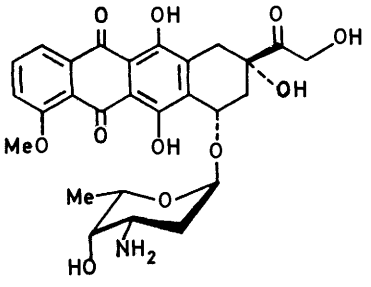
A New Synthetic Approach towards Adriamycin

By **Derek H. R. Barton, Clive C. Dawes, Giovanni Franceschi, Maurizio Foglio, Steven V. Ley,* Philip D. Magnus, William L. Mitchell,** and **Aldemio Temperelli,** Department of Chemistry, Imperial College, London SW7 2AY

An improved route to 3,4-dihydro-2-phenylnaphtho[1,8-*b,c*]furan-5-one (2) and a convenient preparation of furan-3,4-dicarbaldehyde (4) are described. The dihydro-derivative of (2) was condensed with (4) to give 4-(4-formyl-3-furylmethyl)-2-phenylnaphtho[1,8-*b,c*]furan-5-one (5), which after preparation of its 1,3 dithiolan derivative was photocyclised to a polycyclic compound (7). Owing to problems of deprotection of (7) further steps towards adriamycin (1) were abandoned.

THE synthesis of the biologically important molecule adriamycin (1) has received considerable attention over recent years.[1] Our interest [2] in the construction of tetracycline antibiotics using the versatile perinaphthofuran (2) to control regioselectivity prompted us to investigate its use as a suitable precursor for adriamycin.



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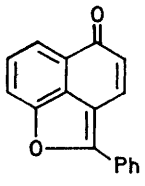


(2)

By analogy it was argued that (2), after hydrogenation, could be condensed with furan-3,4-dicarbaldehyde (4) to furnish (5), which after suitable protection to give (6) could be photocyclised [3] to compound (7). Deprotection of (7) to give the diketone (8) followed by conversion to an isobenzofuran intermediate (9) and subsequent trapping with methyl vinyl ketone could form an adduct (10), which could be reasonably transformed into daunamycinone (11), a compound which had previously been converted to (1) [4] (Scheme 1).

RESULTS AND DISCUSSION

As the preparation of the perinaphthofuran (2) from 1,5-dihydroxynaphthalene and benzoic acid required high temperatures (150 °C), $ZnCl_2$ catalyst, and laborious Soxhlet extraction,[2] a new method of preparation was sought. After considerable experimentation it was found that (2) could most conveniently be prepared in approximately 40-g batches by reaction of 1,5-dihydroxynaphthalene with the Vilsmeier salt of *NN*-dimethylbenzamide ($PhCCl{=}\overset{+}{N}Me_2\ Cl^-$) in 50% yield by direct crystallisation from the reaction mixture. On smaller-scale reactions the yield of (2) could be increased to 90% after chromatography.

Hydrogenation of (2) to the dihydro-derivative (3) had been previously investigated.[2] Although the preparation of furan-3,4-dicarbaldehyde (4) had been described in the literature [5] a new cheap route was developed starting from 1,4-dichlorobut-2-yne giving the dialdehyde in 24% overall yield in reasonable quantities (Scheme 2).

The condensation of the furandicarbaldehyde (4) with the dihydroperinaphthofuran (3) was straightforward. The optimum reaction conditions involved condensation with acetic anhydride and triethylamine at 65 °C with concomitant loss of water and isomerisation of the initially formed exocyclic double bond to give (5) in 60% yield. With quantities of (5) to hand the stage was now set to investigate various methods of cyclisation to produce (7).

In accord with previous work [3] we initially focused our attention on cyclisation of 1,3-dioxolan and tetrahydropyranylcyanohydrin derivatives of (5). However, although these compounds could be prepared readily, attempted cyclisation under a variety of conditions was largely unsuccessful.

