# Formylation and Bromination *ortho* to the Hydroxy-group of 2-Carbonyl-substituted Phenols in the Presence of Titanium(IV) Chloride †

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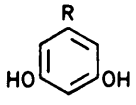
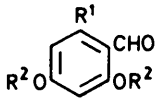
Formylation with dichloromethyl methyl ether and titanium(IV) chloride in dichloromethane, and bromination with bromine and titanium(IV) chloride in dichloromethane, of methyl 2,4-dihydroxybenzoate (16), methyl 2-hydroxy-4-methoxybenzoate (17), ethyl 2-hydroxy-4-methoxy-6-methylbenzoate (21), methyl 2-hydroxy-4-methylbenzoate (24), and 2-hydroxy-4-methoxyacetophenone (25) produce appreciable amounts of 3-substituted products. This selective substitution in the position *ortho* to the hydroxy-group is discussed in terms of a six-membered ring titanium complex.

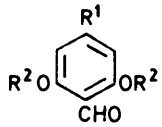
FORMYLATION of phenolic compounds with dichloromethyl methyl ether and titanium(IV) chloride in dichloromethane [1] differs from both the Gattermann method and formylation with ethyl orthoformate and aluminium chloride [1] in that significant formylation *ortho* to the hydroxy-group occurs even when the *para*-position is vacant. Thus 3,5-dihydroxytoluene (orcinol) (1) in both Gattermann [2] and ethyl orthoformate [1] formylation gave exclusively 2,4-dihydroxy-6-methylbenzaldehyde (4) whereas the dichloromethyl methyl ether method gave the former (29%), as well as 2,6-dihydroxy-4-methylbenzaldehyde (9) (19%).[1] We have found that similar results are obtained with 5-ethylbenzene-1,3-diol (2), and 5-propylbenzene-1,3-diol (divarinol) (3). On formylation with ethyl orthoformate and aluminium chloride the phenols (2) and (3) gave as sole products 2,4-dihydroxy-4-ethylbenzaldehyde (5)



(1) R = Me
(2) R = Et
(3) R = Pr



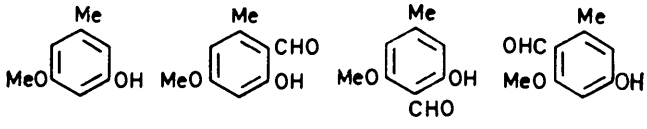
(4) $R^1$ = Me, $R^2$ = H
(5) $R^1$ = Et, $R^2$ = H
(6) $R^1$ = Pr, $R^2$ = H
(7) $R^1$ = Et, $R^2$ = Me
(8) $R^1$ = Et, $R^2$ = Me



(9) $R^1$ = Me, $R^2$ = H
(10) $R^1$ = Et, $R^2$ = Me
(11) $R^1$ = Pr, $R^2$ = Me

and 2,4-dihydroxy-4-propylbenzaldehyde (6), respectively. The structures of these products were apparent from the n.m.r. spectra of the derived methyl ethers, (7) and (8), respectively, in [$^2H_6$]benzene, which both showed AB patterns for the aromatic protons and two 3H singlets due to the methoxy-groups. Formylation of the phenols (2) and (3) with dichloromethyl methyl ether and titanium(IV) chloride gave in each case both of the possible aldehydes, which were separated as their methyl ethers. The n.m.r. spectra of both 4-ethyl-2,6-dimethoxybenzaldehyde (10) and 2,6-dimethoxy-4-propylbenzaldehyde (11) in [$^2H_6$]benzene exhibited 2H singlets for the aromatic protons and 6H singlets due to the methoxy-protons.

With 5-methoxy-3-methylphenol (12) the products of dichloromethyl methyl ether formylation were 2-hydroxy-4-methoxy-6-methylbenzaldehyde (13) (33·4%) and 2-hydroxy-6-methoxy-4-methylbenzaldehyde (14) (7%), the formyl group thus entering the positions *ortho* to the hydroxy-group. In contrast the



(12) (13) (14) (15)

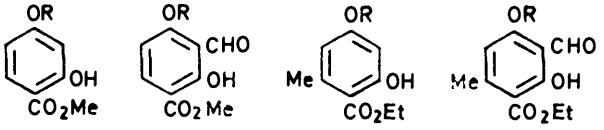
Gattermann method [3,4] gave 4-hydroxy-2-methoxy-6-methylbenzaldehyde (15) as a major product, accompanied by some 2-hydroxy-4-methoxy-6-methylbenzaldehyde (13).

Shah and Laiwalla [5] observed that methyl 2,4-dihydroxybenzoate (16) would only undergo Gattermann formylation with aluminium chloride as catalyst and ether as solvent and that the product was exclusively methyl 3-formyl-2,4-dihydroxybenzoate (18). They attributed this unusual result to the stabilisation of the Kekulé form of the substrate in which the double bond is between the 2-hydroxy-group and the ester substituent by intramolecular hydrogen bond formation, thus facilitating electron release to the 3-position. Using aluminium chloride in ether Whalley [6] found that Gattermann formylation of ethyl 2,4-dihydroxy-6-methylbenzoate (ethyl orsellinate) (20) gave exclusively ethyl 3-formyl-2,4-dihydroxy-6-methylbenzoate (ethyl haematommate) (22). In contrast, Gattermann formylation [7,8] of ethyl orsellinate (20) with zinc chloride in ether gave both of the possible monoaldehydes. This latter evidence appears to throw doubt on the validity of Shah and Laiwalla's explanation of the formation of 3-formylated products when aluminium chloride is used as catalyst.

† Preliminary communication, T. M. Cresp, M. V. Sargent, and J. A. Elix, *Chem. Comm.*, 1972, 214.

