Electrophilic Substitution with Rearrangement. Part 9.[1] Dienones derived from Brominations of *o*-, *m*-, and *p*-Cresol

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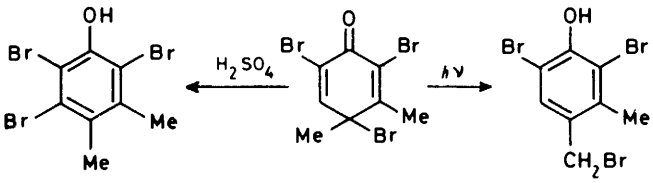
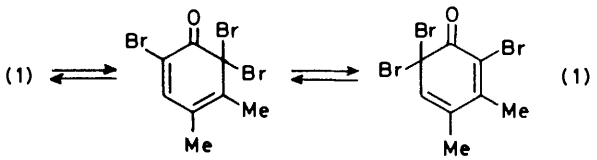
Regiospecific protodebromination of ring-substituted bromophenols derived from 2-, 3-, or 4-methylphenol can be effected by heating them with aqueous hydrogen iodide; the synthetic scope of this reaction has been explored. These di- and poly-bromophenols can generally be converted by further bromination in aqueous acetic acid into dienones, which have now been shown to have the 4-bromo-2,5-dienone rather than the 2-bromo-3,5-dienone structure. The rearrangements of these dienones to ring-substituted polybromophenols by treatment with sulphuric acid have been investigated; where more than one product is formed, the regioselectivity differs from that prevailing in the corresponding direct bromination of the phenol with liquid bromine. The alternative rearrangements of these dienones in aprotic solvents with and without illumination have been compared with results obtained by reaction of the methylphenols with bromine under the same conditions. Characteristic differences between the behaviours of 2-, 3-, and 4-methyl-substituted compounds reflect the specific reactions available to the particular dienones.

In Part 8,[1] the isomerisations of 2,4,6-tribromo-3,4-dimethylcyclohexa-2,5-dienone (1) (obtained by bromination of 3,4-dimethylphenol or of its dibromo-derivative) into (a) 2,5,6-tribromo-3,4-dimethylphenol (2) and (b) 2,6-dibromo-4-bromomethyl-3-methylphenol (3) were



(2) (1) (3)

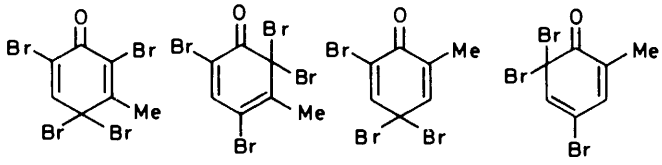
described. Reactions of both these kinds are known for dienones derived from other phenols.[2,3] The structures of these dienones have, however, not always been established fully, since spectroscopic examination is necessary to distinguish between isomeric possibilities. Thus for example (1) and its isomers (4) and (5) potentially comprise a tautomeric system [equation (1)], the mobility of which depends on the conditions in which



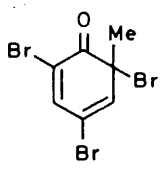
(4) (5)

any one isomer finds itself. Waring[4] has summarised the chemistry of halogen-substituted cyclohexadienones and the methods available up to 1966 for structural assignments in this field.

The regiospecificity of the isomerisation into the side-chain, (1) ⟶ (3), is noteworthy; none of the isomeric 3-bromomethyl compound was detected in the product. It was of interest, however, to know whether a 3- or a 2-methyl group can be attacked in the absence of a 4-methyl group. The 3-methyl-substituted dienone (6) had been described variously as having m.p. 155[5] and 121—124 °C;[2] its isomer (7) had been described as having m.p. 134[6] and 143 °C.[7]

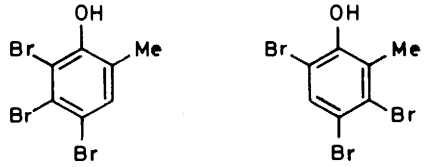


(6) (7) (8) (9)



(10)

A related dienone derived from 2-methylphenol had also been described[8] as being either the 2,5-dienone (8) or the 3,5-dienone (9). The possibility that it was the other 3,5-dienone (10) was not considered, probably on the not entirely conclusive grounds that it was converted by sulphuric acid into the known 4,5,6-tribromo-2-methylphenol (11).



(11) (12)

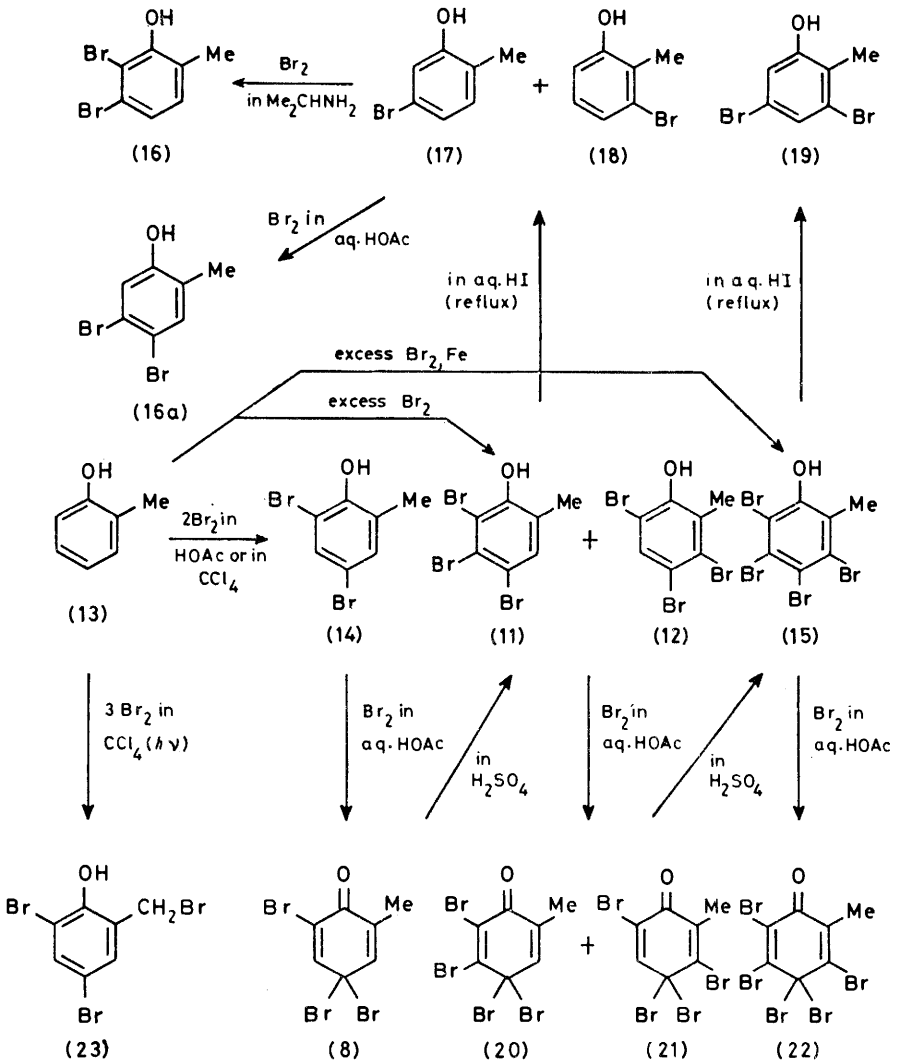
We have, therefore, re-investigated aspects of the brominations of 2-, 3-, and 4-methylphenol, clarifying the structures of some of the accessible dienones and extending our knowledge of the course and regiospecificity of their rearrangements, and of the reactions of the individual phenols. Some further experiments

relating to the bromination of 3,4-dimethylphenol and the rearrangement of 2,4,6-tribromo-3,4-dimethylcyclohexa-2,5-dienone are described.

