# Experiments on the Synthesis of Tetracycline. Part III.[1] Michael-type Cyclisation in the Formation of Ring B

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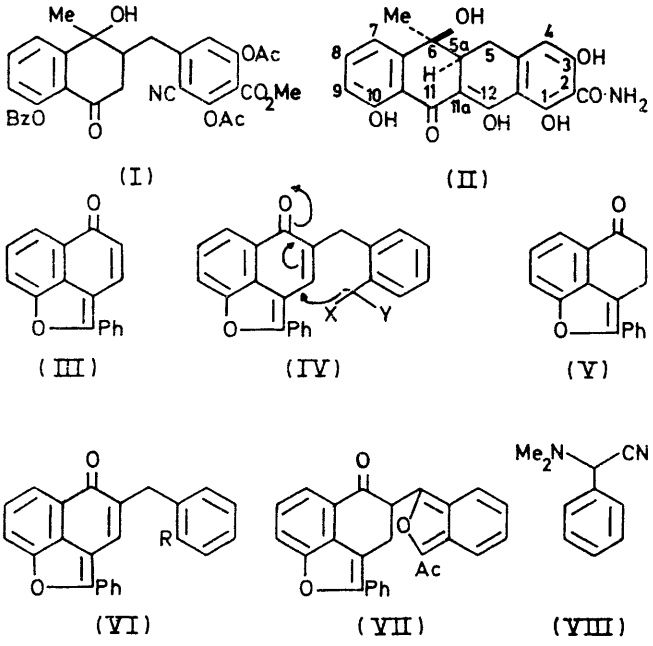
The cyanohydrin tetrahydropyranyl ether {VI; R = CH(CN)·O·CH·[CH$_2$]$_4$·O} formed from 4-(2-formylbenzyl)-2-phenylnaphtho[1,8-*bc*]furan-5-one has been cyclised under basic conditions to 12β-cyano-6aα,7,12,12aα-tetrahydro-12α-tetrahydropyranyloxy-1-phenylnaphthaceno[1,12-*bc*]furan-6-one (XI; R$^1$ = CN, R$^2$ = O·CH·[CH$_2$]$_4$O). This compound has been converted by stepwise reactions into 6-acetoxy-10-hydroxy-5a,11a-dihydronaphthacene-11(6*H*),12(5*H*)-dione (XIII; R = Ac). Work is described in the substituted ring A condensed series that was directed towards a similar objective.



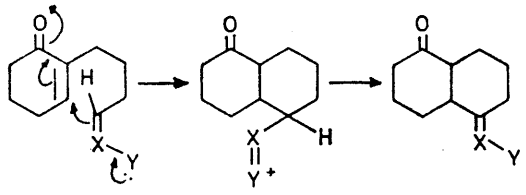
SINCE we had been unable to effect a Dieckmann-type ring closure of our intermediate (I), or related compounds, in the projected synthesis[1] of the tetracyclic substance (II), we investigated possible modifications of the original approach. As the problem resolved itself into a search for methods of forming the 11a,12-bond of structure (II) it became clear that the presence



(I) (II) (III) (IV) (V) (VI) (VII) (VIII)

of a carbonyl group in ring C conjugated with a double bond, as in the CD precursor (III),[1] might enable an intramolecular Michael-type addition of a benzylic anion on to the enone system, as in (IV), to take place. The 12-position eventually carries a keto-function, and consequently some method of reversing the normal polarity of such a function was needed.[2] The substituents X and Y in (IV) must be capable of anion stabilisation and yet readily convertible into a carbonyl group. It was felt that to avoid lengthy work in the ring A substituted series, it would be worthwhile to examine simple unsubstituted model compounds.

Treatment of the dihydronaphthofuran (V) with *o*-phthalaldehyde under conditions of base catalysis gave excellent yields of the endocyclic conjugated keto-aldehyde (VI; R = CHO), $\nu_{max.}$ 2700, 1680, and 1635 cm.$^{-1}$, $\lambda_{max.}$ 250 and 400 nm., τ 5·57br (s, $CH_2$) and −0·40 (CHO). The use of acetic acid–sulphuric acid in this condensation gave a compound whose probable structure (VII) was in keeping with the inference made in Part II[1] as to the participation of *ortho*-substituents. Apparently under basic conditions the initial benzylidene derivative is readily isomerised into the ring-unsaturated form (VI; R = CHO). In agreement, the substance (VI; R = H) was obtained by treatment of the benzylidene derivative prepared earlier[1] with triethylamine. Ring-unsaturated ACD compounds are easily recognised by their characteristic u.v. and i.r. absorptions. Attempts to form the required bond by the use of aldehyde derivatives (the oxime, the phenylhydrazone,[3] the dimethylhydrazone, or the *p*-tolylsulphonylhydrazone) as shown in Scheme 1 were unsuccessful. For this



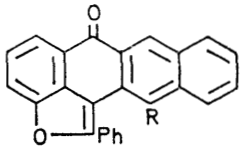
SCHEME 1

reason we turned to 'tetrahedral' aldehyde derivatives, the cyanohydrins. The use of aldehyde cyanohydrin functions to stabilise benzylic carbanions is implicit in the classical Lapworth mechanism of the benzoin condensation;[4] more recently amino-nitriles (VIII) have been *C*-alkylated under basic conditions.[5]

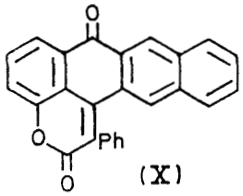
In an attempt to emulate the benzoin condensation, we treated the aldehyde (VI; R = CHO) in ethanol under reflux with sodium cyanide. Two products resulted. The major was the naphthacenofuran (IX; R = H), $\nu_{max.}$ 1640 cm.$^{-1}$, $\lambda_{max.}$ 254, 315, 340, and 420 nm. The minor component, shown to be formed by the reaction of (IX; R = H) with cyanide ion, was a pyrone derivative (X), $\nu_{max.}$ 1710 and 1650 cm.$^{-1}$, $\lambda_{max.}$ 245, 307, 326, 341, 385, and 423 nm. In the

[1] Part II, D. H. R. Barton, B. Halpern, Q. N. Porter, and D. J. Collins, preceding paper.
[2] *Cf.* D. Seebach, *Angew. Chem. Internat. Edn.*, 1969, **8**, 639.
[3] G. J. F. Chittenden and R. D. Guthrie, *J. Chem. Soc.*, 1963, 3658.
[4] W. S. Ide and J. S. Buck, *Org. Reactions*, 1948, **4**, 269.
[5] H. M. Taylor and C. R. Hauser, *J. Amer. Chem. Soc.*, 1960, **28**, 1960.

formation of compound (IX; R = H) the expected cyclisation had occurred, but it had been followed by elimination of water and cyanide ion. Apparent from the formation of the pyrone (X) was the tendency for the

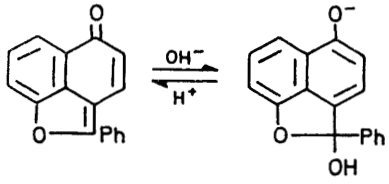


(IX)



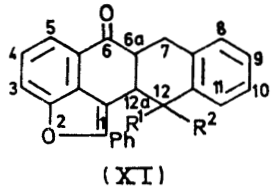
(X)

furan residue to suffer conjugate addition of nucleophiles, an observation which seemed to rationalise the reversible change (400 ⇌ 345 nm.) in the u.v. spectrum of the furan (III) in alkaline media (Scheme 2). Milder conditions were clearly required to avoid the elimination

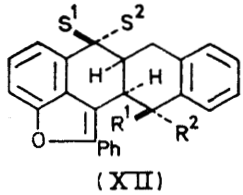


SCHEME 2

reactions, leading to aromatised products. The cyanohydrin [VI; R = CH(CN)·OH], made by treatment of the corresponding aldehyde with aqueous sodium cyanide at 5°, was converted into the corresponding acetate [VI; R = CH(CN)·OAc], $\nu_{max.}$ 1750 and 1640 cm.$^{-1}$. Hydrogen was briskly evolved when this substance was treated with sodium hydride in dimethyl sulphoxide, but the product, formed in 95% yield, was the aromatic phenol (IX; R = OH), $\nu_{max.}$ 3250 and 1665 cm.$^{-1}$, characterised as its acetate (IX; R = OAc), $\lambda_{max.}$ 422 nm. Presuming that the intermediate cyanohydrin acetate (XI; $R^1$ = CN, $R^2$ = OAc) had been hydrolysed under the strongly basic conditions (sodium hydroxide present in sodium hydride) to the diketone (XI; $R^1R^2$ = O), which then suffered base-



(XI)



(XII)

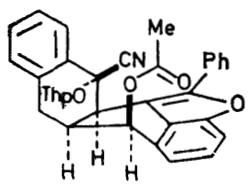
catalysed oxidation to the phenol (IX; R = OH), we next prepared the cyanohydrin benzoate [VI; R = CH(CN)·OBz]. However, under the same conditions this material eliminated benzoic acid and was oxidised to the nitrile (IX; R = CN).

