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Synthetic Studies on Anthracyclinones. XIII.[1] Conversion of Bisanhydro-γ-rhodomycinone into Bisanhydrodaunomycinone

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The synthesis of bisanhydrodaunomycinone (II) was achieved *via* bisanhydro-γ-rhodomycinone (III) by 7 step procedure envolving the transformation of ethyl side chain in III into acetyl group as shown in Chart 2.

The formation of an *ana*-quinone system on methylation of 6,11-dihydroxynaphthacenequinones (II and III) was discussed from infrared and ultraviolet spectral comparison.

Daunomycinone (I) is the aglycone of daunomycin[3] which is a red pigment antibiotic from *Streptomyces peucetius* and *Streptomyces coeruleorubidus*[4,5] and exhibits a potent anti-

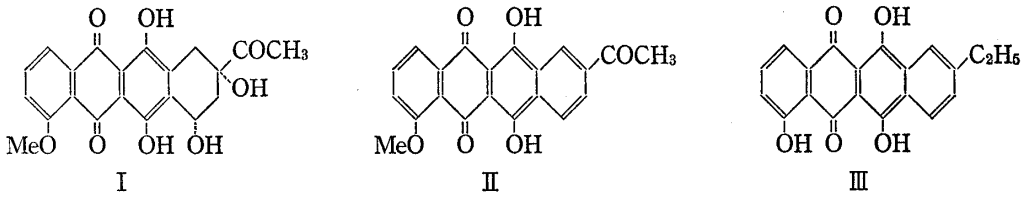

Chart 1

tumour activity,[4,6] and was shown, by Arcamone, *et al*[7] to be 8-acetyl-6,8,10,11-tetrahydroxy-1-methoxy-7,8,9,10-tetrahydronaphthacenequinone (I). They converted I into bisanhydrodaunomycinone (II) by treatment with either acid or alkali.

This paper describes the synthesis[8] of II starting from 8-ethyl-1,6,11-trihydroxynaphthacenequinone (III)[1,9] which is known as bisanhydro-γ-rhodomycinone[10] or bisanhydro-decarbomethoxy-ε-rhodomycinone.[11]

As a model experiment concerning the elaboration of acetyl group in II, the transformation of β-ethylnaphthalene (IV) into β-acetylnaphthalene (V)[12] was investigated. Benzylic

