Experiments on the Synthesis of Tetracycline. Part VI.[1a] Oxidation and Reduction of Potential Ring A Precursors

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The reduction of substituted orcinol derivatives to dihydroaromatic compounds [specifically 2,6-dimethoxy-4-methylcyclohexa-2,5-dienecarboxamide (V)] is described. Attempted application of this reduction to the 3-dimethylamino-derivative (VI; $R^1 = NH_2$, $R^2 = Me$, $R^3 = NMe_2$) was unsuccessful. As an alternative route, the addition of a nitrene to the double bond of an enol ether was studied.

The oxidation of a number of orcinol derivatives to the corresponding hydroxy-quinones is described. Attempts to hydrate these quinones were unsuccessful.

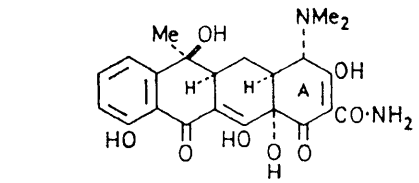
The formation of certain *ortho*-acyloxycyclohexadienones from phenols by use of lead tetra-acetate is described. For the preparation of the starting phenols, boron trichloride is a convenient demethylating agent. Our results indicate that this reagent, contrary to previous reports, may cause selective demethylation *para* to a carbonyl group in certain polyoxygenated benzenes.

As described in part V [1a] we had solved, in principle, the problem of the oxidation level and oxygenation pattern of rings BC and D of tetracycline. The remaining problem involved ring A, which, in our particular synthesis, had to be derived from an aromatic precursor.[1b]

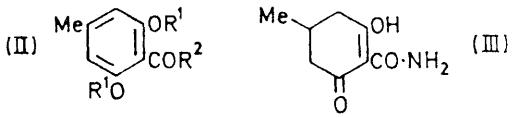
Our first approach was to reduce selectively an aromatic ring A to the dihydro-level of oxidation found in tetracycline (I). Catalytic reduction of the amide (II; $R^1 = H$, $R^2 = NH_2$) gave the β-diketone (III).[2] Similar treatment of the naphthacene (IV) [3] was unsuccessful.

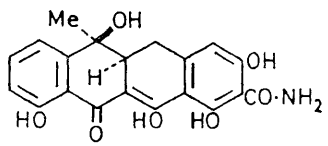
We investigated next the Birch reduction of suitable substituted ring A model compounds. The amide (II; $R^1 = Me$, $R^2 = NH_2$) [4] (see Experimental section), under the Birch reduction conditions described by Kuehne and Lambert,[5] gave the dihydro-amide (V) in good yield. Mild acid hydrolysis gave the known [2] diketo-amide (III). The azo-compound (VI; $R^1 = OH$, $R^2 = H$, $R^3 = N_2Ph$) [6] was methylated to give the dimethoxy-ester (VI; $R^1 = OMe$, $R^2 = Me$, $R^3 = N_2Ph$). Hydrogenolysis gave the amine (VI; $R^1 = OMe$, $R^2 = Me$, $R^3 = NH_2$), which was methylated to afford the dimethylamino-compound (VI; $R^1 = OMe$, $R^2 = Me$, $R^3 = NMe_2$). Hydrolysis to the acid, followed by treatment with oxalyl chloride and ammonia gave the required amide (VI; $R^1 = NH_2$, $R^2 = Me$, $R^3 = NMe_2$). However, Birch reduction [7] reduced the amide grouping, and the total product showed carbonyl absorption at 1705 $cm.^{-1}$.

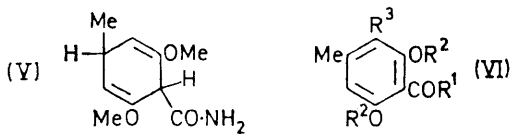
We investigated the idea of reducing the aromatic ring first and then introducing the amine function by the addition of a suitable nitrene to the double bond of the enol ether [8] [as (V)]. Photolytically generated ethoxycarbonylnitrene [9] was therefore treated with 2,5-dihydroanisole; however, the product was a complex mixture. Dihydroanisole reacted with picryl azide [10]



(I)







to give the crystalline enol ether (VII). Acid-catalysed hydrolysis gave picramide and dihydroresorcinol. Scheme 1 summarises the probable mode of formation of the product (VII).

We next examined the possible addition of an electrophilic $\overset{+}{N}Me_2$ system to a suitable enol ether. The pre-

[1] (*a*) Part V, D. H. R. Barton, D. L. J. Clive, P. D. Magnus, and G. Smith, preceding paper; (*b*) J. E. Baldwin, D. H. R. Barton, L. Bould, and P. D. Magnus, *Chem. Comm.*, 1967, 319.

[2] K. Tomino, *J. Pharm. Soc. Japan*, 1958, **78**, 1419 (*Chem. Abs.*, 1959, **53**, 8018a).

[3] A. Green, R. G. Wilkinson, and J. H. Boothe, *J. Amer. Chem. Soc.*, 1960, **82**, 3946.

[4] A. Robertson and R. Robinson, *J. Chem. Soc.*, 1927, 2196.

[5] M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, 1959, **81**, 4278.

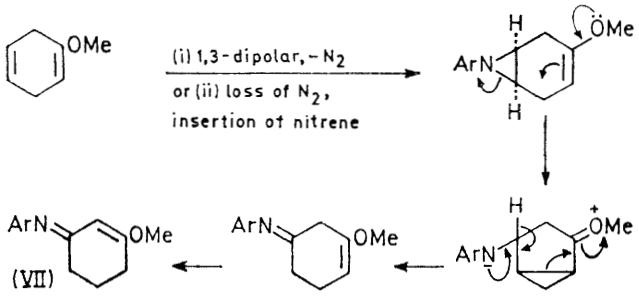
[6] R. Branchini, G. Casini, and C. Mori, *Ann. Chim.* (*Italy*), 1958, **48**, 819.

[7] G. Stork and W. N. White, *J. Amer. Chem. Soc.*, 1956, **78**, 4604.

[8] R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc.*, 1965, 6141.

[9] W. Lwowski and F. P. Woerner, *J. Amer. Chem. Soc.*, 1965, **87**, 5491.

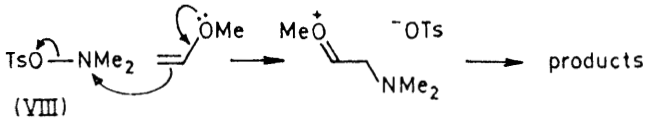
[10] (*a*) A. S. Bailey, J. J. Merer, and J. E. White, *Chem. Comm.*, 1965, 4; (*b*) F. D. Marsh and M. E. Hermes, *J. Amer. Chem. Soc.*, 1964, **86**, 4506.



SCHEME 1

Ar = 2,4,6-trinitrophenyl

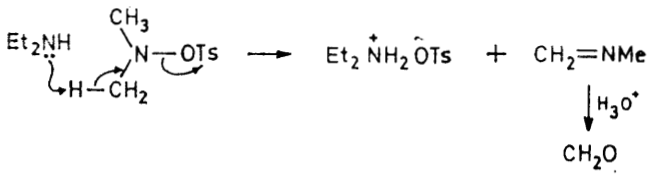
viously unknown toluene-*p*-sulphonate (VIII) was prepared in the hope that it would react with an enol ether as indicated (Scheme 2). However, when the toluene-



SCHEME 2

p-sulphonate (VIII) reacted with 2,5-dihydroresorcinol dimethyl ether or 3-ethoxy-5α-cholest-2-ene under a variety of conditions, no useful result was obtained.

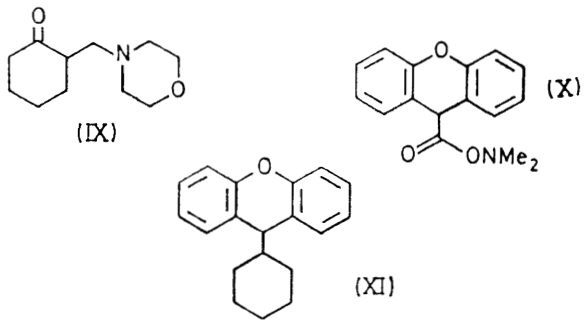
The chemistry of this interesting toluene-*p*-sulphonate was examined briefly. It gave a toluene-*p*-sulphonate salt with diethylamine. Treatment of the total product with acid gave formaldehyde. The reaction can be rationalised as shown in Scheme 3. Treatment of the



SCHEME 3

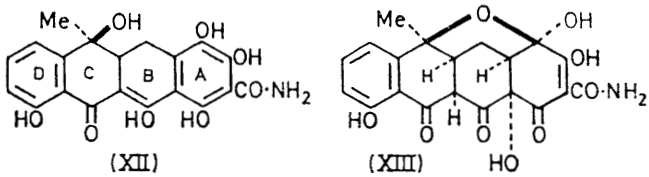
sulphonate (VIII) with the morpholine enamine of cyclohexanone gave, in a Mannich-type reaction, the ketone (IX). The formation of this compound involves an extension of Scheme 3, with appropriate hydrolysis *etc.* Treatment of the toluene-*p*-sulphonate (VIII) with phenylmagnesium bromide gave *NN*-dimethylaniline. Treatment with cyclohexylmagnesium bromide gave dimethylaminocyclohexane, in yields superior to that normally obtained in the reaction between Grignard reagents and *N*-chloro-amines.[11] The reagent (VIII) may therefore be useful for the dimethylamination of bases which do not have affinity for hydrogen.

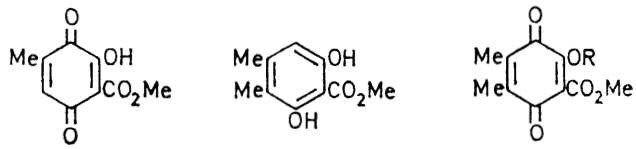
We next investigated free radical addition of $\cdot NMe_2$ to the enol ether function. The photolysis of xanthen-9-carboxylates to give radical products has recently been demonstated.[12] We anticipated that the photolysis of the dimethylhydroxylamine ester (X) would afford $\cdot NMe_2$ radicals which would react in the desired manner. The ester (X) was readily prepared. On photolysis in cyclohexane, 1 mol. of carbon dioxide was

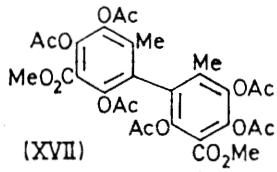


evolved and the hydrocarbon (XI) was formed. In the presence of 3-ethoxy-5α-cholest-2-ene [13] no basic material was produced. We did not pursue the study of the photolysis of compound (X) further, but the reaction deserves a more thorough investigation.

