Synthesis of Intermediates related to 11-Deoxyanthracyclinones†

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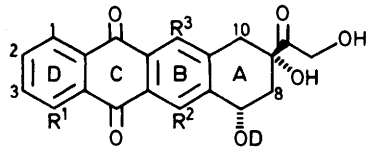
A series of Diels–Alder adducts has been synthesised from 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone (**5**), and the naphthacene (**9b**) has subsequently been converted into the epoxides (**9d**) and (**9e**). Catalytic hydrogenolysis of the ethanonaphthacene (**9a**) gave after work-up in air the 6,11-dione (**11**), whereas hydrogenolysis of the methanonaphthacene (**9f**) gave a condensed leuco quinizarin derivative (**13**). Catalytic hydrogenolysis of the ethylenedioxynaphthacene (**9e**) gave the partially reduced trihydroxy derivative (**15**), the structure of which was established by converting it in two steps into the known trione (**6a**). Compound (**9e**) was also transformed oxidatively into the condensed quinizarin derivative (**16**), and by base-promoted methylation into a compound believed to be the dione (**6d**); the latter was deprotected to give the trione (**6e**).

The widespread clinical use of the antitumour antibiotic adriamycin (**1a**) has generated great interest[1-3] in the total synthesis of this and analogues such as 4-demethoxy- (**1b**),[4] 11-deoxy- (**1c**),[5] and 6-deoxyadriamycin (**1d**). Synthetic routes to compounds in the 11-deoxy,anthracycline category are especially desirable in view of the antitumour activity exhibited by aclacinomycin A,[6] nogalamycin,[7] and the steffimycins.[7]

We report a new approach to the synthesis of compounds related to 11-deoxyanthracyclinones based on the readily available intermediates in an established route to 6,11-dihydroxyanthracyclinones. A successful early Diels–Alder entry [*via* (**2b**) + (**3a**)] to the latter compounds [*e.g.* (**4a**)] was devised by Kende *et al.*[8] and this approach was improved by employing epoxide protection of the internal (**4a–9a**) double bond of quinizarin quinone dienophiles [*cf.* (**5**)].[9] In the present work we have developed a method aimed at achieving the transformation [(**4b**) (equivalent)→(**6a**) and/or (**6b**)] based on the known hydrogenolysis–oxidation sequence (**7a**)→(**8**)→(**7b**)[10] that we recently elaborated.[11]

A series of tetra- and penta-cyclic epoxides (**9a–c**), (**9f**), and (**9g**) were synthesised in good yield (73–95%) by the reported method[9a] from the quinizarin quinone epoxides (**5a**) and (**b**) and the appropriate 1,3-diene [*e.g.* cycloalka-1,3-dienes or (**3b**) and (**3c**)]. The epoxides [*cf.* (**9**)] were always slightly contaminated and appeared to decompose slowly on standing in the solid state at room temperature. Difficulty was experienced in obtaining consistent data from elemental analyses, but the exact masses of the molecular ion for five such epoxides were satisfactory from high resolution mass measurements. The ^{1}H n.m.r. spectra of compounds (**9**) were in accord with the proposed structures with the proviso that the relative stereochemistry of the epoxide ring and the 4a- 12a-hydrogens is probably *cis* but is not unambiguously defined.[9a]

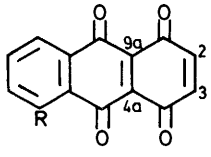
Conversion of the epoxides [*cf.* (**9**)] into the condensed quinizarin derivatives [*e.g.* (**10**)] can be achieved[9a] in two steps {treatment with (i) $Na_2S_2O_4$, and (ii) [O],$PhNO_2$, piperidine} and in principle this would provide model substrates for hydrogenolysis studies in the tetetracyclic series relating to the sequence (**7a**)→(**8**)→(**7b**). It was felt, however, that this sequence could be shortened as the epoxides [*cf.* (**9**)] would be expected to undergo catalytic hydrogenolysis of the epoxide ring and furnish intermediates that might relate to those from the hydrogenolysis of (**10**). In practice, the outcome of catalytic hydrogenolysis [H_2(40 atm), 5% Pd–C, dimethylformamide (DMF), 80 °C] of the epoxides [*cf.* (**9**)] proved to be dependent on the nature of the substituent (R^1) or addend (R–R) on the naphthacene system. For example, hydrogenolysis of the



(**1**)

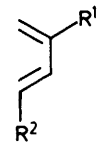
	R^1	R^2	R^3
a;	OMe	OH	OH
b;	H	OH	OH
c;	OMe	OH	H
d;	OMe	H	OH