These experiments indicated the need for a base-stable protecting group for the cyanohydrin. We found that the tetrahydropyranyl ether is adequate for this purpose. The cyanohydrin tetrahydropyranyl ether of acetaldehyde could not be alkylated under basic conditions. The presence of a phenyl substituent in the ether {VI; R = CH(CN)·O·CH·$[CH_2]_4$·O} (prepared in the usual way; $\nu_{max.}$ 2230 and 1640 cm.$^{-1}$) provided sufficient stabilisation for the anion. When this substance was treated, in ethereal solution, with sodium t-butoxide there was formed in good yield, the cyclised ether (XI; $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O), $\nu_{max.}$ 1695 cm.$^{-1}$, $\lambda_{max.}$ 352 nm. (ε 14,300), consistent with the presence of a reduced naphthofuran chromophore.[2] An n.m.r. doublet at τ 5·22 (*J* 6 Hz) was assigned to H-12a, with a *cis* ring junction between rings B and C.

The cyanohydrin (XI; $R^1$ = CN, $R^2$ = OH) was readily regenerated by warming with dilute acid. Concentrated sulphuric acid caused elimination to a mixture of the aromatic nitrile (IX; R = CN), and the derived amide (IX; R = CO·$NH_2$).

The required diketone (XI; $R^1R^2$ = O) was generated when the free cyanohydrin was chromatographed on alumina. It had $\nu_{max.}$ 1680 cm.$^{-1}$, $\lambda_{max.}$ ($CHCl_3$) 264, 281, 299, 310, and 360 nm. The n.m.r. spectrum showed the 12a-proton signal as a doublet, τ 5·20 ($J_{AB}$ 6·20 Hz).[6] These data agree with structure (XII; $S^1S^2$ = O, $R^1R^2$ = O). The suggested intermediacy of this diketone in the base-catalysed condensation of the cyanohydrin [VI; R = CH(CN)·OH] was confirmed by the ready conversion into the phenol (IX; R = OH) in the presence of base and oxygen.

It was now necessary to reduce the 6-keto-function in the naphthacenofuran skeleton of the cyclised material prior to ozonolysis. This was readily achieved by Meerwein–Ponndorf reduction of the cyanohydrin ketone (XI; $R^1$ = CN, $R^2$ = OH), which proceeded with concomitant hydrolysis of the cyanohydrin function, to give the ketol (XII; $S^1$ = OH, $S^2$ = H, $R^1R^2$ = O), $\lambda_{max.}$ 245 and 308 nm., $\nu_{max.}$ 3425 and 1665 cm.$^{-1}$, τ 5·60 (1H, *J* 5·5 Hz) and 5·01 (1H, *J* 3 Hz) (These coupling constants confirm the stereochemistry.) The C-12 ketone group in this molecule is sufficiently sterically hindered by the 1-phenyl substituent to prevent its reduction by this method. Acetylation gave compound (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O), $\nu_{max.}$ 1725 and 1680 cm.$^{-1}$, τ 8·88 (3H, s), 5·51 (1H, *J* 5·5 Hz), and 3·63 (1H, *J* 3 Hz).* The abnormally high-field shift of the acetate methyl group confirms the *cis*-relationship



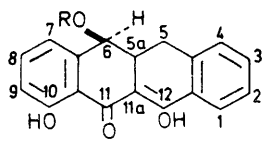
(A)

of H-6 and H-6a. Models show that only in the suggested geometry can ring A effect a strong shielding of these protons [structure (A)]. Reoxidation of the ketol

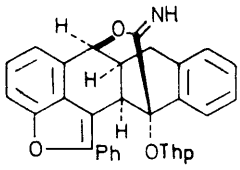
* An identical coupling (3 Hz) occurs in 6-demethyltetracycline.

[6] H. Conroy, *Adv. Org. Chem.*, 1960, **2**, 265.

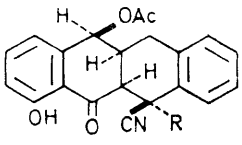
(XII; $S^1$ = OH, $S^2$ = H, $R^1R^2$ = O) with manganese dioxide provided the diketone (XII; $S^1S^2$ = O, $R^1R^2$ = O). The final step in the model sequence was achieved by the ozonolysis of the ketol (XII; $S^1$ = OH, $S^2$ = H, $R^1R^2$ = O) and its derived acetate. The free hydroxy-compound yielded a complex mixture of oxidation products. Ozonolysis of the acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) and chromatography of the product gave a poor yield (6%) of the desired debenzoylated material (XIII; R = Ac), $\lambda_{max.}$ 409 nm. (ε 26,500). The n.m.r. spectrum of this compound showed the C-6 proton signal as a doublet (*J* 3 Hz), and an acetate signal at τ 8·72, again suggesting the correct tetracycline-like relationship between the C-6 hydroxy-function and the BC ring junction. It appears that the presence of the C-12 keto-function in the precursor (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) may cause re-



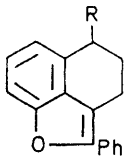

(XIII)



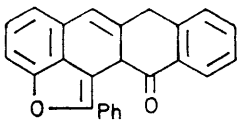

(XIV)



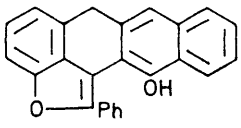

(XV)




(XVI)




(XVII)




(XVIII)

arrangement of an intermediate ozonide.[7] Accordingly we decided to use either the cyanohydrin or its tetrahydropyranyl ether to avoid this difficulty. To this end we investigated the reduction of the cyanohydrin tetrahydropyranyl ether (XII; $S^1S^2$ = O, $R^1$ = CN, $R^2$ = O·CH·[$CH_2$]$_4$·O). The Meerwein–Ponndorf method, which had been useful for the cyanohydrin reduction (see before), led in this case to an interesting compound, the isopropyl ether (XII; $S^1$ = $OPr^i$, $S^2$ = H, $R^1$ = CO·$NH_2$, $R_2$ = O·CH·[$CH_2$]$_4$·O). The structure of this compound was deduced from its spectral data: $\nu_{max.}$ 1695 and 1630 $cm.^{-1}$ (characteristic of a primary amide), $\lambda_{max.}$ 310 nm. (ε 25,000); the n.m.r. spectrum showed signals attributed to an isopropyl ether residue attached at C-6. This substance resisted oxidation and acetylation.

Its formation must involve the addition of isopropoxide ion to the ketone function, which then attacks the cyano-group with formation of an intermediate imido-lactone (XIV). Production of the desired benzylic cation would furnish the amide group. Reduction of this cation by hydride transfer would then afford the structure tentatively proposed. This scheme requires that the ring junction in the precursor ketone should be *cis*, as also was concluded from the n.m.r. spectra, and also that the cyano-function should bear a *trans*-relationship towards the adjacent proton.

The validity of this suggestion was borne out by the finding that prolonged reduction of the ketone (XII; $S^1S^2$ = O, $R^1$ = CN, $R_2$ = O·CH·[$CH_2$]$_4$·O) with lithium tri-t-butoxyaluminium hydride gave rise to the imino-lactone (XIV), $\nu_{max.}$ 3300 and 1655 $cm.^{-1}$, $\lambda_{max.}$ 309 nm. Reduction with sodium borohydride in ethanol gave the same imino-lactone.

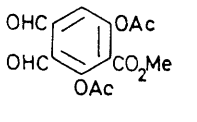
Whereas use of lithium aluminium hydride led to reduction of both ketone and nitrile functions, providing the amine (XII; $S^1$ = OH, $S^2$ = H, $R^1$ = $CH_2$·$NH_2$, $R^2$ = O·CH·[$CH_2$]$_4$·O), $\nu_{max.}$ 3430, 3350, and 3200 $cm.^{-1}$, the more selective reagent, lithium tri-t-butoxyaluminium hydride,[8] when used under controlled conditions (*cf.* above), gave the required alcohol (XII; $S^1$ = OH, $S^2$ = H, $R^1$ = CN, $R^2$ = O·CH·[$CH_2$]$_4$·O), which was acetylated to provide the acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1$ = CN, $R^2$ = O·CH·[$CH_2$]$_4$·O), $\nu_{max.}$ 1730 $cm.^{-1}$. The n.m.r. spectrum demonstrated the *cis* relationship of H-6, H-6a, and H-12a [τ 5·18 (d, *J* 5 Hz) and 3·67 (d, *J* 3 Hz)]. Mild acid hydrolysis gave the free cyanohydrin (XII; $S^1$ = OAc, $S^2$ = H, $R^1$ = CN, $R^2$ = OH). On alumina this cyanohydrin was transformed into the keto-acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O), identical with the previously obtained sample. Ozonolysis of the cyanohydrin tetrahydropyranyl ether (XII; $S^1$ = OAc, $S^2$ = H, $R^1$ = CN, $R^2$ = O·CH·[$CH_2$]$_4$·O) gave the ketone (XV; R = O·CH·[$CH_2$]$_4$·O) in good yield; $\lambda_{max.}$ 264, 270, 275, and 282 nm. Hydrolysis afforded the free cyanohydrin (XV; R = OH), $\nu_{max.}$ 3450, 1745, and 1600 $cm.^{-1}$, τ 8·35 (3H, s) and 3·64 (1H, d *J* 3 Hz), consistent with the proposed structure. Chromatography of this material over alumina gave a poor yield of the required diketone (XIII; R = Ac), $\lambda_{max.}$ 409, 392, 312, 262, and 248 nm., $\nu_{max.}$ 3250, 1735, 1620, 1600, and 1565 $cm.^{-1}$, τ 8·72 (3H) and 3·90 (1H, d, *J* 3 Hz).