Successful cyclisation was achieved using the 1,3-dithiolan derivative (6) under photochemical conditions. The dithiolan was prepared from (5) by a standard procedure and photocyclised using a 750-W tungsten lamp in the presence of lithium hexamethyldisilazide (0.17 equiv.) as catalyst to afford (7) in 80% yield. In typical reactions, 500 mg of (6) could be converted (7) after 3.5 h irradiation in benzene. A dramatic improvement in these reaction conditions could be achieved using a quartz-halogen lamp in an internal-well system. By this method, 500 mg could be similarly cyclised in only 20 min in equally high yield and thus allowed us to build-up quantities of (7). That photocyclisation had taken place to give a *cis*-fused ring system was evident by the ^1H n.m.r. spectrum, which showed 11a-H at τ 5.33 as a doublet, J 5 Hz.

Deprotection of (7) to give the diketone (8), however, proved to be a major problem. A number of literature procedures for the deprotection of 1,3-dithiolans were investigated, the best of which proved to be $Hg(OAc)_2$–H_2O–acetone, which afforded (8) in only 10% yield.

This low yield prompted an investigation into the use of alternative routes. First we prepared the monosulphoxide of (7) in the hope that on warming, the dithiolan ring would open and the intermediate sulphenic acid (12) could be intercepted by the addition of a thiol to give (13). Hydrolysis of (13) would afford the desired diketone (8). Once again under a variety of reaction conditions only very low yields of (8) were obtained.

In a second approach *N*-methyl- and *N*-H-thiazolidine derivatives of (5) were prepared and photocyclised under the usual conditions. Although it was anticipated that the cyclised derivatives should be more easily deprotected, in practice they only reluctantly furnished the diketone in poor yield on hydrolysis.

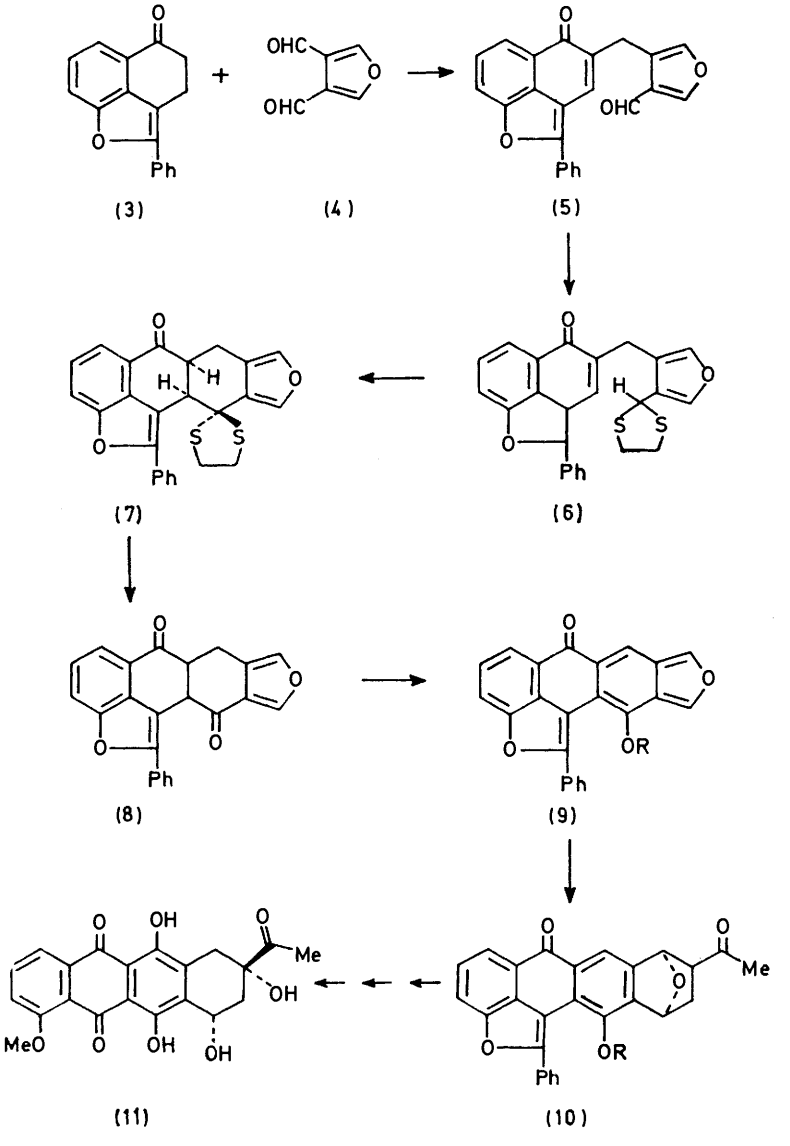
Finally the dehydrogenated dithiolan derivative (14) was prepared from (7) by treatment with selenium dioxide, in the hope that this might hydrolyse more rapidly, and also lead to potential isobenzofuran intermediates (9) required in our synthetic strategy. Attempts to deprotect (14) met with failure, giving either no reaction or leading to mixtures of products which were difficult to characterise.

