Experiments on the Synthesis of Tetracycline. Part II.[1] The Synthesis of Potential Ring A and Ring C–Ring D Components

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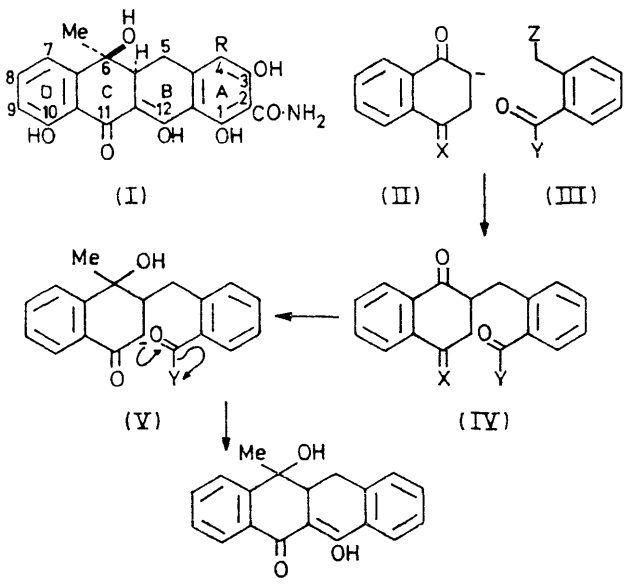
The preparation of 3,4-dihydro-2-phenylnaphtho[1,8-*bc*]furan-5-one and methyl 6-acetoxy-4-diacetoxymethylbenzisoxazole-7-carboxylate, as precursors of the CD ring system and of ring A, respectively, is described. Their condensation to a tricyclic ACD compound and subsequent attempts to transform this into 4-de(dimethylamino)-4a,12a-anhydrotetracycline are presented.

THE reasons for our choice of the tetracyclic molecule (I; R = H or NMe_2) as a synthetic objective have been elaborated in Part I.[1] To these reasons may be added the availability of compounds (I; R = H)[2-4] and (I; R = NMe_2) from degradation of tetracycline.

We hoped that the coupling of a preformed ring A unit, bearing two one-carbon substituents in an *ortho*-relationship, with a CD entity would prove to be a convenient method of synthesis. Thus, the formation of a bond between the ketonic CD precursor (II) and the ring A system (III) should provide a tricyclic compound (IV). The ketonic function in ring C could then be transformed into a carbinol [structure (V)]. Finally, exposure of the masked keto-group in ring C would yield a system of ketone and ester (or their equivalents) conveniently situated for an anionic type cyclisation to the required β-dicarbonyl residue in structure (VI). Having decided upon the outline of this general approach, we then attempted to prepare the two units, correctly substituted as dictated by structure (I).

Preliminary experiments, designed to produce the phenolic ketone (VII) by condensation of 1,5-dihydroxynaphthalene with benzoic acid under catalysis by zinc chloride, yielded only small amounts of this material, along with a new compound shown to be the *peri*-naphthofuran (VIII). [The olefinic protons gave rise to an AB quartet (J 10 Hz) in the n.m.r. spectrum.] Modifications of the reaction conditions increased the yield of the naphthofuran (VIII) to 40%. This protected juglone was hydrogenated (Raney nickel) to give the dihydro-derivative (IX; X = O) [$\nu_{max.}$ 1686 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 275 and 360 nm., n.m.r. spectrum showing



an A_2B_2 multiplet (J_{AB} 6·8 Hz) for the 3- and 4-protons], containing all the structural features required for the CD precursor. It is an α-tetralone unit bearing a

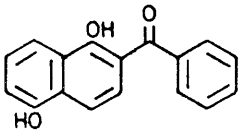
[1] Part I, D. H. R. Barton and P. D. Magnus, preceding paper.

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

[3] A. Green and J. H. Boothe, *J. Amer. Chem. Soc.*, 1960, **82**, 3950.

[4] R. K. Blackwood, H. H. Rennhard, and C. R. Stephens, *J. Amer. Chem. Soc.*, 1960, **82**, 5194.

potential C(11) carbonyl function, which could be revealed by oxidative cleavage of the furan double bond, unmasking at the same time the C(10) oxygen function. To test the use of this material (IX; X = O) in the preparation of the tricyclic ACD structure, it was treated with benzaldehyde in refluxing ethanolic triethylamine. The ketol (X; R = OH), was isolated, and dehydrated to the enone (XI) with toluene-*p*-sulphonyl chloride in



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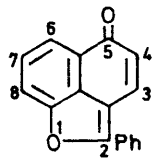

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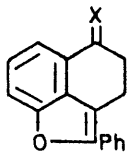

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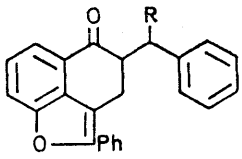

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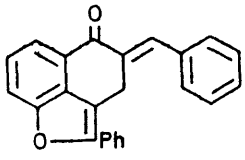

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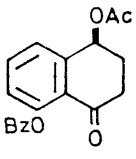

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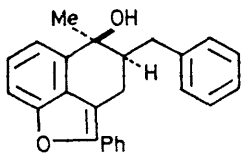

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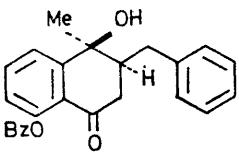

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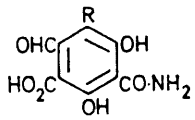

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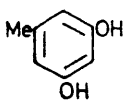

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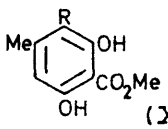


(XVII)

pyridine. The assignment of the illustrated geometry to the groups situated about the enone double bond will be discussed later.

This condensation reaction was simplified by using sulphuric acid in acetic acid [5] to yield directly the enone (XI) in high yield, $\nu_{max.}$ 1665 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 300 and 385 nm., τ 5·57 (d, J 2·5 Hz, 3-H_2). It is of interest that the stereochemistry of the Claisen–Schmidt condensation [6] is such that the product has the carbonyl function *trans* to the larger group at the β-carbon atom. Reduction of the enone (XI) with Raney nickel gave the dihydro-ketone (X; R = H), $\nu_{max.}$ 1681 cm.$^{-1}$, $\lambda_{max.}$ 275 and 355 nm.

Having investigated the potential of (IX; X = O) as a CD precursor we then studied the cleavage of the furan double bond. Ozonolysis of the ketone (VIII) did not yield any tractable product. However, reduction to the alcohol and acetylation gave the ester (IX; X = H,OAc), which was readily ozonised to the keto-benzoate (XII). A reductive work-up of the ozonide was mandatory.

The last relevant aspect of the potential CD unit was investigated by treatment of the ketone (IX; X = O) with methylmagnesium iodide to furnish the tertiary alcohol (IX; X = OH,Me). Similarly, treatment of the model compound (X; R = H) with methylmagnesium iodide gave the carbinol (XIII). Its subsequent cleavage by ozone afforded the keto-benzoate (XIV). Compound (XIII) was formed stereospecifically; it is, therefore, assigned the configuration formed by approach of the methyl carbanion from the less hindered side of the molecule (*trans* to the benzyl group). By these means each of the separate functions required of a CD precursor was successfully tested.

Structure (I) suggested that, in keeping with the projected coupling, the ring A precursor should be of the general form (XV; R = H or NMe_2), or a suitably masked equivalent. Steps to produce such a compound were as follows. Commercially available orcinol (XVI) was carboxylated,[7] and the *p*-orsellinic acid produced was protected from decarboxylation by methylation with potassium hydrogen carbonate–dimethyl sulphate, providing the known ester (XVII; R = H).[8]

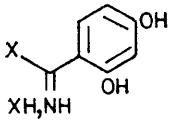
When methyl *p*-orsellinate was stirred with ammonia (*d* 0·880) overnight and the solution was then acidified, large needles of the amide separated (80%). The insolubility of this product militated against formation of the amide function at this stage. Not wishing to carry such a manipulative problem through the synthesis, we left the introduction of this function until later.

Since the initial intention was to produce structure (XV; R = NMe_2), we next considered the introduction of a nitrogen function into the orsellinic ester (XVII; R = H). Although the mononitro-derivative (XVII; R = NO_2) could be produced by direct nitration, failure to oxidise the methyl group in the diacetate (XIX; R^1 = NO_2, R^2 = OMe, R^3 = Ac) to an aldehyde function under Thiele conditions, and also in reactions making use of the labilisation of benzylic hydrogen atoms by *o*-nitro-groups, led us to abandon this sequence.

