooled to 0°. The tin double salt was separated by filtration and suspended in water (750 ml). Sodium hydroxide (500 g) in water (1 l) was added and the mixture was steam-distilled. The product (51) (138·1 g, 88%) was isolated with ether in the usual way.

2-*Bromo*-6-*hydroxytoluene* (52).—The bromotoluidine (51) (40·0 g) was added with stirring on a steam-bath to a mixture of concentrated hydrochloric acid (58 ml) and water (880 ml). The mixture was stirred and cooled to 5° during the dropwise addition over 15 min of a solution of sodium nitrite (15·2 g) in a little water. The solution was stirred at 5° for 10 min and then at room temperature for 1·25 h. The solution was added in a thin stream with stirring to a mixture of concentrated sulphuric acid (80 ml) in water (2 l). It was then heated at 50° with stirring for 15 min and then cooled in ice to room temperature. The mixture was extracted exhaustively with ether and the extract was steam-distilled. The distillate was saturated with salt and the bromo-cresol (52) was isolated with ether. It formed needles (27·5 g, 68%) from light petroleum, m.p. 91—94° (lit.,[17] 95°).

Bromination of 2-*Bromo*-6-*hydroxytoluene* (52).—(a) *With* 1 *mol. equiv. of bromine in dichloromethane.* Bromine (1·88 g) in dichloromethane (10 ml) was added rapidly to a stirred solution of the cresol (52) (2·19 g) in dichloromethane (10 ml). After the rapid disappearance of the bromine colour the mixture was worked up in the usual way. The crude product was steam-distilled and the early distillate was enriched in the more volatile constituent. This material was chromatographed over silica gel with light petroleum as eluant and gave 3,6-dibromo-2-hydroxytoluene (53) (1·11 g, 36%), needles (from pentane), m.p. 42—43° (lit.,[20] 38°) (Found: C, 31·75; H, 2·15. Calc. for $C_7H_6Br_2O$: C, 31·6; H, 2·3%), τ 2·91 and 3·00 (2H, ABq, *J* 8·5 Hz, 4- and 5-H), 4·41 (1H, s, OH), and 7·60 (3H, s, Me). The column was extruded and extracted with ethyl acetate, and the material obtained was combined with the less volatile material from the steam distillation. This crystallised from light petroleum as needles (1·67 g, 53%) of 2,3-*dibromo*-6-*hydroxytoluene* (55), m.p. 81·5—82·5° (Found: C, 32·2; H, 2·1. $C_7H_6Br_2O$ requires C, 31·6; H, 2·3%), τ 2·71 and 3·41 (2H, ABq, 5- and 4-H), 5·22 (1H, s, OH), and 7·59 (3H, s, Me).

(b) *With* 1 *mol. equiv. of bromine in the presence of isopropylamine.* At −30 to −20° a solution of bromine (3·66 g) in dry dichloromethane (9 ml) was added with stirring to a solution of isopropylamine (2 g) in toluene (70 ml). The mixture was cooled to −70° and the cresol (52) (4·27 g) in dry dichloromethane (10 ml) was added over 10 min with stirring. The mixture was stirred in the cooling bath (without further addition of solid CO_2) for 5 h, and then worked up in the usual way (ether). The crude product was chromatographed over a column of silica gel with light petroleum as eluant. Early fractions afforded 3,6-dibromo-2-hydroxytoluene (53) (2·63 g, 43%). Later fractions gave 2,3,5-tribromo-6-hydroxytoluene (56) (1·47 g), needles (from light petroleum), m.p. 90—91° (lit.,[20] 91°), τ 2·49 (1H, s, ArH), 4·50br (1H, s, OH), and 7·61 (3H, s, Me). Starting material (51) (912 mg) was eluted last.

(c) *With* 0·5 *mol. equiv. of bromine in the presence of isopropylamine.* At −20 to −30° a solution of bromine

[35] G. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 1929, 1229.
[36] M. Lounasmaa, *Acta Chem. Scand.*, 1968, **22**, 2388.