The most successful preparation of the diketone (8) came from deprotection of the dithiolan (7) using benzeneseleninic anhydride. Although this reagent had given excellent results with other dithiolans[7] only a 24% yield of diketone (8) could be realised in this case.

Owing to the considerable difficulties which arose due to the poor preparation of the key diketone (8) from (7), this synthetic route was abandoned.

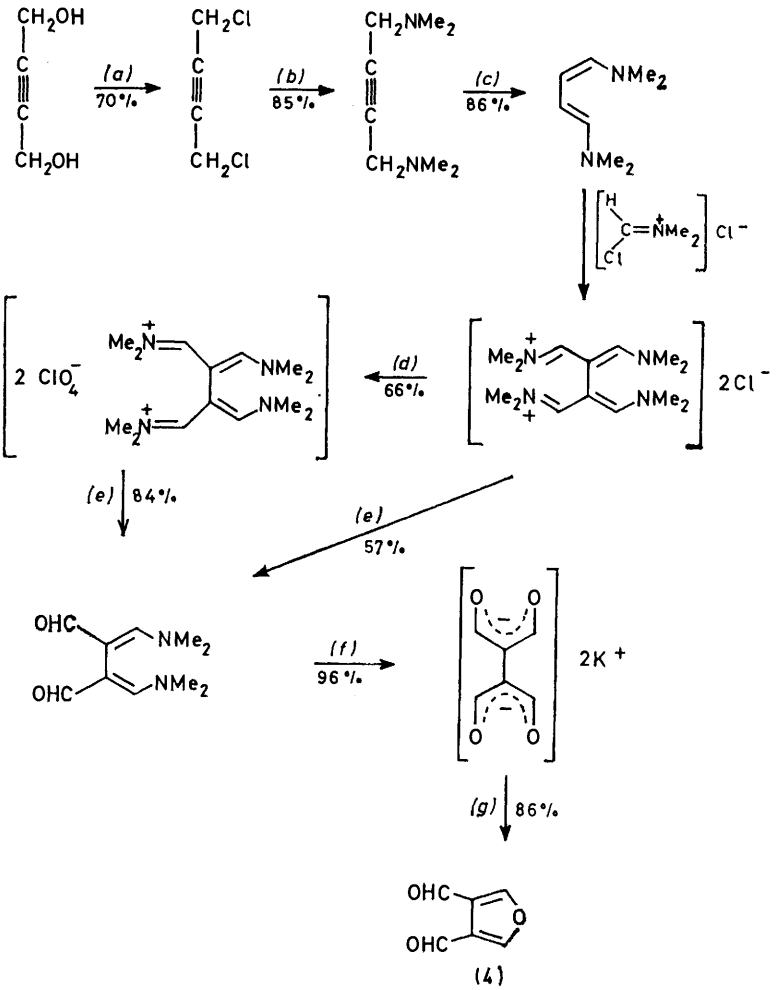
EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were obtained for solutions in $CDCl_3$ ($SiMe_4$ as internal standard) at 60 MHz. Thin-layer and preparative-layer chromatography were carried out on silica gel (Merk GF_{254} Type 60). Light petroleum refers to the fraction of b.p. 60—80 °C. Solutions were dried over sodium sulphate and solvents dried by standard techniques.