As an alternative the attachment of the potential C-12 of (I; R = H) to the ring A precursor was studied. The nitrile function represents a suitable equivalent of a carboxy-group; accordingly we examined its direct introduction into structure (XVII; R = H). Karrer [9] showed that treatment of resorcinol with cyanogen bromide catalysed by zinc chloride gave a complex

[5] V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, 1958, **23**, 789.
[6] H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Amer. Chem. Soc.*, 1959, **81**, 108; H. E. Zimmerman and L. Abramjian, *ibid.*, 1959, **81**, 2086; 1960, **82**, 5459.
[7] A. Robertson and R. Robinson, *J. Chem. Soc.*, 1927, 2199.
[8] P. R. Saraiya and R. C. Shah, *Current Sci.*, 1949, **18**, 218.
[9] P. Karrer, *Helv. Chim. Acta*, 1919, **2**, 89.

(XVIII; X = halogen). We anticipated that treatment of this with base should result in elimination to give the nitrile. Indeed, repetition of Karrer's experiment and subsequent treatment of the complex with collidine gave the desired β-resorcylonitrile.[10] The poor yield in the first step rendered this an inefficient procedure. The classical Gattermann reaction [11,12] provided, however, excellent yields of the formyl derivative (XIX; R^1 = CHO, R^2 = OMe, R^3 = H), $\nu_{max.}$ 1667 and 1640 cm.$^{-1}$. Conversion into the nitrile was accomplished through the oxime (XIX; R^1 = CH:N·OH, R^2 = OMe, R^3 = H), which with acetic anhydride at 95° gave an oxime *O*-acetate, which was pyrolysed at 180° to give the desired nitrile (XIX; R^1 = CN, R^2 = OMe, R^3 = H). When the pyrolysis was conducted at a lower temperature (refluxing xylene), or in acetic anhydride, an isomeric substance, $\nu_{max.}$ 1667 and 1640 cm.$^{-1}$, τ −1·63 (1H, exchanged by D_2O), 1·37 (1H), 3·22 (1H), 5·92 (3H, s), and 7·46 (3H, s) was obtained. This was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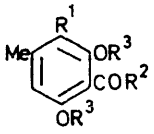
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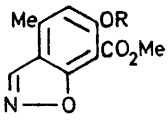
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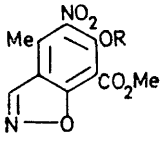
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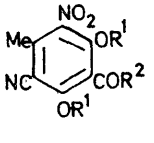
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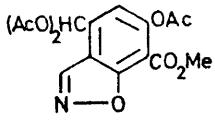
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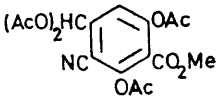
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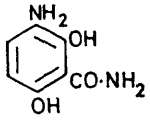
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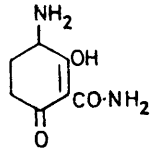
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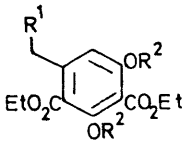
(XXVII)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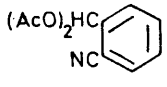

(XXIX)

readily converted with mild base (aqueous ammonia) into the carbamoylnitrile (XIX; R^1 = CN, R^2 = NH_2, R^3 = H). The isomeric substance must be formulated as the isoxazole (XX; R = H). Its formation provides a convenient method of masking a potential carboxy-function.

Mononitration of the isoxazole (XX; R = H) gave the nitroisoxazole (XXI; R = H) in excellent yield. Acetylation in acidic media gave the monoacetate (XXI; R = Ac), whereas under basic conditions the diacetate (XXII; R^1 = Ac, R^2 = OMe) was formed, with concomitant opening of the isoxazole ring. However, attempted oxidation of the methyl group to an aldehyde function in compounds (XXI; R = Ac), (XXII; R^1 = Ac, R^2 = OMe), and the corresponding dimethyl ether (XXII; R^1 = Me, R^2 = OMe) was without success. Reagents which had been reported to work with less substituted nitro-toluenes, *e.g.* *p*-dimethylaminonitrosobenzene [13] and benzaldehyde in the presence of base, and also the Thiele oxidation procedure,[14,15] all, in our hands, yielded no useful results. It appears likely that in hexasubstituted benzenes such as (XXII), steric inhibition of resonance destroys the normal activating effect of the nitro-function on an adjacent methyl group. Such a phenomenon is well known.[16]

Having thus been frustrated in obtaining a suitable hexasubstituted ring A we decided to modify our objective to the 4-de(dimethylamino)-4a,12a-anhydrotetracycline (I; R = H), since the ring A scheme just described did in fact yield a suitable precursor, the benzisoxazole (XX; R = H). Oxidation of the corresponding acetate (XX; R = Ac), $\nu_{max.}$ 1770 and 1739 cm.$^{-1}$, by the Thiele method proceeded in workable yield (30%), to give the diacetoxymethyl derivative (XXIII), $\nu_{max.}$ 1770 and 1739 cm.$^{-1}$. The latter was readily transformed, under basic acetylation conditions, into the nitrile (XXIV). At this stage the construction of a possible ring A precursor was complete.

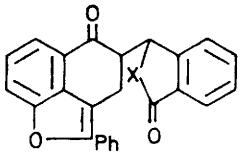
Before we discuss the condensation reaction as such, it is informative to consider briefly two related pieces of work on the ring A series. First, after consideration of the steps required to pass from structure (I; R = NMe_2) back to tetracycline, we felt initially that the aminoresorcinol unit on ring A might be especially sensitive to dihydroreduction, a prediction confirmed by the observation of Tomino [17] that the simple monocyclic model (XXV) was catalytically reduced at pH 7·6, to the cyclohexane-1,3-dione (XXVI), with a functionality characteristic of the tetracyclines. Although we could not reduce the ring A precursor (XIX; R^1 = CN, R^2 = NH_2, R^3 = H) under Tomino's conditions, the possibility that a dimethylamino-group might assist the reduction could not be discounted. Accordingly, the substance (XXVII) was prepared from the nitroamide (XXII, R^1 = H, R^2 = NH_2) by catalytic reduc-

[10] E. Marcus, *Ber.*, 1891, **24**, 3651.
[11] R. Adams and I. Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2373.
[12] W. B. Whalley, *J. Chem. Soc.*, 1949, 3278.
[13] I. Tanasescu and I. Nanu, *Ber.*, 1939, **72**, 1083.
[14] J. Thiele and E. Winter, *Annalen*, 1900, **311**, 353.
[15] E. M. Bavin, R. J. W. Rees, J. M. Robson, M. Seiler, D. E. Seymour, and D. Suddaby, *J. Pharm. Pharmacol.*, 1950, **2**, 764.
[16] R. J. W. Le Fevre, *J. Chem. Soc.*, 1933, 977.
[17] K. Tomino, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 648.

tion and methylation.[18] No uptake was observed when this compound was treated with hydrogen.

The literature records two readily accessible compounds which bear most of the structural requirements of the desired ring A; we therefore examined their potential use in our synthetic scheme. These compounds are the base-catalysed self-condensation product (XXVIII; $R^1 = CO_2Et$, $R^2 = H$)[19] of acetonedicarboxylic ester, and the similar product from acetoacetic ester and acetonedicarboxylic ester (XXVIII; $R^1 = H$, $R^2 = H$).[20] Attempts to oxidise the corresponding diacetates (XXVIII; $R^1 = CO_2Et$, $R^2 =$ Ac, and $R^1 = H$, R = Ac), to the aldehyde (XXVIII; $CH_2R^1 \equiv CHO$, $R^2 = H$), under Thiele conditions and also with selenium dioxide were unsuccessful, and so this alternative pathway to ring A was set aside.