(42·7 g) in dry dichloromethane (100 ml) was added to a stirred solution of isopropylamine (34·5 g) in toluene (1·7 l). The mixture was cooled to −70° and the cresol (52) (100 g) in dry dichloromethane (400 ml) and dry toluene (200 ml) was added over 10 min. The mixture was stirred as before for 6 h and then worked up next day as above. The crude product was crystallised from light petroleum to afford the starting cresol (18·1 g). The mother liquor was concentrated and applied to a column of silica gel which was eluted with light petroleum to afford 3,6-dibromo-2-hydroxytoluene (53) (66·3 g, 97%). Further elution with 20% ethyl acetate–light petroleum gave more starting material (52) (33·7 g).

3,6-*Dibromo*-2-*methoxytoluene* (54).—The foregoing cresol (53) (125·9 g) and dry potassium carbonate (170 g) were stirred at room temperature in acetone (1·5 l) during the addition over 15 min of methyl sulphate (60 ml) in acetone (100 ml). After stirring for a further 4 h the mixture was worked up in the usual way (ether). The crude product was fractionated under diminished pressure to afford the *anisole* (54) (118·3 g, 90%) as an oil, b.p. 85—86° at 0·3 mmHg (Found: C, 34·65; H, 2·65; Br, 56·8. $C_8H_8Br_2O$ requires C, 34·3; H, 2·9; Br, 57·1%); τ 3·81 and 3·86 (2H, ABq, *J* 9·0 Hz, 4- and 5-H), 6·23 (3H, s, OMe), and 7·61 (3H, s, Me).

4-*Bromo*-2-*methoxy*-3-*methylbenzaldehyde* (57).—The foregoing anisole (54) (14·0 g) in dry ether (50 ml) was added over 15 min under dry nitrogen to a solution of phenyllithium (0·075M) in ether (100 ml). The mixture was stirred under nitrogen for 7·5 h then DMF (4·2 g) in ether (50 ml) was added over 10 min and the mixture was stirred for a further 2·5 h. The stirred mixture was cooled in ice and treated with an excess of saturated ammonium chloride solution, and then worked up in the usual way (ether). The oily residue was applied directly to a column of silica gel which was eluted with 0—10% ethyl acetate–light petroleum to afford the *aldehyde* (57) (9·02 g, 79%), needles (from pentane), m.p. 60—60·5° (Found: C, 47·8; H, 4·25; Br, 34·5%; M^+, 230/228. $C_9H_9BrO_2$ requires C, 47·2; H, 3·95; Br, 34·9%; *M*, 230/228), τ −0·27 (1H, s, CHO), 2·49 and 2·59 (2H, ABq, *J* 9·0 Hz, 5- and 6-H), 6·10 (3H, s, OMe), and 7·59 (3H, s, Me).

4-*Bromo*-2-*hydroxy*-3-*methylbenzaldehyde* (58).—The foregoing aldehyde (57) (431 mg) in dry dichloromethane (10 ml) was added at −10° to a stirred solution of boron trichloride (2·0 g) in dry dichloromethane (20 ml). The mixture was stirred at −10° for 30 min and then at room temperature for 15 min and then poured onto ice. The mixture was filtered through kieselguhr and the filtrate was worked up in the usual way (ether). The *aldehyde* (58) crystallised from cold pentane as needles (390 mg, 96%), m.p. 42—43° (Found: C, 44·6; H, 3·05; Br, 37·45. $C_8H_7BrO_2$ requires C, 44·7; H, 3·3; Br, 37·15%), τ −2·41 (1H, s, D_2O exchangeable, OH), −0·69 (1H, s, CHO), 2·79 (2H, apparent s, ArH), and 7·67 (3H, s, Me).