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4) G.F. Gause, *Chem. & Ind.*, **1966**, 1506.
5) G.L. Tong, P. Lim, and L. Goodman, *J. Pharm. Sci.*, **56**, 1691 (1967).
6) A. Di Marco, M. Gaetani, P. Orezzi, B.M. Scarpinato, R. Silvestrini, M. Soldati, T. Dasdia, and L. Valentini, *Nature*, **201**, 706 (1964).
7) *a*) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbieri, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5334 (1964); *b*) F. Arcamone, G. Franceschi, P. Orezzi, S. Penco, and R. Mondelli, *Tetrahedron Letters*, **1968**, 3349; *c*) R.H. Iwamoto, P. Lim, and N.S. Bhacca, *ibid.*, **1968**, 3891; *d*) F. Arcamone, G. Cassinelli, G. Franceschi, R. Mondelli, P. Orezzi, and S. Penco, *Gazz. Chim. Ital.*, **100**, 949 (1970).
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9) H. Brockmann and R. Zunker, *Tetrahedron Letters*, **1966**, 45; H. Brockmann, R. Zunker, and H. Brockmann Jr., *Ann.* **696**, 145 (1966).
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11) H. Brockmann and H. Brockmann, Jr., *Chem. Ber.*, **94**, 2681 (1961).
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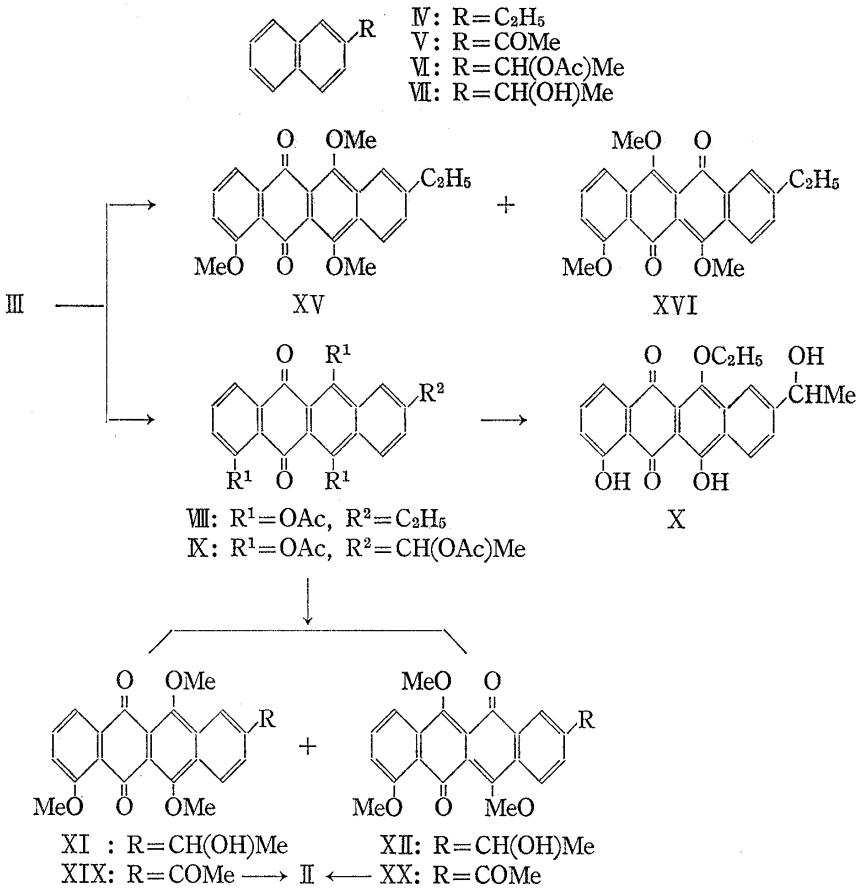


Chart 2

bromination[13] of IV and subsequent acetoxylation gave 2-(1-acetoxyethyl)naphthalene (VI)[14] in 77% yield. Hydrolysis of VI gave 2-(1-hydroxyethyl)naphthalene (VII), which was converted into the desired ketone (V) by Ball oxidation in 81% yield.

A similar procedure was effectively applied to the conversion of III into II.

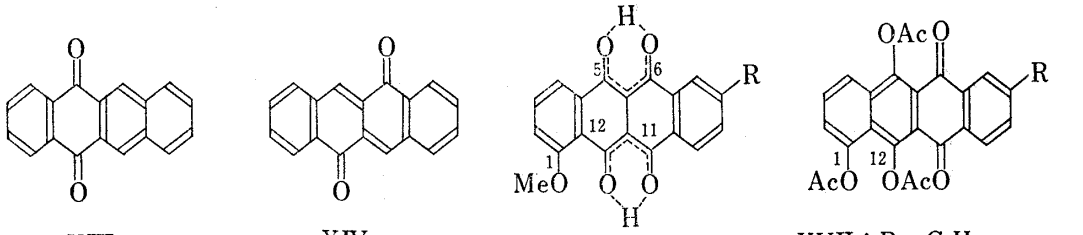
To avoid any aromatic bromination[15] with N-bromosuccinimide, III was acetylated to 1,6,11-triacetoxy-8-ethylnaphthacenequinone (VIII) in 80% yield. Benzylic bromination of VIII with N-bromosuccinimide followed by acetoxylation gave 1,6,11-triacetoxy-8-(1-acetoxyethyl)naphthacenequinone (IX) in 26% yield from VIII.

