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Reactions of Keten Acetals. Part I. A Simple Synthesis of Some Naturally Occurring Anthraquinones[1]

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A study of the condensation of keten acetals with some halonaphthoquinones has led to the simple and regiospecific synthesis of some naturally occurring anthraquinones: catenarin, helminthosporin, emodin, and chrysophanol. The results show unambiguously that a previously proposed mechanism is erroneous. The reaction of these acetals with chloromaleic anhydride also provided a one-step preparation of some substituted phthalic anhydrides.

L'étude de la condensation d'acétals de cétènes avec des halogénonaphtoquinones a permis la synthèse facile et régiospécifique de quelques anthraquinones naturelles: la caténarine, l'helminthosporine, l'émodine et le chrysophanol. Les résultats obtenus démontrent que le mécanisme déjà proposé pour cette réaction est erronée. La réaction de ces acétals avec l'anhydride chloromaléique donne en une seule étape des anhydrides phtaliques substitués.

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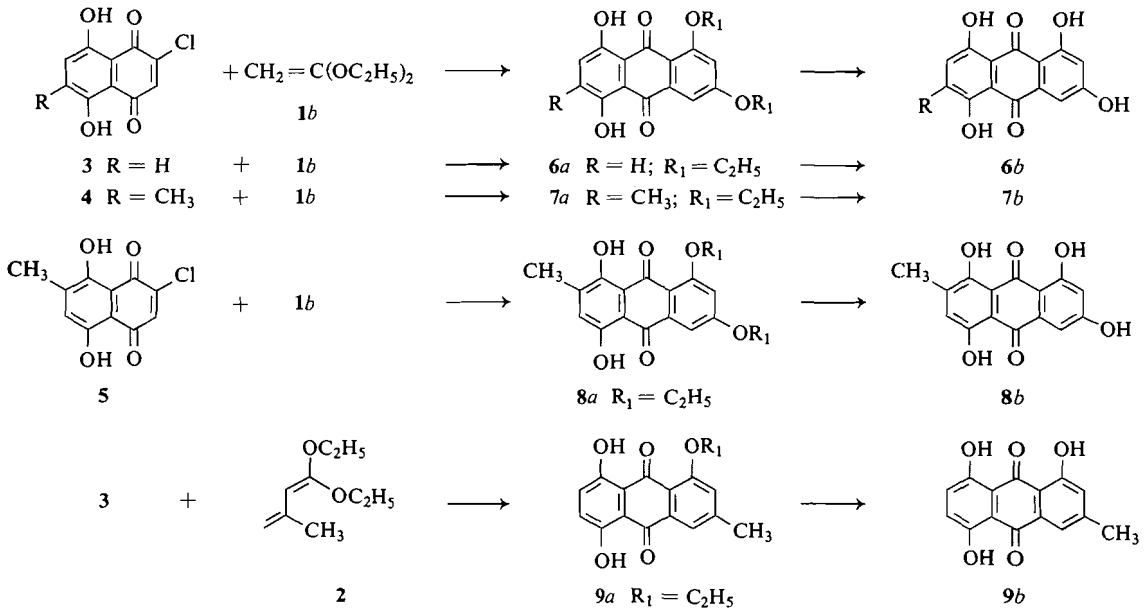
Although keten acetals are very reactive and readily accessible (1, 2), their use in the synthesis of naturally occurring compounds has been considered only rarely. McElvain *et al.* (3–5) have studied the reactions of keten diethyl acetal (**1***b*) with enedione systems and have shown in particular that *p*-benzoquinone, halo-*p*-benzoquinones, and 1,4-naphthoquinone yield 2-ethoxy furans. However under essentially similar conditions 2-bromonaphthoquinone gives a 21% yield of 1,3-diethoxyanthraquinone (xanthopurpurin diethyl ether). Moreover they have proposed mechanisms whereby complex series of processes are initiated by the attack of **1***b*, in the first three cases, on an unsubstituted carbon atom and, in the last instance, on the halogen-bearing one.

The existence of two very different reaction paths and, apparently, modes of attack has led us to examine the factors which determine the course of the reaction and the eventual regiospecificity of the process as applied to the synthesis of anthraquinones. This seemed to be particularly promising since the required isomeric naphthazarins and juglones were known. For ease in identifying the reaction products in mixtures that are often complex, keten dimethyl acetal was used in work of a more exploratory nature, whereas the more readily accessible diethyl acetal was chosen for some of the purely synthetic part. No other particular advantage was found for either of these reagents.

Reactions of Keten Acetals with Halonaphthazarins

It was first established that the presence of the two hydroxyl groups in chloronaphthazarin (**3**) did not prevent or affect a reaction similar to that described for bromonaphthoquinone. Moreover since both 6- and 7-chloro-2-methylnaphthazarin had been identified previously (6), these compounds could readily serve in assessing the proposed dual mode of attack and in providing a very simple synthesis of catenarin (**7***b*). According to McElvain's mechanism, 7-chloro-2-methylnaphthazarin (**5**) should have provided the diethyl ether **7***a*. However the properties of the compound obtained from it, after deethylation, were quite different from those ascribed to catenarin and were correlated to the isomeric substance **8***b*. When carried out with 6-chloro-2-methylnaphthazarin (**4**), the reaction effectively led to the formation of catenarin. In each case, only one quinonic product was obtained as ascertained by t.l.c. and n.m.r. thus clearly establishing that the proposed mechanism is wrong, that only one mode of attack occurs and that the reaction is completely regiospecific. These results were also extended by the reaction of **3** with isopropenylketen diethyl acetal (**2**) which produced **9***a* and thence helminthosporin (**9***b*). In this case the reaction is more efficient

[1]During the preparation of this paper, one of the authors (G.L.) obtained unauthorized patents covering part of the material described here in detail (Fr. 2,112,941; Ger. Offen. 2,144,771–2,144,774).