Wittig Reaction between 2-*Methoxybenzyltriphenylphosphonium Chloride and* 4-*Bromo*-2-*methoxy*-3-*methylbenzaldehyde* (57).—(*a*) Lithium methoxide [from lithium (374 mg)] in absolute methanol (93 ml) was added dropwise over 3 h to a stirred solution of the phosphonium salt (22·6 g) and the aldehyde (57) (9·9 g) in dry DMF (300 ml) at 80—90° (bath) under dry nitrogen. The mixture was then stirred at 80—90° for a further 1·5 h, cooled, and poured into water and worked up in the usual way (light petroleum). The crude product was preadsorbed from dichloromethane on silica gel and chromatographed over a small column of silica gel with light petroleum as eluant. The stilbene (37) (14·3 g, 99%) was obtained as a crystalline solid in which the *cis*-isomer predominated. Repeated crystallisation from pentane gave cis-4-*bromo*-2,2′-*dimethoxy*-3-*methylstilbene* as prisms, m.p. 86—88° (Found: C, 61·3; H, 5·25. $C_{17}H_{17}BrO_2$ requires C, 61·3; H, 5·15%), τ 2·70—3·39 (8H, m, Ar and olefinic H), 6·23 (6H, s, OMe), and 7·68 (3H, s, Me), $\lambda_{max.}$ 217 and 288 nm (ε 21,100 and 10,000).

(*b*) Lithium methoxide [from lithium (709 mg)] in absolute methanol (110 ml) was added dropwise over 1 h to a stirred solution of the phosphonium salt (45·0 g) and the aldehyde (57) (18·7 g) in absolute methanol (600 ml) under dry nitrogen at room temperature. The mixture was stirred at room temperature for 1 h, then under reflux for 2 h, and then most of the methanol was removed under reduced pressure. The solution was diluted with water and worked up in the usual way. The crude product was extracted with boiling light petroleum (5 × 250 ml) and the concentrated extract was chromatographed over a short column of silica gel with 0—2·5% ethyl acetate–light petroleum as eluant to give the stilbene (37) (26·3 g, 97%) as a crystalline mixture of isomers in which the *trans*-isomer predominated. Repeated crystallisation from pentane gave *trans*-4-bromo-2,2′-dimethoxy-3-methylstilbene as plates, m.p. 53—54°, *m/e* 334/332 (M^+), τ 2·34—3·30 (8H, m, Ar and olefinic H), 6·17 and 6·30 (each 3H, s, OMe), and 7·64 (3H, s, Me), $\lambda_{max.}$ 238 and 333 nm (ε 12,300 and 16,200) and $\lambda_{infl.}$ 295 nm (ε 15,100), $\nu_{max.}$ (Nujol) 972 (*trans*-CH=CH) cm^{-1}.

4-*Cyano*-2,2′-*dimethoxy*-3-*methylstilbene* (36).—(*a*) The bromo-stilbene isomers (37) (26·3 g) from the Wittig reaction conducted in methanol, copper(I) cyanide (18·2 g), and dry DMF (87 ml) were heated and stirred under reflux at 155—160° (bath) for 15 h. The cooled mixture was then heated and stirred at 70° for 0·5 h with a solution of hydrated iron(III) chloride (100 g) and concentrated hydrochloric acid (40 ml) in water (200 ml). Work-up in the usual way (ethyl acetate) then gave the crude product which was crystallised from dichloromethane–light petroleum to give the nitrile (13·4 g). The mother liquors were evaporated and the oily residue was applied directly to a column of silica gel (2·8 × 52 cm) which was eluted with 2·5—10% ethyl acetate–light petroleum. A further crop of the nitrile (5·3 g, total yield 85%) resulted. The mixture of isomers on repeated crystallisation from dichloromethane–light petroleum gave the pure trans-*isomer* as needles, m.p. 131—134° (Found: C, 77·6; H, 6·35; N, 4·9. $C_{18}H_{17}NO_2$ requires C, 77·4; H, 6·15; N, 5·0%), τ ($CDCl_3$) 2·20—3·20 (8H, m, Ar and olefinic H), 6·08 and 6·23 (each 3H, s, OMe), and 7·50 (3H, s, Me), $\lambda_{max.}$ 242 and 345 nm (ε 11,400 and 17,500) and $\lambda_{infl.}$ 300 nm (ε 13,800), $\nu_{max.}$ (Nujol) 2220 (CN) and 970 (*trans*-CH=CH) cm^{-1}.

(*b*) The chloro-stilbene isomers (35) (2·89 g) from the Wittig reaction conducted in DMF, copper(I) cyanide (8·9 g), and hexamethylphosphoric triamide (15 ml) were heated at 200—230° (bath) with stirring for 5·5 h. Work-up as before gave the crude product which was preadsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel (total 3·5 × 30 cm) with 5% ethyl acetate–light petroleum as eluant. The nitrile (36) (531 mg, 19%) formed prisms from dichloromethane–light petroleum, m.p. 78—92°. The n.m.r. spectrum showed it to be a *ca.* 1 : 1 mixture of the *cis*- and *trans*-isomers, *m/e* 279 (M^+).