Hydrolysis of IX with potassium hydroxide in aqueous ethanol gave an undesirable monoethyl ether (X) which showed both a non-chelated quinone carbonyl absorption at 1656 cm^{-1} and a chelated one at 1610 cm^{-1} in its infrared (IR) spectrum, and an ethoxyl in nuclear magnetic resonance (NMR) spectrum. Hydrolysis of IX in aqueous methanol followed by methylation with dimethyl sulfate gave two products, 8-(1-hydroxyethyl)-1,6,11-trimethoxynaphthacenequinone (XI) and 8-(1-hydroxyethyl)-1,5,11-trimethoxynaphthacene-6,12-dione (XII) in 40% and 11% yields from IX, respectively.

Both products showed three phenolic methoxyls in NMR spectra and the same molecular ion peak at *m/e* 392 in mass spectra, but their IR spectra were essentially different with each other, especially in aromatic region as shown in Table I. Compound (XII) showed two IR absorption maxima of comparable intensities in aromatic region (at 1602 and 1570 cm^{-1})

13) R.G.R. Bacon, R.G. Guy, and R.S. Irwin, *J. Chem. Soc.*, **1961**, 2436.
14) A preparation of VI by acetylation of the corresponding alcohol (VII) has been reported by Collyer and Kenyon, who prepared VII by reduction of the ketone (V) [T.A. Collyer and J. Kenyon, *J. Chem. Soc.*, **1940**, 676].
15) K. Ueda and I. Yosioka, *Chem. Pharm. Bull.* (Tokyo), **16**, 1521 (1968).

while XI showed a typical aromatic absorption pattern characteristic of naphthacene-(5,12)-quinone system as three bands at 1617, 1587 and 1560 cm^{-1}. The ultraviolet (UV) spectra of these two naphthacenequinones were also found essentially different, suggesting their isomeric relationship in quinoid systems. The possible structures of them were determined by comparison of their IR and UV spectra with those of simple quinones XIII[16] and XIV.[17]



XIII XIV

II : R=Ac
(III′ : R=C_2H_5)
(IX′ : R=CH(OH)Me)

XVII : R=C_2H_5
XVIII : R=CH(OAc)Me

Chart 3

Similar isomer formation was also observed on methylation of III under the same condition, giving two products, 8-ethyl-1,6,11-trimethoxynaphthacenequinone (XV) and its quinoid isomer (XVI). A stepwise ether formation starting with the first methylation on the least hindered C_1-oxygen would lead to the formation of normal and *ana*-quinone[18] resulting from the competitive second methylation on C_5- or C_6-oxygen. A methylation on C_{12}-oxygen would be difficult owing to its considerable steric hindrance by *peri*-methoxyl on C_1. Accordingly the third methylation would occur exclusively on C_{11}-oxygen.

In the case of the triacetate (VIII) or the tetraacetate (IX), there was formed only the normal quinoid system which was readily detected from the aromatic absorptions in IR spectrum (Table I) and confirmed by comparison of the UV spectrum with that of XIII. The most stable acetate would have resulted probably due to the transacylation.[19] The alternative normal quinoid system (XVII or XVIII) would be unfavourable because of their extremely crowded circumstances around *peri*-substituted acetoxyl on C_1 and C_{12}.

Oxidation of XI or XII with manganese dioxide in dry benzene gave 8-acetyl-1,6,11-trimethoxynaphthacenequinone (XIX), mp 224—226°, or 8-acetyl-1,5,11-trimethoxynaphthacene-6,12-dione (XX), mp 192.5—195.0°, in 33% or 39% yield.

Methylation of natural bisanhydrodaunomycinone (II) with dimethyl sulfate also gave two isomeric dimethyl ethers XIX and XX in a ratio of 2 to 1. Synthetic and natural quinone of each pair (XIX,[20] XX) were identical in all respects. The normal quinoid structure of XIX was assigned from its IR and UV spectra.

Partial demethylation[21] of XIX or XX with ten molar equivalents of boron tribromide

16) The normal quinone (XIII) has the spectral data of IR ν_{max}^{KBr} cm^{-1}: 1612, 1583, 1560; UV λ_{max}^{EtOH} mμ (log ε): 238 (4.55), 245 sh (4.51), 283 (4.55), 292 (4.50), 349 (3.62) [T. Tsunoda, *J. Soc. Org. Synthetic Chem.*, 9, 127 (1951)].