[1] H. Gross, A. Rieche, and G. Matthey, *Chem. Ber.*, 1963, **96**, 308.
[2] L. Gattermann and M. Köbner, *Ber.*, 1899, **32**, 279; R. Adams and I. Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2373.
[3] A. St. Pfau, *Helv. Chim. Acta*, 1928, **11**, 864.
[4] D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, 1963, **19**, 1.
[5] R. C. Shah and M. C. Laiwalla, *J. Chem. Soc.*, 1938, 1828.
[6] W. B. Whalley, *J. Chem. Soc.*, 1949, 3278.
[7] F. H. Curd, A. Robertson, and R. J. Stephenson, *J. Chem. Soc.*, 1933, 130.
[8] A. St. Pfau, *Helv. Chim. Acta*, 1933, **16**, 282.

We have therefore investigated the formylation, by dichloromethyl methyl ether and titanium(IV) chloride



(16) R = H (17) R = Me | (18) R = H (19) R = Me | (20) R = H (21) R = Me | (22) R = H (23) R = Me

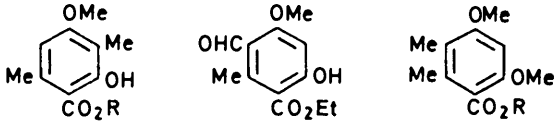
in dichloromethane, of a series of *o*-hydroxy-carbonyl-substituted compounds in which the positions *ortho* and *para* to the hydroxy-group are both vacant. Formylation of methyl 2,4-dihydroxybenzoate (16), methyl 2-hydroxy-4-methoxybenzoate (17), ethyl 2,4-dihydroxy-6-methylbenzoate (20), ethyl 2-hydroxy-4-methoxy-6-methylbenzoate (ethyl everninate) (21), methyl 2-hydroxy-4-methylbenzoate (24), and 2-hydroxy-4-methoxyacetophenone (paeonol) (25) gave predominantly the 3-formyl-substituted products and only traces of the 5-formyl products (see Table). The structures of the products, except in the case of compound (21), were immediately apparent from their

(24) | (25) R = H (26) R = Me

| Substrate | Formylation | $TiCl_4$ bromination |
|---|---|---|
| (16) | 38% 3-CHO | 36% 3-Br |
| | | 30% 5-Br |
| | | 12% 3,5-$Br_2$ [a] |
| (17) | 48% 3-CHO | 48% 3-Br |
| | 8% 5-CNO | 41% 5-Br |
| (18) | 23% 3-CHO | |
| (21) | 49% 3-CHO [b] | 40% 3-Br |
| | 5% 5-CHO | 40% 5-Br |
| (24) | 32% 3-CHO | 32% 3-Br |
| | 5% 5-CHO | 48% 5-Br |
| | | 4% 3,5-$Br_2$ [a] |
| (25) | 32% 3-CHO | 65% 3-Br |
| | 2% 5-CHO | 15% 5-Br |

[a] Unbrominated material was also isolated. [b] See ref. 9.

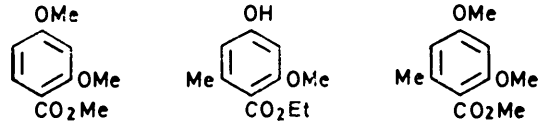
n.m.r. spectra. The major product of formylation of compound (21) was ethyl 3-formyl-2-hydroxy-4-methoxy-6-methylbenzoate (23).[9] This ester was hydrogenated to ethyl rhizinonate (27), which on hydrolysis and methylation [9] gave the corresponding methyl ester,



(27) R = Et (28) R = Me | (29) | (30) R = Et (31) R = Me

methyl 2-hydroxy-4-methoxy-3,6-dimethylbenzoate (28), identical with an authentic sample.[10] Hydrogenation of the minor product, ethyl 5-formyl-2-hydroxy-4-methoxy-6-methylbenzoate (29), followed by methylation, gave the ethyl ester (30).

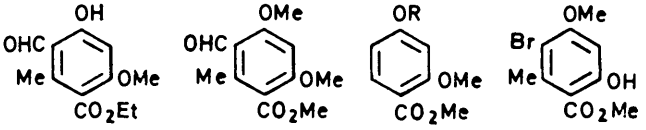
The sole products of formylation of methyl 2,4-dimethoxybenzoate (32), ethyl 4-hydroxy-2-methoxy-6-methylbenzoate (ethyl isoeverninate) (33), methyl 2,4-dimethoxy-6-methylbenzoate (34), and



(32) | (33) | (34)

2,4-methoxyacetophenone (26) were the 5-formyl isomers. The structures of the formylation products of compounds (32) and (26) followed from their n.m.r. spectra. Formylation of compounds (33) and (34) gave the aldehydes (35) and (36), respectively, and these aldehydes could both be related, by suitable transformations, to ethyl 5-formyl-2-hydroxy-4-methoxy-6-methylbenzoate (29).

Formylation of methyl 4-hydroxy-2-methoxybenzoate (37) did not occur at a ring position, but gave methyl 4-formyloxy-2-methoxybenzoate (38), which was iso-



(35) | (36) | (37) R = H (38) R = CHO | (39)

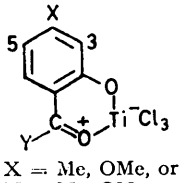
lated by crystallisation of the crude product. This structural assignment was supported by the presence of signals for three aromatic protons and a singlet at $\tau$ 1·68 ($HCO_2^-$) in the n.m.r. The i.r. spectrum showed a carbonyl stretching vibration at 1765 $cm^{-1}$ typical of the formate ester of a phenol.[11] Presumably compound (37), like alcohols,[12] undergoes initial *O*-formylation and the product (38) is insufficiently activated to undergo *C*-formylation. *O*-Formylation appears to be a common side reaction in the formylation of deactivated phenols; thus the n.m.r. spectrum of the crude product from formylation of ethyl isoeverninate (33) exhibited a singlet at $\tau$ 1·62, as well as signals due to the aldehyde (35). The formates are readily hydrolysed to the phenols on chromatography over silica gel and hence were not usually isolated.