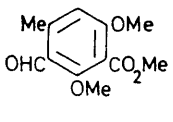
Before we describe the application of this sequence to substituted compounds we wish to mention a reaction of the simple model series. In view of the greater

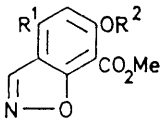
[7] P. S. Bailey, *Chem. Rev.*, 1958, **58**, 927.
[8] H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, 1958, **80**, 5372.

stability of the 6-deoxy-6-demethyltetracyclines,[9] we sought to make this class of compound available from our own synthetic route. We therefore hydrogenolysed the keto-acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) with acid catalysis, to the 6-deoxy-compound (XII; $S^1S^2$ = H, $R^1R^2$ = O) taking advantage of the greater steric hindrance of the 12-keto-group. Although the yield (41%) was acceptable, we tried to improve the conversion by exchanging the C-9 hydroxy-group in the ketol (XII; $S^1$ = OH, $S^2$ = H, $R^1R^2$ = O) for a thioether function. In the case of the naphthofuran (XVI; R = OH),[1] treatment with toluene-α-thiol and acid readily gave the benzyl thioether (XVI; R = S·$CH_2$Ph). This thioether was desulphurised in high yield to the deoxy-compound (XVI; R = H). However, similar treatment of the ketol (XII; $S^1$ = OH, $S^2$ = H, $R^1R^2$ = O) with strong mineral acid caused dehydration to a mixture of two compounds, interconvertible in acid, to which we assign the structures (XVII) and (XVIII) from chemical and spectral data (see Experimental section).

This sequence demonstrated that a phthalaldehyde fragment could be condensed under basic conditions to yield a tricyclic product possessing the ring-unsaturated enone system needed for the Michael reaction. The synthetic objective (II), required, therefore, the preparation of the substituted dialdehyde (XIX). All attempts to make this substance by modification of the already extant ring A precursors were unsuccessful. Attempted oxidation of the methyl group of compound (XXI) led to attack on the formyl function.


(XIX)

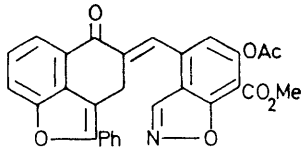

(XXI)

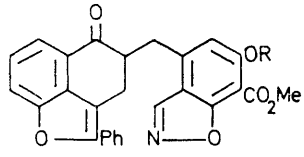

(XX)

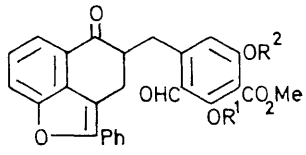
It was apparent that we had to return to the acid-catalysed condensation of the diacetoxymethyl derivative [XX; $R^1$ = $CH(OAc)_2$, $R^2$ = Ac] with the dihydronaphthofuran (V), but before doing so a consideration of two aspects was required. First, in earlier work [1] we had used acetyl protecting groups for the phenolic ring A. As we were unable to make a stable cyanohydrin from salicylaldehyde acetate, but could do so from the corresponding methyl ether, we decided to change the protecting groups for ring A to methyl ether functions. Secondly, as catalytic reduction, required for the isoxazole ring opening, was found in preliminary experiments to reduce the C=C bond of the tricyclic intermediate (XXII) [1] we were forced to adopt the more cumbersome approach of sequential reduction, followed by dehydrogenation. All attempts to rearrange the double bond of (XII) into endocyclic conjugation failed. The simple method of rearrangement with triethylamine as base could not be used because of the extreme sensitivity of the isoxazole to such conditions. Even use of pyridine at 0° gave the hydroxy-nitrile (XXVI; $R^1$ = H, $R^2$ = Ac).

Reduction of compound (XXII) with hydrogen iodide, as described previously,[1] gave, after reacetylation, the acetate (XXIII; R = Ac). The isoxazole was catalytically reduced to provide, in good yield, the phenolic aldehyde (XXIV; $R^1$ = H, $R^2$ = Ac).

Interestingly, reduction of the phenol (XXIII; R = H) gave the hydroxy-nitrile, characterised as its methyl ether (XXVI; $R^1$ = $R^2$ = Me). The aldehyde (XXIV; $R^1$ = H, $R^2$ = Ac) was characterised as its methyl ether, prepared by the Purdie procedure, $\nu_{max.}$ 1760, 1730, 1690, and 1680 cm.$^{-1}$, $\lambda_{max.}$ 265 and 355 nm. Treatment of the aldehyde (XXIV; $R^1$ = Me, $R^2$ = Ac) with sodium methoxide, with the intention of acquiring the phenol (XXIV; $R^1$ = Me, $R^2$ = H), gave the spiro-alcohol (XXV; $R^1$ = H, $R^2$ = H), $\nu_{max.}$ 3400, 1680, and 1665 cm.$^{-1}$. Methylation gave the ether (XXV; $R^1$ = H, $R^2$ = Me), $\nu_{max.}$ 3450, 1725, and 1670 cm.$^{-1}$, which was converted into the acetate (XXV; $R^1$ = Ac, $R^2$ = Me), $\nu_{max.}$ 1740, 1720, and 1685 cm.$^{-1}$,


(XXII)


(XXIII)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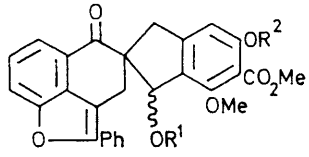
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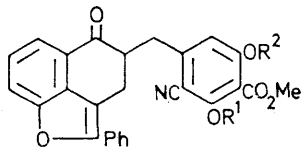
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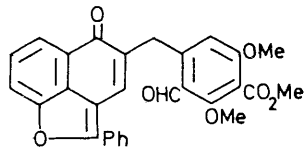
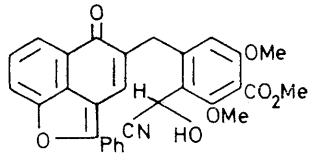
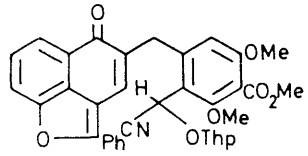

(XXVII)


(XXVIII)


(XXIX)

τ 8·33 (3H, OAc), 7·28 (2H), 6·60 (2H), 6·38—6·13 (9H), 3·56 (1H), and 3·30 (1H) (all singlets except for τ 7·28 which was an AB system).

[9] M. Schach von Wittenau, J. J. Beereboom, R. K. Blackwood, and C. R. Stephens, *J. Amer. Chem. Soc.*, 1962, **84**, 2645.

After these deviations we returned to the known phenolic isoxazole (XXIII; R = H). Methylation gave the ether (XXIII; R = Me), which was hydrogenolysed to the aldehyde (XXIV; $R^1$ = H, $R^2$ = Me). After further methylation the resultant aldehyde (XXIV; $R^1$ = $R^2$ = Me) was refluxed in toluene with dichlorodicyanoquinone (DDQ); the expected shift in the u.v. spectrum slowly occurred ($\lambda_{max.}$ 360 ⟶ 405 nm.). The dehydro-aldehyde (XXVII) was isolated (50%) after extensive chromatography; $\nu_{max.}$ 1735, 1685, and 1635 $cm.^{-1}$.

The cyanohydrin (XXVIII) was prepared as in the model series; treatment with dihydropyran gave the ether (XXIX), $\nu_{max.}$ 1730 and 1640 $cm.^{-1}$, as a mixture of diastereoisomers.

All efforts to cyclise this compound failed. With 1 equiv. of potassium t-butoxide no reaction occurred, whereas use of an excess caused destruction of the ether to give intractable material. The failure of this cyclisation could be attributed to steric hindrance caused by the *o*-methoxy-substituent, or destabilisation of the intermediate anion by the *o*- and *p*-methoxy-groups on ring A. Sodium hydride in dimethylformamide was without effect.

The Michael-type cyclisation was abandoned at this stage, but reactions employing the aldehyde (XXVII) are described in later papers. The route to this important ACD tricyclic aldehyde may be described as the 'benzisoxazole dehydrogenation' path. It involved thirteen stages from orcinol and gave an overall yield of only 0·45%.

## EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage appara tus Unless otherwise stated 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 b.p. 60—80° unless stated to the contrary.

