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REACTIONS OF KETENE ACETALS 15[1]. REGIOSPECIFIC SYNTHESES OF ERYTHROLACCIN AND "7-HYDROXYERYTHROLACCIN".

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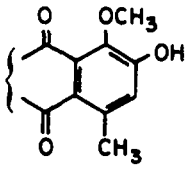
Summary - A new diene, 1,2-dimethoxy-1-trimethylsiloxy-1,3-pentadiene, has been prepared from crotonaldehyde via the cyanohydrin and the β,γ-unsaturated ester. The usefulness of the reagent is demonstrated by advantageous syntheses of the naturally occurring title-compounds and of various partially methylated analogues. The electron-donating substituents on the diene are disposed in order to illustrate the consequence of their opposing electronic effects.

The 1,2-dihydroxy-4-methylbenzo-group has been known to occur in a few natural products[2] such as coleon A and erythrolaccin. Application of classical procedures to the preparation of molecules incorporating this substitution pattern generally have been tedious or unrewarding. With the recent isolation of 8-methoxytrypethelone 7-methyl ether[3] and "7-hydroxyerythrolaccin"[4], the need for more convenient methods of synthesis have indeed become cogent.

A simple and regiospecific approach to the formation of such compounds has previously been proposed[5] using the vinylogous ketene acetal, 1-methoxy-2,4-bistrimethylsiloxy-1,3-pentadiene (1). The structure of this synthon was confirmed by the synthesis of a known derivative (19c) of erythrolaccin, obtained in rather mediocre yield (47%). Moreover the diene is of negligeable usefulness in conjunction with most benzoquinones and gives barely acceptable yields, under very particular circumstances, with 2,6-dichloro- (43% of a very labile product)[5] and 2-chloro-5-methoxybenzoquinone (37%)[6]. In spite of these drawbacks, it does lead directly to compounds of the desired arrangement, specifically in the form of the 1-methyl ether (i).

An alternate solution providing the isomeric 1-hydroxy-2-methoxy-4-methyl pattern (ii) could be



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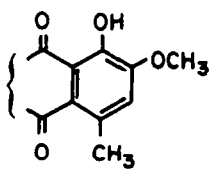
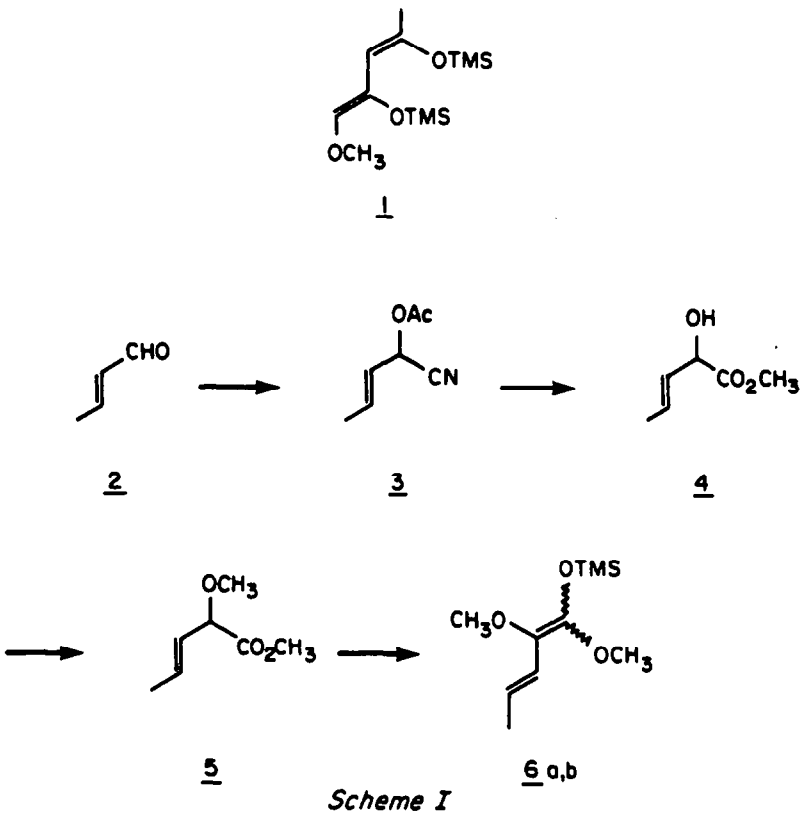


ii

contemplated by application of the appropriate mixed vinylketene acetal, a type of reagent recently shown to be particularly effective for the annulation of benzoquinones[1]. Such a diene, 1,2-dimethoxy-1-trimethylsiloxy-1,3-pentadiene 6a,b, was in fact obtained in four convenient steps from crotonaldehyde (2) through successive methanolysis, etherification and enolsilylation of the cyanohydrin (3) in an overall yield of 54% (Scheme I).

