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REACTIONS OF KETENE ACETALS 16[1]. THE REGIOSPECIFIC SYNTHESIS OF PARTIALLY METHYLATED PURPURINS

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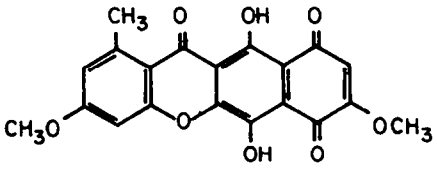
Summary - Two novel vinylketene acetals, 1,4-dimethoxy-1,3-bistrimethylsiloxybutadiene and 1,3,4-trimethoxy-1-trimethylsiloxybutadiene have been prepared in view of their eventual application to the synthesis of the antitumor antibiotic bikaverin. Use of the former in the elaboration of anthraquinones has shown that structures proposed for two natural products, purpurin 1-methyl ether and 8-hydroxypurpurin 1-methyl ether are in fact those of anthragallol derivatives. The second diene has afforded confirmation of the nature of xanthorin 5-methyl ether as well as of a degradation product of bostrycin. A substitution pattern claimed for another natural product, 5-hydroxyanthragallol 2,5-dimethyl ether, is also incorrect.

We have recently shown that naturally occuring 1,4-dihydroxyxanthones can be constructed simply and regiospecifically from halogenated benzoquinones and various salicylates[2]. Extension of this approach to dihalogenated substrates would lead in principle after oxidation, to a xanthenetrione appropriately substituted so as to afford the antitumor antibiotic bikaverin (1) by cycloaddition to the required vinylketene acetal.



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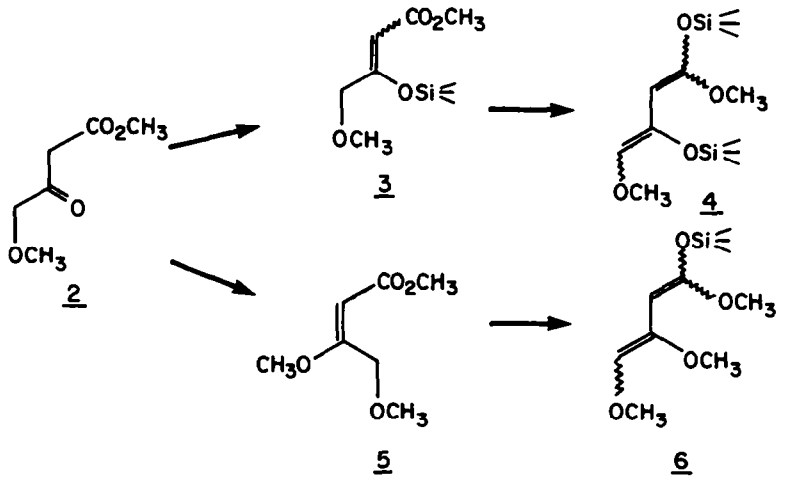
Application of a convergent strategy to this problem would require the synthesis of tetraoxygenated dienes that would not only provide the proper substitution pattern of partially methylated hydroxyl groups but would also show the desired behavior in cycloadditions involving both benzoquinones and xanthenetriones. In this respect, vinylketene dialkylacetals in general and 4-substituted instances in particular have been shown to react unsatisfactorilly with such dienophiles[3]. However the use of mixed acetals (i.e. alkyl trimethylsilyl acetals) can largely overcome this difficulty[4].

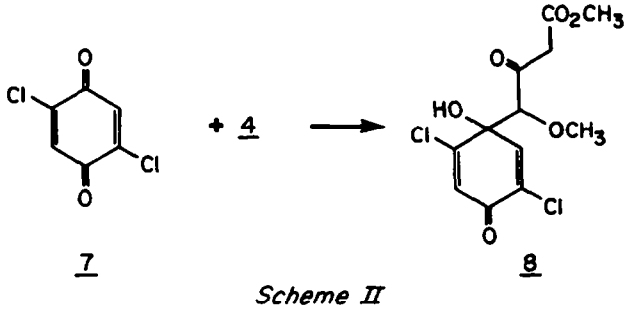
Methyl 4-methoxyacetoacetate (2) readily prepared according to the method of Kato et al.[5a] gave 1,4-dimethoxy-1,3-bistrimethylsiloxybutadiene (4) by means of two consecutive enolsilylations (91 and 85%). The same ester 2 was also converted to the E-enol ether 5 (89%) with methyl orthoformate[6] in methanol and finally to 1,3,4-trimethoxy-1-trimethylsiloxybutadiene (6) in the usual way (92%) (Scheme I).

The anticipated benefical effect of the mixed acetal group on diene 4 did not materialize in reactions with benzoquinones. In the case of the 2,5-dichloro compound 7 only a small amount of the "normal" adduct could be detected. The only product isolated (45%) resulted from addition



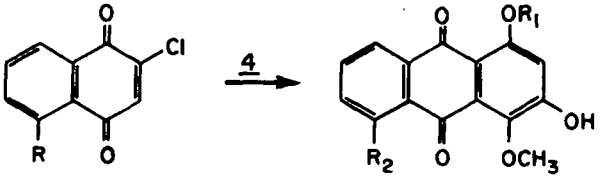
Scheme I

to a quinone carbonyl and was identified as a cyclohexadienone 8 on the basis of spectral characteristics (i.e. two singlets at δ 7.09 and 7.16 for the vinyl protons on the N.M.R. spectrum and I.R. bands at 3420, 1750, 1725 and 1665 cm^{-1} for hydroxyl, ester, saturated and unsaturated ketone functions) (SCHEME II).