EXPERIMENTAL

Most of the materials and methods have been described in earlier Parts.[1] 2-Methylphenol, b.p. 192 °C at 760 mmHg, and 3-methylphenol, b.p. 141 °C at 760 mmHg, were redistilled before use; 4-methylphenol, m.p. 33 °C, was a commercial sample used without further purification. The term 90% acetic acid refers to a mixture of acetic acid (90 cm³) and water (10 cm³). Protodebromination with HI was carried out by heating the bromophenol with a large excess of 55% hydrogen iodide vigorously under reflux, nitrogen being passed through the condenser to remove iodine as it was formed after displacement of positive bromine. Where we refer to reaction under strong illumination, the reaction mixture (kept cool by a rapid current of air) was illuminated in a Pyrex flask with a 1 kW lamp located *ca.* 30 cm from the flask.

(a) *Derivatives of 2-Methylphenol* (*Scheme* 1).—2-Methylphenol (0.1 mol) was dissolved in 90% HOAc (100 cm³), and Br_2 (0.2 mol) was added dropwise with stirring over 5 min at room temperature. After 0.5 h, water was added, and the precipitate was filtered off, washed (H_2O), and recrystallised (CCl_4) giving 4,6-dibromo-2-methylphenol, m.p. 55—56 °C (lit.,[9] 58, 57 °C). This (0.02 mol) was dissolved in acetic acid (200 cm³) and to the solution was added Br_2 (0.022 mol) over 10 min. The mixture was stirred for a further 15 min, and then water and ice were added to precipitate the dienone, which was filtered off and washed with water. In recrystallising this from CCl_4, the mixture was heated to the b.p. of the solvent, but was not maintained at this temperature any longer than was necessary to effect solution. It was then set aside in the dark to cool. The crystalline product was filtered off, and the solvent was removed giving 4,4,6-tribromo-2-methylcyclohexa-2,5-dienone (8), m.p. 105—107 °C (lit.,[8] 100 °C) (Found: C, 24.1; H, 1.7; Active Br, 23.1. Calc. for $C_7H_5Br_3O$: C, 24.4; H, 1.4; Br, 23.2%). It was noted that this compound is unstable, losing HBr and Br_2 on being kept at room temperature. Its u.v. spectrum, with a maximum at 266 nm, establishes that it has the structure



SCHEME 1 Derivatives of 2-methylphenol

indicated, and not either of the isomeric structures (9) or (10).

When this dienone (8), dissolved in chloroform or in carbon tetrachloride, was kept at room temperature for a prolonged period, decomposition of the dienone occurred. After 72 h in the latter solvent, it appeared to have been almost completely converted into 4,6-dibromo-2-methylphenol with small amounts of other compounds, and the colour of bromine was present in the solvent. Thereafter, over a number of days it was observed that a signal in the ^{1}H n.m.r. spectrum at δ 4.42 appeared; its magnitude corresponded to the conversion of *ca.* 20% of the original dienone into 4,6-dibromo-2-bromomethylphenol (23). The identity of the latter compound was confirmed by comparison with the ^{1}H n.m.r. spectrum of an authentic sample prepared by treatment of 2-methylphenol (3.5 g) with bromine (6 cm^3) in CCl_4 (170 cm^3) under strong illumination. After *ca.* 8 h the solvent was evaporated off under reduced pressure to give a crude product containing (from its ^{1}H n.m.r. spectrum) 76% of the required bromomethyl compound together with minor amounts of starting material and the product of disubstitution. Crystallisation from light petroleum (b.p. 60—80 °C) gave 4,6-dibromo-2-bromomethylphenol, m.p. 117—118 °C (lit.,[10] 116—118 °C) having the expected ^{1}H n.m.r. spectrum, with signals at δ 4.42 (2 H, s, CH_2Br), 5.75 (1 H, s, OH), 7.35 (1 H, d, 3- or 5-H, $J_{3,5}$ 2 Hz), and 7.50 (1 H, d, 5- or 3-H, $J_{3,5}$ 2 Hz).

When 4,4,6-tribromo-2-methylcyclohexa-2,5-dienone (8) was treated with sulphuric acid, the product after crystallisation (CCl_4) had m.p. 78.5—80 °C. Its ^{1}H n.m.r. spectrum, examined both before and after crystallisation, showed it to be a mixture of 4,5,6-tribromo-2-methylphenol (11),[8] m.p. 89 °C, and 3,4,6-tribromo-2-methylphenol (12),[8] m.p. 91 °C. Its composition was not changed by crystallisation. A mixture of the same two phenols was obtained by treating 2-methylphenol (10.8 g) with bromine (80 g) added dropwise without solvent over 2 h. The product was left for 7 days and was then crystallised (CCl_4) to give (11) and (12) in approximately equal proportions. This mixture was unchanged in composition on being treated with HBr (45%) in acetic acid at 20 °C for 24 h.

The structures of the two phenols follow from their ^{1}H n.m.r. spectra. The signal for the methyl group in (11) would be expected to be upfield from that for the methyl group in (12), since the latter nucleus is additionally deshielded by the presence of an adjacent bromine atom. Similarly an aromatic hydrogen atom lying between two bromine substituents will be deshielded relative to one lying between methyl and bromine, so the signal for the aromatic proton in (11) would be expected to be upfield from that for the aromatic proton in (12). The spectra of the mixtures contain signals at δ 2.25, 2.45, 7.28, and 7.50; their relative intensities show that those at δ 2.25 and 7.28 represent one component and those at δ 2.45 and 7.50 represent the other; and that the major component in the product obtained by acid-catalysed rearrangement of the preformed dienone is the compound with the less deshielded signals, which must therefore be (11).