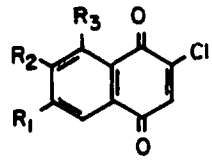


Scheme I

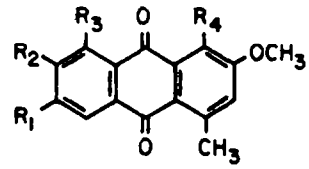
It has previously been shown that the resonance effects of 5- and 7-methoxyl groups hinder nucleophilic attack on the 2-position of 3-chloronaphthoquinones[6] and, in one particular case, lead to a non-regiospecific product[1]. Therefore the opposing electronic effects of substituents on diene 6a,b (those of terminal methyl groups are known to be unexpectedly large[7]), and its consequently reduced polarity should provide an ideal parameter for the study of the regiochemical outcome of this process.

Annulation proceeds very effectively giving good yields of regiospecific products in the case of substrates in which the effects of substituents are complementary and favor an attack on the free position of the quinonic ring[6] (i.e. in 8, 15b,c, 9, 16b and 17; 10a on the other hand appears to be somewhat unstable under these conditions). However when this condition is not met, as with 15a, 16a and 10b, additions occur much more slowly, yields are consistently lower and reaction mixtures invariably contain the non-regiospecific isomer which in the last instance constitutes the major product. This situation can be remedied in the case of 2-chlorojuglones 15a and 16a by prior acetylation or methylation and with 3-chlorojuglone ethers such as 10b by demethylation of the starting material but only with some loss in the flexibility of the method. The corresponding 1-methyl ethers are also generally encountered in this type of reaction[1]; however in the present instances, they seem to occur only in small amounts and were not isolated.

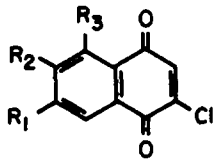
All adducts obtained were directly subjected to pyrolysis at ~ 130° without purification; a process found to be as effective and more rapid than aromatization by adsorption on silica gel. However under these conditions, some products (polymethyl ethers) were partially but selectively demethylated in the peri-position, undoubtedly by the liberated hydrogen chloride. Thus the 2-chlorojuglone ethers 15c, 16b and 17 gave 13, 2 and 13% yields respectively of the cleaved compounds 18b, 19a and 20a which could readily be identified by spectral means. The mono- 18a and dimethyl 18b ethers are moreover derivatives of the deoxygenated product obtained by Cameron *et al.*[4] by treatment of erythrolaccin by $AlCl_3$ at high temperature. On the other hand, the dimethyl ether 19a obtained from the 2-chlorojuglone 16a is apparently the same as a substance previously



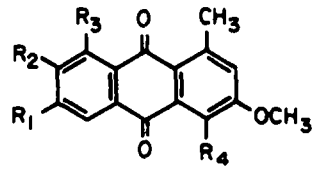
#	R_1	R_2	R_3
7	H	H	H
8	H	H	OH
9	OCH_3	H	OH
10a	OH	OCH_3	OH
10b	OCH_3	OCH_3	OCH_3



#	R_1	R_2	R_3	R_4
11a	H	H	H	OH
11b	H	H	H	OCH_3
12a	H	H	OH	OH
12b	H	H	OCH_3	OCH_3
13	OCH_3	H	OH	OH
14	OCH_3	OCH_3	OCH_3	OCH_3



#	R_1	R_2	R_3
15a	H	H	OH
15b	H	H	OAc
15c	H	H	OCH_3
16a	OCH_3	H	OH
16b	OCH_3	H	OCH_3
17	OCH_3	OCH_3	OCH_3

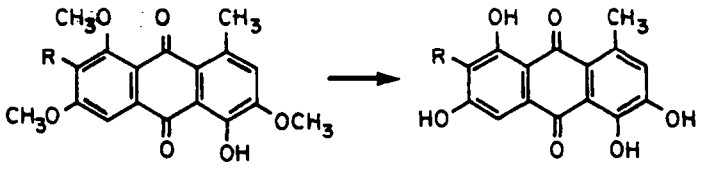


#	R_1	R_2	R_3	R_4
18a	H	H	OH	OH
18b	H	H	OCH_3	OH
19a	OCH_3	H	OH	OH
19b	OCH_3	H	OCH_3	OH
19c	OCH_3	H	OCH_3	OCH_3
20a	OCH_3	OCH_3	OH	OH
20b	OCH_3	OCH_3	OCH_3	OH
20c	OCH_3	OCH_3	OCH_3	OCH_3

prepared by Venkataraman *et al.*[9] in the course of their work on erythrolaccin.

