Reactions of Ketene Acetals. 10.[1] Total Syntheses of the Anthraquinones Rubrocomatulin Pentamethyl Ether, 2-Acetylemodin, 2-Acetyl-5-hydroxyemodin Tetramethyl Ether, and Xanthorin

Jean-Louis Grandmaison and Paul Brassard*

Department of Chemistry, Laval University, Quebec, Canada G1K 7P4

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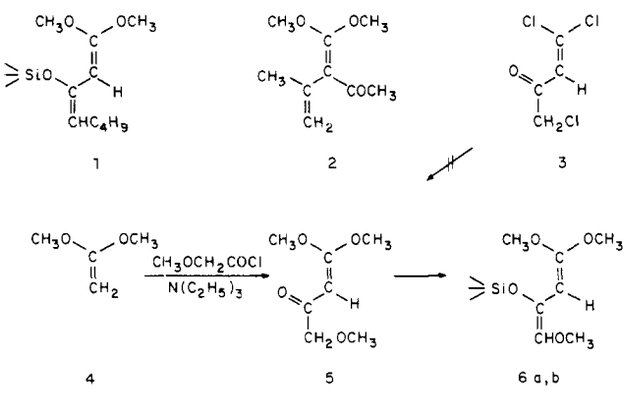
Some new or recently prepared conjugated ketene acetals such as 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene, 1,1-dimethoxy-3-trimethylsilyloxyocta-1,3-diene, and 2-acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene have been used in cycloaddition-type reactions for first or improved syntheses of the title compounds.

Conjugated ketene acetals[1-3] (1,1-dialkoxybutadienes) or the vinylogues of ketene acetals[4] have recently been used for the facile and regiospecific synthesis of a number of naturally occurring naphthoquinones and anthraquinones. These reagents have the advantage of being easy to prepare and quite reactive toward most quinonic substrates. Moreover they have been modified so as to introduce up to three groups with the desired orientation in a single annelating step. Some dienes previously obtained in this laboratory have now been applied to the synthesis of some highly substituted anthraquinones and a new reagent, 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene (**6a,b**), has been prepared in order to extend the scope and usefulness of the method (Scheme I).

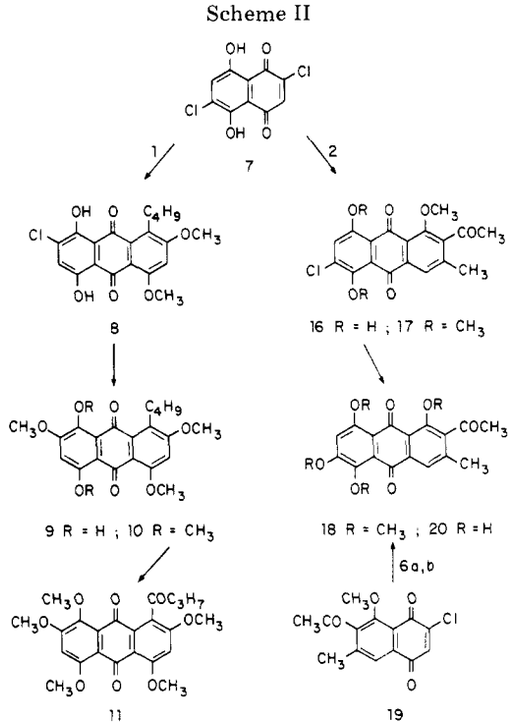
The synthesis of penta-*O*-methylrubrocomatulin (**11**), the tetramethyl ether of a crinoid pigment,[5] was attempted by first condensing 2,6-dichloronaphthazarin (**7**) with 1,1-dimethoxy-3-trimethylsilyloxyocta-1,3-diene[2] (**1**) (Scheme II). Pyrolysis of the adduct, hydrolysis of the silyl ether, and partial methylation gave a 56% yield of 1-butyl-7-chloro-5,8-dihydroxy-2,4-dimethoxyanthraquinone (**8**). Finally the remaining chlorine was substituted (76%) according to a recent procedure[6] using sodium methoxide and copper(I) iodide. Complete methylation of this trimethyl ether (**10**) under the usual conditions followed by photooxidation[2] as in the syntheses of rhodolamprometrin and rhodocomatulin provided rubrocomatulin pentamethyl ether, which was indistinguishable in all respects from a sample of the authentic material.

