Tetrahedron Vol. 40, No. 22, pp. 4579 to 4583, 1984
Printed in Great Britain.

0040–4020/84 $3.00 + .00
© 1984 Pergamon Press Ltd.

THE SYNTHESIS OF ANTHRACYCLINONES—II

THE SYNTHESIS OF 7,9-BISDEOXYCARMINOMYCINONE AND -DAUNOMYCINONE

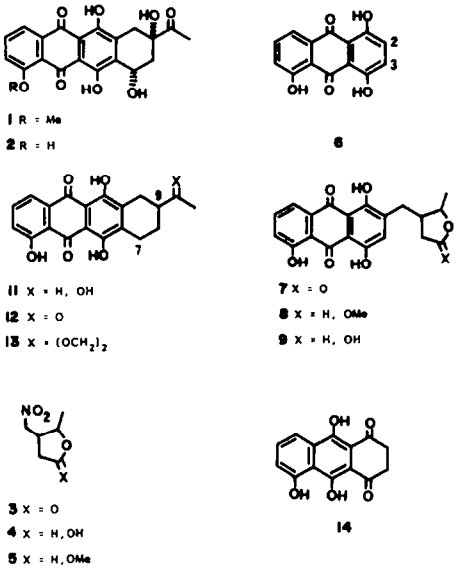
ALISON E. ASHCROFT, DAVID T. DAVIES and JAMES K. SUTHERLAND*
Chemistry Department, The Victoria University of Manchester, Manchester M13 9PL.

(*Received in USA* 17 *April* 1984)

Abstract—7,9-Bisdeoxycarminomycinone has been synthesised from 5-hydroxyquinizarin by two annelation routes involving nitronate addition to C-2 and aldol condensation at C-3. 4-Demethoxy-7,9-bisdeoxydaunomycinone has been synthesised efficiently by similar methods.

THE aglycones of the therapeutically useful anthracycline antibiotics have been the object of many synthetic studies. Numerous elegant and ingenious strategies have been devised to produce isomerically pure intermediates as precursors for daunomycione (**1**) and its 11-deoxyderivative following the original synthesis of Wong.[1] Four general approaches have been successful in solving the problem of regiochemical control. The syntheses of Kende,[2] Johnson,[3] Braun,[4] and Rao[5] have used selective Friedel-Crafts acylation to form ring C, while a variety of ingenious Michael condensations have been used to form ring B in the syntheses of Parker[6] and Kende,[7] rings B and C in the Hauser syntheses,[8] and ring C in the Swenton[9] and Keay[10] approaches. Regioselective Diels–Alder reactions formed the basis of the elegant syntheses of Kelly[11] (forming ring A) and Kishi[12] (forming ring B); the latter synthesis also forms ring A enantioselectively. Diels–Alder control in formation of ring B is also the cornerstone of the Gesson synthesis.[13] The final approach, adopted in the Sih route,[14] uses a regiocontrolled formation of ring A. So far, the Kishi route is the only example of a regio- and enantiochemically controlled synthesis; however, there are a number of promising methods which may well be applicable to the enantioselective synthesis of **1** and its 11-deoxyderivative, notably the use of chiral dienes by Stoodley,[15] the chiral epoxidation route of Cava,[16] and the chiral reduction of Terashima.[17] Other interesting approaches which show promise in solving the regiochemical problem are those of Baldwin[18] and Rutledge.[19]

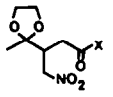
Our decision to use 5-hydroxyquinizarin (**6**) as starting material for the synthesis of **1** and **2** required development of methods for regioselective substitution at C-2 and/or C-3. In Part 1,[20] we showed that reaction of *leuco*-5-hydroxyquinizarin (**14**) with aldehydes under Marschalk conditions (NaOH—H_2O) gave alkyl-5-hydroxyquinizarins with useful regioselectivity (2:3 = 9:1) while reaction under Lewis conditions (Pr^{i}OH-piperidinium acetate) reversed this selectivity (2:3 = 1:7). The most complete regiochemical control was obtained in the addition of nitronates to 5-hydroxyquinizarin when only the 2-alkyl isomer was isolated. This result was the key to our first synthesis of 7,9-bisdeoxycarminomycinone (**2**) which began with the bromination of ethyl laevulinate to a 1:4 mixture of the 2- and 3-bromoesters. Dehydrobromination of the mixture gave ethyl 4-oxopent-2-enoate (89%) which



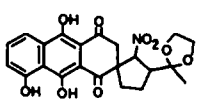
was reduced to ethyl 4-hydroxypent-2-enoate with $NaBH_4$—MeOH (82%). Michael addition of nitromethane to the hydroxy ester[21] was followed by *in situ* lactonisation to give the nitro compounds† (**3**). Attempts to alkylate 5-hydroxyquinizarin with **3** gave only 8% of the alkylation products (**7**); a control experiment established that under the basic conditions of the alkylation the ½-life of the lactones (**3**) was *ca* 4 hr, perhaps accounting for low yield. The nitrolactones (**3**) were converted to more stable substrates by reduction with Bu^i_2AlH[22] to the lactols† **4** (74%) and conversion to the methyl ethers **5** (74%).

