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Experiments Directed Towards the Synthesis of Anthracyclinones. XI* A New Diels–Alder Entry to (±)-4-Demethoxydaunomycinone

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Abstract

The cycloaddition of 2-acetoxybuta-1,3-diene to the external double bond of quinizarinquinone proceeds in high yield in benzene at 55°. The resulting adduct has been converted into a key intermediate for 4-demethoxydaunomycinone synthesis.

Pericyclic reactions have played a pivotal role in the search for synthetic routes from anthraquinones to new anthracyclines.[1] For example, we recently completed a synthesis[2] of 4-demethoxydaunomycinone (1) in which the key intermediate (2) was synthesized from quinizarin by sequential reductive Claisen rearrangements.[3] Others have used the Diels–Alder addition of a suitable diene to a protected anthradiquinone,[4] or of a relatively electron-deficient diene such as chloroprene to the external double bond of the unprotected diquinone.[5] In the course of this latter investigation Terashima *et al.*[5] found that 2-acetoxybuta-1,3-diene was unsuitable for addition to quinizarinquinone (6) since the cycloadduct (7) was obtained in only 16% yield. We now report conditions which allow the synthesis of (7) in 83% yield, and its conversion into the functionalized anthraquinone (3), the parent phenol of the intermediate (2), thereby bringing about a convergence of these two synthetic strategies.

* Part X, *Aust. J. Chem.*, 1986, **39**, 487.

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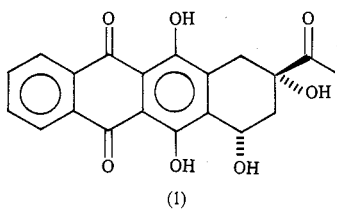

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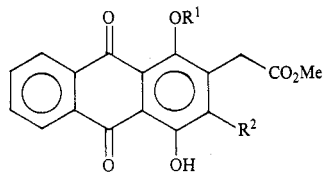
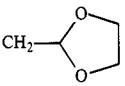
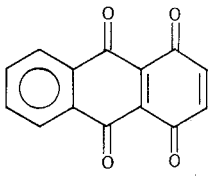


	R^1	R^2
(2)	Me	$CH(OMe)_2$
(3)	H	$CH(OMe)_2$
(4)	H	$CH_2CH(OMe)_2$
(5)	H	



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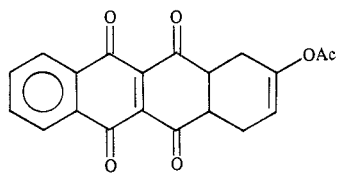

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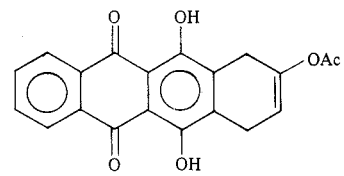

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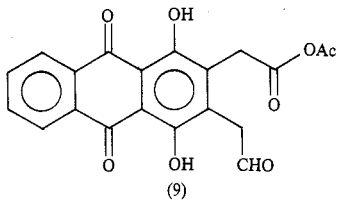

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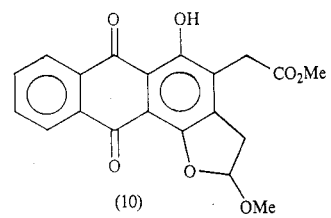

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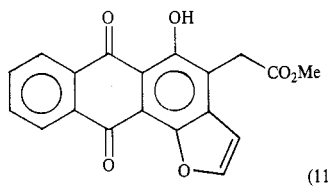

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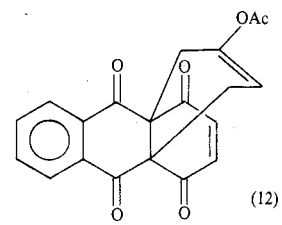

(12)