D = daunosaminyl



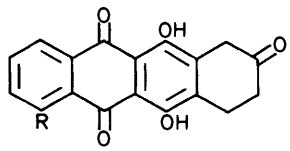
(**2**)

a; R = H
b; R = OMe



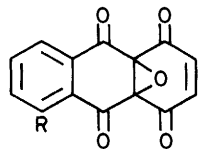
(**3**)

a; R^1 = OAc, R^2 = H
b; R^1 = $OSiMe_3$, R^2 = H
c; R^1 = $OSiMe_3$, R^2 = OMe



(**4**)

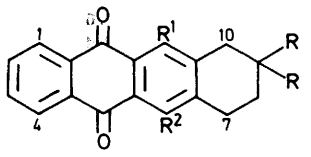
a; R = OMe
b; R = H



(**5**)

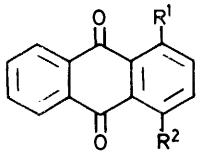
a; R = H
b; R = OMe

† Preliminary communication, P. N. Preston, T. Winwick, and J. O. Morley, *J. Chem. Soc., Chem. Commun.*, 1984, 307.

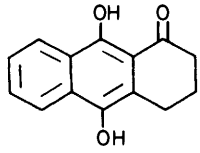


(6)

	R^1	R^2	R,R
a;	H	OH	O
b;	OH	H	O
c;	H	OH	OCH_2CH_2O
d;	H	OMe	OCH_2CH_2O
e;	H	OMe	O

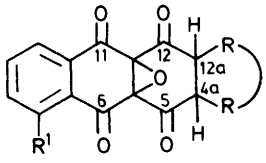


(7)



(8)

a; $R^1 = R^2 = OH$
b; $R^1 = OH$, $R^2 = H$



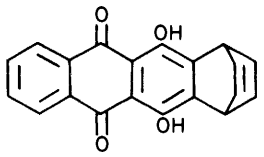
(9)

	R^1	R–R
a;	H	–CHCH=CHCHCH$_2$CH$_2$–
b;	H	$-CH_2C(OSiMe_3)=CHCH_2-$
c;	H	$-CH_2C(OSiMe_3)=CHCHOMe$
d;	H	$-CH_2COCH_2CH_2-$
e;	H	$-CH_2C(OCH_2CH_2O)CH_2CH_2-$
f;	OMe	–CHCH=CHCHCH$_2$–
g;	OMe	–CHCH=CHCHCH$_2$CH$_2$–

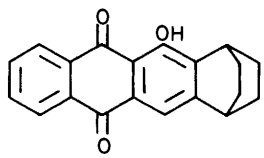
cyclohexadiene adduct (**9a**) gave, after work-up in air, the 12-hydroxy-6,11-dione derivative (**11**) (51%) presumably [*cf.* (**7a**)→(**8**)→(**7b**)] *via* the condensed anthracenone (**12**). In contrast, hydrogenation of the cyclopentadiene adduct (**9f**) derived from 5-methoxy-4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone (**5b**) gave a leuco compound (**13**) (30%) and a complex residue from which derivatives analogous to (**11**) or (**12**) could not be isolated.

Following the successful transformation of the model compound of type (**9a**)→(**11**), we turned our attention to the sequence relating to the synthesis of (**6a**) and/or (**6b**) or more elaborate intermediates related to anthracyclinones with a 7-oxygen-containing substituent. Catalytic hydrogenolysis of the epoxide adduct (**9c**) from (**5a**) and 4-methoxy-2-trimethylsiloxybuta-1,3-diene (**3c**) gave a complex product from which no pure compounds could be isolated. The epoxide substrate for hydrogenolysis was therefore simplified by converting [(HCl, tetrahydrofuran (THF)] the 2-trimethylsiloxybuta-1,3-diene adduct (**9c**) into the pentaone derivative (**9d**) (96%) and thence into the protected tetraone (**9e**).

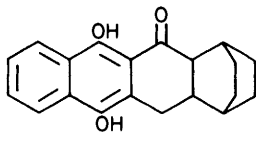
Chemical reduction ($Na_2S_2O_4$) of this tetraone (**9e**) gave the expected leuco derivative (**14**) (*cf.* ref. 9*a*) but catalytic hydrogenation gave a surprising result compared with the earlier transformations [*cf.* (**9a**)→(**11**) and (**9f**)→(**13**)]. A single compound was isolated chromatographically in 28% yield from a complex product. From analytical and spectroscopic data (see Experimental section), a condensed anthranol structure [*cf.* (**15**)] was assigned to this product although the definitive regiochemical formulation (**15**) was only determined after subsequent chemical reactions. When a yellow solution of compound (**15**) in dimethyl sulphoxide was allowed to stand in air for two weeks it slowly turned red and the condensed quinizarin derivative (**16**) was isolated in 82% yield. Treatment of the naphthacenone (**15**) with potassium carbonate in



