Naturally Occurring Compounds related to Phenalenone. Part IV.[1] Some Transformations and Molecular Rearrangements of Compounds in the Herqueinone Series

By J. S. Brooks and G. A. Morrison,* Department of Organic Chemistry, The University, Leeds LS2 9JT

Dihydroherqueinone di- and tri-methyl ethers (2b and c) have been oxidised to the 6a-hydroxy-1,6-diketone (4); the epimeric 5,6-glycols (3b) have been shown to undergo rearrangement to bridged ketones (1,5-methanonaphth-[1,8-*cd*]oxocin-12-ones) (7) when treated with boron trifluoride–ether.

WE have previously shown [1-3] that herqueinone (1) has the structure and absolute configuration illustrated, and that isoherqueinone, which is co-extracted with it from the mycelium of *P. herquei*, differs only in the configuration of the asymmetric centre in the side chain. Hydrogenation of the herqueinone–isoherqueinone mixture obtained from the mycelium, followed by methylation under appropriate conditions affords dihydroherqueinone mono-, di-, and tri-methyl ethers (2a—c). As previously reported,[1] these compounds (obtained as described), even when chromatographically pure, contain some of the corresponding compounds arising from isoherqueinone. The dimethyl ethers of dihydroherqueinone and dihydroisoherqueinone give the epimeric glycols A and B (3a), respectively, upon reduction with

lithium aluminium hydride whilst the corresponding tri-methyl ethers afford glycols C and D (3b), respectively. All four glycols have been obtained pure. The relative stereochemistry implied in formula (3) has been proposed tentatively on the basis of their n.m.r. spectra.[1] We now describe some oxidations of dihydroherqueinone di- and tri-methyl ethers, and some acid-catalysed rearrangements of glycols C and D.
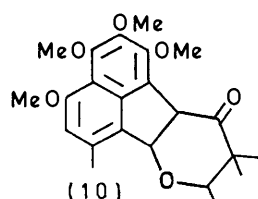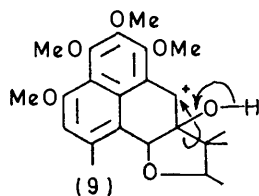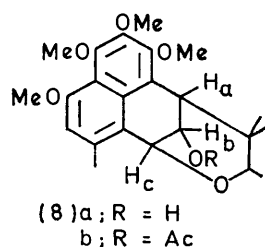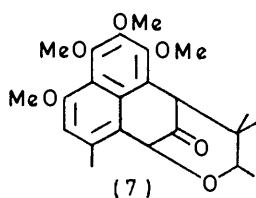
Treatment of the dimethyl ether (2b) (containing a small amount of dihydroisoherqueinone dimethyl ether, as judged by its n.m.r. spectrum) with *m*-chloroperbenzoic acid in wet chloroform, with toluene-*p*-sulphonic acid as catalyst, gave a quantitative yield of the diketone (4). The same material was obtained by similar treat-

[1] Part III, J. S. Brooks and G. A. Morrison, *J.C.S. Perkin I*, 1972, 421.

[2] J. S. Brooks and G. A. Morrison, *Tetrahedron Letters*, 1970, 963.

[3] J. S. Brooks and G. A. Morrison, *Chem. Comm.*, 1971, 1359.

ment of the trimethyl ether (2c); oxidation of the tri-methyl ether with chromic acid also gave the diketone (4), but in only 9% yield. As expected, the diketone (4) obtained by each procedure contained a small amount

OMe
HO 9 8 OH
         7
O   1   6   O
     2   5   OH
        3   4
              O
         (1) H

OMe
R²O   OR¹
R³O   O
                 OH
              O
(2)a; R¹ = R³ = H , R² = Me
   b; R¹ = R² = Me , R³ = H
   c; R¹ = R² = R³ = Me

OMe
MeO   OMe
            H
R O   OH
               OH
      H   O
          H
(3)a; R = H
   b; R = Me

OMe
MeO   OMe
            OH
O   O
              OH
         O
(4)

OMe
MeO   OMe
O   O
               OH
     HO   O
(5)

OMe
MeO   OMe
HO   O
O   OH
         O
(6)

OMe
MeO   OMe
MeO   O
         O
(7)

OMe
MeO   OMe
               Ha
MeO   Hb
              OR
         Hc   O
(8)a; R = H
   b; R = Ac

OMe
MeO   OMe
MeO   O—H
         O
(9)

OMe
MeO   OMe
MeO   O
         O
(10)
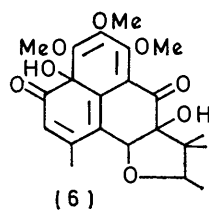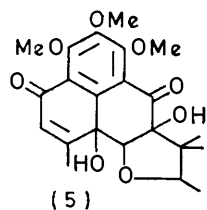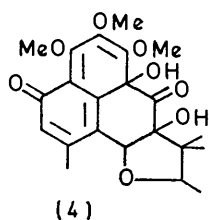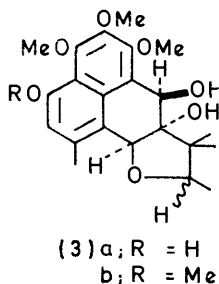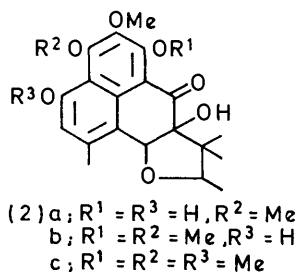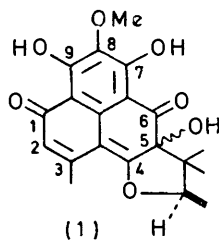
of the isomeric material (as indicated by the n.m.r. spectrum: see Experimental section) arising from the impurity in the starting materials. The structure of the diketone (4) followed from its spectra (see Experimental section) and from the observation that brief treatment (0·5 min) with zinc and acetic acid reduced it to dihydro-