Methyl 2,2'-Dimethoxy-3-methylstilbene-4-carboxylate (39).—The foregoing nitrile (36) as a mixture of isomers (23·2 g), potassium hydroxide (232 g), water (450 ml), and ethanol (280 ml) were stirred and heated under reflux for 68 h when the evolution of ammonia could no longer be detected. The mixture was cooled and diluted with water and worked up as usual (ethyl acetate) to give the crude acid (40). A sample on repeated crystallisation from dichloromethane–light petroleum gave prisms, m.p. 173—174° (presumably the *trans*-isomer). The crude acid was stirred at room temperature for 16 h with methyl sulphate (19 ml), dry potassium carbonate (55 g), and dry DMF (60 ml). Work-up in the usual way (ethyl acetate) gave the ester (39) (25·9 g, 99%) as a mixture of isomers. Repeated crystallisation of a sample from methanol gave the trans-*isomer* as microscopic needles, m.p. 77—78° (Found: C, 73·1; H, 6·35. $C_{19}H_{20}O_4$ requires C, 73·05; H, 6·45%), τ 2·29—3·39 (8H, m, Ar and olefinic H), 6·19, 6·21, and 6·32 (each 3H, s, OMe), and 7·52 (3H, s, Me), $\lambda_{max.}$ 244 and 345 nm (ε 10,400 and 20,200) and $\lambda_{infl.}$ 300 nm (14,000), $\nu_{max.}$ (Nujol) 1710 (CO) and 970 (*trans*-CH=CH) cm^{-1}. The pure isomer (434 mg) and a small crystal of iodine were heated under reflux in nitrobenzene (3 ml) for 0·5 h. Water (25 ml), methanol (50 ml), and potassium hydroxide (5 g) were then added and the mixture was again boiled under reflux for 2 h. The nitrobenzene was removed in steam and the isolated acid was esterified ($MeOH–H_2SO_4$). The ester after one crystallisation from aqueous methanol had m.p. and mixed m.p. 76—77°.

4-Methoxycarbonylbenzyltriphenylphosphonium Bromide.—Methyl 4-bromomethylbenzoate [37] (22·9 g) and triphenylphosphine (26·2 g) were heated under reflux in dry benzene (50 ml) for 13 h. The mixture was cooled, and the phosphonium salt (44·7 g, 91%) was separated by filtration, washed with dry ether, and dried *in vacuo* at 56°. It formed *prisms* from dichloromethane–dry ether, m.p. 232—235° (Found: C, 65·85; H, 5·0; Br, 16·7, 16·2. $C_{27}H_{24}BrO_2P$ requires C, 66·0; H, 4·9; Br, 16·25%).

Methyl 2-Methoxystilbene-4'-carboxylate (59).—The foregoing phosphonium salt (42·3 g) and 2-methoxybenzaldehyde (14·1 g) were stirred in dry methanol (350 ml) under dry nitrogen during the dropwise addition over 35 min at room temperature of lithium methoxide [from lithium (600 mg)] in dry methanol (100 ml). The mixture was then heated under reflux for 2 h, potassium hydroxide (15 g) in water (150 ml) was added, and reflux was continued for a further 14 h. The crude acid, obtained in the usual way, was esterified ($MeOH–H_2SO_4$) to give the stilbene (59) (18·4 g, 80%) as an oily mixture of isomers. The mixture (808 mg) and a small crystal of iodine were heated under reflux for 0·5 h in nitrobenzene (8 ml). Potassium hydroxide (6 g), water (20 ml), and methanol (50 ml) were then added and the mixture was heated under reflux for 3 h. The nitrobenzene was driven off in steam and the acid was isolated as usual and esterified ($MeOH–H_2SO_4$). The trans-*isomer* (243 mg) crystallised from methanol (charcoal) as needles, m.p. 63—64° (Found: C, 76·0; H, 6·35. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%), $\lambda_{max.}$ 237 and 347 nm (ε 9500 and 19,100) and $\lambda_{infl.}$ 295 (14,100), $\nu_{max.}$ (Nujol) 1710 (CO) and 974 (*trans*-CH=CH) cm^{-1}.