Our synthetic objective was then modified to 4a,12a-anhydro-4-hydroxy-4-de(dimethylamino)tetracycline (XII),[14] or an equivalent derivative. Compound (XII) is easily obtained by pyrolysis of tetracycline methyl



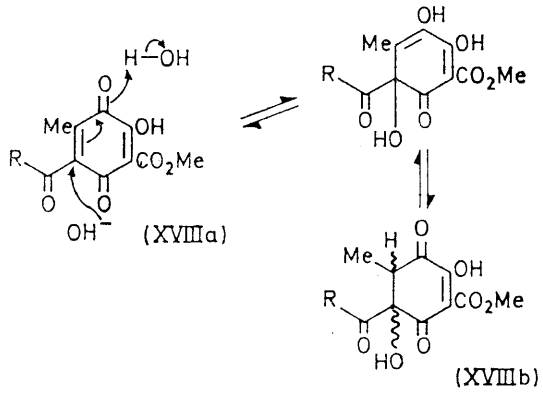




betaine.[14] It may be dehydrated to 4-hydroxy-6-methylpretetramid, a biosynthetic precursor of the tetracyclines, and a compound of some synthetic interest in its own right.[15] There is the possibility of oxidative hydroxylation and dearomatisation of ring A and conversion into tetracycline *via* the epoxide (XIII).[16] For

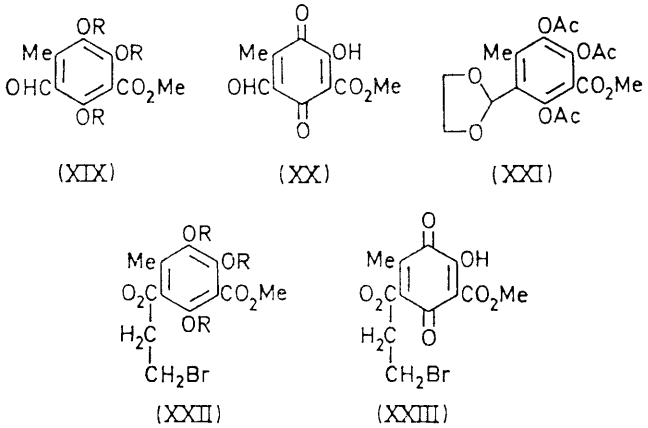
[11] G. H. Coleman, *J. Amer. Chem. Soc.*, 1933, **55**, 3001.
[12] D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 1965, 3571.
[13] C. Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003.
[14] J. J. Hlavka, P. Bitha, and J. H. Boothe, *J. Amer. Chem. Soc.*, 1965, **87**, 1795.
[15] (*a*) J. R. D. McCormick, U. H. Joachim, E. R. Jensen, S. Johnson, and N. O. Sjolander, *J. Amer. Chem. Soc.*, 1965, **87**, 1793; (*b*) J. R. D. McCormick and E. R. Jensen, *J. Amer. Chem. Soc.*, 1965, **87**, 1794.
[16] (*a*) R. K. Blackwood and C. R. Stephens, *Canad. J. Chem.* 1965, **43**, 1382; (*b*) R. K. Blackwood and C. R. Stephens, *J. Amer. Chem. Soc.* 1964, **86**, 2736.

these reasons we next studied the introduction of a C-4 hydroxy-group into orcinol derivatives.



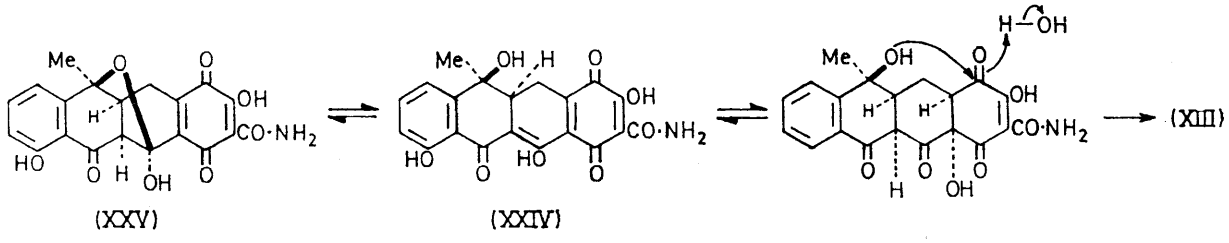
SCHEME 4

Methyl *p*-orsellinate was treated with an excess of Frémy's salt [17] to give the quinone (XIV) (87%). This was reduced and acetylated to give the triacetate (VI; R^1 = OMe, R^2 = Ac, R^3 = OAc) in over 90% yield. Oxidation of compound (XV) (see Experimental section) with Frémy's salt afforded the quinone (XVI; R = H) in excellent yield. If these oxidations were conducted in strongly alkaline solution (0·1N-NaOH) dimeric products [of type (XVII)] were isolated (see Experimental section). Hassall and Winters [18a] have recently carried out some analogous oxidations with Frémy's salt.



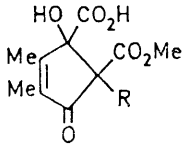
The possibility of converting a 2-hydroxy-quinone (XVIIIa) into an enedione (XVIIIb), as in Scheme 4, was investigated. Compound (VI; R^1 = OMe, R^2 = H, R^3 = OH), made by hydrogenation of the quinone (XIV), was formylated with the Gattermann complex [18b] to give the aldehyde (XIX; R = H) in excellent yield. Oxidation of the aldehyde with dichlorodicyano-*p*-benzoquinone (DDQ) gave the quinone (XX) in high yield. Acetylation of the aldehyde gave the triacetate (XIX; R = Ac). Attempted oxidation of the formyl group with conventional reagents was unsuccessful. The required oxidation level was obtained by the following indirect method. The acetate (XIX; R = Ac) was converted into its acetal (XXI) by transacetalisation with butan-2-one ethylene acetal. Treatment of the acetal (XXI) with *N*-bromosuccinimide gave the ester (XXII; R = Ac).[19] Deacetylation with methanolic hydrogen chloride to the triol (XXII; R = H), followed by oxidation with DDQ gave the quinone (XXIII). In a study of the possible hydration of quinones (XX) and (XXIII) experiments were performed under both basic and acidic conditions. No hydration was observed. However, in the case of the tetracyclic quinone (XXIV) it is conceivable that acetal formation might capture the intermediate and prevent the reverse process [(XIII) ⟶ (XXIV)]. It is also possible that this process would have biosynthetic significance.

Oxidation of the naphthacene (XII) [14] in dioxan with DDQ gave the quinone (XXIV) as a red crystalline solid, $\lambda_{max.}$ (dioxan) 257, 340, and 382 nm. (ε 18,000, 9190, and 5890), $\lambda_{max.}$ (0·01N-HCl) 261, 342, and 428 nm. (ε 17,600, 8210, and 12,600). These data suggest that the quinone exists in tautomeric equilibrium with the 6,12-hemiacetal (XXV). Attempted hydration of the quinone (XXIV) under acidic, basic, and aqueous photolytic conditions led to no useful result. For the conversion (XXIV) ⟶ (XIII) the following must occur: first, hydration of 4a,12a-double bond from the α-face with the hydroxy-group at C-12a; second, ketonisation, without β-elimination, of the potential 11,12-β-diketone, with retention of the C-4 ketone system; and third, intramolecular cyclisation from C-6 to C-4 to form the hemiacetal (XIII). The 11,12-diketone system in (XXIV) could be prevented from enolising by halogenating C-11a [20] with *N*-chlorosuccinimide, thus increasing the driving force for hydration (more positive C-12a).

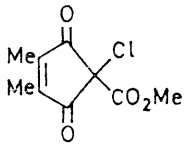


[17] H.-J. Teuber and G. Staiger, *Chem. Ber.*, 1955, **88**, 802.
[18] (*a*) C. H. Hassall and T. E. Winters, *Chem. Comm.*, 1967, 77; (*b*) C. Grundmann and A. Kreutzberger, *J. Amer. Chem. Soc.*, 1954, **76**, 632.
[19] J. D. Prugh and W. C. McCarthy, *Tetrahedron Letters*, 1966, 1351.
[20] R. K. Blackwood, J. J. Beereboom, H. H. Rennhard, M. Sehach von Wittenau, and C. R. Stephens, *J. Amer. Chem. Soc.*, 1963, **85**, 3943.

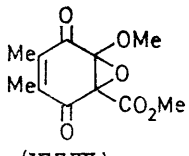
In model experiments the quinone (XVI; R = H) was treated with hypochlorous acid to give the cyclopentane derivative (XXVI; R = Cl). The n.m.r. spectrum of the latter showed the presence of two methyl groups on a double bond. Oxidation of compound (XXVI; R = Cl) with lead tetra-acetate gave the



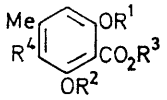
(XXVI)



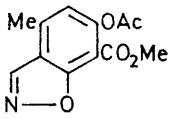
(XXVII)



(XXVIII)



(XXIX)

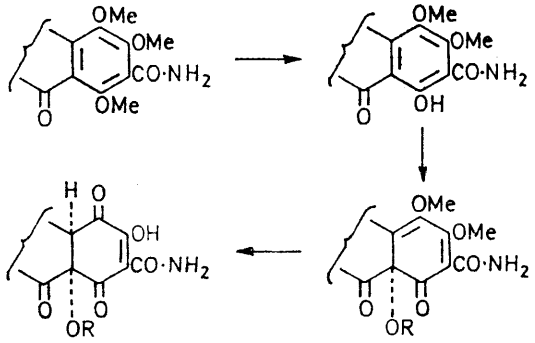


(XXX)

dione (XXVII). A similar ring contraction in the reaction of phenols with chlorinating agents has been reported.[21] It is clear that this type of oxidising agent could not be used for the hydroxylation of the quinone (XXIV).

An alternative approach to 12a-hydroxylation involves epoxidation of the 4a,12a-double bond of the quinone (XXIV), followed by the appropriate reduction step. The model quinone (XVI; R = Me) gave upon treatment with basic hydrogen peroxide the ring-contracted product (XXVI; R = OH),[22] whereas treatment with *m*-chloroperbenzoic acid gave the epoxide (XXVIII). Since only the 2,3-double bond could be attacked oxidatively this epoxidation approach was set aside.

With the problem of 12a-hydroxylation and concomitant dearomatisation remaining unsolved, we investigated the oxidation of phenols to *o*-hydroxy- (or a protected equivalent) cyclohexadienones (Scheme 5).



SCHEME 5

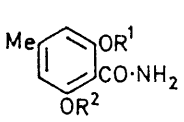
As described in Part VII it became necessary to protect the hydroxy-groups in ring A by methylation. The selective demethylation step is described here as it provided us with suitable compounds with which to test Scheme 5. When compound (XXIX; $R^1 = R^2 = R^3 = Me$, $R^4 = H$) was treated with sodium borohydride–iodine,[23,24] the phenol (XXIX; $R^1 = Me$, $R^2 = R^3 = R^4 = H$) was isolated in good yield. This phenolic acid was stable to further treatment with the borohydride–iodine reagent. In an extension of the reaction to compound (XXIX; $R^1 = R^2 = R^3 = R^4 = Me$), the phenolic acid (XXIX; $R^1 = R^4 = Me$, $R^2 = R^3 = H$) was formed in excellent yield. Methylation of this with diazomethane gave the ester (XXIX; $R^1 = R^3 = R^4 = Me$, $R^2 = H$). Demethylation of the aldehyde (XXIX; $R^1 = R^2 = R^3 = Me$, $R^4 = CHO$) with boron trichloride[25a] gave the phenol (XXIX; $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = CHO$), which upon hydrogenolysis gave a product identical with the ester (XXIX; $R^1 = R^3 = R^4 = Me$, $R^2 = H$). To establish the structure of the boron trichloride demethylation product it was acetylated. The resulting acetate (XXIX; $R^1 = R^3 = Me$, $R^2 = Ac$, $R^4 = CHO$) was different from the acetate (XXIX; $R^1 = Ac$, $R^2 = R^3 = Me$, $R^4 = CHO$),[25b] prepared by hydrogenation of the benzisoxazole (XXX) followed by methylation.