When the cycloaddition was applied to naphthoquinones 16b and 17 excellent yields were obtained of tri-O-methylerythrolaccin 19b (93%) and "tetra-O-methyl-7-hydroxyerythrolaccin" 20b (84%) which could be converted efficiently to the natural products 19d and 20d by treatment with $AlCl_3$-NaCl at 180° or even better with pyridinium chloride at 160° (i.e. 94% and 98% yields respectively). Methylation of 19b gave a permethylated derivative of erythrolaccin (19c) indistinguishable in all respects with a sample obtained earlier[5], while both completely demethylated substances 19d and 20d showed physical properties comparable to the extensive data of the literature[2,4,9,10] (Scheme II).

The reaction of diene 6a,b with benzoquinones was not examined in detail after it was ascertained that yields remained low (36% with quinone 21, while diene 1 gives 37% of an analogous compound) in spite of the fact that the reagent was a vinylketene mixed acetal. Attempts to improve the outcome by use of a more electrophilic quinone such as 22 gave an adduct in fair yield (63%) that could not be aromatized. An IR band at 1735 cm^{-1}, strong U.V. absorption at 243 nm and the presence of doublets (J = 3.0 Hz) at δ 7.14 and 7.30 in the NMR spectrum confirm the suspicion

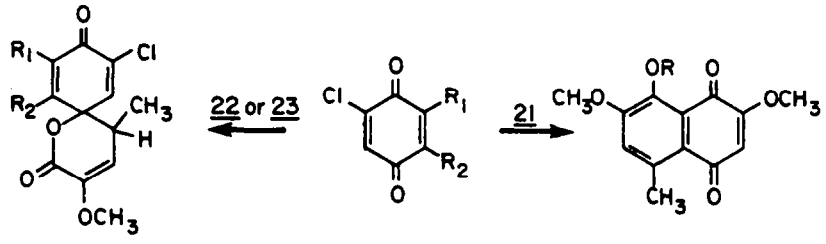


#	R
19b	H
20b	OCH_3

#	R
19d	H
20d	OH

Scheme II

that a different kind of product is formed and indicate that the adduct is in fact the cyclohexadienonespirolactone 25 (Scheme III). This type of compound is somewhat similar to the cyclohexadienonespiropyrans[11] obtained earlier by Barltrop and Hesp but accessible only by photochemical means. The position of the chlorine atoms were substantiated by the NMR spectrum of an analogous product 26, formed in low yield (20% from quinone 23), which shows the cyclohexadienone protons at δ 6.63 and 7.13. The competitive formation of this novel type of product probably accounts for the fact that many other dienes react unsatisfactorily with benzoquinones.



#	R_1	R_2
25	Cl	H
26	H	Cl

#	R_1	R_2
21	OCH_3	H
22	Cl	H
23	H	Cl

#	R
24a	H
24b	CH_3

Scheme III

EXPERIMENTAL

All melting points were taken for samples in capillary tubes with a Thomas-Hoover Apparatus and are not corrected. The UV spectra were determined on a Hewlett-Packard 8450A spectrophotometer, the IR spectra on a Beckman Model IR-4250 instrument and calibrated with a film of polystyrene. NMR spectra were recorded with a Bruker HX-90 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. Merck silica gel $60F_{254}$, for dry column chromatography was used throughout in a product to adsorbent ratio of 1:50-100. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Preparation of 1,2-dimethoxy-1-trimethylsiloxy-1,3-pentadiene (6a,b)

Methyl 2-methoxy-3-pentenoate (5).

A mixture of methyl 2-hydroxy-3-pentenoate[12,13] (4) (65.1 g; 0.50 mol), CH_3I (213 g; 1.50 mol) and freshly prepared Ag_2O (232 g; 1.00 mol) in dry chloroform (1.5 L) was stirred for 4 h, filtered and evaporated. Distillation of the residue gave 5 (66.3 g; 92%), b.p. 75-78°/16 mm; IR ν_{max} (film) 2830, 1745, 1670 and 970 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (3H, dd, J = 6.5, 1.5 Hz, 5-H), 3.38 (3H, s, 2-OCH_3), 3.77 (3H, s, 1-OCH_3), 4.21 (1H, dd, J = 7.5, 0.5 Hz, 2-H), 5.50 (1H, ddq, J = 15.5,

7.5, 1.5 Hz, 3-H) and 5.94 (1H, ddq, J = 15.5, 6.5, 0.5 Hz, 4-H); mass spectrum: m/e 144 (M^+).