Reaction of 5-hydroxyquinizarin, NaOMe, and the diastereoisomeric ethers (**5**) in a molar ratio of 1:1.4:3 in boiling MeOH gave the alkylation products **8** (67%); most of the unreacted ethers could be recovered. When **5**, **6**, and NaOMe in a 1:1:3 ratio were boiled in MeOH no reaction occurred, supporting the view that the nitronate anion reacts with 5-hydroxyquinizarin not its monoanion. 300 MHz NMR spectroscopy of **8** indicated the presence of all four possible diastereoisomers, showing methoxyl resonances at δ 3.38, 3.36, 3.34, and 3.31 in a ratio of 1:3:2.5:3. Hydrolysis of **8** with HCl—H_2O gave the lactols (**9**) whose

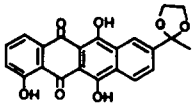
† A mixture of diastereoisomers.



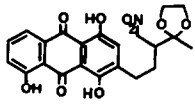
15 X = OEt
16 X = H



17



18



10

insolubility made characterisation difficult: however, on oxidation with pyridinium chlorochromate, they gave products identical to the lactones (7) obtained previously. Reduction of the lactols (9) with $Na_2S_2O_4$—NaOH—H_2O gave the tetracyclic alcohols† 11 (67%) which were oxidised to 7,9-bisdeoxycarminomycinone 12 (67%) with pyridinium chlorochromate. The 300 MHz n.m.r. spectrum of 12 confirmed that the material obtained was regiochemically pure, showing only three hydroxyl resonances at δ_H 12.25, 12.82, and 13.60; we have found hydroxyl resonances of quinizarin derivatives to be highly sensitive to structural changes in a molecule and to be one of the best criteria for purity. Final proof of structure came from conversion of 12 to 7,9-bisdeoxydaunomycinone and comparison with an authentic sample. The transformation of 12 to its 4-methyl ether was carried out in two ways, neither of them efficient. In the first the ketone 12 was converted to a mixture of di- and tri-methyl ethers using MeI—K_2CO_3—Me_2CO and the crude mixture oxidised with Ag_2O—HNO_3—H_2O[23] to give the 4-monomethyl ether (16%). Secondly, reaction of 12 with a large excess of CH_2N_2[24] gave unchanged 12 (48%), the 4-ether (16%), and another monomethyl ether (8%) to which the 6-methyl ether structure was assigned since its IR spectrum showed only H-bonded quinone carbonyl groups (ν_{max} 1600 cm^{-1}) to be present. The 6-methyl ether regenerated the ketone 12 (70%) on reaction with $AlCl_3$.

Since an hydroxyl on C-7 is a common feature of all the anthracyclinones and it is likely that the immediate product of cyclisation of the lactol is the C-7 hydroxylated *leuco*-compound, attempts were made to intercept this intermediate; all attempts to prepare the alcohol (or its oxidation product) using Marschalk variations led either to starting material or the known tetracycle (11). Reduction of the lactol (9) with Zn—AcOH gave the *leuco*-derivative which cyclised with piperidinium acetate-Pr^{i}OH to the tetracycle 11 (61%); attempted cyclisation under acidic conditions did not form products in acceptable yields.

Reaction of the nitrolactols (4) with 5-hydroxyquinizarin could, if reactions occurred in the correct order, give tetracyclic products in a one-pot reaction; in the event the lactols were unstable under the reaction conditions but three products were isolated in low yield and two identified as the lactols (9) (7%) and its methyl ethers (8) (2%). A control experiment established that under the reaction conditions 9 was converted to 8 in 58% yield. The third product (2%) was pentacyclic, δ_H 14.40 (1H, s), 13.52 (1H, s), 13.20 (1H, s), 7.85 (1H, dd), 7.48 (1H, t), 7.25 (1H, dd), 5.55 (1H, m), 4.00 (1H, bq). On reduction with $Na_2S_2O_4$ it was converted to the tetracyclic alcohols (11), suggesting that it was either the 7,13-ether or the 10,13-ether.