Diels–Alder addition of 2-acetoxybuta-1,3-diene to quinizarin quinone (6)[6] in benzene at 55° for 4 days gave the tetrone (7) (83%) which on treatment with sodium acetate in glacial acetic acid afforded 2-acetoxy-5,12-dihydroxy-1,4-dihydronaphthacene-6,11-dione (8) (91%). Ozonolysis of the latter compound with reductive workup gave an unstable compound identified but not characterized as the aldehydo anhydride (9). When the crude ozonolysis product was treated with trimethyl orthoformate/methanol/*p*-toluenesulfonic acid the acetal (4) was obtained in 23% yield along with the dihydrofuran (10) (36%). On the other hand when the methanol in the latter reaction was replaced by ethane-1,2-diol the dioxolan (5) was obtained as the sole product (80%). Treatment of either the dihydrofuran (10), or the dimethyl acetal (4), or the ethylene acetal (5) with Eaton's reagent[7] gave the benzofuran (11) in yields of 70%, 47% and 77% respectively. In a sequence involving ozonolysis, acetal formation and treatment with Eaton's reagent without purification of intermediates, the enol acetate (8) was converted into the furano ester (11) in

[6] Fieser, L. F., and Fieser, M., 'Reagents for Organic Synthesis' Vol. 1, p. 538 (John Wiley: New York 1967).

[7] Eaton, P. E., Carlson, G. R., and Lee, J. T., *J. Org. Chem.*, 1973, **38**, 4071.

62% yield. Ozonolysis of the latter product and acetal formation with trimethyl orthoformate/methanol/*p*-toluenesulfonic acid afforded the desired ester (3) (95%).

Although the overall yield of (3) (45%) is inferior to that of (2) (68%),[2] the cycloaddition route obviates the need for a subsequent demethylation. It also may prove superior for anthracyclinone synthons containing functionality which is incompatible with the reducing conditions required for Claisen rearrangements.

Experimental

For general experimental details see Part I.[8]

2-Acetoxy-1,4,4a,12a-tetrahydronaphthacene-5,6,11,12-tetrone (7)

A suspension of quinizarinquinone (6)[6] (0·26 g, 1·10 mmol) in 2-acetoxybuta-1,3-diene (0·36 g, 3·18 mmol) and benzene (12 ml) was stirred at 55° for 4 days. The mixture was cooled and a tan-coloured solid was removed. The solid was washed with hexane and dried under reduced pressure to give 2-acetoxy-1,4,4a,12a-tetrahydronaphthacene-5,6,11,12-tetrone (0·32 g, 83%), m.p. 199–203° (dec.) [lit.[9] 200–203° (dec.)]. ν_{max} 1745 (OAc), 1710, 1665, 1590, 1280, 1215, 1125, 905 cm^{-1}. *m/z* 352, 350 (M), 348, 310, 308, 306 ($M-H_2-CH_2CO$), 240 ($MH_2-C_6H_8O_2$), 43 (CH_3CO, 100%). Concentration of the filtrate under reduced pressure gave an orange oil (59 mg) which was shown by ^1H n.m.r. analysis to contain quinizarin, quinizarinquinone and the internal Diels–Alder adduct (12) in a 1 : 1 : 2 ratio. δ_H 2·12, s, $OCOCH_3$ of (12), 2·67–3·00, m, H 11, 14 of (12); 5·36–5·63, m, H 13 of (12); 6·80, s, H 2,3 of (12); 6·88, s, H 7,8 of (6), 12·90, s, OH of quinizarin.

2-Acetoxy-5,12-dihydroxy-1,4-dihydronaphthacene-6,11-dione (8)

A suspension of the tetrone (7) (0·22 g, 0·67 mmol) in glacial acetic acid (7 ml) was stirred for 10 min at 125–130°. Sodium acetate (0·11 g, 1·3 mmol) was added, and the mixture was heated for a further 10 min, which gave a red solution. The mixture was cooled and then diluted with water (30 ml). The resultant red solid was filtered, washed with water and ether, and dried under reduced pressure to give 2-acetoxy-5,12-dihydroxy-1,4-dihydronaphthacene-6,11-dione (0·20 g, 91%), m.p. 207–210° (lit.[9] 208–210°). ν_{max} 1750 (OAc), 1620 (quinone CO) 1580, 1420, 1235, 1200, 1100 cm^{-1}. δ_H 2·20, s, $OCOCH_3$; 3·45–3·58, m, 4H, H 1,4; 5·48–5·68, m, H 3; 7·67–7·95; m, 2H, H 8,9; 8·13–8·33, m, 2H, H 7,10; 13·25, 13·28, 2s, 5,12-OH. *m/z* 350 (M), 308 ($M-C_2H_2O$), 290 ($M-CH_3CO_2H$), 280 (308 − CO), 43 (CH_3CO).