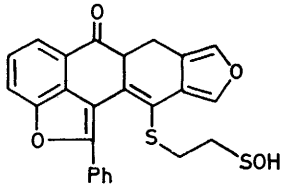
SCHEME 1

The Preparation of 2-Phenylnaphtho[1,8-b,c]*furan-5-one* (2).—Phosgene (160 g, 1.616 mol) was condensed at −78 °C in a 1-l three-necked round-bottomed flask, and



SCHEME 2 (*a*) $POCl_3$, $PhNMe_2$; (*b*) Me_2NH anhydrous; (*c*) Na; (*d*) $NaClO_4$; (*e*) aqueous K_2CO_3, 70 °C; (*f*) KOH; (*g*) H_2SO_4

dichloromethane (300 ml) was added under nitrogen, with stirring. Dimethylbenzamide (120 g, 0.805 mol) in dichloromethane (100 ml) was added dropwise at 0 °C, and the reaction left overnight at room temperature. The



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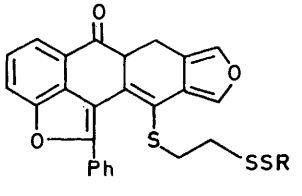

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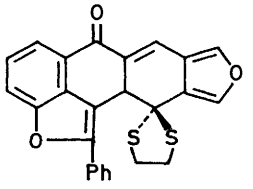

(14)

solvent and excess of phosgene were removed from the reaction mixture by evaporation *in vacuo*, at room temperature overnight, to leave a hard, white solid.

In the same flask, the hard white solid was finely powdered and subsequently mixed intimately with 1,5-dihydroxynaphthalene (51.2 g, 0.320 mol). The flask was equipped with a strong mechanical stirrer (a large Teflon paddle or a Hirschberg stirrer), a nitrogen inlet, and a condenser with a drying tube. The flask was placed in a carefully equilibrated oil-bath, set at 80—82 °C. With vigorous stirring, a solution of triethylamine (160 g, 2.317 mol) and nitrobenzene (120 ml) were rapidly added *via* the condenser (15 s). Throughout the following 40 min, the temperature was maintained as closely as possible to 80—83 °C. The reaction was cooled, and chloroform then ice–water was added. The organic layer was separated, and the aqueous phase was further extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated at room temperature under reduced pressure. Ethanol was added until there was *ca.* 550 ml of solution, and the solution set aside to crystallise overnight at 0 °C. The crystals were filtered off, and washed first with a little cold ethanol, and then with light petroleum, until free of nitrobenzene. The yellow crystals were dried *in vacuo* to afford the perinaphthofuran (2) (37.2 g, 47%), m.p. 137—137.5 °C (from ethanol) (lit.,[2] 137—137.5 °C).

3,4-*Dihydro*-2-*phenylnaphtho*[1,8-b,c]*furan*-5-*one* (3).— Perinaphthofuran (2) (1.00 g, 4.06 mmol) was dissolved in toluene (100 ml) and hydrogenated over alcohol-free W-2

Raney nickel at 40—50 °C and atmospheric pressure. The catalyst was filtered off and replenished as necessary, until the reaction was complete (t.l.c.). When complete the catalyst and solvent were removed, and the residue crystallised from methanol, to give dihydronaphthofuran (3) (0.68 g, 68%), m.p. 113—114 °C (lit.,[2] 113—114 °C).

1,4-Dichlorobut-2-yne.—This was prepared by the literature method,[9] b.p. 56—59.5 °C at 13 mmHg, n_D^{19} 1.508 6 (lit.,[9] 68—69 °C at 17 mmHg, n_D^{19} 1.507 2); τ 5.8 (4 H, s, 2 × CH_2Cl).