SCHEME I

and produces a much higher yield than with the unconjugated acetals (Scheme 1).

Reactions of Keten Acetals with Bromojuglones

For a more detailed study of the reaction, 2- and 3-bromojuglones were chosen since numerous synthetic applications could be envisaged. Upon adding 3-bromojuglone (**14**) to the theoretical amount (5 equiv.)[2] of keten dimethyl acetal (**1***a*) in the absence of solvent a vigorous reaction ensues and a 60% yield of 1,3-dimethoxy-8-hydroxyanthraquinone (**19***a*) is produced and could be converted into the known 1,3,8-trimethoxyanthraquinone. Under similar conditions 2-bromojuglone (**18**) reacts slowly even at 100° and gives 1,3-dimethoxy-5-hydroxyanthraquinone (53%) and, after methylation, the known 1,3,5-trimethoxyanthraquinone. In both cases t.l.c. revealed no trace of the other isomer. These reactions, therefore, establish that the process is also completely regiospecific in the case of juglones and, though electronic effects modify sharply the reactivity, they do not alter the product-determining step.

The only convenient starting material available for the synthesis of the important natural product emodin (**22***b*) by this method is 8-chloro-7-methyljuglone (**13**). By successive bromination and dehydrobromination of three 8-chlorojuglones the corresponding 3-bromo derivatives were obtained in high yields. The structures were assumed to be those predicted on the basis of the work of Thomson (7) on juglone itself (**10**) and were established unambiguously but indirectly by the substitution patterns in the anthraquinones obtained from them (Scheme 2). By varying the ratios of the reactants, the solvents, the reaction times, and by adding a catalyst ($Hg(OAc)_2$) (8) known to be effective in a reaction of enol ethers, no marked effects were observed. The results are summarized in Table 1. These experiments did establish that an excess of keten acetals should be avoided, that the best results are obtained in the absence of solvent and that free *peri*-hydroxyl groups favor the reaction (Scheme 3). Under these conditions no starting material or other quinonic by-product is isolated or detected. However when only 2 equiv. of **1***a* are used, a small amount (8%) of another substance is formed which probably is methyl (3-bromo-8-chloro-5-hydroxy-7-methylnaphthoquinonyl-2)-acetate. During chromatography (silica gel) the bromine is lost in part and the product could not be adequately purified. The reaction of 3-bromo-8-chlorojuglone (**15**) with isopropenylketen diethyl acetal was also found

[2]During the condensation hydrogen bromide and methanol are eliminated, which react further with the keten acetal.

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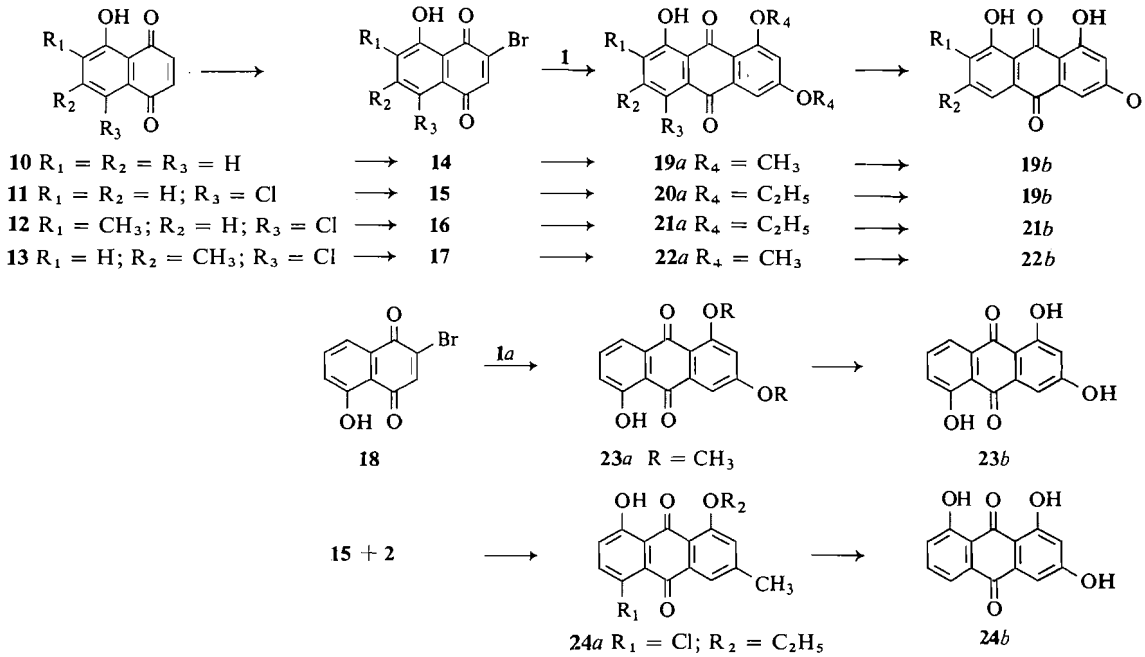

SCHEME 2

TABLE 1. Condensation of 3-bromo-8-chloro-7-methyljuglone (**17**) (600 mg) with keten dimethyl acetal (**1***a*)

Equivalents of acetal	Solvent	Conditions	Yield of **22***a* (%)
2	C_6H_6 (10 ml)	Refluxed 10 min	13
5	C_6H_6 (10 ml)	Refluxed 10 min	25
7	C_6H_6 (10 ml)	Refluxed 10 min	12
3	C_6H_6 (10 ml)	Refluxed 12 h	22
5	C_6H_6 (10 ml)	Refluxed 12 h	30
8	C_6H_6 (10 ml)	Refluxed 12 h	23
5	C_6H_6 (10 ml)	$Hg(OAc)_2$ (32 mg) Refluxed 12 h	19
5	DME (10 ml)	Refluxed 12 h	26
5	C_6H_6 (200 ml)	Refluxed 12 h	19
5	None	100 °C 1 h	57

to be particularly efficient giving a good yield of the corresponding chloroanthraquinone (**24***a*). However a reaction carried out with a chloroketen acetal in the hope of obtaining conveniently substituted chloroanthraquinones was disappointing as the reagent was found to be insufficiently reactive.