This deduction was confirmed by conversion of the mixture of phenols containing excess of (11) into a mixture of dienones by treating it with bromine in 90% acetic acid in the manner described earlier for the preparation of the dienone (8). The product, worked up in the usual way, and formed in good yield, was a mixture of the expected 2,5-dienones (20) and (21), $\lambda_{max.}$ (HOAc) 270 nm ($\varepsilon_{max.}$ 10 700). Its ^{13}C n.m.r. spectrum allowed assignment of one set of peaks to the major component from the intensities of the signals, despite the fact that nuclear Overhauser enhancement affects quantitative interpretation of the integration of the signals. The signal for the single proton-bearing unsaturated carbon in the minor component could be recognised in the undecoupled spectrum as a doublet, whereas that in the major component was a doublet of quartets, split by a ^1J coupling with the attached proton and a ^3J coupling with the protons of the methyl group. The major component is therefore (20) and the minor component is (21), whence the structures of the phenols from which they were derived were respectively (11) and (12).

The mixture containing 88% of (11) (1 g) was heated under reflux with HI (55%; 10 cm^3), nitrogen being passed through the condenser to remove iodine as it was formed. The solid which collected in the condenser was removed with diethyl ether; the resulting solution was washed (aq. $Na_2S_2O_3$, H_2O) and dried ($MgSO_4$). Removal of the solvent gave a mixture of 5-bromo- (17) and 3-bromo-2-methylphenol (18) (ratio 9 : 1). By chromatographing the mixture on silica gel, with CCl_4 as eluant, 5-bromo-2-methylphenol was obtained, m.p. 78 °C (lit.,[8,11] 80, 78 °C).

A portion (0.18 g) of the mixture of 5- and 3-bromo-2-methylphenol containing the former in large excess was treated in 90% acetic acid (10 cm^3) with 0.95 mol equiv. bromine in the same solvent at room temperature. After 10 min, most of the product was precipitated by adding water and the bromophenol was recovered by extraction into diethyl ether. Preparative t.l.c. using $CHCl_3$ as solvent gave nearly pure 4,5-dibromo-2-methylphenol, m.p. 92—93° after recrystallisation from light petroleum (b.p. 60—80 °C). Its ^{1}H n.m.r. spectrum had the two aromatic signals (singlets) characteristic of a dibromo-2-methylphenol with no aromatic protons adjacent.

Specific *ortho*-bromination [12,13] of the purified 5-bromo-2-methylphenol with bromine and isopropylamine in a mixture of dichloromethane and toluene at −70 °C gave 5,6-dibromo-2-methylphenol (16), m.p. 86 °C. It is not clear (see Discussion section) which of these isomeric dibromo-2-methylphenols has been prepared before.[8]

The mixture of dienones (20) and (21), containing (20) in considerable excess, was powdered and stirred with sulphuric acid (15 cm^3) at room temperature for 2 h. The resulting material was poured onto crushed ice (60 g), and the precipitate was filtered off, washed (H_2O), and crystallised (CCl_4) to give 3,4,5,6-tetrabromo-2-methylphenol (15), m.p. 204—207 °C (lit.,[14] 205 °C). This phenol was obtained also by reaction of 2-methylphenol with excess of bromine when iron was used as a catalyst.[14] On protodebromination with HI it gave 3,5-dibromo-2-methylphenol (19), m.p. 100—102 °C (lit.,[15] 98—101 °C) in 89% yield. This was accompanied by a tribromo-2-methylphenol (probably 3,5,6-tribromo-2-methylphenol) from which it could be separated by recrystallisation (CCl_4) or chromatography. 3,4,5,6-Tetrabromo-2-methylphenol (2.2 g) on being treated with bromine (0.5 cm^3) in 90% acetic acid (100 cm^3) at room temperature gave 3,4,4,5,6-*pentabromo-2-methylcyclohexa-2,5-dienone* (22), m.p. 117—119 °C (decomp.), $\lambda_{max.}$ (HOAc) 270 nm ($\varepsilon_{max.}$ 12 400) (Found: C, 16.5; H, 0.9; Br, 80.0. $C_7H_3Br_5O$ requires C, 16.7; H, 0.6; Br, 79.5%).

(b) *Derivatives of 3-Methylphenol* (*Scheme* 2).—2,4,6-Tribromo-3-methylphenol (25) was prepared from 3-methylphenol (0.28 mol) and the theoretical quantity of bromine, which was added in acetic acid (20 cm^3) over 15

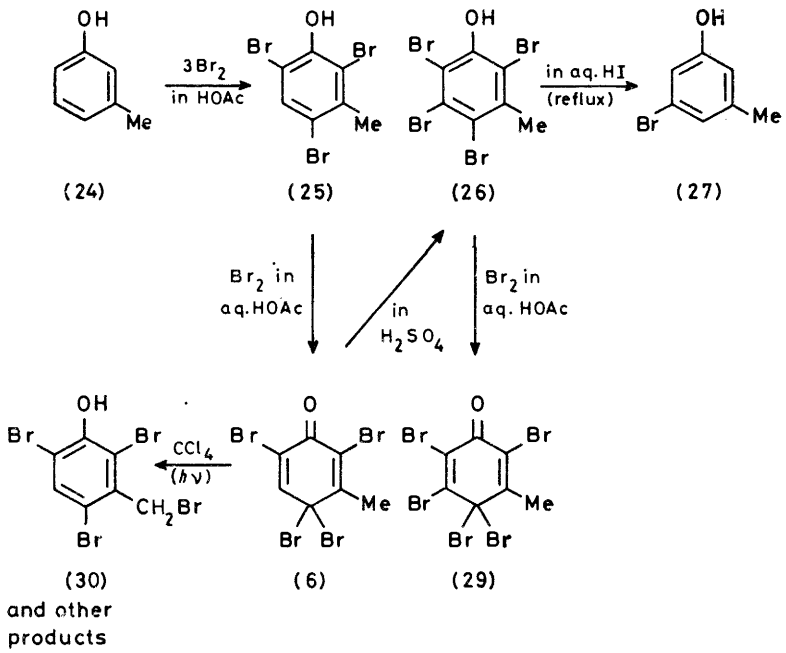
min. Water was then added, and the precipitate was filtered off and crystallised from n-hexane or from carbon tetrachloride to give needles, m.p. 81 °C (lit.,[16] 81 °C). This phenol (0.01 mol) was treated with bromine (0.01 mol) in 90% acetic acid (75 cm³) over *ca.* 2 min. The mixture was stirred for 5 min. Water was then added to precipitate the product, which was recrystallised (CCl_4) to give 2,4,4,6-tetrabromo-3-methylcyclohexa-2,5-dienone (6), m.p. 141—142 °C, $\lambda_{max.}$ (HOAc) 276 nm (ε 13 700) (Found: C, 19.6; H, 1.1; Br, 75.2. Calc. for $C_7H_4Br_4O$: C, 19.8; H, 0.95; Br, 75.4%). This clearly is the compound described by Denivelle and Fort [5] as having m.p. 155°, $\lambda_{max.}$ 278—279 nm ($\varepsilon_{max.}$ 13 800). 2,4,4,6-Tetrabromo-3-methylcyclohexa-2,5-dienone (2 g) was suspended in sulphuric acid (15 ml, 96%). The mixture was stirred for 30 min, allowed to stand overnight, and then added to water (100 ml). The resulting precipitate after recrystallisation from carbon tetrachloride gave 2,4,5,6-tetrabromo-3-methylphenol (26), m.p. 194—195 °C (lit.,[17,18] 196, 194 °C).