4-(2-*Formylbenzyl*)-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (VI; R = CHO).—3,4-Dihydro-2-phenylnaphtho[1,8-*bc*]-furan-5-one (V) [1] (8 g.) and *o*-phthalaldehyde (6 g.) in ethanol (160 ml.) and triethylamine (24 ml.) were refluxed under nitrogen for 8 hr. After 18 hr. at room temperature the product was filtered off and recrystallised from dichloromethane–di-isopropyl ether. Work-up of the mother liquors by addition of di-isopropyl ether provided, in combination with the first crop, a total yield of 80%. The *aldehyde* (VI; R = CHO) had m.p. 142—144°, $\lambda_{max.}$ 250 and 400 nm. (ε 22,000 and 32,000), $\nu_{max.}$ 2700, 1680, and 1635 $cm.^{-1}$, τ 5·57 (2H, s) and −0·40 (1H, s) (Found: C, 82·35; H, 4·7. $C_{25}H_{16}O_3$ requires C, 82·40; H, 4·45%).

The following derivatives of the aldehyde (VI; R = CHO) were prepared: oxime, m.p. 201°; phenylhydrazone, m.p. (from ethanol) 175—176°; NN-*dimethylhydrazone*, m.p. (from ethanol) 90—92°, $\nu_{max.}$ 1635 and 1615 $cm.^{-1}$, $\lambda_{max.}$ 270, 295, and 402 nm. (ε 20,000, 20,400, and 26,100) (Found: C, 79·4; H, 5·6; N, 6·8. $C_{27}H_{22}N_2O_2$ requires C, 79·8; H, 5·5; N, 6·9%); and the p-*tolylsulphonylhydrazone*, m.p. (from methanol) 213—215°, $\nu_{max.}$ 3140 and 1630 $cm.^{-1}$ (Found: C, 73·3; H, 5·4; O, 11·0. $C_{35}H_{27}N_2O_4S$ requires C, 73·5; H, 4·8; O, 11·2%). Attempts to cyclise these derivatives, under both basic and acidic conditions, were unsuccessful.

4-*Benzyl*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (VI; R = H).— 4-Benzylidene-3,4-dihydro-2-phenylnaphtho[1,8-*bc*]-furan-5-one [1] (100 mg.) in triethylamine (5 ml.) was heated under reflux overnight. Removal of the triethylamine, followed by chromatography on alumina (G3) in benzene, gave the *benzyl derivative* (VI; R = H) (94%), m.p. (from ethanol) 153°, $\nu_{max.}$ 1643 $cm.^{-1}$, τ 6·02br (2H, s) (Found: C, 85·7; H, 5·0. $C_{24}H_{16}O_2$ requires C, 85·7; H, 4·8%).

4-(3-*Acetylisobenzofuran*-1-*yl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (VII).—The dihydronaphthofuran (V) (460 mg.) and *o*-phthalaldehyde (500 mg.) in acetic acid (5 ml.) and concentrated sulphuric acid (0·1 ml.) were stored in the dark at room temperature for 4·5 hr. The *product* (VII) was crystallised twice from acetone–ethanol (200 mg.), m.p. 170°, and further purified by chromatography on alumina (G3), m.p. 175—177°, $\lambda_{max.}$ 260 and 360 nm., $\nu_{max.}$ 2630, 1670, and 1610 $cm.^{-1}$ (Found: C, 79·7; H, 4·45. $C_{27}H_{18}O_4$ requires C, 79·8; H, 4·45%).

1-*Phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (IX; R = H).—The condensed aldehyde (VI; R = CHO) (488 mg.) in hot ethanol (50 ml.) was heated under reflux for 35 min. with an aqueous solution of sodium cyanide (110 mg. in 5 ml.), until the maximum at 400 nm. no longer decreased. The *product* (IX; R = H) crystallised on cooling, m.p. 245°, $\lambda_{max.}$ 254, 315, 340, and 420 nm. (ε 78,000, 22,000, 20,000, and 12,000), $\nu_{max.}$ 1640 $cm.^{-1}$ (Found: C, 86·85; H, 4·25. $C_{22}H_{14}O_2$ requires C, 86·7; H, 4·9%). The n.m.r. spectrum showed only aromatic protons.

The residue from the mother liquors was chromatographed on alumina to yield the ketone (IX; R = H) (5 mg.) and 1-*phenylnaphthaceno*[1,12-bc]*pyran*-2,7-*dione* (X) (150 mg.), m.p. 313—315° (from benzene), $\lambda_{max.}$ 245, 307, 326, 341, 385, and 423 nm. (ε 50,000, 25,000, 25,000, 25,000, 19,000, and 10,000), $\nu_{max.}$ 1710 and 1650 $cm.^{-1}$ (Found: C, 83·25; H, 3·85. $C_{26}H_{14}O_3$ requires C, 83·4; H, 3·75%). The same compound was obtained when the naphthacenofuran (IX; R = H) was heated under reflux in ethanol with sodium cyanide for 18 hr.

4-[2-(*Cyanohydroxymethyl*)*benzyl*]-2-*phenylnaphtho*[1,8-bc]-*furan*-5-*one* [VI; R = CH(CN)·OH].—The aldehyde (VI; R = CHO) (1·82 g.) in tetrahydrofuran (37 ml.) at 5° was treated with an aqueous solution of sodium cyanide (270 mg. in 10 ml.) added dropwise [after each addition the solution was neutralised with sulphuric acid (0·5N; 11 ml.)] during 20 min. at 0° and the mixture was stirred for a further 1 hr. The product was extracted with chloroform, washed with water, and dried. Evaporation of the extract to 2/3 bulk gave crystals of the *cyanohydrin* [VI; R = CH(CN)·OH] (1·75 g.), m.p. 168—171°, $\lambda_{max.}$ 267 and 400 nm. (ε 57,000 and 27,900), $\nu_{max.}$ 3300 and 1640 $cm.^{-1}$, τ ($Me_2SO$) 5·93 (2H) and 3·92 (1H, s) (Found: C, 80·0; H, 4·7; N, 3·4. $C_{26}H_{17}NO_3$ requires C, 79·8; H, 4·4; N, 3·6%).

The cyanohydrin [VI; R = CH(CN)·OH] (500 mg.) was acetylated overnight, at room temperature, with pyridine (6 ml.) and acetic anhydride (6 ml.). The *acetate* [VI; R = CH(CN)·OAc] was crystallised from benzene (yield 510 mg.); m.p. 167°, $\lambda_{max.}$ 268 and 403 nm. (ε 68,000 and 31,000), $\nu_{max.}$ 1750 and 1640 $cm.^{-1}$ (Found: C, 77·35; H, 4·35; N, 3·35. $C_{28}H_{19}NO_4$ requires C, 77·6; H, 4·4; N, 3·25%).

12-*Hydroxy*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (IX; R = OH).—The cyanohydrin acetate [VI; R = CH(CN)·OAc] (100 mg.) was added to a suspension of sodium hydride (60 mg.; 50% dispersion) in dry dimethyl sulphoxide (15 ml.). When hydrogen evolution had ceased (1 hr.), acetic acid was added and the mixture was diluted with water. The precipitate was chromatographed over G3 alumina to give yellow plates of the *naphthacenofuran* (IX; R = OH) (78 mg.), m.p. 260° (decomp.), $\nu_{max.}$ 3250 and 1665 cm.$^{-1}$ (Found: C, 83·2; H, 3·85. $C_{25}H_{14}O_3$ requires C, 82·85; H, 3·9%). The *acetate* (IX; R = OAc), obtained in the usual way, was purified by sublimation (180°/$10^{-4}$ mm.); m.p. 287°, $\lambda_{max.}$ 252, 318, 342, and 422 nm. (ε 7000, 21,000, 20,000, and 40,000), $\nu_{max.}$ 1750 and 1665 cm.$^{-1}$ (Found: C, 79·95; H, 4·05. $C_{27}H_{16}O_4$ requires C, 80·2; H, 4·0%).

12-*Cyano*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (IX; R = CN).—The cyanohydrin [VI; R = CH(CN)·OH] (109 mg.) in pyridine (5 ml.) was treated with benzoyl chloride (0·1 ml.) for 18 hr. at room temperature. The product, obtained by chromatography over alumina (G3), could not be crystallised (yield 153 mg.); $\nu_{max.}$ 1710 and 1640 cm.$^{-1}$.

This material (150 mg.) in dry dimethyl sulphoxide (7 ml.) was treated with sodium hydride (60 mg.; 50% oil dispersion). After 2 hr. excess of hydride was destroyed with acetic acid and the product was obtained by dilution with water. Chromatography over alumina (G3) gave yellow crystals of the *cyano-compound* (IX; R = CN) (108 mg.), m.p. (from benzene) 307°, $\nu_{max.}$ 2240 and 1660 cm.$^{-1}$ (Found: C, 84·25; H, 3·6. $C_{26}H_{13}NO_2$ requires C, 84·1; H, 3·5%).

