Studies related to Anthracyclines. Part 1. Some Diels–Alder Reactions of 4a,9a-Epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetrone [1]

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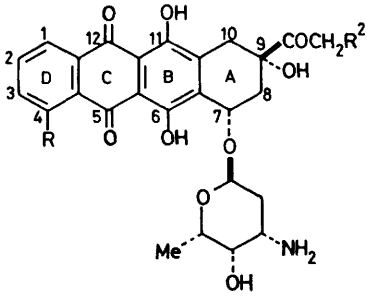
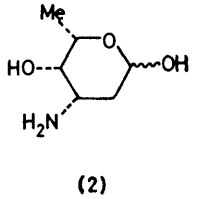
The title compound (5b), prepared by the oxidation of anthracene-1,4,9,10-tetrone (4) with *m*-chloroperbenzoic acid, undergoes Diels–Alder reactions with cyclohexa-1,3-diene, cyclopentadiene, and 2-methylbuta-1,3-diene to give 5a,11a-epoxy-1,4-ethano-1,4,4a,5a,11a,12a-hexahydronaphthacene-5,6,11,12-tetrone (7a), 5a,11a-epoxy-1,4,4a,5a,11a,12a-hexahydro-1,4-methanonaphthacene-5,6,11,12-tetrone (7b), and 5a,11a-epoxy-1,4,4a,5a,11a,12a-hexahydro-2-methylnaphthacene-5,6,11,12-tetrone (12), respectively. The foregoing cycloadducts, which are isolated as single stereoisomers, are assigned their stereo-structures on the assumption that the cycloaddition reactions occur by way of the least hindered *endo*-transition states. Reduction of the cycloadducts (7a), (7b), and (12) to give 1,4-ethano-1,4,4a,12a-tetrahydro-6,11-dihydroxynaphthacene-5,16-dione (10a), 1,4,4a,12a-tetrahydro-6,11-dihydroxy-1,4-methanonaphthacene-5,12-dione (10b), and 1,4,4a,12a-tetrahydro-6,11-dihydroxy-2-methylnaphthacene-5,12-dione (13), respectively, is achieved by using zinc in acetic acid or sodium dithionite in aqueous methanol. Lead(IV) acetate in acetic acid converts the diones (10a), (10b), and (13) into 1,4-ethano-1,4,4a,12a-tetrahydronaphthacene-5,6,11,12-tetrone (9a), 1,4,4a,12a-tetrahydro-1,4-methanonaphthacene-5,6,11,12-tetrone (9b), and 1,4,4a,12a-tetrahydro-2-methylnaphthacene-5,6,11,12-tetrones (14), respectively. Aromatisation of the tetrones (9a), (9b), and (14) occurs in the presence of triethylamine to give the corresponding quinizarin derivatives (8a), (8b), and (15).

ADRIAMYCIN (1a) and daunomycin (1b), members of the anthracycline group of antibiotics, are of considerable current interest because of their potent antitumour properties.[2] The clinical utility of these derivatives,

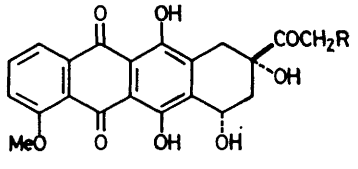


(1)

a; R^1 = OMe, R^2 = OH
b; R^1 = OMe, R^2 = H
c; R^1 = R^2 = OH
d; R^1 = R^2 = H



(2)



(3)

a; R = OH
b; R = H

however, is limited by dose-related cardiotoxicities. In consequence, an intense effort is being devoted to the derivation of analogues of the antibiotics in the hope of eliminating or reducing the toxic side-effects.

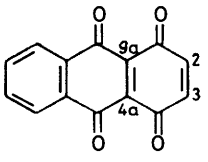
The coupling of appropriately protected derivatives of (L)-daunonosamine (2) and adriamycinone (3a) or daunomycinone (3b) has been described. In principle, anthracycline analogues containing novel sugars and/or modified aglycones may be prepared by this procedure.[2]

To acquire a better understanding of structure–activity relationships involving anthracycline derivatives, we have initiated a programme aimed at the total synthesis of analogues with altered aglycones. At the outset of our work it was known that the 4-methoxy group of ring D was not essential since carminomycin (1c) also displayed pronounced cytotoxic activity.[3] Our initial objective therefore was to prepare derivatives, with modifications to ring A, which lacked the 4-substituent of ring D. Significantly, a recent report [4] has revealed that 4-demethoxydaunomycin (1d) is 8—10 times more active than daunomycin (1b).

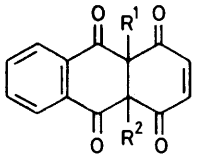
In principle, a simple and versatile approach to precursors of the required anthracyclinones involves the cycloaddition of a 1,3-diene at the 2,3-positions of the readily available tetrone (4). In practice, however, this route is limited by the tendency of many dienes to react preferentially with the 4a,9a-double bond.[5-7] No obvious correlation exists between the structure of the diene and the site of its cycloaddition, although 2-alkyl-substituted buta-1,3-dienes add predominantly to the 4a,9a-double bond. An obvious solution to the foregoing problem involves the protection of the internal double bond of the tetrone (4). The choice of the substituents R^1 and R^2 in such a protected compound, *i.e.* (5), is governed by three considerations. First, it is desirable that they can be added exclusively to the 4a,9a-double bond of the tetrone (4). Secondly, they should not interfere with the dienophilic properties of compound (5). Thirdly, they should be capable of elimination from the derived cycloadducts.

A compound of type (5) has been described by Inhoffen *et al.*;[5] thus treatment of the tetrone (4) with bromine and acetic acid in the presence of lead(II) acetate afforded the bromo-acetate (5a). The structure of the product

was inferred on the basis of its elemental composition and its conversion into quinizarin (6a) by sodium dithionite. We repeated the foregoing preparation; the spectroscopic properties of the isolated bromo-acetate (5a) were in accord with its assigned structure.