Scheme II

At this point in the attempt to prepare specific naphthopurpurin derivatives we became aware of the isolation[7] of numerous anthraquinones from callus cultures of *Cinchona ledgeriana*. Two new compounds in particular identified as purpurin 1-methyl ether and 8-hydroxypurpurin 1-methyl ether showed N.M.R. data that appeared inconsistent with these structures (i.e. 3-H signals δ 7.46 and 7.45). These would seem to be more appropriately ascribed to peri-protons. Nevertheless cycloaddition of diene 4 to 2-chloronaphthoquinone (9) and to 5-acetoxy-2-chloronaphthoquinone (10) was carried out and after aromatization gave the corresponding anthraquinones of unambiguous structure (11 and 13). As expected the compounds revealed physical properties at complete variance with those of the natural products (SCHEME III).



	R
9	H
10	OAc

	R_1	R_2
11	H	H
12	CH_3	H
13	H	OH

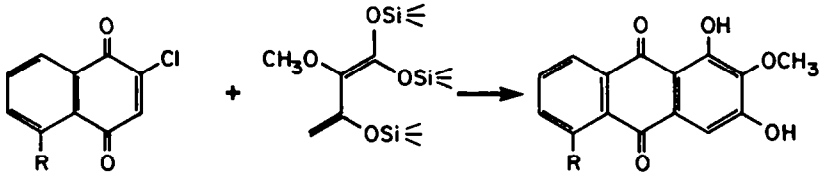
Scheme III

Careful scrutiny of the published data and reference to previous results strongly suggested, in spite of the inexplicable absence of m.p.'s, that the substances in question were actually anthragallol 2-methyl ether (16) and 5-hydroxyanthragallol 2-methyl ether (17). Comparison of their spectral properties with those of the former (previously prepared in this laboratory[8]) and of the latter obtained from quinone 10 and 2-methoxy-1,1,3-tristrimethylsiloxybutadiene (15) confirmed this hypothesis.

In the original structural assignments, importance is given to a prominent peak corresponding to $[M-H_2O]^+$ in the mass spectrum as proof of the presence of a peri-methoxyl group. It has now been observed that authentic purpurin 1-methyl ethers do not provide such a criterion. The fact that anthragallol 2-methyl ethers do give an intense peak in this area stresses once again the unreliability[9] of this occurrence as a diagnostic test.

On the other hand, anthragallol 2-methyl ethers appear to give a characteristic N.M.R. signal at $\delta \sim 4.15$ in $CDCl_3$ solution corresponding to the hindered methoxyl group (purpurin 1-methyl ethers do not exhibit this shielding effect). Moreover such contiguously substituted compounds also show U.V. absorption at 485 nm in methanolic hydroxide, a band considered to be typical of 1,3-dihydroxyanthraquinones[10].

A third product obtained from *Cinchona ledgeriana* was identified as 5-hydroxyanthragallol 2,5-dimethyl ether (18). Such a structure can readily be verified by reaction of 2-chlorojuglone methyl ether (14) with diene 15. The synthetic anthraquinone 18 isolated in 86% yield was obviously quite different from the natural product, all the more so since the selective demethylation already carried out would have given a substance on hand, the one now known to be 5-hydroxyanthragallol 2-methyl ether (17). Indeed the natural compound does not give the characteristic U.V. absorption at 485 nm and the available evidence does not suggest another structure unequivocally. However it is quite probably 5-hydroxyanthragallol 1,3-dimethyl ether since the 1,2- and 3,5-dimethyl ethers can be excluded on chemical or spectral grounds (SCHEME IV).



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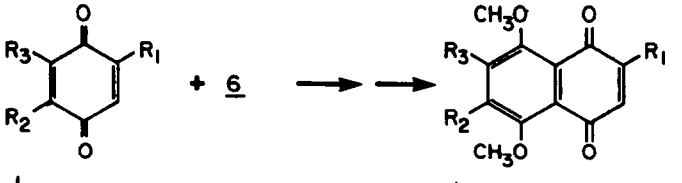
	R
9	H
10	OAc
14	OCH_3

	R
16	H
17	OH
18	OCH_3

Scheme IV

Reactions of 1,3,4-trimethoxy-1-trimethylsiloxybutadiene (6) with benzoquinones (7,19,20 and 21) were only slightly more successful than in the case of diene 4 and after methylation of the crude product did not give more than 14% of the desired naphthoquinones (SCHEME V). The major



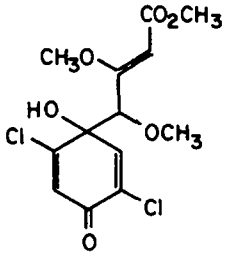
	R_1	R_2	R_3
7	Cl	Cl	H
19	Cl	H	Cl
20	OCH_3	Cl	H
21	OCH_3	H	Cl

	R_1	R_2	R_3
22	Cl	H	OCH_3
23	Cl	OCH_3	H
24	OCH_3	H	OCH_3
25	OCH_3	OCH_3	H

Scheme V

part of the product was invariably constituted of one or more adducts resulting from addition to carbonyl groups. In the reactions of diene 6 to quinone 7 for instance, an 84% of such a product 26, analogous to substance 8, could be isolated along with only 5-6% of naphthoquinone 22. Various attempts were made to modify the outcome of this reaction, however changes in solvent (C_6H_6, THF, DMF, CH_3CN) and addition of a Lewis acid ($SnCl_4$) or CuI did not materially improve the distribution of products.