(10)



(11)



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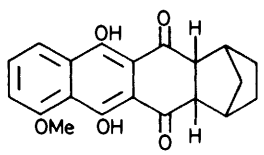

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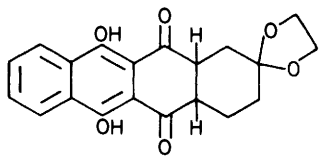

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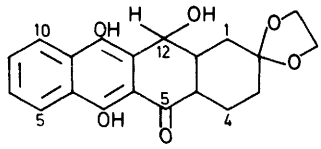
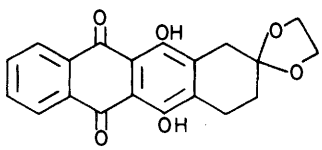


(15)



(16)

methanol under reflux caused dehydration with concomitant oxidation to give the tetrahydronaphthacene-6,11-dione (**6c**) in 85% yield. The regiochemical outcome of the sequence (**9e**)→(**15**)→(**6c**) was unambiguously defined by the conversion of compound (**6c**) into the tetrahydronaphthacene-2,6,11-trione (**6a**) using hydrochloric acid in tetrahydrofuran; the latter product (**6a**) was identical* (m.p., u.v., i.r., n.m.r., and mass spectra) with the compound prepared by Gesson *et al.*[12] by a Diels–Alder route, but different from the isomer (**6b**) prepared by Gesson *et al.* by an analogous method.[13] An additional compound, presumed also to be related to 11-deoxyanthracyclinones, was prepared by treating the naphthacenone (**15**) with methyl toluene-*p*-sulphonate and potassium carbonate in *o*-dichlorobenzene under reflux giving the dione (**6d**) in 53% yield; deprotection of the latter compound (**6d**) gave the trione (**6e**).

The successful hydrogenolysis of equivalents [*cf.* (**9**)] of 6,11-dihydroxyanthracyclinone intermediates [*cf.* (**4**)] achieved in this work provides encouragement to extend the studies to suitably ring A protected derivatives of natural and synthetic anthracyclinones.

Experimental

Anthracene-1,4,9,10-tetraone (**2a**) and 4a,9a-epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetraone (**5a**) were prepared by a reported procedure.[9a] Palladium on charcoal catalyst (5%) was purchased from Koch-Light. Catalytic hydrogenation experiments were carried out in rocking Baskerville autoclaves (300 ml and 1 l capacity) or in a 150-ml Berghof autoclave fitted with a magnetic stirrer.

Preparation of 5-*Methoxyanthracene*-1,4,9,10-*tetraone* (**2b**).— 1,4-Dihydroxy-5-methoxyanthraquinone[14] (18.0 g, 66.6 mmol) was added to a stirred suspension of lead(IV) acetate (45.0 g, 101 mmol) in glacial acetic acid (300 cm^3). After 0.5 h the product was filtered and the brown precipitate was washed with water and dried *in vacuo* over phosphorus pentaoxide. The product 5-*methoxyanthracene*-1,4,9,10-*tetraone* (**2b**) (15.3 g, 85%), δ[$(CD_3)_2SO$] 4.00 (3H, s), 6.9 (2 H, s), and 7.4—7.8 (3 H, m), was converted without further purification into the epoxide (**5b**).

Preparation of 4a,9a-*Epoxy*-5-*methoxy*-4a,9a-*dihydroanthracene*-1,4,9,10-*tetraone* (**5b**).— *m*-Chloroperbenzoic acid (20.5 g, 112 mmol) was added in portions to a stirred ice-cooled suspension of the tetraone (**2b**) (15.0 g, 56.0 mmol) in dichloromethane (1 l). The mixture was warmed to room temperature, allowed to stand for 1 h, and filtered. Solvent was evaporated from the filtrate and the residue was chromatographed (silica gel, diethyl ether eluant) to give (after trituration with dichloromethane) yellow 4a,9a-*epoxy*-5-*methoxy*-4a,9a-*dihydroanthracene*-1,4,9,10-*tetraone* (**5b**) (7.8 g, 41% based on 1,4-dihydroxy-5-methoxyanthraquinone), m.p. 205—220 °C (decomp.); δ[$(CD_3)_2SO$] 3.95 (3 H, s), 6.7 (2 H, s), and 7.3—7.8 (3 H, m); $\nu_{max.}$(KBr) 3 100, 3 050, 1 720, 1 675, 1 608, 1 586, 1 472, 1 441, 1 325, 1 280, 1 235, 1 192, 1 108, 1 092, 1 075, 1 032, 952, 912, 890, 842, 785, and 722 cm^{-1}; *m/z* 284 ($M^{+\cdot}$); $\lambda_{max.}$(MeOH) 211, 228, and 340 nm (Found: C, 62.8; H, 2.7%; $M^{+\cdot}$ 286.047. $C_{15}H_8O_6$ requires C, 63.38; H, 2.81%; $M^{+\cdot}$ 286.047).