1,4-Bis(dimethylamino)but-2-yne.—To a stirred solution of dimethylamine (340 g, 7.56 mol) in benzene (1.5 l), in a flask fitted with a solid CO_2–acetone condenser, was added 1,4-dichlorobut-2-yne (150 g, 1.22 mol) at 5—20 °C during 1 h. After 4 h, the reaction was allowed to warm to room temperature and left for 16 h, and finally heated at 40—50 °C for 1 h. The solution was cooled, and ether (1 l) was added. The filtered solution was evaporated, filtered, and distilled to give 1,4-bis(dimethylamino)but-2-yne (145 g, 85%), b.p. 75.5 °C at 22 mmHg, n_D^{20} 1.455 3 (lit.,[9] b.p. 92 °C at 31 mmHg, n_D^{20} 1.456 1); τ 6.69 (4 H, s, 2 × CH_2) and 7.69 (12 H, s, 2 × NMe_2).

cis,trans-*1,4-Bis(dimethylamino)buta-1,3-diene.*—In a 250-ml three-necked round-bottomed flask, equipped with a Hirschberg stirrer and nitrogen inlet, a dropping funnel, and a condenser with drying tube, was prepared a dispersion of sodium (0.75 g, 33 mmol) in xylene (10 ml). Hexane (25 ml) was added with vigorous stirring at 75—80 °C (external temperature), followed by the addition of 1,4-bis(dimethylamino)but-2-yne (75.0 g, 536 mmol) during 2 h. When cool, the contents of the flask were distilled directly affording *cis,trans*-1,4-bis(dimethylamino)buta-1,3-diene (64.6 g, 86%), b.p. 68—72 °C at 5 mmHg, n_D^{20} 1.549 (lit.,[10] 85% yield, b.p. 75—80 °C at 7 mmHg, n_D^{20} 1.549). The i.r. spectrum agreed with that in the literature.[10]

2,3-Diformyl-1,4-bis(dimethylamino)buta-1,3-diene.— The diene prepared as above (2.00 g, 14.3 mmol), in DMF (1.5 ml) and chloroform (7 ml), was added during 30 min, to (chloromethylene)dimethylammonium chloride[11] (9.15 g, 71.5 mmol) in DMF (10.7 ml) and chloroform (36 ml), with stirring, under nitrogen, at −30 to 0 °C. After 20 h, ice (10.7 g) was added at 0 °C, and the organic layer extracted into water (2 × 6 ml). Saturated aqueous potassium carbonate was added to the combined aqueous extracts, under nitrogen, with stirring, until neutral; a further portion (42 ml) was then added at 70 °C, during 40 min. After 30 min, the solution was extracted into benzene–ethanol (1 : 1) (4 × 50 ml). The combined, dried (K_2CO_3) extracts were evaporated, and the solid residue dissolved in hot dioxan, from which 2,3-diformyl-1,4-bis(dimethylamino)-buta-1,3-diene crystallised (1.60 g, 57%), m.p. 171—172 °C (lit.,[12] 172.5—173 °C); $\nu_{max.}$ (Nujol) 1 590br cm^{-1}; τ 1.01 (2 H, s, CHO), 3.03 (2 H, s, =CH–), and 6.92 (12 H, s, 2 × NMe_2).

Ethane-1,1,2,2-tetracarbaldehyde Dipotassium Salt.—The diformyldiamino-diene as above (29.4 g, 0.15 mol) was added to potassium hydroxide (85% pure, 20.0 g, 0.30 mol) in water (150 ml), under nitrogen, and stirred for 3 h at room temperature. After evaporation, the product was washed with hot ethanol, to give 1,1,2,2-ethanetetracarbaldehyde dipotassium salt (31.8 g, 97%); $\nu_{max.}$ (Nujol) 1 550 (br) cm^{-1} (lit.,[5a] 1 640 cm^{-1}); τ (D_2O, external $SiMe_4$) 2.28 (2 H, s) and 6.17 (2 H, s).