With naphthoquinones the cycloaddition of diene 6 proceeded normally. 2-Chloro-6-methylnaphthoquinone (27) in particular gave 7-methylpurpurin trimethyl ether (29) (after methylation) which upon selective demethylation and acetylation provided a product identical to the diacetate of 7-methylpurpurin 2-methyl ether (30), a degradation product of bostrycin[11a]. 7-Methylpurpurin 2-methyl ether has recently been isolated from a natural source[11b]. Application of the process to 3-chloro-7-methyljuglone (28) was quite efficient in overall yield but also considerably more complex. Pyrolysis of the crude adduct under vacuum gave four products which could readily be separated by chromatography and identified by spectral means: physcion, a product of reductive elimination (2%), xanthorin 5-methyl ether (31) (43%), xanthorin 5,8-dimethyl ether (32) (12%) and 6-norxanthorin 5,8-dimethyl ether (33) (38%) (an unusual type of demethylation induced by evolved HCl). This first synthesis of xanthorin 5-methyl ether (31) has in the meantime provided unambiguous confirmation of the structure deduced for a natural product recently isolated from the root bark of *Ventilago calyculata* Tul[12] (SCHEME VI). (Original samples of the compounds described as purpurin 1-methyl ether, 8-hydroxypurpurin 1-methyl ether and 5-hydroxyanthragallol 2,5-dimethyl ether appear to be unavailable).



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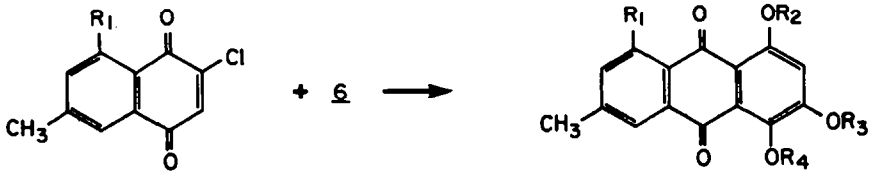

	R_1
27	H
28	OH

	R_1	R_2	R_3	R_4
29	H	CH_3	CH_3	CH_3
30	H	Ac	CH_3	Ac
31	OH	H	CH_3	CH_3
32	OH	CH_3	CH_3	CH_3
33	OH	CH_3	H	CH_3

Scheme VI

Experimental

All m.p.s were taken for samples in capillary tubes with a Thomas-Hoover apparatus and are not corrected. The U.V. spectra were determined on a Hewlett-Packard 8450A spectrophotometer, the I.R. spectra on a Beckman model IR-4250 instrument and calibrated with a film of polystyrene. N.M.R. spectra were recorded with a Varian XL-200 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. Ether refers to diethyl ether.

Preparation of dienes

Methyl 4-methoxy-3-oxobutanoate (2).

To a boiling solution of sodium methoxide prepared from sodium (21.0 g; 0.90 mol) and absolute methanol (500 mL) was added (40 min) methyl 4-bromo-3-oxobutanoate[15] (58.5 g; 0.30 mol) in the same solvent (60 mL). The mixture was refluxed for 10 min, cooled, neutralized with 6N HCl (110 mL), filtered and evaporated under vacuum. After pouring into water (500 mL) and extracting with CH_2Cl_2, the crude product was distilled under vacuum and gave ester 2 (27.0 g; 62%), b.p. 42-5°C/0.2 mm Hg (lit.[56] b.p. 89°C/8.5 mm Hg); IR ν_{max} (film) 1750, 1720, 1655 and 1635 cm^{-1}; NMR ($CDCl_3$) δ (keto from) 3.43 (s, 4-OCH_3), 3.53 (s, 2-H_2), 3.75 (s, 1-OCH_3) and 4.08 (s, 4-H_2) and (enol form) ~ 4.00 (s, 4-H_2), 5.29 (s, 2-H) and 11.88 (s, 3-OH).

Methyl (E)- and (Z)-4-methoxy-3-trimethylsiloxy-2-butenoate (3).

To a fine suspension of fused $ZnCl_2$ (550 mg) in dry triethylamine (30.5 g; 0.30 mol) were added (~ 1h) ester 2 (20.3 g; 0.14 mol) in anhydrous benzene (40 mL) and then (~ 1h) chlorotrimethylsilane (29.8 g; 0.27 mol)[14]. After stirring overnight at 45°C, the mixture was filtered, evaporated, diluted with petroleum ether (b.p. 30-60°C) (300 mL) and filtered again. After repeating this operation, the residue was distilled under vacuum and yielded enol ether 3 (27.6 g; 91%), b.p. 75-7°/1.4 mm Hg as a 1:1 mixture of stereoisomers; IR ν_{max} (film) 1720, 1630, 1250 and 845 cm^{-1}; NMR ($CDCl_3$) δ 0.27 and 0.29 [2s, 3-$OSi(CH_3)_3$], 3.37 (s, 4-OCH_3), 3.67 and 3.68 (2s, 1-OCH_3), 3.79 [d, J=1.3 Hz, (Z)-4-H_2], 4.48 [s, (E)-4-H_2], 5.26 [s, (E)-2-H] and 5.37 [t, J=1.3 Hz, (Z)-2-H]. (Found: C, 49.36; H, 8.29; Si, 12.46. Calc. for $C_9H_{18}O_4Si$: C, 49.51; H, 8.31; Si, 12.86).

1,4-Dimethoxy-1,3-bistrimethylsiloxy-1,3-butadiene (4).