These results in which *C*-formylation occurs almost exclusively at the 3-position of the *o*-hydroxy-carbonyl compounds studied, and solely at the 5-position in the *o*-methoxy-carbonyl compounds, suggested to us that a six-membered ring titanium complex might be the species responsible for the direction of electrophilic substitution in the case of the *o*-hydroxy-carbonyl compounds. To test this hypothesis we investigated the bromination

[9] T. M. Cresp, J. A. Elix, S. Kurokawa, and M. V. Sargent, *Austral. J. Chem.*, 1972, **25**, 2167.
[10] Y. Asahina and H. Akagi, *Ber.*, 1955, **68**, 1130.
[11] S. Sofuka, J. Muramatsu, and H. Hagitani, *Bull. Chem. Soc. Japan*, 1967, **40**, 2942.
[12] A. Rieche and H. Gross, *Chem. Ber.*, 1959, **92**, 83.

of compounds (16), (17), (21), (24), and (25) in the presence of an excess of titanium(IV) chloride. In the absence of this reagent the products were exclusively the 5-bromo-compounds, but in the presence of an excess of this reagent appreciable proportions of the 3-bromo-compounds resulted (see Table). The structures of the products are assigned on the basis of their n.m.r. spectra, except for ethyl everninate (21). In this case the structural assignments were made by analogy with methyl everninate, which is known [13] to give the 5-bromo-compound (39) in the absence of titanium(IV) chloride.

Collman [14] has observed that transition-metal complexes of β-diketones undergo electrophilic substitution



(40) X = Me, OMe, or OH
Y = Me, OMe, or OEt

in a manner analogous to aromatic compounds. We believe that the species undergoing electrophilic substitution in our experiments is a titanium complex (40) of the *o*-hydroxy-carbonyl compound. Since substitition occurs at the 3-position it appears that there is a degree of bond fixation in the benzene ring of these complexes, and by analogy with Collman's work they may be regarded as having naphthalene-like character. The metal chelate system behaves as a fused aromatic nucleus such that the 3-position constitutes the most reactive α-position of this naphthalenoid system. This view is supported by the fact that when less than a molar equivalent of titanium(IV) chloride is used in the bromination of methyl 2-hydroxy-4-methoxybenzoate (17) the amount of 5-brominated product increases at the expense of the 3-brominated product. The results of Shah and Laiwalla, and Whalley (see before) may be rationalised in the same way.

## EXPERIMENTAL

General directions have been given previously.[13]

(A) *Preparation of Substrates.—Methyl 4-hydroxy-2-methoxybenzoate* (37). Methyl 4-benzyloxy-2-methoxybenzoate [15] (2·71 g) in ethyl acetate (120 ml) was shaken in hydrogen with 10% palladised charcoal (150 mg) and palladium chloride (10 mg) until absorption ceased. The crude product crystallised from dichloromethane–light petroleum to give the *phenol* as needles (1·50 g, 83%), m.p. 152—153° (Found: C, 59·5; H, 5·85%; *M*, 182. $C_9H_{10}O_4$ requires C, 59·35; H, 5·55%; *M*, 182).

*Ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate*. Ethyl orsellinate (20) (7·5 g), potassium carbonate (15 g), and benzyl chloride (5·3 g) were stirred and heated under reflux in acetone (100 ml) for 22 h. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and with saturated brine, and dried ($Na_2SO_4$). The oily product left on removal of the solvent was passed through a column of silica gel (3·2 × 40 cm) with 2·5% ethyl acetate–light petroleum as eluant. The *phenol* (5·19 g, 47%) formed prisms from light petroleum, m.p. 53—54° (Found: C, 70·95; H, 6·45. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·35%), τ −1·88 (1H, s, OH), 2·67 (5H, s, Ph), 3·67 (2H, s, ArH), 4·99 (2H, s, $CH_2$), 5·64 (2H, q, $CH_2{\cdot}CH_3$), 7·53 (3H, s, Me), and 8·62 (3H, t, $CH_2{\cdot}CH_3$).

*Ethyl 4-hydroxy-2-methoxy-6-methylbenzoate* (33). Ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate was methylated in the usual way with dimethyl sulphate, potassium carbonate, and acetone. The crude product was hydrogenolysed as before and the product was crystallised from ether–light petroleum to afford needles of the *isoeverninate* (33) (79%), m.p. 76—77° (Found: C, 63·15; H, 6·65. $C_{11}H_{14}O_4$ requires C, 62·85; H, 6·7%), τ 3·77 (2H, s, ArH), 5·49 (2H, q, $CH_2{\cdot}CH_3$), 6·36 (3H, s, OMe), 7·78 (3H, s, Me), and 8·62 (3H, t, $CH_2{\cdot}CH_3$).