This phenol (0.005 mol) was suspended in 55% HI (50 ml) and heated under reflux for 3.5 h, nitrogen being passed through the condenser. The resulting product was extracted from the aqueous solution with $CHCl_3$ (4 × 30 cm³), and the combined portions of $CHCl_3$ were washed ($Na_2S_2O_3$, then H_2O), and dried ($MgSO_4$). After removal of the solvent, the residue was distilled at *ca.* 0.1 mmHg to give 5-bromo-3-methylphenol (27) (0.75 g, 85%) as needles, m.p. 52 °C (lit.,[17] 54 °C).

2,4,5,6-Tetrabromo-3-methylphenol (10^{-3} mol) was treated with bromine (2 × 10^{-3} mol) in 90% acetic acid (75 cm³) at room temperature. The mixture was stirred for 30 min before water was added to precipitate *2,4,4,5,6-pentabromo-3-methylcyclohexa-2,5-dienone* (29), m.p. 132—133 °C (decomp.), $\lambda_{max.}$ (HOAc) 280 nm ($\varepsilon_{max.}$ 13 900) (Found: C, 16.5; H, 0.7; Br, 78.4. $C_7H_3Br_5O$ requires C, 16.7; H, 0.6; Br. 79.5%).

The rearrangement of 2,4,4,6-tetrabromo-3-methylcyclohexa-2,5-dienone in CCl_4 under powerful illumination gave a mixture of products including at least one bromomethylphenol, probably 2,4,6-tribromo-3-bromomethylphenol (30). A complex mixture including bromomethylphenols was also obtained from the reaction of 3-methylphenol with 4 mol equiv. of bromine in carbon tetrachloride under powerful illumination.

(c) *Derivatives of 4-Methylphenol* (*Scheme* 3).—To 4-methylphenol (0.32 mol) in 90% acetic acid (750 cm³), bromine (0.96 mol) was added dropwise over *ca.* 20 min. The mixture was stirred for a further 30 min, and ice (400 g) was added. The mixture was stirred for 1 h, after which