Furan-3,4-dicarbaldehyde.—The finely powdered dipotassium salt as above (60.4 g, 227 mol) was added in small quantities to vigorously stirred concentrated sulphuric acid (400 ml) under nitrogen, at room temperature over 3 h. After a further 15 min, the reaction was poured onto ice (2 l). The solution was extracted first with chloroform and then with ether. The combined organic extracts were dried (K_2CO_3 and Na_2SO_4) and evaporated to yield the crude furan-3,4-dicarbaldehyde (4) (29.4 g, 86%). Recrystallisation from ether–light petroleum gave the pure dialdehyde (4), m.p. 78.5—80 °C (lit.,[5a] 77—78 °C); $\lambda_{max.}$ (EtOH) 261 (ε 4 200) nm; $\nu_{max.}$ (Nujol) 1 680 (CHO) cm^{-1}; τ −0.24 (2 H, s, CHO) and 1.83 (2 H, s, =CH–); *m/e* 124 (M^+), 96 (M^+ − CO), and 68 (M^+ − 2CO).

Preparation of 4-[(4-Formyl-3-furyl)methyl]-2-phenylnaphtho[1,8-b,c]furan-5-one (5).—The dihydronaphthofuran (3) (10.00 g, 40.3 mmol) and the dialdehyde (4) (5.00 g, 40.3 mmol) in acetic anhydride (20 ml) and triethylamine (20 ml) were stirred under nitrogen, at 60 °C, for 3 d. The precipitate was filtered off, washed with ethanol–water (1 : 1), and recrystallised from acetone–dichloromethane to yield 4-[(4-*formyl*-3-*furyl*)*methyl*]-2-*phenylnaphtho*[1,8-b,c]-*furan-5-one* (5) (8.55 g, 60%), m.p. 209—211.5 °C; $\lambda_{max.}$ ($CHCl_3$) 267 (ε 22 600) and 401 (30 800) nm; $\nu_{max.}$ (CH_2Cl_2) 2 720 (H–CO), 1 696 (CHO), 1 644 (enone), 1 591 (aromatic), 1 570, 1 540, 1 063, 1 053, and 1 028 cm^{-1}; τ 0.00 (1 H, s, CHO), 1.68—2.64 (10 H, m, aromatic), and 5.95 (2 H, s, CH_2); *m/e* 354 (M^+) and 326 (M^+ − CO) (Found: C, 78.0; H, 4.05. $C_{23}H_{14}O_4$ requires C, 77.95; H, 4.0%).

4-{[4-(1,3-*Dithiolan*-2-*yl*)-3-*furyl*]*methyl*}-2-*phenylnaphtho*-[1,8-b,c]*furan-5-one* (6).—Ethane-1,2-dithiol (5.0 ml, 59.7 mmol), followed by boron trifluoride–ether complex (5.0 ml, 29.8 mmol), were added to a vigorously stirred suspension of the aldehyde (3) (5.00 g, 14.1 mmol) in acetic acid (30 ml), under nitrogen, at room temperature. After 1 h, water was added, and the mixture neutralised with solid sodium hydrogencarbonate. The mixture was extracted into chloroform (4 × 100 ml), and the combined extracts were dried (Na_2SO_4). After addition of ethanol, the solution was evaporated until 4-{[4-(1,3-*dithiolan*-2-*yl*)-3-*furyl*]-*methyl*}-2-*phenylnaphtho*[1,8-b,c]*furan-5-one* (6) crystallised (5.71 g, 94%), m.p. 169.5—171 °C; $\lambda_{max.}$ ($CHCl_3$) 267 (ε 17 700) and 401 nm (14 600); $\nu_{max.}$ ($CHCl_3$) 1 638 (enone), 1 608, 1 581 (aromatic), and 1 562 cm^{-1}; τ 1.74—2.81 (11 H, m, aromatic and olefinic), 4.40 (1 H, s, methine), 6.08 (2 H, s, CH_2), and 6.68 (4 H, s, SCH_2CH_2S); *m/e* 430 (M^+) and 369 (M^+ − EtS) (Found: C, 69.95; H, 4.15. $C_{25}H_{18}O_3S_2$ requires C, 69.75; H, 4.2%).