(B) *Formylation Reactions with Ethyl Orthoformate.—5-Ethylbenzene-1,3-diol* (2). The diol (2) [16] (0·95 g) and ethyl orthoformate (8·9 g) in benzene (30 ml) were stirred rapidly at 0°, aluminium chloride (2·2 g) was added, and the mixture was stirred for 10 min and then poured into ice-cold 5% hydrochloric acid. The mixture was extracted with ether and the extract washed with water, and dried ($MgSO_4$). The dark oily residue left on removal of the ether was chromatographed over silica gel with 20% ether–light petroleum as eluant to give *6-ethyl-2,4-dihydroxybenzaldehyde* (5) (0·43 g, 38%), which formed needles from ether–light petroleum, m.p. 100° (Found: C, 65·2; H, 6·0%; *M*, 166. $C_9H_{10}O_3$ requires C, 65·05; H, 6·05%; *M*, 166), τ −2·54 (1H, s, OH), −0·15 (1H, s, CHO), 2·38br (1H, s, OH), 3·64 (2H, s, ArH), 7·12 (2H, q, $CH_2{\cdot}CH_3$), and 8·72 (3H, t, $CH_2{\cdot}CH_3$). This on methylation with methyl iodide and potassium carbonate in *NN*-dimethylformide at room temperature gave *6-ethyl-2,4-dimethoxybenzaldehyde* (7), as an oil, b.p. 90° (bath) at 1 mmHg (Found: C, 67·9; H, 7·2%; *M*, 194. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%; *M*, 194), τ ($C_6D_6$) −0·82 (1H, s, CHO), 3·67 and 3·81 (2H, dd, *J* 3·0 Hz, ArH), 6·55 and 6·67 (each 3H, s, OMe), 6·84 (2H, q, $CH_2{\cdot}CH_3$), and 8·72 (3H, t, $CH_2{\cdot}CH_3$), $\nu_{max.}$ (film) 1675 (CO) $cm^{-1}$.

*5-Propylbenzene-1,3-diol* (3). The diol (3) [17] (3·23 g) and ethyl orthoformate (64·5 g) in benzene (150 ml) were treated with aluminium chloride (22 g) as in the preceding experiment. Chromatography as before gave *2,4-dihydroxy-6-propylbenzaldehyde* (6) (0·8 g, 21%) as a pale yellow oil which slowly crystallised to form prisms, m.p. 48—50° (Found: *M*, 180·0785. $C_{10}H_{12}O_3$ requires *M*, 180·0786), τ −2·45 (1H, s, OH), −0·06 (1H, s, CHO), 3·20br (1H, s, OH), 3·71 (2H, s, ArH), 7·19 (2H, t, $CH_2{\cdot}CH_2{\cdot}CH_3$), 8·33 (2H, m, $CH_2{\cdot}CH_2{\cdot}CH_3$), and 9·04 (3H, t, $CH_2{\cdot}CH_2{\cdot}CH_3$). On methylation as before it yielded *2,4-dimethoxy-6-propylbenzaldehyde* (8) as an oil, b.p. 90° (bath) at 0·6 mmHg (Found: C, 68·8; H, 7·6%; *M*, 208. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%; *M*, 208), τ ($C_6D_6$) −0·85 (1H, s, CHO), 3·68 and 3·82 (2H, dd, *J* 3·0 Hz, ArH), 6·60 and 6·71 (each 3H, s, OMe), 6·87 (2H, t, $CH_2{\cdot}CH_2{\cdot}CH_3$), 8·31 (2H, m, $CH_2{\cdot}CH_2{\cdot}CH_3$), and 8·98 (3H, t, $CH_2{\cdot}CH_2{\cdot}CH_3$), $\nu_{max.}$ (film) 1675 (CO) $cm^{-1}$.

[13] J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, G. Vinciguerra, and J. A. Elix, *J. Chem. Soc.* (*C*), 1971, 3495.
[14] J. P. Collman, *Angew. Chem.*, 1965, **77**, 154.
[15] K. G. Dave, S. A. Telang, and K. Venkataraman, *J. Sci. Ind. Res., India*, 1960, **19***B*, 470 (*Chem. Abs.*, 1961, **55**, 16,531).
[16] K. Mosbach, *Acta Chem. Scand.*, 1964, **18**, 1591.
[17] A. Sonn and W. Scheffer, *J. prakt. Chem.*, 1911, [2] **83**, 38.

(C) *Formylation Reactions with Dichloromethyl Methyl Ether.—General procedure.* To the phenol (10 mmol) and dichloromethyl methyl ether (2·5 ml) in dichloromethane at 0° was added with stirring a solution of titanium(IV) chloride (4·4 ml) in dichloromethane (5 ml) during 0·5 h. The cooling bath was removed; the mixture was stirred for a further 1 h, poured into ice–water, and extracted with ether. The extract was washed in turn with sodium hydrogen carbonate solution, water, and saturated brine, and dried ($Na_2SO_4$). The residue left on removal of the solvent was, unless stated otherwise, preadsorbed onto silica gel and chromatographed over a column of silica gel with a mixture of ethyl acetate–light petroleum of suitable polarity as eluant.

*5-Ethylbenzene-1,3-diol* (2). The mixture of aldehydes, which migrated as one spot on t.l.c. in a variety of solvent systems, was methylated with methyl iodide and potassium carbonate in *NN*-dimethylformamide at room temperature for 16 h. The methylated products were separated by chromatography over a silica gel plate (100 × 20 × 0·1 cm) developed with 40% ether–light petroleum. Two bands developed which were removed in turn and extracted with ether. The faster-running band yielded 6-ethyl-2,4-dimethoxybenzaldehyde (7) (20%), identical with that already described. The other band yielded *4-ethyl-2,6-dimethoxybenzaldehyde* (10) (16·5%), as an oil, b.p. 90° (bath) at 0·8 mmHg (Found: C, 68·2; H, 7·1%; *M*, 194. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%; *M*, 194), τ ($C_6D_6$) −0·91 (1H, s, CHO), 3·79 (2H, s, ArH), 6·56 (6H, s, OMe), 7·58 (2H, q, $CH_2{\cdot}CH_3$), and 8·90 (3H, t, $CH_2{\cdot}CH_3$), $\nu_{max.}$ (film) 1680 (CO) $cm^{-1}$.