To a solution of LDA prepared in the usual way from anhydrous diisopropylamine (12.2 g; 0.12 mol) in THF (120 mL) and a 1.6 M solution of n-butyllithium in hexane (80.0 mL; 0.13 mol) at 0°C then cooled to -78°C, was added (2h) a mixture of ester 3 (26.2 g; 0.12 mol) in THF (30 mL) and after 20 min chlorotrimethylsilane (13.6 g; 0.12 mol) (2h). The mixture was allowed to warm to room temperature, evaporated under vacuum, diluted with petroleum ether (b.p. 30-60°C) (300 mL) and filtered. After repeating this operation, the residue was distilled and yielded diene 4 mainly (~ 80%) as one isomer (29.8 g; 85%), b.p. 75-78°C/0.3 mm Hg; IR ν_{max} (film) 1680, 1620, 1255, 1220 and 845 cm^{-1}; NMR ($CDCl_3$) δ (principal isomer) 0.16 and 0.22 [2x9H, 2s, 1,3-$OSi(CH_3)_3$], 3.51 and 3.58 (2x3H, 2s, 1,4-OCH_3), 4.38 (1H, s, 2-H) and 5.68 (1H, s, 4-H). (This diene is somewhat unstable and a correct analysis could not be obtained).

Methyl (E)-3,4-dimethoxy-2-butenoate (5).

A mixture of methyl 4-methoxy-3-oxobutanoate (2) (21.9 g; 0.15 mol), methyl orthoformate (18.5 g; 0.18 mol), p-toluenesulfonic acid (0.4 g) and absolute methanol (50 mL) was refluxed for 10h, concentrated and heated at 100°C for 2h under a vacuum of 15 mm Hg. The residue, dissolved in ether, washed with 2% NaOH gave upon distillation enol ether 5 (21.4 g; 89%), b.p. 53-4°C/0.2 mm Hg; IR ν_{max} (film) 1720 and 1635 cm^{-1}; NMR ($CDCl_3$) δ 3.42 (3H, s, 4-OCH_3), 3.70 and 3.71 (2x3H, 2s, 1,3-OCH_3), 4.58 (2H, s, 4-H_2) and 5.15 (1H, s, 2-H); mass spectrum: m/e 160 [M]+. (Found: C, 52,49; H, 7.82. Calc. for $C_7H_{12}O_4$: C, 52.40; H, 7.55).

1,3,4-Trimethoxy-1-trimethylsiloxy-1,3-butadiene (6).

In a preparation similar to that of diene 4, butenoate 5 (16.0 g; 0.10 mol), diisopropylamine (11.1 g; 0.11 mol), n-butyllithium (0.12 mol) and chlorotrimethylsilane (16.3 g; 0.15 mol) gave diene 6 [in the form of one predominant isomer (~ 80%)] (21.3 g; 92%), b.p. 72-76°C/0.35 mm Hg; IR ν_{max} (film) 1675, 1615, 1250 and 840 cm^{-1}; RMN ($CDCl_3$) δ (for principal isomer) 0.22 [9H, s, 1-$OSi(CH_3)_3$], 3.49, 3.54 and 3.60 (3x3H, 3s, 1,3,4-OCH_3), 4.39 (1H, s, 2-H) and 5.75 (1H, s, 4-H). (Found: C, 51.40; H, 8.77; Si, 11.70. Calc. for $C_{10}H_{20}O_4Si$: C, 51.69; H, 8.68; Si, 12.08).

Reactions of diene 4.

a) With benzoquinones.

General method A: A solution of the diene (2.20-2.60 mmol) in anhydrous benzene (5 mL) is added slowly (5-10 min) to the quinone (2.00 mmol) in the same solvent (15 mL). The reaction mixture is stirred at room temperature (0.5-4.0 h) and slowly filtered through a column of silica gel.

Methyl 4-(2,5-dichloro-1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)-4-methoxy-3-oxobutanoate 8.

The crude product obtained from diene 4 (2.50 mmol) and 2,5-dichlorobenzoquinone (7) according to method A (4h) was submitted to chromatography (C_6H_6 then C_6H_6-CH_3CO_2Et 20:1). Repetition of this operation (CH_2Cl_2) gave a fraction consisting mostly of dichloro-2,5-hydroquinone (137 mg) followed by ester 8 (291 mg; 45%) (a colorless oil that could not be further purified without decomposition); UV λ_{max} (MeOH) (log ε) 224 (3.95) and 296 (3.58) nm; IR ν_{max} (film) 3420 br, 1750, 1725 and 1665 cm^{-1}; NMR ($CDCl_3$) δ (keto form) 3.53 (s, 4-OCH_3), 3.75 (s, 1-OCH_3), 3.80 (s, 2-H_2), 5.20 (s, 4-H), 5.41 (s, 1'-OH), 7.09 (s,

3'-H) and 7.16 (s, 6'-H), (enol form ~ 15%) 3.46 (s, 4-OCH_3), 3.79 (s, 1-OCH_3), 5.37 (s, 1'-OH), 5.47 and 5.72 (2s, 2-H and 4-H), 7.09 (s, 3'-H), 7.23 (s, 6'-H) and 11.94 (s, 3-OH); mass spectrum: m/e 322/324/326 $[M]^+$ (< 1) and 145 (100).

b) With naphthoquinones.

General method B: To a solution of the naphthoquinone (1.00 mmol) in dry benzene (3 mL) is added (~ 10 min) the diene (1.50 mmol) in the same solvent (2 mL). The mixture is stirred at room temperature and the crude adduct is aromatized by slow percolation through a column of silica gel.