1-*Phenyl*-6a,7,11,11a-*tetrahydrofuro*[3,4-f]*naphtho*[1,8-b,c]*furan*-11-*spiro*-2′-(1′,3′-*dithiolan*)-6-*one* (7).—Argon was bubbled through refluxing dry benzene (1 l) contained in an internal-well photolysis unit. The dithiolan (16) (500 mg, 1.16 mmol), followed by lithium hexamethyldisilazide (44.8 mg, 0.26 mmol), were added and irradiation with a 650-W quartz-halogen lamp (Atlas Co.) was begun. When the reaction was judged to be complete by u.v. (22 min), the irradiation was stopped, and the benzene removed. The residue in chloroform (200 ml) was washed with saturated aqueous potassium dihydrogenphosphate (100 ml), separated, and the aqueous phase extracted with chloroform (50 ml). The combined organic layers were washed with water (100 ml), separated, and the aqueous washings extracted with chloroform (50 ml). The combined organic extracts were dried (Na_2SO_4), evaporated, and the residue crystallised from chloroform–ethanol to give the *title compound* (7) (310 mg, 62%), m.p. 203—205 °C; concentration of the mother-liquors afforded a second crop of (7) (125 mg,

25%); $\lambda_{max.}$ ($CHCl_3$) 279 (ε 23 100) and 353 nm (15 100); $\nu_{max.}$ ($CHCl_3$), 1 696 (C=O) and 1 617 (aromatic) cm^{-1}; τ 1.80—2.93 (10 H, m, aromatic), 5.33 (1 H, d, *J* 5 Hz, 11a-H), and 5.70—8.46; *m/e* 430 (M^+), 184 ($C_8H_8S_2O$), and 156 (base peak) (Found: C, 69.7; H, 4.4. $C_{25}H_{18}O_3S_2$ requires C, 69.75; H, 4.2%).

1-*Phenyl*-7,11a-*dihydrofuro*[3,4-f]*naphtho*[1,8-b,c]*furan*-6,11(6aH)-*dione* (8).—Dichloromethane (2 ml) was added with stirring to the dithiolan (7) (86 mg, 0.20 mmol) and benzeneseleninic anhydride (48 mg, 0.13 mmol) at room temperature under argon. After 30 min, the solvent was removed and the residue chromatographed over Kieselgel H (Type 60). Elution with benzene removed the by-products, but elution with ether yielded the *dione* (8) as two fractions, one of which crystallised and was isolated by filtration (17 mg, 24%), m.p. 240—242 °C, whilst the other upon evaporation gave an oil (13 mg, 18%); $\lambda_{max.}$ ($CHCl_3$) 295 and 355 nm; $\nu_{max.}$ ($CHCl_3$) 1.693 cm^{-1}; τ (at 100 MHz) 1.88—2.88 (10 H, m, aromatic), 5.38 (1 H, d, *J* 6.5 Hz, 9a-H), 5.98—6.52 (2 H, m, 6a-H and 7β-H), and 6.98—7.40 (1 H, m, 7α-H); *m/e* 354 (M^+) and 108 ($C_6H_4O_2$) (Found: C, 78.0; H, 4.0. $C_{23}H_{14}O_4$ requires C, 77.95; H, 4.0%).

1-*Phenyl*-11,11a-*dihydrofuro*[3,4-f]*naphtho*[1,8-b,c]*furan*-11-*spiro*-2′-(1′,3′-*dithiolan*)-6-*one* (14).—The dithiolan (7) (0.5 g) was dissolved in pyridine (50 ml) to which a small amount of water had been added. To this stirred solution was added SeO_2 (0.5 g) and the mixture warmed at 100 °C for 1 h. After evaporation of pyridine the residue was dissolved in benzene and water. The benzene layer was dried over Na_2SO_4 and evaporated to yield the crude product. Crystallisation from acetone gave *compound* (14) (0.4 g), m.p. 238—240 °C; $\lambda_{max.}$ ($CHCl_3$) 1 660 cm^{-1}; $\nu_{max.}$ ($CHCl_3$) 305 and 395 nm; *m/e* 428 (M^+) (Found: C, 69.75; H, 3.85. $C_{25}H_{16}O_3S_2$ requires C, 70.1; H, 3.75%).

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