At this point we were able to tackle the third stage of the projected synthesis, the condensation of ring A with the CD entity. As noted above, the acid-catalysed Cromwell conditions[5] were satisfactory in the simple benzaldehyde case. However, the presence of an *o*-nitrile function in the more complex example (XXIX) led to a predictable complication. Thus treatment of the dihydronaphthofuran (IX; X = O) with *o*-cyanobenzaldehyde diacetate (XXIX), under the usual conditions of acid catalysis gave the phthalide (XXX; X = O) as a result of intramolecular trapping of the intermediate ketol. Phthalide formation was also accompanied by an impaired yield in the condensation. The use of basic catalysis with the free aldehyde from the diacetate (XXIX) was no better, insofar as the lactam (XXX; X = NH) was isolated. For these



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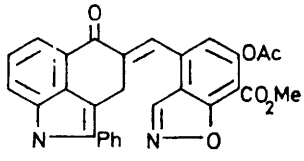

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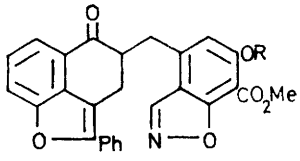

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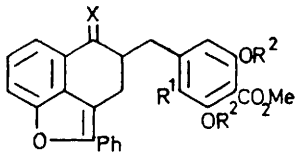

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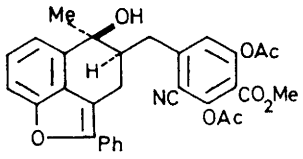

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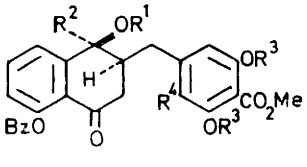

(XXXV)

reasons we turned to the benzisoxazole (XXIII) and were able to effect the acid-catalysed condensation in *ca.* 50% yield to provide the ACD precursor (XXXI), $\lambda_{max.}$ 307 and 405 nm., $\nu_{max.}$ 1760, 1740, and 1670 cm.$^{-1}$, probably with *trans* geometry. Although this substance resisted hydrogenation conditions (Raney nickel) previously employed for the simple benzylidene model (XI), and although more vigorous catalysts attacked the isoxazole first, the double bond was readily reduced with dry hydrogen iodide in acetic acid, thereby providing the substance (XXXII; R = Ac), $\lambda_{max.}$ 265 and 355 nm., $\nu_{max.}$ 1780, 1730, and 1686 cm.$^{-1}$. The use of dry hydrogen iodide as a specific reductant deserves further investigation. The isoxazole (XXXII; R = Ac) was, as expected from previous experience, transformed in pyridine with acetic anhydride into the nitrile (XXXIII; $R^1 = CN$, $R^1 = Ac$, X = O). Since we had shown that ring A in this compound was only deacetylated by methylmagnesium iodide we proceeded to the Grignard reaction of compound (XXXIII; $R^1 = CN$, $R^2 = Ac$, X = O) and were able to isolate, after reacetylation, the required carbinol (XXXIII; $R^1 = CN$, $R^2 = Ac$, X = Me,OH), $\lambda_{max.}$ 305 and 320 nm., $\nu_{max.}$ 3450, 2235, 1770, and 1735 cm.$^{-1}$. Although no definitive stereochemical evidence is available the same argument that was used for structure (XIII) is applicable here. The tricyclic carbinol may be written as in (XXXIV).

Having thoroughly demonstrated the use of ozone for cleavage of the furanoid ring system in the simple models (see before), we treated the tricyclic product (XXXIV) with ozone, and subjected the product (XXXV; $R^1 = H$, $R^2 = Me$, $R^3 = Ac$, $R^4 = CN$) to basic cyclisation conditions (sodium hydride, potassium t-butoxide, sodium triphenylmethanide, and lithium di-isopropylamide). There was no indication of the desired cyclisation (u.v. spectroscopy). Since, however, we could not condense benzonitrile with cyclohexanone under similar conditions, we felt that the difficulty lay in the relative inertness of the cyano-group.

Treatment of the benzisoxazole (XXXII; R = H) with hydrogen over palladium–carbon gave, after hydrolytic work-up, the aldehyde (XXXIII; $R^1 =$ CHO, $R^2 = H$, X = O), $\nu_{max.}$ 1667 and 1635 cm.$^{-1}$. Acetylation gave a diacetate (XXXIII; $R^1 =$ CHO, $R^2 =$ Ac, X = O), $\nu_{max.}$ 1780, 1740, 1710, and 1690 cm.$^{-1}$. Subsequent oxidation with chromic acid, and treatment of the resulting acid with diazomethane, afforded the diester (XXXIII; $R^1 = CO_2Me$, $R^2 =$ Ac, X = O), $\nu_{max.}$ 1780, 1740, and 1690 cm.$^{-1}$. Reduction with potassium borohydride and acetylation of the crude product gave the compound (XXXIII; $R^1 = CO_2Me$, $R^2 =$ Ac, X = H,OAc). Ozonolysis provided compound (XXXV; $R^1 =$ Ac, $R^2 = H$, $R^3 =$ Ac, $R^4 = CO_2Me$). This compound could not be cyclised with sodium hydride under conditions in which cyclohexanone readily condensed with methyl benzoate. No hydrogen evolution could be detected. It is possible that the improved anion cyclisation conditions developed

[18] R. Baltzly, *J. Amer. Chem. Soc.*, 1953, **75**, 6038.
[19] W. Theilacker and W. Schmid, *Annalen*, 1950, **570**, 15.
[20] G. Koller and E. Krakauer, *Monatsh.*, 1929, **53**, 931.

by Muxfeldt [21] after our work had been completed would be successful. We have not had occasion to repeat our work.

In view of these difficulties we decided to abandon the attempt to induce closure of ring B by a Dieckmann-type reaction, as elaborated above.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. Unless otherwise specified, u.v. spectra were measured for solutions in ethanol and i.r. spectra for Nujol mulls. N.m.r. spectra were taken for solutions in deuteriochloroform at 20°, with tetramethylsilane as internal standard. Light petroleum refers to the fraction of b.p. 40—60° unless stated to the contrary.

2-Phenylnaphtho[1,8-bc]*furan-5-one* (VIII).—To a rapidly stirred mixture of 1,5-dihydroxynaphthalene (20 g.) and benzoic acid (30 g.) at 150° was added finely divided zinc chloride (17 g.) during 5 min. Stirring was continued for 1 hr., at 150°, then the mixture was poured into saturated sodium hydrogen carbonate solution (500 ml.) and stirred for 1 hr. The solid product was dried and powdered, and then stirred for 2 hr. with 5% sodium hydroxide solution; the solid residue was dried and extracted (Soxhlet) with benzene. When the extracts were colourless, the benzene solution was boiled with charcoal (2 g.) and evaporated to dryness. The product formed orange needles of the *naphthofuran* (VIII) (38%), m.p. 137—137·5° (from ethanol), $\nu_{max.}$ 1645 cm.$^{-1}$, $\lambda_{max.}$ 265 and 395 nm. (ε 16,000 and 31,500), τ 2·10 and 3·35 (ABq, J_{AB} 10 Hz) (Found: C, 82·7; H, 4·1. $C_{17}H_{10}O_2$ requires C, 82·9; H, 4·1%).

3,4-Dihydro-2-phenylnaphtho[1,8-bc]*furan-5-one* (IX; X = O).—The naphthofuran (VIII) (2·2 g.) in dry benzene (120 ml.) was hydrogenated over alcohol-free W-2 Raney nickel at room temperature and atmospheric pressure. After 1·5 hr. (uptake 174 ml.) the solvent was removed and the residue chromatographed in benzene on G-3 alumina. Evaporation of the first fractions and addition of methanol gave large pale yellow laths of the *dihydronaphthofuran* (IX; X = O) (1·5 g.), m.p. 113—114°, $\nu_{max.}$ 1686 cm.$^{-1}$, $\lambda_{max.}$ 275 and 360 nm. (ε 22,500 and 14,800), τ 6·58 and 7·07 (4H, A_2B_2m, J_{AB} 6·8 Hz) (Found: C, 82·6; H, 5·2. $C_{17}H_{12}O_2$ requires C, 82·85; H, 4·85%).

3,4-Dihydro-4-(α-hydroxybenzyl)-2-phenylnaphtho[1,8-bc]*furan-5-one* (X; R = OH).—The dihydro-compound (IX; X = O) (1·17 g.), benzaldehyde (600 mg.), and triethylamine (6 drops) in ethanol (30 ml.) were refluxed for 14 hr. Removal of the solvent (reduced pressure) and crystallisation of the product from benzene–light petroleum (b.p. 60—80°) gave the *ketol* (X; R = OH) as orange needles, m.p. 158—159°, $\nu_{max.}$ 3490 and 1686 cm.$^{-1}$, $\lambda_{max.}$ 275 and 360 nm. (ε 23,000 and 13,800) (Found: C, 81·3; H, 5·25. $C_{24}H_{18}O_3$ requires C, 81·3; H, 5·1%).