17) The *ana*-quinone (XIV) shows IR ν_{max}^{KBr} cm^{-1}: 1583, 1543; UV λ_{max}^{EtOH} mμ (log ε): 271 (4.70), 455 (4.08), 483 (4.05) [C. Dufraisse and J. Houpillart, *Compt. rend.*, **206**, 756 (1938)].

18) The 5,11-dichloro-*ana*-quinone system of naphthacene was previously reported: L.N. Goldyrev and I. Ya. Postovskii, *J. Gen. Chem.*, **11**, 429, 451 (1941) [*C.A.*, **35**, 6589[1-6] (1941)].

19) *a*) S. Alvarado, F. Farina, and J.L. Martin, *Tetrahedron Letters*, **1970**, 3377; *b*) H. Brockmann, H. Greve, and A. Zeeck, *Tetrahedron Letters*, **1971**, 1929.

20) Bisanhydrodaunomycinone dimethyl ether supplied by Dr. F. Arcamone was identical with XIX.

21) A methoxyl on terminal aromatic ring in naphthacenequinone system has been found less reactive to demethylation under a mild condition. *cf.* Z. Horii, T. Momose, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **13**, 797 (1965).

gave II, which was identical with natural bisanhydrodaunomycinone in all respects.

The authors are grateful to Dr. J.R. Berman of National Cancer Institute (USA) for his kind supply of daunomycin and to Dr. F. Arcamone of Instituto Richerche Farmitalia (Italy) for his kind supply of bisanhydrodaunomycinone dimethyl ether.

Table I. Aromatic Absorptions in IR Spectra of VIII, IX, XI, XII, XIII, XIV, XV, XVI, XIX, and XX in KBr Disk

Compound	XIII	XI	XV	XIX	VIII	IX	XIV	XII[a)]	XVI	XX
cm^{-1}	1612 m.	1617 w.	1614 w.	1608 m.	1618 m.	1623 w.	1583 s.	1602 m.	1599 s.	1600 m.
	1583 s.	1587 s.	1585 s.	1585 s.	1597 m.	1592 m.	1543 m.	1570 m.	1570 m.	1569 m.
	1560 m.	1560 w.	1562 w.	1551 w.	1567 w.	1570 w.				

s.=strong, m.=medium, w.=weak; *a*) in $CHCl_3$

Experimental[22)]

2-(1-Acetoxyethyl)naphthalene (VI)[14)]——A mixture of 2-(1-bromoethyl)naphthalene[13)] (4.3 g), AcOK (7.2 g) and AcOH (100 ml) was refluxed for 20 hr and evaporated. To the residue was added benzene (100 ml), and the mixture was washed with H_2O, satd. $NaHCO_3$ and then H_2O, then dried and evaporated. The residue was fractionated *in vacuo* to give 3.0 g (76.6%) of a yellow viscous oil (bp 149°/4 mmHg) (lit.[14)] bp 172°/15 mmHg). IR ν_{max}^{film} cm^{-1}: 1733 (C=O), 1600 (arom.).

2-(1-Hydroxyethyl)naphthalene (VII)[14)]——A mixture of VI (1.4 g), EtOH (5 ml) and KOH (0.6 g) was refluxed for 3 hr. The reaction mixture was poured into ice water, and the mixture was extracted with ether (20 ml×3). The extract was washed with dil. HCl and then with H_2O. The ethereal layer was dried and evaporated to give 0.7 g (63.0%) of VII as pale yellow crystals, mp 69—71° (lit.[14)] 71—72°). IR ν_{max}^{Nujol} cm^{-1}: 3250 (OH), 1595 (arom.).