The conversion of the chlorinated anthraquinone ethers (**20***a*–**22***a*, **24***a*) to the polyhydroxyanthraquinones (**19***b*, **21***b*, **22***b*, **24***b*) can be carried out efficiently by known methods either (*A*) by reduction with sodium hydrosulfite (9, 10) followed by demethylation with aluminium chloride at 180° (11) or (*B*) by treatment with hydriodic acid and red phosphorus followed by reoxidation with chromic acid (12).

Reactions of Keten Acetals with Chloromaleic Anhydride

Keten dimethyl and diethyl acetals (**1***a*, *b*) as well as isopropenylketen diethyl acetal (**2**) have been found to react vigorously with chloromaleic anhydride and to give directly in moderate yields 3,5-dimethoxy- 3,5-diethoxy- and 3-eth-

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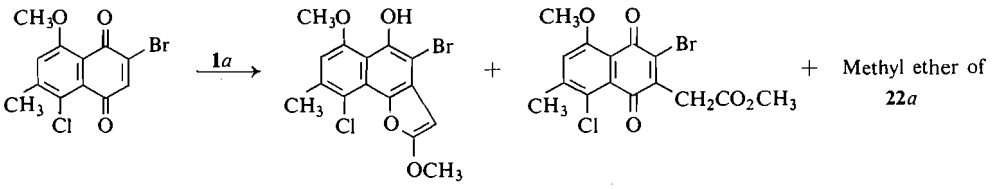
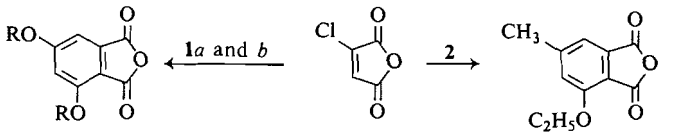


25 26

SCHEME 3



27a R = CH_3
27b R = C_2H_5

28

SCHEME 4

oxy-5-methylphthalic anhydrides. These reactions, therefore, provide very convenient syntheses of these important intermediates (Scheme 4).

Conclusion

In conclusion, this paper illustrates a few very practical syntheses of anthraquinones and numerous other applications of the procedure can be envisaged with minor modifications of the method. The original mechanism proposed by McElvain has been found to be erroneous but no other can be proposed with certainty at present. The intermediate formation of a zwitterion followed by a 1,4-dipolar addition of keten acetal and a triple elimination seems to represent the most plausible series of processes; however, a mechanism involving an oxidative step, as suggested by the reaction with a juglone ether cannot be discounted.

Since all benzoquinones and some naphthoquinones invariably yield 2-alkoxy furans numerous attempts have been made to decrease the ease with which this course is taken. Condensations involving various dibenzoquinones, dihalobenzoquinones (with or without the addition of Lewis acids), and halogenated benzoquinone imines, imides, and chloroimides have not given encouraging results.

Experimental

Reactions of Keten and Isopropenylketen Diethyl Acetal with Chloronaphthazarins

General Procedure a

To a solution of 1.0 g of the chloronaphthazarin (3–5) in 10 ml of anhydrous benzene are added 5 equiv. of keten diethyl acetal (**1***b*) (2). The solution which darkens immediately is allowed to stand for 1 h and then refluxed for 1 h. The crystals that separate on cooling are washed with petroleum ether (b.p. 30–60°) and recrystallized from the appropriate solvent.

1,3-Diethoxy-5,8-dihydroxyanthraquinone (**6***a*) is obtained from chloronaphthazarin (**3**) (13), m.p. 203–204° (toluene) (23%); λ_{max} (EtOH) 230, 277.5, 296, 470, 490 nm (log ε 4.59, 4.32, 4.03, 4.07, 4.04); ν_{max} (KBr) 1610 (sh), 1598 cm^{-1}; δ (90 MHz) ($CDCl_3$) 1.47 t (J = 7.0 Hz) (3-OCH_2CH_3), 1.57 t (J = 7.0 Hz) (1-OCH_2CH_3), 4.20 q (J = 7.0 Hz) (1,3-OCH_2—), 6.72 d (J = 2.5 Hz) (2-CH), 7.19 s (6,7-CH), 7.42 d (J = 2.5 Hz) (4-CH), 12.75 s and 13.44 s (5,8-OH).

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.46; H, 4.90.

6,8-Diethoxy-1,4-dihydroxy-3-methylanthraquinone (**7***a*) is prepared from 6-chloro-2-methylnaphthazarin (**4**) (6), m.p. 174–175° (benzene) (34%); λ_{max} (EtOH) 231.5, 277, 300 (sh), 480 nm (log ε 4.60, 4.31, 4.04, 4.12); ν_{max} (KBr) 1615 (sh), 1595 (sh), 1580 cm^{-1}; δ (90 MHz) ($CDCl_3$) 1.47 t (J = 7.0 Hz) (6-OCH_2CH_3), 1.57 t (J = 7.0 Hz) (8-OCH_2CH_3), 2.33 s (3-CH_3), 4.22 q (J = 7.0 Hz) (6,8-OCH_2—), 6.72 d (J = 2.2 Hz) (7-CH), 7.04 s (2-CH), 7.42 d (J = 2.2 Hz) (5-CH), 12.83 s and 13.88 s (1,4-OH).

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.29. Found: C, 66.23; H, 5.33.