2-Acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene[1] (**2**), obtained earlier by us from pent-3-en-2-one and ketene dimethyl acetal for the preparation of stypandrone, has now been applied to the synthesis of two coccid pigments recently isolated by Banks and Cameron.[7] A first attempt at condensing the foregoing diene with 2-chloro-6,8-dimethoxynaphthoquinone[1] (**12**) in boiling benzene followed by pyrolysis at 135 °C produced no anthraquinonic material; however, bringing the components together in refluxing xylene gave a 50% yield of

Scheme I



Scheme II



the expected product 2-acetyl-1,6,8-trimethoxy-3-methylanthraquinone (**14**) (Scheme III).

It is now well established that 3-halojuglones are more reactive than the corresponding ethers toward ketene acetals and 1,1-dialkoxybutadienes and consistently produce higher yields. Consequently the 8-methyl ether of the chosen substrate (**12**) was cleaved by anhydrous aluminium chloride. The resultant juglone (**13**) reacted with the same diene (**2**) and gave a 78% yield of acetylemodin trimethyl ether (**14**) after methylation. This compound was then demethylated by a brief contact with a semisolid mixture of aluminium and sodium chlorides at 90 °C and yielded a substance which was indistinguishable from the natural product (**15**). A partial synthesis[8] of this compound had been carried out earlier starting from natural stypandrone.

The synthesis of another coccid pigment, 2-acetyl-5-hydroxyemodin (**20**), could at this point then be envisaged using the same diene and 2,6-dichloronaphthazarin (**7**) (Scheme II). The condensation of these two compounds proceeded smoothly and gave an 81% yield of 2-acetyl-6-chloro-5,8-dihydroxy-1-methoxy-3-methylanthraquinone (**16**). Substitution of the remaining chlorine by methoxide (followed by complete methylation) proved to be unexpectedly difficult, being accompanied by considerable decomposition. In an initial attempt the process was interrupted after 6 h; the product, after methylation, yielded mainly a derivative (**17**)

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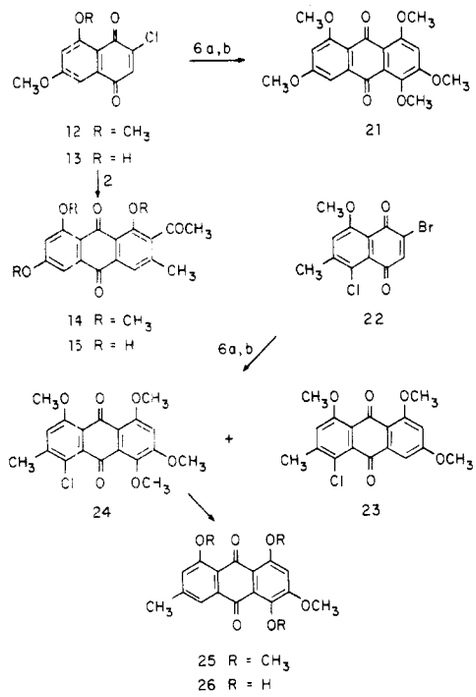
Scheme III



of the substrate (59%) and only 6% of the desired substance (**18**). By extending the reaction time to 12 h the substitution product could be increased to 13% while only 16% of the unreacted material could be recovered. Attempted demethylation of the tetramethyl ether as before gave a large number of products which were not isolated.

At this point a more satisfactory method of forming the 1,2,4-trihydroxylated ring was explored. In a first approach 1,4,4-trichlorobut-3-en-2-one (**3**) was obtained according to the procedure used for the 4,4-dichloro compound. It was expected that methoxydehalogenation involving all or, more selectively, the ethylenic chlorines could be realized; however, all attempts to carry out the substitutions yielded only intractable tars. On the other hand, the addition of ketene dimethyl acetal to methoxyketene (prepared in situ) using a method established[10,11] for other such substrates, gave only one product, 1,4,4-trimethoxybut-3-en-2-one (**5**), in a 39% yield which could be increased to 56% by using excess ketene acetal (3 equiv) (Scheme I). The enolsilylation of this substance according to Danishefsky and Kitahara[12] as adapted to acylketene acetals[2] gave a 71% yield of the desired diene, 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene as a mixture of the *E* and *Z* isomers (**6a,b**).