*5-Propylbenzene-1,3-diol* (3). Separation of the mixture of aldehydes was only achieved after methylation, as for compound (2). The faster-running band yielded 2,4-dimethoxy-6-propylbenzaldehyde (8) (15%), identical with that already described. The other band yielded *2,6-dimethoxy-4-propylbenzaldehyde* (11) (10·6%), as an oil, b.p. 110° (bath) at 0·6 mmHg (Found: C, 69·1; H, 7·2%; *M*, 208. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%; *M*, 208), τ ($C_6D_6$) −0·91 (1H, s, CHO), 3·78 (2H, s, ArH), 6·60 (6H, s, OMe), 7·61 (2H, t, $CH_2{\cdot}CH_2{\cdot}CH_3$), 8·47 (2H, m, $CH_2{\cdot}CH_2{\cdot}CH_3$), and 9·12 (3H, t, $CH_2{\cdot}CH_2{\cdot}CH_3$), $\nu_{max.}$ (film) 1680 (CO) $cm^{-1}$.

*5-Methoxy-3-methylphenol* [13] (12). Chromatography of the crude product gave 2-hydroxy-6-methoxy-4-methylbenzaldehyde (14) (7%), which formed needles from methanol, m.p. 77—78° (lit.,[18] 78°), τ ($CCl_4$) −1·92 (1H, s, OH), −0·21 (1H, s, CHO), 3·73br (1H, s, ArH), 3·91br (1H, s, ArH), 6·16 (3H, s, OMe), and 7·70 (3H, s, Me). This was followed by 2-hydroxy-4-methoxy-6-methylbenzaldehyde (13) (33·4%), which formed blades from methanol, m.p. 63—64° (lit.,[3] 63°), τ ($CCl_4$) −2·32 (1H, s, OH), −0·01 (1H, s, CHO), 3·88 (s, 2H, ArH), 6·22 (3H, s, OMe), and 7·52 (3H, s, Me).

*Methyl 2,4-dihydroxybenzoate* (16). Chromatography of the crude product gave methyl 3-formyl-2,4-dihydroxybenzoate (18) (38%), which formed needles, from dichloromethane–light petroleum, m.p. 137—138° (lit.,[5] 138—140°), τ −2·59 (1H, s, OH), −2·03 (1H, s, OH), −0·49 (1H, s, CHO), 2·06 and 3·56 (2H, dd, *J* 9·0 Hz, ArH), and 6·05 (3H, s, OMe).

*Methyl 2-hydroxy-4-methoxybenzoate* (17). Chromatography of the crude product yielded the starting material (35%), followed by *methyl 5-formyl-2-hydroxy-4-methoxybenzoate* (8%), which formed blades, from dichloromethane–light petroleum, m.p. 155—155·5° (Found: C, 56·9; H, 4·8. $C_{10}H_{10}O_5$ requires C, 57·15; H, 4·8%), τ −1·50 (1H, s, OH), −0·39 (1H, s, CHO), 1·60 (1H, s, 6-H), 3·52 (1H, s, 3-H), and 6·03 (6H, s, OMe). A sample hydrogenated in glacial acetic acid over 10% palladised charcoal gave *methyl 2-hydroxy-4-methoxy-5-methylbenzoate*, which formed prisms from dichloromethane–light petroleum, m.p. 95—96° (Found: C, 61·2; H, 6·15. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·15%), τ −0·87 (1H, s, OH), 2·47br (1H, s, 6-H), 3·60 (1H, s, 3-H), 6·10 and 6·17 (each 3H, s, OMe), and 7·89 (3H, s, Me). Later fractions gave methyl 3-formyl-2-hydroxy-4-methoxybenzoate (19) (48%), which formed plates from dichloromethane–light petroleum, m.p. 120—121° (lit.,[5] 121—122°), τ −2·66 (1H, s, OH) −0·41 (1H, s, CHO), 1·92 and 3·58 (2H, dd, *J* 9·0 Hz, 5- and 6-H), and 6·02 and 6·09 (each 3H, s, Me).

*Ethyl 2,4-dihydroxy-6-methylbenzoate* (20). The crude product was steam-distilled and the distillate afforded ethyl 3-formyl-2,4-dihydroxy-6-methylbenzoate (22) (23%), m.p. and mixed m.p. 110—112° (lit.,[19] 111—112°) Only traces of the isomeric aldehyde were detected in the non-volatile residue.

*Ethyl 2-hydroxy-4-methoxy-6-methylbenzoate* (21). This experiment has been previously described by us.[9] A sample of the minor product, ethyl 5-formyl-2-hydroxy-4-methoxy-6-methylbenzoate (29), was hydrogenated in glacial acetic acid over 10% palladised charcoal, and the crude product was methylated with dimethyl sulphate and potassium carbonate in acetone to give *ethyl 2,4-dimethoxy-5,6-dimethylbenzoate* (30) as plates, from pentane, m.p. 62—63° (Found: C, 65·75; H, 7·8%; *M*, 238. $C_{13}H_{18}O_4$ requires C, 65·55; H, 7·6%; *M*, 238), τ ($CCl_4$) 3·79 (1H, s, ArH), 5·73 (2H, q, $CH_2{\cdot}CH_3$), 6·27 and 6·28 (each 3H, s, OMe), 7·89 and 7·99 (each 3H, s, Me), and 8·69 (3H, t, $CH_2{\cdot}CH_3$). On hydrolysis with aqueous ethanolic sodium hydroxide this gave the *acid*, which formed plates from methanol, m.p. 214—215° (Found: C, 63·1; H, 6·8%; *M*, 210. $C_{11}H_{14}O_4$ requires C, 62·85; H, 6·7%; *M*, 210). Methylation of the acid with dimethyl sulphate and potassium carbonate in acetone gave the *methyl ester* (31), which formed platelets from light petroleum, m.p. 77—78° (Found: *M*, 224. $C_{12}H_{16}O_4$ requires *M*, 224).