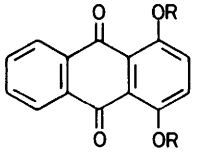


(4)



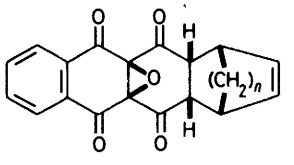
(5)

a; R^1 = OAc, R^2 = Br
b; R^1, R^2 = O
c; R^1 = H, R^2 = *m*-$ClC_6H_4CO_3$



(6)

a; R = H
b; R = $B(OAc)_2$



(7)

a; *n* = 2
b; *n* = 1

To examine its dienophilic properties, the bromo-acetate (5a) was treated with cyclopentadiene in benzene; no reaction occurred at room temperature and at 60 °C dimerisation of the diene resulted. Inhoffen *et al.* reported that quinizarin (6a) was produced when the bromo-acetate (5a) was treated with 1-acetoxybuta-1,3-diene.[5] Clearly, the bromine and acetoxy substituents are inadequate protectors of the internal double bond of the tetrone (4).

When treated with 1 mol. equiv. of *m*-chloroperbenzoic acid in dichloromethane for 2 days, the tetrone (4) afforded the oxiran (5b), which was isolated (50% after recrystallisation) as pale yellow needles. Interestingly, the oxidation proceeded more rapidly (*ca.* 2 h) and in better yield [50% based upon (6a)] when a non-recrystallised sample of the tetrone (4) * was employed. An unusual feature of the foregoing reaction is the observed site selectivity since it is well established that electron-withdrawing groups dampen the reactivities of alkenes towards peracids.[8] Possibly the oxidation involves the initial addition of *m*-chloroperbenzoic acid to the 4a,9a-double bond to give the adduct (5c) which subsequently eliminates *m*-chlorobenzoic acid to give the oxiran (5b).

To examine its dienophilic properties, the oxiran (5b) was initially treated with cyclohexa-1,3-diene in benzene; after 2 h under reflux, the cycloadduct (7a) was isolated in 78% yield. The stereochemistry of the product (7a), which was obtained as a single stereoisomer, was inferred on the expectation that the cycloaddition occurred by way of the least hindered *endo*-transition state.

Having demonstrated the dienophilic character of the oxiran (5b) attention was turned to the conversion of the cycloadduct (7a) into the quinizarin (8a). The last described compound was prepared (60%), in a parallel study, by the triethylamine-induced isomerisation of the cycloadduct (9a), itself obtained (70%) from the reaction † of cyclohexa-1,3-diene with the tetrone (4). Again the stereochemistry of the product (9a), which was isolated as a single stereoisomer, was inferred on the basis of the *endo*-addition rule. Attempts to convert the oxiran (7a) into the tetrone (9a) were unrewarding. However, in the presence of zinc and acetic acid, the oxiran (7a) was converted into the leucoquinizarin (10a), which was obtained in 60% yield after silica gel chromatography.‡ Oxidation of the leucoquinizarin (10a) with lead(IV) acetate in acetic acid afforded (73%) a material which was identical with the cycloadduct (9a). This result confirmed that the cycloaddition reactions of the oxiran (5b) and the tetrone (4) with cyclohexa-1,3-diene shared a common stereoselectivity.

Having established the methodology for effecting the Diels–Alder reaction at the 2,3-double bond of the tetrone (4), some further examples were examined. The oxiran (5b) reacted rapidly with cyclopentadiene in benzene at room temperature to give a single cycloadduct (88%), presumed to be the stereoisomer (7b). By contrast, a *ca.* 1.3 : 1 mixture of diadducts and internal monoadducts was produced when the tetrone (4) was similarly treated with cyclopentadiene. Reduction of the cycloadduct (7b) to the leucoquinizarin (8b) was effected by using either zinc in acetic acid § or sodium dithionite in aqueous methanol; the latter procedure was more efficient (70%) than the former (40%) and it was not necessary to purify the product by silica gel chromatography. Oxidation of the leucoquinizarin (8b) with lead(IV) acetate in acetic acid gave the tetrone (9b) (90%), which was isomerized to the quinizarin (8b) (75%) by triethylamine in benzene.

Whilst the above work was in progress, Birch *et al.* reported [9] that treatment of quinizarin (6a) with boron triacetate gave the boroacetate (6b) which underwent Diels–Alder cycloadditions, presumably by way of the less stable tautomer (11). By using cyclopentadiene, a 2.6 : 1 mixture of the leucoquinizarin (10b) and its *exo*-isomer was isolated after hydrolysis. Oxidation of either adduct using nitrobenzene and a catalytic quantity of piperidine led to the quinizarin (8b). The m.p. of the *endo*-isomer (10b) (143—144 °C) and of the quinizarin (8b) (225—227 °C), reported by Birch *et al.*, were similar to those observed for the corresponding compounds described in the present study (m.p. 147—148 and 222—224 °C).

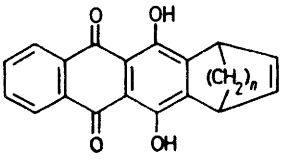
* The preparation of the tetrone (4) involves oxidation of quinizarin (6a) with lead(IV) acetate in acetic acid (see Experimental section); presumably, traces of lead salts in the crude product promote the oxidation.

† A low yield (*ca.* 2%) of the internal cycloadduct, as a mixture of stereoisomers, was also isolated (see Experimental section).

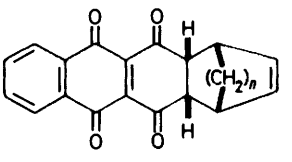
‡ A second material, obtained in a somewhat impure state, was also isolated from the reaction; its structure was not elucidated.

§ A second material, m.p. 256—258 °C, was also isolated from this reaction; its structure was not established.