Treatment of the amide (XXXI; $R^1 = R^2 = Me$) with the sodium borohydride–iodine reagent gave the hydroxy-amide (XXXI; $R^1 = Me$, $R^2 = H$). Application of this procedure to compound (XXXII; $R^1 = R^2 = R^3 = Me$) gave an extremely slow reaction leading to a mixture of two hydroxy-acids (XXXII; $R^1 = R^2 = H$, $R^3 = Me$) and (XXXII; $R^1 = Me$, $R^2 = R^3 = H$), in low yield.

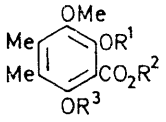
Since the boron trichloride demethylation of the ether (XXIX; $R^1 = R^2 = R^3 = Me$, $R^4 = CHO$) to the phenol (XXIX; $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = CHO$) took place rapidly, in 98% yield at −76°, it was decided to pursue studies with this reagent.[25a] Saponification of the ester (XXIX; $R^1 = R^2 = R^3 = Me$, $R^4 = CHO$), and treatment of the resulting acid (XXIX; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = CHO$), with thionyl chloride–dimethylformamide,[26] followed by ammonia (*d* 0·880) gave the amide (XXXIII; R = Me). When this was treated with boron trichloride in dichloromethane at −76°, the hydroxy-amide (XXXIII; R = H) was isolated in good yield. Its structure was established as follows. 2,6-Dihydroxy-4-methylbenzamide (XXXI; $R^1 = R^2 = H$) was methylated with methyl iodide–potassium carbonate in acetone to give compound (XXXI, $R^1 = Me$, $R^2 = H$). Formylation of this material with dichloromethyl methyl ether and aluminium trichloride[27] gave the *o*-hydroxy-aldehyde (XXXIII; R = H).

[21] C. J. Moye and S. Sternhell, *Austral. J. Chem.*, 1966, **19**, 2107.
[22] J. F. Corbett, *J. Chem. Soc.*, 1967, 611.
[23] L. H. Long and G. F. Freeguard, *Chem. and Ind.*, 1965, 223.
[24] G. F. Freeguard and L. H. Long, *Chem. and Ind.*, 1964, 1582.
[25] (*a*) 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; (*b*) Part III, E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner, and M. Slaytor, *J. Chem. Soc.* (*C*), 1971, 2175.
[26] (*a*) H. H. Bosshard and Hch. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1659; (*b*) H. H. Bosshard, R. Mory, M. Schmid, and Hch. Zollinger, *ibid.*, p. 1653.
[27] A. Rieche, H. Gross, and E. Höft, *Chem. Ber.*, 1960, **93**, 88.

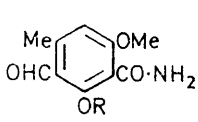
Compound (XXXII; $R^1 = R^2 = R^3 = Me$) was treated with boron trichloride in dichloromethane at −76° then at room temperature. The completely demethylated compound (XXXIV) was isolated. Methylation of the triol (XIX; R = H) gave the trimethyl ether (XIX; R = Me). Treatment of this with boron trichloride at −80° gave compound (XXXVII) and not the expected product (XXXV). Hydrogenation of the aldehyde (XXXVII) gave the dimethyl derivative (XXXVIII). The desired isomer (XXXVI) was unambiguously synthesised as follows. Treatment of the



(XXXI)



(XXXII)



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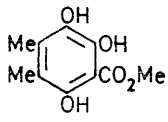

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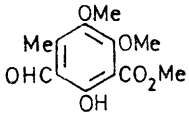
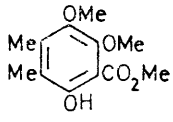
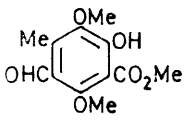


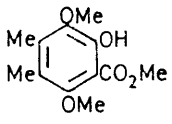
(XXXV)



(XXXVI)



(XXXVII)



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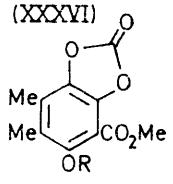
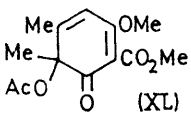


(XXXIX)



(XL)

triol (XXXIV) with phosgene in pyridine gave the cyclic carbonate (XXXIX; R = H). Benzoylation then gave the benzoate (XXXIX; R = Bz) and removal of the cyclic carbonate group with dilute acid followed by methylation gave the dimethoxy-benzoate (XXXII; $R^1 = R^2 = Me$, $R^3 = Bz$). Hydrolysis with sodium methoxide in methanol then gave the phenol (XXXVI). Boron trichloride has gained a reputation for selective demethylation *ortho* to a carbonyl group. Our results demonstrate that caution must be observed when extending this selectivity to a polymethoxylated system.

We were now in a position to examine the oxidation of these model compounds. The hydroxy-aldehyde (XXIX; $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = CHO$) was inert to tetraethylammonium periodate and sodium periodate, and converted into an intractable mixture by lead tetra-acetate. However, treatment of the phenol (XXIX; $R^1 = R^3 = R^4 = Me$, $R^2 = H$) in methanol with lead tetra-acetate and a trace of boron trifluoride–ether gave a clean rapid reaction. The product had $\nu_{max.}$ 1733 and 1660 cm.$^{-1}$, $\lambda_{max.}$ 224 and 324 nm. (ε 9940 and 4410). The n.m.r. spectrum exhibited one methyl signal at τ 8·55 and suggested the structure (XL). The possibility of using lead tetra-acetate oxidation for the introduction of the 12a-hydroxy-group was thus demonstrated.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. U.v. spectra were run for solutions in ethanol, i.r. spectra for Nujol mulls, and n.m.r. spectra for solutions in deuteriochloroform unless otherwise stated. Light petroleum refers to the fraction of b.p. 40—60°. Sodium sulphate was used for drying solutions prior to evaporation.

2,6-Dimethoxy-4-methylbenzamide (II; $R^1 = Me$, $R^2 = NH_2$).—2,6-Dimethoxy-4-methylbenzoic acid (2·79 g.) in thionyl chloride (50 ml.) was heated under reflux for 4 hr. (exclusion of moisture). The excess of reagent was evaporated off and the residue [$\nu_{max.}$ ($CHCl_3$) 1790 cm.$^{-1}$] in dry benzene (50 ml.) was treated with dry, gaseous ammonia. The mixture was filtered and the solid was washed thoroughly with water. The dry amide (1·91 g.), $\nu_{max.}$ 3540, 3430, and 1675 cm.$^{-1}$, was used for the next stage. A portion recrystallised from benzene had m.p. 201—205° (lit.,[28] 199°).

2,6-Dimethoxy-4-methylcyclohexa-2,5-dienecarboxamide (V).—Sodium (370 mg., in small pieces) was added rapidly with stirring to 2,6-dimethoxy-4-methylbenzamide (543 mg.) in liquid ammonia (50 ml.) and absolute ethanol (9 ml.). After the resulting blue colour had faded, ammonium chloride (2·7 g.) was added and the ammonia was evaporated off. The residue was mixed with water (50 ml.) and extracted with dichloromethane. The organic phase was separated, dried, and evaporated to leave the crude product (423 mg.), $\nu_{max.}$ 3500, 3400, 1690, and 1680 cm.$^{-1}$. Two recrystallisations from chloroform–ether furnished the *dihydro-amide* (V) (70 mg.), m.p. 172—177°, τ 4·1br (2H), 5·22 (2H, d, *J* 2 Hz), 6·38 (6H, s), and 8·87 (3H, d, *J* 8 Hz). An analytical sample had m.p. 185—189° (Found: C, 61·25; H, 7·8; N, 7·4. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·7; N, 7·1%).

4-Methyl-2,6-dioxocyclohexanecarboxamide (III).[2]—2,6-Dimethoxy-4-methylbenzamide (540 mg.) was reduced by the method already described and the crude product in ethanol (22 ml.) and hydrochloric acid (6N; 30 drops) was kept for 2·3 hr. at room temperature (u.v. control). The solution was evaporated below 55° and the residue was warmed with saturated aqueous sodium hydrogen carbonate (10 ml.). Insoluble material was removed. Acidification (conc. hydrochloric acid) of the cooled filtrate afforded the crystalline β-diketone (153 mg.), m.p. 138—148·5°. Recrystallised twice from aqueous methanol this had m.p. 146—150° (lit.,[2] 146—150°).

Methyl 2,6-Dimethoxy-4-methyl-3-phenylazobenzoate (VI; $R^3 = N_2Ph$, $R^2 = Me$, $R^1 = OMe$).—2,6-Dihydroxy-4-methyl-3-phenylazobenzoic acid[6] (9·48 g.), anhydrous potassium carbonate (19·60 g.), and dimethyl sulphate (10·6 ml.) in dry acetone (*ca.* 250 ml.) were heated under reflux with stirring. Potassium carbonate and dimethyl sulphate (9·8 g. and 5·3 ml., respectively) were added after 15 hr. and again after 41 hr. After a further 4—5 hr. more potassium carbonate (4·0 g.) was added and the reaction was continued for 43 hr. The mixture was filtered, the solid was washed with dry acetone, and the

[1]P. R. Saraiya and R. C. Shah, *Current Sci.*, 1949, **18**, 218.

combined filtrates were evaporated. The residue was chromatographed over alumina (with benzene) and crystallised from aqueous ethanol to give the *dimethoxy-ester* (8·61 g.), m.p. 118—121°, $\nu_{max.}$ 2880 and 1725 cm.$^{-1}$, τ 197—2·59 (5H, m), 3·37 (1H, s), 6·05, 6·11, and 6·13 (each 3H, s), and 7·47 (3H, s). An analytical sample had m.p. 120·5—121° (Found: C, 65·2; H, 5·95; N, 8·7. $C_{17}H_{18}N_2O_4$ requires C, 65·0; H, 5·8; N, 8·9%).

Methyl 3-Amino-2,6-dimethoxy-4-methylbenzoate (VI; $R^3 = NH_2$, $R^2 = Me$, $R^1 = OMe$).—Methyl 2,6-dimethoxy-4-methyl-3-phenylazobenzoate (4·5 g.) in methanol (85 ml.) containing conc. hydrochloric acid (4·5 ml.) was hydrogenated over Adams catalyst (94 mg.). The mixture was filtered, made alkaline (saturated aqueous sodium hydrogen carbonate), and extracted with dichloromethane. The purple organic solution was dried and evaporated, and the residue was extracted with several portions of boiling ether. The combined extracts were filtered, concentrated, and cooled to *ca.* −60° to give the crude amine (2·28 g.), m.p. 90—100°, $\nu_{max.}$ 3490, 3410, 2860, and 1725 cm.$^{-1}$, suitable for the next stage.

Methyl 3-Dimethylamino-2,6-dimethoxy-4-methylbenzoate (VI; $R^3 = NMe_2$, $R^2 = Me$, $R^1 = OMe$).—Anhydrous potassium carbonate (2·1 g.) and dimethyl sulphate (0·55 ml.) were added to methyl 3-amino-2,6-dimethoxy-4-methylbenzoate (314 mg.) in dry acetone (*ca.* 6 ml.). The mixture was refluxed with stirring overnight, filtered, and evaporated to dryness; the residue was taken up in chloroform, washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The product was chromatographed over alumina with benzene to give the *dimethylamino-derivative* (291 mg.), m.p. (from light petroleum) 71—72°, $\nu_{max.}$ 2860, 2800, and 1723 cm.$^{-1}$, τ 3·50 (1H), 6·10, 6·23, and 6·25 (9H), 7·27 (6H), and 7·72 (3H) (Found: C, 61·45; H, 7·4; N, 5·6. $C_{13}H_{19}NO_4$ requires C, 61·65; H, 7·55; N, 5·55%).