6,8-Diethoxy-1,4-dihydroxy-2-methylanthraquinone (**8***a*) is obtained from 7-chloro-2-methylnaphthazarin (**5**) (6), m.p. 186–187° (toluene) (47%); λ_{max} (EtOH) 231.5, 275, 301 (sh), 480 nm (log ε 4.56, 4.28, 4.01, 4.06); ν_{max} (KBr) 1618, 1590, 1575 cm^{-1}; δ (90 MHz) ($CDCl_3$) 1.47 t (J = 7.0 Hz) (6-OCH_2 CH_3), 1.56 t (J = 7.0 Hz) (8-OCH_2CH_3), 2.30 s (2-CH_3), 4.18 q (J = 7.0 Hz) (6,8-OCH_2—), 6.68 d (J = 2.5 Hz) (7-CH), 7.08 s (3-CH), 7.39 d (J = 2.5 Hz) (5-CH), 13.16 s and 13.48 s (1,4-OH).

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.29. Found: C, 66.92; H, 5.25.

1-Ethoxy-5,8-dihydroxy-3-methylanthraquinone (*9a*): Equimolar quantities of chloronaphthazarin (1 g) and isopropenylketen diethyl acetal (**2**) (14) are dissolved in anhydrous benzene (10 ml). The reaction mixture is then refluxed for 1 h, cooled, and diluted with a small amount

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of petroleum ether. The precipitated solid is recrystallized from petroleum ether, m.p. 186–187° (72%); λ_{max} (EtOH) 230, 255, 287 (sh), 475 nm (log ε 4.59, 4.12, 3.86, 3.98); ν_{max} (KBr) 1622, 1596 cm^{-1}; δ (90 MHz) ($CDCl_3$) 1.58 t (J = 7.0 Hz) (1-OCH_2CH_3), 2.47 s (3-CH_3), 4.34 q (J = 7.0 Hz), 7.07 bs (2-CH), 7.73 bs (4-CH), 7.21 s (6,7-CH), 12.82 s and 13.32 s (5,8-OH).

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.51; H, 4.62.

Polyhydroxyanthraquinones (from Naphthazarins)

The diethoxy or ethoxy methyl dihydroxyanthraquinone (**7***a*–**9***a*) (500 mg) is added to a solution of 5 g of anhydrous $AlCl_3$ in 20 ml of nitrobenzene. The mixture is stirred for 24 h at 80° and then poured into 500 ml of ice and water. The nitrobenzene is extracted with petroleum ether and the aqueous solution heated to 80°. Upon cooling, crystals of the deethylated compound are recovered and crystallized from the appropriate solvent.

1,4,6,8-Tetrahydroxy-3-methylanthraquinone (catenarin) (**7***b*) from **7***a*, m.p. 244–246° (EtOH) (90%) (lit. (15) m.p. 246°); λ_{max} (EtOH) 231, 255.5, 279, 302, 475, 490, 505 (sh), 515 (sh) nm (log ε 4.46, 4.17, 4.19, 3.99, 4.07, 4.11, 4.02, 3.95); ν_{max} (KBr) 3300, 1610 (sh), 1598 cm^{-1}; δ (90 MHz) ($(CD_3)_2SO$) 2.09 s (3-CH_3), 6.40 d (J = 2.5 Hz) (7-CH), 6.87 d (J = 2.5 Hz) (5-CH), 6.94 s (2-CH), 11.90 s and 12.90 s (1,4,8-OH).

Tetraacetate, m.p. 235° (lit. (15) m.p. 234–235°).

1,4,6,8-Tetrahydroxy-2-methylanthraquinone (**8***b*) from **8***a*, m.p. 273–274° (EtOH) (90%); λ_{max} 231.5, 252.5, 280.5, 300, 485, 505, 515 nm (log ε 4.51, 4.20, 4.26, 4.05, 4.18, 4.08, 4.02); ν_{max} (KBr) 3338, 1602, 1590 (sh) cm^{-1}; δ (90 MHz) ($(CD_3)_2SO$) 2.14 (2-CH_3), 6.45 d (J = 2.0 Hz) (7-CH), 6.95 d (J = 2.0 Hz) (5-CH), 6.98 s (3-CH), 11.89 s, 12.28 s and 12.50 s (1,4,8-OH).

Anal. Calcd. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52. Found: C, 63.13; H, 3.43.

Tetraacetate, m.p. 221°.

1,5,8-Trihydroxy-3-methylanthraquinone (helminthosporin) (**9***b*) from **9***a*, m.p. 226–227° (pyridine) (almost quantitative) (lit. (16) m.p. 226–227°); λ_{max} (EtOH) 231, 255, 289, 480 (sh), 490, 510 (sh), 520 (sh) nm (log ε 4.67, 4.30, 3.95, 4.11, 4.13, 4.01, 3.91); ν_{max} (KBr) 1598 cm^{-1}; δ (90 MHz) ($CDCl_3$) 2.47 s (3-CH_3), 7.10 bs (2-CH), 7.69 bs (4-CH), 7.28 s (6,7-CH), 12.08 s, 12.27 s and 12.97 s (1,5,8-OH).

Triacetate, m.p. 223° (lit. (16) m.p. 224°).

8-Chlorojuglones

These compounds were prepared according to Cooke *et al.* (17, 18).

8-Chlorojuglone (**11**), m.p. 197–198° (lit. (17) m.p. 201°); λ_{max} (EtOH) 211.5, 254, 430 nm (log ε 4.51, 4.14, 3.66); ν_{max} (KBr) 1665, 1645, 1600 cm^{-1}; δ (60 MHz) ($CDCl_3$) 7.01 s (2,3-CH), 7.50 dd (J = 9.5 Hz; Δν = 24.2 Hz) (6,7-CH), 12.65 s (5-OH).