2,4-Dihydroxy-1-methoxyanthraquinone (purpurin 1-methyl ether) (11) and 2-hydroxy-1,4-dimethoxyanthraquinone (purpurin 1,4-dimethyl ether) (12).

Application of method B to diene 4 and 2-chloronaphthoquinone[15] (9) (11h) gave a crude product which was aromatized on silica gel (C_6H_6 then C_6H_6-CH_3CO_2Et 1:1) and separated by chromatography, (C_6H_6-CH_3CO_2Et 5:1). A first band yielded anthraquinone 11 (129 mg; 48%), m.p. 230°C (95% EtOH); UV λ_{max} (MeOH) (log ε) 248 (4.44), 263 sh (4.16), 285 (4.14) and 430 (3.83) nm; IR ν_{max} (KBr) 3200 br, 1655, 1630, 1595 and 1580 cm^{-1}; NMR ($CDCl_3$) 3.99 (3H, s, 1-OCH_3), 6.87 (2H, s, 2-OH and 3-H), 7.75-7.83 (2H, m, 6,7-H), 8.25-8.32 (2H, m, 5,8-H) and 13.54 (1H, s, 4-OH); mass spectrum: m/e 270 $[M]^+$ (82), 252 $[M-H_2O]^+$ (10) and 241 $[M-CHO]^+$ (23). (Found: C, 66.43; H, 3.61. Calc. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73).

A second zone (C_6H_6-CH_3CO_2Et 1:1) consisted of anthraquinone 12 (11 mg; 4%), m.p. 229.5°C (95% EtOH); UV λ_{max} (MeOH) (log ε) 229 sh (4.39), 243 (4.47), 280 (4.31) and 410 (3.83) nm; IR ν_{max} (KBr) 3130 br, 1670, 1635, 1595, 1575 and 1555 cm^{-1}; NMR ($CDCl_3$) δ 3.98 and 3.99 (2x3H, 2s, 1,4-OCH_3), 6.80 (1H, s, 2-OH), 6.98 (1H, s, 3-H), 7.66-7.80 (2H, m, 6,7-H) and 8.15-8.25 (2H, m, 5,8-H); mass spectrum: m/e 284 $[M]^+$. (Found: C, 67.83; H, 4.10. Calc. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25).

2,4,8-Trihydroxy-1-methoxyanthraquinone (8-hydroxy purpurin 1-methyl ether) (13).

In a similar reaction (method B) using diene 4 and 5-acetoxy-2-chloronaphthoquinone[16] (10) [28h - an additional portion of the diene (0.50 mmol) was added after 25h] aromatization (C_6H_6-CH_3CO_2Et 10:1 then 5:1) gave the monoacetate of 13 which was hydrolyzed by refluxing (8h) in a mixture of 10% aqueous HCl (10 mL) and methanol (100 mL). Purification of the crude material by chromatography (C_6H_6-CH_3CO_2Et 5:1) gave anthraquinone 13 (142 mg; 50%), m.p. 242.5°C (95% EtOH); UV λ_{max} (MeOH) (log ε) 232 (4.39), 249 (4.30), 270 sh (4.10), 290 (4.11), 335 (3.40) and 442 (4.04) nm; IR ν_{max} (KBr) 3370 br, 1615 and 1555 cm^{-1}; NMR ($CDCl_3$) 4.00 (3H, s, 1-OCH_3), 6.87 (1H, s, 2-OH), 6.88 (1H, s, 3-H), 7.30 (1H, dd, J=8.3, 1.3 Hz, 7-H), 7.67 (1H, t, J=8.3, 7.6 Hz, 6-H), 7.83 (1H, dd, J=7.6, 1.3 Hz, 5-H) and 12.81 and 13.62 (2x1H, 2s, 4,8-OH); mass spectrum: m/e 286 $[M]^+$ (75), 271 $[M-CH_3]^+$ (12), 268 $[M-H_2O]^+$ (24) and 257 $[M-CHO]^+$ (19). (Found: C, 63.14; H, 3.45. Calc. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52).

Reactions of diene 15 with naphthoquinones.

1,3-Dihydroxy-2-methoxyanthraquinone (anthragallol 2-methyl ether) 16.

Anthraquinone 16 was prepared earlier[8]; NMR ($CDCl_3$) δ 4.15 (3H, s, 2-OCH_3), 6.49 (1H, s, 3-OH), 7.47 (1H, s, 4-H), 7.74-7.83 (2H, m, 6,7-H), 8.22-8.33 (2H, m, 5,8-H) and 13.14 (1H, s, 1-OH); mass spectrum: m/e 270 $[M]^+$ (93), 252 $[M-H_2O]^+$ (56) and 241 $[M-CHO]^+$ (7).

1,3,5-Trihydroxy-2-methoxyanthraquinone (5-hydroxyanthragallol 2-methyl ether) (17).