Dehydration of the Ketol (X; R = OH).—The alcohol (X; R = OH) (35 mg.) and toluene-*p*-sulphonyl chloride (17 mg.) were kept in pyridine (1·0 ml.) for 12 hr. Acidification with 4N-hydrochloric acid gave *4-benzylidene-3,4-dihydro-2-phenylnaphtho*[1,8-bc]*furan-5-one* (XI) (25 mg.), m.p. 189—190° (from benzene), $\nu_{max.}$ 1665 cm.$^{-1}$, $\lambda_{max.}$ 300 and 385 nm. (ε 33,000 and 9100), τ 5·57 [2H, C(3)H_2, J 2·5 Hz (allylic coupling)] (Found: C, 85·5; H, 4·8. $C_{24}H_{16}O_2$ requires C, 85·7; H, 4·8%).

The same product was obtained by direct condensation as follows. The dihydro-compound (IX; X = O) (160 mg.) and benzaldehyde (0·1 ml.) in glacial acetic acid (1 ml.) were treated with conc. sulphuric acid (0·08 ml.). After 18 hr. at room temperature the product was filtered off and recrystallised from benzene (yield 170 mg.).

4-Benzyl-3,4-dihydro-2-phenylnaphtho[1,8-bc]*furan-5-one* (X; R = H).—The benzylidene derivative (XI) (1·65 g.) was reduced in benzene over Raney nickel. After absorption of 1 mol. of hydrogen the *dihydro-compound* (X; R = H) (1·17 g.) was isolated; m.p. 126—127° (from methanol), $\nu_{max.}$ ($CHCl_3$) 1681 cm.$^{-1}$, $\lambda_{max.}$ 275 and 355 nm. (ε 17,000 and 10,700), τ 2·2—2·9 (13H, aromatic) and 5·7—7·5 (5H) (Found: C, 85·4; H, 5·3. $C_{24}H_{18}O_2$ requires C, 85·2; H, 5·4%).

3,4-Dihydro-2-phenylnaphtho[1,8-bc]*furan-5-ol* (IX; X = H,OH).—The dihydro-compound (IX; X = O) (240 mg.) in ethanol (50 ml.) was hydrogenated over palladium–charcoal (5%). After uptake of 1 mol. of hydrogen the catalyst was filtered off and the ethanolic solution was concentrated. Dilution with water gave cream needles of the *alcohol* (IX; X = H,OH) (200 mg.), m.p. 135·5—136°, $\nu_{max.}$ 3560, 3400, 1631, and 1607 cm.$^{-1}$, τ 6·90 (2H), 7·88 (2H), 4·99 (1H), and 7·77 (1H, exchanged by D_2O) (Found: C, 81·7; H, 5·9. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·7%). The same product was obtained by reduction with sodium borohydride.

3,4-Dihydro-2-phenylnaphtho[1,8-bc]*furan-5-yl Acetate* (IX; X = H,OAc) (with D. L. J. Clive).—Acetic anhydride (10 ml.) was added to the alcohol (IX; X = H,OH) (963 mg.) in dry pyridine (10 ml.). The mixture was stirred at room temperature for 3·7 hr. and evaporated below 40°, and the residue was chromatographed over silica gel (2 × 14 cm.) in benzene–chloroform. The product gave the *acetate* (IX; X = H,OAc) (898 mg.), m.p. 89—91·5° (from light petroleum), $\nu_{max.}$ 1723 cm.$^{-1}$, τ 2·1—2·95 (8H), 3·8 (1H, t, J 4·5 Hz), 6·85 (2H), 7·75 (2H), and 7·93 (3H, Ac) (Found: C, 78·05; H, 5·5. $C_{19}H_{16}O_3$ requires C, 78·05; H, 5·5%).

4-Acetoxy-8-benzoyloxy-3,4-dihydronaphthalen-1(2H)*-one* (XII) (with D. L. J. Clive).—The acetate (IX; X = H,OAc) (398 mg.) in dry chloroform (60 ml.; stabilised with methanol) and dry methanol (75 ml.) was ozonised at −80° for *ca.* 15 hr. The mixture was warmed to −30°, excess of ozone was removed with a stream of nitrogen, and a cold solution (−30°) of triphenylphosphine (1 g.) in chloroform was added dropwise. After 30 min. at *ca.* −30° the solution was evaporated below 30° and the residue was chromatographed on silica gel (2 × 15 cm.) in benzene–chloroform to obtain the *keto-benzoate* (XII) (238 mg.), m.p. 124—128° (from ethanol), $\nu_{max.}$ 1737 and 1679 cm.$^{-1}$, τ 1·7—2·99 (8H), 3·87 (1H, t, J 5 Hz), 7·4 (2H), 7·7 (2H), and 7·92 (3H, Ac), $\lambda_{max.}$ 233 and 286 nm. (ε 22,760 and 2763) (Found: C, 70·6; H, 4·9. $C_{19}H_{16}O_5$ requires C, 70·35; H, 4·95%).

3,4-Dihydro-5-methyl-2-phenylnaphtho[1,8-bc]*furan-5-ol* (IX; X = Me,OH).—The dihydro-compound (IX; X = O) (1·1 g.) in ether (50 ml.) was added dropwise with stirring to methylmagnesium iodide [from methyl iodide (860 mg.) and magnesium (150 mg.)] in ether (8 ml.). The solution was refluxed for 1 hr., cooled, and decomposed with aqueous ammonium chloride to yield the *carbinol* (IX; X = Me,OH), m.p. 90—91° (from light petroleum), $\nu_{max.}$ 3360 cm.$^{-1}$, $\lambda_{max.}$ 230, 245, 294, 304, and 320 nm. (ε 12,600, 8350, 24,180, 30,800, and 25,000), τ 2·05—2·80

[21] H. Muxfeldt, G. Hardtmann, F. Kathawala, E. Vedejs, and J. B. Mooberry, *J. Amer. Chem. Soc.*, 1968, **90**, 6534 and earlier papers by Muxfeldt and his collaborators.

(8H), 6·90 (2H, t, *J* 6 Hz), 7·93 (2H, t, *J* 6 Hz), 8·32 (3H, s), and 8·04 (1H, OH, exchanged with D_2O) (Found: C, 81·8; H, 6·1. $C_{18}H_{16}O_2$ requires C, 81·7; H, 6·3%).

4-Benzyl-3,4-dihydro-5-methyl-2-phenylnaphtho[1,8-bc]-*furan-5-ol* (XIII).—The benzyl compound (X; R = H) (300 mg.) in ether (20 ml.) was added during 30 min. to a stirred solution of methylmagnesium iodide [from methyl iodide (0·22 ml.) and magnesium (150 mg.)] in ether (7 ml.). The mixture was refluxed for 1 hr., stirred overnight, and decomposed with ice and ammonium chloride. Removal of the solvent from the organic extract gave the *carbinol* (XIII), m.p. 128—129° [from light petroleum (b.p. 60—80°)], $\nu_{max.}$ 3590 cm.$^{-1}$, $\lambda_{max.}$ 306 and 321 nm. (ε 21,500 and 16,900) (Found: C, 84·7; H, 6·6. $C_{25}H_{22}O_2$ requires C, 84·8; H, 6·3%).

8-Benzoyloxy-3-benzyl-3,4-dihydro-4-hydroxy-4-methylnaphthalen-1(2H)*-one* (XIV).—The alcohol (XIII) (150 mg.) was ozonised in chloroform (5 ml.) at −20° (u.v. spectral control). After removal of excess of ozone with a stream of nitrogen, and work-up with potassium iodide solution, evaporation of the solvent gave a non-crystalline product (XIV), $\nu_{max.}$ 3560 and 1686 cm.$^{-1}$, characterised as the *2,4-dinitrophenylhydrazone*, m.p. (from ethyl acetate) 255—257° (Found: N, 10·1. $C_{31}H_{26}N_4O_7$ requires N, 10·4%).