8-Chloro-6-methyljuglone (**12**) was prepared from 20.0 g of 5-chloro-2-methoxytoluene, 24.0 g of maleic anhydride, 226 g of anhydrous $AlCl_3$ and 50 g of NaCl by heating at 200° for 2 min. The crude material obtained after hydrolysis was extracted (Soxhlet) with petroleum ether (b.p. 30–60°) and chromatographed on silica gel (benzene), m.p. 160.5–161.0° (petroleum ether) (24%); λ_{max} (EtOH) 217, 258, 338, 430 nm (log ε 4.35, 3.93, 4.14, 3.43); ν_{max} (KBr) 1670, 1645, 1597 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.35 s (6-CH_3), 6.95 s (2,3-CH), 7.53 s (7-CH), 13.10 s (5-OH).

Anal. Calcd. for $C_{11}H_7ClO_3$: C, 59.64; H, 3.17. Found: C, 59.59; H, 3.09.

8-Chloro-7-methyljuglone (**13**), m.p. 158–159° (lit. (18) m.p. 159–161°); λ_{max} (EtOH) 217, 256, 340, 425 nm (log ε 4.54, 4.12, 3.11, 3.69); ν_{max} (KBr) 1670, 1655, 1615 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.52 s (7-CH_3), 6.99 s (2,3-CH), 7.25 s (6-CH), 12.60 s (5-OH).

3-Bromo-8-chlorojuglones

These quinones are prepared by the methods of Wheeler and Scott (19) and Thomson (7). A suspension of the chlorojuglone (**11**–**13**) (1 to 3 g) and a five-fold excess of Br_2 in CCl_4 (4 to 12 ml) is stirred for 5 h at room temperature and evaporated to dryness under vacuum. The residue dissolved in absolute ethanol (12 to 36 ml) is refluxed for 3 min and a nearly quantitative yield of the 3-bromo-8-chlorojuglone (**16**–**18**) is obtained on cooling.

3-Bromo-8-chlorojuglone (**15**) is obtained from **11**, m.p. 202–203° (dichloroethane); λ_{max} (EtOH) 216, 260, 285, 435 nm (log ε 4.41, 3.86 3.92, 3.62); ν_{max} (KBr) 1655, 1635, 1595 cm^{-1}; δ (90 MHz) ($(CD_3)_2CO$) 7.59 s (2-CH), 7.59 dd (J = 9.5 Hz; Δν = 19.3 Hz) (6,7-CH), 12.30 s (5-OH).

Anal. Calcd. for $C_{10}H_4BrClO_3$: C, 41.77; H, 1.39. Found: C, 41.91; H, 1.40.

3-Bromo-8-chloro-6-methyljuglone (**16**) from **12**, m.p. 144–145° (CCl_4); λ_{max} (EtOH) 221, 265 (sh), 290, 440 nm (log ε 4.43, 3.83, 3.91, 3.62); ν_{max} (KBr) 1650, 1635, 1600 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.35 s (6-CH_3), 7.46 s (2-CH), 7.52 s (7-CH), 12.65 s (5-OH).

Anal. Calcd. for $C_{11}H_6BrClO_3$: C, 43.82; H, 2.01. Found: C, 44.03; H, 1.91.

3-Bromo-8-chloro-7-methyljuglone (**17**) from **13**, m.p. 187.5–188.0° (EtOH); λ_{max} (EtOH) 221, 259, 289, 435 nm (log ε 4.31, 3.67, 3.79, 3.60); ν_{max} (KBr) 1666, 1640, 1600 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.52 s (7-CH_3), 7.28 s (2-CH), 7.51 s (6-CH), 12.40 s (5-OH).

Anal. Calcd. for $C_{11}H_6BrClO_3$: C, 43.82; H, 2.01. Found: C, 43.58; H, 2.10.

3-Bromo-8-chloro-5-methoxy-7-methylnaphthoquinone (methyl ether of **17**): The juglone **17** (1.0 g) is dissolved in 20 ml of $CHCl_3$, two portions of iodomethane (1.0 ml) and Ag_2O (0.6 g) are added at 6 h intervals and the mixture stirred at room temperature for 14 h. The methyl ether is obtained in almost quantitative yield, m.p. 205–206° (dichloroethane); λ_{max} (EtOH) 219, 258, 280 (sh), 415 nm (log ε 4.53, 4.10, 4.04, 3.62); ν_{max} (KBr) 1665, 1662, 1583 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.54 s (7-CH_3), 4.02 s (5-OCH_3), 7.28 s (6-CH), 7.43 s (2-CH).

Anal. Calcd. for $C_{12}H_8BrClO_3$: C, 45.67; H, 2.55. Found: C, 45.79; H, 2.45.

Reactions of Keten and Isopropenylketen Acetals with Bromojuglones

General Procedure b

Keten dimethyl acetal (**1***a*) (20)[3] (1.04 g; 0.0118 mol) is added all at once to the bromojuglone (0.00238 mol). A vigorous reaction ensues and the mixture is kept at 100° for 1 h. The volatile by-products are then evaporated under vacuum and the residue chromatographed on 100 g

[3]In this procedure, ref. 20, benzene is advantageously replaced by xylene.

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of silica gel. A mixture of benzene and ether (19:1) elutes the 8-hydroxy-1,3-dimethoxyanthraquinone.

8-Hydroxy-1,3-dimethoxyanthraquinone (**19***a*) was obtained from **14** (7), m.p. 217.5–218° (EtOH and sublimed) (61%); λ_{max} (EtOH) 222, 242, 270 (sh), 279, 420 nm (log ε 4.54, 4.14, 4.30, 4.33, 4.02); ν_{max} (KBr) 1666, 1625, 1596 cm^{-1}; δ (60 MHz) ($CDCl_3$) 4.03 s (3-OCH_3), 4.08 s (1-OCH_3), 6.87 d (J = 2.5 Hz) (2-CH), 7.45 d (J = 2.5 Hz) (4-CH), 7.5–8.0 m (5,6,7-CH), 13.30 s (8-OH).