2-Acetylnaphthalene (V)[12)]——A mixture of VII (1.0 g), dry benzene (10 ml) and active manganese dioxide[23)] (4.0 g) was stirred at room temperature for 3 days. The manganese dioxide was removed, and the filtrate was evaporated. The residue was fractionated *in vacuo* to give 0.8 g (80.9%) of V as a colorless oil (bp 183—186°/35 mmHg), which solidified to colorless crystals, mp 52—54° (lit.[12)] mp 53°). IR ν_{max}^{Nujol} cm^{-1}: 1678 (C=O), 1630 (arom.).

1,6,11-Triacetoxy-8-ethylnaphthacenequinone (VIII)——A mixture of 8-ethyl-1,6,11-trihydroxynaphthacenequinone[1,9)] (III, 1.1 g), pyridine (12 ml) and Ac_2O (6 ml) was heated at 80° for 1 hr. Resulting yellow solution was poured into ice water to give yellow precipitates, which were collected, washed with H_2O and dried to give 1.22 g (80.4%) of VIII as yellow crystals (from benzene), mp 251—255°. *Anal.* Calcd. for $C_{26}H_{20}O_8$: C, 67.82; H, 4.38. Found: C, 67.63; H, 4.24. IR ν_{max}^{KBr} cm^{-1}: 1764 (OAc), 1667 (C=O), 1618, 1597, 1567 (arom.). NMR (in $CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 2.45, 2.58, 2.64 (9H, each s, -OAc ×3), 2.75 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$). UV $\lambda_{max}^{CHCl_3}$ mμ (log ε): 251 (4.65), 290 sh (4.43), 300 (4.46), 401 (3.83).

1,6,11-Triacetoxy-8-(1-acetoxyethyl)naphthacenequinone (IX)——A mixture of VIII (8.0 g), N-bromosuccinimide (6.16 g), dry CCl_4 (570 ml) and benzoyl peroxide (catalytic amounts) was refluxed with stirring for 10 hr. The cooled mixture was filtered, and the filtrate was evaporated to give 4.8 g of an orange paste which showed a positive Beilstein test. To this were added AcOK (9.6 g), Ac_2O (60 ml) and AcOH (60 ml), and the mixture was refluxed for 6 hr. The reaction mixture was evaporated, and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to give 5.0 g of a dark red paste. To this were added pyridine (50 ml) and Ac_2O (25 ml), and the temperature was maintained at 80° for 1 hr. The reaction mixture was poured into ice water to give yellow precipitates, which were collected, washed with H_2O and dried. These precipitates (4.2 g) were chromatographed on silica gel (84 g) in $CHCl_3$. The later fraction gave 2.37 g (26.3%) of IX as yellow crystals (from benzene), mp 205.0—205.5°. *Anal.* Calcd. for $C_{28}H_{22}O_{10}$: C, 64.86; H, 4.28. Found: C, 64.77; H, 4.31. IR ν_{max}^{KBr} cm^{-1}: 1772 (aromatic OAc), 1747 (aliphatic OAc), 1678 (C=O), 1623, 1592, 1570 (arom.). NMR (in $CDCl_3$) δ: 2.62, 2.56, 2.42, 2.09 (12H, each s, -OAc×4), 1.59 (3H, d, J=7 Hz, $-CH(OAc)C\underline{H}_3$), 6.02 (1H, q, J=7 Hz, $-C\underline{H}(OAc)CH_3$). UV $\lambda_{max}^{CHCl_3}$ mμ (log ε): 245 (4.61), 276 sh (4.35), 287 (4.40), 298 (4.42), 396 (3.81).

22) Melting points and boiling points are uncorrected. Organic extracts were dried over anhyd. Na_2SO_4. The NMR spectra were measured at 60 Mc with tetramethylsilane as the internal standard.

23) J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, and T. Walker, *J. Chem. Soc.*, **1952**, 1094.