Synthesis of the Diels–Alder Adducts of 4a,9a-*Epoxytetraones* (**5a**) *and* (**5b**).— 5a,11a-*Epoxy*-1,4-*ethano*-1,4,4a,5a,11a,12a-*hexahydronaphthacene*-5,6,11,12-*tetraone* (**9a**). This compound (73%), m.p. 208—212 °C (decomp.) [lit.,[9a] 208—212 °C (decomp.)] was prepared from the tetraone (**2a**) and cyclohexa-1,3-diene according to a literature procedure.[9a]

5a,11a-*Epoxy*-2-*trimethylsiloxy*-1,4,4a,5a,11a,12a-*hexahydronaphthacene*-5,6,11,12-*tetraone* (**9b**). 2-Trimethylsiloxybuta-1,3-diene[15] (11.3 g, 79 mmol) was added to a stirred suspension of the epoxy tetraone (**5a**) (10.0 g, 39.4 mmol) in dichloromethane (500 cm^3). After 3 days at room temperature, the solvent was evaporated under reduced pressure and the residue was recrystallised from dichloromethane–light petroleum to yield the colourless title compound (**9b**) (14.0 g, 90%), m.p. 205—207 °C; δ[$(CD_3)_2SO$] 0.18 (9 H, s, Me_3SiO), 2.00 (2 H, m, 1- or 4-H), 2.40 (2 H, m, 1- or 4-H), 3.20 (1 H, m, 4a, or 12a-H), 3.55 (1 H, m, 4a- or 12a-H), 4.75 (1 H, m, 3-H), and 7.90 (4 H, m, ArH).

5a,11a-*Epoxy*-4-*methoxy*-2-*trimethylsiloxy*-1,4,4a,5a,11a,-12a-*hexahydronaphthacene*-5,6,11,12-*tetraone* (**9c**). 4-Methoxy-2-trimethylsiloxybuta-1,3-diene[16] (7.4 g, 43.3 mmol) was added to a stirred suspension of the epoxy tetraone (**5a**) (10.0g, 39.4 mmol) in dichloromethane (200 cm^3). After 10 min the solvent was evaporated under reduced pressure and the residual colourless solid was recrystallised from dichloromethane–light petroleum (b.p. 40—60 °C) to give the colourless title *compound* (**9c**) (15.9 g, 95%), m.p. 175—178 °C; δ($CDCl_3$) 0.18 (9 H, s, Me_3SiO), 2.10 (1 H, dd, *J* 7 and 18 Hz, 1-H), 2.75 (1 H, d, *J* 18 Hz, 1-H), 3.04 (4 H, m, MeO + 12a-H), 3.53 (1 H, t, *J* 6 Hz, 4a-H), 4.20 (1 H, t, *J* 5 Hz, 4-H), 5.05(1 H, d, *J* 6 Hz, 3-H), 7.75 (2 H, m, ArH), and 8.00 (2 H, m, ArH); $\nu_{max.}$(KBr) 2 950, 1 755, 1 730, 1 695, 1 655, 1 595, 1 415, 1 380, 1 340, 1 285, 1 265, 1 250, 1 065, 990, 895, 845, 765, and 705 cm^{-1}; *m/z* 426 (M^+) $\lambda_{max.}$(MeOH) 212, 230, and 258 nm (Found: C, 61.0; H, 5.1; $M^{+\cdot}$ 426.113. $C_{22}H_{22}O_7Si$ requires C, 62.00; H, 5.16%; $M^{+\cdot}$ 426.113).

5a,11a-*Epoxy*-7-*methoxy*-1,4-*methano*-1,4,4a,5a,11a,12a-*hexahydronaphthacene*-5,6,11,12-*tetraone* (**9f**). Cyclopentadiene (0.3 g, 4.54 mmol) was added to a stirred suspension of the epoxy tetraone (**5b**) (0.5 g, 1.76 mmol). After 1 h the precipitate was filtered off and recrystallised from chloroform–light petroleum (b.p. 40—60 °C) to give the yellow title *compound* (**9f**) (0.47 g, 76%), m.p. 190—210 °C (decomp.); δ($CDCl_3$) 1.40 (2 H, m, $CHCH_2CH$), 3.25 (2 H, m, $CHCH_2CH$), 3.65 (2 H, m, $COCHCHCO$), 3.95 (3 H, s, OMe), 6.10 (2 H, m, $CHCH{=}CHCH$), and 7.2—7.8 (3 H, m, ArH); $\nu_{max.}$(KBr) 2 970, 2 930, 1 725, 1 680, 1 580, 1 460, 1 295, 1 265, 1 060, and 675 cm^{-1} (Found: C, 67.85; H, 3.7. $C_{20}H_{14}O_6$ requires C, 68.57; H, 4.00%). The molecular ion was of very low intensity and an accurate mass measurement of the molecular ion was not made.