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.80; H, 4.35.

1,3,8-Trimethoxyanthraquinone was prepared by refluxing for 3 h a mixture of **19***a* (0.21 g), dimethyl sulfate (1.8 g), anhydrous K_2CO_3 (2.0 g) and acetone (20 ml), m.p. 194.5–195.0° (EtOH) (85%) (lit. (21) m.p. 195–196°); λ_{max} (EtOH) 219, 275, 395 nm (log ε 4.51, 4.38, 3.89); ν_{max} (KBr) 1660, 1603 cm^{-1}; δ (60 MHz) ($CDCl_3$) 3.99 s, 4.01 s and 4.03 s (1,3,8-OCH_3), 6.84 d (J = 2.5 Hz) (2-CH), 7.3–8.0 m (4,5,6,7-CH).

5-Hydroxy-1,3-dimethoxyanthraquinone (**23***a*) from **18** (22), m.p. 199–199.5° (EtOH and sublimed) (53%); λ_{max} (EtOH) 228, 248, 278, 404 nm (log ε 4.49, 4.12, 4.31, 3.99); ν_{max} (KBr) 1665, 1645, 1605 cm^{-1}; δ (60 MHz) ($CDCl_3$) 4.01 s (3-OCH_3), 4.04 s (1-OCH_3), 6.85 d (J = 2.5 Hz) (2-CH), 7.52 d (J = 2.5 Hz) (4-CH), 7.2–7.9 m (5,7,8-CH), 12.40 s (5-OH).

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.85; H, 4.05.

1,3,5-Trimethoxyanthraquinone was prepared from **23***a* as above for the 1,3,8-isomer, m.p. 201.5–202° (EtOH) (85%) (lit. (23) m.p. 203°); λ_{max} (EtOH) 226, 276, 283 nm (log ε 4.51, 4.39, 4.01); ν_{max} (KBr) 1660, 1605 cm^{-1}; δ (60 MHz) ($CDCl_3$) 3.98 s, 4.02 s and 4.06 s (1,3,5-OCH_3), 6.80 d (J = 2.5 Hz) (2-CH), 7.48 d (J = 2.5 Hz) (4-CH), 7.2–8.0 m (6,7,8-CH).

4-Chloro-1-hydroxy-6,8-dimethoxy-3-methylanthraquinone (**22***a*) from **17**, m.p. 213–213.5° (EtOH and sublimed) (57%); λ_{max} (EtOH) 227, 271, 282 (sh), 430 nm (log ε 4.57, 4.31, 4.27, 4.02); ν_{max} (KBr) 1677, 1625, 1592 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.45 s (3-CH_3), 3.97 s (6-OCH_3), 4.00 s (8-OCH_3), 6.75 d (J = 2.5 Hz) (7-CH), 7.20 s (2-CH), 7.43 d (J = 2.5 Hz) (5-CH), 13.60 s (1-OH).

Anal. Calcd. for $C_{17}H_{13}ClO_5$: C, 61.36; H, 3.93; Found: C, 61.31; H, 3.86.

General Procedure a (see first Section)

This method gave products analogous to the foregoing.

5-Chloro-1,3-diethoxy-8-hydroxyanthraquinone (**20***a*) from **15** and **1***b*, m.p. 182–182° (benzene – petroleum ether) (33%); λ_{max} (EtOH) 223, 229 (sh), 271, 422, 430, 437 nm (log ε 4.46, 4.43, 4.27, 4.00, 4.00, 4.00); ν_{max} (KBr) 1670, 1631, 1626, 1598 cm^{-1}; δ (90 MHz) ($CDCl_3$) 1.46 t (J = 7.0 Hz) (3-OCH_2CH_3), 1.59 t (J = 7.0 Hz) (1-OCH_2CH_3), 4.19 q (J = 7.0 Hz) (1,3-OCH_2—), 6.72 d (J = 2.5 Hz) (2-CH), 7.33 d (J = 2.5 Hz) (4-CH), 7.34 dd (J = 8.5 Hz; Δν = 32.9 Hz) (7,6-CH), 13.74 s (8-OH).

Anal. Calcd. for $C_{18}H_{15}ClO_5$: C, 62.34; H, 4.35. Found: C, 62.72; H, 4.26.

4-Chloro-6,8-diethoxy-1-hydroxy-2-methylanthraquinone (**21***a*) from **16**, m.p. 160–161° (petroleum ether) (40%); ν_{max} (KBr) 1671, 1630, 1600 cm^{-1}; δ (60 MHz) ($CDCl_3$) 1.49 t (J = 7.5 Hz) (6-OCH_2CH_3), 1.56 t (J = 7.5 Hz) (8-OCH_2CH_3), 2.34 s (2-CH_3), 4.23 q (J = 7.5 Hz) (6,8-OCH_2—), 6.69 d (J = 2.5 Hz) (7-CH), 7.38 d (J = 2.5 Hz) (5-CH), 7.44 s (3-CH).

Anal. Calcd. for $C_{19}H_{17}ClO_5$: C, 63.23; H, 4.75. Found: C, 63.06; H, 4.92.

4-Chloro-6,8-diethoxy-1-hydroxy-3-methylanthraquinone (**22***a'*, R_4 = C_2H_5) from **17**, m.p. 198–199° (petroleum ether) (40%).

Anal. Calcd. for $C_{19}H_{17}ClO_4$: C, 63.25; H, 4.75. Found: C, 63.35; H, 4.57.