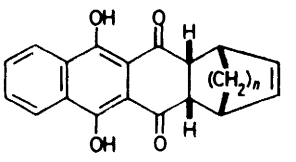
In earlier work, it was reported that 2-methylbuta-1,3-diene reacted with the 4a,9a-double bond of the tetrone (4) to give the internal cycloadduct.[7] When heated with isoprene in boiling benzene, the oxiran (5b) was converted into a single product (95%), presumed to be the stereoisomer (12). Reduction of the cycloadduct (12) to the leucoquinizarin (13) was effected by using either zinc in acetic acid or sodium dithionite in aqueous methanol; the latter procedure was more effective (35%) than the former (20%), although, in each case, it was necessary to purify the product by silica gel chromatography.* Oxidation of the leucoquinizarin (13) with lead(IV) acetate in acetic acid gave the tetrone (14) (87%) which was isomerized to the quinizarin (15) (90%) by triethylamine in dichloromethane.



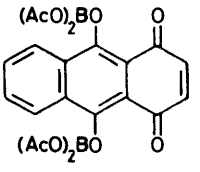
(8)
a; $n = 2$
b; $n = 1$



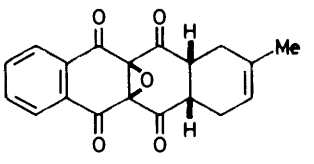
(9)
a; $n = 2$
b; $n = 1$



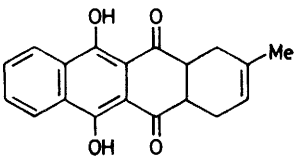
(10)
a; $n = 2$
b; $n = 1$



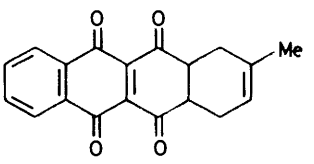
(11)



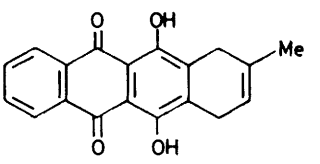
(12)



(13)



(14)



(15)

The foregoing results considerably extend the scope of the Diels–Alder route to anthracyclinone analogues; in principle, they allow for the derivation of compounds with a wide range of functionality in ring A. The conversion of the quinizarin derivatives (10a), (10b), and (15), and related compounds, into anthracyclinone analogues is under investigation.

EXPERIMENTAL

Benzene was dried over sodium wire. Cyclopentadiene was prepared by the destructive distillation of dicyclopentadiene [10] and used immediately. All other solvents and chemicals were employed as purchased.

Column chromatography was effected, under pressure, using Merck Kieselgel H (Type 60). T.l.c. was performed on Schleicher and Schüll plastic sheets coated with silica gel (F1500 LS 254); the plates were initially examined under u.v. light from a Mineralight UVSL 58 source and then developed with an aqueous potassium permanganate spray.

Evaporations were carried out at *ca.* 40 °C using a Buchi rotary evaporator. M.p.s were determined using a Kofler hot-stage apparatus. I.r. spectra were measured using a Hilger and Watts Infrascan. A Unicam SP 800 spectrometer was employed to determine u.v. spectra. N.m.r. spectra refer to tetramethylsilane as the internal standard; the spectra were measured at 60 MHz using a Varian EM 360 spectrometer. Mass spectra were determined using an A.E.I. MS9 spectrometer operating at 70 eV. Microanalyses were performed using a Hewlett–Packard 185 CHN Analyser.

Reaction of 1,4-*Dihydroxyanthraquinone* (6a) *with Lead*(IV)-*Acetate*.[11]—The anthraquinone (6a) (20.0 g, 83.3 mmol), lead(IV) acetate (40 g, 90.2 mmol), and acetic acid (50 cm^3) were ground together in a mortar. Within 5 min the mixture became viscous and dark red in colour. After a further 10 min the mixture was filtered and the precipitate, after washing thoroughly with distilled water, was dried (*in vacuo*, P_2O_5). The crude product (18.3 g) was dissolved in nitrobenzene (270 cm^3) at 80 °C and, after filtration, the cooled solution was diluted with carbon disulphide (540 cm^3). The yellow-brown needles of anthracene-1,4,9,10-tetrone (4) (10.0 g, 50%) were collected and dried (*in vacuo*, $CaCl_2$); m.p. 208—210 °C (decomp.) (lit.,[11] 212—213 °C); $\nu_{max.}$ (KBr) 1 700 and 1 680 (CO), 1 654, 1 620, and 1 590 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 254 (ε 14 900) and 365 nm (1 700); δ ($CDCl_3$) 6.93 (2 H, s, COCH:CHCO) and 7.7—8.2 (4 H, m, C_6H_4); *m/e* 240 (MH_2^+, base peak).

Reaction of Anthracene-1,4,9,10-*tetrone* (4) *with Bromine in Acetic Acid*.[5]—A stirred mixture of the unrecrystallised tetrone (4) (1.00 g, *ca.* 4.2 mmol) and lead(II) acetate (5.00 g, 15.4 mmol) in acetic acid (100 cm^3), cooled in an ice-bath,

*A second material, m.p. 153—155 °C, was also isolated from these reactions; it was not identified.

was treated dropwise over 10 min with a solution of bromine (0.2 cm³, *ca.* 3.8 mmol) in acetic acid (20 cm³). After a further 15 min the mixture was filtered and the filtrate was poured into water. The precipitate was dried (*in vacuo*, P_2O_5) to give a brown solid (0.695 g) which was purified by silica gel chromatography ($CHCl_3$ as eluant). Recrystallisation of the chromatographed product from benzene–light petroleum (b.p. 60—80 °C) gave 4a-acetoxy-9a-bromo-4a,9a-dihydroanthracene-1,4,9,10-tetrone (5a) [0.380 g, 22% based upon (6a)] as a yellow solid, m.p. 156 °C (lit.,[5] 157 °C); $\nu_{max.}$ (KBr) 1 765 (ester CO), 1 715br and 1 685 (CO), and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 213sh (ε 14 100), 232 (25 800), 263sh (7 200), and 309 nm (2 000) [lit.,[5] $\lambda_{max.}$ (MeOH) 228 nm (ε 26 200)]; δ ($CDCl_3$) 2.24 (3 H, s, MeCO), 6.94 (2 H, s, COCH:CHCO), and 7.7—8.3 (4 H, m, C_6H_4); *m/e* 336/334 ($M^+ - C_2H_2O$) and 255 ($M^+ - C_2H_2BrO$, base peak).