The usefulness of this new diene was first tested by reaction with 2-chloro-8-hydroxy-6-methoxynaphthoquinone (**13**) in refluxing benzene followed by pyrolysis and methylation in the usual manner (Scheme III). A 78% yield of 1,2,4,5,7-pentamethoxyanthraquinone (**21**) was obtained, which unfortunately could not be compared with a sample of the substance described earlier. However all physical and spectral characteristics of the two preparations are concordant including the fact that on crystallization from benzene and petroleum ether dimorphous yellow and brown crystals are formed.[13] A second experiment involved a condensation with 6-acetyl-3-chloro-5-methoxy-7-methylnaphthoquinone (**19**)[1] and, in this case, gave an excellent yield of 2-acetyl-5-hydroxyemodin tetramethyl ether (**18**) which up to this point had been difficult to prepare (vide supra). Finally a reaction with 2-bromo-5-chloro-8-methoxy-6-methylnaphthoquinone (**22**) yielded the expected 4-chloro-1,5,6,8-tetramethoxy-3-methylanthraquinone (**24**; 38%) along with 10% of an unexpected product, 4-chloroemodin trimethyl ether (**23**). The formation of this compound requires a reductive elimination of bromine and methoxyl and is analogous to a process known to occur in the presence of ethanol[14] at ~150 °C, a condition which exists during the pyrolytic stage. The chloroanthraquinone (**24**) could then be reduced with hydrazine and palladium[15] to the trimethyl ether of xanthorin (**25**; 29%).

Experimental Section

Melting points were taken for samples in capillary tubes with a Thomas-Hoover apparatus (calibrated thermometer). The IR and UV spectra were determined with Beckman IR-12 and DK-1A spectrophotometers, respectively. The NMR spectra were recorded with Hitachi-Perkin-Elmer R-24A and Bruker HX-90 spectrometers (tetramethysilane as internal standard). The mass spectra were obtained with a Varian M-66 spectrometer. Davison silica gel No. 923 was used for column chromatography, Baker-7G silica gel for preparative TLC, and Woelm silica gel, activity III, for dry column chromatography.

1,4,4-Trichlorobut-3-en-2-one (3). This substance was prepared according to the procedure described for the 4,4-dichloro compound[9] from chloroacetyl chloride (113 g, 1.00 mol), anhydrous aluminium chloride (133 g, 1.00 mol) and 1,1-dichloroethylene (97.0 g, 1.00 mol). Steam distillation and fractionation of the crude product gave the trichlorobutanone **3** (82.0 g, 47%): bp 52–53 °C (0.5 mm Hg); mp 45–48 °C; IR ν_{max} (carbon tetrachloride) 1730 (C=O) and 1600 (C=C) cm^{-1}; NMR δ (60 MHz, $CDCl_3$) 4.05 (2 H, s, 1-H_2) and 6.95 (1 H, s, 3-H). Anal. Calcd for $C_4H_3Cl_3O$: C, 27.70; H, 1.74; Cl, 61.33. Found: C, 27.77; H, 1.76; Cl, 60.99.

1,4,4-Trimethoxybut-3-en-2-one (5). To a mixture of ketene dimethyl acetal[16] (**4**; 16.5 g, 0.188 mol) and triethylamine (7.50 g, 0.0740 mol) in anhydrous ethyl ether (60 mL) was added (1.5 h) under nitrogen a solution of methoxyacetyl chloride (6.80 g, 0.0627 mol) in the same solvent (20 mL). The reaction mixture was stirred for 4 h at room temperature, filtered, and evaporated. Distillation of the residue gave the trimethoxybutenone **5** (5.6 g, 56%): bp 95–103 °C (0.3 mm Hg); mp 46–48 °C; IR ν_{max} (film) 1650 (C=O) and 1600 (C=C) cm^{-1}; NMR δ (60 MHz, $CDCl_3$) 3.48 (3 H, s, 1-OCH_3), 3.88 and 3.95 (6 H, 2s, 4,4-OCH_3), 4.14 (2 H, s, 1-H_2), and 4.93 (1 H, s, 3-H). Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.75; H, 7.28.