The synthesis is attractive in that it offers high regioselectivity but it requires two protection–deprotection steps. In order to eliminate one of these we prepared the nitroaldehyde (16) from ethyl 4-oxopent-2-enoate which was first converted to the acetal using Hase's conditions[25] (90%). Michael addition of nitromethane to the acetal in CH_3CN—DBU gave the nitroester 15 (54%) which was reduced with Bu^i_2 AlH-hexane-PhMe to the aldehyde (16) (85%) [ν_{max} 2880, 1725 cm^{-1}; δ_H 9.78 (1H, bs), 4.61 (1H, dd, J = 13 and 6 Hz), 4.34 (1H, dd, J = 13 and 7 Hz), 3.96 (4H, m), 3.26 (1H, m), 2.70 (1H, dd, J = 18 and 3 Hz), 2.51 (1H, dd, J = 13 and 7 Hz), 1.30 (3H, s)]. Condensation of the aldehyde (16) with *leuco*-5-hydroxyquinizarin in Pr^{i}OH containing piperidinium acetate gave the nitro-compound (10) (55%) along with the C-2 alkylated regioisomer (11%); crystallisation from Me_2CO gave pure 10 (40%). On heating with NaOMe—MeOH 10 was cyclised to the tetracycle (13) (85%) which on hydrolysis with CF_3CO_2H—H_2O gave the ketone (12) identical to that obtained by the previous route. Reaction of the nitro-compound (10) with NaOMe—MeOH at ambient temperature partially converted it into a yellow isomer, the UV, visible, and NMR (above δ 6.0) spectra of which were identical to those of *leuco*-5-hydroxyquinizarin. Additionally, the ^{1}H NMR spectrum showed resonances at δ_H 5.92 (1H, d, J = 7 Hz), 4.04 (4H, m), 3.42 (1H, q, J = 7 Hz), 2.92 (2H, s), 2.10 (2H, m), 1.84 (2H, m), 1.38 (3H, s) leading us to assign the *spiro*-structure (17). On melting, 17 reverted to 10 and a partial reversion occurred on reaction of the pure *spiro*-compound with NaOMe—MeOH while boiling with NaOMe—MeOH converted it to tetracycle (13).

The tetracyclic ketal (13) could be formed in a "one-pot" process if, after formation of the alkylation product with Pr^{i}OH-piperidinium acetate, piperidine was added and the mixture boiled under reflux for a further 16 hr. After chromatography a 5 : 1 mixture of 13 and its regioisomer (49%) was isolated along with the naphthacene (18) (4%) and 1,5-dihydroxyanthraquinone.‡ A single crystallisation of the isomer mixture improved it to a 12 : 1 isomer ratio.

These experiments demonstrate the flexibility of the double alkylation approach and show that initial nitroalkylation can be regiospecific while the Lewis alkylation is only regioselective. However, if the unwanted regioisomer can be readily removed at some stage it does offer the advantage of being two steps shorter.

† This arises from a known piperidine catalysed dehydration of the *leuco*-compound.[20]

Reaction of the nitro-ether (5) with quinizarin gave an adduct which was converted to 4-demethoxy-7,9-bisdeoxydaunomycinone in 28% overall yield by the route described for the synthesis of 12.

EXPERIMENTAL

NMR spectra were measured in $CDCl_3$ at 300 MHz unless indicated to the contrary. "Worked up in the usual way" implies dilution with brine, extraction with the solvent indicated, drying of the organic solution with $MgSO_4$ or Na_2SO_4, filtration, and concentration *in vacuo*.

Ethyl 4-hydroxypent-2-enoate. $NaBH_4$ (203 mg) was added to a stirred soln of ethyl 4-oxopent-2-enoate (2.025 g) in MeOH (40 ml). After 1 hr work-up in the usal way by Et_2O (3 × 100 ml) extraction gave the *hydroxyester* (1.677 g), b.p. 115°/0.1 mmHg; δ_H (CCl_4, 60 MHz) 6.82 (1H, dd, J = 16 and 4 Hz), 5.86 (1H, dd J = 16 and 2 Hz), 4.35 (1H, m), 4.15 (2H, q J = 6 Hz), 1.32 (3H, d, J = 6 Hz), 1.30 (3H, t, J = 6 Hz); (Found: C, 58.0; H, 8.5; M^+ 144.0781. $C_7H_{12}O_3$ requires: C, 58.3; H, 8.4%; M^+ 144.0786).

Nitrolactones (3). Ethyl 4-hydroxypent-2-enoate (6.724 g) was added over 30 min to a mixture of CH_3NO_2 (10 ml), Triton B (3.32 ml), and Bu^{t}OH (4.67 ml) at 20°. The solution was then warmed at 50° for 99 h. Further portions of Triton B (1.16 ml) were added after 27 and 89 hr and CH_3NO_2 (2.5 ml) and Bu^{t}OH (1.17 ml) after 89 hr. After neutralisation with 6 MHCl work-up in the usual way with CH_2Cl_2 (200 ml) extraction gave the *nitrolactone* 3 (5.894 g) as a brown oil. A sample was purified by chromatography on silica gel, eluting with CH_2Cl_2, ν_{max} 1770 cm^{-1}, g.c.-m.s. showed two components *m/e* 159 in 1:1 ratio; (Found: C, 45.2; H, 5.8. $C_6H_9NO_4$ requires C, 45.3; H, 5.7%).