U.v. Irradiation of Methyl 2,2'-Dimethoxy-3-methylstilbene-4-carboxylate (39).—The ester (39) (2·015 g) and iodine (80 mg) in cyclohexane (700 ml) were stirred and irradiated with a Hanovia 500 W medium pressure mercury lamp surrounded by a Pyrex cooling jacket immersed in the solution. The solvent was removed and the residue was preadsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel with 2·5—5% ethyl acetate–light petroleum as eluant. Early fractions gave *methyl 1-methoxy-2-methylphenanthrene-3-carboxylate* (45) (283 mg, 16%), needles (from methanol), m.p. 81—82° (Found: C, 77·5; H, 6·0%; M^+, 280. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·75%; *M*, 280), τ 0·99 (1H, s, 4-H), 1·32 (1H, m, 5-H), 1·91—2·10 (5H, m, 6-, 7-, 8-, 9-, and 10-H), 6·03 and 6·11 (each 3H, s, OMe), and 7·33 (3H, s, Me). Later fractions yielded *methyl 1,8-dimethoxy-2-methylphenanthrene-3-carboxylate* (42) (706 mg, 35%), glistening prisms (from chloroform–methanol), m.p. 166—167° (Found: C, 73·8; H, 5·85%; M^+, 310. $C_{19}H_{18}O_4$ requires C, 73·55; H, 5·85%; *M*, 310), τ ($CDCl_3$) 1·00 (1H, s, 4-H), 1·74 (1H, d, $J_{5,6}$ 8·0 Hz, 5-H), 1·76 and 2·00 (2H, ABq, $J_{9,10}$ 9·0 Hz, 9- and 10-H), 2·46 (1H, dd, $J_{5,6} = J_{6,7}$ 8·0 Hz, 6-H), 3·05 (1H, d, $J_{6,7}$ 8·0 Hz, 7-H), 6·03 (6H, s, OMe), 6·10 (3H, s, OMe), and 7·32 (3H, s, Me).

U.v. Irradiation of 4-Cyano-2,2'-dimethoxy-3-methylsilbene (36).—The stilbene (36) (360 mg) and iodine (35 mg) were irradiated in cyclohexane (600 ml) as before. Chromatography as before with 2·5—5% ethyl acetate light-petroleum as eluant gave *3-cyano-1-methoxy-2-methylphenanthrene* (46) (34 mg, 11%), needles (from methanol), m.p. 131—132° (Found: N, 5·75%; M^+, 247. $C_{17}H_{13}NO$ requires N, 5·65%; *M*, 247), τ ($CDCl_3$) 1·29 (1H, s, 4-H), 1·46 (1H, m, 5-H), 1·98—2·44 (5H, m, 6-, 7-, 8-, 9-, and 10-H), 6·08 (3H, s, OMe), and 8·71 (3H, s, Me). This was followed by *3-cyano-1,8-dimethoxy-2-methylphenanthrene* (41) (111 mg, 31%), needles (from methanol), m.p. 199·5—200° (Found: C, 77·65; H, 5·4; N, 4·9%; M^+, 277. $C_{18}H_{15}NO_2$ requires C, 77·95; H, 5·45; N, 5·05%; *M*, 277), τ ($CDCl_3$) 1·26 (1H, s, 4-H), 1·57 and 1·96 (2H, ABq, $J_{9,10}$ 9·0 Hz, 9- and 10-H), 1·82 (1H, d, $J_{5,6}$ 8·0 Hz, 5-H), 2·35 (1H, dd, $J_{5,6} = J_{6,7}$ 8·0 Hz, 6-H), 2·92 (1H, d, $J_{6,7}$ 8·0 Hz, 7-H), 5·92 and 6·05 (each 3H, s, OMe), and 7·35 (3H, s, Me).