(*E*)- and (*Z*)-1,1,4-Trimethoxy-3-trimethylsilyloxybuta-1,3-diene (6a,b). To a solution of 1,4,4-trimethoxybut-3-en-2-one (**5**; 10.3 g, 0.0644 mol) and triethylamine (14.6 g, 0.145 mol) in anhydrous benzene (20 mL) was added (15 min) chlorotrimethylsilane (13.2 g, 0.122 mol). The temperature of the reaction mixture rose slightly and was kept at 40 °C for 3 h. After stirring for 24 h at room temperature, the suspension was filtered and evaporated. The residue upon distillation gave the dienes **6a,b** (10.6 g, 71%): bp 68–76 °C (0.3 mm Hg); IR ν_{max} (film) 1654, 1630 (C=C), and 835 (Si–C str) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 0.19, 0.27, and 0.29 (3s, 3-$OSi(CH_3)_3$), 3.36, 3.52, 3.57, and 3.64 (4s, 1,1,4-OCH_3), 3.78 and 3.91 (2s, 2-H), 4.48 and 5.79 (2s, 4-H). The mixture is very unstable but can be kept for 2 weeks at −20 °C.

1-Butyl-7-chloro-5,8-dihydroxy-2,4-dimethoxyanthraquinone (8). A mixture of 2,6-dichloronaphthazarin[17,18] (**7**; 100 mg, 0.380 mmol), 1,1-dimethoxy-3-trimethylsilyloxyocta-1,3-diene[2] (**1**; 140 mg, 0.390 mmol), and anhydrous benzene (5 mL) was refluxed for 2 h and evaporated to dryness. The residue was heated at 150 °C for 1 h and hydrolyzed by boiling for 30 min in a solution of methanol (5 mL) and 5% hydrochloric acid (3 mL). The crude product, extracted with chloroform was selectively methylated by refluxing for 15 h with dimethyl sulfate (235 mg) and anhydrous potassium carbonate (50 mg) (both added in several portions) in dry acetone (15 mL). Purification by chromatography on silica gel (dry column, chloroform) gave the expected anthraquinone **8** (84 mg, 56%): mp 200–201 °C (acetone); UV λ_{max} (ethanol) 238, 258, 287, 296 sh, 480, and 495 nm (log ϵ 4.58, 4.07, 4.10, 4.04, 4.08, and 4.07); IR ν_{max} (KBr) 1650 and 1625 (chelated C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 0.97 (3 H, ~t, $J \sim 6.0$ Hz, 4′-H), 1.31–1.64 (4 H, m, 2′,3′-H_2), 3.09 (2 H, ~t, $J \sim 6.5$ Hz, 1′-H_2), 3.97 and 4.03 (6 H, 2s, 2,4-OCH_3), 6.72 (1 H, br s, 3-H), 7.30 (1 H, s, 6-H), 13.28 and 13.39 (2 H, 2s, 5,8-OH); *m/e* 392/390 (M^+). Anal. Calcd for $C_{20}H_{19}ClO_6$: C, 61.46; H, 4.90; Cl, 9.08. Found: C, 61.73; H, 5.11; Cl, 9.01.

1-Butyl-2,4,5,7,8-pentamethoxyanthraquinone (10). A suspension of 1-butyl-7-chloro-5,8-dihydroxy-2,4-dimethoxyanthraquinone (**8**) (35 mg, 0.0854 mmol), sodium methoxide (1.00 g), copper(I) iodide (35 mg) in anhydrous methanol (5 mL), and dry dimethylformamide (5 mL) was refluxed for 24 h, poured into water, and acidified. Chromatography of the crude product (dry column,

chloroform) gave 1-butyl-5,8-dihydroxy-2,4,7-trimethoxyanthraquinone (**9**; 28 mg). The foregoing material (40 mg) was methylated in the usual way [dimethyl sulfate (200 mg), potassium carbonate (500 mg), and dry acetone (5 mL) for 3 h] and after purification by chromatography (dry column, chloroform) gave the pentamethoxyanthraquinone **10** (21 mg, 50%): mp 166–167 °C (petroleum ether, bp 90–120 °C); UV λ_{max} (ethanol) 227, 262, 288, and 400 nm (log ϵ 4.47, 4.18, 4.16, and 3.86); IR ν_{max} (KBr) 1670 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 0.94 (3 H, ~t, $J \sim 7.0$ Hz, 4'-H_3), 1.22–1.67 (4 H, m, 2',3'-H_2), 2.91 (2 H, ~t, $J \sim 7.0$ Hz, 1'-H_2), 3.90, 3.92, and 3.96 (2 × 3 H and 1 × 9 H, 3s, 2,4,5,7,8-OCH_3), 6.62 and 6.68 (2 H, 2s, 3,6-H); *m/e* 414 (M^+). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.31; H, 6.31.