Methyl 2,6-Dihydroxy-p-toluoate (XVII; R = H).—2,6-Dihydroxy-*p*-toluic acid was prepared in 95% yield by heating orcinol (3,5-dihydroxytoluene) with potassium hydrogen carbonate and glycerol, under carbon dioxide at 116°.[7] The crude acid was carefully dried on a steam-bath, and methylated as follows. The dry acid (110 g.) in dry acetone (550 ml.) was treated with sodium hydrogen carbonate (75 g.). Dimethyl sulphate (78 ml.) was added, and the whole suspension was gently refluxed for 10 hr. The mixture was cooled to room temperature and filtered. The filtrate was concentrated to *ca.* 70 ml. and treated with methanol (150 ml.). Large needles of the ester separated (95%); m.p. 98—99°, $\nu_{max.}$ 3500 and 1670 cm.$^{-1}$, τ 0·52 (2H, exchanged by D_2O), 3·77 (2H), 6·03 (3H), and 7·82 (3H).[7]

2,6-Dihydroxy-4-methylbenzamide.—Methyl 2,6-dihydroxy-*p*-toluoate (1 g.) was shaken with concentrated ammonia (7 ml.) and water (5 ml.) for 18 hr. Acidification with 6N-hydrochloric acid gave a precipitate which was filtered off, washed with ether, and recrystallised from aqueous ethanol to give the *amide* (900 mg.), m.p. 242°, $\nu_{max.}$ 3425, 3175, and 1667 cm.$^{-1}$ (Found: C, 57·55; H, 5·8; N, 8·25. $C_8H_9NO_3$ requires C, 57·5; H, 5·45; N, 8·4%).

Methylation of this amide with dimethyl sulphate in aqueous sodium hydroxide gave the known 2,6-dimethoxy-4-methylbenzamide.[7]

Methyl 2,6-Dihydroxy-3-nitro-p-toluoate (XVII; R = NO_2).—Methyl 2,6-dihydroxy-*p*-toluoate (1·1 g.) in acetic acid (10 ml.) was nitrated with nitric acid (*d* 1·2; 1·2 ml.) at 15°. The product, which crystallised from the reaction mixture, furnished the *ester* (630 mg.), m.p. 164—165° (from methanol), $\nu_{max.}$ 3420, 1690, and 1546 cm.$^{-1}$, τ 7·59 (3H, s), 5·89 (3H, s), 3·59 (1H, s), −0·98 (1H), −0·49 (1H) (the last two exchanged with D_2O) (Found: C, 47·9; H, 4·3; N, 5·95. $C_9H_9NO_6$ requires C, 47·6; H, 4·0; N, 6·15%).

Methyl 2,6-Diacetoxy-4-methyl-3-nitrobenzoate.—The nitro-ester (XVII; R = NO_2) (1·87 g.) was treated with acetic anhydride (10 ml.) and sodium acetate (1·5 g.) at 95° for 1 hr. Quenching in ice–water provided the *diacetate* (2·1 g.), m.p. 90° [from light petroleum (b.p. 60—80°)], $\nu_{max.}$ 1770, 1724, and 1538 cm.$^{-1}$, τ 3·00 (1H), 6·18 (3H), 7·62 (3H), 7·74 (3H), and 7·76 (3H) (Found: C, 50·55; H, 4·4; N, 4·45. $C_{13}H_{13}NO_8$ requires C, 50·15; H, 4·2; N, 4·50%).

Oxidation of Methyl 2,6-Diacetoxy-4-methyl-3-nitrobenzoate.—The ester (2 g.), in acetic anhydride (20 ml.) and acetic acid (20 ml.), was treated with concentrated sulphuric acid (3·2 ml.), with the temperature of the mixture kept below 5°. Chromium trioxide (3·7 g.) was added with stirring during 45 min. and the mixture was kept for 6 hr. at 0—5°. Addition to ice–water caused the product to separate slowly. After extraction with benzene the residue was recrystallised from light petroleum (b.p. 60—80°)–ether, to give 3,5-diacetoxy-4-methoxycarbonyl-2-nitrobenzoic acid (1·07 g.), m.p. 168°. Treatment with ethereal diazomethane gave the *dimethyl ester*, m.p. (from benzene–light petroleum) 107—108°, $\nu_{max.}$ 1780, 1728, and 1564 cm.$^{-1}$, τ 2·33 (1H), 6·10 (3H), 6·12 (3H), 7·69 (3H), and 7·72 (3H) (Found: C, 47·1; H, 3·9; N, 4·0; Ac, 24·4. $C_{14}H_{13}NO_{10}$ requires C, 47·3; H, 3·7; N, 3·9; Ac, 24·2%).

Direct Introduction of a Nitrile Group into Resorcinol.—Resorcinol (10 g.) and cyanogen bromide (5 g.) in anhydrous ether (150 ml.) were treated with zinc chloride (3 g.). Hydrogen chloride was passed through the solution for 3 hr., the ether was decanted, and the product (XVIII) (3·25 g.) was washed with ether. The complex (XVIII) (2 g.) in collidine (20 ml.) was heated at 95° for 18 hr. Dilution with water, acidification, and extraction with ether gave β-resorcylonitrile (500 mg.), m.p. and mixed m.p.[9] 179°, $\nu_{max.}$ 2240 cm.$^{-1}$.

Methyl 3-Formyl-2,6-dihydroxy-p-toluoate (XIX; R^1 = CHO, R^2 = OMe, R^3 = H).—Aluminium chloride (8 g.) in anhydrous ether (50 ml.) was added with stirring to a solution of methyl 2,6-dihydroxy-*p*-toluoate (3·8 g.) in ether (75 ml.) containing zinc cyanide (3 equiv.) at 0°. The mixture was saturated with hydrogen chloride at 0°, and after 3 hr. the crystalline complex that had separated was filtered off, washed with ether, dissolved in water (500 ml.) and left overnight. The *aldehyde* was produced as pale yellow needles (3·6 g.), m.p. 147° (from methanol), $\nu_{max.}$ 1667 and 1640 cm.$^{-1}$, τ 7·43 (3H), 5·96 (3H), 3·66 (1H), −0·05 (1H), −2·43 (1H), and −3·97 (1H) (the last two exchanged with D_2O) (Found: C, 56·95; H, 4·75. $C_{10}H_{10}O_5$ requires C, 57·15; H, 4·8%). On a 100 g. scale the conditions were also satisfactory.

Methyl 2,6-Dihydroxy-3-hydroxyiminomethyl-p-toluoate (XIX; R^1 = CH:N·OH, R^2 = OMe, R^3 = H).—Hydroxylamine hydrochloride (1·8 g.) and anhydrous sodium acetate (3·3 g.) in water (9 ml.) was added to methyl 3-formyl-2,6-dihydroxy-*p*-toluoate (2 g.) in absolute ethanol (125 ml.) at 70°. After 30 min. the mixture was cooled to 0° and the *oxime* was filtered off, washed with water, and recrystallised from ethanol (yield 1·8 g.); m.p. 204—205°, $\nu_{max.}$ 3390 and 1667 cm.$^{-1}$, τ 7·70 (3H, s), 6·10 (3H, s), 3·72 (1H, s), 1·64 (1H, s), −0·99 (1H, s), and −1·90 (1H, s) (Found: C, 53·5; H, 5·05; N, 5·9. $C_{10}H_{11}NO_5$ requires C, 53·35; H, 4·9; N, 6·2%).

Methyl 3-Acetoxyiminomethyl-2,6-dihydroxy-p-toluoate.—The oxime (1·34 g.) in acetic anhydride (3·5 ml.) was warmed to 95° for a few min. until a clear solution resulted. On cooling, the *O-acetate* precipitated (yield 1·37 g.); m.p. 125° (from methanol), $\nu_{max.}$ 3333, 1760, and 1667 cm.$^{-1}$ (Found: N, 5·3. $C_{12}H_{13}NO_6$ requires N, 5·5%).

Methyl 3-Cyano-2,6-dihydroxy-p-toluoate (XIX; R^1 = CN, R^2 = OMe, R^3 = H).—The foregoing oxime *O*-acetate

(100 mg.) was heated to 180°. The product gave white *needles* (40 mg.), m.p. 180—182° (from methanol), $\nu_{max.}$ 3333 and 2230 cm.$^{-1}$ (Found: C, 57·85; H, 4·3; N, 6·85. $C_{10}H_9NO_4$ requires C, 57·5; H, 4·4; N, 6·75%).

Methyl 6-Hydroxy-4-methylbenzisoxazole-7-carboxylate (XX; R = H).—The foregoing oxime *O*-acetate was heated to 140—150° and the remaining traces of acetic acid were then removed under vacuum. The *benzisoxazole* (XX; R = H) had m.p. 168° (from methanol), $\nu_{max.}$ 1667 and 1640 cm.$^{-1}$, τ −1·63 (1H, exchanged with D_2O), 1·37 (1H), 3·22 (1H), 5·92 (3H), and 7·46 (3H) (Found: C, 57·85; H, 4·4; N, 6·85. $C_{10}H_9NO_4$ requires C, 57·95; H, 4·4; N, 6·75%).