3-Dimethylamino-2,6-dimethoxy-4-methylbenzoic Acid (VI; $R^3 = NMe_2$, $R^2 = Me$, $R^1 = OH$).—Methyl 3-dimethylamino-2,6-dimethoxy-4-methylbenzoate (169 mg.), aqueous sodium hydroxide (4N; 2·55 ml.), and ethanol (5·1 ml.) were heated under reflux for 5—6 hr. [t.l.c. control]. The clear solution was cooled, diluted with water, and extracted with ether. The aqueous layer was acidified (acetic acid) and continuously extracted with ether for 15 hr. Evaporation of the extract gave the crude amino-acid (140 mg.), $\nu_{max.}$ 2860, 2800, and 1720 cm.$^{-1}$. This compound was used directly for the next stage.

3-Dimethylamino-2,6-dimethoxy-4-methylbenzamide (VI; $R^3 = NMe_2$, $R^2 = Me$, $R^1 = NH_2$).—3-Dimethylamino-2,6-dimethoxy-4-methylbenzoic acid (204 mg.) in oxalyl chloride (1 ml.) was kept for 15 min. at room temperature and then heated under reflux gently for 2 hr. The solvent was removed and the residue, in anhydrous benzene, was treated with dry gaseous ammonia. The resulting mixture was added to saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic solution was dried and evaporated to give the *amide* (125 mg.), m.p. (from benzene) 176—180°, $\nu_{max.}$ 3520, 3430, 2890, 2820, 1678, and 1600 cm.$^{-1}$ (Found: C, 61·4; H, 7·8; N, 11·6%; M^+, 238·131095. $C_{12}H_{18}N_2O_3$ requires C, 60·5; H, 7·6; N, 11·8%; *M*, 238·131734), τ 3·48 (1H, s), 4·0 (2H), 6·13 and 6·19 (6H), 7·21 (6H, s), and 7·68 (3H, s).

Attempted Reduction of the Amide (VI; $R^3 = NMe_2$, $R^2 = Me$, $R^1 = NH_2$).—Sodium (70 mg., in several pieces) was added rapidly with stirring to the amide (141 mg.) in dry liquid ammonia (50 ml.) and absolute ethanol (1·8 ml.). A fleeting blue colour was produced and after 5 min., ammonium chloride (1 g.) was added to the colourless solution. The ammonia was evaporated off, water was added to the residue, and the mixture was extracted with dichloromethane. The organic solution was dried and evaporated to give a partially crystalline oil, $\nu_{max.}$ 3520, 3420, 2880, 1705, and 1680 cm.$^{-1}$. T.l.c. showed, besides starting material, two slower-running substances. Dissolution of the total product in ethanol containing hydrochloric acid (6N; several drops) produced slight changes in the u.v. spectrum but no peak developed at 260 nm., even on heating.

Other procedures were tried, with the same result.

Photolysis of Ethyl Azidoformate in the Presence of 2,5-Dihydroanisole.—Ethyl azidoformate (1·31 g.)[29,30] and 2,5-dihydroanisole (1·12 g.) in cyclohexane (*ca.* 60 ml.; distilled from sodium) were irradiated with a low-pressure mercury lamp (nitrogen stirring) for 5 hr. (disappearance of ethyl azidoformate). The solvent was removed to leave an oil, $\nu_{max.}$ (film) 3380, 2200w, 1720, 1687, and 1672 cm.$^{-1}$, which contained at least six components. Other procedures were tried, some without solvent, and the same result was obtained.

Reaction Between Picryl Azide and 2,5-Dihydroanisole.—Picryl azide[31] (354 mg., free from ethanol) was added to 2,5-dihydroanisole (6 ml.) and the mixture was stirred in the dark under nitrogen. Gas was evolved, a red colour developed, and the homogeneous mixture became warm. The mixture was cooled and kept at room temperature for 20 hr., by which time a yellow precipitate had formed. The mixture was filtered and the solid was washed with light petroleum, dried, and chromatographed on G3 alumina with benzene to give N-(*3-methoxycyclohex-2-enylidene*)*picrylamine* (VII) (312 mg.), m.p. (from methanol) 158—162°, $\lambda_{max.}$ 253 and 323 nm. (ε 24,060 and 15,330), $\nu_{max.}$ 1640, 1615, 1592, and 1340 cm.$^{-1}$, τ 1·02 (2H, s), 4·60 (1H, s), 6·23 (3H, s), 7·52 (4H, m), and 7·93 (2H, m) (Found: C, 46·3; H, 3·55; N, 16·4. $C_{13}H_{12}N_4O_7$ requires C, 46·4; H, 3·6; N, 16·65%).

Hydrochloric acid (6N; 5 drops) was added to *N*-(3-methoxycyclohex-2-enylidene)picrylamine (60 mg.) in dioxan (4 ml.). The mixture was kept at 80° for 8 hr., evaporated to small bulk, saturated with sodium chloride, and extracted with chloroform. The extract was dried and evaporated, and the residue (61 mg.) was chromatographed over silica gel with chloroform. Picramide (18 mg.) [m.p., mixed m.p., i.r. spectrum (Nujol)] was obtained. Further elution with ethyl acetate–acetic acid (9 : 1) gave dihydroresorcinol. This (10 mg.) in saturated aqueous sodium hydrogen carbonate (1 ml.) and water (0·5 ml.) was treated at 0° with aqueous benzenediazonium chloride. The precipitate was chromatographed over alumina with chloroform to give the pure azo-dye (9 mg.), identical (m.p., mixed m.p., i.r. spectrum) with authentic material.

NN-*Dimethyl*-O-p-*tolylsulphonylhydroxylamine* (VIII).—*NN*-Dimethylhydroxylamine hydrochloride[32] (1·074 g.) in chloroform (250 ml.) was cooled to room temperature and triethylamine (2·228 g.) in dry chloroform (6 ml.) was added. The mixture was stirred and cooled in an ice-bath

[29] M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, 1908, 72.
[30] R. J. Cotter and W. F. Beach, *J. Org. Chem.*, 1964, **29**, 751.
[31] (*a*) O. L. Brady and H. V. Horton, *J. Chem. Soc.*, 1925, 2230; (*b*) E. Schrader, *Ber.*, 1917, **50**, 777.
[32] A. C. Cope and E. Ciganek, *Org. Synth.*, Coll. Vol. IV, p. 612.

during dropwise addition of dry toluene-*p*-sulphonyl chloride (1·906 g.) in chloroform (15 ml.). The stirring was continued overnight in the dark at room temperature. Washing with water (40 ml.) and evaporation at room temperature gave the *product* (1·305 g.), which was stored in a refrigerator *in vacuo* over calcium chloride. It decomposed slowly and was repurified by chromatography over silica gel; $\nu_{max.}$ 1600, 1380, 1190, and 1180 cm.$^{-1}$, m.p. 87—89: (from light petroleum or cyclohexane) (Found: C, 50·6; H, 6·65; N, 6·45; S, 15·55. $C_9H_{13}NO_3S$ requires C, 50·2; H, 6·1; N, 6·5; S, 14·9%), τ 2·03—2·70 (4H), 7·37 (6H, s), and 7·55 (3H, s).

Action of Base on NN-*Dimethyl*-O-p-*tolylsulphonylhydroxylamine*.—Diethylamine (*ca.* 4 ml.) and the toluene-*p*-sulphonate (138 mg.) in benzene (1 ml.) were kept for 14 hr. at room temperature. The salt of diethylamine and toluene-*p*-sulphonic acid [m.p., mixed m.p., i.r. spectrum (Nujol)] was filtered off; the filtrate was acidified with hydrochloric acid (6N) and steam distilled. The vapours were passed into a saturated aqueous solution of dimedone; formaldehyde dimedone derivative (26 mg.) was obtained (m.p. and mixed m.p.).

Reaction between 4-(*Cyclohex*-1-*enyl*)*morpholine and* NN-*Dimethyl*-O-p-*tolylsulphonylhydroxylamine*.—The hydroxylamine (207 mg.) and 4-(cyclohex-1-enyl)morpholine[33] (329 mg.) in dry benzene (*ca.* 4 ml.) were stirred at room temperature for 15 hr. The mixture was diluted with ether and extracted with hydrochloric acid (6N), and the aqueous layer was evaporated. The residue had $\nu_{max.}$ 1708 cm.$^{-1}$. The ketonic component was isolated as the crystalline 2,4-dinitrophenylhydrazone (23 mg.) of 2-(morpholinomethyl)-cyclohexanone, identical with an authentic sample (m.p., mixed m.p.; see following experiment).

2-(*Morpholinomethyl*)*cyclohexanone* 2,4-*Dinitrophenylhydrazone*.—The method of Harradence and Lions[34] was used to prepare 2-(morpholinomethyl)cyclohexanone (IX). The 2,4-*dinitrophenylhydrazone* had m.p. (from ethyl acetate) 154—158° (Found: C, 54·2; H, 6·4; N, 18·5. $C_{17}H_{23}N_5O_5$ requires C, 54·1; H, 6·15; N, 18·55%).

Reaction of NN-*Dimethyl*-O-p-*tolylsulphonylhydroxylamine with Grignard Reagents*.—(*a*) A suspension of *NN*-dimethyl-*O*-tosylhydroxylamine (295 mg.) in ether was added to phenylmagnesium bromide in ether (excess) with stirring. After 10 min. at room temperature the excess of Grignard reagents was destroyed with water and the mixture was diluted with aqueous sodium hydrogen carbonate and extracted with ether. The extract was washed with hydrochloric acid (6N) and the aqueous solution was evaporated to leave *NN*-dimethylaniline hydrochloride (124 mg.), identified by comparison with an authentic sample.

The free base (82 mg.), liberated by treatment with aqueous sodium hydrogen carbonate, was treated with picric acid in ethanol to give *NN*-dimethylaniline picrate (m.p., mixed m.p., i.r. spectrum).

(*b*) *NN*-Dimethyl-*O*-*p*-tolylsulphonylhydroxylamine (311 mg.) in ether (15 ml.) was added dropwise with stirring to an excess of cyclohexylmagnesium bromide in ether. A thick white precipitate formed, but dissolved within 10 min. At this stage the mixture was worked up as in (*a*). The crystalline hydrochloride (35 mg.) showed signals in its n.m.r. spectrum (deuterium oxide) at τ 7·0 (6H, s) and 7·5—9·2 (11H). The identification was confirmed by comparison (m.p., mixed m.p., i.r. spectrum) with an authentic sample.[18a]

NN-*Dimethyl*-O-(*xanthen*-9-*carbonyl*)*hydroxylamine* (X).—Xanthen-9-carbonyl chloride[12] (490 mg.) was stirred for 5 min. at 0° with *NN*-dimethylhydroxylamine hydrochloride (197 mg.) in dry pyridine (3 ml.). Stirring was continued at room temperature for 1·5 hr. (protection from light). The solution was poured into a mixture of ice and hydrochloric acid (N), and extracted with ether. The organic layer was washed with ice-cold aqueous sodium hydroxide (N) and then with water. The solution was dried and evaporated below 40° to give the crude product (403 mg.), $\nu_{max.}$ 1749 cm.$^{-1}$. Recrystallisation from light petroleum afforded the *ester* (X) (304 mg.), m.p. 60—63°, τ 2·81 (m), 5·05 (1H, s), and 7·39 (6H, s). An analytical sample had m.p. 65·5—66·5° (Found: C, 71·1; H, 5·75; N, 5·5. $C_{16}H_{15}NO_3$ requires C, 71·35; H, 5·6; N, 5·2%).