E,E- and Z,E-1,2-Dimethoxy-1-trimethylsiloxy-1,3-pentadiene (6a,b).
To a solution of LDA prepared in the usual way with n-BuLi (0.12 mol; 1.4 M in hexane) and diisopropylamine (0.11 mol) in dry THF (100 mL) at 0° then cooled to -78° were added (45 min) the foregoing ester 5 (14.4 g; 0.10 mol) in THF (20 mL) then after 30 min, a solution of TMSCl (16.3 g; 0.15 mol) in the same solvent (30 mL) (3 h). The reaction mixture was allowed to warm to room temperature, evaporated, diluted with dry petroleum ether, b.p. 30-60° (500 mL), filtered and evaporated, diluted with dry petroleum ether, b.p. 30-60° (500 mL), filtered and evaporated again. Upon distillation, the residue gives a mixture of diastereoisomeric dienes 6a,b (isomer a predominates in this mixture but isomer b is the major component when the method of Corey and Gross is applied[14]), b.p. 47-48°/0.3 mm (18.3 g; 85%); IR ν_{max} (film) 1658, 1635, 1442, 1245 and 865 cm^{-1}; NMR ($CDCl_3$) δ 0.26 and 0.24 (2s, 1-OTMS), 1.78 (dd, J = 6.5, 1.2 Hz, 5-H), 3.50, 3.57 and 3.56, 3.70 (4s, 1,2-OCH_3), 5.58 and 5.62 (2 dq, J = 15.5, 6.5 Hz, 4-H) and 6.13 and 6.01 (2 dq, J = 15.5, 1.2 Hz, 3-H). (Found: C, 55.61; H, 9.16; Si, 13.09. Calc. for $C_{10}H_{20}SiO_3$: C, 55.52; H, 9.32; Si, 12.98).

Reactions with naphthoquinones.

General method A. A solution of the diene 6a,b (3.00 mmol) in dry benzene (5 mL) is added (30 min) to a suspension of the chloronaphthoquinone (2.00 mmol) in the same solvent (5 mL) at 5-10°. The reaction mixture is stirred at room temperature for 1 h, refluxed until the quinone had disappeared, evaporated, pyrolyzed at 130° in an open flask for 1 h and finally separated by chromatography, eluting with CH_2Cl_2 unless otherwise indicated.

1-Hydroxy-2-methoxy-4-methylanthraquinone (11a).
Anthraquinone 11a was obtained from naphthoquinone 7 (reflux time 5 h) after chromatography (CH_2Cl_2-CCl_4 2:1) (411 mg; 77%), m.p. 212.5° (CH_2ClCH_2Cl-C_2H_5OH); IR ν_{max} (KBr) 1655, 1628, 1590 and 1580 cm^{-1}; UV λ_{max} (CH_3OH) 249, 277 and 424 nm (log ε 4.51, 4.12 and 3.82); NMR ($CDCl_3$) δ 2.76 (3H, s, 4-CH_3), 4.03 (3H, s, 2-OCH_3), 6.93 (1H, s, 3-H), 7.67-7.89 (2H, m, 6,7-H), 8.19-8.37 (2H, m, 5,8-H) and 13.67 (1H, s, 1-OH); mass spectrum: m/e 268 (M^+). (Found: C, 71.72; H, 4.64. Calc. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51).

1,2-Dimethoxy-4-methylanthraquinone (11b).
Methylation [$(CH_3)_2SO_4$ (16.00 mmol), K_2CO_3 (17.60 mmol), acetone (150 mL) refluxed 3d] of the crude product obtained as in the preceding paragraph after chromatography (CH_2Cl_2) gave 11b (447 mg; 79%), m.p. 147.0-147.5° (C_2H_5OH); IR ν_{max} (KBr) 1675, 1660, 1595, 1580 and 1545 cm^{-1}; UV λ_{max} (CH_3OH) 225, 244, 270 and 376 nm (log ε 4.31, 4.34, 4.38 and 3.70); NMR ($CDCl_3$) δ 2.83 (3H, s, 4-CH_3), 4.02 (6H, s, 1,2-OCH_3), 7.06 (1H, s, 3-H), 7.64-7.84 (2H, m, 6,7-H) and 8.12-8.32 (2H, m, 5,8-H); mass spectrum: m/e 282 (M^+). (Found: C, 72.24; H, 5.05. Calc. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00).

1,8-Dihydroxy-2-methoxy-4-methylanthraquinone (12a).
The cycloaddition with 3-chlorojuglone[15,16] (8) (reflux time 2 h) afforded 12a (486 mg; 86%), m.p. 216.0-216.5° (CH_2ClCH_2Cl-C_2H_5OH) (lit.[10] m.p. 206-207°); IR ν_{max} (KBr) 1655, 1623 and 1600 cm^{-1}; UV λ_{max} (CH_3OH) 232, 251, 289 and 446 nm (log ε 4.46, 4.34, 4.09 and 4.03); NMR ($CDCl_3$) δ 2.74 (3H, s, 4-CH_3), 4.03 (3H, s, 2-OCH_3), 6.96 (1H, s, 3-H), 7.26 (1H, dd, J = 7.5, 2.0 Hz, 7-H), 7.69 (1H, t, J = 7.5 Hz, 6-H), 7.82 (1H, dd, J = 7.5, 2.0 Hz, 5-H) and 12.02 and 13.04 (2 x 1H, 2s, 1,8-OH); mass spectrum: m/e 284 (M^+). (Found: C, 67.80; H, 4.30. Calc. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25).