Alternatively the oxime (XIX; R^1 = CH:N·OH, R^2 = OMe, R^3 = H) (480 mg.) was heated with acetic anhydride (3·6 ml.) at 100° for 1 hr. The solution was poured into ice–water and the crystalline benzisoxazole separated (80%).

3-Cyano-2,6-dihydroxy-4-methylbenzamide (XIX; R^1 = CN, R^2 = NH_2, R^3 = H).—The benzisoxazole (XX; R = H) (100 mg.) was dissolved in concentrated ammonia (2 ml.) and water (1·5 ml.) by warming on a steam-bath. After 18 hr. at room temperature acidification produced the *amide* (XIX; R^1 = CN, R^2 = NH_2, R^3 = H) (90 mg.), m.p. 271° (from methanol), $\nu_{max.}$ 3333, 3077, 2463, and 1675 cm.$^{-1}$, τ 7·63 (3H, s), 3·59 (1H, s), and 1·78 (2H, two broad signals showing exchange with D_2O) (Found: C, 56·2; H, 4·4; N, 14·45. $C_9H_8N_2O_3$ requires C, 56·25; H, 4·2; N, 14·6%).

Methyl 6-Hydroxy-4-methyl-5-nitrobenzisoxazole-7-carboxylate (XXI; R = H).—The benzisoxazole (XX; R = H) (330 mg.) in concentrated sulphuric acid (5 ml.) at 0° was treated with nitric acid (0·5 ml.; *d* 1·4) and sulphuric acid (2 ml.) with cooling. After 1·5 hr. at room temperature the reaction was quenched with ice; the *nitro-derivative* formed pale yellow needles (300 mg.), m.p. 194—195° (from methanol), $\nu_{max.}$ 1667 and 1538 cm.$^{-1}$, τ 7·41 (3H, s), 5·88 (3H, s), 2·40 (1H, s), and 1·03br (1H, s, OH) (Found: C, 47·75; H, 3·4; N, 10·85. $C_{10}H_8N_2O_6$ requires C, 47·6; H, 3·2; N, 11·1%).

Methyl 6-Acetoxy-4-methyl-5-nitrobenzisoxazole-7-carboxylate (XXI; R = Ac).—The nitrobenzisoxazole (XXI; R = H) (140 mg.) was treated with acetic anhydride (3 ml.) and sulphuric acid (1 drop) at room temperature for 18 hr. Quenching with ice–water provided the *acetate* (XXI; R = Ac) (140 mg.), m.p. 145° (from methanol), $\nu_{max.}$ 1780 and 1739 cm.$^{-1}$ (Found: C, 49·25; H, 3·45; N, 9·15; Ac, 11·9. $C_{12}H_{10}N_2O_7$ requires C, 49·0; H, 3·45; N, 9·5; Ac, 11·3%).

Methyl 2,6-Diacetoxy-3-cyano-4-methyl-5-nitrobenzoate (XXII; R^1 = Ac, R^2 = OMe).—The nitrobenzisoxazole (XXI; R = H) (140 mg.), acetic anhydride (3 ml.), and sodium acetate (130 mg.) were heated at 95° for 2 hr. The mixture was quenched with ice–water, and the *diacetate* (XXII; R^1 = Ac, R^2 = OMe) was recrystallised from ether or methanol (yield 130 mg.); m.p. 126—127°, $\nu_{max.}$ 1780, 1739, and 2465 cm.$^{-1}$, τ 7·69 (3H, s), 7·58 (3H, s), 7·39 (3H, s), and 6·10 (3H, s) (Found: C, 50·0; H, 3·6; N, 8·35; Ac, 22·1. $C_{14}H_{12}N_2O_8$ requires C, 49·9; H, 3·85; N, 8·4; Ac, 22·45%).

Methyl 3-Cyano-2,6-dimethoxy-4-methyl-5-nitrobenzoate (XXII; R^1 = Me, R^2 = OMe).—The nitrobenzisoxazole (XXI; R = H) (500 mg.) was refluxed in dry acetone (25 ml.) with dimethyl sulphate (1·3 g.) and potassium carbonate (2 g.) for 14 hr. The filtered solution was concentrated and washed with aqueous sodium carbonate at 50°. Extraction with benzene provided the *dimethyl ether* (XXII; R^1 = Me, R^2 = OMe) (500 mg.), m.p. 87° (from ether), $\nu_{max.}$ 2240 and 1739 cm.$^{-1}$ (Found: C, 51·7; H, 4·35; N, 9·8. $C_{12}H_{12}N_2O_6$ requires C, 51·45; H, 4·3; N, 10·0%).

Attempted Oxidation of the Diacetoxy-nitro-compound (XXII; R^1 = Ac, R^2 = OMe) *and the Nitrobenzisoxazole* (XXI; R = Ac) *by Thiele's Method.*—Both acetyl derivatives were recovered unchanged after treatment with chromic acid (from chromium trioxide and sulphuric acid) in acetic acid–acetic anhydride at 0—5° for 3 hr.

Attempted Condensations of the Dimethyl Ether (XXII; R^1 = Me, R^2 = OMe) with *p-Nitrosodimethylaniline and with Benzaldehyde.*—The dimethyl ether was recovered unchanged after exposure to benzaldehyde and piperidine at 170° for 2 hr.

Treatment of the dimethyl ether (240 mg.) in piperidine (0·8 ml.) with *p*-nitrosodimethylaniline (130 mg.) and iodine (10 mg.) at room temperature for 1 week gave *methyl 3-cyano-2-hydroxy-6-methoxy-4-methyl-5-nitrobenzoate* (XXII; R^1 = H and Me, R^2 = OMe) (100 mg.), m.p. 131° (from methanol), $\nu_{max.}$ 2240 and 1667 cm.$^{-1}$ (Found: C, 49·35; H, 3·65; N, 10·35. $C_{11}H_{10}N_2O_6$ requires C, 49·65; H, 3·9; N, 10·5%).

Methyl 6-Acetoxy-4-methylbenzisoxazole-7-carboxylate (XX; R = Ac).—The hydroxybenzisoxazole (XX; R = H) (330 mg.) in acetic anhydride (6 ml.) and sulphuric acid (4 drops) was kept at room temperature for 18 hr. After quenching with ice–water the product was recrystallised from ether or methanol to give the *acetate* (330 mg.), m.p. 137°, $\nu_{max.}$ 1780 and 1739 cm.$^{-1}$, τ 1·24 (1H), 3·07 (1H), 6·00 (3H), 7·40 (3H), and 7·60 (3H) (Found: C, 57·55; H, 4·45; N, 5·6; Ac, 17·5. $C_{12}H_{11}NO_5$ requires C, 57·85; H, 4·45; N, 5·6; Ac, 17·3%).

Methyl 6-Acetoxy-4-diacetoxymethylbenzisoxazole-7-carboxylate (XXIII).—The acetoxybenzisoxazole (XX; R = Ac) (3·6 g.) in acetic acid (45 ml.) and acetic anhydride (45 ml.) at 0° was treated with concentrated sulphuric acid (7·2 ml.) below 5°. After addition of chromium trioxide (8·4 g.) the mixture was stirred for 4 hr., quenched with ice–water (375 ml.), and stirred for 1 hr., then left at 0° for 18 hr. The precipitate was dissolved in benzene (charcoal) and the solvent was removed; the residue gave the *diacetoxymethyl derivative* (XXIII) (1·25 g.), m.p. 122° (from methanol), $\nu_{max.}$ 1770 and 1739 cm.$^{-1}$, τ 0·97 (1H), 2·05 (1H), 2·65 (1H), 5·95 (3H), and 7·58 and 7·82 (9H) (Found: C, 52·5; H, 4·1; N, 3·75; Ac, 35·55. $C_{16}H_{15}NO_9$ requires C, 52·6; H, 4·15; N, 3·85; Ac, 35·35%).

The mother liquors from the oxidation, after a further 6 days, deposited *6-acetoxy-7-methoxycarbonylbenzisoxazole-4-carboxylic acid* (700 mg.), m.p. 163—164°, $\nu_{max.}$ 1770, 1739, and 1704 cm.$^{-1}$, τ 7·60 (3H), 5·98 (3H), 2·15 (1H), 0·75 (1H), −0·99 (1H, exchanged by D_2O) (Found: C, 51·9; H, 3·6; N, 5·0. $C_{12}H_9NO_7$ requires C, 51·6; H, 3·25; N, 5·0%).