8-(1-Hydroxyethyl)-1,6,11-trimethoxynaphthacenequinone (XI) and 8-(1-Hydroxyethyl)-1,5,11-trimethoxynaphthacene-6,12-dione (XII)——A mixture of IX (3.28 g), MeOH (290 ml), H_2O (290 ml) and KOH (2.85 g) was refluxed for 3 hr under N_2. The reaction mixture was poured into ice water, and the mixture was acidified with conc. HCl to give dark red precipitates, which were collected, washed with H_2O and dried. This crude quinone (1.68 g) was chromatographed on silica gel (34 g) in $CHCl_3$. The later fraction gave 1.45 g of dark red crystals which showed a hydroxyl absorption at 3350 cm^{-1} in IR spectrum (nujol). A mixture of these dark red crystals (140 mg), Me_2SO_4 (300 mg), K_2CO_3 (4.0 g) and acetone (7 ml) was refluxed for 14 hr and evaporated. To the residue were added H_2O and aq. NH_3. The mixture was extracted with $CHCl_3$ (20 ml×3), and the extract was washed with water, dried and evaporated. The reddish orange glassy residue (186 mg) was chromatographed on alumina (8 g) in benzene to give 157 mg of an orange glassy substance, which was again chromatographed on silica gel (3.2 g) in ether. The earlier fraction gave 26 mg (10.5 %) of XII as an orange viscous oil, and the later fraction gave 98 mg (39.7%) of XI as orange needles (from ether), mp 91—94°. Both the oil and the crystals showed a negative $FeCl_3$ test.

Compound (XI): *Anal.* Calcd. for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.11, H, 5.23. IR ν_{max}^{KBr} cm^{-1}: 3470 (OH), 1670 (C=O), 1617, 1587, 1560 (arom.). NMR (in $CDCl_3$) δ: 1.60 (3H, d, J=7 Hz, -CH(OH)C$\underline{H}_3$), 4.03, 4.09, 4.14 (9H, each s, -OC$\underline{H}_3$×3), 5.16 (1H, q, J=7 Hz, -C$\underline{H}$(OH)CH_3). UV λ_{max}^{EtOH} mμ (log ε): 242 (4.70), 252 sh (4.68), 290 sh (4.36), 298 (4.40), 406 (4.09). Mass Spectrum *m/e*: 392 (M^+).

Compound (XII): *Anal.* Calcd. for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.57; H, 5.40. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1664 (C=O), 1602, 1570 (arom.). NMR (in $CDCl_3$) δ: 1.54 (3H, d, J=7 Hz, -CH(OH)C$\underline{H}_3$), 4.03 (3H, s, -OCH_3), 4.07 (6H, s, OC$\underline{H}_3$×2), 5.04 (1H, q, J=7 Hz, -C$\underline{H}$(OH)CH_3). UV λ_{max}^{EtOH} mμ (log ε): 259 (4.86), 288 sh (4.39), 300 sh (4.23), 430 (4.11). Mass Spectrum *m/e*: 392 (M^+).

8-Acetyl-1,6,11-trimethoxynaphthacenequinone (Bisanhydrodaunomycinone Dimethyl Ether) (XIX)——A mixture of XI (161 mg), MnO_2 (350 mg) and dry benzene (7 ml) was stirred for 12 hr at room temperature. Inorganic material was removed, and the filtrate was evaporated to give 129 mg of yellow crystals, which were chromatographed on silica gel (2.6 g) in $CHCl_3$. The earlier fraction was evaporated, and the residue was recrystallized from ether to give 53 mg (32.9%) of XIX as yellow needles, mp 224—226° (lit.[7d] mp 230—231° (from AcOH) for natural bisanydrodaunomycinone dimethyl ether). *Anal.* Calcd. for $C_{23}H_{18}O_6$: C, 70.76; H, 4.65. Found: C, 70.54; H, 4.73. IR ν_{max}^{KBr} cm^{-1}: 1680 (acetyl C=O), 1674, 1660 (quinone C=O), 1608, 1585, 1551 (arom.). NMR (in $CDCl_3$) δ: 2.78 (3H, s, -COC$\underline{H}_3$), 4.07 (6H, s, -OC$\underline{H}_3$×2), 4.20 (3H, s, -OC$\underline{H}_3$). UV λ_{max}^{EtOH} mμ (log ε): 263 (4.74), 302 sh (4.27), 405 (4.10). Mass Spectrum *m/e*: 390 (M^+).