1,2,8-Trimethoxy-4-methylanthraquinone (12b).
When the crude product from the foregoing reaction was methylated as for compound 11b (28h) and purified in the same way, 12b was isolated (494 mg; 79%), m.p. 182.0-182.5° (C_2H_5OH); IR ν_{max} (KBr) 1670, 1650, 1585 and 1550 cm^{-1}; UV λ_{max} (CH_3OH) 223, 266 and 370 nm (log ε 4.46, 4.35 and 3.94); NMR ($CDCl_3$) δ 2.77 (3H, s, 4-CH_3), 3.99, 4.02 and 4.03 (3 x 3H, 3s, 1,2,8-OCH_3), 6.98 (1H, s, 3-H), 7.26 (1H, dd, J = 8.0, 2.0 Hz, 7-H), 7.64 (1H, t, J = 8.0 Hz, 6-H) and 7.80 (1H, dd, J = 8.0, 2.0 Hz, 5-H); mass spectrum: m/e 312 (M^+). (Found: C, 69.33; H, 5.19. Calc. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16).

1,8-Dihydroxy-2,6-dimethoxy-4-methylanthraquinone (13).
Application of the general method (reflux time 6 h) to the chloromethoxyjuglone 9[11] yielded 13 (504 mg; 80%), m.p. 242.5-243.0° (CH_2ClCH_2Cl-C_2H_5OH); IR ν_{max} (KBr) 1660, 1620, 1605, 1580 and 1500 cm^{-1}; UV λ_{max} (CH_3OH) 230, 249, 278, 307 (sh) and 440 nm (log ε 4.53, 4.19, 4.41, 4.08, and 4.15); NMR ($CDCl_3$) δ 2.77 (3H, s, 4-CH_3), 3.96 and 4.03 (2 x 3H, 2s, 2,6-OCH_3), 6.68 (1H, d, J = 2.5 Hz, 7-H), 6.94 (1H, s, 3-H), 7.38 (1H, d, J = 2.5 Hz, 5-H) and 12.23 and 13.18 (2 x 1H, 2s, 1,8-OH); mass spectrum: m/e 314 (M^+). (Found: C, 64.92; H, 4.57. Calc. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49).

1,2,3,7,8-Pentamethoxy-5-methylanthraquinone (14).

a) Chlorojuglone 10a[6] afforded an analogous product (reflux time 7 d) which was converted to the pentamethyl ether 14 in the usual way (6d) and isolated by chromatography (C_6H_6-$CH_3CO_2C_2H_5$ 10:1) (292 mg; 39%), m.p. 158.0-158.5° (C_2H_5OH); IR ν_{max} (KBr) 1678, 1660, 1580 and 1552 cm^{-1}; UV λ_{max} (CH_3OH) 219, 280 and 358 nm (log δ 4.38, 4.58 and 3.86); NMR ($CDCl_3$) δ 2.74 (3H, s, 5-CH_3), 4.01, 4.02, 4.04 and 4.06 (15H, 4s, 1,2,3,7,8-OCH_3), 6.98 (1H, s, 6-H) and 7.54 (1H, s, 4-H); mass spectrum: m/e 372 (M^+). (Found: C, 64.78; H, 5.43. Calc. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41).

b) A similar reaction using naphthoquinone 10b[6] (reflux time 9 d) after methylation in the usual way (20 h) gave 20c (195 mg; 26%) (vide infra); a second zone consisted of quinone 14 (141 mg; 19%).

1,5-Dihydroxy-2-methoxy-4-methylanthraquinone (18a).

a) A reaction mixture obtained with 2-chlorojuglone[15,16] (15a) (reflux time 6 h) afforded 18a (333 mg; 59%), m.p. 229.0-229.5° (CH_2ClCH_2Cl-C_2H_5OH); IR ν_{max} (KBr) 1617 and 1590 cm^{-1}; UV λ_{max}

(CH_3OH) 231, 253, 293 and 454 nm (log ε 4.46, 4.39, 4.09 and 4.06); NMR ($CDCl_3$) δ 2.78 (3H, s, 4-CH_3), 4.03 (3H, s, 2-OCH_3), 6.96 (1H, s, 3-H), 7.32 (1H, dd, J = 8.0, 1.5 Hz, 6-H), 7.66 (1H, t, J = 8.0 Hz, 7-H), 7.85 (1H, dd, J = 8.0, 1.5 Hz, 8-H) and 13.21 and 13.81 (2 x 1H, 2s, 1,5-OH); mass spectrum: m/e 284 (M^+). (Found: C, 67.82; H, 4.37. Calc. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25).