5a,11a-*Epoxy*-7-*methoxy*-1,4-*ethano*-1,4,4a,5a,11a,12a-*hexahydronaphthacene*-5,6,11,12-*tetraone* (**9g**). Cyclohexa-1,3-diene (0.28 g, 0.35 mmol) and the epoxytetraone (**5b**) (0.5 g, 1.76 mmol) were heated after reflux in benzene (5 ml). After 3 h the mixture was cooled and the precipitate separated and recrystallised from chloroform to give the yellow title *compound* (**9g**) (0.48g, 75%), m.p. 200—220 °C (decomp.); δ($CDCl_3$) 1.25—1.60 (4 H, m, $CHCH_2CH_2CH$), 3.11 (2 H, br, s, $CHCH_2CH_2CH$), 3.48 (2 H, s, 4a- 12a-H), 3.96 (3 H, s, OMe), 6.22 (2 H, m, CH=CH), 7.35 (1 H, m, ArH), and 7.82 (2 H, m, ArH); $\nu_{max.}$ 2 930, 2 860, 1 725, 1 680, 1 575, 1 460, 1 270, 1 250, 1 070, 910, and 690 cm^{-1}; $\lambda_{max.}$(MeOH) 208, 238, and 350nm (Found: C, 67.0; H, 4.3. $C_{21}H_{16}O_6$ requires C, 69.23; H, 4.39%).

Preparation of 5a,11a-*epoxy*-1,2,3,4,4a,5a,11a,12a-*octahydronaphthacene*-2,5,6,11,12-*pentaone* (**9d**). A solution of the tetraone (**9b**) (12.0 g, 30.3 mmol) in 2M-hydrochloric acid (4 cm^3) and tetrahydrofuran (200 cm^3) was allowed to stand at room temperature for 2 h. The resulting precipitate was separated and recrystallised from dichloromethane to give the colourless title *compound* (**9d**) (9.4 g, 96%), m.p. 200—220 °C (decomp.); δ[$(CD_3)_2SO$] 2.00—3.00 (6 H, m, 1-, 1-, 3-, 3-, 4-, 4-H), 4.00 (1 H m, 4a-H), 4.40 (1 H, m, 12a-H), and 8.25 (4 H, m, ArH); $\nu_{max.}$ 1 740, 1 590, 1 305, and 1 285 cm^{-1} (Found: C, 65.9;

* We thank Professor J. P. Gesson for generously providing samples of (**6a**) and (**6b**).

H, 3.6%; $M^{+\bullet}$ 324.063. $C_{18}H_{12}O_6$ requires C, 66.66; H, 3.7%; $M^{+\bullet}$ 324.065).

Preparation of 5a,11a-*epoxy*-2,2-*ethylenedioxy*-1,2,3,4,4a,5a,11a-*octahydronaphthacene*-5,6,11,12-*tetraone* (**9e**). The epoxy pentaone (**9d**) (8.0 g, 22.6 mmol), ethylene glycol (2.8 g, 45.2 mmol), and toluene-*p*-sulphonic acid (0.1 g) were heated under reflux for 2 h in dichloromethane (400 cm^3); during this time, water was removed from the mixture with a Dean–Stark apparatus. The product was filtered, the filtrate was evaporated under reduced pressure, and the residue was recrystallised from dichloromethane to yield the colourless title *compound* (**9e**) (7.01 g, 78%), *m*.p. 185—200 °C (decomp.); δ[$(CD_3)_2SO$] 1.50—2.50 (6 H, m, 1-, 1-, 3-, 3-, 4-, 4-H), 3.42 (2 H, s, 4a-, 12a-H), 3.90 (4 H, m, OCH_2CH_2O), and 7.98 (4 H, m, ArH); *m*/*z* 368 (M^+); $\nu_{max.}$(KBr) 2 960, 2 950, 1 730, 1 710, 1 680, 1 585, 1 290, 1 095, 1 030, 935, 890, 875, 790, 745, and 705 cm^{-1} $\lambda_{max.}$(MeOH), 205, 228, and 258 nm (Found: C, 64.6; H, 4.2%; $M^{+\bullet}$ 368.089.$C_{20}H_{16}O_7$ requires C, 65.22; H, 4.34%; $M^{+\bullet}$ 368.091).