4-{2-[*Cyano*(*tetrahydropyranyloxy*)*methyl*]*benzyl*}-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* [VI; R = CH(CN)·O·CH·$[CH_2]_4$·O].—The cyanohydrin [VI; R = CH(CN)·OH] (900 mg.) in refluxing dry benzene (100 ml.) containing 2,3-dihydropyran (10 ml.) was treated with concentrated hydrochloric acid (9 drops). After 2 hr. under reflux the solution was cooled, washed with saturated sodium hydrogen carbonate solution (100 ml.), and evaporated. Chromatography of the residue over alumina (G3) gave the *cyanohydrin ether* (754 mg., 70%), m.p. (from benzene–di-isopropyl ether) 146—148°, $\lambda_{max.}$ 267 and 402 nm. (ε 17,000 and 22,000), $\nu_{max.}$ 2230 and 1640 cm.$^{-1}$, τ 5·89 (2H, s), and 4·16 and 4·00 (1H, mixture of diastereoisomers) (Found: C, 78·2; H, 5·55; N, 2·85. $C_{31}H_{25}NO_4$ requires C, 78·3; H, 5·3; N, 2·95%).

12β-*Cyano*-6aα,7,12,12aα-*tetrahydro*-12α-*tetrahydropyranyloxy*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (XI; R¹ = CN, R² = O·CH·$[CH_2]_4$·O).—Anhydrous sodium t-butoxide (1 mol., in t-butyl alcohol) was added to the cyanohydrin ether {VI; R = CH(CN)·O·CH·$[CH_2]_4$·O} (490 mg.) in ether (350 ml.) under reflux. After 1 hr. the solution was quenched with water and neutralised ($CO_2$), and the ethereal phase was evaporated. Chromatography of the residue over alumina (G3) gave crystals of the *cyclic product* (XI; R¹ = CN, R² = O·CH·$[CH_2]_4$·O). Recrystallised from chloroform–benzene (yield 305 mg., 62%), this had m.p. 215—218°, $\lambda_{max.}$ 277 and 352 nm. (ε 20,700 and 14,300), $\nu_{max.}$ 1695 cm.$^{-1}$, τ 5·22 (1H, d, *J* 6 Hz) and signals for 12 aromatic H (Found: C, 78·4; H, 5·55; N, 2·85. $C_{31}H_{25}NO_4$ requires C, 78·3; H, 5·3; N, 2·95%).

12β-*Cyano*-6aα,7,12,12aα-*tetrahydro*-12α-*hydroxy*-1-*phenylnaphthaceno*[1,12-bc]*furan*-6-*one* (XI; R¹ = CN, R² = OH).—The tetracyclic ether (XI; R¹ = CN, R² = O·CH·$[CH_2]_4$·O) (600 mg.) in ethanol (60 ml.) and dilute hydrochloric acid (12 ml.) was heated under reflux for 30 min. After addition of water (75 ml.) the solution was cooled to 0° and the *cyanohydrin* (XI; R¹ = CN, R² = OH) thereby obtained was recrystallised from chloroform–benzene (yield 372 mg., 75%); m.p. 219—222°, $\lambda_{max.}$ 259 and 358 nm. (ε 28,200 and 12,200), $\nu_{max.}$ 3400, 1700, and 1670 cm.$^{-1}$ (Found: C, 80·05; H, 4·35; N, 3·45. $C_{26}H_{17}NO_3$ requires C, 79·8; H, 4·4; N, 3·6%).

Treatment of this product with cold concentrated sulphuric acid gave the aromatic nitrile (IX; R = CN), identical (m.p. and mixed m.p.) with the material described above.

6aα,12aα-*Dihydro*-1-*phenyl*-7H-*naphthaceno*[1,12-bc]-*furan*-6,12-*dione* (XII; S¹S² = O, R¹R² = O).—The cyclic cyanohydrin (XI; R¹ = CN, R² = OH) (100 mg.) in benzene was slowly eluted through a column of G3 alumina. Evaporation of the eluate gave the *diketone* (XII; S¹S² = O, R¹R² = O) (74 mg., 76%), m.p. 234—235° (from benzene), $\nu_{max.}$ 1680 cm.$^{-1}$, τ 5·20 (1H, d, *J* 6·5 Hz), $\lambda_{max.}$ 264, 281, 299, 310, and 360 nm. (ε 25,580, 18,690, 15,740, 13,380, and 12,590) (Found: C, 82·1; H, 4·6. $C_{25}H_{16}O_3$ requires C, 82·4; H, 4·45%). Treatment of this substance with base in the presence of air gave the phenol (IX; R = OH).

6aα,7-*Dihydro*-6β-*hydroxy*-1-*phenyl*-6H-*naphthaceno*-[1,12-bc]*furan*-12(12aαH)-*one* (XII; S¹ = OH, S² = H, R¹R² = O).—The cyanohydrin (XI; R¹ = CN, R² = OH) (350 mg.) in absolute propan-2-ol (42 ml.) and toluene (28 ml.) was heated under reflux with aluminium isopropoxide (1·4 g.) in propan-2-ol (7 ml.). After 18 hr. the cooled solution was quenched with water and extracted with chloroform. The residue obtained by evaporation of the solvent was chromatographed over alumina (G3) to provide the *ketol* (XII; S¹ = OH, S² = H, R¹R² = O) (151 mg., 46%), m.p. 190—191° (from di-isopropyl ether–benzene), $\lambda_{max.}$ 245 and 308 nm. (ε 16,000 and 24,000), $\nu_{max.}$ 3425 and 1665 cm.$^{-1}$, τ 5·60 (1H, *J* 5·5 Hz) and 5·01 (1H, *J* 3 Hz) (Found: C, 83·45; H, 5·3. $C_{25}H_{18}O_3,C_6H_6$ requires C, 83·75; H, 5·45%).

When this product (20 mg.) was shaken in dry benzene with manganese dioxide (500 mg.) for 18 hr. it was converted into the diketone (XI; R¹R² = O), identical (m.p. and mixed m.p.) with an authentic specimen.

Acetylation of the ketol (XII; S¹ = OH, S² = H, R¹R² = O) (100 mg.) in pyridine (5 ml.) and acetic anhydride (2 ml.) at room temperature for 18 hr. gave the *acetate* (XII; S¹ = OAc, S² = H, R¹R² = O). After chromatography over alumina and crystallisation from benzene–di-isopropyl ether (yield 74 mg., 80%), this had m.p. 234—236°, $\nu_{max.}$ 1725 and 1680 cm.$^{-1}$, τ 8·88 (3H, s), 5·51 (1H, d, *J* 5·5 Hz), 3·63 (1H, d, *J* 3 Hz) (Found: C, 80·1; H, 5·0. $C_{27}H_{20}O_4,0{\cdot}33C_6H_6$ requires C, 80·2; H, 5·10%).

*Ozonolysis of the Ketol* (XII; S¹ = OH, S² = H, R¹R² = O).—The ketol (40 mg.) in methanol (12 ml.) containing pyridine (10 mg.) was ozonolysed at −60° for 12 min. After removal of excess of ozone with nitrogen the residue was hydrogenated (5% palladium–charcoal) at −60° for 30 min. The product, a yellow oil, had $\nu_{max.}$ 1735, 1680, 1600, and 3450 cm.$^{-1}$, $\lambda_{max.}$ 405 and 387 nm. T.l.c. indicated the presence of several products, which could not be separated.

6aα,7,12,12aα-*Tetrahydro*-6β-*isopropoxy*-1-*phenyl*-12α-

*tetrahydropyranyloxy*-6H-*naphthaceno*[1,12-bc]*furan*-12β-*carboxamide* (XII; $S^1$ = OPr$^i$, $S^2$ = H, $R^1$ = CO·$NH_2$, $R^2$ = O·CH·$[CH_2]_4$·O).—The ketone (XI; $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O) (400 mg.) in absolute propan-2-ol (50 ml.) containing aluminium isopropoxide (500 mg.) was heated under reflux for 18 hr., then cooled. Water (100 ml.) was added and the solution was extracted with chloroform. Chromatography of the extract over alumina gave the *amide* (160 mg., 38%), m.p. 226—229° (from benzene–di-isopropyl ether), $\lambda_{max.}$ 310 nm. (ε 25,900), $\nu_{max.}$ 3470, 3330, 3220, 1695, and 1630 cm.$^{-1}$, τ 9·20 (6H, d, *J* 6 Hz), 5·56 (1H, d, *J* 6 Hz), and 5·19 (1H, d, *J* 3 Hz) (Found: C, 75·9; H, 6·6; O, 15·3; active H, 0·42. $C_{34}H_{35}NO_5$ requires C, 75·95; H, 6·55; O, 14·9; active H, 0·38%).