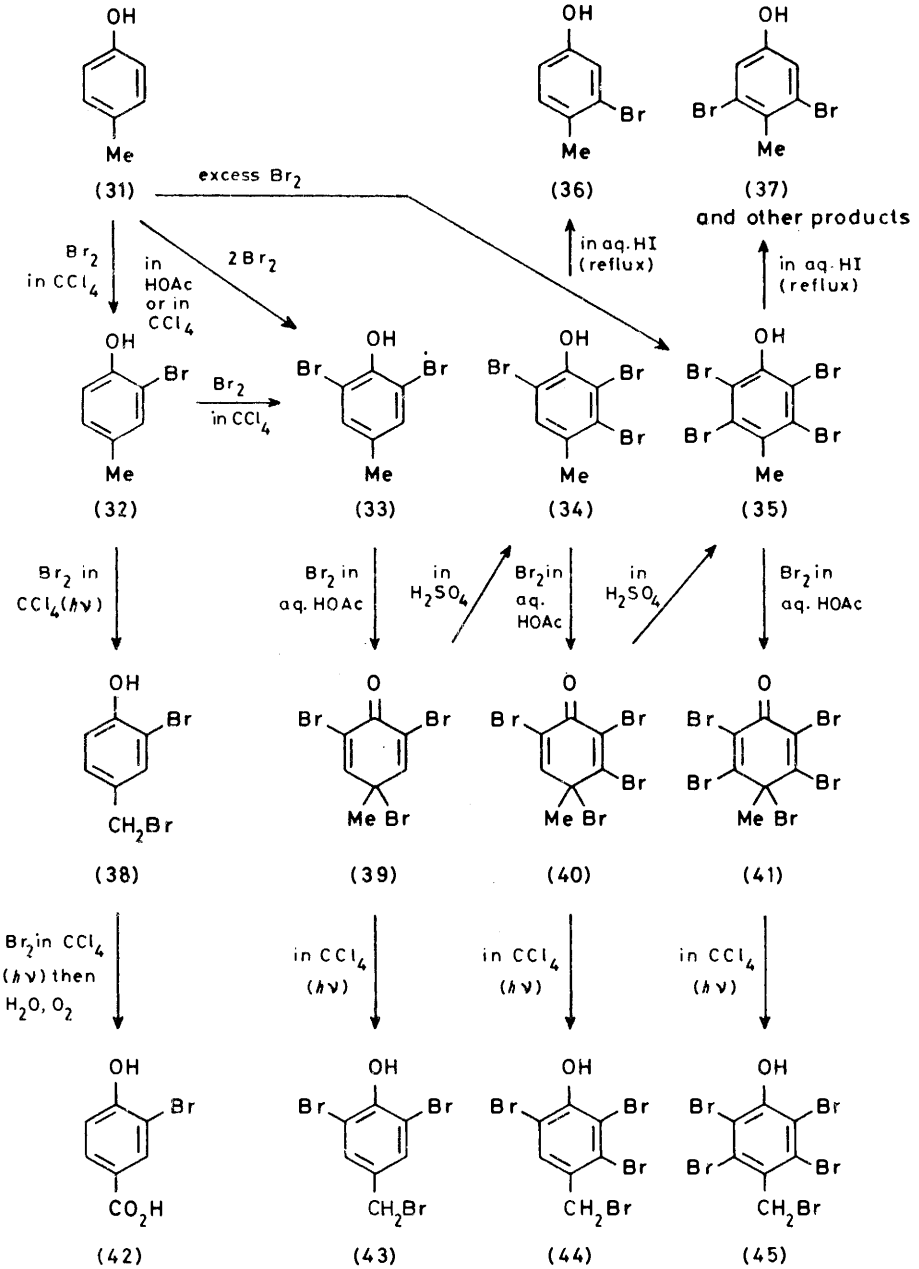


SCHEME 2 Derivatives of 3-methylphenol

pure water (500 cm³) was added. The precipitate was filtered off, washed (H_2O), and crystallised (CCl_4) to give 2,4,6-tribromo-4-methylcyclohexa-2,5-dienone (39) as needles, m.p. 104—105 °C (decomp.) (lit.,[19] 102—105 °C), $\lambda_{max.}$ (HOAc) 270 nm ($\varepsilon_{max.}$ 10 800) (Found: C, 24.8; H, 1.6; Br, 69.6. Calc. for $C_5H_7Br_3O$: C, 24.4; H, 1.5; Br, 69.5%). This dienone (1 g), on being allowed to stand in solution in carbon tetrachloride (100 cm³) for several days, being exposed to laboratory daylight intermittently, or on being kept similarly in $CDCl_3$ (0.2 g in 0.5 cm³), or on being allowed to stand in the solid phase for a prolonged period, gave nearly quantitatively 2,6-dibromo-4-bromomethylphenol (43) which, after recrystallisation (CCl_4), had m.p. 151 °C (lit.,[19] 150 °C). The same dienone (4.5 g) was stirred with sulphuric acid (30 cm³) for 45 min and allowed to stand overnight. The mixture was then poured onto ice (100 g), and the resulting precipitate was collected and crystallised (CCl_4) to give 2,3,6-tribromo-4-methylphenol (34), m.p. 106 °C (lit.,[20-22] 102 °C). This phenol was refluxed with excess of aq. HI (55%) for 9 h, nitrogen being passed through the condenser. The mixture was cooled to room temperature and after 2 days the precipitate was filtered off, washed (aq. $Na_2S_2O_3$, then H_2O), and chromatographed

on silica gel, hexane–benzene–diethyl ether (2 : 1 : 1 v/v) being used as eluant. Appropriate fractions were bulked to give 3-bromo-4-methylphenol (36) (86%), m.p. 51 °C (lit.,[23,24] 54—55 °C) (Found: C, 45.1; H, 3.8; Br, 43.0. Calc. for C_7H_7BrO: C, 45.0; H, 3.8; Br, 42.7%).

1.2; Br, 74.5. $C_7H_4Br_4O$ requires C, 19.8; H, 0.94; Br, 75.5%). On being treated with sulphuric acid as was described for 2,4,6-tribromo-4-methylcyclohexa-2,5-dienone it gave quantitatively 2,3,5,6-tetrabromo-4-methylphenol (35) (which could also be prepared from bromine and *p*-



SCHEME 3 Derivatives of 4-methylphenol

2,3,6-Tribromo-4-methylphenol (1.25 g) in 90% HOAc (50 cm³) was treated with Br_2 (0.6 g) dropwise over *ca.* 1 min. The mixture was stirred for 1 h, and then water (25 cm³) was added. The resulting precipitate was filtered off, washed (H_2O), and crystallised (CCl_4) to give 2,3,4,6-*tetrabromo*-4-*methylcyclohexa*-2,5-*dienone* (40) as needles from carbon tetrachloride, m.p. 109—111 °C (decomp.), $\lambda_{max.}$ (HOAc) 275 nm ($\varepsilon_{max.}$ 13 000) (Found: C, 21.0; H,

cresol),[20] m.p. 199 °C (lit.,[18,20-22] 196, 198—199 °C). This phenol (1.5 g) was dissolved in 90% HOAc (150 cm³) by gentle warming. Bromine (0.3 cm³) was added dropwise and the mixture was stirred for 30 min. Water was then added and the precipitate was filtered off, washed (H_2O), and crystallised (CCl_4) to give 2,3,4,5,6-pentabromo-4-methylcyclohexa-2,5-dienone (41),[24] m.p. 135—136 °C (decomp.), $\lambda_{max.}$ (HOAc) 279 nm ($\varepsilon_{max.}$ 14 650) (Found: C,

16.6; H, 0.6; Br, 79.9. Calc. for $C_7H_3Br_5O$: C, 16.7; H, 0.6; Br, 79.5%). On being allowed to stand in carbon tetrachloride for *ca.* 10 days, this dienone gave a mixture containing 2,3,5,6-tetrabromo-4-bromomethylphenol (45), m.p. 183—184 °C (lit.,[21,22] 182 °C), which was prepared for reference by treating 2,3,5,6-tetrabromo-4-methylphenol with bromine in CCl_4 under strong illumination. The dienone from 2,3,6-tribromo-4-methylphenol also gave a bromomethyl derivative on being kept in CCl_4 for some days.

When 2,3,5,6-tetrabromo-4-methylphenol was heated under reflux with aqueous HI for 8.5 h, all the starting material was gone, but the product was a complex mixture, which from its ^1H n.m.r. spectrum appeared to contain 3,5-dibromo-4-methylphenol. Successive chromatography and recrystallisation from light petroleum, aqueous acetic acid, and aqueous ethanol gave a product, m.p. 109—111° (lit.,[22] 109°), having the expected ^1H n.m.r. spectrum (see Supplementary Publication), but still containing an unidentified impurity, as judged by a singlet attributable to a methyl group in up to 15%; we were unsuccessful in removing this.

When acetic acid, or aqueous acetic acid, is used as solvent for the monobromination of 4-methylphenol, the product contains both some starting material and 2,6-dibromo-4-methylphenol. A more satisfactory product is obtained by carrying out the bromination in CCl_4 as solvent. 4-Methylphenol (3.5 g) in CCl_4 (150 cm^3) was treated with bromine (5.2 g) in the dark. After 0.5 h, the solvent and hydrogen bromide was removed *in vacuo*, and from the residue 2-bromo-4-methylphenol (32) was recovered.

When excess of bromine was used, and the reaction mixture was kept in the dark, 2,6-dibromo-4-methylphenol (33) was the product. The bromination of a stirred solution of 4-methylphenol (4.35 g) and bromine (6.3 cm^3) in dry CCl_4 (170 cm^3) under strong illumination at a temperature not exceeding 30 °C took a different course. The composition of the reaction mixture was monitored at intervals by ^1H n.m.r. spectroscopy. After 5 min the main product had a signal at δ 4.35 and was presumably 2-bromo-4-bromomethylphenol (38). After 1.5 h the reaction mixture contained 2-bromo-4-dibromomethylphenol as the major product. After *ca.* 3 h, reaction to form the dibromomethyl compound was complete, and removal of solvent gave a greenish oil which on being kept in contact with moist air gave 3-bromo-4-hydroxybenzoic acid (42).

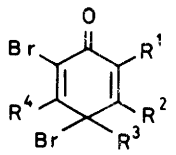
(d) *Reactions of* 3,4-*Dimethylphenol.*—3,4-Dimethylphenol (4.3 g) was treated with excess (18 g) of bromine in CCl_4 (170 cm^3) at room temperature under strong illumination. The ^1H n.m.r. spectrum showed that the product was a complex mixture of several mono- and di-bromomethyl compounds. By contrast, the rearrangement of 2,4,6-tribromo-3,4-dimethylcyclohexa-2,5-dienone in CCl_4 at room temperature under normal laboratory illumination, or in the dark, gave only 2,6-dibromo-4-bromomethyl-3-methylphenol.

(e) ^1H *and* ^{13}C *N.m.r. Spectra.*—The ^1H n.m.r. spectra of the phenols described in this work were determined by using a Varian T-60 n.m.r. spectrometer, usually in $CDCl_3$ as solvent with tetramethylsilane as internal standard. They are given in Supplementary Publication No. SUP 22896 (46 pp.),* and are all consistent with the structures ascribed to them. For the dienones, data for which are provided similarly, the positions and multiplicities of the signals are summarised in Table 1.