Methyl 2,6-Diacetoxy-3-cyano-4-diacetoxymethylbenzoate (XXIV).—The diacetoxymethylbenzisoxazole (XXIII) (550 mg.) in pyridine (5 ml.) and acetic anhydride (2 ml.) was kept at room temperature for 18 hr. After quenching with dilute hydrochloric acid (15 ml.; 6N) the *product* was recrystallised from methanol (yield 500 mg.), m.p. 126°, $\nu_{max.}$ 1780 and 1724 cm.$^{-1}$, τ 7·87 (6H), 7·65 (3H), 7·73 (3H), 6·18 (3H), and 2·28 [1H, $(AcO)_2CH$] (Found: C, 52·95; H, 4·45. $C_{18}H_{17}NO_{10}$ requires C, 53·1; H, 4·2%).

3-Cyano-2,6-dihydroxy-4-methyl-5-nitrobenzamide (XXII;

$R^1 = H$, $R^2 = NH_2$).—The nitrobenzisoxazole (XXI; R = H) (1·0 g.), concentrated ammonia (20 ml.), and water (4 ml.) were warmed at 50—60° for 24 hr. Water (20 ml.) was added, and the crystalline salt was redissolved by warming. The cooled solution was stirred with ice and concentrated hydrochloric acid (25 ml.) and the product was washed with water and dried (100°). Recrystallisation from methanol gave the *amide* (XXII; $R^1 = H$, $R^2 = NH_2$) as feathery needles, m.p. 241—243°, $\nu_{max.}$ 3450, 3230, 2240, 1670, and 1595 cm.$^{-1}$ (Found: C, 45·75; H, 3·05; N, 17·5. $C_9H_7N_3O_5$ requires C, 45·55; H, 3·0; N, 17·7%).

3-*Cyano*-5-*dimethylamino*-2,6-*dihydroxy*-4-*methylbenzamide* (XXVII).—The nitro-compound (XXII; $R^1 = H$, $R^2 = NH_2$) (99 mg.) was hydrogenated over Adams catalyst (51 mg.) in formic acid (6·0 ml.). After absorption of 3 mol. of hydrogen, formalin (1 ml.) was added, and the mixture was refluxed for 4 hr. The cooled solution was acidified with conc. hydrochloric acid, the catalyst was removed, and the solution was evaporated *in vacuo*. Trituration of the residue with ethanol gave granular crystals of the amine hydrochloride (63 mg.), m.p. 193—195° (from ethanol).

Ethyl 3,5-*Diacetoxy*-2,4-*diethoxycarbonylphenylacetate* (XXVIII; $R^1 = CO_2Et$, $R^2 = Ac$).—The dihydroxy-compound (XXVIII; $R^1 = CO_2Et$, R = H) (300 mg.), prepared as described elsewhere,[19] in acetic anhydride (6 ml.) and sodium acetate (600 mg.) was warmed on a steam-bath for 2 hr.; the mixture was quenched with ice–water and the product was recrystallised from ether–light petroleum to give the *diacetate* (300 mg.), m.p. 52°, $\nu_{max.}$ 1770, 1724, and 1712 cm.$^{-1}$, τ 8·3—8·8 (complex, 9H), 7·70 (3H), 7·68 (3H), 6·13 (2H), 5·4—5·9 (complex, 6H), and 2·92 (1H) (Found: C, 56·65; H, 5·8. $C_{20}H_{24}O_{10}$ requires C, 56·6; H, 5·7%).

Diethyl 2,6-*Diacetoxy*-4-*methylisophthalate* (XXVIII; $R^1 = H$, $R^2 = Ac$).—The dihydroxy-compound [20] (XVIII; $R^1 = H$, $R^2 = H$) (100 mg.) in acetic anhydride (5 ml.) and sodium acetate (200 mg.) was warmed on a steam-bath for 2 hr.; the mixture was quenched with ice–water and the product was recrystallised from ether–light petroleum to give the *diacetate* (100 mg.), m.p. 66°, $\nu_{max.}$ 1780 and 1724 cm.$^{-1}$ (Found: C, 58·3; H, 5·6. $C_{17}H_{20}O_8$ requires C, 58·0; H, 5·7%).

3,4-*Dihydro*-2-*phenyl*-4-*phthalidylnaphtho*[1,8-bc]*furan*-5-*one* (XXX; X = O).—The dihydronaphthofuran (IX; X = O) (480 mg.) and *o*-cyanobenzaldehyde diacetate (XXIX) (460 mg.) in acetic acid (8·0 ml.) and sulphuric acid (0·1 ml.) were kept at room temperature for 18 hr. The yellow precipitate was recrystallised from Methylcellosolve to give the *phthalide* (XXX; X = O) (700 mg.), m.p. 239—240°, $\nu_{max.}$ 1760 and 1666 cm.$^{-1}$ (Found: C, 78·9; H, 4·4. $C_{25}H_{16}O_4$ requires C, 78·9; H, 4·2%).

3,4-*Dihydro*-4-(3-*oxoisoindolin*-1-*yl*)-2-*phenylnaphtho*-[1,8-bc]*furan*-5-*one* (XXX; X = NH).—The dihydronaphthofuran (IX; X = O) (123 mg.) and *o*-cyanobenzaldehyde (103 mg.) in ethanol (4·0 ml.) containing triethylamine (3 drops) were refluxed for 3 hr. The solution was cooled and the *product* (XXX; X = NH) was recrystallised from ethyl acetate; m.p. 281—282°, $\nu_{max.}$ 1718 and 1686 cm.$^{-1}$ (Found: C, 79·0; H, 4·9; N, 3·8. $C_{25}H_{17}NO_3$ requires C, 79·1; H, 4·5; N, 3·7%).

4-(6-*Acetoxy*-7-*methoxycarbonylbenzisoxazol*-4-*ylmethylene*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXXI).—The diacetoxymethylbenzisoxazole (XXIII) (240 mg.) and the dihydronaphthfuran (IX; X = O) (160 mg.) in glacial acetic acid (1·75 ml.) containing concentrated sulphuric acid (3 drops) were kept at room temperature for 18 hr. The *product* (XXXI) was recrystallised from toluene (yield 190 mg.); m.p. 240—241°, $\lambda_{max.}$ ($CHCl_3$) 307 and 405 nm. (ε 29,400 and 6800) $\nu_{max.}$ 1760, 1740, and 1670 cm.$^{-1}$ (Found: C, 70·65; H, 4·05; N, 2·8. $C_{29}H_{19}NO_7$ requires C, 70·6; H, 3·9; N, 2·85%).

3,4-*Dihydro*-4-(6-*Hydroxy*-7-*methoxycarbonylbenzisoxazol*-4-*ylmethyl*)-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXXII; R = H).—The benzylidene compound (XXXI) (1·0 g.) in a solution of 30% anhydrous hydrogen iodide in acetic acid (35 ml.) was shaken for 6 hr. at room temperature. The product that crystallised was washed thoroughly with methanol and recrystallised from acetone to give the *ketone* (XXXII; R = H) (560 mg.), m.p. 218—219°, $\nu_{max.}$ 1670 and 1656 cm.$^{-1}$, τ 6·94 (2H), 5·0—7·0 (3H), 6·01 (3H), 2·98 (1H), (aromatics, 8H), and 0·96 (1H of isoxazole) (Found: C, 71·7; H, 4·4. $C_{27}H_{19}NO_6$ requires C, 71·5; H, 4·2%).

4-(6-*Acetoxy*-7-*methoxycarbonylbenzisoxazol*-4-*ylmethyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXXII; R = Ac).—The phenol (XXXII; R = H) (420 mg.) in acetic anhydride (10 ml.) and sulphuric acid (1 drop) was warmed at 95° for 6 hr. The mixture was quenched in ice–water and stirred for 2 hr. The *acetate* (420 mg.) had m.p. 196—197° (from acetone–ethanol), $\lambda_{max.}$ 265 and 355 nm. (ε 31,500 and 12,400), $\nu_{max.}$ 1780, 1730, and 1686 cm.$^{-1}$, τ 7·61 (3H), 6·01 (3H), 2·98 (1H), 0·96 (1H), (complex aromatics, 8H), and 5·0—7·0 (5H, complex) (Found: C, 70·3; H, 4·45; N, 2·8. $C_{29}H_{21}NO_7$ requires C, 70·3; H, 4·3; N, 2·8%).