Reaction of 4a-*Acetoxy*-9a-*bromo*-4a,9a-*dihydroanthracene*-1,4,9,10-*tetrone* (5a) *with Cyclopentadiene*.—Cyclopentadiene (2 cm³) was added to a solution of the tetrone (5a) (0.100 g, 0.27 mmol) in benzene (5 cm³). No reaction occurred at room temperature (5 h) and so the solution was heated under reflux. Evaporation after 10 h gave an oily residue which contained the tetrone (15a) and dicyclopentadiene (t.l.c. and n.m.r. spectroscopy).

Reaction of Anthracene-1,4,9,10-*tetrone* (4) *with* m-*Chloroperbenzoic Acid*.—(*a*) A stirred solution of the tetrone (4) (4.00 g, 16.8 mmol) in dichloromethane (50 cm³) was treated with 85% *m*-chloroperbenzoic acid (3.19 g, 15.7 mmol). After 48 h the solution was washed with dilute sodium hydrogencarbonate solution and dried ($MgSO_4$). Evaporation and crystallisation of the residue from chloroform gave 4a,9a-*epoxy*-4a,9a-*dihydroanthracene*-1,4,9,10-*tetrone* (5b) (2.13 g, 50%), as yellow needles, m.p. 166—180 °C (decomp.); $\nu_{max.}$ (KBr) 1 725 and 1 680 (CO), 1 620, and 1 595 cm^{-1}; $\lambda_{max.}$ (EtOH) 212sh (ε 15 100) and 233 nm (18 800); δ ($CDCl_3$) 6.76 (2 H, s, COCH:CHCO) and 7.8—8.3 (4 H, m, C_6H_4); *m/e* 254 (M^+) and 82 ($C_4H_2O_2^+$, base peak) (Found: C, 65.9; H, 2.4. $C_{14}H_6O_5$ requires C, 66.15; H, 2.35%).

(*b*) A stirred ice-cooled solution of the unrecrystallised tetrone (4) (14.8 g, *ca.* 62.2 mmol) in dichloromethane (300 cm³) was treated portionwise over 5 min with 85% *m*-chloroperbenzoic acid (12.0 g, 59.1 mmol) and then the mixture was allowed to warm to room temperature. After 2 h, the mixture was filtered, washed with sodium hydrogencarbonate solution, and dried ($MgSO_4$). Evaporation and crystallisation of the residue from chloroform gave the tetrone (5b) [8.53 g, 50% based upon (6a)].

Reaction of 4a,9a-*Epoxy*-4a,9a-*dihydroanthracene*-1,4,9,10-*tetrone* (5b) *with Cyclohexa*-1,3-*diene*.—The tetrone (5b) (0.508 g, 2 mmol) and cyclohexa-1,3-diene (0.320 g, 4 mmol) were heated under reflux in benzene (4 cm³). After 2 h the mixture was ice-cooled and the precipitate collected by filtration. Recrystallisation of the solid from chloroform gave 5a,11a-*epoxy*-1,4-*ethano*-1,4,4a,5a,11a,12a-*hexahydronapththacene*-5,6,11,12-*tetrone* (7a) (0.520 g, 78%) as a solid, m.p. 208—212 °C (decomp.); $\nu_{max.}$ (KBr) 1 750sh, 1 730, and 1 690 (CO), and 1 595 cm^{-1}; $\lambda_{max.}$ (EtOH) 206 (ε 4 900), 236 (8 300), 266 (2 600), and 312 nm (1 000); δ ($CDCl_3$; 90 MHz *) 1.40—1.67 (4 H, m, $CHCH_2CH_2CH$), 3.03 br (2 H, s, $CHCH_2CH_2CH$), 3.52 (2 H, s, COCHCHCO), 6.19—6.28 (2 H, m, CHCH:CHCH), and 7.78—7.90 and 8.01—8.17 (each 2 H, m, C_6H_4); *m/e* 334 (M^+) and 80 ($C_6H_8^+$, base peak) (Found: C, 72.2; H, 4.1. $C_{20}H_{14}O_5$ requires C, 71.85; H, 4.2%).

Reaction of Anthracene-1,4,9,10-*tetrone* (4) *with Cyclohexa*-1,3-*diene*.—A solution of the tetrone (4) (4.00 g, 16.8 mmol) and cyclohexa-1,3-diene (1.40 g, 17.5 mmol) was heated under reflux in benzene (40 cm³). After 4 h the mixture was ice-cooled and the precipitated 1,4-*ethano*-1,4,4a,12a-*tetrahydronaphthacene*-5,6,11,12-*tetrone* (9a) (3.58 g, 67%) was collected as salmon-pink crystals; m.p. >340 °C (from $CHCl_3$–Et_2O); $\nu_{max.}$ (KBr) 1 710 and 1 665 (CO), and 1 595 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (ε 20 400), 230 (16 200), 262 (14 300), 270 (11 300), 284sh (8 100), and 356 nm (3 800); δ ($CDCl_3$) 1.32—1.96 (4 H, m, $CHCH_2CH_2CH$), 3.39—3.65 (2 H, m, $CHCH_2CH_2CH$), 3.55 (2 H, s, COCHCHCO), 6.32—6.35 (2 H, m, CHCH:CHCH), and 7.91—8.42 (4 H, m, C_6H_4); *m/e* 318 (M^+) and 290 ($M^+ - CO$, base peak) (Found: C, 75.45; H, 4.45%; M^+, 318.0918. $C_{20}H_{14}O_4$ requires C, 75.45; H, 4.4%; *M*, 318.0892).