Hydrogenation of 5a,11a-*Epoxy*-1,4-*ethano*-1,4,4a,5a,11a,-12a-*hexahydronaphthacene*-5,6,11,12-*tetraone* (**9a**).—The epoxide (**9a**) (6.0 g, 18 mmol) in DMF (250 cm^3) was hydrogenated (40 atm H_2) over 5% Pd-C (0.7 g) for 15 h at 80 °C. The product was filtered through Celite and added to ice-cold water (200 cm^3). The red precipitate was washed with cold water, dried *in vacuo* at 60 °C, and recrystallised from DMF to give red 12-*hydroxy*-1,4-*ethano*-1,2,3,4-*tetrahydronaphthacene*-6,11-*dione* (**11**) (2.8 g, 51%), m.p. 241—244 °C; δ($CDCl_3$) 1.55 (4 H, m), 1.85 (4 H, m), 3.65 (2 H, s, 1- and 4-H), 7.80 (2 H, m, ArH), 7.84 (1 H, m, ArH), 8.0 (1 H, s, ArH), 8.35 (1 H, m, ArH), and 13.72 (1 H, s, exch, OH); $\nu_{max.}$(KBr) 2 940, 2 860, 1 645, 1 625, 1 595, 1 500, 1 450, 1 380, 1 355, 1 340, 1 290, 1 280, 970, 895, 845, 820, and 760 cm^{-1}; *m*/*z* 304 ($M^{+\bullet}$) (Found: C, 78.5; H, 5.2. $C_{20}H_{16}O_3$ requires C, 78.94; H, 5.26%).

Hydrogenation of 5a,11a-*Epoxy*-7-*methoxy*-1,4-*methano*-1,4,-4a,5a,11a,12a-*hexahydronaphthacene*-5,6,11,12-*tetraone* (**9f**).—The tetraone (**9f**) (2.5 g, 7 mmol) in DMF (60 cm^3) was hydrogenated (40 atm H_2) over 5% Pd-C (0.1 g) for 15 h at 80 °C. The product was filtered through Celite and the solvent evaporated from the filtrate under reduced pressure. The brown oily residue was chromatographed on silica gel (ethyl acetate–light petroleum eluant) to give yellow 6,11-*dihydroxy*-7-*methoxy*-1,4-*methano*-1,2,3,4,4a,12a-*hexahydronaphthacene*-5,12-*dione* (**13**) (0.76 g, 30%), m.p. 198—200 °C; δ_H($CDCl_3$) 1.20—1.70 (6 H, m, 2-, 2-, 3-, 3-H and $CHCH_2CH$), 3.05 (2 H, br, s, 1-and 4-H), 3.20 (2 H, br, s, 4a- and 12a-H), 4.00 (3 H, s, MeO), 7.20 (1 H, d, *J* 8 Hz, ArH), 7.70 (1 H, t, *J* 8 Hz, ArH), 8.10 (1 H, d, *J* 8 Hz, ArH), 14.70 (1 H, s, exch., OH), and 15.95 (1 H, s, exch, OH); $\nu_{max.}$(KBr) 2 940, 2 860, 1 580, 1 445, 1 400, 1 335, 1 235, 1 160, 1 065, 1 040, 900, 810, and 770 cm^{-1}; $\lambda_{max.}$ (MeOH) 256, 274, 279, 420, and 445 nm (Found: C, 70.2; H, 5.1. $C_{20}H_{18}O_5$ requires C, 71.00; H, 5.33%).

Preparation of 2,2-*Ethylenedioxy*-6,11-*dihydroxy*-1,2,3,4,4a,-12a-*hexahydronaphthacene*-5,12-*dione* (**14**).—Sodium dithionite (0.75 g) in water (2 cm^3) was added to the epoxide (**9e**) (0.5 g, 1.4 mmol) in methanol (100 cm^3). The yellow product was acidified (dil. HCl), poured into water and then extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow oil which was recrystallised from methanol to give the yellow title *compound* (**14**) (0.30 g, 62%), m.p. 172—174 °C; δ($CDCl_3$) 1.75—1.90 (5 H, m, 1-, 3-, 3-, 4-, 4-H), 2.50—2.60 (1 H, m, 1-H), 3.20—3.40 (2 H, m, 4a -and 12a-H), 3.96 (4 H, m, OCH_2CH_2O), 7.78 (2 H, m, ArH), 8.48 (2 H, m, ArH), 13.72 (1 H, s, exch., OH), and 13.77 (1 H, s, exch. OH); *m*/*z* 354 ($M^{+\bullet}$); $\lambda_{max.}$(MeOH) 238, 250, 278, 296, and 416 nm; $\nu_{max.}$(KBr) 2 940, 2 860, 1 615, 1 580, 1 450, 1 400, 1 340, 1 240, 1 160, 1 065, 1 045, and 900 cm^{-1} (Found: C, 67.0; H, 5.1%; $M^{+\bullet}$, 354.110. $C_{20}H_{18}O_6$ requires C, 67.80; H, 5.08%; $M^{+\bullet}$ 354.112).