U.v. Irradiation of Methyl 2-Methoxystilbene-4'-carboxylate (59).—The stilbene (59) (3·00 g) and iodine (120 mg) in light petroleum (600 ml) were irradiated as before for 15 h. The crude product was chromatographed as before with 2·5% ethyl acetate–light petroleum as eluant. The first material to be eluted was methyl phenanthrene-3-carboxylate (161 mg, 6%), needles (from light petroleum), m.p. 93—93·5° (lit.,[38] 95—95·5°), *m/e* 236 (M^+), τ 0·68 (1H, s, $W_{\frac{1}{2}}$ 4 Hz, 4-H), 1·27 (1H, m, 5-H), 1·88 (1H, dd, $J_{2,4}$ 1·0, $J_{1,2}$ 9·0 Hz, 2-H), 2·08—2·55 (6H, m, 1-, 6-, 7-, 8-, 9-, and 10-H), and 6·06 (3H, s, Me), $\nu_{max.}$ (Nujol) 1715 (CO) cm^{-1}. Later fractions gave *methyl 8-methoxyphenanthrene-3-carboxylate* (60) (691 mg, 17%), needles (from methanol), m.p. 112—113° (Found: C, 76·8; H, 5·5. $C_{17}H_{14}O_3$ requires C, 76·65; H, 5·3%), τ ($CDCl_3$) 0·74 (1H, s, $W_{\frac{1}{2}}$ 3 Hz, 4-H), 1·60—2·46 (6H, m, 1-, 2-, 5-, 6-, 9-, and 10-H), 3·15 (1H, d, 7-H), and 6·06 (6H, s, OMe).

1,8-Dimethoxy-2-methylphenanthren-3-ylmethanol (43).—The ester (42) (2·625 g) in dry tetrahydrofuran (195 ml) was added with stirring to lithium aluminium hydride (2·38 g) in dry tetrahydrofuran (65 ml) and the mixture was then heated under reflux with stirring for 2·5 h. Work-up in the usual way (saturated aqueous NH_4Cl) and isolation with ethyl acetate gave the *alcohol* (43) (2·38 g, 99%), needles (from methanol), m.p. 155—156° (Found: C, 76·35; H,

[37] W. Davies and W. H. Perkin, jun., *J. Chem. Soc.*, 1922, 2202.
[38] E. Mosettig and J. van de Kamp, *J. Amer. Chem. Soc.*, 1932, **54**, 3328.

6·8. $C_{18}H_{18}O_3$ requires C, 76·55; H, 6·55%), τ ($CDCl_3$) 1·58 (1H, s, 4-H), 1·74 and 2·01 (2H, ABq, $J_{9,10}$ 9·5 Hz, 9- and 10-H), 1·76 (1H, d, $J_{5,6}$ 8·0 Hz, 5-H), 2·47 (1H, dd, $J_{5,6} = J_{6,7}$ 8·0 Hz, 6-H), 3·05 (1H, d, $J_{6,7}$ 8·0 Hz, 7-H), 5·15 (2H, s, CH_2OH), 5·98 and 6·10 (each 3H, s, OMe), and 7·56 (3H, s, Me).

1,8-Dimethoxy-2-methylphenanthrene-3-carbaldehyde (44).—The foregoing alcohol (43) (2·46 g) and manganese dioxide (25·7 g) (prepared by the method of Mancera *et al.*,[26] and further activated by azeotropic distillation with benzene) were heated under reflux in chloroform with stirring for 30 h. The manganese dioxide was separated by filtration and washed well with hot chloroform. The solvent was removed and the residue was crystallised from methanol to afford the *aldehyde* (44) (2·23 g, 92%), as needles, m.p. 116—118° on rapid heating. On slow heating the needles changed to plates, m.p. 139—141° (Found: C, 77·6; H, 5·85%; M^+, 280. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·75%; *M*, 280), τ ($CDCl_3$) −0·38 (1H, s, CHO), 1·21 (1H, s, 4-H), 1·62 and 2·00 (2H, ABq, $J_{9,10}$ 9·0 Hz, 9- and 10-H), 1·76 (1H, d, $J_{5,6}$ 8·0 Hz, 5-H), 2·42 (1H, dd, $J_{5,6} = J_{6,7}$ 8·0 Hz, 6-H), 3·01 (1H, d, $J_{6,7}$ 8·0 Hz, 7-H), 5·98 and 6·10 (each 3H, s, OMe), and 7·07 (3H, s, Me).