Photolysis of NN-*Dimethyl*-O-(*xanthen*-9-*carbonyl*)*hydroxylamine in Cyclohexane*.—The hydroxylamine ester (X) (134 mg.) in boiling cyclohexane (*ca.* 50 ml.) was irradiated for 3 hr. in quartz apparatus with a high-pressure mercury lamp. During this time a stream of dry nitrogen was passed through the mixture and the exit gases were led through two wash bottles containing aqueous barium hydroxide. The photolysis solution was cooled, decanted from a small amount of insoluble material, diluted with ether, extracted with hydrochloric acid (N), dried, and evaporated. The residue (116 mg.), which contained no starting material, was chromatographed over alumina with benzene. Fractional sublimation and recrystallisation from ethanol afforded 9-cyclohexylxanthen (XI), τ 2·97 (8H), 6·3 (1H, s), and 8·2—9·3 (11H). Further chromatography over alumina with light petroleum gave pure 9-*cyclohexylxanthen* (13 mg.), m.p. (from ethanol) 106·5—108° (Found: C, 86·65; H, 7·65. $C_{19}H_{20}O$ requires C, 86·3; H, 7·65%). Barium carbonate (286 mg.) was obtained from the first wash bottle.

3-*Hydroxy*-4-*methoxycarbonyl*-2,5-*toluquinone* (XIV).—Methyl 2,6-dihydroxy-*p*-toluoate (296 mg.) in ethanol (100 ml.) was stirred, and Frémy's salt (3·35 g.) in water (100 ml.) was added. After 1 hr. the mixture was extracted with chloroform. The dried extract was evaporated to yield orange-yellow crystals of the *quinone* (XIV), m.p. 115—116° (from benzene–light petroleum), $\nu_{max.}$ 3400, 1670, and 1590 cm.$^{-1}$, $\lambda_{max.}$ 209, 263, and 327 nm. (ε 14,200, 14,900, and 1480), τ 7·93 and 7·77 (3H), 6·03 and 5·97 (3H), 3·72 (1H, s), and 0·45 (1H, s, exchanged by D_2O) (Found: C, 55·3; H, 4·3. $C_9H_8O_5$ requires C, 55·1; H, 4·1%).

Methyl 2,3,6-*Triacetoxy*-4-*methylbenzoate* (VI; R^3 = OAc, R^2 = Ac, R^1 = OMe).—The quinone (XIV) (180 mg.) in sulphurous acid solution (10 ml.) was heated at 95° for 2 hr. The mixture was cooled to room temperature and extracted with ether. Evaporation of the dried extract gave an oil. This oil in acetic anhydride (3 ml.) and pyridine (3 ml.) was kept at room temperature. After 20 hr. the mixture was quenched in 2N-hydrochloric acid (25 ml.) and extracted with chloroform. The dried extract was evaporated, and the residue was chromatographed on alumina. Crystallisation from methanol gave the *triacetate* (VI; R^3 = OAc, R^2 = Ac, R^1 = OMe) (235 mg.), m.p. 144—145°, $\nu_{max.}$ 1780 and 1742 cm.$^{-1}$, $\lambda_{max.}$ 204 and 272 nm. (ε 30,800 and 16,800), τ 7·74 (12H, m), 6·17 (3H, s), and

[33] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207.

[34] R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. New South Wales*, 1939, **72**, 233.

3·07 (1H, s) (Found: C, 55·9; H, 4·8. $C_{15}H_{16}O_8$ requires C, 55·6; H, 5·0%).

Methyl 2,6-*Dihydroxy*-3,4-*dimethylbenzoate* (XV).—Methyl 2-formyl-2,6-dihydroxy-*p*-toluoate (1·0 g.) was hydrogenated in glacial acetic acid (100 ml.) over prereduced 10% palladium–carbon (100 mg.) until hydrogen uptake ceased to give the crystalline ester [35] (XV) (820 mg.), m.p. 108—109°, τ 7·93 (3H, s), 7·77 (3H, s), 5·94 (3H, s), 3·65 (1H, s), 0·79 (1H, exchanged by D_2O), and −0·14 (1H, exchanged by D_2O).

3-*Hydroxy*-4-*methoxycarbonyl*-6-*methyl*-2,5-*toluquinone* (XVI; R = H).—Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (XV) (130 mg.) in ethanol (50 ml.) was treated with Frémy's salt (2·0 g.) in water (90 ml.) containing sodium acetate (M; 10 ml.). After 18 hr. at room temperature the solution was acidified with dilute hydrochloric acid and extracted with chloroform. The dried chloroform solution was evaporated and the residue gave the *quinone* (XVI; R = H) (132 mg.), m.p. 68° (from ether–di-isopropyl ether), $\nu_{max.}$ 1678, 1660, and 1643 cm.$^{-1}$, $\lambda_{max.}$ 208, 272, and 396 nm. (ε 9440, 17,800, and 920), τ 7·92 (6H, s), 6·00 (3H, s), and −2·73 to −1·38 (1H, exchanged by D_2O) (Found: C, 57·1; H, 4·7. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

Basic Frémy's Salt Oxidation of Methyl 2,6-*Dihydroxy*-p-*toluoate*.—The ester (500 mg.) in dimethylformamide (20 ml.) and aqueous sodium hydroxide solution (0·1N; 28 ml.) was treated with Frémy's salt (5·0 g.) in water (100 ml.) and sodium hydroxide (4N; 2·5 ml.) was added. After 1 hr. the mixture was acidified with 6N-hydrochloric acid and extracted with chloroform. Evaporation of the dried extract gave a solid which was reduced with zinc dust (5 g.) in dimethylformamide (10 ml.) and glacial acetic acid (10 ml.) at 0°. The mixture was filtered, treated with acetic anhydride (3 ml.) and pyridine (3 ml.) at room temperature, quenched in ice-cold dilute hydrochloric acid, and extracted with chloroform. Evaporated of the dried extract and chromatography of the residue on alumina followed by crystallisation from benzene–light petroleum gave the *hexa-acetate* (XVII) (85 mg.), m.p. 225—227°, $\nu_{max.}$ 1778 and 1727 cm.$^{-1}$, $\lambda_{max.}$ 210 and 285 nm. (ε 54,800 and 5180), τ 8·07, 7·70, and 6·18 (ratio 2 : 2 : 1), *m/e* 582 (M^+, $C_{30}H_{30}O_{16}$) (Found: C, 55·7; H, 4·5. $C_{30}H_{30}O_{16}$ requires C, 55·8; H, 4·7%).

Methyl 2,3,6-*Trihydroxy*-4-*methylbenzoate* (VI; R^3 = OH, R^2 = H, R^1 = OMe).—The quinone (XIV) (289 mg.) in ether (70 ml.) was hydrogenated over 8% palladium–carbon at atmospheric pressure and room temperature. When the uptake of hydrogen ceased the catalyst was filtered off and the ether removed at 0° under a stream of nitrogen. The crystalline residue (270 mg.) gave pure *ester* (VI; R^3 = OH, R^2 = H, R^1 = OMe), m.p. 82° (from aqueous methanol), $\nu_{max.}$ 3560, 3450, and 1670 cm.$^{-1}$, $\lambda_{max.}$ 323, 255, and 221 nm. (ε 3440, 13,100, and 19,500), τ 7·70 (3H, s), 5·88 (3H, s), 3·62 (1H, s), and 1·25 (1H, s), 0·34 (1H, s), and 0·08 (1H, s) (all exchanged by D_2O) (Found: C, 54·4; H, 5·0. $C_9H_{10}O_5$ requires C, 54·6; H, 5·1%).

Methyl 3-*Formyl*-2,5,6-*trihydroxy*-4-*methylbenzoate* (XIX; R = H).—The phenol (VI; R^3 = OH, R^2 = H, R^1 = OMe) (730 mg.) in dry ether (250 ml.) was stirred with the Gattermann [18b] complex (from dry hydrogen chloride and hydrogen cyanide) (4 g.) and aluminium trichloride (5 g.) for 5 hr. Evaporation of the ether and addition of water [containing conc. hydrochloric acid (10 ml.)] to the dark red residue, followed by warming at 90°, gave yellow crystals of the *aldehyde* (XIX; R = H), m.p. (from chloroform) 202°, $\nu_{max.}$ ($CHCl_3$) 3570, 1660, and 1640 cm.$^{-1}$, $\lambda_{max.}$ 305 and 256 nm. (ε 1840 and 27,500), τ 7·50 (3H, s), 5·98 (3H, s), −0·12 (1H, s), −1·50 (1H, s), −2·60 (1H, s), and −3·00 (1H, s) (last 4H exchanged by D_2O), *m/e* 226 (M^+, $C_{10}H_{10}O_6$) (Found: C, 53·2; H, 4·6. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·5%).

6-*Formyl*-3-*hydroxy*-4-*methoxycarbonyl*-2,5-*toluquinone* (XX).—The aldehyde (XIX; R = H) (76 mg.) in chloroform (25 ml.) was stirred with DDQ (77 mg.) at room temperature for 2·5 hr. The hydroquinone ($DDQH_2$) was filtered off and the solution was evaporated. The residue gave yellow nuggets of the *quinone* (XX) (73 mg.), m.p. 145° (from benzene–light petroleum), $\nu_{max.}$ 1706, 1684, and 1664 cm.$^{-1}$, $\lambda_{max.}$ 206, 272, and 376 nm. (ε 11,400, 13,500, and 470), τ 7·54 (3H, s), 5·84 (3H, s), −0·56 (1H, s), and −2·0br (1H, exchanged by D_2O) (Found: C, 53·5; H, 3·8. $C_{10}H_8O_6$ requires C, 53·6; H, 3·6%).

Methyl 2,3,6-*Triacetoxy*-5-*formyl*-4-*methylbenzoate* (XIX; R = Ac).—Methyl 3-formyl-2,5,6-trihydroxy-4-methylbenzoate (XIX; R = H) (450 mg.) in acetic anhydride (15 ml.) and pyridine (15 ml.) was heated at 90° for 15 min. The mixture was quenched in ice–water containing conc. hydrochloric acid (3 ml.). The solid was filtered off and gave (from benzene–light petroleum) the *triacetate* (XIX; R = Ac) (560 mg.), m.p. 112—114°, $\nu_{max.}$ 1780, 1735, and 1690 cm.$^{-1}$, $\lambda_{max.}$ 219, 249, and 300 nm. (ε 28,600, 9210, and 1780), τ 7·71 (3H, s), 7·66 (6H, s), 7·54 (3H, s), 6·13 (3H, s), and −0·30 (1H, s) (Found: C, 54·7; H, 4·3. $C_{16}H_{16}O_9$ requires C, 54·6; H, 4·6%].