*The Imino-lactone* (XIV; R = H).—The ketone (XI; $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O) (500 mg.) in tetrahydrofuran (100 ml.) was treated with lithium tri-t-butoxyaluminium hydride (1 g.) at room temperature for 24 hr. Work-up by pouring into water, extraction, and recrystallisation from benzene–light petroleum (b.p. 30—40°) gave the *imino-lactone* (XIV; R = H) in variable yield, m.p. 198—200°, $\lambda_{max.}$ 309 nm. (ε 24,600), $\nu_{max.}$ 3300 and 1655 cm.$^{-1}$ (Found: C, 77·7; H, 5·75; O, 13·15. $C_{31}H_{27}NO_4$ requires C, 77·95; H, 5·7; O, 13·4%). The same imino-lactone was obtained by reducing the ketone (XI; $R^1$ = CN; $R^2$ = O·CH·$[CH_2]_4$·O) with sodium borohydride in ethanol.

12β-*Aminomethyl*-6aα,7,12,12aα-*tetrahydro*-1-*phenyl*-12α-*tetrahydropyranyloxy*-6H-*naphthaceno*[1,12-bc]*furan*-6β-*ol* (XII; $S^1$ = OH, $S^2$ = H, $R^1$ = $CH_2$·$NH_2$, $R^2$ = O·CH·$[CH_2]_4$·O).—The cyanohydrin ether (XI; $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O) was reduced in ethereal solution with lithium aluminium hydride at room temperature. Chromatography of the product over alumina afforded the *amine*, m.p. 232—235° (decomp.) (from benzene–di-isopropyl ether), $\nu_{max.}$ 3430, 3350, and 3200 cm.$^{-1}$ (Found: C, 77·55; H, 6·95; N, 2·45. $C_{31}H_{31}NO_4$ requires C, 77·3; H, 6·5; N, 2·9%).

6aα,7,12,12aα-*Tetrahydro*-6β-*hydroxy*-1-*phenyl*-12α-*tetrahydropyranyloxy*-6H-*naphthaceno*[1,12-bc]*furan*-12β-*carbonitrile* (XII; $S^1$ = OH, $S^2$ = H, $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O).—The ketone (XI; $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O) (585 mg.) in tetrahydrofuran (150 ml.) was treated with lithium tri-t-butoxyaluminium hydride (750 mg.) and stirred at room temperature [u.v. control (350 nm.)]. Two-thirds of the solvent was removed in vacuum, and the solution was added to water. The product, extracted with chloroform, was crystallised from ethyl acetate–light petroleum to give the *alcohol* (347 mg.), m.p. 175°, $\lambda_{max.}$ 308 nm. (ε 18,600), $\nu_{max.}$ 3550 cm.$^{-1}$ (Found: C, 78·4; H, 5·6; O, 13·5. $C_{31}H_{27}NO_4$ requires C, 78·4; H, 5·7; O, 13·4%).

Acetylation of this material (102 mg.) in chloroform (10 ml.) containing acetic anhydride (5 ml.) and pyridine (5 ml.) at room temperature for 18 hr., followed by chromatography of the product over G3 alumina, gave the *acetate* (XII; $S^1$ = OAc, $S^2$ = H, $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O) (97 mg.), m.p. 205—209° (from di-isopropyl ether), $\lambda_{max.}$ 310 nm. (ε 21,000), $\nu_{max.}$ 1730 cm.$^{-1}$, τ 8·80 (3H), 5·18 (1H, d, *J* 5 Hz), and 3·67 (1H, d, *J* 3 Hz) (Found: C, 76·1; H, 5·9. $C_{33}H_{29}NO_5$ requires C, 76·3; H, 5·65%).

This substance was correlated with the earlier described keto-acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) by sequential acid hydrolysis to the cyanohydrin (XII; $S^1$ = OAc, $S^2$ = H, $R^1$ = CN, $R^2$ = OH), followed by chromatography over alumina (G3). The keto-acetate obtained (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) was identical (m.p. and mixed m.p.) with an authentic sample.

6β-*Acetoxy*-5,5a,6,11,11a,12-*hexahydro*-10-*hydroxy*-11-*oxo*-12α-*tetrahydropyranyloxynaphthacene*-12β-*carbonitrile* (XV; R = O·CH·$[CH_2]_4$·O).—The tetrahydropyranyl ether (XII; $S^1$ = OAc, $S^2$ = H, $R^1$ = CN, $R^2$ = O·CH·$[CH_2]_4$·O) (140 mg.) in dry chloroform (20 ml.) at −20° was ozonised for 40 min. The excess of ozone was removed in a stream of nitrogen, and the solution was shaken with aqueous potassium iodide and sodium thiosulphate, acidified with carbon dioxide, and evaporated. The residue was chromatographed over acid-washed alumina (G5) to yield the *cyanohydrin ether* (59 mg., 48%), m.p. 183—185° (from di-isopropyl ether) (Found: C, 69·8; H, 5·55. $C_{26}H_{25}NO_6$ requires C, 69·8; H, 5·65%).

6β-*Acetoxy*-5,5a,6,11,11a,12-*hexahydro*-10,12α-*dihydroxy*-11-*oxonaphthacene*-12β-*carbonitrile* (XV; R = OH).—The tetrahydropyranyl ether (XV; R = O·CH·$[CH_2]_4$·O) (38 mg.) was warmed on a steam-bath in ethanol (10 ml.) containing hydrochloric acid (25%; 5 drops). Water (20 ml.) was added and the solution was cooled to 0°. Crystallisation from benzene–di-isopropyl ether gave the *cyanohydrin* (XV; R = OH) (28 mg., 90%), m.p. 193° (decomp.), $\lambda_{max.}$ 264, 271, 275, and 285 nm. (ε 1500, 1700, 1700, and 1250), $\nu_{max.}$ 3450, 1745, and 1600 cm.$^{-1}$, τ 8·35 (3H) and 3·64 (1H, d, *J* 3 Hz) (Found: C, 69·8; H, 4·8. $C_{21}H_{17}NO_5$ requires C, 69·4; H, 4·7%).

6β-*Acetoxy*-5a,11a-*dihydronaphthacene*-11(6H),12(5H)-*dione* (XIII; R = Ac).—The oxo-cyanohydrin (XV; R = OH) (18 mg.) was dissolved in benzene and treated, at room temperature, with alumina (G5). The air-dried alumina was extracted (Soxhlet) with chloroform. The non-crystalline product was identical in u.v. spectrum ($\lambda_{max.}$ 392 and 440 nm.) and t.l.c. behaviour with the substance (XIII; R = Ac) produced by ozonolysis of the keto-acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) as in the following procedure.

The keto-acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) (250 mg.) in chloroform (8 ml.) and anhydrous methanol (8 ml.) containing pyridine (2—3 drops) was ozonised at −60° for 50 min. The excess of ozone was removed (nitrogen) and the still cooled solution was hydrogenated (5% palladium–calcium carbonate; 20 mg.). Chromatography over silica gel–Celite '545' (1 : 1 w/w) gave the *naphthacene* (XIII; R = Ac) (13·2 mg., 6%), m.p. (from light petroleum) 169—171°, $\lambda_{max.}$ 409, 392, 312, 262, and 248 nm. (ε 26,500, 29,700, 6140, 10,900, and 12,500), $\nu_{max.}$ 3250, 1735, 1620, 1600, and 1565 cm.$^{-1}$, τ 8·72 (3H) and 3·90 (1H, d, *J* 3 Hz) (Found: C, 71·75; H, 4·85. $C_{20}H_{16}O_5$ requires C, 71·45; H, 4·8%), $M^+$ 336 ($C_{20}H_{16}O_5$).

6a,7-*Dihydro*-1-*phenyl*-6H-*naphthaceno*[1,12-bc]*furan*-12(12aH)-*one* (XII; $S^1S^2$ = H, $R^1R^2$ = O) (with N. J. A. Gutteridge).—The keto-acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R$ = O) (200 mg.) in glacial acetic acid (50 ml.) containing hydrochloric acid (1 ml.) was hydrogenolysed

over prereduced 10% palladium–carbon. After absorption of 2 mol. (90 min.) the filtered solution was cooled to 0° (solid $CO_2$) and added to ice–water. Extraction with chloroform (under $CO_2$) and evaporation of the extract at room temperature gave an oil, which was chromatographed on alumina (G3) to yield the *deoxy-compound* (XII; $S^1 = S^2 = H$, $R^1R^2 = O$) (70 mg., 41%), m.p. (from light petroleum) 207—208°, $\lambda_{max.}$ 320, 306, 294, 257, 247, and 239 nm. (ε 17,000, 27,000, 24,000, 14,600, 19,700, and 18,200), τ 8·73 (1H), 5·58 (1H), and 6·51—7·10 (4H, m) (Found: C, 85·2; H, 5·25. $C_{25}H_{18}O_2$ requires C, 85·7; H, 5·2%).