The ^{13}C n.m.r. spectra of the bromodienones were determined similarly by using a JEOL FX-60 instrument. Standard techniques were used for observation of the required spectral characteristics; the relevant spectra are also given in SUP 22896. Full consideration of the findings is deferred awaiting completion of a comparative study of these and the related hydroxy- and nitro-dienones; in the present paper, the discussion is confined to those aspects of the spectra which define the structures of the dienones and the absence of significant proportions of equilibrium amounts of other isomers in their solutions. Of the two dienones (39) and (46) that could be derived from 2,6-dibromo-4-methylphenol, it is clear that (39) would have five, and (46) would have seven different ^{13}C signals in the fully decoupled spectrum. The spectrum of the relevant dienone has five signals; no significant signals which could be attributed either to impurity or to the presence of the second isomer in equilibrium are apparent. The fully

TABLE 1

The ^1H n.m.r. spectra of the bromodienones [a]

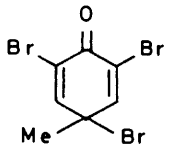


Compound no.	Substituent				Chemical shift [b] (multiplicity)			
	R1	R2	R3	R4	R1	R2	R3	R4
(8)	Me	H	Br	H	2.05 (d, *J* 1—2 Hz)	7.05 (m)		7.61 (d, *J* 2—3 Hz)
(20)	Me	H	Br	Br	2.10 (s)	7.05 (s)		
(21)	Me	Br	Br	H	2.26 (s)			8.04 (s)
(22)	Me	Br	Br	Br	2.25 (s)			
(6)	Br	Me	Br	H		2.62 (s)		7.86 (s)
(29)	Br	Me	Br	Br		2.75 (s)		
(39)	Br	H	Me	H		7.50 (s)	2.00 (s)	7.50 (s)
(40)	Br	Br	Me	H			2.10 (s)	7.70 (s)
(41)	Br	Br	Me	Br			2.40 (s)	

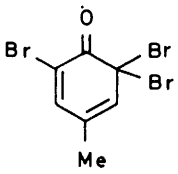
[a] Spectra were measured as solutions in $CDCl_3$. [b] p.p.m. from tetramethylsilane.

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1979, Index issue.

undecoupled spectum confirms the conclusion that the structure is (39) and not (46). The results are given in Table 2.



(39)



(46)

It has been shown by Hollenstein and Philipsborn [26] and by Rieker and Berger [27] that the chemical shifts for C-1 in extensive series of alkyl-substituted 2,5-dienones lie in the range δ 178—187 p.p.m., whereas those for the corresponding 2,4-dienones lie in a substantially higher range (δ 192—205 p.p.m.). All the dienones examined in this work have signals for C-1 in a range δ 168—176 p.p.m., as is shown by the results given in Table 3. In our view, therefore, they are all 2,5-dienones, and their spectra generally do not show the presence of significant proportions of isomers.

TABLE 2

Details of the ^{13}C n.m.r. spectrum of 2,4,6-tribromo-4-methylcyclohexa-2,5-dienone

Peak position (p.p.m.) downfield from Me_4Si in proton-decoupled spectrum	Multiplicity fully undecoupled spectrum	Assignment	Couplings
171.2	t	C-1	^3J with 3- and 5-H
150.1	d of m (approx. pentets)	C-3, -5	^1J (C-3 with 3-H, C-5 with 5-H)
			^3J (C-3 with 5-H, C-5 with 3-H)
			^3J (with methyl hydrogens)
123.8	d	C-2, -6	^2J (C-2 with 3-H, C-6 with 5-H)
54.4	q (poorly resolved)	C-4	^2J (C-4 with methyl hydrogens)
30.0	q	CH_3	^1J (methyl with attached hydrogens)

TABLE 3

Chemical shifts (p.p.m. downfield from tetramethylsilane) for C-1 in the ^{13}C n.m.r. spectra of substituted cyclohexa-2,5-dienones in $CDCl_3$

Substituents in dienone						Chemical shift of signal for C-1 [δ (p.p.m.)]
2	3	4	4	5	6	
Me	H	Br	Br	H	Br	176.0
Me	Br	Br	Br	H	Br	173.3
Me	H	Br	Br	Br	Br	174.5
Me	Br	Br	Br	Br	Br	172.1
Br	Me	Br	Br	H	Br	170.0
Br	Me	Br	Br	Br	Br	168.3
Br	H	Me	Br	H	Br	171.2
Br	Br	Me	Br	H	Br	169.8
Br	Br	Me	Br	Br	Br	168.2

DISCUSSION

Many workers have contributed to our knowledge of the bromination of methylphenols, as is indicated by the papers already cited. Despite this, the literature relating to the compounds which can be derived in this way is confusing, in part conflicting, and in part incorrect. The reactions carried out in the course of the present work are summarised in Schemes 1—3.

(a) *Reactions of the Methylphenols and their Bromo-derivatives with Bromine.*—A wide variety of conditions have been used successfully for the bromination of phenol and its derivatives. Treatment with molecular bromine in a solvent (*e.g.* acetic acid, dichloromethane, chloroform, or carbon tetrachloride) normally gives nearly quantitative bromination, with substitution first *para* to the hydroxy-group if this position is vacant, and then at vacant *ortho*-positions. Literature descriptions of the formation of (14), (25), and (33) in this way have been confirmed in the course of this work. Reactions can be more easily stopped at the stage of monobromination with dipolar aprotic than with hydroxylic solvents.

Pearson *et al.*[12] have described a method for bromination specifically *ortho* to a hydroxy-group, so that the normal preference for *para*-bromination can be reversed. Cresp *et al.*[13] have used this procedure for the preparation of 3,6-dibromo-2-methylphenol from 3-bromo-2-methylphenol, and we have used it for the preparation of 5,6-dibromo-2-methylphenol (16) from 5-bromo-2-methylphenol. Our product, m.p. 86 °C, was characterised by its ^1H n.m.r. spectrum in which an *ortho*-coupling ($J_{3,4}$ 8 Hz) is evident. Previously Janney [8] had recorded its preparation (m.p. 94 °C) from 5-bromo-2-methylphenol and bromine in the presence of iron. The catalyst might possibly have modified the orientation, so it is not in our view certain whether this preparation gave 5,6- or 4,5-dibromo-2-methylphenol or a mixture of the two; but by treating 5-bromo-2-methylphenol with bromine in aqueous acetic acid we obtained as the main product authentic 4,5-dibromo-2-methylphenol (16a), m.p. 92—93°, having the expected ^1H n.m.r. spectrum.