5-Chloro-1-ethoxy-8-hydroxy-3-methylanthraquinone (**24***a*) from **15** and isopropenylketen diethyl acetal (**2**) as for **9***a*, m.p. 212–213° (benzene – petroleum ether) (75%); λ_{max} (EtOH) 226.5, 260, 277 (sh), 420, 432 nm (log ε 4.61, 4.29, 4.04, 3.97, 3.96); ν_{max} (KBr) 1676, 1635 (sh), 1631, 1600 cm^{-1}; δ (90 MHz) ($CDCl_3$) 1.58 t (J = 7.0 Hz) (1-OCH_2CH_3), 2.49 s (3-CH), 4.30 q (J = 7.0 Hz) (1-OCH_2—), 7.08 bs (2-CH), 7.37 dd (J = 9.0 Hz; Δν = 33.40 Hz) (7,6-CH), 7.69 bs (4-CH), 13.58 s (8-OH).

Anal. Calcd. for $C_{17}H_{12}ClO_4$: C, 64.66; H, 3.84. Found: C, 64.32; H, 3.95.

Reaction of Keten Dimethyl Acetal with 3-Bromo-8-chloro-5-methoxy-7-methylnaphthoquinone

A mixture of the methyl ether of **17**, (0.631 g; 0.002 mol) and keten dimethyl acetal (**1***a*) (0.88 g; 0.01 mol) is heated at 120° for 1 h and then at 140° for ½ h. The volatile by-products are then evaporated under vacuum and the residue chromatographed on 100 g of silica gel. Benzene elutes 0.032 g (5%) of 4-bromo-9-chloro-5-hydroxy-2,6-dimethoxy-8-methylnaphtho[1,2-*b*]furan (**25**), a colorless and unstable compound which is slowly converted into **26**; ν_{max} ($CHCl_3$) 3345, 1605 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.51 s (8-CH_3), 4.10 s (2,6-OCH_3), 5.78 s (3-CH), 6.68 s (7-CH), 10.40 s (5-OH).

A mixture of benzene and ether (19:1) next elutes 0.285 g (38%) of methyl 3-bromo-8-chloro-5-methoxy-7-methylnaphthoquinonylacetate (**26**), m.p. 171.0–171.5° (CCl_4); λ_{max} (EtOH) 219, 259, 381, 415 nm (log ε 4.38, 3.96, 3.88, 3.55); ν_{max} (KBr) 1730, 1678 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.51 s (7-CH_3), 3.77 s (CO_2CH_3), 3.90 s (—CH_2—), 4.01 s (5-OCH_3), 7.28 s (6-CH).

Anal. Calcd. for $C_{15}H_{12}BrClO_5$: C, 46.47; H, 3.12. Found: C, 46.22; H, 3.08.

Upon flushing the column with ethyl acetate and separating the residue by preparative t.l.c., 0.041 g (6%) of 4-chloro-1,6,8-trimethoxy-3-methylanthraquinone (methyl ether of **22***a*) is obtained, m.p. 219.5–220° (EtOH); λ_{max} (EtOH) 221, 273, 400 nm (log ε 4.28, 4.00, 3.51); ν_{max} (KBr) 1668, 1601 cm^{-1}; δ (60 MHz) ($CDCl_3$) 2.52 s (3-CH_3), 3.99 s, 4.00 s and 4.01 s (1,6,8-OCH_3), 6.78 d (J = 2.5 Hz) (7-CH), 7.25 s (2-CH), 7.29 d (J = 2.5 Hz) (5-CH).

Anal. Calcd. for $C_{18}H_{15}ClO_5$: C, 62.34; H, 4.36. Found: C, 62.44; H, 4.12.

Polyhydroxyanthraquinones (from Juglones)

Method A (Reduction Step)

To a solution of NaOH (1.4 g) in equal volumes of ethanol and water (40 ml each) is added the 5-chloro 8-hydroxy-1,3-dimethoxy anthraquinone (7.16×10^{-4} mol) and $Na_2S_2O_4$ (7.7 g). The mixture is stirred for 18 h under nitrogen and then aerated for 1 h, acidified with dilute HCl and extracted with chloroform.

1-Hydroxy-3-methyl-6,8-dimethoxyanthraquinone from **22***a*, m.p. 211.0° (EtOH) (94%); λ_{max} (EtOH) 225, 269, 280, 298, 430 nm (log ε 4.57, 4.29, 4.31, 4.05, 4,00); ν_{max} (KBr) 1670, 1632, 1595 cm^{-1}; δ (60 MHz) ($CDCl_3$)

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2.44 bs (3-CH_3), 3.99 s (6-OCH_3), 4.03 s (8-OCH_3), 6.79 d (J = 2.5 Hz) (7-CH), 7.11 bs (2-CH), 7.45 d (J = 2.5 Hz) (5-CH), 7.60 bs (4-CH), 13.10 s (8-OH).

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.70; H, 4.51.

Method A (Demethylation Step)

To a molten mixture of $AlCl_3$ (10.0 g) and NaCl (2.0 g) at 180° is added at once the hydroxy dimethoxy anthraquinone (**19***a*, **23***a*, or the preceding compound) (100 mg). After cooling to 120° the melt is hydrolyzed with ice (300 g) and concentrated HCl (10 ml). The precipitate is extracted with chloroform and the organic solution washed with water, dried and evaporated to dryness.

1,3,5-Trihydroxyanthraquinone (**23***b*) from **18**, m.p. 320–322° dec. (benzene) (84%) (lit. (23) m.p. 314–315°); λ_{max} (EtOH) 227, 246, 280, 322, 415 nm (log ε 4.31, 4.13, 4.19, 3.38, 3.92); ν_{max} (KBr) 1610, 1580 (sh) cm^{-1}; δ (90 MHz) ($(CD_3)_2SO$) 6.52 d (J = 2.0 Hz) (2-CH), 7.06 d (J = 2.0 Hz) (4-CH), 7.17–7.90 m (6,7,8-CH), 12.28 and 12.64 2 s (1,5-OH).