General Ozonolysis Procedure

A solution of ozone, preformed by bubbling ozone into dichloromethane at −78° was standardized by titration with sodium thiosulfate (0·1 M) in the presence of an excess of potassium iodide in a 1 : 1 mixture of acetic acid and water. The required amount of ozone solution was then added to a solution of the substrate in dichloromethane at −78°. The reaction was maintained at −78° for 1 h, dimethyl sulfide (0·5 ml) was added, and the mixture was then warmed to room temperature over 1 h.

Ozonolysis of 2-Acetoxy-5,12-dihydroxy-1,4-dihydronaphthacene-6,11-dione

(A) The dione (8) (96 mg, 0·27 mmol) was treated with ozone (0·33 mmol). The solvent and excess of dimethyl sulfide were removed under reduced pressure, and the resulting red-brown solid was dissolved in dichloromethane, washed with water and dried. Solvent was removed under reduced pressure to give acetic [1,4-dihydroxy-9,10-dioxo-3-(2′-oxoethyl)-9,10-dihydroanthracen-2-yl]acetic anhydride (9) as a red-orange solid, unstable to chromatography. ν_{max} (KBr) 3700–3150 (OH, H-bonded), 1820, 1725 (anhydride), 1670 (CHO), 1640 (quinone CO), 1595, 1420, 1260 cm^{-1}. δ_H 2·27, s, $OCOCH_3$; 3·83–4·06, m, 4H, $ArCH_2$; 7·66–8·06, m, 2H, H 6,7; 8·16–8·50, m, 2H, H 5,8; 9·73–9·87, br t, CHO; 13·30, s, OH; 13·36, s, OH.

[8] Roberts, J. L., Rutledge, P. S., and Trebilcock, M. J., *Aust. J. Chem.*, 1977, **30**, 1553.
[9] Mills, J., Ph.D. Thesis, University of Rochester, 1977.

(B) The dione (8) (76 mg, 0·22 mmol) was treated with ozone (0·32 mmol), solvent and excess of dimethyl sulfide were removed under reduced pressure, and the residue was heated under reflux with trimethyl orthoformate (2·0 ml, 18 mmol) and *p*-toluenesulfonic acid (30 mg, 0·17 mmol) in dry methanol (50 ml) for 40 min. Workup gave an orange solid (90 mg) which on flash chromatography (hexane/acetone 99 : 1) yielded two compounds:

(i) *Methyl [3-(2′,2′-dimethoxyethyl)-1,4-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl]acetate* (4) (20 mg, 23%) crystallized from chloroform/hexane as orange needles, m.p. 163·5–165° (Found: C, 63·3; H, 4·9. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%). λ_{max} 233sh (log ε 4·19), 251 (4·45), 287 (3·90), 490 (3·87), 523sh (3.62). ν_{max} 3600–3300 (OH), 1745 (CO_2Me), 1630 (quinone CO), 1595, 1400, 1210 cm^{-1}. δ_H 3·12, d, *J* 5 Hz, 2H, $CH_2CH(OMe)_2$; 3·38, s, 6H, OCH_3; 3·72, s, CO_2CH_3; 3·98, s, 2H, CH_2CO_2Me; 4·57, t, *J* 5 Hz, $CH(OMe)_2$; 7·68–7·95, m, 2H, H 6,7; 8·13–8·33, m, 2H, H 5,8; 13·52, s, OH; 13·57, s, OH. δ_C 31·8, CH_2CO_2Me;[A]* 32·2, C 1′;[A] 52·2, CO_2CH_3; 54·5, 2-OCH_3 of acetal; 104·3, C 2′; 110·8, C 2;[B] 111·0, C 9a;[B] 126·8, C 5,8; 135·9, C 4a;[C] 133·4, C 8a, 10a; 134·3, C 6,7; 137·9, C 3;[C] 156·8, C 1,4; 170·6, CO_2Me; 186·2; 186·5, C 9,10. *m/z* 400 (M), 368, (M − MeOH), 308 (M − HCO_2Me − MeOH).