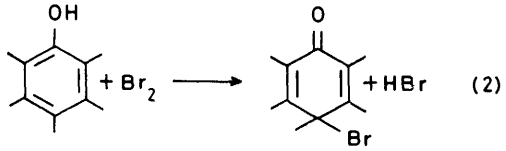
Polybromination of the methylphenols can be effected by treating the liquid or solid phenol with excess of liquid bromine. It has been confirmed that this procedure when applied to 3-methylphenol gives the fully ring-brominated derivative (26); similarly 4-methylphenol gives (35). With 2-methylphenol it had been reported [22] that 4,5,6-tribromo-2-methylphenol (11) is the major product. In our experience, however, the product is a mixture of the isomers (11) and (12), formed in approximately equal amount, and in our hands only partly separated by chromatography on silica gel or alumina, light petroleum (b.p. 60—80 °C), ethyl acetate, and several other solvents having been tried as eluants. We have confirmed that the fully ring-brominated derivative (15) can be prepared by using excess of bromine and iron as a catalyst.[28,29]

The mechanism by which bromine is introduced *meta* to a hydroxy-group in these brominations is not certain.

It is possible that the reactions involve the formation and acid-catalysed rearrangement of bromodienones, as in the reactions described below. If so, the regioselectivity of the rearrangement which gives (11) and (12) differs according to the conditions of reaction; a marked predominance of (11) is obtained in the reaction of (8) with sulphuric acid, whereas approximately equal proportions of the two isomers are formed by treating 2-methylphenol with liquid bromine.

(b) *Protodebromination of Polybromophenols.*—In Part 8,[1] the preparation was described of two new bromo-substituted 3,4-dimethylphenols by protodebromination of 2,5,6-tribromo-3,4-dimethylphenol with aqueous hydrogen iodide followed by bromination of the product. In the present paper, we have shown that this method of protodebromination can be applied to other polybromophenols, and that it appears to be superior to the method of Kohn *et al.*,[15,17,30] in which the polybromophenol is treated with aluminium trichloride and benzene. Thus we have obtained 3,5-dibromo-2-methylphenol (19) from 3,4,5,6-tetrabromo-2-methylphenol (15) in 84% yield. The same reaction was effected by Kohn and Jawetz [15] by using aluminium trichloride and benzene, but the yield was much poorer. Similarly the mixture of 4,5,6- and 3,4,6-tribromo-2-methylphenols (11) and (12) gave in good yield a mixture of 5-bromo- (17) and 3-bromo-2-methylphenol (18), from which the former could be obtained by careful chromatography. It has been shown also that 2,4,5,6-tetrabromo-3-methylphenol (26) gives 5-bromo-3-methylphenol in 85% yield. Kohn and Weissberg [17] carried out the same reaction in poorer yield by using excess of benzene and aluminium chloride. They were unsuccessful in preparing 3-bromo-4-methylphenol (36) from 2,3,6-tribromo-4-methylphenol (34) by their method, whereas by using hydrogen iodide an 86% yield has now been obtained. The corresponding reaction of 2,3,5,6-tetrabromo-4-methylphenol (35) gave a slightly impure material, though its m.p. agreed with that reported in the literature. We failed also to purify it through its acetate.

(c) *Preparation of Bromodienones by Bromination of Phenols.*—The bromodienones (6), (8), (20) and (21) as a mixture, (22), (29), (39), (40), and (41) have been prepared from the corresponding bromophenols by reaction with bromine in aqueous (90%) acetic acid. The presence of water is necessary to enable the reaction to proceed to completion; in anhydrous acetic acid, the equilibrium of equation (2) (which is itself affected by the



(2)

formation of hydrogen tribromide by the equilibrium $Br_2 + HBr \rightleftharpoons HBr_3$) is less favourable to the formation of the dienone.

The dienones are formed quite rapidly at room temperature, and most of them can easily be isolated in nearly quantitative yield. Their u.v. spectra (see SUP 22896) establish, through the existence in each case of a broad maximum at 270—280 nm, with an extinction coefficient in the range 9 000—14 000, and little absorption in the region 320—400 nm, that they are *para-* rather than *ortho*-dienones. Thus the structures previously accorded [5,7,19] to compounds (6) and (39) are confirmed, and the uncertainty [8] concerning the structure of (8) is resolved.

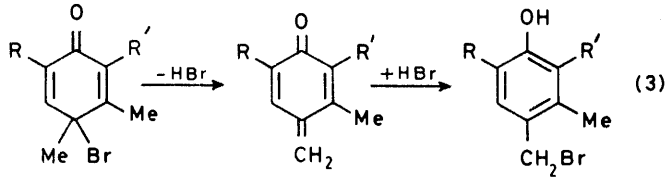
Denivelle and Fort [5] have previously described the preparation of the dienone (6) by bromination of 3-methylphenol in a number of solvents. The u.v. spectrum which they recorded had within experimental error the same characteristics as ours; we have, however, been unable to reproduce their m.p. of 155 °C. In our hands the m.p. was 141—142 °C after recrystallisation from several solvents. It seems likely that the same compound was obtained by Foster [6] and by Fries and Volk,[7] who attributed to it the *ortho*-dienone structure, and it is possible that two crystalline forms of this dienone exist.

(d) *Rearrangement of Bromodienones to Ring-substituted Bromophenols.*—Any of the bromodienones (8), (20), (21), (6), (39), or (40), when stirred in suspension with concentrated sulphuric acid at room temperature, give nearly quantitatively the product of 1,2-shift of bromine. This type of reaction, which we reported [1,31] for the dienone derived from 2,6-dibromo-3,4-dimethylphenol, had earlier [2,8] been described for (6) and for (8). In the latter case, in which the migrating group has a choice of positions to move to, the earlier report [8] had indicated that only (11) was obtained. In fact, however, the reaction is regioselective rather than regiospecific; both (11) and (12) are formed, though (11) predominates to the extent of *ca.* 88%. Similar rearrangements of 4-chloro-4-methylcyclohexa-2,5-dienones have recently been described.[32]

The stages leading to polybromophenols by the formation of dienones and their rearrangement with sulphuric acid are usually clean and nearly quantitative, so this type of route is often preferable to the alternative, in which the appropriate phenol is treated with excess of bromine, sometimes at elevated temperatures or in the presence of a catalyst.