3-Cyano-1,8-dimethoxy-2-methylphenanthrene (41).—The foregoing aldehyde (44) (670 mg), hydroxylamine hydrochloride (340 mg), and sodium acetate trihydrate (860 mg) were heated under reflux in ethanol (160 ml) and water (20 ml) for 5 h. Most of the ethanol was removed by distillation and the residue was diluted with water and worked up in the usual way (ethyl acetate). The crude product was heated under reflux in acetic anhydride (10 ml) for 1 h, and then poured into water. The crude product was collected by filtration, preadsorbed from dichloromethane on silica gel, and filtered through a short column of silica gel with 5% ethyl acetate–light petroleum as eluant. The nitrile (41) (590 mg, 89%) formed prisms from methanol and was identical with that obtained previously.

1,8-Dimethoxy-2-methyl-3-(4-methylpentanoyl)phenanthrene (63).—(*a*) Isopentyl alcohol was prepared by the method of Huston and Agett.[39] The fraction b.p. 129—132° was converted into the bromide by the method of Vogel.[40] Magnesium (670 mg) was activated by the method of Mendel[41] and the Grignard reagent was prepared in the usual way from isopentyl bromide (3·75 g) and dry tetrahydrofuran (40 ml) under dry nitrogen. After the addition (0·5 h) the mixture was heated under reflux for 0·5 h and then the foregoing nitrile (41) (600 mg) was added over 0·5 h at reflux. Heating and stirring were continued for 18 h and the mixture was then cooled. An excess of dilute hydrochloric acid was added and the mixture was heated under reflux for 0·5 h. The cooled mixture was worked up in the usual way (dichloromethane). Chromatography of the crude product over silica gel with 2·5—5% ethyl acetate–light petroleum gave the *ketone* (63), needles (from methanol) (38 mg, 5%), m.p. 82—84°, raised to 86—87° after recrystallisation (Found: C, 79·25; H, 7·2%; M^+, 350. $C_{23}H_{26}O_3$ requires C, 78·8; H, 7·5%; *M*, 350), τ ($CDCl_3$) 1·38 (1H, s, 4-H), 1·64 and 1·96 (2H, ABq, $J_{9,10}$ 9·0 Hz, 9- and 10-H), 1·81 (1H, d, $J_{5,6}$ 8·0 Hz, 5-H), 2·42 (1H, dd, $J_{5,6} = J_{6,7}$ 8·0 Hz, 6-H), 3·00 (1H, d, $J_{6,7}$ 8·0 Hz, 7-H), 5·98 and 6·09 (each 3H, s, OMe), 6·95 (2H, deformed t, $COCH_2CH_2CHMe_2$), 7·47 (3H, s, ArMe), 8·31 (3H, m, $COCH_2CH_2CHMe_2$), and 9·01 (6H, d, side chain Me).

(*b*) The Grignard reagent was prepared from isopentyl bromide (3·75 g) and activated magnesium (670 mg) in dry ether (80 ml) under dry nitrogen in the usual way. The aldehyde (44) (740 mg) in dry tetrahydrofuran (60 ml) was added dropwise to the solution under gentle reflux. More dry tetrahydrofuran (20 ml) was added and the whole was heated under reflux with stirring for 4 h. An excess of saturated aqueous ammonium chloride was added to the cooled mixture which was then worked up in the usual way (ethyl acetate). The crude product was dissolved in acetone (15 ml) and Jones reagent (2·4 ml) was added dropwise to the stirred solution at room temperature. The mixture was then stirred for 0·5 h and worked up as usual (dichloromethane). The crude product was preadsorbed on silica gel and chromatographed over a column of silica gel with 2·5% ethyl acetate–light petroleum as eluant. The first material eluted was the required ketone (63) which formed needles (514 mg, 56%) from methanol, m.p. 86—87°. Later fractions gave *8-methoxy-7-methyl-6-(4-methylpentanoyl)-1,4-phenanthraquinone* (65) (41 mg), clusters of orange needles (from dichloromethane–light petroleum), m.p. 127—128° (Found: C, 74·95; H, 6·5. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·35%), τ ($CDCl_3$) 0·33 (1H, s, 5-H), 1·53 and 1·81 (2H, ABq, *J* 8·0 Hz, 9- and 10-H), 3·05 (2H, s, 2- and 3-H), 6·10 (3H, s, OMe), 6·92 (2H, deformed t, $COCH_2CH_2CHMe_2$), 7·49 (3H, s, ArMe), 8·29 (3H, m, $COCH_2CH_2CHMe_2$), and 9·01 (6H, d, side chain Me).