*Methyl 2-hydroxy-4-methylbenzoate* (24). Early fractions from chromatography of the crude product gave the starting material (24) (19%), followed by *methyl 3-formyl-2-hydroxy-4-methylbenzoate* (32%), which formed prisms from dichloromethane–light petroleum, m.p. 113—114° (Found: *M*, 194·0577. $C_{10}H_{10}O_4$ requires *M*, 194·0579), τ −1·59 (1H, s, OH), −0·64 (1H, s, CHO), 2·16 and 3·31 (2H, dd, *J* 9·0 Hz, 6- and 5-H), 6·02 (3H, s, OMe), and 7·37 (3H, s, Me). Later fractions gave *methyl 5-formyl-2-hydroxy-4-methylbenzoate* (5%), which formed needles from dichloromethane–light petroleum, m.p. 124—125° (Found: *M*, 194·0579. $C_{10}H_{10}O_4$ requires *M*, 194·0579), τ −1·49 (1H, s, OH), −0·37 (1H, s, CHO), 1·76 (1H, s, 6-H), 3·20 (1H, s, 3-H), 6·03 (3H, s, OMe), and 7·37 (3H, s, Me).

*2-Hydroxy-4-methoxyacetophenone* (25). Early fractions from chromatography of the crude product gave the starting material (25) (54%), followed by *5-formyl-2-hydroxy-4-methoxyacetophenone* (2%), which formed pale yellow needles from ether–light petroleum, m.p. 129—130·5°

[18] Y. Asahina and I. Yosioka, *Ber.*, 1936, **69**, 1367.
[19] A. St. Pfau, *Helv. Chim. Acta*, 1926, **9**, 650.

(Found: C, 62·0; H, 5·25. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%), τ −3·21 (1H, s, OH), −0·34 (1H, s, CHO), 1·68 (1H, s, 6-H), 3·51 (1H, s, 3-H), 6·01 (3H, s, OMe), and 7·36 (3H, s, COMe). Later fractions gave *3-formyl-2-hydroxy-4-methoxyacetophenone* (32%), which formed pale yellow needles from ether–light petroleum, m.p. 124—125° (Found: C, 62·2; H, 4·85. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%), τ −3·32 (1H, s, OH), −0·43 (1H, s, CHO), 1·87 and 3·49 (2H, dd, *J* 9·0 Hz, 6- and 5-H), 6·01 (3H, s, OMe), and 7·36 (3H, s, COMe).

*Methyl 2,4-dimethoxybenzoate* (32). Crystallisation of the crude product gave methyl 5-formyl-2,4-dimethoxybenzoate (67%), which formed needles from dichloromethane–light petroleum, m.p. 172—173° (lit.,[20] 167°), τ −0·31 (1H, s, CHO), 1·57 (1H, s, 6-H), 3·49 (1H, s, 3-H), 6·00 (6H, s, OMe), and 6·13 (3H, s, OMe).

*Ethyl 4-hydroxy-2-methoxy-6-methylbenzoate* (33). Chromatography of the crude product gave *ethyl 5-formyl-4-hydroxy-2-methoxy-6-methylbenzoate* (35) (53%), which formed blades from dichloromethane–light petroleum, m.p. 139—140° (Found: C, 60·55; H, 6·1. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%), τ −2·80 (1H, s, OH), −0·22 (1H, s, CHO), 3·68 (1H, s, ArH), 5·59 (2H, q, $CH_2$·$CH_3$), 6·11 (3H, s, OMe), 7·49 (3H, s, Me), and 8·60 (3H, t, $CH_2$·$CH_3$). On hydrogenation in glacial acetic acid over palladised charcoal this gave *ethyl 4-hydroxy-2-methoxy-5,6-dimethylbenzoate*, which formed plates from dichloromethane–light petroleum, m.p. 111—112° (Found: C, 64·3; H, 6·9. $C_{12}H_{16}O_4$ requires C, 64·25; H, 7·2%), τ 3·77 (1H, s, ArH), 3·98br (1H, s, OH), 5·60 (2H, q, $CH_2$·$CH_3$), 6·36 (3H, s, OMe), 7·82 and 7·93 (each 3H, s, Me), and 8·62 (3H, t, $CH_2$·$CH_3$). On methylation with dimethyl sulphate and potassium carbonate in acetone this gave the ester (30), identical with that prepared before. Later fractions gave the starting material (38%).

*Methyl 2,4-dimethoxy-6-methylbenzoate* (34). On chromatography of the crude product the early fractions gave the starting material (53%); this was followed by *methyl 5-formyl-2,4-dimethoxy-6-methylbenzoate* (36) (16·5%), which formed blades from dichloromethane–light petroleum, m.p. 125—126° (Found: C, 60·45; H, 5·9%; *M*, 238. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%; *M*, 238), τ −0·47 (1H, s, CHO), 3·62 (1H, s, ArH), 6·08 (3H, s, OMe), 6·10 (6H, s, OMe), and 7·51 (3H, s, Me). On hydrogenation in glacial acetic acid over 10% palladised charcoal it gave the ester (31), identical with that prepared before.

*2,4-Dimethoxyacetophenone* (26). Crystallisation of the crude product from dichloromethane–light petroleum gave 5-formyl-2,4-dimethoxyacetophenone (52%) as prisms, m.p. 169—170° (lit.,[20] 167°), τ −0·43 (1H, s, CHO), 1·59 (1H, s, 6-H), 3·47 (1H, s, 3-H), 5·93 (6H, s, OMe), and 7·40 (3H, s, COMe).