Quinone Lactones (7). Na (31 mg) was added to MeOH (55 ml) and after evolution of H_2 ceased, 1,4,5-trihydroxyanthraquinone (256 mg) and 3 (446 mg) were dissolved in the soln which was boiled under reflux for 52 hr. After acidification with 10M HCl the ppt was filtered off, washed with H_2O, dried (246 mg), and chromatographed on silica gel, eluting with CH_2Cl_2 to give the *lactones* 7 (80 mg), m.p. 214–216° (CH_3Cl_2), ν_{max} 1770 cm^{-1}; λ_{max}^{EtOH} 233 (ε 7285), 254 (4320), 290 (2100), 462 (1850), 482 (2100), 498 (2220), 513 (2000), 528 nm (1850); δ_H 12.91 (1H, s), 12.69 (1H, s), 12.05 (1H, s), 7.83 (1H, dd, J = 7 and 2 Hz), 7.71 (1H, t, J = 7 Hz), 7.35 (1H, dd, J = 7 and 2 Hz), 7.15 (1H, s), 4.45 (1H, m), 1.40 (1½H, d, J = 7 Hz), 1.28 (1½H, J = 7 Hz). (M^+ 368.0889; $C_{20}H_{16}O_7$ requires: 368.0896).

Nitrolactol ethers (5). Bu^i_2AlH (43.65 ml of a 1M hexane soln) was added over 15 min to a stirred soln of 3 (5.894 g) in PhMe (60 ml) cooled to −78°. Further Bu^i_2AlH was added after 2 hr (21.83 ml), 4 hr (21.83 ml), and 5 hr (10.92 ml). After 5.5 hr MeOH (28 ml) was added, the cooling bath removed, and H_2O (28 ml) added when the mixture reached room temp. The gelatinous mixture was dried *in vacuo* and thoroughly extracted with Et_2O (4 × 100 ml). Concentration of the dried extracts gave the *lactols* (4) (4.44 g), δ_H 5.55 (1H, m), *m/e* C.I. (NH_3) 179 ($M^+ + 18$).

Conc. H_2SO_4 (0.05 ml) was added to 4 (437 mg) in MeOH (18 ml) at 0°. After 2 hr work-up in the usual way by Et_2O extraction (2 × 200 ml) gave the *lactol ethers* 5 (374 mg). Prep. TLC gave a sample, δ_H (60 MHz) 4.98 (1H, m), 5.55 (2H, m), 3.90 (1H, m), 3.28 (3H, bs), 1.26 (3H, m); g.c.-m.s. showed 4 components, *m/e* 144 ($M^+ - OMe$); (Found: C, 48.1; H, 7.3; N, 8.3. $C_7H_{13}NO_4$ requires: C, 48.0; H, 7.5; N, 8.0%).

Lactol ethers (8). The ethers 5 (887 mg) and 6 (433 mg) in MeOH (90 ml) containing NaOMe (*ex* 54 mg Na) were boiled under reflux for 45 hr under a N_2 atm. After acidification with 10 MHCl and dilution with H_2O (100 ml) the ppt was filtered off, washed with H_2O, dried and recrystallised from CH_2Cl_2-pentane to give the *ethers* 8 (395 mg), m.p. 160–5°, δ_H 13.03, 13.01, 12.98, 12.74, 12.72, 12.25, 12.16 (all singlets integrating for 3H), 7.88 (1H, dd, J = 7 and 2 Hz), 7.71 (1H, t, J = 7 Hz), 7.30 (1H, dd, J = 7 and 2 Hz), 2.84 (1H, s), 4.95 (1H, m), 3.38, 3.36, 3.34, 3.31 (all singlets integrating for 3H); (Found: C, 65.9; H, 5.3; M^+ 384.1212. $C_{21}H_{20}O_7$ requires: C, 65.6; H, 5.3; M^+ 384.1209).

Extraction of the aqueous filtrate with $CHCl_2$ (2 × 100 ml) and work-up in the usual way gave recovered nitrolactol ether (619 mg).

Tetracyclic alcohols (11)

(a) 1 MHCl (1 ml) was added to 8 (58 mg) in $MeOCH_2CH_2OMe$ (5 ml) and the mixture stirred at ambient temp for 70 hr. After dilution with H_2O (40 ml), extraction with CH_2Cl_2 (2 × 40 ml) and work-up in the usual way gave 9 (47 mg) m.p. 250° (dec), (M^+ 370.1049. $C_{20}H_{18}O_7$ requires: 370.1052).

The lactol 9 (262 mg) was dissolved in 1% NaOH—H_2O (155 ml) at 90° under a N_2 atm. A 2% $Na_2S_2O_4$—H_2O soln was added until the purple colour had changed to yellow. After 3 hr a stream of air was passed through the cooled soln which became purple. After acidification with 10 MHCl the mixture was extracted with CH_2Cl_2 (4 × 125 ml) and worked up in the usual way to give the *alcohols* 11 (168 mg), m.p. 95–7°, δ_H 13.62 (1H, s), 12.85 (1H, s), 12.27 (1H, s), 7.88 (1H, dd, J = 7 and 2 Hz), 7.65 (1H, t, J = 7 Hz), 7.25 (1H, dd, J = 7 and 2 Hz), 1.53 (3H, d, J = 6 Hz); (M^+ 354.1099. $C_{20}H_{18}O_6$ requires 354.1103).