5-*Benzylthio*-4,5-*dihydro*-2-*phenyl*-3H-*naphtho*[1,8-bc]-*furan* (XVI; R = S·$CH_2$Ph) (with N. J. A. Gutteridge).—The alcohol (XVI; R = OH) [1] (250 mg.) in benzene (2·5 ml.) was heated under reflux with toluene-*p*-sulphonic acid (10 mg.) and toluene-α-thiol (0·23 ml.) for 3 hr. The cooled mixture was washed with sodium hydrogen carbonate solution, and then extracted with chloroform. Evaporation of the extract afforded the *thioether* (XVI; R = S·$CH_2$Ph) (320 mg., 98%), m.p. 98° (from light petroleum), $\lambda_{max.}$ 323, 309, 299, 248, and 234 nm. (ε 25,900, 32,100, 26,400, 10,800, and 15,300), τ 7·76 (2H), 6·91 (2H), 6·22 (2H), and 5·84 (1H) (Found: C, 80·55; H, 6·0; S, 8·8. $C_{24}H_{20}OS$ requires C, 80·9; H, 5·65; S, 9·0%).

When the substance (XVI; R = S·$CH_2$Ph) (250 mg.) was refluxed with Raney nickel in benzene for 5 hr., the *deoxy-compound* (XVI; R = H) was obtained. Chromatographed on alumina and recrystallised from light petroleum (117 mg., 71%), this had m.p. 53—55° and was identical with the authentic material prepared by direct hydrogenolysis of 3,4-dihydro-2-phenylnaphtho[1,8-*bc*]furan-5-one over 10% palladium–carbon; yield 84%, m.p. 55°, $\lambda_{max.}$ 320, 306, 253, and 230 nm. (ε 24,900, 32,300, 12,700, and 21,400), $\nu_{max.}$ 1621 and 1054 cm.$^{-1}$, τ 7·95 (2H), 7·19 (2H), and 7·03 (2H) (Found: C, 87·1; H, 5·75. $C_{17}H_{14}O$ requires C, 87·15; H, 6·0%).

1-*Phenyl*-7H-*naphthaceno*[1,12-bc]*furan*-12(12aH)-*one* (XVII) (with N. J. A. Gutteridge).—The keto-acetate (XII; $S^1$ = OAc, $S^2$ = H, $R^1R^2$ = O) (250 mg.) in dry benzene (150 ml.) was heated with toluene-*p*-sulphonic acid (a few crystals) under reflux under nitrogen for 16 hr. The cooled solution was poured into aqueous sodium hydrogen carbonate and extracted with chloroform; the extract was dried and evaporated. The residue was chromatographed on alumina (G3). Elution with benzene gave two fractions: (a) the *ketone* (XVII) (158 mg., 73%), m.p. (from benzene) 201°, $\lambda_{max.}$ 412, 318, 306, 281, and 231 nm. (ε 5000, 5900, 7000, 31,000, and 34,000), $\nu_{max.}$ 1660, 1635, 1608, and 1585 cm.$^{-1}$, *m/e* 348 ($M^+$, accurate mass corresponding to $C_{25}H_{16}O_2$); (b) phenol (XVIII) (46 mg., 21%), m.p. 202—204°, $\lambda_{max.}$ 306, 289, and 256 nm. $\nu_{max.}$ 3550, 1660, 1608, and 1577 cm.$^{-1}$, τ 5·32 (2H); the *mono-acetate* had m.p. (from benzene) 291—220°, $\lambda_{max.}$ 322, 285, 275, 248, and 223 nm. (ε 14,000, 25,000, 26,000, 28,000, and 42,000), $\nu_{max.}$ 1761, 1605, and 1567 cm.$^{-1}$, τ 8·79 (3H, s, shielded by 1-Ph) and 5·40 (2H) (Found: C, 83·2; H, 4·9. $C_{27}H_{18}O_3$ requires C, 83·05; H, 4·65%).

*Methyl* 3-*Formyl*-2,6-*dimethoxy*-4-*methylbenzoate* (XXI).—Methyl 3-formyl-2,6-dihydroxy-4-methylbenzoate (100 mg.) in acetone (25 ml.) containing potassium carbonate (1 g.) and methyl iodide (1 ml.) was heated under gentle reflux for 24 hr. Further portions (1 ml.) of methyl iodide were added after 4 and 10 hr. The cooled solution was poured into dilute sodium hydroxide solution; the mixture was extracted with chloroform and the extracts were dried and evaporated. The *dimethyl ether* (XXI) crystallised from cyclohexane as white needles (79 mg., 70%), m.p. 97—99°, $\lambda_{max.}$ 276, 233, and 210 nm., $\nu_{max.}$ 1735 and 1680 cm.$^{-1}$, τ 7·40 (3H), 6·11 (3H), 6·08 (3H), 6·06 (3H), 3·42 (1H), and −0·35 (1H) (Found: C, 60·55; H, 5·95. $C_{12}H_{14}O_5$ requires C, 60·50; H, 5·9%).

*Dehydrogenation of* 3,4-*Dihydro*-2-*phenylnaphtho*[1,8-bc]-*furan*-5-*one* (V).—The dihydro-compound (V) (106 mg.) and dichlorodicyano-*p*-benzoquinone (103 mg.) in toluene (12 ml.) were heated under reflux for 6 hr. The solution was cooled, decanted from the crystalline material, and chromatographed on alumina (G3). Elution with chloroform–benzene gave 2-phenylnaphtho[1,8-*bc*]furan-5-one (82 mg.), m.p. and mixed m.p.[1] 140°.

4-(5-*Acetoxy*-2-*formyl*-3-*hydroxy*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXIV; $R^1$ = H, $R^2$ = Ac).—The acetate (XXIII; R = Ac) [1] (40 mg.) in dry dimethylformamide (8 ml.) containing glacial acetic acid (1 ml.) and prereduced 5% palladium–charcoal (10 mg.) was hydrogenolysed until 1·05 mol. of hydrogen had been taken up. The solution was filtered into 2N-hydrochloric acid (25 ml.) and extracted with benzene. The extract was dried ($Na_2SO_4$) and evaporated to yield an oil. Crystallisation from chloroform and ether gave pale yellow needles (30 mg.) of the *aldehyde phenol* (XXIV; $R^1$ = H, $R^2$ = Ac), m.p. 243°, $\nu_{max.}$ 1755 and 1675 cm.$^{-1}$, $\lambda_{max.}$ 356 nm. (ε 15,200) (Found: C, 70·1; H, 4·4. $C_{29}H_{22}O_8$ requires C, 69·85; H, 4·45%).

4-(5-*Acetoxy*-2-*formyl*-3-*methoxy*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXIV; $R^1$ = Me, $R^2$ = Ac).—The aldehyde phenol (XXIV; $R^1$ = H, $R^2$ = Ac) (75 mg.) in chloroform (15 ml.) and benzene (15 ml.) containing methyl iodide (1 ml.) and silver oxide (100 mg.) was shaken for 2 days, and the silver residues were filtered off through Celite 545. The solvent was evaporated off to leave an orange oil, which was chromatographed on G3 acid alumina, to yield the *methyl ether* (XXIV; $R^1$ = Me, $R^2$ = Ac) (52 mg.), as pale yellow needles (from chloroform–ether), m.p. 181—182°, $\nu_{max.}$ 1760, 1730, 1690, and 1680 cm.$^{-1}$, $\lambda_{max.}$ 265 and 355 nm. (ε 27,200 and 14,900), τ 7·72 (3H), 6·07 (6H), 3·01 (1H), and −0·50 (1H) (all s) (Found: C, 70·45; H, 4·7. $C_{30}H_{24}O_8$ requires C, 70·3; H, 4·7%).

*Methyl* 3′,4′-*Dihydro*-1,5-*dihydroxy*-7-*methoxy*-5′-*oxo*-2′-*phenylspiro*{*indane*-2,4′-*naphtho*[1,8-bc]*furan*}-6-*carboxylate* (XXV; $R^1$ = $R^2$ = H). The aldehyde (XXIV; $R^1$ = Me, $R^2$ = Ac) (250 mg.) in methanolic 0·2N-sodium methoxide (15 ml.) was heated under reflux under nitrogen for 40 min. The solution was poured into 6N-hydrochloric acid and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give an oil, which yielded white crystals of the *phenol* (XXV; $R^1$ = $R^2$ = H), m.p. (from benzene) 230—233°, $\nu_{max.}$ 3400, 1680, and 1665 cm.$^{-1}$, $\lambda_{max.}$ 260, 275, and 356 nm. (ε 23,700, 22,100, and 13,300) (Found: C, 71·35; H, 4·8. $C_{28}H_{22}O_7$ requires C, 71·5; H, 4·7%).

Methylation with methyl iodide–silver oxide gave the *ether* (XXV; $R^1$ = H, $R^2$ = Me), $\nu_{max.}$ 3450, 1725, and 1670 cm.$^{-1}$. Acetylation of this product gave the *acetate* (XXV; $R^1$ = Ac, $R^2$ = Me), m.p. (from benzene–light petroleum) 224—226°, $\nu_{max.}$ 1740, 1720, and 1685 cm.$^{-1}$, $\lambda_{max.}$ 275 and 354 nm. (ε 22,200 and 12,900), τ 8·33 (3H), 7·28 (2H), 6·60 (2H), 6·38 (3H), 6·13 (6H), 3·56 (1H), and

3·30 (1H) (Found: C, 70·85; H, 4·95. $C_{31}H_{26}O_8$ requires C, 70·7; H, 5·0%).