A slower-moving band was identified as the isomeric 12a (57 mg; 10%).

b) A similar reaction using naphthoquinone 15b[15] (reflux time 6 h) gave 18a (409 mg; 72%) after hydrolysis [CH_3OH (25 mL), aq. 5% HCl (10 mL)-reflux 2 h] and chromatography of the crude product.

1-Hydroxy-2,5-dimethoxy-4-methylanthraquinone (18b).

A reaction of the usual diene with juglone ether 15c[17] (reflux time 2 d) gave the demethylated product 18a (75 mg; 13%), while the main product consisted of 18b (449 mg; 75%), m.p. 199° (CH_2ClCH_2Cl-C_2H_5OH); IR ν_{max} (KBr) 1655, 1635 and 1585 cm^{-1}; UV λ_{max} (CH_3OH) 230, 251, 283 and 430 nm (log ε 4.41, 4.42, 4.11 and 3.92); NMR ($CDCl_3$) δ 2.74 (3H, s, 4-CH_3), 4.01 and 4.05 (2 x 3H, 2s, 2,5-OCH_3), 6.95 (1H, s, 3-H), 7.36 (1H, dd, J = 8.0, 1.5 Hz, 6-H), 7.69 (1H, t, J = 8.0 Hz, 7-H), 7.96 (1H, dd, J = 8.0, 1.5 Hz, 8-H) and 13.42 (1H, s, 1-OH); mass spectrum: m/e 298 (M^+). (Found: C, 68.73; H, 4.69. Calc. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73).

1,5-Dihydroxy-2,7-dimethoxy-4-methylanthraquinone (19a) (Erythrolaccin 2,7-dimethyl ether).

A mixture obtained using naphthoquinone 16a[1] was allowed to stand at room temperature for 2 d, refluxed for 2 h, pyrolyzed and gave 19a (123 mg; 39%), m.p. 238.0-238.5° (CH_2ClCH_2Cl) (lit.[9] m.p. 224°); IR ν_{max} (KBr) 1645, 1615, 1600, 1590 and 1555 cm^{-1}; UV λ_{max} (CH_3OH) 229, 262, 292 and 456 nm (log ε 4.55, 4.40, 4.30 and 4.09); NMR ($CDCl_3$) δ 2.79 (3H, s, 4-CH_3), 3.96 and 4.04 (2 x 3H, 2s, 2,7-OCH_3), 6.75 (1H, d, J = 2.5 Hz, 6-H), 6.96 (1H, s, 3-H), 7.39 (1H, d, J = 2.5 Hz, 8-H) and 13.49 and 13.76 (2 x 1H, 2s, 1,5-OH); mass spectrum: m/e 314 (M^+). (Found: C, 65.14; H, 4.58. Calc. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49).

A second band consisted of the isomer 13a (8 mg; 3%).

1-Hydroxy-2,5,7-trimethoxy-4-methylanthraquinone (19b) (Erythrolaccin 2,5,7-trimethyl ether).

An analogous reaction with 16b[1], (Method A; reflux time 24 h), after chromatography yielded 19a (14 mg; 2%) and the major product 19b (613 mg; 93%), m.p. 221.0-221.5° (CH_2ClCH_2Cl-C_2H_5OH); IR ν_{max} (KBr) 1657, 1630, 1595 and 1565 cm^{-1}; UV λ_{max} (CH_3OH) 227, 273 and 436 nm (log ε 4.51, 4.36 and 3.92); NMR ($CDCl_3$) δ 2.73 (3H, s, 4-CH_3), 3.97 and 4.00 (3H, 6H, 2s, 2,5,7-OCH_3), 6.80 (1H, d, J = 2.5 Hz, 6-H), 6.94 (1H, s, 3-H), 7.43 (1H, d, J = 2.5 Hz, 8-H) and 13.41 (1H, s, 1-OH); mass spectrum: m/e 328 (M^+). (Found: C, 66.09; H, 5.05. Calc. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91).

Methylation of the foregoing compound 19b (164 mg; 0.50 mmol) in the usual way (cf product 11b) (2 d) provided erythrolaccin tetramethyl ether 19c (157 mg; 92%), m.p. 158° (C_2H_5OH) (lit.[5,18] m.p. 155-156°; [10] 159°, [19] 159-160°) indistinguishable from a sample prepared earlier[5].

5-Hydroxy-1,2,3,6-tetramethoxy-8-methylanthraquinone (20b) ("7-Hydroxyerythrolaccin 3,6,7,8-tetramethyl ether").