8-Acetyl-1,5,11-trimethoxynaphthacene-6,12-dione (XX)——Oxidation of XII (105 mg) with MnO_2 (230 mg) in dry benzene (5 ml) was carried out in a similar manner to that for XIX. Inorganic material was removed, and the filtrate was evaporated to give 100 mg of orange crystals, which were recrystallized from ether to give 41 mg (39.0%) of XX as orange needles, mp 192—195°. *Anal.* Calcd. for $C_{23}H_{20}O_6$: C, 70.76; H, 4.65. Found: C, 70.54; H, 4.41. IR ν_{max}^{KBr} cm^{-1}: 1688 (acetyl C=O), 1669, 1663 (quinone C=O), 1600, 1569 (arom.). NMR (in $CDCl_3$) δ: 2.72 (3H, s, -COC$\underline{H}_3$), 4.07 (6H, s, -OC$\underline{H}_3$×2), 4.12 (3H, s, -OC$\underline{H}_3$). UV λ_{max}^{EtOH} mμ (log ε): 264 (4.61), 444 (3.76). Mass Spectrum *m/e*: 390 (M^+).

Methylation of Natural Bisanhydrodaunomycinone——A mixture of natural bisanhydrodaunomycinone (II, 50 mg), Me_2SO_4 (70 mg), K_2CO_3 (8 g) and acetone (15 ml) was refluxed for 54 hr and evaporated. To this were added H_2O (20 ml) and aq. NH_3, and the mixture was extracted with $CHCl_3$ (10 ml×4). The extract was washed with H_2O, dried and evaporated to give brown crystals. The starting material (8 mg) less soluble in $CHCl_3$ was filtered off, and the filtrate was evaporated to give 22 mg of orange crystals, which were chromatographed on silica gel thin layer in ether. The fraction which has a higher *Rf* value gave 4 mg of orange crystals, which were recrystallized from ether to give 0.5 mg (1.1% on subtraction of recovered II) of XX as orange crystals, mp 192.5—195.0°. The fraction which has a lower *Rf* value gave 11 mg of yellow crystals. Recrystallization from ether gave 1.0 mg (2.2% on subtraction of recovered II) of XIX as yellow crystals, mp 223—225°. The ether, XIX or XX, from natural bisanhydrodaunomycinone was identified with the synthetic sample by comparison of their infrared and mass spectra, thin layer chromatography and melthing points and by mixed melthing point determination.

Bisanhydrodaunomycinone (II) (Partial Demethylation of XIX or XX)——A cooled solution of XIX (39 mg) in dry CH_2Cl_2 (4 ml) was mixed, at −60°, with a cooled solution of BBr_3 (230 mg, 10 molar equivalents) in dry CH_2Cl_2 (2 ml), and the mixture was allowed to warm up to room temperature and then stood for 1 hr, and poured onto cracked ice. The mixture was extracted with $CHCl_3$ (40 ml×4), and the extract was washed with H_2O, dried and evaporated. The resulting red amorphous substance (37 mg) was chromatographed on silica gel thin layer in $CHCl_3$. The red zone on thin layer gave 28 mg of dark red crystals, which were recrystallized from $CHCl_3$ to afford 17 mg (47.0%) of II as red needles, mp 320—325° (lit.[7a,d] mp 325—330° from AcOH). The reaction employing 5 molar equivalents of BBr_3 gave II in 23.0% yield. Demethylation of XX (19.5 mg) with BBr_3 (95 mg) in a similar manner also gave II (7 mg, 38.9%). *Anal.* Calcd. for $C_{21}H_{14}O_6$: C, 69.61; H, 3.89. Found: C, 69.42; H, 3.92. IR ν_{max}^{KBr} cm^{-1}: 1683 (acetyl C=O), 1615, 1605, 1575, 1560, 1542 (arom.). NMR (in $CDCl_3$) δ: 2.89 (3H, s, -COC$\underline{H}_3$), 4.02 (3H, s, -OC$\underline{H}_3$). Mass Spectrum *m/e*: 362 (M^+). Compound (II) from XIX or XX, and natural bisanhydrodaunomycinone were completely identical in comparison of their infrared spectra, mass spectra, thin layer chromatography, melting points and mixed melting point.