A mixture of 5-acetoxy-2-chloronaphthoquinone[16] (10) (1.00 mmol) and diene 15[8] (2.00 mmol) in benzene (5 mL) was refluxed for 16h and evaporated. The residue was heated at 60°C for 4h, hydrolyzed (5h) as for compound 13 and upon purification by chromatography (C_6H_6-CH_3CO_2Et 5:1) gave anthraquinone 17 (247 mg; 86%), m.p. 236.0-236.5°C (MeOH); UV λ_{max} (log ε) 253 (4.19), 281 (4.43) and 420 (4.05) nm; IR ν_{max} (KBr) 3440 br, 1630, 1605, 1585 and 1570 cm^{-1}; NMR ($CDCl_3$) δ 4.17 (3H, s, 2-OCH_3), 6.51 (1H, s, 3-OH), 7.29 (1H, dd, J=8.1, 1.5 Hz, 6-H), 7.47 (1H, s, 4-H), 7.66 (1H, t, J=8.1, 7.7 Hz, 7-H), 7.82 (1H, dd, J=7.7, 1.5 Hz, 8-H) and 12.63 and 13.18 (2x1H, 2s, 1,5-OH); mass spectrum: m/e 286 $[M]^+$ (73), 271 $[M-CH_3]^+$ (10), 269 $[M-OH]^+$ (10), 268 $[M-H_2O]^+$ (61) and 257 $[M-CHO]^+$ (10). (Found: C, 62.84; H, 3.34. Calc. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52).

1,3-Dihydroxy-2,5-dimethoxyanthraquinone (5-hydroxyanthragallol 2,5-dimethyl ether) (18).

The residue obtained from a reaction using 5-methoxy-2-chloronaphthoquinone[17] (14) and similar to the preceding one was heated at 70°C for 3.5h. Crystallization of the crude product from 95% EtOH gave anthraquinone 18 (258 mg; 86%), decomposes above 290°C; UV λ_{max} (MeOH) (log ε) 244 (4.18), 279 (4.44) and 400 (4.00) nm; IR ν_{max} (KBr) 3280 br, 1655, 1625, 1595, 1580 and 1565 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (3H, s, 5-OCH_3), 4.13 (3H, s, 2-OCH_3), 6.47 (1H, s, 3-OH), 7.34 (1H, dd, J=7.7, 1.1 Hz, 6-H), 7.41 (1H, s, 4-H), 7.72 (1H, t, J=7.7 Hz, 7-H), 7.96 (1H, dd, J=7.7, 1.1 Hz, 8-H) and 12.99 (1H, s, 1-OH); NMR (DMSO-d_6) 3.84 and 3.94 (2x3H, 2s, 2,5-OCH_3), 7.16 (1H, s, 4-H), 7.57 (1H, dd, J_{obs} = 5.7, 4.0 Hz, 6-H), 7.83 and 7.84 (2H, 2d, J_{obs} = 4.0, 5.7 Hz, 7,8-H) and 12.75 (1H, s, 1-OH); mass spectrum: m/e 300 $[M]^+$ (86), 285 $[M-CH_3]^+$ (10), 283 $[M-OH]^+$ (18), 282 $[M-H_2O]^+$ (3) and 271 $[M-CHO]^+$ (9). (Found: C, 63.93; H, 3.99. Calc. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03).

Reactions of diene 6

a) With benzoquinones

Methyl 4-(2,5-dichloro-1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)-3,4-dimethoxy-2-butenoate (26) and 2-chloro-5,7,8-trimethoxynaphthoquinone (22).

The reaction mixture obtained from 2,5-dichlorobenzoquinone (7) and diene 6 (2.20 mmol) according to method A (30 min) was separated (C_6H_6 then C_6H_6-CH_3CO_2Et 1:1) into several fractions. The intermediate colorless band consisted of ester 26 (567 mg; 84%), m.p.

146.5-147.0°C (CH_2Cl_2-pentane); UV λ_{max} (MeOH) (log ε) 228 (4.21) and 296 (3.60) nm; IR ν_{max} (KBr) 3260 br, 1690, 1660 and 1635 cm^{-1}; NMR ($CDCl_3$) δ 3.46 (3H, s, 4-OCH_3), 3.72 (3H, s, 1-OCH_3), 4.03 (3H, s, 3-OCH_3), 5.37 and 5.69 (2x1H, 2s, 2-H and 4-H), 5.40 (1H, s, 1'-OH), 7.09 (1H, s, 3'-H) and 7.17 (1H, s, 6'-H); mass spectrum: m/e 336/338 $[M]^+$ (<1) and 159 (100). (Found: C, 46.25; H, 4.21; Cl, 21.23. Calc. for $C_{13}H_{14}O_6Cl_2$: C, 46.31; H, 4.18; Cl, 21.03).

The quinonic head and tail fractions were methylated with excess CH_3I (0.5 mL) and Ag_2O (0.5 g) in chloroform (25 mL) and after chromatography (C_6H_6-CH_3CO_2Et 5:1) gave naphthoquinone 22 (26 to 33 mg; 5-6%), m.p. 182.5-183.0°C (CCl_4); UV λ_{max} (MeOH) (log ε) 220 (4.58), 242 sh (3.91), 248 sh (3.99), 254 sh (4.08), 260 sh (4.15), 271 (4.21) and 438 (3.67) nm; IR ν_{max} (KBr) 1675, 1650, 1615, 1585, 1580 and 1545 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (3H, s, 7-OCH_3), 4.00 (6H, s, 5,8-OCH_3), 6.78 (1H, s, 6-H) and 7.03 (1H, s, 3-H); mass spectrum: m/e 282/284 $[M]^+$. (Found: C, 55.51; H, 4.01; Cl, 12.90. Calc. for $C_{13}H_{11}O_5Cl$: C, 55.24; H, 3.92; Cl, 12.54).

2-Chloro-5,6,8-trimethoxynaphthoquinone (23).