4-(3,5-*Diacetoxy*-2-*cyano*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXXIII; $R^1 = CN$, $R^2 = Ac$, X = O).—The benzisoxazole (XXXII; R = Ac) (100 mg.) in pyiridine (2·0 ml.) and acetic anhydride (0·25 ml.) was kept at room temperature for 18 hr. The mixture was quenched in ice–water containing hydrochloric acid. The *nitrile* (XXXIII; $R^1 = CN$, $R^2 = Ac$) formed needles (90 mg.), m.p. 171·5—172° (from methanol–acetone), $\lambda_{max.}$ 265 and 355 nm. (ε 25,100 and 13,500), $\nu_{max.}$ 2203, 1770, 1724, and 1675 cm.$^{-1}$ (Found: C, 69·1; H, 4·45. $C_{31}H_{23}NO_8$ requires C, 69·3; H, 4·3%).

4-(3,5-*Diacetoxy*-2-*cyano*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-5-*methyl*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*ol* (XXXIII; $R^1 = CN$, $R^2 = Ac$, X = OH,Me).—The nitrile (XXXIII; $R^1 = CN$, $R^2 = Ac$, X = O) (350 mg.) in dry tetrahydrofuran (20 ml.) was added dropwise during 40 min. to a stirred solution of methylmagnesium iodide [from methyl iodide (880 mg.) and magnesium (560 mg.)] in tetrahydrofuran (8 ml.) at −5°. The mixture was stirred at 0° for 14 hr. and worked up with ammonium chloride. After reacetylation (pyridine–acetic anhydride) the product was dissolved in ethanol, cooled to 0°, and treated with water. The *methylcarbinol* (200 mg.), purified twice in this manner, had m.p. 96—97°, $\lambda_{max.}$ 305 and 320 nm. (ε 22,400 and 16,000), $\nu_{max.}$ 3450, 2235, 1770, and 1735 cm.$^{-1}$ (Found: C, 69·8; H, 5·25. $C_{32}H_{27}NO_8$ requires C, 69·4; H, 4·9%).

8-*Benzoyloxy*-3-(3,5-*diacetoxy*-2-*cyano*-4-*methoxycarbonylbenzyl*)-4-*hydroxy*-4-*methylnaphthalen*-1(2H)-*one* (XXXV; $R^1 = H$, $R^2 = Me$, $R^3 = Ac$, $R^4 = CN$).—The tertiary alcohol (XXXIV) (200 mg.) was ozonised in chloroform (20 ml.) at −20° (u.v. control, 305 nm.). After removal of excess of ozone with nitrogen the solution was shaken with

potassium iodide and washed with sodium thiosulphate. The *ketone* (XXXV; R^1 = H, R^2 = Me, R^3 = Ac, R^4 = CN), obtained by evaporation, was recrystallised from ethyl acetate–light petroleum; m.p. 101—103°, $\nu_{max.}$ 3500, 2222, 1742, and 1686 cm.$^{-1}$, $\lambda_{max.}$ 225, 260, and 322 nm. (ε 20,600, 5900, and 1400) (Found: C, 65·2; H, 5·1. $C_{32}H_{27}NO_{10}$ requires C, 65·6; H, 4·6%).

Attempts to Cyclise the Benzylnaphthalene (XXXV; R^1 = H, R^2 = Me, R^3 = Ac, R^4 = CN).—The tetralone and increasing amounts of sodium hydride in benzene, toluene, tetrahydrofuran, and dioxan were refluxed under nitrogen, for up to 10 days. After destruction of excess of hydride with glacial acetic acid only starting material could be recovered. No cyclisation could be achieved with triphenylmethylsodium in ether, with potassium t-butoxide in benzene, or with lithium di-isopropylamide in ether or tetrahydrofuran.

Cyclohexanone could not be condensed with benzonitrile with sodium hydride in toluene or with potassium t-butoxide in benzene at reflux temperature.

4-(2-*Formyl*-3,5-*dihydroxy*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXXIII; R^1 = CHO, R^2 = H, X = O).—The benzisoxazole (XXXII; R = H) (50 mg.) in dimethylformamide (7 ml.) was treated with hydrogen over prereduced palladium–charcoal (40 mg.). After absorption of 1 mol. of hydrogen, the catalyst was removed and the solution was diluted with water (10 ml.). Recrystallised from ethanol–acetone, the *aldehyde* (30 mg.) had m.p. 183—184°, $\nu_{max.}$ 1667—1635 cm.$^{-1}$, $\lambda_{max.}$ 265 and 357 nm. (ε 24,000 and 12,800) (Found: C, 70·9; H, 4·5. $C_{27}H_{20}O_7$ requires C, 71·0; H, 4·4%).

4-(3,5-*Diacetoxy*-2-*formyl*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXXIII; R^1 = CHO, R^2 = Ac, X = O).—The aldehyde (XXXIII; R^1 = CHO, R^2 = H, X = O) (400 mg.) in pyridine (5 ml.) and acetic anhydride (1·5 ml.) was kept at room temperature for 18 hr. The *diacetate*, obtained in the usual way, was recrystallised from ethanol–acetone (400 mg.); m.p. 186°, $\nu_{max.}$ 1780, 1740, 1710, and 1690 cm.$^{-1}$ (Found: C, 68·8; H, 4·4. $C_{31}H_{24}O_9$ requires C, 68·9; H, 4·5%).

4-(3,5-*Diacetoxy*-2,4-*dimethoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXXIII; R^1 = CO_2Me, R^2 = Ac, X = O).—The aldehyde (XXXIII; R^1 = CHO, R^2 = Ac, X = O) (220 mg.) in acetic acid (15 ml.) at 80° was treated with aqueous chromium trioxide (2·0 ml.; 55 mg. per ml.) and maintained at 80° for 3 hr. Addition of water provided the acid (XXXIII; R^1 = CO_2H, R^2 = Ac, X = O) which was esterified (diazomethane in tetrahydrofuran) to the *diester* (XXXIII; R^1 = CO_2Me, R^2 = Ac, X = O) (90 mg.), m.p. 219—220° (from methanol), $\nu_{max.}$ 1780, 1740, and 1690 cm.$^{-1}$, $\lambda_{max.}$ 264 and 355 nm. (ε 21,400 and 12,200) (Found: C, 67·7; H, 4·6. $C_{32}H_{26}O_{10}$ requires C, 67·4; H, 4·6%).

4-(3,5-*Diacetoxy*-2,4-*dimethoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*yl Acetate* (XXXIII; R^1 = CO_2Me, R^2 = Ac, X = H,OAc).—The diester (XXXIII; R^1 = CO_2Me, R^2 = Ac, X = O) (75 mg.) in methanol (120 ml.) was stirred with potassium borohydride (64 mg.) at room temperature for 30 min. and the mixture was then added to ice–water (100 ml.) containing acetic acid (2 ml.). The crude dried product was treated with acetic anhydride (1·5 ml.) and sodium acetate (200 mg.) at 95° for 2 hr. Work-up in the usual way gave the *ester* (XXXIII; R^1 = CO_2Me, R^2 = Ac, X = H,OAc) (61 mg.), m.p. (from methanol) 181—182°, $\nu_{max.}$ 1777 and 1735—1745 cm.$^{-1}$, $\lambda_{max.}$ 306 and 320 nm. (ε 27,800 and 21,400) (Found: C, 66·6; H, 4·8. $C_{34}H_{30}O_{11}$ requires C, 66·45; H, 4·9%).

4-*Acetoxy*-8-*benzoyloxy*-3-(3,5-*diacetoxy*-2,4-*dimethoxycarbonylbenzyl*)-3,4-*dihydronaphthalen*-1(2H)*one* (XXXV; R^1 = Ac, R^2 = H, R^3 = Ac, R^4 = CO_2Me).—The acetoxy-derivative (XXXIII; R^1 = CO_2Me, R^2 = Ac, X = H,OAc) (61 mg.) in chloroform (5 ml.) was ozonised at −20° (u.v. control, 308 nm.). The product was worked up as before and reacetylated in pyridine (1 ml.) and acetic anhydride (0·2 ml.) at room temperature for 18 hr. The ketone so formed (38 mg.), m.p. (from methanol) 103—105°, $\nu_{max.}$ 1770, 1740, and 1686 cm.$^{-1}$ did not give a satisfactory analysis owing to solvation.

Treatment of this ketone with sodium hydride (excess) in refluxing toluene did not lead to the desired cyclisation (u.v. spectroscopy).

We thank Drs. J. E. Baldwin and P. D. Magnus for their help in the preparation of this manuscript.

[0/2122 *Received, December 14th,* 1970]