1-Butanoyl-2,4,5,7,8-pentamethoxyanthraquinone (11). Oxygen was bubbled into a solution of 1-butyl-2,4,5,7,8-pentamethoxyanthraquinone (**10**; 17 mg, 0.041 mmol) in ethanol (5 mL) which was simultaneously heated under reflux and irradiated with two 375-W floodlamps (2 h). The residue obtained after evaporation of the solvent was chromatographed on silica gel (dry column, chloroform). The product was purified by preparative TLC (chloroform–methanol, 40:1) and gave the acylanthraquinone **11** (4 mg, 22%) (methanol), mp 150–152 °C and 210–211 °C (lit.[5] 152–153.5 °C and 214– 215 °C), identical (mmp, TLC in five solvent systems, and IR spectra) with an authenic sample.

2-Chloro-8-hydroxy-6-methoxynaphthoquinone (13). To a suspension of anhydrous aluminium chloride (1.50 g) in redistilled nitrobenzene (6 mL) was added 2-chloro-6,8-dimethoxynaphthoquinone[1] (**12**; 250 mg, 0.990 mmol). The mixture was stirred for 1 h at room temperature then poured into water containing concentrated hydrochloric acid (50 mL) and agitation is continued 15 h. Petroleum ether (bp 65–110 °C) (300 mL) is then added and the heterogenous mixture is filtered. The residue consisted of the expected juglone **13** (215 mg, 91%): mp 177–178 °C (petroleum ether, bp 90–120 °C, benzene); UV λ_{max} (ethanol) 220, 273, 283 sh, and 445 nm (log ϵ 4.59, 4.15, 4.03, and 3.81); IR ν_{max} (KBr) 1670 (C=O) and 1640 (chelated C=O) cm^{-1}; NMR (60 MHz, $CDCl_3$) 3.95 (3 H, s, 6-OCH_3), 6.71 (1 H, d, J = 2.5 Hz, 7-H), 7.19 (1 H, s, 3-H), 7.25 (1 H, d, J = 2.5 Hz, 5-H), and 11.95 (1 H, s, 8-OH); *m/e* 240/238 (M^+). Anal. Calcd for $C_{11}H_7ClO_4$: C, 55.36; H, 2.96; Cl, 14.86. Found: C, 55.59; H, 2.93; Cl, 15.00

2-Acetyl-1,6,8-trimethoxy-3-methylanthraquinone (14). (a) A mixture of 2-chloro-6,8-dimethoxynaphthoquinone (**12**; 100 mg, 0.397 mmol) and 2-acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene[1] (**2**; 220 mg, 1.38 mmol) in xylene (5 mL) was refluxed for 20 h. Purification by column chromatography (chloroform) followed by preparative TLC (benzene–ethyl acetate, 9:1) gave 2-acetylemodin trimethyl ether (**14**; 70 mg, 50%): mp 220–221 °C (methanol); UV λ_{max} (chloroform) 278, 400 nm (log ϵ 4.32, 3.73); IR ν_{max} (KBr) 1710 (hindered CH_3CO–) and 1665 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.34 (3 H, s, 3-CH_3), 2.54 (3 H, s, 2-$COCH_3$), 3.92, 3.96, and 3.98 (9 H, 3 s, 1,6,8-OCH_3), 6.76 (1 H, d, J = 2.5 Hz, 7-H), 7.31 (1 H, d, J = 2.5 Hz, 5-H), and 7.83 (1 H, s, 4-H); *m/e* 354 (M^+). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.92; H, 5.18.

(b) 2-Chloro-8-hydroxy-6-methoxynaphthoquinone (190 mg, 0.797 mmol) and the acetylbutadiene **2** (380 mg, 2.38 mmol) were refluxed in xylene (5 mL) for 8 h. The crude product was separated by chromatography (dry column, chloroform), methylated in the usual way [dimethyl sulfate (500 mg), potassium carbonate (500 mg), and acetone (10 mL) for 3 h], and rechromatographed (benzene–ethyl acetate, 9:1) giving the same anthraquinone **14** (220 mg, 78%).

2-Acetyl-1,6,8-trihydroxy-3-methylanthraquinone (2-Acetylemodin, 15). 2-Acetyl-1,6,8-trimethoxy-3-methylanthraquinone (**14**, 22 mg) was stirred in a mixture of anhydrous aluminium chloride (5.0 g) and sodium chloride (1.0 g) for 5 min at 90 °C. The cooled reaction mixture was hydrolyzed with ice (20 g) and concentrated hydrochloric acid (5 mL) then extracted with ethyl acetate. Purification of the crude product by preparative TLC (chloroform–methanol, 100:1) gave 2-acetylemodin (10 mg, 53%) indistinguishable from a sample of the authentic material (mmp, IR spectra, and TLC in five solvent systems).