A similar reaction mixture obtained from 2,6-dichlorobenzoquinone (19) and diene 6 (2.20 mmol) (30 min) was fractionated on silica gel (C_6H_6, C_6H_6-CH_3CO_2Et 10:1 and C_6H_6-CH_3CO_2Et 1:1). The colored portions were methylated as for compound 22 and upon purification by chromatography (C_6H_6-CH_3CO_2Et 5:1) afforded naphthoquinone 23 (58 mg; 10%), m.p. 169.0° (CCl_4); UV λ_{max} (MeOH) (log ε) 221 (4.64), 237 (4.02), 243 (4.06), 248 (4.15), 254 (4.24), 260 (4.27), 270 (4.26) and 436 (3.74) nm; IR ν_{max} (KBr) 1670, 1655, 1620, 1585 and 1550 cm^{-1}; NMR ($CDCl_3$) δ 3.87 (3H, s, 6-OCH_3), 4.00 and 4.01 (2x3H, 2s, 5,8-OCH_3), 6.75 (1H, s, 7-H) and 7.03 (1H, s, 3-H); mass spectrum: m/e 282/284 $[M]^+$. (Found: C, 55.24; H, 3.91; Cl, 12.60. Calc. for $C_{13}H_{11}O_5Cl$: C, 55.24; H, 3.92; Cl, 12.54).

2,5,7,8-Tetramethoxynaphthoquinone (mompain tetramethyl ether) (24).

In an analogous case, 5-chloro-2-methoxybenzoquinone[17] (20) and diene 6 (2.40 mmol) (method A-2h) were heated to reflux for 1.5h (0.4 mmol of diene being added after 1h). Aromatization (with recovery of 49% of 20) and methylation of the naphthoquinonic fractions as for 22 provided, after chromatography (C_6H_6-CH_3CO_2Et 1:1), the expected naphthoquinone (24), (27 mg; 5%), m.p. 164.0-164.5°C (CCl_4) (lit.[18] 169-171°); UV λ_{max} (MeOH) (log ε) 218 (4.54), 243 sh (3.97), 249 sh (4.05), 254 sh (4.14), 260 sh (4.22), 265 (4.24), 290 (4.03) and 428 (3.68) nm; IR ν_{max} (KBr) 1675, 1635, 1625, 1590 and 1555 cm^{-1}; NMR. ($CDCl_3$) δ 3.82 and 3.88 (2x3H, 2s, 2,7-OCH_3), 3.98 and 3.99 (2x3H, 2s, 5,8-OCH_3), 5.99 (1H, s, 3-H) and 6.78 (1H, s, 6-H); mass spectrum: m/e 278 $[M]^+$. (Found: C, 60.55; H, 5.14. Calc. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07).

2,5,6,8-Tetramethoxynaphthoquinone (25).

Application of method A (1.5h) to 6-chloro-2-methoxybenzoquinone[17] (21) and diene 6 (2.50 mmol) gave a mixture which was aromatized on silica gel (C_6H_6-CH_3CO_2Et 20:1, then 1:1). The colored fractions were methylated in the usual way and upon purification by chromatography (C_6H_6-CH_3CO_2Et 1:2) yielded naphthoquinone 25 (77 mg; 14%), m.p. 192-193°C (CCl_4-95% EtOH); UV λ_{max} (MeOH) (log ε) 276 (4.18), 288 sh (4.16) and 422 (3.72) nm; IR ν_{max} (KBr) 1670, 1655, 1630, 1585 and 1555 cm^{-1}; NMR ($CDCl_3$) δ 3.83 and 3.86 (2x3H, 2s, 2,6-OCH_3), 3.99 (6H, s, 5,8-OCH_3), 5.98 (1H, s, 3-H) and 6.71 (1H, s, 7-H); mass spectrum: m/e 278 $[M]^+$. (Found: C, 60.43; H, 5.11. Calc. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07).

b) With naphthoquinones.

General method C: To 1.00 mmol of the naphthoquinone in dry benzene (7 mL) is added (5-7 min) diene 6 in the same solvent (3 mL). When the cycloaddition appears to be complete, the solvent is evaporated and the residue pyrolyzed at 100°C for 1h under a vacuum of ~30 mm Hg.

1,2,4-Trimethoxy-7-methylanthraquinone (29).

When method C was applied to 2-chloro-6-methylnaphthoquinone[15] (27) and diene 6 (2.00 mmol) (48h at reflux temperature) and the residue was methylated [$(CH_3)_2SO_4$ (4.00 mmol), K_2CO_3 (4.40 mmol), $(CH_3)_2CO$ (50 mL), reflux 77h], anthraquinone 29 was isolated in the usual way and purified by chromatography (C_6H_6-CH_3CO_2Et 2:1) (181 mg; 58%), m.p. 153-154°C (CCl_4); UV λ_{max} (MeOH) (log ε) 245 sh (4.45), 248 (4.51), 254 (4.55), 260 (4.49), 280 sh (4.35) and 404 (3.85) nm; IR ν_{max} (KBr) 1675, 1655, 1605, 1590, 1580 and 1555 cm^{-1}; NMR ($CDCl_3$) δ 2.48 (3H, s, 7-CH_3), 3.95 (3H, s, 2-OCH_3), 4.01 and 4.04 (2x3H, 2s, 1,4-OCH_3), 6.81 (1H, s, 3-H), 7.51 (1H, br d, J = 7.9 Hz, 6-H), 7.93 (1H, br s, 8-H) and 8.09 (1H, d, J = 7.9 Hz, 5-H); mass spectrum: m/e 312 $[M]^+$.

1,4-Diacetoxy-2-methoxy-7-methylanthraquinone (30).