Hydrogenation of 5,11a-*Epoxy*-2,2-*ethylenedioxy*-1,2,3,4,4a,-5a,11a,12a-*octahydronaphthacene*-5,6,11,12-*tetraone* (**9e**).—The epoxide(**9e**) (5.0 g, 13.6 mmol) in DMF (200 ml) was hydrogenated (40 atm H_2) over palladium (0.2 g; 5% Pd—C) for 15 h at 80 °C. The product was filtered through Celite and the solvent was evaporated under reduced pressure. The resulting dark brown oily residue was purified chromatographically (ether–light petroleum, 1:1 as eluant) yielding bright yellow 2,2-*ethylenedioxy*-6,11,12-*trihydroxynaphthacen*-5-*one* (**15**) (1.3 g, 28%), m.p. 188—190 °C (from dichloromethane); δ($CDCl_3$) 1.58 (s, H_2O, exch.), 1.25—2.00 (5 H, m), 2.60—2.95 (4 H, m), 3.95 (4 H, m, OCH_2CH_2O), 5.69 (1 H, t, *J* 5 Hz, 12-H), 7.63 (2 H, m, Ar-H), 8.20 (1 H, d, *J* 8 Hz, ArH), 8.40(1 H, d, *J* 8 Hz, ArH), 9.24 (1 H, s, exch, 11-OH), and 14.20 (1 H, s, exch., 6-OH); $\nu_{max.}$3 390, 3 320, 3 170, 2 950, 2 900, 1 620, 1 595, 1 580, 1 475, 1 450, 1 400, 1 380, 1 360, 1 285, 1 235, 1 120, 1 080, 1 045, and 770 cm^{-1}; *m*/*z* 356 ($M^{+\bullet}$); $\lambda_{max.}$(MeOH) 220, 272, and 410 nm (Found: C, 64.1; H, 5.5; $C_{20}H_{20}O_6 \cdot H_2O$ requires C, 64.17; H, 5.88%).

Reactions of the Naphthacen-5-one Derivative (**15**).—(a) *Air oxidation.* A yellow solution of the naphthacen-5-one (**15**) (0.05 g, 0.14 mmol) in dimethyl sulphoxide (1 cm^3) was allowed to stand in an open vessel in air for 2 weeks. The red precipitate was washed with water and dried *in vacuo* at 70 °C to give 2,2-*ethylenedioxy*-5,12-*dihydroxy*-1,2,3,4-*tetrahydronaphthacene*-6,11-*dione* (**16**) (0.04 g, 82%), m.p. 235—237 °C (from dichloromethane–light petroleum); $\nu_{max.}$(KBr) 2 960, 1 620, 1 585, 1 440, 1 400,1 230, 1 110, and 1 055 cm^{-1}; δ($CDCl)_3$) 2.05 (2 H, t, *J* 7 Hz, 3-, 3-H), 3.06 (4 H, m, 1-, 1-, 4-, 4-H), 4.10 (4 H, s, OCH_2CH_2O), 7.81 (2 H, m, Ar-H) 8.32 (2 H, m, ArH), 13.46 (1 H, s, exch., OH), and 13.47 (1 H, s, exch., OH); $\lambda_{max.}$ (MeOH) 256, 269, 455, and 480 nm; *m*/*z* 352 (Found: C, 65.7; H, 4.55%; $M^{+\bullet}$, 352.094. $C_{20}H_{16}O_6 \cdot H_2O$ requires C, 64.86; H, 4.86%; $M^{+\bullet}$ 352.096).

(b) *Dehydration–oxidation.* The naphthacen-5-one (**15**) (0.25 g, 0.7 mmol), potassium carbonate (0.1 g), and methanol (40 cm^3) were heated under reflux for 0.5 h. Upon cooling, orange 2,2-*ethylendioxy*-5-*hydroxy*-1,2,3,4-*tetrahydronaphthacene*-6,11-*dione* (**6c**) (0.21 g, 85%) crystallised, m.p. 225—227 °C (from MeOH), δ($CDCl_3$) 2.00 (2 H, t, *J* 7 Hz, 3-H), 3.05 (4 H, m, 1-, 1-, 4-, 4-H), 4.05 (4 H, s, OCH_2CH_2O), 7.54 (1 H, s, ArH), 7.78 (2 H, m, ArH), 8.27 (2 H, m, ArH), and 13.04 (1 H, s, exch., OH); $\nu_{max.}$(KBr) 2 900, 1 670, 1 635, 1 590, 1 480, 1 415, 1 385, 1 360, 1 325, 1 295, 1 275, 1 260, 1 245, 1 140, 1 110, 1 055, 1 005, 790, and 720 cm^{-1}; *m*/*z* 336 ($M^{+\bullet}$); $\lambda_{max.}$(MeOH) 205, 262, 244, and 405 nm (Found: C, 70.8; H, 4.7. $C_{20}H_{16}O_5$ requires C, 71.43; H, 4.76%).