2-Acetyl-6-chloro-5,8-dihydroxy-1-methoxy-3-methylanthraquinone (16). A mixture of 2,6-dichloronaphthazarin[17,18] (**7**; 120 mg, 0.463 mmol), 2-acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene (**2**; 220 mg, 1.38 mmol), and 2 mL of xylene was stirred at 115 °C for 4 h, cooled, and chromatographed (dry column, benzene) and gave the chloroanthraquinone **16** (135 mg, 81%): mp 186–188 °C (benzene–petroleum ether, bp 65–110 °C); UV λ_{max} (ethanol) 233, 257 and 475 nm (log ϵ 4.40, 4.39, and 3.96); IR ν_{max} (KBr) 1710 (CH_3CO) and 1640 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.41 (3 H, s, 3-CH_3), 2.58 (3 H, s, 2-$COCH_3$), 3.91 (3 H, s, 1-OCH_3), 7.42 (1 H, s, 7-H), 8.04 (1 H, s, 4-H), 13.03 and 13.28 (2 H, 2s, 5,8-OH); *m/e* 362/360 (M^+). Anal. Calcd for $C_{18}H_{13}ClO_6$: C, 59.93; H, 3.63; Cl, 9.83. Found: C, 59.84; H, 3.39; Cl, 9.52.

2-Acetyl-1,5,6,8-tetramethoxy-3-methylanthraquinone (18). (a) A suspension of 2-acetyl-6-chloro-5,8-dihydroxy-1-methoxy-3-methylanthraquinone (**16**; 100 mg, 0.278 mmol), sodium methoxide (2.35 g, 43.5 mmol), and copper(I) iodide (100 mg, 0.524 mmol) in methanol (10 mL) and dimethylformamide (10 mL) was refluxed for 12 h, poured into ice water, acidified, and extracted with chloroform. The crude product was methylated in the usual way [methyl sulfate (1.50 g in three portions), potassium carbonate (1.50 g), and acetone (20 mL) for 24 h] and by chromatography (dry column, chloroform) gave a mixture of two substances. These were separated on a second column (benzene). A first zone consisted of 2-acetyl-6-chloro-1,5,8-trimethoxy-3-methylanthraquinone (**17**; 16 mg, 15%): mp 198–199 °C (benzene–petroleum ether, bp 90–120 °C); IR ν_{max} (KBr) 1685 (CH_3CO–) and 1670 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.33 (3 H, br s, 3-CH_3), 2.52 (3 H, s, 2-$COCH_3$), 3.91 and 3.98 (3 H and 6 H, 2s, 1,5,8-OCH_3), 7.33 (1 H, s, 7-H), and 7.74 (1 H, br s, 4-H); *m/e* 390/388 (M^+). Anal. Calcd for $C_{20}H_{17}ClO_6$: C, 61.78; H, 4.41; Cl, 9.12. Found: C, 62.22; H, 4.50; Cl, 9.09. A more polar mixture of solvents (benzene–ethyl acetate, 9:1) eluted the desired anthraquinone **18** (14 mg, 13%): mp 154–155 °C (benzene–petroleum ether, bp 90–120 °C); UV λ_{max} (ethanol) 227, 252, 281, and 410 nm (log ϵ 4.41, 4.36, 4.21, and 3.83); IR ν_{max} (KBr) 1700 (CH_3CO–) and 1675 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.33 (3 H, br s, 3-CH_3), 2.53 (3 H, s, 2-$COCH_3$), 3.92, 3.94, and 3.99 (3 H, 3 H, and 6 H, 3s, 1,5,6,8-OCH_3), 6.82 (1 H, s, 7-H) and 7.76 (1 H, br s, 4-H); *m/e* 384 (M^+). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.78; H, 5.26.