6-Ethoxy-1,11-dihydroxy-8-(1-hydroxyethyl)naphthacenequinone (X)——A mixture of IX (500 mg), KOH (430 mg), EtOH (44 ml) and H_2O (44 ml) was refluxed for 3 hr under N_2. The reaction mixture was poured into ice water, and the solution was acidified with conc. HCl. The resulting precipitates were collected, washed with H_2O and dried. The dark red precipitates (310 mg) were chromatographed on silica gel (6.2 g) in $CHCl_3$. The later fraction gave 158 mg (46.8%) of X as dark red needles (from $CHCl_3$), mp 228—230°. *Anal.* Calcd. for $C_{22}H_{18}O_6$: C, 69.83; H, 4.80. Found: C, 69.61; H, 4.67. IR ν_{max}^{KBr} cm^{-1}: 3497 (OH), 1656 (C=O), 1610, 1594, 1561 (arom.). NMR (in CF_3COOD) δ: 1.68 (3H, t, J=6.6 Hz, $-OCH_2C\underline{H}_3$), 1.78 (3H, d, J=6.6 Hz, $-CH(OH)C\underline{H}_3$), 4.46 (2H, q, J=6.6 Hz, $-OC\underline{H}_2CH_3$), 5.36 (1H, q, J=6.6 Hz, $-C\underline{H}(OH)CH_3$). Mass Spectrum *m/e*: 378 (M^+).

8-Ethyl-1,6,11-trimethoxynaphthacenequinone (XV) and 8-Ethyl-1,5,11-trimethoxynaphthacene-6,12-dione (XVI)——A mixture of III (100 mg), Me_2SO_4 (230 mg), K_2CO_3 (3 g) and acetone (5 ml) was refluxed for 32 hr and evaporated. To the residue were added H_2O and aq. NH_3, and the mixture was extracted with $CHCl_3$ (10 ml×4). The extract was washed with H_2O, and dried, and evaporated. The resulting orange red paste (125 mg) was chromatographed on alumina (2.5 g) in benzene. The earlier fraction gave a yellow paste (97 mg), which was chromatographed on silica gel thin layer in isopropyl ether. The fraction which has a higher *Rf* value gave 47 mg of yellow crystals. Recrystallization from *n*-hexane gave 18 mg (16.1%) of XVI as yellow needles, mp 103—107°. *Anal.* Calcd. for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.50; H, 5.25. IR ν_{max}^{KBr} cm^{-1}: 1668 (C=O), 1599, 1570 (arom.). NMR (in $CDCl_3$) δ: 1.32 (3H, t, J=8 Hz, $-CH_2C\underline{H}_3$), 2.81 (2H, q, J=8 Hz, $-C\underline{H}_2CH_3$), 4.05 (6H, s, $-OC\underline{H}_3\times2$), 4.11 (3H, s, $-OC\underline{H}_3$). UV λ_{max}^{EtOH} mμ (log ε): 260 (4.76), 430 (4.02). The fraction which has a lower *Rf* value gave 54 mg of yellow crystals. Recrystallization from isopropyl ether gave 21 mg (18.7%) of XV as yellow needles, mp 127—129°. *Anal.* Calcd. for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.13; H, 5.20. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O), 1614, 1585, 1562 (arom.). NMR (in $CDCl_3$) δ: 1.37 (3H, t, J=8 Hz, $-CH_2C\underline{H}_3$), 2.89 (2H, q, J=8 Hz, $-C\underline{H}_2CH_3$), 4.02, 4.15, 4.17 (9H, each s, $-OC\underline{H}_3\times3$). UV λ_{max}^{EtOH} mμ (log ε): 241 (4.67), 251 (4.65), 287 sh (4.31), 298 (4.36), 406 (4.03).