(b) A suspension of Raney Ni and EtOH was added to a soln of the 9 (10 mg) in 5% K_2CO_3—H_2O (10 ml) until the purple colour had changed to yellow. After 1 hr the filtered mixture was acidified with 10 MHCl and extracted with $CHCl_3$ (2 × 20 ml). Work-up in the usual way gave 11 (4 mg).

(c) Zn dust was added to a stirred soln of 9 (5 mg) in CH_3CO_2H (2 ml) and CF_3CO_2H (0.002 ml) under a N_2 atm. After 1 hr the filtered soln was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (2 × 10 ml). Work-up in the usual way gave a yellow solid which was dissolved in Pr^{i}OH (2 ml) and piperidinium acetate (73 mg) added. The mixture was boiled with reflux under a N_2 atm for 3 hr, cooled, H_2O (20 ml) added, and the soln extracted with $CHCl_3$ (20 ml). The $CHCl_3$ soln was extracted with 1% NaOH—H_2O (25 ml) and a stream of air passed through the aqueous soln until it was purple. The soln was acidified with 10 MHCl and extracted with $CHCl_3$ (2 × 20 ml). Work-up in the usual way gave 11 (3 mg).

7,9-*Bisdeoxycarminomycinone* (12)

(a) Pyridinium chlorochromate (50 mg) was added to a stirred soln of 11 (21 mg) in CH_2Cl_2 (0.5 ml). After 80 min the mixture was diluted with Et_2O (10 ml) and worked up in the usual way to give 12 (14 mg), which was purified by sublimation (200° 0.1 mmHg), m.p. 211° (lit. 188–192°), ν_{max} 1705 cm^{-1}, δ_H 13.60 (1H, s), 12.82 (1H, s), 12.25 (1H, s), 7.85 (1H, dd, J = 7 and 2 Hz), 7.65 (1H, t, J = 7 Hz), 7.30 (1H, dd, J = 7 and 2 Hz), 2.30 (3H, s). (Found: C, 68.0; H, 4.5; M^+ 352.0949. $C_{18}H_{13}O_5$ requires: C, 68.2; H, 4.6%; M^+ 352.0947).

(b) H_2O (0.1 ml) was added to a soln of 13 (94 mg) in CF_3CO_2H (30 ml). After 1 hr the solvent was evaporated and the residue dissolved in CH_2Cl_2 (100 ml) and work-up in the usual way gave 12 (84 mg) identical to the material prepared previously.

7,9-*Bisdeoxydaunomycinone*

(a) The ketone 12 (8 mg) in Me_2CO (2 ml) containing K_2CO_3 (10 mg) and CH_3I (0.04 ml) was boiled with reflux for 27 hr. K_2CO_3 (10 mg) and CH_3I (0.04 ml) were added after 17 and 23 hr. After evaporation of the solvent the residue was extracted with CH_2Cl_2 (10 ml), the mixture filtered and the filtrate evaporated to give a yellow oil which was dissolved in Me_2CO (1 ml). AgO (14 mg) and 6.3 MHNO_3 (0.2 ml) were added to the boiling soln; similar portions were added after 45 min and 1 hr. After 1.5 hr H_2O (15 ml) was added and the soln extracted with CH_2Cl_2. The organic phase was shaken with 4% $Na_2S_2O_4$—H_2O (2 × 12 ml), dried, and concentrated to give an oil which was purified on TLC (CH_2Cl_2) to give 7,9-bisdeoxydaunomycinone (2 mg), m.p. 240°, which was shown to be identical with an authentic sample by mixed m.p., TLC, NMR and mass spectra.

(b) CH_2N_2 (24 mg) in CH_2Cl_2 (4 ml) was added to 12 (6 mg)

in CH_2Cl_2 (4 ml) at 0°. After 0.5 hr CH_3CO_2H was added to destroy excess CH_2N_2. Evaporation of solvent gave a solid which on TLC (CH_2Cl_2) yielded starting material (3 mg), 7,9-bisdeoxydaunomycinone (1 mg), and the 6-methylether, m.p. 245–9°, ν_{max} 1705, 1600 cm^{-1}, λ_{max} 255 (3660), 292 (1710), 405 (850), 440 (1220), 465 (1340), 493 (1100), 515 (850), 530 nm (ε 730), δ_H 13.73 (1H, s), 13.05 (1H, s), 7.80 (1H, dd, J = 7 and 1.5 Hz), 7.60 (1H, t, J = 7 Hz), 7.05 (1H, m), 3.86 (3H, s), 2.25 (3H, s), (M^+ 366.1110. $C_{21}H_{18}O_6$ requires: M^+ 366.1103).

Reaction of the 6-methylether with $AlCl_3$ in PhH gave **12**.

4-Demethoxy-7,9-bisdeoxydaunomycinone. The title compound was prepared by a similar sequence of reactions starting from quinizarin.