Concentration of the mother-liquor afforded a further batch of crystals (0.100 g, 2%), which were bright yellow in colour; the material, present as a *ca.* 1 : 1 mixture of isomers, was 5a,9a-(*cyclohex*-5-*en*-1,4-*ylene*)-4a,9a-*dihydroanthracene*-1,4,9,19-*tetrone*, m.p. 248—250 °C (from $CHCl_3$–Et_2O); $\nu_{max.}$ (KBr) 1 705sh, 1 695 and 1 675 (CO), and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 208sh (ε 20 000), 227 (48 000), and 302 nm (2 900); δ ($CDCl_3$) 1.18—1.63 (4 H, m, $CHCH_2CH_2CH$), 4.03—4.30 (2 H, m, $CHCH_2CH_2CH$), 6.35 (2 H, t, separation 4 Hz, CHCH:CHCH), 6.62 and 6.75 (each 1 H, s, COCH:CHCO), and 7.65—8.05 (4 H, m, C_6H_4) [irradiation at 1.40 caused the m at 4.03—4.30 to simplify to a br t (separation 4 Hz), irradiation at 4.16 caused the m at 1.18—1.63 to simplify and the t at 6.35 to collapse to an s, irradiation at 6.35 caused the m at 4.03—4.30 to collapse to a br s]; *m/e* 318 (M^+) and 290 ($C_{19}H_{14}O_3^+$, base peak) (Found: C, 74.85; H, 4.2. $C_{20}H_{14}O_4$ requires C, 75.45; H, 4.4%).

Reaction of 1,4-*Ethano*-1,4,4a,12a-*tetrahydronaphthacene*-5,6,11,12-*tetrone* (9a) *with Triethylamine*.—The tetrone (9a) (1.70 g, 5.35 mmol) and triethylamine (1 cm³) in benzene (50 cm³) were heated under reflux for 5 h. After cooling in ice, the precipitated 1,4-*ethano*-1,4-*dihydro*-5,12-*dihydroxynaphthacene*-6,11-*dione* (8a) (1.00 g, 59%) was collected as deep red crystals, m.p. >340 °C (from $CHCl_3$); $\nu_{max.}$ (KBr) 1 620 (CO) and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 206 (ε 14 100), 253sh (22 800), 258 (24 900), 287 (3 800), 468sh (14 400), 492 (5 100), and 529 nm (3 300); δ ($CDCl_3$) 1.38—1.72 (4 H, m, $CHCH_2CH_2CH$), 4.60—4.85 (2 H, m, $CHCH_2CH_2CH$), 6.55 (2 H, t, separation 4 Hz, CHCH:CHCH), and 7.71—7.98 and 8.25—8.49 (each 2 H, m, C_6H_4); *m/e* 318 (M^+) and 290 ($M^+ - CO$, base peak) (Found: C, 75.9; H, 4.2. $C_{20}H_{14}O_4$ requires C, 75.45; H, 4.4%).

Reaction of 5a,11a-*Epoxy*-1,4-*ethano*-1,4,4a,5a,11a,12a-*hexahydronaphthacene*-5,6,11,12-*tetrone* (7a) *with Zinc in Acetic Acid*.—A stirred solution of the tetrone (7a) (0.334 g, 1 mmol) in acetic acid (20 cm³) was treated with powdered zinc (0.654 g, 10 mmol). After 24 h the mixture was partitioned between chloroform and water. The organic layer was washed several times with dilute sodium hydrogencarbonate solution, dried ($MgSO_4$), and evaporated to leave an orange solid which contained two major components (t.l.c.). These were partially fractionated by silica gel chromatography (light petroleum–EtOAc as eluant).

The first eluted material (0.190 g, 60%), obtained as orange crystals, was 1,4-*ethano*-1,4,4a,12a-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (10a), m.p. 203—204 °C

* Because of solubility problems this spectrum was determined using a Bruker Spectrospin HE 90E operating in the Fourier transform mode; 2 565 s scans were made.

(from $CHCl_3$–EtO_2); $\nu_{max.}$ (KBr) 1 620 and 1 600 (CO) and 1 580 cm^{-1}; $\lambda_{max.}$ (EtOH) 208 (ε 8 100), 245sh (20 000), 255 (20 800), 270sh (18 000), 282 (13 600), 290 (13 300), 390sh (2 400), 404 (10 700), and 424 nm (10 700); δ ($CDCl_3$) 1.30—2.00 (4 H, m, $CHCH_2CH_2CH$), 3.25 (2 H, s, COCHCHCO), 3.35—3.65 (2 H, s, $CHCH_2CH_2CH$), 6.20 (2 H, t, separation 4 Hz, CHC*H*:C*H*CH), 7.6—7.9 and 8.2—8.5 (each 2 H, m, C_6H_4), and 15.80 (2 H, s, exchanged with D_2O) (irradiation at 3.25 caused the t at 6.20 to collapse to an s, irradiation at 6.20 caused the br s at 3.35—3.65 to sharpen); *m/e* 320 (M^+) and 240 ($M^+ - C_6H_8$, base peak) (Found: C, 75.35; H, 4.9%; M^+, 320.1065. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%; *M*, 320.1049).

The second eluted material (0.100 g) was not obtained in a pure state and its structure was not elucidated.

Reaction of 1,4-*Ethano*-1,4,4a,12a-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (10a) *with Lead*(IV) *Acetate*.—A stirred solution of the dione (10a) (0.080 g, 0.25 mmol) in acetic acid (5 cm^3) was treated with lead(IV) acetate (0.133 g, 0.30 mmol). After 0.5 h the pink solution was diluted with water and extracted with chloroform. The organic layer was washed with sodium hydrogencarbonate solution, dried ($MgSO_4$), and evaporated to give a material (0.058 g, 73%) which was identical (i.r. and mass spectroscopy) with the tetrone (9a).