*Methyl 4-hydroxy-2-methoxybenzoate* (37). Crystallisation of the crude product from dichloromethane–light petroleum gave *methyl 4-formyloxy-2-methoxybenzoate* (38) (67%), which formed plates, m.p. 75—77° (Found: C, 57·3; H, 4·55%: *M*, 210. $C_{10}H_{10}O_5$ requires C, 57·15; H, 4·8%; *M*, 210), τ 1·68 (1H, s, O·CHO), 2·15 (1H, d, *J* 9·0 Hz, 3-H), 3·25 (2H, m, 5- and 6-H), and 6·12 (6H, s, OMe), $\nu_{max.}$ (Nujol) 1765 (CO) and 1730 (CO) $cm^{-1}$.

(C) *Bromination Reactions.—General procedure.* To the substrate (5 mmol) in dichloromethane (10 ml) was added titanium(IV) chloride (12·5 mmol) followed by bromine (5 mmol) with stirring. After 5 min the mixture was poured into water and ice and stirred rapidly. The mixture was then extracted with ether and the extract washed in turn with water, saturated sodium hydrogen carbonate solution, and saturated brine, and dried ($Na_2SO_4$). The crude products left on removal of the solvent were treated as described later. When the experiments were repeated in the absence of titanium(IV) chloride the sole products were the 5-bromo-compounds, which were isolated in almost quantitative yield.

*Methyl 2,4-dihydroxybenzoate* (16). An efficient separation of the products could not be achieved and the total material was therefore methylated with dimethyl sulphate and potassium carbonate in acetone. This crude product was preadsorbed from dichloromethane onto silica gel and chromatographed over a column of silica gel with 5—10% ethyl acetate–light petroleum as eluant. Early fractions afforded *methyl 3,5-dibromo-2,4-dimethoxybenzoate* (12%), which crystallised from pentane as needles, m.p. 53—54° (Found: C, 34·15; H, 2·85. $C_{10}H_{10}Br_2O_4$ requires C, 33·9; H, 2·85%), τ ($CCl_4$) 2·06 (1H, s, ArH), and 6·09 and 6·11 (9H, each s, OMe). Further elution gave *methyl 3-bromo-2,4-dimethoxybenzoate* (36%), which crystallised from light petroleum as plates, m.p. 60—61° (Found: C, 43·95; H, 4·1. $C_{10}H_{11}BrO_4$ requires C, 43·65; H, 4·05%), τ 2·17 and 3·30 (2H, dd, *J* 9·0 Hz, 6- and 5-H), and 6·06 and 6·09 (9H, each s, OMe). On hydrolysis with aqueous methanolic potassium hydroxide this gave the corresponding *acid*, which formed plates from dichloromethane, m.p. 174—175° (Found: C, 41·1; H, 3·3. $C_9H_9BrO_4$ requires C, 41·4; H, 3·45%). Later fractions gave methyl 2,4-dimethoxybenzoate (21%) as an oil, identical with an authentic sample.[21] This was followed by methyl 5-bromo-2,4-dimethoxybenzoate (30%), which formed needles from dichloromethane–light petroleum, m.p. 117—118° (lit.,[22] 117°), τ ($CCl_4$) 1·98 (1H, s, 6-H), 3·56 (1H, s, 3-H), and 6·06, 6·08, and 6·14 (each 3H, s, OMe).

*Methyl 2-hydroxy-4-methoxybenzoate* (17). (*a*) The crude product 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 methyl 5-bromo-2-hydroxy-4-methoxybenzoate (41%), which crystallised from dichloromethane–light petroleum as needles, m.p. 143—144° (lit.,[22] 143°) (Found: C, 41·0; H, 3·65. Calc. for $C_9H_9BrO_4$: C, 41·4; H, 3·45%), τ −0·94 (1H, s, OH), 2·00 (1H, s, 6-H), 3·52 (1H, s, 3-H), and 6·07 (6H, s, OMe). Later fractions gave *methyl 3-bromo-2-hydroxy-4-methoxybenzoate* (48%), which crystallised as prisms, m.p. 118—119°, from dichloromethane–light petroleum (Found: C, 41·65; H, 3·35. $C_9H_9BrO_4$ requires C, 41·4; H, 3·45%), τ −1·41 (1H, s, OH), and 2·23 and 3·45 (2H, dd, *J* 9·0 Hz, 6- and 5-H).

(*b*) When this experiment was repeated with 1 mol. equiv. of titanium(IV) chloride and the crude product analysed by n.m.r. spectroscopy it was found to contain the 3-bromo-compound (46%) and the 5-bromo-compound (54%). When 0·5 mol. equiv. of titanium(IV) chloride was used the proportions were: 3-bromo-compound 35%; 5-bromo-compound 65%.

*Ethyl 2-hydroxy-4-methoxy-6-methylbenzoate* (21). The crude product was preadsorbed from dichloromethane onto silica gel and chromatographed over a column of silica gel. Elution with 5% ethyl acetate–light petroleum gave

[20] K. P. Mathai and S. Sethna, *J. Indian Chem. Soc.*, 1963, **40**, 347.

[21] W. H. Perkin, jun., and E. Schiess, *J. Chem. Soc.*, 1904, 159.

[22] G. P. Rice, *J. Amer. Chem. Soc.*, 1926, **48**, 3125.