Quinizarin + ether **5** → 5-deoxy **8** (62%), m.p. 148–150° (M^+ 368.1264 $C_{21}H_{20}O_6$ requires: M^+ 368.1260). → 5-deoxy(**9**) (90%) m.p. 116–120° M^+ 354.1094). $C_{20}H_{18}O_6$ requires: M^+ 354.1103 → 4-deoxy **11** (84%), m.p. 190–196° (M^+ 338.1158. $C_{20}H_{18}O_5$ requires: M^+ 338.1154) → 4-deoxy **12** (58%), m.p. 188–190°. (Found: C, 71.4; H, 5.1; M^+ 336.0998. $C_{20}H_{16}O_5$ requires: C, 71.4; H, 4.8%; M^+ 336.0998).

Reaction of nitrolactols (**4**) *with 5-hydroxyquinizarin* (**6**). 5-Hydroxyquinizarin (182 mg), NaOMe (*ex* 23 mg Na), MeOH (38 ml) and **4** were boiled with reflux for 45 hr under a N_2 atm. Acidification with 10 MHCl gave a red soild which was washed with H_2O and dried (146 mg). TLC (CH_2Cl_2) of a portion (20 mg) gave **6** (8 mg), an *ether* (2 mg), m.p. 185–192°, λ_{max} 237 (3060), 256 (2590), 297 (740), 435 (420), 463 (850), 484 (1060), 495 (1270), 518 (950), 532 nm (ε 950), δ_H 14.40 (1H, s), 13.52 (1H, s), 13.20 (1H, s), 7.85 (1H, dd, J = 7 and 2 Hz), 7.58 (1H, t, J = 7 Hz), 7.25 (dd, J = 7 and 2 Hz), 5.55 (1H, m), 4.00 (1H, q, J = 7 Hz) (M^+ 352.0943. $C_{20}H_{16}O_6$ requires: 352.0947). Reduction of the ether with 1% $Na_2S_2O_4$—H_2O gave **11**. The third component isolated from the reaction mixture was **8** (2 mg) and the final component was identified as **9** (8 mg). A control experiment established that **9** was converted into **8** under the conditions of reaction.

Ethyl 4-ethylenedioxypent-2-enoate. Ethyl-4-oxopent-2-enoate (872 mg), $(CH_2OH)_2$ (750 mg), $BF_3 \cdot OEt_2$ (0.2 ml), and $HC(OEt)_3$ (1.8 g) in PhH (25 ml) were boiled with reflux for 18 hr. The mixture was added to 3% $NaHCO_3$—H_2O (50 ml) and worked-up in the usual way to give the *acetal* (1.2 g). A sample was purified by distillation (Found: C, 57.5; H, 7.6; M^+ 186.0894. $C_9H_{14}O_4$ requires: C, 58.1; H, 7.6%; M^+ 186.0842), δ_H 6.78 (1H, d, J = 17 Hz), 6.07 (1H, d, J = 17 Hz), 3.95 (4H, m), 1.53 (3H, s).

Ethyl 4-ethylenedioxy-(3-nitromethyl-pentanoate (**15**). A soln of ethyl 4-ethylenedioxypent-3-enoate (7.62 g), CH_3NO_2 (4.9 g), and diazabicycloundecane (6.84 g) in CH_3CN (70 ml) was stirred under a N_2 atm for 16 hr. H_2O saturated with NH_4Cl (200 ml) was added and the mixture extracted with Et_2O (2 × 100 ml). Work-up in the usual way gave the *ester* **15** (5.74 g) after dry column chromatography. (Found: C, 48.4; H, 7.1; N, 6.1. $C_{10}H_{17}NO_6$ requires: C, 48.6; H, 6.9; N, 5.7%), δ_H 4.60 (1H, dd, J = 12.6 and 6.3 Hz), 4.40 (1H, dd, J = 12.6 and 6.3 Hz), 3.96 (4H, s), 3.17 (1H, m), 2.24 (1H, dd, J = 15.4 and 5.6 Hz), 2.37 (1H, dd, J = 15.4 and 5.6 Hz), 1.27 (3H, s).

4-Ethylenedioxy-(3-nitromethyl)-pentanal (**16**). Bu^i_2AlH (10 ml of a 1M hexane soln) was added over 10 min to a cooled (−78°) soln of **15** (2.1 g) in PhMe (200 ml) under a N_2 atm. After 1 hr CH_3OH (1 ml) was added and the soln warmed to 3° when sat Na_2SO_4—H_2O (5 ml) was added followed by Na_2SO_4 (10 g). The semi-solid residue was extracted with Et_2O (200 ml) and the extract passed through a short silica gel column. Evaporation of the eluate gave the *aldehyde* **16** (1.47 g). (Found: C, 46.8; H, 6.3; N, 7.2. $C_8H_{13}NO_5$ requires: C, 47.3; H, 6.5; N, 6.9%), δ_H 9.78 (1H, bs), 4.61 (1H, dd, J = 13 and 6 Hz), 4.34 (1H, dd, J = 13 and 7 Hz), 3.96 (4H, m), 3.26 (1H, m), 2.70 (1H, dd, J = 18 and 3 Hz), 2.51 (1H, dd, J = 18 and 7 Hz), 1.30 (3H, s).