Methyl 2,3,6-*Triacetoxy*-5-*ethylenedioxymethyl*-4-*methylbenzoate* (XXI).—The aldehyde (XIX; R = Ac) (207 mg.) in dry benzene (10 ml.) and butan-2-one ethylene acetal (1·5 ml.) were treated with boron trifluoride (40% ethereal solution; 0·1 ml.). After 15 min. the mixture was poured into water (20 ml.) containing triethylamine (0·5 ml.). The benzene layer was separated and dried. Evaporation, and crystallisation from benzene–light petroleum, gave the *triacetate* (XXI) (171 mg.), m.p. 176—177°, $\nu_{max.}$ 1770 and 1720 cm.$^{-1}$, $\lambda_{max.}$ 207 and 283 nm. (ε 31,800 and 2140), τ 7·74 (12H, m), 6·23 (3H, s), 5·97 (4H, d), and 4·09 (1H, s) (Found: C, 54·7; H, 5·0. $C_{18}H_{20}O_{10}$ requires C, 54·5; H, 5·1%).

Methyl 2,3,6-*Triacetoxy*-5-(2-*bromoethoxycarbonyl*)-4-*methylbenzoate* (XXII; R = Ac).—The acetal (XXI) (88 mg.) in dry benzene (25 ml.) was treated with *N*-bromosuccinimide (40 mg.), and the mixture was refluxed for 3 hr. The solvent was evaporated off and the residue was stirred with carbon tetrachloride. Filtration and evaporation of the filtrate gave a colourless solid. Crystallisation from chloroform–light petroleum gave the *bromo-ester* (XXII; R = Ac) (100 mg., 94%), m.p. 94—97°, $\nu_{max.}$ 1770, 1750, 1730, and 1720 cm.$^{-1}$, $\lambda_{max.}$ 207 and 284 nm. (ε 35,000 and 2070), τ 7·92 (9H, s), 7·66 (3H, s), 6·39 (2H, t, *J* 6 Hz), 6·16 (3H, s), and 5·35 (2H, t, *J* 6 Hz) (Found: C, 45·6; H, 3·9; Br, 16·5. $C_{18}H_{19}BrO_{10}$ requires C, 45·5; H, 4·0; Br, 16·8%).

Methyl 3-(2-*Bromoethoxycarbonyl*)-2,5,6-*trihydroxy*-4-*methylbenzoate* (XXII; R = H).—The triacetate (XXII; R = Ac) (200 mg.) in methanolic hydrogen chloride (5N; 25 ml.) was stirred under nitrogen for 3 hr. at room temperature. Evaporation, and crystallisation from ether–light petroleum, gave the *phenol* (XXII; R = H) (102 mg.), m.p. 111—113°, $\nu_{max.}$ 3500, 1660, and 1640 cm.$^{-1}$, $\lambda_{max.}$ 202,

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237, 247, and 347 nm. (ε 12,400, 20,700, 16,100, and 6930), τ 7·50 (3H, s), 6·23 (2H, t, *J* 5·8 Hz), 5·93 (3H, s), 5·30 (2H, t, *J* 5·8 Hz), −1·53 (1H, exchanged by D_2O), and −1·90 (2H, exchanged by D_2O) (Found: C, 41·5; H, 3·5. $C_{12}H_{13}BrO_7$ requires C, 41·3; H, 3·7%).

6-(2-*Bromoethoxycarbonyl*)-3-*hydroxy*-4-*methoxycarbonyl*-2,5-*toluquinone* (XXIII).—The phenol (XXII; R = H) (48·3 mg.) in chloroform (20 ml.) was treated with DDQ (33·6 mg.) under nitrogen for 45 min. at room temperature. The solution was filtered and evaporated to give the orange *quinone* (XXIII) (45 mg.), m.p. 116—118°, $\nu_{max.}$ 1660 and 1640 cm.$^{-1}$, $\lambda_{max.}$ 204, 214, and 269 nm. (ε 11,800, 10,300, and 11,700), τ 7·82 (3H, s), 6·35 (2H, t, *J* 5·8 Hz), 5·94 (3H, s), and 5·30 (2H, t, *J* 5·8 Hz) (Found: C, 41·6; H, 3·0. $C_{12}H_{11}BrO_7$ requires C, 41·5; H, 3·2%).

Hydration Reactions.—The experimental conditions refer to both quinones (XXIII) and (XX). The quinone (25 mg.) in dioxan (10 ml.) and water (3 ml.) gave a red solution of the anion (acidification provided the quinone). The solution was stirred at room temperature and sodium hydroxide (0·1N) was added dropwise. The reaction was followed by u.v. spectroscopy. Acidification gave the unchanged quinone in quantitative yield.

The quinone (15 mg.) in water (25 ml.) and dioxan (10 ml.) was treated with hydrochloric acid (2 ml.). After 5 hr. no change was observed and the quinone was recovered unchanged.

Preparation of the 4a,12a-*Anhydro*-4-*hydroxy*-4-*de*(*dimethylamino*)*tetracycline* (XII).[14]—Tetracycline hydrochloride (10 g.) in water (200 ml.) was treated with aqueous sodium acetate at 0° until the pH was 4·5. The pale yellow crystals were filtered off, washed with water and ether, and dried *in vacuo* (yield 8·2 g., 90%).

The tetracycline base (10 g.) in tetrahydrofuran (200 ml.) and methyl iodide (24 ml.) was protected from light and kept at room temperature for 4 days. The crystals were filtered off and dried *in vacuo* (yield 11·5 g., 87%).

Tetracycline methiodide (13·1 g.) in water (550 ml.) was rapidly filtered and sufficient aqueous sodium acetate was added to give pH 4·5. The solution was cooled to 0°. The tetracycline methyl betaine (9·6 g., 93·8%) was filtered off, washed with water, acetone, and ether, and dried *in vacuo*.

Dry tetracycline methyl betaine (660 mg.) was suspended in dry acetonitrile (4·5 ml.; distilled three times from calcium hydride), heated under reflux under nitrogen for 4·75 hr., and cooled. The orange crystals were filtered off and dried *in vacuo* to give the derivative (XII) (449 mg., 76·5%).

4a,12a-*Anhydro*-4-*de*(*dimethylamino*)-4-*oxotetracycline* (XXIV).— 4a,12a-Anhydro-4-hydroxy-4-de(dimethylamino)tetracycline (XII) (1·10 g.) in dry dioxan (150 ml.) was stirred under nitrogen with DDQ (632 mg.) for 20 hr. The solution was filtered and the solvent was evaporated off at room temperature to give a dark red oil. Trituration with ether gave the *quinone* (XXIV) (893 mg.), m.p. (wide range) > 250°, $\nu_{max.}$ 3500, 3400, 3280, 1667, and 1625 cm.$^{-1}$, $\lambda_{max.}$ (dioxan) 257, 340, and 382 nm. (ε 18,000, 9190, and 5890), $\lambda_{max.}$ methanolic 0·01M-HCl) 261, 342, and 428 nm. (ε 17,600, 8210, and 12,600), τ 8·36 and 8·43 (and others) (Found: C, 60·4; H, 3·5; N, 3·3. $C_{20}H_{15}NO_8$ requires C, 60·5; H, 3·8; N, 3·5%).

5-*Chloro*-1-*hydroxy*-5-*methoxycarbonyl*-2,3-*dimethyl*-4-*oxocyclopent*-2-*enecarboxylic Acid* (XXVI; R = Cl).—The quinone (XVI; R = H) (206 mg.) in dioxan (10 ml.), water (10 ml.), and hydrochloric acid (6N; 20 ml.) was treated with a solution of sodium hypochlorite (10%). After 2 min. the mixture was extracted with ether. The extract was dried and evaporated to give a pale yellow oil which slowly crystallised. Recrystallisation from benzene–light petroleum gave the unsaturated ketone (XXVI; R = Cl) (142 mg.), m.p. 84—85°, $\nu_{max.}$ 3520, 3400, 2560, 1745, and 1723 cm.$^{-1}$, $\lambda_{max.}$ 241 nm. (ε 7800), τ 8·07 (3H, s), 7·96 (3H, s), 6·21 (3H, s), and 4·83 (2H, exchanged by D_2O).

Treatment of the ketone (XXVI; R = Cl) (71 mg.) in ether (10 ml.) with ethereal diazomethane gave *dimethyl* 1-*chloro*-2-*hydroxy*-3,4-*dimethyl*-5-*oxocyclopent*-3-*ene*-1,2-*dicarboxylate* (69 mg.), m.p. (from chloroform–light petroleum) 140—142°, $\nu_{max.}$ 3480, 1750, and 1722 cm.$^{-1}$, $\lambda_{max.}$ 239 nm. (ε 10,400), τ 7·99, 7·93, 6·26, and 6·20 (all 3H, s) and 5·69 (1H, s, exchanged by D_2O) (Found: C, 47·6; H, 4·6. $C_{11}H_{13}ClO_6$ requires C, 47·7; H, 4·7%).

Methyl 1-*Chloro*-3,4-*dimethyl*-2,5-*dioxocyclopent*-3-*ene*-1-*carboxylate* (XXVII).—The cyclopentenone (XXVI; R = Cl) (48 mg.) in dry benzene (20 ml.) was stirred at room temperature with lead tetra-acetate (82 mg.) for 30 min. The solution was filtered, poured into water (100 ml.), and extracted with ether. Evaporation of the dried extract and crystallisation from light petroleum gave the *enedione* (XXVII) (31 mg.), m.p. 89—90°, $\nu_{max.}$ 1770 and 1709 cm.$^{-1}$, $\lambda_{max.}$ 224 nm. (ε 12,380), τ 7·84 (6H, s) and 6·20 (3H, s) (Found: C, 50·0; H, 4·2; Cl, 16·6. $C_9H_9ClO_4$ requires C, 49·9; H, 4·2; Cl, 16·4%).

3-*Methoxy*-4-*methoxycarbonyl*-6-*methyl*-2,5-*toluquinone* (XVI; R = Me).—The quinone (XVI; R = H) (204 mg.) in methanol (2 ml.) was treated with diazomethane in ether. The solvent was evaporated off and the residue was crystallised from ether–di-isopropyl ether to give the *methyl ether* (XVI; R = Me) (180 mg.), m.p. 70—71°, $\nu_{max.}$ 1735, 1672, 1647, 1636, and 1616 cm.$^{-1}$, $\lambda_{max.}$ 273 nm. (ε 15,490), τ 7·96 (6H, s), and 6·08 and 5·96 (3H singlets) (Found: C, 60·0; H, 5·5. $C_{11}H_{12}O_5$ requires C, 59·9; H, 5·4%).

1,5-*Dihydroxy*-5-*methoxycarbonyl*-2,3-*dimethyl*-4-*oxocyclopent*-2-*enecarboxylic Acid* (XXVI; R = OH).—The methoxy-quinone (XVI; R = Me) (70 mg.) in water (2 ml.) and methanol (2 ml.) was treated with aqueous sodium peroxide (50%; 0·1 ml.). After being stirred at room temperature for 2 hr. the solution was acidified and extracted with dichloromethane. Evaporation of the dried extract and crystallisation of the residue from ether gave the *diol* (XXVI; R = OH) (18·1 mg.), m.p. 160—165°, $\lambda_{max.}$ 238 nm. (ε 8300), τ 8·12, 8·05, 6·23, and 6·20 (all 3H singlets), and 5·93 (1H, exchanged by D_2O) (Found: C, 50·9; H, 5·4. $C_{11}H_{14}O_7$ requires C, 51·2; H, 5·5%).