(b) A mixture of 7-acetyl-2-chloro-8-methoxy-6-methylnaphthoquinone[1] (**19**; 170 mg, 0.610 mmol), 1,1,4-trimethoxy-3-trimethylsilyloxybuta-1,3-diene (**6a,b**; 375 mg, 1.62 mmol; added in three portions), and anhydrous benzene (5 mL) was refluxed for 3 h and evaporated to dryness. The residue was heated at 150 °C for 1 h, hydrolyzed by boiling in a solution of methanol (5 mL) and 5% hydrochloric acid (2.5 mL) for 15 min, extracted with chloroform, and methylated in the usual way. The crude product was purified by dry column chromatography (chloroform) and preparative TLC (chloroform) and gave the same anthraquinone **18** (202 mg, 86%). This product was identical (mmp, IR spectra, and TLC in five solvent systems) with the tetramethyl ether obtained in the usual way from a sample of authentic 2-acetyl-5-hydroxyemodin (**20**) (dimethyl sulfate and potassium carbonate in boiling acetone).

1,2,4,5,7-Pentamethoxyanthraquinone (21). By an analogous procedure (compound **18**, method b) using 2-chloro-8-hydroxy-6-methoxynaphthoquinone (**13**; 225 mg, 0.943 mmol) and 1,1,4-trimethoxy-3-trimethylsilyloxybutadiene (**6a,b**; 450 mg, 1.94 mmol) in benzene (5 mL), the pentamethoxyanthraquinone **21** was obtained after pyrolysis, hydrolysis, methylation, and dry column chromatography (benzene–ethyl acetate, 1:1) (273 mg, 78%): mp 189.5–190 °C (benzene–petroleum ether, bp 90–120 °C) (lit.[13] 193 °C); UV λ_{max} (ethanol) 225, 285, and 415 nm (log ϵ 4.59, 4.36, and 3.85); IR ν_{max} (KBr) 1670 and 1655 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 3.92, 3.96, 3.98, and 3.99 (3 H, 6 H, 3 H, 3 H, 4s, 1,2,4,5,7-OCH_3), 6.71 (1 H, d, J = 2.0 Hz, 6-H), 6.79 (1 H, s, 3-H), and 7.22 (1 H, d, J = 2.0 Hz, 8-H); *m/e* 358 (M^+). Anal. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C, 63.74; H, 5.27.

4-Chloro-1,5,6,8-tetramethoxy-3-methylanthraquinone (24). From a similar reaction mixture prepared with 2-bromo-5-chloro-8-methoxy-6-methylnaphthoquinone[19] (**22**; 490 mg, 1.55 mmol) and trimethoxytrimethylsilyloxybutadiene (**6a,b**; 800 mg, 3.44 mmol) in benzene (25 mL, 4 h) was obtained (after pyrolysis, hydrolysis, and methylation) by dry column chromatography (benzene–ethyl acetate, 9:1) a fast moving zone consisting of 4-chloro-1,6,8-trimethoxy-3-methylanthraquinone (**23**; 52 mg, 10%), mp 217–218.5 °C, which was identical in all respects with a sample obtained earlier.[19] Elution with a 1:1 mixture of benzene and ethyl acetate gave the trimethyl ether of chloroxanthorin (**24**; 221 mg, 38%): mp 209.5–210 °C (benzene–petroleum ether, bp 90–120 °C) (lit.[20] mp 210–211 °C); UV λ_{max} (ethanol) 226, 258, and 400 nm (log ϵ 4.52, 4.33, and 3.97); IR ν_{max} (KBr) 1680 and 1670 (C=O) cm^{-1}; NMR δ (90 MHz, $CDCl_3$) 2.47 (3 H, s, 3-CH_3), 3.94 and 3.97 (2 × 6 H, 2s, 1,5,6,8-OCH_3), 6.71 (1 H, s, 7-H), and 7.07 (1 H, s, 2-H); *m/e* 378 ($M^+ + 2$), 376 (M^+). Anal. Calcd for $C_{19}H_{17}ClO_6$: C, 60.56; H, 4.55; Cl, 9.41. Found: C, 60.99; H, 4.77; Cl, 9.40.