Reaction of 4a,9a-*Epoxy*-4a,9a-*dihydranthracene*-1,4,9,10-*tetrone* (5b) *with Cyclopentadiene*.—Cyclopentadiene (0.500 g, 7.58 mmol) was added to a stirred mixture of the tetrone (5b) (0.700 g, 2.76 mmol) in benzene (10 cm^3). After 0.5 h the crystals of 5a,11a-*epoxy*-1,4,4a,5a,11a,12a-*hexahydro*-1,4-*methanonaphthacene*-5,6,11,12-*tetrone* (7b) (0.770 g, 87%) were collected by filtration, m.p. 208—220 °C (decomp.); $\nu_{max.}$ (KBr) 1 730 and 1 690 (CO) and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (ε 9 000), 237 (22 200), 265 (7 000), and 311 nm (2 300); δ ($CDCl_3$) 1.27—1.67 (2 H, m, $CHCH_2CH$), 3.24—3.44 (2 H, m, $CHCH_2CH$), 3.74br (2 H, s, COCHCHCO), 6.22br (2 H, s, CHC*H*:C*H*CH), and 7.7—7.9 and 8.0—8.2 (each 2 H, m, C_6H_4); *m/e* 320 (M^+) and 66 ($C_5H_6^+$, base peak) (Found: C, 71.35; H, 3.8. $C_{19}H_{12}O_5$ requires C, 71.25; H, 3.75%).

Reaction of Anthracene-1,4,9,10-*tetrone* (4) *with Cyclopentadiene*.—Cyclopentadiene (3.33 g, 50 mmol) was added to a stirred mixture of the tetrone (4) (1.19 g, 5 mmol) in benzene (100 cm^3). Evaporation after 3 h left a residue (1.57 g) which was a *ca.* 1.3 : 1 mixture of a diadduct and an internal monoadduct (n.m.r. spectroscopy); there was no evidence for the presence of the external monoadduct (9b).

Reaction of 5a,11a-*Epoxy*-1,4,4a,5a,11a,12a-*hexahydro*-1,4-*methano*-5,6,11,12-*naphthacene*-5,6,11,12-*tetrone* (7b) *with Zinc in Acetic Acid*.—The tetrone (7b) (0.320 g, 1 mmol) was added to a stirred mixture of powdered zinc (0.654 g, 10 mmol) and acetic acid (10 cm^3). After 1.5 h the mixture was diluted with water and extracted with chloroform. The organic layer was washed with sodium hydrogencarbonate solution, dried ($MgSO_4$), and evaporated to leave a product which was a mixture of two major materials (t.l.c.). The mixture was fractionated by silica gel chromatography (light petroleum–EtOAc as eluant).

The first eluted material, obtained as an orange-yellow solid (0.122 g, 40%), was 1,4,4a,12a-*tetrahydro*-6,11-*dihydroxy*-1,4-*methanonaphthacene*-5,10-*dione* (10b), m.p. 147–148 °C (from $CHCl_3$–Et_2O); $\nu_{max.}$ (KBr) 1 620 and 1 605 (CO), and 1 590sh cm^{-1}; $\lambda_{max.}$ (EtOH) 204 (ε 12 500), 245 (25 700), 255 (26 800), 281 (22 800), 289 (21 200), 386sh (9 300), 405 (13 300), and 425 nm (13 500); δ ($CDCl_3$) 1.60—1.70 (2 H, m, $CHCH_2CH$), 3.55—3.65 (2 H, m, $CHCH_2CH$), 3.75—3.92 (2 H, m, COCHCHCO), 6.17 (2 H, t, separation 2 Hz, CHC*H*:C*H*CH), 7.82—7.98 and 8.50—8.66 (each 2 H, m, C_6H_4), and 15.79 (2 H, s, exchanged with D_2O) (irradiation at 3.84 caused the signals at 1.60—1.70 and 6.17 to collapse to s); *m/e* 306 (M^+) and 240 ($M^+ - C_5H_6$, base peak) (Found: C, 74.7; H, 4.65%; M^+, 306.0886. $C_{19}H_{14}O_4$ requires C, 74.5; H, 4.6%; *M*, 306.0892).

The second eluted material (0.080 g), isolated as a pale yellow solid, m.p. 256—258 °C, was not identified.

Reaction of 5a,11a-*Epoxy*-1,4,4a,5a,11a,12a-*hexahydro*-1,4-*methano*-5,6,11,12-*naphthacene*-5,6,11,12-*tetrone* (7b) *with Sodium Dithionite*.—A stirred solution of the tetrone (7b) (0.640 g, 2 mmol) in methanol (10 cm^3) was treated dropwise with sodium dithionite (0.960 g, 5.5 mmol) dissolved in distilled water (2 cm^3). After 6 h the red solution was acidified with dilute hydrochloric acid and partitioned between chloroform and water. After washing with sodium hydrogencarbonate solution, the organic layer was dried ($MgSO_4$) and evaporated to give the dione (10b) (0.430 g, 70%) (n.m.r.spectroscopy), as an orange solid.

Reaction of 1,4,4a,12a-*Tetrahydro*-6,11-*dihydroxy*-1,4-*methano*-5,12-*naphthacene*-5,12-*dione* (10b) *with Lead*(IV) *Acetate*.—A stirred solution of the dione (10b) (0.306 g, 1 mmol) in acetic acid (5 cm^3) was treated with lead(IV) acetate (0.488 g, 1.1 mmol). After 1 h the pink solution was diluted with chloroform and washed with sodium hydrogencarbonate solution. Evaporation of the dried ($MgSO_4$) organic layer left a residue which was recrystallised from chloroform–ether to give 1,4,4a,12a-*tetrahydro*-1,4-*methanonaphthacene*-5,6,11,12-*tetrone* (9b) (0.274 g, 90%), as a pink solid, m.p. 158—159 °C; $\nu_{max.}$ (KBr) 1 705 and 1 660 (CO), and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 237 (ε 14 000), 263 (11 000), 272sh (10 000), 278 (7 100), 311 (3 900), 325 (3 900), and 356 nm (4 600); δ ($CDCl_3$) 1.4—1.85 (4 H, m, $CHCH_2CH$), 3.45—3.65br (2 H, s, $CHCH_2CH$), 3.68 (2 H, s, COCHCHCO), 6.10—6.25 (2 H, m, CHC*H*:C*H*CH), and 7.6—8.1 (4 H, m, C_6H_4) [irradiation at 3.55 caused the signals at 1.4—1.85 to sharpen to an ABq (*J* 10 Hz) and those at 6.10—6.25 to collapse to an s]; *m/e* 304 (M^+, base peak) (Found: C, 74.6; H, 3.95. $C_{19}H_{12}O_4$ requires C, 75.0; H, 3.95%).