Methyl 1,6-*Epoxy*-6-*methoxy*-3,4-*dimethyl*-2,5-*dioxocyclohex*-3-*enecarboxylate* (XXVIII).—The methoxy-quinone (XVI; R = Me) (54 mg.) in dry benzene (5 ml.) was treated with *m*-chloroperbenzoic acid (85%; 100 mg.) and stirred under nitrogen for 2 hr. at room temperature. The solvent was evaporated off and the residue was washed with ether (25 ml.). The ether solution was washed with aqueous sodium hydrogen carbonate followed by water, and dried. Evaporation and crystallisation from di-isopropyl ether gave the *epoxide* (XXVIII) (44·3 mg.), m.p. 92—94°, $\nu_{max.}$ 1762 and 1691 cm.$^{-1}$, τ 7·97 (6H, s), 6·20 (3H, s), and 6·08 (3H, s) (Found: C, 54·9; H, 5·1. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%).

Demethylation of the Dimethoxy-ester (XXIX; $R^1 = R^2 = R^3$ = Me, R^4 = H) *with Sodium Borohydride–Iodine*.[23,24]—

The dimethoxy-ester (290 mg.) in chloroform (10 ml.) was treated with sodium borohydride (200 mg.) and iodine (500 mg.). After 3 hr. at room temperature the mixture was poured into aqueous sodium hydroxide (0·1N; 10 ml.) and extracted with ether. Acidification of the aqueous basic solution and crystallisation of the precipitate from ethanol gave 2-hydroxy-6-methoxy-4-methylbenzoic acid [35] (XXIX; R^1 = Me, R^2 = R^3 = R^4 = H) (220 mg.).

2-Hydroxy-6-methoxy-3,4-dimethylbenzoic Acid (XXIX; R^1 = R^4 = Me, R^2 = R^3 = H).—The ester (XXIX; R^1 = R^2 = R^3 = R^4 = Me) (470 mg.) was treated as just described to give the *acid* (XXIX; R^1 = R^4 = Me, R^2 = R^3 = H) (370 mg.), m.p. (from benzene) 167—168°, $\nu_{max.}$ 3170 and 1690 cm.$^{-1}$, τ −2·50 (1H, s, exchanged by D_2O), 3·68 (1H, s), 5·97 (3H, s), 7·69 (3H, s), and 7·90 (3H, s) (Found: C, 60·9; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

Methylation of the Acid (XXIX; R^1 = R^4 = Me, R^3 = R^2 = H).—The acid (310 mg.) in ether was treated with ethereal diazomethane until the yellow colour persisted. The solvent was removed and the residue was crystallised from light petroleum to give the *methyl ester* (XXIX; R^4 = R^3 = R^1 = Me, R^2 = H), m.p. 78—79°, $\nu_{max.}$ 1645—1610 cm.$^{-1}$, τ −1·87 (1H, s, exchanged by D_2O), 3·73 (1H, s), 6·04 (3H, s), 6·16 (3H, s), 7·71 (3H, s), and 7·89 (3H, s) (Found: C, 62·6; H, 6·8. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%).

Methyl 3-Formyl-2-hydroxy-6-methoxy-4-methylbenzoate (XXIX; R^4 = CHO, R^1 = R^3 = Me, R^2 = H).—The aldehyde (XXIX; R^4 = CHO, R^1 = R^2 = R^3 = Me) (287 mg.) in dichloromethane (20 ml.) at −76° was treated with boron trichloride (1 ml.). After 7 min. the solution was quenched in water (100 ml.) and extracted with dichloromethane (2 × 50 ml.). Evaporation of the dried extract and crystallisation of the residue from benzene–light petroleum gave the *aldehyde* (XXIX; R^4 = CHO, R^1 = R^3 = Me, R^2 = H) (263 mg.), m.p. 137°, $\nu_{max.}$ 3400—3100, 1720, and 1640 cm.$^{-1}$, $\lambda_{max.}$ 322, 286, 238, and 206 nm. (ε 5200, 14,500, 14,400, and 10,700), τ 7·38 (3H, s), 6·07 (3H, s), 6·05 (3H, s), 3·67 (1H, s), −0·23 (1H, s), and −2·61 (1H, s, exchanged by D_2O) (Found: C, 58·9; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

Hydrogenation of the Aldehyde (XXIX; R^4 = CHO, R^1 = R^3 = Me, R^2 = H).—The aldehyde (490 mg.) in glacial acetic acid (20 ml.) was hydrogenated over 10% palladium–carbon (50 mg.) for 5 hr. The mixture was filtered and diluted with water. Crystallisation from light petroleum gave the *dimethyl derivative* (XXIX; R^4 = R^3 = R^1 = Me, R^2 = H) (370 mg., 80%), identical (m.p., mixed m.p.) with the product from treatment of (XXIX; R^1 = R^4 = Me, R^3 = R^2 = H) with diazomethane.

Acetylation of the Ester (XXIX; R^4 = CHO, R^1 = R^3 = Me, R^2 = H).—The hydroxy-aldehyde (XXIX; R^4 = CHO, R^1 = R^3 = Me, R^2 = H) (84 mg.) in dry pyridine (3 ml.) and acetic anhydride (3 ml.) was heated at 90° for 0·5 hr.; the mixture was then evaporated to dryness. The residue gave the *acetate* (XXIX; R^1 = R^3 = Me, R^2 = Ac, R^4 = CHO) (71 mg.), m.p. 162° (from benzene–light petroleum), $\nu_{max.}$ 1773, 1732, and 1694 cm.$^{-1}$, τ 7·63 (3H, s), 7·30 (3H, s), 6·06 (6H, s), 3·24 (1H, s), and −0·25 (1H, s) (Found: C, 58·3; H, 5·1. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%). The isomeric acetate (XXIX; R^2 = R^3 = Me, R^1 = Ac, R^4 = CHO) prepared from the benzisoxazole (XXX) had m.p. 106° and a different i.r. spectrum (Nujol) and a mixed m.p. was depressed.

Reaction of 2,6-Dimethoxy-4-methylbenzamide (XXXI; R^1 = R^2 = Me) *with Sodium Borohydride–Iodine.*—The amide (XXXI; R^1 = R^2 = Me) (470 mg.) gave, after being stirred in chloroform with sodium borohydride–iodine (as before) for 18 hr., the hydroxy-amide (XXXI; R^1 = Me, R^2 = H) (190 mg.), m.p. 169—171°, identical with the material prepared by methylation of 2,6-dihydroxy-4-methylbenzamide (m.p. and mixed m.p.).

Methyl 2,3,6-Trimethoxy-4,5-dimethylbenzoate (XXXII; R^1 = R^2 = R^3 = Me).—The quinone (XVI; R = H) (150 mg.) in dry benzene (2·5 ml.) was hydrogenated over 10% palladium–barium sulphate until the uptake ceased. The product gave the *hydroquinone* (XXXIV) (145 mg.), m.p. 133—134° (from benzene–light petroleum), $\nu_{max.}$ 3400 and 1675 cm.$^{-1}$, $\lambda_{max.}$ 208, 224, 265, and 355 nm. (ε 13,600, 11,200, 13,800, and 3630), τ 7·90 (3H, s), 7·70 (3H, s), 5·95 (3H, s), 5·16—4·21 (1H, exchanged by D_2O), and 1·16—0·70 (1H, exchanged by D_2O) (Found: C, 56·7; H, 5·8. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%).

The hydroquinone (XXXIV) (800 mg.) in acetone (100 ml.) was treated with methyl iodide (20 ml.) and anhydrous potassium carbonate (5 g.). The suspension was heated under reflux for 15 hr., then poured into water (100 ml.). Extraction with dichloromethane (3 × 50 ml.) and evaporation of the dried extract gave a thick oil. Chromatography of this oil over alumina (G3) [with benzene–light petroleum (1 : 1)] gave the *trimethyl ether* (XXXII; R^1 = R^2 = R^3 = Me) (740 mg.) as an oil, $\nu_{max.}$ 2950, 1734, and 1600 cm.$^{-1}$, τ 7·82 (3H, s), 7·78 (3H, s), 6·26 (3H, s), 6·19 (3H, s), 6·13 (3H, s), and 6·08 (3H, s) (Found: C, 61·6; H, 7·0. $C_{18}H_{18}O_5$ requires C, 61·4; H, 7·1%).

Reaction of Methyl 2,3,6-Trimethoxy-4,5-dimethylbenzoate (XXXII; R^1 = R^2 = R^3 = Me) *with Sodium Borohydride–Iodine.*—The ester (XXXII; R^1 = R^2 = R^3 = Me) (61 mg.) in dichloromethane (4 ml.) was treated with sodium borohydride (14 mg.). To this suspension was slowly added iodine (40 mg.) in dichloromethane (2 ml.). After 7 days at room temperature water (10 ml.) was added to the mixture, followed by 6N-hydrochloric acid (3 ml.). The dichloromethane layer was washed with a saturated aqueous solution of sodium carbonate. The basic layer was separated, neutralised, and extracted with dichloromethane. Evaporation of the dried extract gave an oily residue (24 mg.), $\nu_{max.}$ ($CHCl_3$) 3400—2600, 1700, and 1610 cm.$^{-1}$. The n.m.r. spectrum of the crude product had signals indicative of a mixture of compounds (XXXII; R^1 = R^2 = H, R^3 = Me) and (XXXII; R^3 = R^2 = H, R^1 = Me).

3-Formyl-2,6-dimethoxy-4-methylbenzoic Acid (XXIX; R^1 = R^2 = Me, R^3 = H, R^4 = CHO).—The ester (XXIX; R^1 = R^2 = R^3 = Me, R^4 = CHO) (2·108 g.) in ethanol (25 ml.) under nitrogen was treated with 4N-sodium hydroxide (1·1 ml.). The mixture was heated under reflux for 4 hr., cooled, acidified with 6N-hydrochloric acid, and extracted with chloroform (3 × 100 ml.). Evaporation of the dried extract gave the *acid* (XXIX; R^1 = R^2 = Me, R^3 = H, R^4 = CHO) (1·92 g.), m.p. (from benzene–ethyl acetate) 176—178°, $\nu_{max.}$ 3200—3000, 2700—2500, 1702, 1675, and 1606 cm.$^{-1}$, τ 7·34 (3H, s), 6·04 (3H, s), 5·99 (3H, s), 3·38 (1H, s), 0·48br (1H, s, exchanged by D_2O), and −0·43 (1H, s) (Found: C, 58·9; H, 5·4. $C_{11}H_{12}O_5$ requires C, 58·9; H. 5·4%).

3-Formyl-2,6-dimethoxy-4-methylbenzamide (XXXIII; R = Me).—The acid (XXIX; R^1 = R^2 = Me, R^3 = H, R^4 = CHO) (1·385 g.) in dry benzene (30 ml.), thionyl chloride (1·0 g.), and dimethylformamide (0·5 ml.) was

heated under reflux for 2·75 hr. The solution was cooled to room temperature, poured into ammonia (*d* 0·880; 100 ml.), and stirred vigorously for 15 min. The benzene layer was separated, dried, and evaporated to give the *amide* (XXXIII; R = Me) (1·04 g.), m.p. (from chloroform) 242—244°, $\nu_{max.}$ 3420, 3200, 1690, 1668, and 1608 cm.$^{-1}$, τ 7·42 (3H, s), 6·11 (3H, s), 6·08 (3H, s), 3·26 (1H, s), 2·64br (1H, s), 2·40br (1H, s), and −0·30 (1H, s) (Found: C, 59·3; H, 6·0; N, 6·1. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·9; N, 6·3%).