A cycloaddition involving naphthoquinone 17[6] (reflux time 3 d) afforded 1,5-dihydroxy-2,3,6-trimethoxy-8-methylanthraquinone (20a) (87 mg; 13%), m.p. 219-220° (CH_2ClCH_2Cl-C_2H_5OH); IR ν_{max} (KBr) 1625, 1592 and 1560 cm^{-1}; UV λ_{max} (CH_3OH) 229, 275, 318 and 456 nm (log ε 4.45, 4.53, 3.97 and 4.11); NMR ($CDCl_3$) δ 2.76 (3H, s, 8-CH_3), 4.02 and 4.06 (3H, 6H, 2s, 2,3,6-OCH_3), 6.91 (1H, s, 7-H), 7.44 (1H, s, 4-H) and 13.52 and 13.88 (2 x 1H, 2s, 1,5-OH); mass spectrum: m/e 344 (M^+). (Found: C, 62.82; H, 4.67. Calc. for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68).

A slower-moving zone gave the major product 20b (604 mg; 84%), m.p. 188.0-188.5° (CH_2ClCH_2Cl-C_2H_5OH); IR ν_{max} (KBr) 1660, 1630 and 1585 cm^{-1}; UV λ_{max} (CH_3OH) 224, 274 and 426 nm (log ε 4.36, 4.54 and 3.86); NMR ($CDCl_3$) δ 2.71 (3H, s, 8-CH_3), 3.99, 4.00, 4.02 and 4.04 (4 x 3H, 4s, 1,2,3,6-OCH_3), 6.91 (1H, s, 7-H), 7.64 (1H, s, 4-H) and 13.42 (1H, s, 5-OH); mass spectrum: m/e 358 (M^+). (Found: C, 63.55; H, 5.19. Calc. for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06).

1,2,3,5,6-Pentamethoxy-8-methylanthraquinone (20c) ("7-Hydroxyerythrolaccin pentamethyl ether").

Methylation [CH_3I (1.0 mL), Ag_2O (2.0 g), $CHCl_3$ (50 mL) - 2 days at 25°] of the crude product obtained from 1 mmol of 17 gave the permethylated derivative 20c (264 mg; 71%), m.p. 168-169° (C_2H_5OH); IR ν_{max} (KBr) 1665, 1578 and 1553 cm^{-1}; UV λ_{max} (CH_3OH) 218, 279 and 354 nm (log ε 4.41, 4.55 and 3.77); NMR ($CDCl_3$) δ 2.74 (3H, s, 8-CH_3), 4.00, 4.01, 4.03 and 4.04 (15H, 4s, 1,2,3,5,6-OCH_3), 7.03 (1H, s, 7-H) and 7.56 (1H, s, 4-H); mass spectrum: m/e 372 (M^+). (Found: C, 64.77; H, 5.47. Calc. for $C_{20}H_{20}O_7$: C, 64.51; H. 4.41).

Demethylations

Method B. In a typical procedure 1.00 mmol of a polymethylated anthraquinone was added to a melt of $AlCl_3$ (30.0 g) and NaCl (6.0 g) at 180° and the mixture stirred at the same temperature for 5-10 min, cooled, hydrolyzed with 5% HCl (600 mL) and extracted with ethyl acetate.

Method C. A mixture of the quinone (1.00 mmol) and pyridinium chloride (0.50 mol) was kept at 160° under nitrogen for 17-24h, cooled, hydrolyzed and extracted as above.

1,2,5,7-Tetrahydroxy-4-methylanthraquinone (19d) (Erythrolaccin).

a) Application of method B to quinone 19b followed by chromatography on silica gel deactivated with 2% oxalic acid ($CH_3CO_2C_2H_5$) gave the natural product 19d (262 mg; 92%), m.p. 315° (decomp.) (99% C_2H_5OH) [lit.[10] m.p. 314° (decomp.)]; IR ν_{max} (KBr) 3370 (br), 1617, 1595 (sh) and 1560 cm^{-1}; UV λ_{max} (C_2H_5OH) 229, 264, 293 and 464 nm (log ε 4.42, 4.26, 4.25 and 3.94); NMR (DMSO-d_6) δ 2.48 (3H, s, 4-CH_3), 6.49 (1H, d, J = 2.5 Hz, 6-H), 6.91 (1H, s, 3-H), 7.01 (1H, d, J = 2.5 Hz, 8-H) and 13.28 (1H, s, 1- or 5-OH); mass spectrum: m/e 286 (M^+). (Found: C, 62.84; H, 3.58. Calc. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52).

b) Method C gave quinone 19d (268 mg; 94%) which was purified as in the preceding paragraph.