1,3,8-Trihydroxyanthraquinone (**19***b*) from **19***a*, m.p. 287–287.5° dec. (EtOH) (98%) (lit. (21) m.p. 287–288°); λ_{max} (EtOH) 215, 245, 265, 285, 321, 430 nm (log ε 4.44, 4.23, 4.21, 4.25, 3.53, 4.02); ν_{max} (KBr) 1670, 1620, 1575 cm^{-1}; δ (90 MHz) ($(CD_3)_2SO$) 6.55 d (J = 2.0 Hz) (2-CH), 7.09 d (J = 2.0 Hz) (4-CH), 7.20–7.90 m (5,6,7-CH), 11.96 bs (1,8-CH).

1,6,8-Trihydroxy-3-methylanthraquinone (emodin) (**22***b*), from 1-hydroxy-6,8-dimethoxy-3-methylanthraquinone, m.p. 258–259° dec. (MeOH) (96%) (lit. (10) m.p. 259–260° dec.); λ_{max} (EtOH) 221, 253, 266, 289, 438 nm (log ε 4.41, 4.15, 4.12, 4.19, 3.94); ν_{max} (KBr) 1680, 1631, 1598 cm^{-1}; δ (90 MHz) ($(CD_3)_2SO$) 2.37 bs (3-CH_3), 6.52 d (J = 2.5 Hz) (7-CH), 7.03 d (5-CH), 7.04 d (2-CH), 7.36 d (J = 1.5 Hz) (4-CH), 11.93 and 12.02 2 s (1,8-OH).

Method B

To a solution of a 5-chloro-1,3-diethoxy 8-hydroxy anthraquinone or 5-chloro-1-ethoxy 8-hydroxy-3-methyl anthraquinone (1.0 g) in acetic acid (20 ml) are added hydriodic acid (d = 1.57) (1.0 ml) and red phosphorus (1.0 g). The mixture is refluxed for 5 h, poured in ice and water and filtered after several hours. The crystalline product is then extracted with chloroform and the residue, upon evaporation of the solvent, oxidized with an equal weight of chromic oxide in acetic acid (50 ml) at 60° for 0.5 h. The polyhydroxylated anthraquinone is then recovered by dilution with water and extraction by chloroform.

1,3,8-Trihydroxyanthraquinone (**19***b*) from **20***b*, m.p. 287° (ethyl acetate) (85%).

Triacetate, m.p. 194–195° (lit. (21) m.p. 195°).

1,6,8-Trihydroxy-2-methylanthraquinone (**21***b*) from **21***a*, m.p. 287–288° (EtOH) (74%) (lit. (24) m.p. 283–284°); λ_{max} (EtOH) 225, 251, 272, 290, 433 nm (log ε 4.43, 4.14, 4.25, 4.21, 3.98); ν_{max} (KBr) 1665, 1613 cm^{-1}; δ (90 MHz) ($(CD_3)_2SO$) 2.19 s (2-CH_3), 6.49 d (J = 2.0 Hz) (7-CH), 7.00 d (J = 2.0 Hz) (5-CH), 7.46 s (3,4-CH), 11.89 and 12.28 2 s (1,8-OH).

Triacetate, m.p. 205.5–206° (lit. (24) m.p. 204°).

1,6,8-Trihydroxy-3-methylanthraquinone (emodin) (**22***b*) from **22***a*′, m.p. 256° (acetic acid) (80%).

Triacetate, m.p. 193° (lit. (25) m.p. 193–194°).

1,8-Dihydroxy-3-methylanthraquinone (chrysophanol) (**24***b*) from **24***a*, m.p. 192–193° (EtOH) (66%) (lit. (26) m.p. 196°); λ_{max} (EtOH) 226, 256, 277, 287, 425 nm (log ε 4.58, 4.32, 3.98, 4.01, 4.02); ν_{max} (KBr) 1676, 1625, 1604 cm^{-1}; δ (90 MHz) ($CDCl_3$) 2.45 s (3-CH_3), 7.10 bs (2-CH), 7.65 bs (4-CH), 7.2–8.0 m (5,6,7-CH), 11.97 and 12.08 2 s (1,8-OH).

Diacetate, m.p. 206–208° (lit. (27) m.p. 208°).

Reactions of Keten and Isopropenylketen Acetals with Chloromaleic Anhydride

To a solution of chloromaleic anhydride (2.64 g), 0.020 mol) in anhydrous ethyl ether (20 ml) is added rapidly 0.10 mol of the keten acetal (**1***a* or **1***b*) or 0.04 mol of isopropenylketen diethyl acetal (**2**). After the vigorous reaction has subsided, the reaction mixture is allowed to rest for 12 h at room temperature and then filtered.

3,5-Dimethoxyphthalic anhydride (**27***a*), m.p. 148–149° (petroleum ether) (32%) (lit. (28) m.p. 149°); ν_{max} (KBr) 1845, 1790, 1770 cm^{-1}; δ (60 MHz) ($CDCl_3$) 4.03 s (5-OCH_3), 4.08 s (3-OCH_3), 6.86 d (J = 2.0 Hz) (4-CH), 7.11 d (J = 2.0 Hz) (6-CH).

3,5-Diethoxyphthalic anhydride (**27***b*), m.p. 137° (dioxan–cyclohexane) (37%) (lit. (29) m.p. 130°).

3-Ethoxy-5-methylphthalic anhydride (**28**), m.p. 158–159° (acetone) (50%); ν_{max} (KBr) 1837, 1775 cm^{-1}; δ (60 MHz) ($(CD_3)_2CO$) 1.46 t (J = 7.0 Hz) (3-OCH_2CH_3), 2.54 s (5-CH_3), 4.34 q (J = 7.0 Hz) (3-OCH_2—), 7.38 m (2,4-CH).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.13; H, 4.66.

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