The aldehyde was converted to its *dimethylacetal* (MeOH, $HC(OMe)_3$, *p*-$MeC_6H_4SO_3H$). (Found: C, 48.2; H, 7.8; N, 6.0. $C_{10}H_{19}NO_6$ requires: C, 48.2; H, 7.7; N, 5.6%).

Reaction of the acetal aldehyde (**16**) *with* leuco-5-*hydroxyquinizarin.* The aldehyde **16** (165 mg) in CH_2Cl_2 (5 ml) was added to *leuco*-5-hydroxyquinizarin (202 mg) suspended in Pr^iOH (40 ml), followed by addition of freshly prepared piperidinium acetate (100 mg). After boiling with reflux under a N_2 atm for 3 hr the cooled mixture was added to brine (150 ml) and extracted with CH_2Cl_2 (1 × 150, 1 × 50 ml). Work-up in the usual way gave a red solid which on dry column chromatography (Silicagel 60G; hexane—CH_2Cl_2) gave the mixture of 2- and 3-substituted isomers (229 mg). Crystallisation from Me_2CO gave the *nitrocompound* **10** (138 mg), m.p. 185–7°. (Found: C, 59.3; H, 4.7; N, 3.1, M^+ 443.1215. $C_{22}H_{21}NO_9$ requires: C, 59.6; H, 4.8; N, 3.2%; M^+ 443.1216), δ_H 13.06 (1H, s), 12.75 (1H, s), 12.20 (1H, s), 7.86 (1H, dd, J = 8 and 1 Hz), 7.70 (1H, t, J = 8 Hz), 7.29 (1H, dd, J = 8 and 1 Hz), 7.18 (1H, s), 4.62 (1H, dd, J = 13 and 7 Hz), 4.37 (1H, dd, J = 13 and 6 Hz), 3.96 (4H, m), 1.70 (3H, s).

Cyclisation of (**10**)

(a) A stirred suspension of **10** (222 mg) in MeOH (10 ml) was mixed with 1M NaOMe—MeOH (0.5 ml). After 30 min acidification with 2 MHCl and work-up in the usual way with CH_2Cl_2 (1 × 100, 1 × 50 ml) gave a brown solid which was chromatographed (Silicagel G; CH_2Cl_2) to give recovered starting material (69 mg) and then the *spiro*-**17** (54 mg), m.p. 165–170° (dec) (M^+ 443.1216. $C_{22}H_{21}NO_9$ requires: M^+ 443.1216) · λ^{EtOH}_{max} 395 (7500), 418 (13,200), 440 nm (ε 15,900), δ_H 15.37 (1H, s), 13.30 (1H, s), 10.24 (1H, s), 8.00 (1H, dd, J = 8 and 1 Hz), 7.70 (1H, t, J = 8 Hz), 7.22 (1H, dd, J = 8 and 1 Hz), 5.92 (1H, d, J = 7 Hz), 4.04 (4H, m), 3.42 (1H, q, J = 7 Hz), 2.29 (2H, s), 2.10 (2H, m), 2.00 (1H, m), 1.84 (1H, m), 1.38 (3H, s). On melting the compound reverted to starting material.

(b) 1 MNaOMe—MeOH (1.2 ml) was added to a suspension of **10** (3 mg) in MeOH (10 ml) and the soln boiled with reflux for 10 hr under a N_2 atm. After acidification with 2MHCl the mixture was evaporated to dryness and the residue extracted with CH_2Cl_2 (25 ml) and worked up in the usual way to give a solid which purified by dry column chromatography (Silicagel G—CH_2Cl_2) to give the *tetracycle* **13** (23 mg), m.p. 210–3° CH_2Cl_2-hexane). (Found: C, 66.9; H, 4.9; M^+ 396.1202; $C_{22}H_{20}O_7$ requires: C, 66.7; H, 5.1%; M^+ 396.1209), δ_H 13.65 (1H, s), 12.79 (1H, s), 12.28 (1H, s), 7.83 (1H, dd, J = 8 and 1 Hz), 7.68 (1H, t, J = 8 Hz), 7.26 (1H, dd, J = 8 and 1 Hz), 4.00 (4H, m), 1.40 (3H, s).