The foregoing quinone 29 (150 mg; 0.48 mmol) was selectively demethylated by refluxing for 30 min in a mixture of 49% HBr (15 mL) and CH_3COOH (10 mL). The precipitated solid upon acetylation [Ac_2O (3 mL) - conc. H_2SO_4] gave anthraquinone 30, (112 mg; 63%), m.p. 253.0-254.5°C ($CHCl_3$-95% EtOH), (lit.[11a] m.p. 238-243°C; lit.[11c] 242-248°C); UV λ_{max} (MeOH) (log ε) 265 (4.53), 281 sh (4.28), 337 sh (3.69) and 363 (3.70) nm; NMR ($CDCl_3$) δ 2.48, 2.49 and 2.50 (3x3H, 3s, 7-CH_3 and 1,4-OAc), 3.95 (3H, s, 2-OCH_3), 6.94 (1H, s, 3-H), 7.53 (1H, br d, J = 8.2 Hz, 6-H), 7.95 (1H, br s, 8-H) and 8.06 (1H, d, J = 8.2 Hz, 5-H); mass spectrum: m/e 368 $[M]^+$ (1), 326 (13) and 284 (100). (Found: C, 65.53; H, 4.56. Calc. for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38).

4,5-Dihydroxy-1,2-dimethoxy-7-methylanthraquinone (xanthorin 5-methyl ether) (31), 1,2,4-trimethoxy-5-hydroxy-7-methylanthraquinone (xanthorin 5,8-dimethyl ether) (32) and 2,5-dihydroxy-1,4-dimethoxy-7-methylanthraquinone (6-norxanthorin 5,8-dimethyl ether) (33).

Application of method C to 3-chloro-5-hydroxy-7-methylnaphthoquinone[4] (28) and diene 6 (1.25 mmol) (6h at R.T.) gave several products separated by chromatography (C_6H_6-CH_3CO_2Et 20:1).

A first band consisted of 1,8-dihydroxy-3-methoxy-6-methylanthraquinone (physcion) (6 mg; 2%), m.p. 201-202°C ($CHCl_3$-95% EtOH) (lit.[4] m.p. 206.0-206.5°C).

A second zone (C_6H_6-CH_3CO_2Et 10:1) yielded anthraquinone 31 (134 mg; 43%), m.p. 253.5-254.0°C (CH_2Cl-CH_2Cl) (lit.[12] m.p. 252°C) shown to be identical to the natural product[12]; UV λ_{max}^{MeOH} (log ε) 227 (4.56), 254 (4.40), 296 (4.16) and 444 (4.14) nm; IR ν_{max} (KBr) 3420, 1675, 1630, 1602, 1580 and 1550 cm^{-1}; NMR ($CDCl_3$) δ 2.44 (3H, s, 7-CH_3), 3.92 (3H, s, 2-OCH_3), 3.97 (3H, s, 1-OCH_3), 6.70 (1H, s, 3-H), 7.05 (1H, br s, 6-H), 7.59 (1H, br s, 8-H) and 12.06 and 12.98 (2x1H, 2s, 4,5-OH); mass spectrum: m/e 314 $[M]^+$. (Found: C, 65.29; H, 4.74. Calc. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49).

Further elution (C_6H_6-CH_3CO_2Et 5:1) provided anthraquinone 32 (38 mg; 12%), m.p. 190.0-190.5°C (CCl_4-95% EtOH); UV λ_{max}^{MeOH} (log ε) 227 (4.65), 254 (4.34), 260 (4.29), 290 (4.26) and 432 (4.06) nm; IR ν_{max} (KBr) 1670, 1630, 1580 and 1550 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (3H, s, 7-CH_3), 3.93 (3H, s, 2-OCH_3), 4.02 and 4.06 (2x3H, 2s, 1,4-OCH_3), 6.81 (1H, s, 3-H), 7.03 (1H, br s, 6-H), 7.49 (1H, br s, 8-H) and 12.97 (1H, s, 5-OH); mass spectrum: m/e 328 $[M]^+$. (Found: C, 65.55; H, 5.16. Calc. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91).

A final band (C_6H_6-CH_3CO_2Et 1:1) gave anthraquinone 33 (121 mg; 38%), m.p. 232.0-232.5°C (C_6H_6); UV λ_{max}^{MeOH} (log ε) 225 (4.63), 250 sh (4.34), 254 (4.37), 260 (4.34), 290 (4.31) and 440 (4.05) nm; IR ν_{max} (KBr) 3380 br, 3320 br, 1670, 1630, 1585 and 1545 cm^{-1}; NMR ($CDCl_3$), δ 2.43 (3H, s, 7-CH_3), 3.96 and 4.02 (2x3H, 2s, 1,4-OCH_3), 6.83 (1H, s, 2-OH), 6.97 (1H, s, 3-H), 7.06 (1H, br s, 6-H), 7.52 (1H, br s, 8-H) and 13.00 (1H, s, 5-OH); mass spectrum: m/e 314 $[M]^+$. (Found: C, 65.01; H, 4.62. Calc. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49). When the foregoing reaction mixture was aromatized on silica gel, the following distribution of products was obtained: physcion (2%), 31 (41%), 32 (5%) and 33 (40%).

1,2,4,5-Tetramethoxy-7-methylanthraquinone.

The preceding crude reaction mixture as well as compounds 31 and 33 have been converted to the permethylated derivative [$(CH_3)_2SO_4$, K_2CO_3, $(CH_3)_2CO$], m.p. 186.5-187.0°C (toluene-petroleum ether, b.p. 90-120°C) (lit.[19] m.p. 185-186°C) and found to be identical to a previously prepared sample (NMR and TLC in four solvent systems).

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