4-(2-*Cyano*-3,5-*dimethoxy*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXVI; $R^1 = R^2 = Me$).—The hydroxybenzisoxazole (XXIII; R = H) (1·1 g.) in dry dimethylformamide (100 ml.) containing 5% palladium–charcoal (200 mg.) was hydrogenolysed until 1·1 mol. of hydrogen had been taken up. The solution was filtered into 2N-hydrochloric acid and the resulting solid was separated by filtration and dried *in vacuo*. The solid was redissolved in chloroform and benzene containing methyl iodide (5 ml.) and silver oxide (2 g.) and shaken for 18 hr. The solution was filtered through Celite 545 and evaporated to yield an oil, which was chromatographed on G3 alumina. The major fraction from the column was evaporated to an oil, which yielded yellow crystals of the *nitrile* (XXVI; $R^1 = R^2 = Me$) (110 mg.), m.p. 163—164° (from methanol), $\nu_{max.}$ 2270, 1735, and 1685 cm.$^{-1}$, $\tau$ 6·19 (3H), 6·08 (3H), 5·99 (3H), and 3·28 (1H) (Found: C, 72·65; H, 5·0; N, 2·5. $C_{29}H_{23}NO_6$ requires C, 72·35; H, 4·8; N, 2·9%).

3,4-*Dihydro*-4-(6-*methoxy*-7-*methoxycarbonylbenzisoxazol*-4-*ylmethyl*)-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXIII; R = Me).—The hydroxybenzisoxazole (XXIII; R = H) (100 mg.) in chloroform (10 ml.) and benzene (10 ml.) containing methyl iodide (2 ml.) and silver oxide (200 mg.) was shaken overnight. The mixture was filtered through Celite 545 and evaporated to yield an oil. This oil crystallised from benzene–di-isopropyl ether to give yellow needles of the *ether* (XXIII; $R^1 = Me$) (87 mg., 85%), m.p. 190—192°, $\nu_{max.}$ 1690 and 1680 cm.$^{-1}$, $\tau$ 6·16 (3H), 6·01 (3H), 3·18 (1H), and 1·37 (1H) (Found: C, 72·0; H, 4·79; N, 2·95. $C_{28}H_{21}NO_6$ requires C, 71·95; H, 4·55; N, 3·0%).

4-(2-*Formyl*-3-*hydroxy*-5-*methoxy*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXIV; $R^1 = H$, $R^2 = Me$).—The methoxybenzisoxazole (XXIII; R = Me) (400 mg.) in dimethylformamide (90 ml.) containing acetic acid (10 ml.) and prereduced 5% palladium–charcoal (200 mg.) was hydrogenolysed until 1·05 mol. of hydrogen had been taken up. The solution was filtered into 2N-hydrochloric acid (400 ml.) and extracted with chloroform. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give an oil, which was treated with acetone–ethanol to yield the *phenol* (XXIV; $R^1 = H$, $R^2 = Me$) (215 mg., 54%), m.p. 206—208°, $\nu_{max.}$ 1725, 1690, and 1640 cm.$^{-1}$, $\lambda_{max.}$ 238, 277, 326, and 347 nm., $\tau$ 6·29 (3H), 6·08 (3H), 3·74 (1H), −0·25 (1H), and −2·53 (1H, exchanged with $D_2O$) (Found: C, 71·9; H, 4·95. $C_{28}H_{22}O_7$ requires C, 71·5; H, 4·7%).

4-(2-*Formyl*-3,5-*dimethoxy*-4-*methoxycarbonylbenzyl*)-3,4-*dihydro*-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXIV; $R^1 = R^2 = Me$).—The aldehyde (XXIV; $R^1 = H$, $R^2 = Me$) in chloroform (10 ml.) and benzene (10 ml.) containing methyl iodide (2 ml.) and silver oxide (200 mg.) was shaken for 30 hr. at room temperature. The mixture was filtered through Celite 545 and evaporated to produce an orange oil. This oil was chromatographed on G3 alumina (5% ethyl acetate–benzene) to give the *methyl ether* (XXIV; $R^1 = R^2 = Me$), which formed needles (99 mg.), m.p. 187—189° (from chloroform–ether), $\nu_{max.}$ 1730, 1690, and 1680 cm.$^{-1}$, $\lambda_{max.}$ 237, 276, and 358 nm. ($\varepsilon$ 27,900, 30,100, and 13,400), $\tau$ 6·20 (3H), 6·08 (3H), 6·04 (3H), 3·35 (1H), and −0·35 (1H) (Found: C, 72·1; H, 5·1. $C_{29}H_{24}O_7$ requires C, 71·9; H, 5·0%).

4-(2-*Formyl*-3,5-*dimethoxy*-4-*methoxycarbonylbenzyl*)-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXVII).—The aldehyde (XXIV; $R^1 = R^2 = Me$) (300 mg.) and 2,3-dichloro-5,6-dicyanobenzoquinone (700 mg.) in dry toluene (70 ml.) were heated under reflux under nitrogen for 30 hr. After cooling, a black solid was filtered off. The solution was evaporated to yield an oily residue which, in benzene, was chromatographed on G3 alumina. The fraction containing the required product was further chromatographed over silica gel (1 part) and Celite (2 parts). Elution with 20% acetone–light petroleum gave bright yellow crystals of the *dehydro-aldehyde* (XXVII) (174 mg.), m.p. 181—184° (from benzene–di-isopropyl ether), $\nu_{max.}$ 1735, 1685, and 1635 cm.$^{-1}$, $\lambda_{max.}$ 270 and 405 nm. ($\varepsilon$ 27,000 and 29,000), $\tau$ 6·12 (3H), 6·07 (6H), 5·53 (2H), 3·00 (1H), and −0·50 (1H) (Found: C, 75·15; H, 5·25. $C_{29}H_{22}O_7,C_6H_6$ requires C, 75·0; H, 5·05%).

4-{2-[*Cyano*(*hydroxy*)*methyl*]-3,5-*dimethoxy*-4-*methoxycarbonylbenzyl*}-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXVIII).—The aldehyde (XXVII) (200 mg.) in redistilled tetrahydrofuran (20 ml.) was stirred at 0° while aqueous sodium cyanide (0·45; 1 ml.) was added. The solution was carefully neutralised by dropwise addition of 0·24N-sulphuric acid. Further portions (1 ml.) of sodium cyanide solution were added (the mixture was neutralised each time with sulphuric acid) until the reaction was shown to be complete by t.l.c. The solution was poured into chloroform and the organic layer was washed with water and dried ($Na_2SO_4$). Careful evaporation gave an oil, which crystallised from chloroform–ether to give the *cyanohydrin* (XXVIII) (152 mg., 84%), m.p. 182—185°, $\nu_{max.}$ 3300, 1735, and 1635 cm.$^{-1}$, $\tau$ 6·32 (3H), 6·10 (3H), 6·06 (3H), 4·00 (1H), and 3·43 (1H) (Found: C, 70·9; H, 4·7; N, 2·6. $C_{30}H_{23}NO_7$ requires C, 70·7; H, 4·55; N, 2·75%).

4-{2-[*Cyano*(*tetrahydropyranyloxy*)*methyl*]-3,5-*dimethoxy*-4-*methoxycarbonylbenzyl*}-2-*phenylnaphtho*[1,8-bc]*furan*-5-*one* (XXIX).—The cyanohydrin (XXVIII) (117 mg.) and 2,3-dihydropyran (1 ml.) in benzene (50 ml.) were heated under reflux, with addition of conc. hydrochloric acid (1 drop). After 2·5 hr. the cooled solution was poured into dilute sodium hydrogen carbonate solution; the benzene layer was separated, washed with water, and dried ($Na_2SO_4$). The oily product was chromatographed on G3 neutral alumina. Elution with benzene gave the *cyanopyranyl ether* (XXIX) (90 mg., 66%), m.p. (from di-isopropyl ether) 191—194°, $\nu_{max.}$ 1730 and 1640 cm.$^{-1}$, $\lambda_{max.}$ 210, 266, and 403 nm. ($\varepsilon$ 44,100, 14,100, and 21,700), $\tau$ 8·40 (6H), 6·29 and 6·25 (3H), 6·08 (3H), 6·06 (3H), 5·69 (2H), 4·03 and 3·93 (1H), and 3·43 (1H) (Found: C, 70·55; H, 5·2; N, 2·3. $C_{35}H_{31}NO_8$ requires C, 70·8; H, 5·25; N, 2·35%).

*Attempted Cyclisation of the Tetrahydropyranyl Ether* (XXIX).—The ether (XXIX) (24 mg.) in dry ether (50 ml.) was heated under reflux under nitrogen. Sodium t-butoxide (1 mol.) in t-butyl alcohol was added, and the refluxing was continued overnight. Only starting material was obtained. Use of an excess of potassium t-butoxide produced many decomposition products.

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