Reaction of 1,4,4a,12a-*Tetrahydro*-1,4-*methanonaphthacene*-5,6,11,12-*tetrone* (9b) *with Triethylamine*.—The tetrone (9b) (0.152 g, 0.5 mmol) was heated under reflux in benzene (5 cm^3) containing a few drops of triethylamine. After 5 h the deep red solution was partitioned between chloroform and dilute hydrochloric acid. The dried ($MgSO_4$) organic layer was evaporated and the residue was recrystallised from chloroform–ether to give 1,4-*dihydro*-5,12-*dihydroxy*-1,4-*methanonaphthacene*-6,11-*dione* (8b) (0.114 g, 75%), as a red solid, m.p. 222—224 °C; $\nu_{max.}$ (KBr) 1 620 (CO) and 1 585 cm^{-1}; $\lambda_{max.}$ (EtOH) 210 (ε 21 800), 220sh (13 200), 247sh (34 400), 262 (43 100), 474sh (8 600), 490 (9 400), and 524 nm (5 600); δ($CDCl_3$) 2.35—2.45br (2 H, s, $CHCH_2CH$), 4.30—4.50 (2 H, m, $CHCH_2CH$), 6.85—6.95 (2 H, m, CHC*H*:C*H*CH), 7.6—7.9 and 8.1—8.4 (each 2 H, m, C_6H_4), and 12.78 (2 H, s, 2 × OH) (irradiation at 4.40 caused the signal at 6.85—6.95 to collapse to an s, irradiation at 6.90 caused the signal at 4.30—4.50 to sharpen to a br s); *m/e* 304 (M^+, base peak) (Found: C, 74.8; H, 4.25. $C_{19}H_{12}O$ requires C, 75.0; H, 3.95%).

Reaction of 4a,9a-*Epoxy*-4a,9a-*dihydro*-1,4,9,10-*anthracene*-1,4,9,10-*tetrone* (5b) *with* 2-*Methylbuta*-1,3-*diene*.—A solution of the tetrone (5b) (2.40 g, 10 mmol) and isoprene (*ca.*

2 cm³, *ca.* 20 mmol) in benzene (50 cm³) was heated under reflux. Evaporation after 24 h left a syrup which crystallised on addition of ether. The filtered white solid was 5a,11a-*epoxy*-1,4,4a,5a,11a,12a-*hexahydro*-2-*methylnaphthacene*-5,6,11,12-*tetrone* (12) (3.06 g, 95%), m.p. 152—154 °C (decomp.) (from $CHCl_3$–Et_2O); $\nu_{max.}$ (KBr) 1 735 and 1 695 (CO), and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 212 (ε 8 900), 234 (12 900), 255 (8 400), and 300sh nm (2 100); δ ($CDCl_3$) 1.74br (3 H, s, MeC:C), 2.0—2.45 (4 H, m, $CH_2CHCHCH_2$), 3.32—3.66 (2 H, m, COCHCHCO), 5.26—5.60 (1 H, m, C:C*H*CH_2), and 7.65—8.2 (4 H, m, C_6H_4) (irradiation at 2.26 caused the signal at 3.32—3.66 to sharpen and that at 5.26—5.60 to collapse to a br s); *m/e* 322 (M^+) and 173 (base peak) (Found: C, 70.5; H, 4.15. $C_{19}H_{14}O_5$ requires C, 70.8; H, 4.35%).

Reaction of 5a,11a-*Epoxy*-1,4,4a,5a,11a,12a-*hexahydro*-2-*methylnaphthacene*-5,6,11,12-*tetrone* (12) *with Zinc.*—Powdered zinc (3.27 g, 50 mmol) was added to a stirred solution of the tetrone (12) (1.61 g, 5 mmol) in acetic acid (50 cm³). After 24 h the yellow solution was partitioned between chloroform and water. The organic layer was washed with sodium hydrogencarbonate solution, dried ($MgSO_4$), and evaporated to leave a yellow solid which was a mixture of two major components (t.l.c.). The mixture was fractionated by silica gel chromatography (light petroleum–EtOAc as eluant).

The first eluted material (0.308 g, 20%), isolated as an orange solid, was 1,4,4a,12a-*tetrahydro*-6,11-*dihydroxy*-2-*methylnaphthacene*-5,12-*dione* (13); m.p. 238—239 °C (from EtOAc–light petroleum); $\nu_{max.}$ (KBr) 1 640 and 1 615 (CO), and 1 580 cm^{-1}; $\lambda_{max.}$ (EtOH) 208 (ε 11 700), 237 (25 300), 251 (25 000), 280 (18 500), 288 (16 600), 386sh (6 200), 400 (9 900), 418 (9 900), and 423 nm (9 200); δ ($CDCl_3$) 1.74br (3 H, s, MeC:C), 2.18—2.74 (4 H, m, $CH_2CHCHCH_2$), 3.18—3.48 (2 H, m, COCHCHCO), 5.33—5.61 (1 H, m, C:C*H*CH_2), 7.6—7.95 and 8.25—8.6 (each 2 H, m, C_6H_4), and 13.40 (2 H, s, 2 × OH) (irradiation at 2.42 caused the signal at 5.33—5.61 to collapse to a br s); *m/e* 308 (M^+) and 240 ($M^+ - C_5H_8$, base peak) (Found: C, 73.95; H, 5.2. $C_{19}H_{16}O_4$ requires C, 74.05; H, 5.2%).

The second eluted material (0.483 g), isolated as a bright yellow solid, m.p. 153—155° (from $CHCl_3$–Et_2O), was not identified.