1,3,4,8-Tetramethoxy-6-methylanthraquinone (25). The reductive dehalogenation[15] of 4-chloro-1,5,6,8-tetramethoxy-3-methylanthraquinone (**24**) was carried out by refluxing a mixture of this quinone (76 mg, 0.202 mmol), 100% hydrazine hydrate (83.5 mg, 1.67 mmol; added in three portions of 10.0, 24.5, and 49.0 mg), 10% palladized charcoal (100 mg), and ethanol (13 mL) for 3 h. Chromatog-

raphy of the crude product (dry column, chloroform) gave the expected anthraquinone **25** (20 mg, 29%): mp 185–186 °C (toluene–petroleum ether, bp 90–120 °C) (lit.[21] 185–186 °C;[22] 189–190 °C); UV λ_{max} (chloroform) 280 and 406 nm (log ϵ 3.96 and 3.38); IR ν_{max} (KBr) 1665 (C=O) cm^{-1}; NMR δ (60 MHz, $CDCl_3$) 2.40 (3 H, s, 6-CH_3), 3.90 and 3.95 (3 H and 9 H, 2s, 1,3,4,8-OCH_3), 6.75 (1 H, s, 2-H), 7.00 (1 H, br s, 7-H), and 7.50 (1 H, br s, 5-H); *m/e* 342 (M^+). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.77; H, 5.35. Demethylation of this compound (17 mg) according to Tanaka and Kaneko[21] gave xanthorin (6 mg, 40%), mp 247–248 °C (acetic acid) (lit.[21] 244–246 °C; lit.[22] 253 °C; lit.[23] 250–251 °C) indistinguishable from a sample of the authentic material (mmp, IR spectra, and TLC in four solvent systems).

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Registry No.—**1**, 61539-63-7; **2**, 65120-61-8; **3**, 41501-60-4; **4**, 922-69-0; **5**, 65120-62-9; **6a**, 65120-63-0; **6b**, 65120-64-1; **7**, 13719-93-2; **8**, 65120-65-2; **9**, 65120-66-3; **10**, 65120-67-4; **11**, 65120-68-5; **12**, 57165-99-8; **13**, 65120-69-6; **14**, 65120-70-9; **15**, 32013-63-1; **16**, 65120-71-0; **17**, 65120-72-1; **18**, 65120-73-2; **19**, 65120-74-3; **20**, 32013-66-4; **21**, 1989-44-2; **22**, 52431-64-8; **23**, 52431-72-8; **24**, 37567-67-2; chloroacetyl chloride, 79-04-9; 1,1-dichloroethylene, 75-35-4; methoxyacetyl chloride, 38870-89-2; chlorotrimethylsilane, 75-77-4; xanthorin, 17526-15-7.

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Biosynthesis of α-Naphthocyclinone[1]

Karsten Schröder and Heinz G. Floss*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

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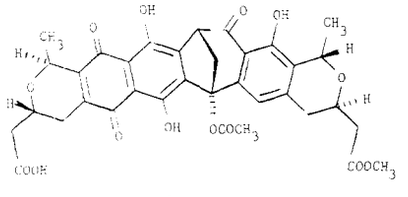
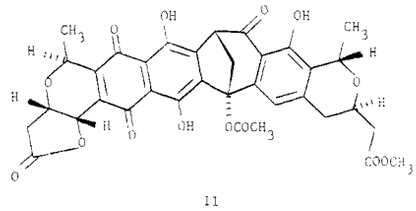
The biosynthesis of α-naphthocyclinone in *Streptomyces arenae* was studied by feeding experiments with sodium [1-^{13}C]- and [2-^{13}C]acetate and diethyl [2-^{13}C]malonate followed by ^{13}C NMR analysis. The compound is derived entirely from acetate/malonate units by the polyketide pathway, and the labeling pattern is consistent with its formation from two benzoisochroman quinone units. Surprisingly, [2-^{13}C]malonate labels both the starter and the chain extension units, but not the acetoxy group. Possible explanations of the latter finding are suggested.

The naphthocyclinones are a series of closely related pigments which were isolated from cultures of *Streptomyces arenae*, strain Tü 495.[2] Some of the compounds, β- and γ-naphthocyclinone (I and II, Scheme I), exhibit antibacterial activity against gram-positive organisms. Their structure elucidation by Zeeck's group showed[2,3] that the naphthocy-

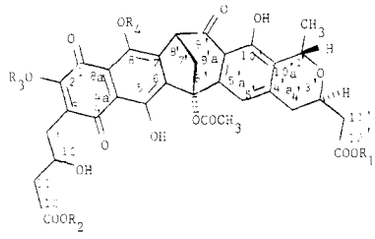
Scheme I. Structures of Naphthocyclinones



I



II



III: R_1=CH_3, R_2=R_3=R_4=H, α-naphthocyclinone
IV: R_1=R_2=R_3=R_4=H, α-naphthocyclinone acid
V: R_1=R_2=R_3=CH_3, R_4=H
VI: R_1=R_2=R_3=R_4=CH_3

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