(ii) *Methyl (5-hydroxy-2-methoxy-6,11-dioxo-2,3,6,11-tetrahydroanthra[1,2-b]furan-4-yl)acetate* (10) (28 mg, 36%) crystallized from chloroform/hexane as fine orange needles, m.p. 215–216° (Found: C, 65·2; H, 4·4%; $M^{+\bullet}$, 368·0897. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4%; $M^{+\bullet}$, 368·0891). λ_{max} 234sh (log ε 4·24), 252 (4·46), 280 (3·97), 456 (3·87). ν_{max} (KBr) 3650–3300 (OH), 1730 (CO_2Me), 1670 (quinone CO), 1630 (quinone CO, H-bonded), 1590, 1210, 930 cm^{-1}. δ_H 3·06–3·33, m, 2H, H 3; 3·63, s, CO_2CH_3; 3·73, br s, 5H, 2-OCH_3, CH_2CO_2Me; 5·83–6·00, m, 2H, H 2; 7·68, m, 2H, H 8,9; 8·33, m, 2H, H 7,10; 13·71, s, 5-OH. δ_C 32·6, CH_2CO_2Me; 35·4, C 3; 52·4, CO_2CH_3; 56·4, 2-OCH_3; 108·3, C 2; 112·7, C 4;[A] 112·9, C 5a;[A] 126·5, C 7;[B] 126·9, C 10;[B] 127·7, C 11a; 132·8, C 10a;[C] 134·1, C 6a;[C] 133·4, C 8;[D] 134·3, C 9;[D] 139·9, C 3a; 151·9, OC(OMe); 157·7, C 5; 169·9; CO_2Me; 180·7, C 11; 186·7, C 6. *m/z* 368 (M), 337 (M − OCH_3), 308 (M − HCO_2Me).

Methyl [3-(1′,3′-Dioxolan-2′-ylmethyl)-1,4-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl]acetate (5)

The dione (8) (0·13 g, 0·36 mmol) was treated with ozone (0·54 mmol), solvent and excess of dimethyl sulfide were removed under reduced pressure and the residue was treated under reflux with trimethyl orthoformate (2 ml, 18 mmol), and *p*-toluenesulfonic acid (10 mg, 0·06 mmol) in ethylene glycol (35 ml) for 2 h. Workup gave a red solid (0·16 g) which after flash chromatography (hexane/acetone, 99 : 1) gave the *methyl ester* (5) (0·12 g, 80%), m.p. 199–200·5° (Found: $M^{+\bullet}$, 398·1014. $C_{21}H_{18}O_8$ requires $M^{+\bullet}$, 398·1002). λ_{max} 228sh (log ε 4·24), 257 (4·66), 292 (4·02), 489 (4·06), 521sh (3·85). ν_{max} (KBr) 3600–3300 (OH), 1745 (CO_2Me) 1625 (quinone CO, H-bonded), 1590, 1395, 1210, 1170 cm^{-1}. δ_H 3·22, d, *J* 5 Hz, 2H, CH_2CHO_2; 3·73, s, CO_2CH_3; 3·90, m, 4H, $CH(C_2H_4O_2)$; 4·00, s, 2H, CH_2CO_2Me; 5·17, t, *J* 5 Hz, CH_2CHO_2; 7·65–7·93, m, 2H, H 6,7; 8·1–8·3, m, 2H, H 5,8; 13·47, s, OH; 13·47, 13·52, 2s, OH. δ_C 31·8, CH_2CO_2Me; 32·4, CH_2CHO_2; 52·2, CO_2CH_3; 64·9, $-OCH_2CH_2O-$; 102·7, CH_2CHO_2; 110·9, 111·0, C 2,9a; 126·8, C 5,8; 133·2, C 8a,10a; 134·2, C 6,7; 135·7; C 4a; 137·0, C 3; 156·6, 156·8, C 1,4; 170·4, CO_2Me; 186·2, 186·4, C 9,10. *m/z* 398 (M), 366 (M − CH_3OH), 338 (M − $C_2H_4O_2$).