Reaction of 5a,11a-*Epoxy*-1,4-4a,11a,12a-*hexahydro*-2-*methylnaphthacene*-5,6,11,12-*tetrone* (12) *with Sodium Dithionite.*—A stirred solution of the tetrone (12) (0.332 g, 1 mmol) in methanol (5 cm³) was treated dropwise with sodium dithionite (0.522 g, 3 mmol) dissolved in distilled water (1 cm³). After 5 h the yellow solution was acidified with dilute hydrochloric acid and partitioned between chloroform and water. The organic layer was washed with sodium hydrogencarbonate solution, dried ($MgSO_4$), and evaporated to leave a yellow solid which was mainly a mixture of two compounds (t.l.c.). The mixture was fractionated by silica gel chromatography (light petroleum–EtOAc as eluant).

The first eluted compound (0.108 g, 35%) was identical with the dione (13) (n.m.r. and i.r. spectroscopy).

The second eluted material (0.065 g) was identical (n.m.r. spectroscopy) with the unidentified yellow solid, obtained from the reduction of the tetrone (12) with zinc in acetic acid.

* The melting point (287—288 °C) quoted for this compound in the preliminary communication [1] is incorrect.

† This spectrum was determined as described in the footnote on p. 1010; 5 125 s scans were made.

Reaction of 1,4,4a,12a-*Tetrahydro*-6,11-*dihydroxy*-2-*methylnaphthacene*-5,12-*dione* (13) *with Lead*(IV) *Acetate.*—A stirred solution of the dione (13) (0.306 g, 1 mmol) in acetic acid (5 cm³) was treated with lead(IV) acetate (0.488 g, 1.1 mmol). After 2 h the pink solution was diluted with chloroform and washed with sodium hydrogencarbonate solution. Evaporation of the dried ($MgSO_4$) organic layer left 1,4,4a,12a-*tetrahydro*-2-*methylnaphthacene*-5,6,11,12-*tetrone* (14) (0.266 g, 87%), as a pink solid, m.p. 273 °C (decomp.) (from $CHCl_3$–Et_2O); $\nu_{max.}$ (KBr) 1 710 and 1 665 (CO) and 1 595 cm^{-1}; $\lambda_{max.}$ (EtOH) 218 (ε 18 400), 233 (18 000), 257 (16 900), 322 (4 300), 400 (1 600), and 420 nm (1 000); δ ($CDCl_3$) 1.77br (3 H, s, MeC:C), 2.2—2.5 (4 H, m, $CH_2CHCHCH_2$), 3.4—3.8 (2 H, m, COCHCHCO), 5.35—5.60 (1 H, m, C:C*H*CH_2), and 7.7—8.2 (4 H, m, C_6H_4) (irradiation at 2.35 caused the signal at 3.4—3.8 to sharpen and that at 5.35—5.60 to collapse to a br s); *m/e* 306 (M^+, base peak) (Found: C, 74.35; H, 4.55. $C_{19}H_{14}O_4$ requires C, 74.5; H, 4.6%).

Reaction of 1,4,4a,12a-*Tetrahydro*-2-*methylnaphthacene*-5,6,11,12-*tetrone* (13) *with Triethylamine.*—A solution of the tetrone (13) (0.306 g, 1 mmol) in dichloromethane (5 cm³) was treated with a few drops of triethylamine. A precipitate rapidly formed and after 5 min the mixture was diluted with chloroform and washed with dilute hydrochloric acid followed by sodium hydrogencarbonate solution. Evaporation of the dried ($MgSO_4$) organic layer gave 1,4-*dihydro*-5,12-*dihydroxy*-2-*methylnaphthacene*-6,11-*dione* (15) (0.276 g, 90%), as a red solid, m.p. 255—261 °C (decomp.) * (from $CHCl_3$); $\nu_{max.}$ (KBr) 1 625 (CO) and 1 585 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (ε 9 600), 227 (8 500), 258 (19 600), 285sh (4 800), 325 (1 700), 456 (4 600), 485 (5 900), and 515 nm (4 400); δ ($CDCl_3$; 90 MHz †) 1.65br (3 H, s, C:CMe), 3.35br (4 H, s, CH_2C:CCH_2), 5.5—5.6 (1 H, m, C:C*H*CH_2), 7.74—7.86 and 8.28—8.41 (each 2 H, m, C_6H_4), and 12.57 and 12.60 (each 1 H, s, 2 × OH) (addition of D_2O caused the signal at 13.4 to disappear); *m/e* 306 (M^+, base peak) (Found: 74.8; H, 4.25. $C_{19}H_{14}O_4$ requires C, 74.5; H, 4.6%).

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REFERENCES

[1] Preliminary communication, M. Chandler and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1978, 998.
[2] F. Arcamone, in 'Topics in Antibiotic Chemistry,' ed. P. G. Sammes, Ellis Horwood, Chichester, 1978, vol. 2, p. 99.
[3] M. C. Wani, H. L. Taylor, M. E. Wall, A. T. McPhail, and K. D. Onan, *J. Amer. Chem. Soc.*, 1975, **97**, 5955; G. R. Pettit, J. J. Einck, C. L. Herald, R. H. Ode, R. B. Von Dreale, P. Brown, M. G. Brazhnikova, and G. F. Gause, *ibid.*, p. 7387.
[4] F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. Di Marco, A. M. Casazza, G. Pratesi, and R. Reggiani, *Cancer Treatment Reports*, 1976, **60**, 829.
[5] H. H. Inhoffen, M. Muxfeldt, V. Kappe, and J. Heimann-Trosien, *Chem. Ber.*, 1957, **90**, 1448.
[6] W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, 1976, **41**, 2296.
[7] T. R. Kelly, R. N. Goerner, jun., J. W. Gillard, and B. K. Prazak, *Tetrahedron Letters*, 1976, 3869.
[8] D. Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692.
[9] A. M. Birch, A. J. H. Mercer, A. M. Chippendale, and C. W. Greenhalgh, *J.C.S. Chem. Comm.*, 1977, 745.
[10] G. Wilkinson, *Org. Syntheses*, 1956, **36**, 33.
[11] O. Dimroth and V. Hilcken, *Ber.*, 1921, **54**, 3050.