3-*Formyl*-2-*hydroxy*-6-*methoxy*-4-*methylbenzamide* (XXXIII; R = H).—The amide (XXXIII; R = Me) (78 mg.) in dichloromethane (10 ml.) at −76° was treated with boron trichloride (10 drops). After 5 min. at −76° the solution was poured on ice. The dichloromethane layer was separated, dried, and evaporated to give the *amide* (XXXIII; R = H) (61 mg.), m.p. (from dimethyl sulphoxide) 255—257°, $\nu_{max.}$ 3370, 3200, 1660, and 1608 cm.$^{-1}$, τ 7·52 (3H, s), 6·07 (3H, s), 3·53 (1H, s), 1·88br (2H, s), −0·37 (1H, s), and −5·53 (1H, s, exchanged by D_2O) (Found: C, 57·2; H, 5·3; N, 6·4. $C_{10}H_{11}NO_4$ requires C, 57·4; H, 5·3; N, 6·7%).

2-*Hydroxy*-6-*methoxy*-4-*methylbenzamide* (XXXI; R^1 = Me, R^2 = H).—2,6-Dihydroxy-4-methylbenzamide (1·0 g.) in dry acetone (100 ml.) and methyl iodide (5 ml.) was heated with anhydrous potassium carbonate (4 g.) under reflux for 2·75 hr. Work up in the usual way gave the *methyl ether* (XXXI; R^1 = Me, R^2 = H) (0·948 g.), m.p. (from benzene) 169—171°, $\nu_{max.}$ 3410, 3300, 3190, 1645, 1624, and 1586 cm.$^{-1}$, τ 7·57 (3H, s), 6·04 (3H, s), 3·70 (1H, s), 3·50 (1H, s), 2·25br (1H, s), 1·90br (1H, s), and −3·88 (1H, s, exchanged by D_2O) (Found: C, 59·7; H, 6·3; N, 7·6. $C_9H_{11}NO_3$ requires C, 59·7; H, 6·1; N, 7·7%).

Formylation of 2-*Hydroxy*-6-*methoxy*-4-*methylbenzamide* (XXXI; R^1 = Me, R^2 = H).—The hydroxy-amide (218 mg.) in dry dichloromethane (30 ml.) and dichloromethyl methyl ether (1·0 ml.) was treated with aluminium trichloride (700 mg.) at 0°. The mixture was stirred at room temperature for 1 hr., then poured into water (100 ml.). Evaporation of the dried dichloromethane layer gave the aldehyde (XXXIII; R = H) (194 mg.), identical (Nujol i.r. spectrum, m.p., and mixed m.p.) with the material prepared by demethylation.

Attempted Demethylation of the Trimethyl Ether (XXXII; R^1 = R^2 = R^3 = Me).—The trimethyl ether (70 mg.) in dry dichloromethane (20 ml.) was cooled to −76° and boron trichloride (1 ml.) was added. No reaction occurred. Upon warming to room temperature and work-up in the usual way the phenol (XXXVI) was isolated in 40% yield.

Methyl 3-*Formyl*-2,5,6-*trimethoxy*-4-*methylbenzoate* (XIX; R = Me).—The trihydroxy-aldehyde (XIX; R = H) (1·67 g.) in acetone (100 ml.) was heated with dimethyl sulphate (3·5 g.) and potassium carbonate (3·8 g.) under reflux for 4·5 hr. and then poured into water (200 ml.). Extraction with chloroform, and evaporation of the dried extract gave a yellow oil. Chromatography of this oil on alumina (with benzene) gave the *trimethyl ether* (XIX; R = Me) (1·52 g.), as an oil, $\nu_{max.}$ 1731 and 1686 cm.$^{-1}$, $\lambda_{max.}$ 227, 268, and 313 nm. (ε 16,000, 8740, and 2390), τ 7·34, 6·20, and 6·08 (all 3H singlets), 6·00 (6H, s), and −0·40 (1H, s) (Found: C, 58·3; H, 6·2. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

Monodemethylation of Methyl 3-*Formyl*-2,5,6-*trimethoxy*-4-*methylbenzoate* (XIX; R = Me).—The aldehyde (702 mg.) in dichloromethane (15 ml.) at −80° was treated with boron trichloride (2 ml.). After 6 min. the mixture was quenched in water (25 ml.). The dichloromethane layer was separated and dried. Evaporation, and crystallisation of the residue from benzene–light petroleum, gave *methyl* 3-*formyl*-2-*hydroxy*-5,6-*dimethoxy*-4-*methylbenzoate* (XXXVII) (507 mg.), m.p. 93—95°, $\nu_{max.}$ 1723 and 1663 cm.$^{-1}$, $\lambda_{max.}$ 240, 277, and 345 nm. (ε 17,500, 7500, and 3520), τ 7·43, 6·19, 6·13, and 5·95 (all 3H singlets), −0·40 (1H, s), and −1·90 (1H, exchanged by D_2O) (Found: 56·5; H, 5·4. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·6%).

Methyl 2-*Hydroxy*-3,6-*dimethoxy*-4,5-*dimethylbenzoate* (XXXVIII).—The aldehyde (XXXVII) (266 mg.) in glacial acetic acid (100 ml.) was hydrogenated over pre-reduced 10% palladium–charcoal (50 mg.) until hydrogen absorption ceased. The product gave the *dimethylphenol* (XXXVIII) (186 mg.), m.p. 89° (from light petroleum), $\nu_{max.}$ 1660 cm.$^{-1}$, $\lambda_{max.}$ 256 and 327 nm. (ε 6010 and 1130), τ 7·88, 7·79, 6·34, 6·23, and 6·04 (all 3H singlets), and −1·03 (1H, exchanged by D_2O) (Found: C, 60·0; H, 6·5. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

Reaction of Methyl 2,3,6-*Trihydroxy*-4,5-*dimethylbenzoate* (XXXIV) *with Phosgene*.—The phenol (XXXIV) (1 g.) in toluene (30 ml.) at 0° and dry pyridine (5 ml.) was treated under nitrogen with phosgene in toluene (5%; 10 ml.). After 10 min. the mixture was poured into ice-cold hydrochloric acid (N; 25 ml.). The toluene layer was separated and the aqueous phase was extracted with ether (2 × 100 ml.). The combined extracts were dried and evaporated to yield the *carbonate* (XXXIX; R = H) (665 mg.), m.p. (from benzene) 167—168°, $\nu_{max.}$ 3180, 1836, and 1681 cm.$^{-1}$, $\lambda_{max.}$ 247 and 327 nm. (ε 9970 and 3760), τ 7·80, 7·65, and 5·95 (all 3H singlets) (Found: C, 55·5; H, 4·2. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%).

Benzoylation of the Carbonate (XXXIX; R = H).—The carbonate (1·27 g.) in pyridine (15 ml.) was treated with benzoyl chloride (800 mg.). After 2·5 hr. at room temperature the solution was poured into dilute hydrochloric acid (50 ml.). The product was filtered off and dried. Crystallisation from benzene–light petroleum gave the *benzoate* (XXXIX; R = Bz) (1·40 g.), m.p. 127—128°, $\nu_{max.}$ 1844, 1829, 1733, and 1720 cm.$^{-1}$, τ 7·81, 7·61, and 6·22 (all 3H singlets), 2·56 (3H, m), and 1·78 (2H, m) (Found: C, 63·0; H, 4·2. $C_{18}H_{14}O_7$ requires C, 63·2; H, 4·1%).

Methyl 2-*Benzoyloxy*-5,6-*dimethoxy*-3,4-*dimethylbenzoate* (XXXII; R^1 = R^2 = Me, R^3 = Bz).—The carbonate (XXXIX; R = Bz) (500 mg.) in tetrahydrofuran (50 ml.) and dilute hydrochloric acid (N; 50 ml.) was heated at 90° for 10 min. Water (50 ml.) was added and the mixture was extracted with dichloromethane. Evaporation of the dried extract and crystallisation from benzene–light petroleum gave the *diester* (345 mg.), m.p. 190—192°, $\nu_{max.}$ 3420, 1713, and 1672 cm.$^{-1}$, $\lambda_{max.}$ 227, 260, and 331 nm. (ε 31,700, 11,200, and 3840), τ 7·94, 7·73, and 6·39 (3H, singlets), 5·00 (1H, exchanged by D_2O), 2·75 (3H, m), 1·7 (2H, m), and −1·27 (1H, exchanged by D_2O) (Found: C, 64·5; H, 5·0. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%).

This catechol (317 mg.) in acetone (30 ml.) and dimethyl sulphate (320 mg.) was heated under reflux with potassium carbonate (800 mg.) for 2 hr. The mixture was poured into water (100 ml.) and extracted with dichloromethane. Evaporation of the dried extract and crystallisation of the residue from light petroleum gave the *dimethyl ether* (XXXII; R^1 = R^2 = Me, R^3 = Bz) (300 mg.), m.p. 92—93°, $\nu_{max.}$ 1740 cm.$^{-1}$, $\lambda_{max.}$ 230 and 275 nm. (ε 19,000 and 2310), τ 7·94, 7·76, 6·33, 6·19, and 6·10 (3H singlets),

2·80 (3H, m), and 1·72 (2H, m) (Found: C, 66·4; H, 5·9. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·9%).

Methyl 2-Hydroxy-5,6-dimethoxy-3,4-dimethylbenzoate (XXXVI).—Sodium (300 mg.) in dry methanol (10 ml.) was added to the benzoate (XXXII; $R^1 = R^2 = Me$, $R^3 =$ Bz) (300 mg.) in methanol (25 ml.). After 5 min. at room temperature the mixture was poured into water, acidified, and extracted with dichloromethane. Evaporation of the dried extract gave the *phenol* (XXXVI) (190 mg.), m.p. 38°, $\nu_{max.}$ 1662 cm.$^{-1}$, $\lambda_{max.}$ 255 and 327 nm. (ε 10,200 and 3920), τ 7·87, 7·78, 6·26, 6·17, and 6·03 (3H singlets) and −1·30 (1H, exchanged by D_2O) (Found: C, 60·0; H, 6·6. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%).

Oxidation of the Phenol (XXIX; $R^1 = R^3 = R^4 = Me$, $R^2 = H$) *with Lead Tetra-acetate*.—The phenol (50 mg.) in methanol (10 ml.) was stirred with lead tetra-acetate (200 mg.) and boron trifluoride–ether (0·25 ml.) at room temperature for 15 min. The mixture was quenched in water (20 ml.) and extracted with dichloromethane. Evaporation of the dried extract and crystallisation of the residue from benzene–light petroleum gave the *acetate* (XL) (25·5 mg.), m.p. 180—186°, $\nu_{max.}$ 1733 and 1660 cm.$^{-1}$, $\lambda_{max.}$ 224 and 324 nm. (ε 9940 and 4410), τ 8·55, 8·10, 7·92, 6·12, and 6·08 (3H singlets) and 3·80 (1H, m) (Found: C, 58·3; H, 6·0. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

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