(c) A mixture of *leuco*-**14** (260 mg), the aldehyde **16** (124 mg), and piperidinium acetate (62 mg) in Pr^iOH (55 ml) was boiled with reflux for 5 hr under a N_2 atm. Piperidine (450 mg) was then added and the mixture boiled under reflux for a further 16 hr. After acidification with 2MHCl work-up in the usual way with CH_2Cl_2 (1 × 200, 1 × 50 ml) afforded a solid which was purified by dry column chromatography (Silicagel G—CH_2Cl_2) to give 1,5-dihydroxyanthraquinone (24 mg), 5-hydroxyquinizarin (76 mg), the *naphthacene* **18** (10 mg), m.p. 241–3° ($CHCl_3$-hexane) (M^+ 392.0895. $C_{22}H_{16}O_7$ requires: 392.0896), λ^{EtOH}_{max} 460 (3400), 490 (6200), 525 nm (ε 6400), δ_H 15.30 (1H, s), 14.30 (1H, s), 12.50 (1H, s), 8.68 (1H, d, J = 1 Hz), 8.54 (1H, d, J = 8 Hz), 8.00 (1H, dd, J = 8 and 1 Hz), 7.98 (1H, dd, J = 8 and 1 Hz), 7.76 (1H, t, J = 8 Hz), 7.34 (1H, dd, J = 8 and 1 Hz), 4.17 (2H, m), 3.88 (2H, m), 1.81 (3H, s), and finally a 5:1 mixture (118 mg) of **13** and its positional isomer.

Acknowledgements—We wish to thank the S.E.R.C. for financial support, I.C.I. Organics Division for supplies of chemicals and Dr. F. Johnson, S.U.N.Y., for an authentic sample of 7,9-bisdeoxydaunomycionone.

REFERENCES

[1] C. M. Wong, R. Schwenk, D. Popein and T. L. Ho, *Can. J. Chem.* **51**, 466 (1973).
[2] A. S. Kende, J. A. Belltire, T. J. Bentley, E. Hume and J. Airey, *J. Am. Chem. Soc.* **97**, 4425 (1975).
[3] K. S. Kim, E. Vanotti, A. Surato and F. Johnson, *J. Am. Chem. Soc.* **101**, 2483 (1979).

[4] M. Braun, *Tetrahedron Letters* 3781 (1980).
[5] A. V. Rama Rao, K. B. Reddy and A. R. Mehendale, *J. Chem. Soc. Chem. Comm.* 564 (1983).
[6] K. A. Parker and J. Kallmerton, *J. Am. Chem. Soc.* **102**, 5881 (1980).
[7] A. S. Kende, J. Rizzi and J. Reimer, *Tetrahedron Letters* 121 (1979).
[8] F. M. Hauser and S. Prassana, *J. Am. Chem. Soc.* **103**, 6378 (1981); F. M. Hauser and D. Mal, *Ibid.* **105**, 5688 (1983).
[9] M. G. Dolson, B. L. Chenard and J. S. Swenton, *J. Am. Chem. Soc.* **103**, 5263 (1981).
[10] B. A. Keay and R. Rodrigo, *Can. J. Chem.* **61**, 637 (1983).
[11] T. R. Kelly, J. Vaya and L. Ananthasubramanian, *J. Am. Chem. Soc.* **102**, 5983 (1980).
[12] H. Sekizaka, M. Jung, J. M. McNamara and Y. Kishi, *J. Am. Chem. Soc.* **104**, 7372 (1982).
[13a] J. P. Geeson and M. Mondon, *J. Chem. Soc. Chem. Comm.* 421 (1982); [b] R. K. Boeckmann and S. H. Cheon, *J. Am. Chem. Soc.* **105**, 4112 (1983).
[14] F. Sujuki, S. Trenbeath, R. D. Gleim and C. H. Sih, *J. Am. Chem. Soc.* **100**, 2272 (1978).
[15] R. C. Gupta, P. A. Harland and R. J. Stoodley, *J. Chem. Soc. Chem. Comm.* 754 (1983).
[16] M. P. Cava and D. Dominguez, *J. Org. Chem.* **48**, 2820 (1983).
[17] S. Terashima, N. Tanno and K. Koga, *Tetrahedron Letters* 2753 (1980).
[18] J. E. Baldwin and A. J. Rajeckas, *Tetrahedron* **38**, 3097 (1982).
[19] I. K. Boddy, P. J. Boniface, R. C. Cambie, P. A. Craw, D. S. Larsen, H. McDonald, P. S. Rutledge and P. D. Woodgate, *Tetrahedron Letters* 4407 (1982); R. S. Cambie, D. S. Larsen, H. McDonald, P. S. Rutledge and P. D. Woodgate, *Tetrahedron Letters* 2319 (1983).
[20] L. M. Harwood, P. Towers and J. K. Sutherland, *Can. J. Chem.* accepted for publication.
[21] N. J. Leonard and G. L. Shoemaker, *J. Am. Chem. Soc.* **71**, 1876 (1949); N. J. Leonard and D. L. Felley, *ibid*, **72**, 2537 (1950).
[22] I. Schmidlin and A. Wettstein, *Helv. Chim. Acta* **46**, 2799 (1963).
[23] C. D. Snyder and H. Rapaport, *J. Am. Chem. Soc.* **94**, 227 (1972).
[24] R. J. Blade and P. Hodge, *J. Chem. Soc. Chem. Comm.*, 85 (1979).
[25] T. A. Hase, A. Ourila and C. Holmberg, *J. Org. Chem.* **46**, 3137 (1981).