1,8-Diacetoxy-2-methyl-3-(4-methylpentanoyl)phenanthrene (64).—The ketone (68) (450 mg) in dry dichloromethane (10 ml) was added dropwise to a stirred solution of boron tribromide (2 g) in dry dichloromethane (10 ml) at −78°. The cooling bath was removed and the mixture was stirred for a further 12 h and then the solution was evaporated under diminished pressure. The residue was heated on a steam-bath for 1·5 h with a mixture of acetic anhydride (4 ml) and pyridine (4 ml). The solvents were removed under diminished pressure and the residue was preadsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel with 10—20% ethyl acetate–light petroleum as eluant. The *phenanthrene* (64) formed needles (from methanol) (250 mg, 48%), m.p. 157° (Found: C, 74·3; H, 6·4. $C_{25}H_{26}O_5$ requires C, 73·85; H, 6·45%), τ ($CDCl_3$) 1·31 (1H, s, 4-H), 1·58 (1H, dd, $J_{5,6}$ 8·0, $J_{5,7}$ 1·0 Hz, 5-H), 2·12 and 2·39 (2H, ABq, $J_{9,10}$ 9·0 Hz, 9- and 10-H), 2·39 (1H, dd, $J_{5,6} = J_{6,7}$ 8·0 Hz, 6-H), 2·66 (1H, dd, $J_{6,7}$ 8·0, $J_{5,7}$ 1·0 Hz, 7-H), 6·95 (2H, deformed t, $COCH_2CH_2CHMe_2$), 7·53, 7·55, and 7·59 (each 3H, s, 2 × MeCO and ArMe), 8·30 (3H, m, $COCH_2CH_2CHMe_2$), and 9·01 (6H, d, side chain Me).

Piloquinone [*1,8-Dihydroxy-2-methyl-3-(4-methylpentanoyl)-9,10-phenanthraquinone*] (1).—The foregoing phenanthrene (64) (90 mg) was stirred at 70° in acetic acid (5 ml) during the dropwise addition of chromium trioxide (100 mg) in acetic acid (1 ml) and water (0·6 ml). The mixture was maintained at 70° for 1·75 h, then poured into water, and worked up as usual (dichloromethane). The crude product was dissolved in methanol (20 ml), 1% aqueous sodium hydroxide solution (15 drops) was added, and the whole was stirred under nitrogen at room temperature for 0·5 h. Dilute hydrochloric acid was added and the mixture was worked up as usual (ethyl acetate). The crude product was preadsorbed from dichloromethane on silica gel and

[39] R. C. Huston and A. H. Agett, *J. Org. Chem.*, 1941, **6**, 127.
[40] A. Vogel, 'A Text-book of Practical Organic Chemistry,' 3rd edn., Longmans, London, 1956, p. 279.
[41] A. Mendel, *J. Organometallic Chem.*, 1966, **6**, 97.

chromatographed over a column of silica gel with 2·5—5% ethyl acetate–light petroleum. The *quinone* (15 mg, 18%) formed needles from ether–light petroleum, m.p. and mixed m.p. 176—179° (lit.,[4] 176—178°) (Found: C, 71·65; H, 5·5. $C_{21}H_{20}O_5$ requires C, 71·6; H, 5·7%). The mass and n.m.r. spectra were identical with those of the natural material. The synthetic and natural materials had the same R_F on t.l.c. in several solvent systems.

Some of this work was carried out during a study leave (to R. G. F. G.) from the University of Cape Town, and financial support of the South African C.S.I.R. is gratefully acknowledged. Thanks are also due to the Lilly Research Centre, Erl Wood Manor, Windlesham, for partial financial support, and to Dr. J. Polonsky for the gift of natural piloquinone.

[4/904 *Received, 7th May,* 1974]