(c) *Reaction with methyl toluene*-p-*sulphonate.* The naphthacen-5-one (**15**) (0.10 g, 0.3 mmol) methyl toluene-*p*-sulphonate (0.17 g 0.9 mmol), potassium carbonate (0.1 g), and *o*-dichlorobenzene (10 cm^3) were heated under reflux for 15 h. The product was poured into water and extracted with diethyl ether. The ether extract was washed with water and evaporated under reduced pressure to give a brown oily residue. This material was chromatographed (silica gel, diethyl ether–light petroleum eluant) to give yellow 2,2-*ethylenedioxy*-5-*methoxy*-1,2,3,4-*tetrahydronaphthacene*-6,11-*dione* (**6d**) (0.052 g, 53%), m.p. 202—204 °C (from diethyl ether–light petroleum); δ(CDCl) 2.00 (2 H, t, *J* 7 Hz, 3-H), 3.10 (4 H, m, 1-, 1-, 4-, 4-H), 3.92 (3 H, s, MeO), 4.05 (4 H, s, OCH_2CH_2O), 7.75 (2 H, m, ArH), 7.84 (1 H, s, ArH), and 8.25 (2 H, m, ArH); *m*/*z* 350 ($M^{+\bullet}$); $\nu_{max.}$(KBr) 2 950, 2 870, 1 665, 1 580, 1 445, 1 335, 1 260, 1 110, 1 055, 1 005, 970,

945, 835, 760, and 715 cm^{-1}; $\lambda_{max.}$(MeOH) 218, 255, and 342 nm (Found: C, 71.7; H, 4.95. $C_{21}H_{18}O_5$ requires C, 72.0; H, 5.14%).

Preparation of 5-Hydroxy-1,2,3,4-tetrahydronaphthacene-2,-6,11-trione (**6a**).—The naphthacene-6,11-dione (**6c**) (0.1 g, 0.2 mmol) was heated under reflux with a catalytic amount of 10M-hydrochloric acid in tetrahydrofuran (20 cm^3) for 0.5 h. The product was added to aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic extract was dried ($MgSO_4$) and evaporated under reduced pressure to give the dark yellow title compound (**6a**) (0.08 g, 92%), m.p. 245—247 °C (from chloroform) (lit.,[12] 245—247 °C); δ($CDCl_3$) 2.62 (2 H, t, *J* 7 Hz, 3-, 3-H), 3.25 (2 H, t, *J* 7 Hz, 4-, 4-H), 3.71 (2 H, s, 1-, 1-H), 7.60 (1 H, s, ArH), 7.84 (2 H, m, ArH), 8.33 (2 H, m, ArH), and 13.09 (1 H, s, exch., OH); $\nu_{max.}$(KBr) 1 725, 1 665, 1 630, 1 590, 1 570,1 275, 995, 790, and 715 cm^{-1}; $\lambda_{max.}$(MeOH) 205, 246, 262, 315, and 405 nm.

Preparation of 5-Methoxy-1,2,3,4-tetrahydronaphthacene-2,-6,11-trione (**6e**).—The naphthacene-6,11-dione (**6d**) (0.04 g, 0.114 mmol), 2M-HCl (0.5 cm^3), and methanol (6 cm^3) were heated under reflux for 15 h. The product was poured into water and extracted with dichloromethane. The organic extract was dried ($MgSO_4$) and evaporated to leave an oily residue, chromatographic purification [silica gel; diethyl ether–light petroleum ether (2:1) eluant] of which gave the yellow title compound (**6e**) (0.02 g, 54%), darkens at 103 °C, m.p. 135 °C (decomp.); δ($CDCl_3$) 2.59 (2 H, t, *J* 7 Hz, 3-, 3-H), 3.30 (2 H, t, *J* 7 Hz, 4-, 4-H) 3.74 (2 H, s, 1-, 1-H), 3.96 (3 H, s, MeO), 7.85 (2 H, m, ArH), 7.93 (1 H, s, ArH), and 8.27 (2 H, m, ArH); *m/z* 306 ($M^{+\bullet}$); $\nu_{max.}$(KBr) 2 920, 1 700, 1 670, 1 580, 1 260, and 710 cm^{-1}; $\lambda_{max.}$(MeOH) 222, 263, and 269 nm. This sample turned red on standing and could not be obtained analytically pure.

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