*ethyl* 5-*bromo*-2-*hydroxy*-4-*methoxy*-6-*methylbenzoate* (40%), which crystallised as needles, m.p. 112—113°, from dichloromethane–light petroleum (Found: C, 45·4; H, 4·6. $C_{11}H_{13}BrO_4$ requires C, 45·7; H, 4·55%), τ −1·58 (1H, s, OH), 3·61 (1H, s, ArH), 5·57 (2H, q, $CH_2$·$CH_3$), 6·09 (3H, s, OMe), 7·30 (3H, s, Me), and 8·56 (3H, t, $CH_2$·$CH_3$). Further elution gave *ethyl* 3-*bromo*-2-*hydroxy*-4-*methoxy*-6-*methylbenzoate* (40%), which formed needles, m.p. 161—161·5°, from dichloromethane–light petroleum (Found: C, 45·25; H, 4·5. $C_{11}H_{13}BrO_4$ requires C, 45·7; H, 4·55%), τ −2·51 (1H, s, OH), 3·56 (1H, s, ArH), 5·56 (2H, q, $CH_2$·$CH_3$), 6·06 (3H, s, OMe), 7·45 (3H, s, Me), and 8·57 (3H, t, $CH_2$·$CH_3$).

*Methyl* 2-*hydroxy*-4-*methylbenzoate* (24). In the absence of titanium(IV) chloride this gave methyl 5-bromo-2-hydroxy-4-methylbenzoate, which crystallised from light petroleum as plates, m.p. 46—47° (lit.,[23] 48°), τ −0·58 (1H, s, OH), 2·03br (1H, s, 6-H), 3·11br (1H, s, 3-H), 6·06 (3H, s, OMe), and 7·61 (3H, s, Me). On methylation with dimethyl sulphate and potassium carbonate in acetone this gave methyl 5-bromo-2-methoxy-4-methylbenzoate, which crystallised from light petroleum as prisms, m.p. 58—59° (lit.,[23] 45—46°), τ ($CCl_4$) 2·13br (1H, s, 6-H), 3·22br (1H, s, 3-H), 6·18 (6H, s, OMe), and 7·60 (3H, s, Me). The crude product obtained from the experiment conducted in the presence of titanium(IV) chloride was only poorly resolved on t.l.c. in a number of solvent systems; it was therefore methylated with dimethyl sulphate and potassium carbonate in acetone. The crude methylated product was chromatographed over a column of silica gel with 2·5—10% ethyl acetate–light petroleum as eluant. Early fractions afforded *methyl* 3,5-*dibromo*-2-*methoxy*-4-*methylbenzoate* (4%), which formed needles from pentane, m.p. 55—56° (Found: C, 35·85; H, 3·05. $C_{10}H_{10}Br_2O_3$ requires C, 35·55; H, 3·0%), τ ($CCl_4$) 2·09 (1H, s, ArH), 6·12 (6H, s, OMe), and 7·38 (3H, s, Me). Later fractions gave methyl 3-bromo-2-methoxy-4-methylbenzoate (32%), as an oil, τ ($CCl_4$) 2·41 and 3·01 (2H, ABq, *J* 9·0 Hz, 6- and 5-H), 6·12 (6H, s, OMe), and 7·54 (3H, s, Me). On hydrolysis with aqueous methanolic sodium hydroxide it gave the corresponding acid, which formed needles from methanol, m.p. 141—142° (lit.,[24] 137—138°). Further elution gave a mixture of methyl 5-bromo-2-methoxy-4-methylbenzoate (79·5 mol.%, 48% yield), and methyl 2-methyl-4-methylbenzoate (20·5 mol.%, 9% yield), which was analysed by g.l.c. [Perkin-Elmer model 880; 5% XE-60 on Chromosorb W column (0·067 in × 10 ft); injection temp. 180°; column temp. 140°; nitrogen flow rate 28·6 ml $min^{-1}$]. Under these conditions the bromo-compound had a retention time of 6·4 min and methyl 2-methoxy-4-methylbenzoate, prepared by methylation of compound (24), b.p. 155—156° at 30 mmHg (lit.,[25] 137—139° at 14 mmHg), had a retention time of 2·0 min.

2-*Hydroxy*-4-*methoxyacetophenone* (25). The crude product was preadsorbed from dichloromethane onto silica gel and chromatographed over a column of silica gel, which was eluted with 5—10% ethyl acetate–light petroleum. Early fractions afforded 5-bromo-2-hydroxy-4-methoxyacetophenone (15%), which crystallised from dichloromethane–light petroleum as needles, m.p. 172—172·5° (lit.,[26] 169—170°; lit.,[27] 172—174°), τ −2·68 (1H, s, OH), 2·17 (1H, s, 6-H), 3·58 (1H, s, 3-H), 6·09 (3H, s, OMe), and 7·47 (3H, s, COMe). Further elution gave 3-*bromo*-2-*hydroxy*-4-*methoxy*-*acetophenone* (65%), which formed needles from dichloromethane–light petroleum, m.p. 130—131° (Found: C, 44·45; H, 3·85. $C_9H_9BrO_3$ requires C, 44·1; H, 3·7%), τ −3·29 (1H, s, OH), 2·32 and 3·52 (2H, dd, *J* 9·0 Hz, 6- and 5-H), 6·04 (3H, s, OMe), and 7·41 (3H, s, COMe).

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[23] R. von Walther and W. Zipper, *J. prakt. Chem.*, 1915, [2] **91**, 364.
[24] N. Meldrum and C. N. Bamji, *J. Indian Chem. Soc.*, 1936, **13**, 641.
[25] R. Anschütz, H. Aschenberg, H. Kuckert, F. Krone, K. Riepenkröger, and C. Zerbe, *Annalen*, 1925, **442**, 18.
[26] N. P. Kirjalov, *Zhur. obshchei Khim.*, 1946, **16**, 1527.
[27] J. Shinoda, D. Sato, and M. Kawagoye, *J. Pharm. Soc. Japan*, 1932, **52**, 766.