(e) *Rearrangement of Bromodienones to Bromomethylphenols.*—The dienones (39)—(41) derived from 4-methylphenol undergo easy rearrangement to give the corresponding bromomethylphenols (43)—(45), respectively. Rearrangements of this kind are well known,[1,3,14,16] and are sometimes described as quino-bromide rearrangements. They occur both in the solid state and in solution, and are accelerated by the use of higher temperatures. In our experience, and that of others,[33] the crystalline dienones become less susceptible to rearrangement when traces of impurities are removed by recrystallisation. We found that the very highly brominated

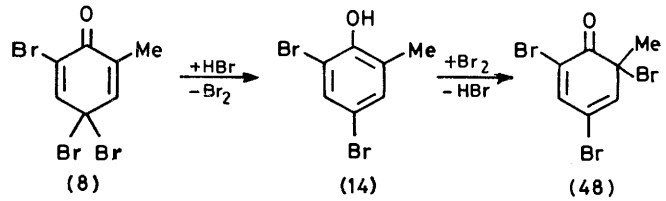
dienones (40) and (41) were converted rather sluggishly and not quite cleanly into their bromomethyl derivatives (44) and (45). In other cases, and especially for dienones containing electron-releasing substituents, these reactions can be nearly quantitative, as for 4-bromo-4-methyl-2,6-di-t-butylcyclohexa-2,5-dienone,[33] of 2,4,6-tribromo-4-methylcyclohexa-2,5-dienone (39) (this paper), and of 2,4,6-tribromo-3,4-dimethylcyclohexa-2,5-dienone.[1] For the last of these reactions, it was found that exposure of solutions to ordinary laboratory illumination increased the rate of the reaction by a small factor. The regiospecificity of this particular quinobromide rearrangement was notable; no 2,6-dibromo-3-bromomethyl-4-methylphenol was formed. It has been recognised by several groups of workers, including ourselves,[1,3,33] that these rearrangements show indications of the incursion of homolytic processes. Despite this, they have generally been considered to be probably heterolytic in character. Both homolytic and heterolytic mechanisms are available for elimination of hydrogen bromide from unsaturated ketones,[34] so a methylenequinone [*e.g.* (47)] could be an intermediate in either type of pathway [reaction (3)]. It has been



(3)

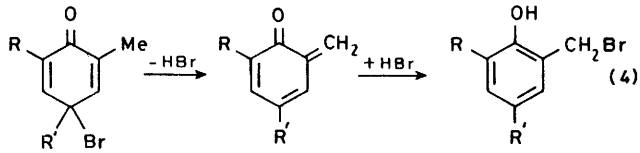
(47)

shown [35] that simple methylenequinones can be prepared in dilute solution in carbon tetrachloride. Although they have a considerable tendency to polymerise, it seems clear from their properties that the final stage of sequence (3) would be rapid, so this type of sequence is a reasonable representation of the rearrangements of our 4-methyl-substituted dienones to 4-bromomethylphenols under normal laboratory conditions.



(8) (14) (48)

4-Bromo-2,5-dienones containing an *ortho*-methyl group [*e.g.* (8)] could conceivably react through a pathway such as that shown in reaction (4) by a 1,4-elimination of hydrogen bromide analogous with the 1,2-elimination shown in reaction (3). The dienone (8) [R = R′ = Br in sequence (4)] does not, however, appear to rearrange in this way. Instead, when (8) is kept in solution in carbon tetrachloride, it reverts gradually to a mixture which includes bromine and the derived phenol, and only then begins to give the side-chain-brominated product. Presumably catalytic amounts of hydrogen bromide are produced by a side-reaction, and sequence (5) then follows. Because this conversion proceeds under conditions which allow the very regiospecific reaction of 2,4,6-tribromo-3,4-dimethylcyclo-

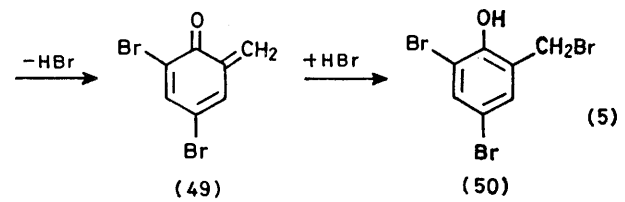


(4)

hexa-2,5-dienone, it seems reasonable to suppose that the intermediate *ortho*-dienone (48) and *ortho*-methylenequinone (49) are intermediates, but it is possible that the methyl group is brominated directly in a homolytic process.

It would be expected that the polybromodienone (6) derived from 3-methylphenol would not give a similar reaction. Although it is more stable than the dienones derived from 2- or from 4-methylphenol, on strong illumination in CCl_4 it gives a mixture in which 2,4,6-tribromo-3-bromomethylphenol is probably the main component, and no products which could be derived by further bromination of the bromomethyl group were detected.

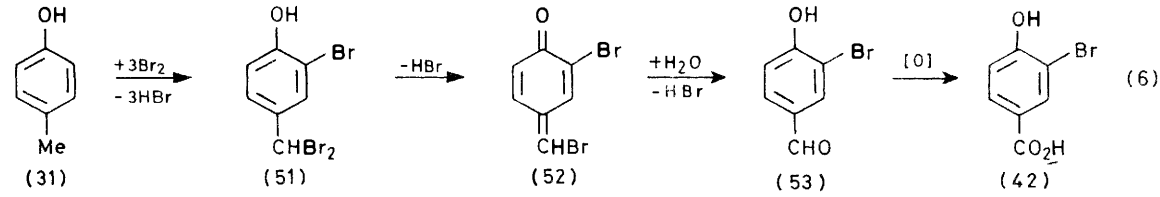
(f) *Bromination of Methylphenols under Strong Illumination.*—Many heavily brominated bromomethyl compounds have been prepared by earlier workers by heating the corresponding bromo-substituted phenol with excess of bromine in a sealed tube.[10,14,21,30] Under these conditions, equilibria of the type shown in equation (2) are set up; but it is not known whether the substrate undergoing reaction is the phenol or the dienone, whether the reaction is homolytic or heterolytic, or whether (if the reaction is homolytic) the source of bromine atoms is bromine or the bromodienone. We have shown that much milder conditions can be used for these brominations. Thus 2-methylphenol on treatment with excess of bromine for some hours under strong illumination, the temperature being kept below



(49) (50)

(5)

30 °C, gives 4,6-dibromo-2-bromomethylphenol (23) in good yield. The corresponding reaction of 3-methylphenol gives a complex mixture of products, which include bromomethyl and dibromomethyl compounds. With 4-methylphenol, it was found that the reaction (which in the absence of illumination proceeds slowly to give 2,6-dibromo-4-methylphenol) became diverted at the point at which only one bromine substituent had been introduced into the ring, and thence there was obtained ultimately in good yield 3-bromo-4-hydroxybenzoic acid. With 3,4-dimethylphenol, the ^1H n.m.r.



spectrum showed that the product was a complex mixture of bromomethyl and dibromomethyl compounds.

It is clear that these reactions are less regiospecific than those prevailing when the quinobromide rearrangement of a pre-formed bromodienone is allowed to proceed spontaneously in the solid phase or in an aprotic solvent with or without the normal laboratory illumination. Probably, therefore they involve bromine atoms. There are several possible ways in which 3-bromo-4-hydroxybenzoic acid could be formed from 4-methylphenol; one of these is shown in reaction (6). The 1,6-elimination of hydrogen bromide (51) ⟶ (52) has known analogies in the chemistry of 4-dibromomethylphenols.[36]

[0/373 *Received*, 7*th March*, 1980]

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