1,2,3,5,6-Pentahydroxy-8-methylanthraquinone (20d) ("7-Hydroxyerythrolaccin").

a) Method B applied to 20b (0.50 mmol) gave the polyhydroxylated compound 20d (113 mg; 72%), no m.p., decomp. > 340° (CH_3OH) (lit.[4] no m.p., decomp. > 320°); IR ν_{max} (KBr) 3410 (br), 1610, 1595 (sh) and 1560 cm^{-1}; UV λ_{max} (CH_3OH containing 1% HCO_2H) 285, 322 (sh) and 454 nm (log ε 4.44, 3.82 and 3.96); NMR (DMSO-d_6) δ 2.57 (3H, s, 8-CH_3), 6.96 (1H, s, 7-H) and 7.23 (1H, s, 4-H); mass spectrum: m/e 302 (M^+). (Found: C, 59.77; H, 3.51. Calc. for $C_{15}H_{10}O_7$: C, 59.61; H, 3.33).

b) Use of method C with 20b gave 20d (296 mg; 98%).

Reactions with benzoquinones

5-Hydroxy-3,6-dimethoxy-8-methylnaphthoquinone (24a).

A reaction between 2-chloro-6-methoxybenzoquinone[20] 21 (345 mg; 2.00 mmol) and diene 6a,b (541 mg; 2.50 mmol) according to method A (the mixture is allowed to stand for 3 h at room temperature - refluxing is unnecessary) gave naphthoquinone 24a (181 mg; 36%), m.p. 215.5-216.0° (CH_3OH); IR ν_{max} (KBr) 1630, 1612, 1595 and 1565 cm^{-1}; UV λ_{max} (CH_3OH) 223, 268, 295 and 450 nm (log ε 4.40, 4.05, 3.98 and 3.67); NMR ($CDCl_3$) δ 2.67 (3H, s, 8-CH_3), 3.90 and 4.00 (2 x 3H, 2s, 3,6-OCH_3), 6.11 (1H, s, 2-H), 6.90 (1H, s, 7-H) and 14.09 (1H, s, 5-OH); mass spectrum: m/e 248 (M^+). (Found: C, 62.73; H, 4.71. Calc. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87).

Methylation [CH_3I-Ag_2O] of the preceding compound 24a and purification by chromatography (C_6H_6-$CH_3CO_2C_2H_5$ 5:1) gave the triether 24b (65%), m.p. 186.5-187.5° (CH_3OH) (lit.[4] 185.0-186.5°) indistinguishable from a sample obtained previously.

8,10-Dichloro-3-methoxy-5-methyl-1-oxaspiro [5.5]undeca-3,7,10-triene-2,9-dione (25).

In an analogous experiment diene 6a,b (2.50 mmol) in dry THF (5 mL) was added (30 min) to a suspension of 2,6-dichlorobenzoquinone (22) (2.00 mmol) in the same solvent (5 mL) at -78°. The mixture was allowed to stand for 3 h at room temperature, stirred with water (5 mL; 1 h), further diluted and extracted with CH_2Cl_2. The residue was taken up in CCl_4 and upon addition of petroleum ether (b.p. 65-110°) gave the lactone 25 (366 mg; 65%), m.p. 226.5-227.0° (CH_2ClCH_2Cl-C_6H_6); IR ν_{max} (KBr) 1735, 1695, 1642 and 1610 cm^{-1}; UV λ_{max} (CH_3OH) 243 and 297 nm (log ε 4.02 and 3.29); NMR ($CDCl_3$) δ 1.16 (3H, d, J = 7.5 Hz, 5-CH_3), 3.19 (1H, dq, J = 7.5, 3.0 Hz, 5-H), 3.77 (3H, s, 3-OCH_3), 5.47 (1H, d, J = 3.0 Hz, 4-H) and 7.14 and 7.30 (2 x 1H, 2d, J = 3.0 Hz, 7,11-H); mass spectrum: m/e 290/288 (M^+). (Found: C, 49.84; H, 3.60; Cl, 24.80. Calc. for $C_{12}H_{10}Cl_2O_4$: C, 49.85; H, 3.49; Cl, 24.53).

7,10-Dichloro-3-methoxy-5-methyl-1-oxaspiro [5.5]undeca-3,7,10-triene-2,9-dione (26).

A similar reaction with quinone 23 gave 26 (20%), m.p. 184.5-185.0° (C_6H_6); UV λ_{max} (CH_3OH) 240 and 290 (sh) nm (log ε 4.16 and 3.30); NMR ($CDCl_3$) δ 1.13 (3H, d, J = 7.5 Hz, 5-CH_3), 3.33 (1H, dq, J = 7.5, 2.5 Hz, 5-H), 3.73 (3H, s, 3-OCH_3), 5.36 (1H, d, J = 2.5 Hz, 4-H), 6.63 (1H, s, 8-H) and 7.13 (1H, s, 11-H); mass spectrum: m/e 292/290/288 (M^+). (Found: C, 50.07; H, 3.51; Cl, 24.90. Calc. for $C_{12}H_{10}Cl_2O_4$: C, 49.85; H, 3.49; Cl, 24.53).

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