Methyl (5-Hydroxy-6,11-dioxo-6,11-dihydroanthra[1,2-b]furan-4-yl)acetate (11)

(A) *From methyl (5-hydroxy-2-methoxy-6,11-dioxo-2,3,6,11-tetrahydroanthra[1,2-b]furan-4-yl)acetate.*—The dihydrofuran (10) (25 mg, 0·068 mmol) was stirred in methanesulfonic acid/phosphorus(v) oxide (Eaton's reagent[7]) (1 ml) for 1 h. The mixture was poured into water (50 ml) and extracted into dichloromethane. The organic layer was dried with magnesium sulfate and the solvent was removed under reduced pressure to yield an orange solid (26 mg). P.l.c. (dichloromethane/hexane, 1 : 1) gave the *furano ester* (11) (16 mg, 70%) which crystallized from dichloromethane as orange needles, m.p. 236–238° (Found: C, 68·1; H, 3·6. $C_{19}H_{12}O_6$ requires C, 67·9; H, 3·6%). λ_{max} 223 (log ε 4·18), 255 (4·47), 274 (4·26), 433 (3·87). ν_{max} 1740 (CO_2Me), 1670 (quinone CO), 1635 (quinone CO, H-bonded), 1595, 1400, 1295, 1005,

* Pairs of superscript letters indicate that the signals may be interchanged.

935 cm^{-1}. δ_H 3·70, s, CO_2CH_3; 3·97, s, 2H, CH_2CO_2Me; 6·80, d, *J* 3 Hz, H 3; 7·67–7·83, m, 2H, H 8,9; 7·91, d, *J* 3 Hz, H 2; 8·20–8·37, m, 2H, H 7,10; 13·17, s, OH. *m/z* 336 (M), 304 (M − MeOH), 277 (M − $C_2H_3O_2$), 249 (M − $C_2H_3O_2$ − CO).

(B) *From methyl [3-(2′,2′-dimethoxyethyl)-1,4-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl]acetate.*—The acetal (4) (12 mg, 0·029 mmol) was treated with Eaton's reagent as above for 2 h. Workup gave the furano ester (11) (4·7 mg, 47%).

(C) *From methyl [3-(1′,3′-dioxolan-2′-ylmethyl)-1,4-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl]acetate.*—The ethylene acetal (5) (20 mg, 0·05 mmol) was treated with Eaton's reagent for 2 h. Workup gave the furano ester (11) (13 mg, 77%).

(D) *From 2-acetoxy-1,4-dihydro-5,12-dihydroxynaphthacene-6,11-dione.*—The dione (8) (0·10 g, 0·29 mmol) was treated successively as above with ozone (0·44 mmol) in dichloromethane, dry methanol (50 ml) containing trimethyl orthoformate (2 ml, 18 mmol) and *p*-toluenesulfonic acid (10 mg) for 2 h and then with Eaton's reagent for 1 h. Workup and flash chromatography (dichloromethane/hexane, 1 : 1) gave the furano ester (11) (61 mg, 62%).

Methyl [1,4-Dihydroxy-3-dimethoxymethyl-9,10-dioxo-9,10-dihydroanthracen-2-yl]acetate (3)

The furano ester (11) (30 mg, 0·089 mmol) was treated successively with ozone (0·14 mmol) in dichloromethane, and dimethyl sulfide. The product was heated under reflux in dry methanol (30 ml) containing trimethyl orthoformate (1·5 ml, 14 mmol) and *p*-toluenesulfonic acid (10 mg) for 1 h. Workup and flash chromatography (dichloromethane/hexane) gave the ester (3) (31 mg, 95%) which crystallized from dichloromethane/hexane as fine red needles, m.p. 170–171° (lit.[2] 170–171°). The spectral properties were identical with those of an authentic sample.

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