herqueinone dimethyl ether. Reduction with zinc and acetic acid for 2 h afforded glycol A (3a). Structures (5) and (6), which might equally well arise in the peroxy-acid oxidation and which would also be easily reduced to dihydroherqueinone dimethyl ether, are excluded since they would not account for the band at 1710 cm⁻¹ in the i.r. spectrum of the oxidation product.

When glycol C (3b) was treated for 1 h at 0° with boron trifluoride–ether the major product (72% yield) was the skeletally rearranged ketone (7), designated ketone I. Reduction of ketone I with lithium alumin-ium hydride gave the corresponding alcohol (8a) from which the acetate (8b) was obtained by treatment with acetic anhydride and pyridine. The spectra of ketone I are fully in accord with structure (7). In particular, the

N.m.r. spectra of ketones I, II, and III

	Ketone I (7)	Ketone II (7)	Ketone III [De-O-methyl-(7)]
CMe₂	9·19 (s)	9·23 (s)	9·20 (s)
	8·83 (s)	8·81 (s)	8·86 (s)
O·CHMe	9·04 (d,	9·03 (d,	9·06 (d,
	J 6·5 Hz)	J 6·5 Hz)	J 6·5 Hz)
ArMe	7·49 (s)	7·49 (s)	7·52 (s)
ArOMe	6·06 (s, 6H)	6·12 (s)	6·06 (s, 6H)
	6·02 (s)	6·04 (s, 9H)	5·94 (s)
	5·98 (s)		
O·CHMe	6·49 (q,	6·40 (q,	6·53 (q,
	J 6·5 Hz)	J 6·5 Hz)	J 6·5 Hz)
CMe₂·CH(Ar)·CO	6·21 (d,	6·31 (d,	6·29 (d,
	J 2 Hz)	J 2 Hz)	J 2 Hz)
O·CH(Ar)·CO	5·02 (d,	4·82 (d,	5·09 (d,
	J 2 Hz)	J 2 Hz)	J 2 Hz)
ArH	3·28 (s)	3·40 (s)	3·37 (s)
OH			0·70 (s)

n.m.r. spectrum (Table) exhibits coupling (J 2 Hz) be-tween the benzylic protons in agreement with the associ-ated W-conformation.[4] N.m.r. double irradiation ex-periments on the acetate (8b) (see Experimental section) clearly indicated that the protons H_a, H_b, and H_c were all coupled with each other (J_ac 2·5, J_ab 3, J_bc 2 Hz).

If the relative stereochemistry of glycol C is correctly represented in formula (3)[1] it is unlikely that ketone I arises by a concerted rearrangement. Presumably an intermediate benzylic carbonium ion rearranges as indicated in formula (9). Migration of the 2,3-bond of the tetrahydrofuran ring would produce compound (10); this structure for ketone I is excluded by the n.m.r. data and also by the failure of ketone I to undergo dehydro-genation with 2,3-dichloro-5,6-dicyano-p-benzoquinone. A compound possessing structure (10) would be expected to undergo dehydrogenation readily to give an acenaph-thylene derivative. Ketone I also failed to undergo bromination with NNN-trimethylanilinium tribromide in accord with its formulation as a non-enolisable ketone. Finally, the high carbonyl stretching frequency (1735 cm⁻¹) observed for ketone I [and also for ketones II and III (see later)] may be regarded as resulting from a

⁴ Cf. L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, London, 1969, p. 334.

combination of ring strain and the inductive effect of the α-oxygen substituent in structure (7); a compound possessing structure (10) would be expected to absorb at the usual frequency for six-membered cyclic ketones (ca. 1715 cm⁻¹).

Treatment of glycol D (3b) with boron trifluoride-ether gave a compound (ketone II) which exhibited spectra similar to those of ketone I (see Table and Experimental section). The two compounds are regarded as being epimeric at the asymmetric centre carrying the C-methyl group. A third ketone (ketone III) was prepared from glycol C (3b) by treatment with hydrochloric acid in dioxan. From its analysis and spectroscopic properties (Table and Experimental section) it is thought to be a de-O-methyl derivative of ketone I (7).

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Unicam SP 1000 G spectrophotometer or on a Perkin-Elmer 125 instrument. U.v. spectra were recorded on a Unicam SP 800 spectrophotometer (95% ethanol as solvent). N.m.r. spectra were recorded on a Varian A60A instrument, with deuteriochloroform as solvent, except for the double-irradiation experiments which were carried out on a Bruker HFX₅ 90 MHz instrument. Mass spectra were recorded on an A.E.I. MS 902 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for chloroform solutions in a 1 dm cell. T.l.c. was carried out on plates coated with Merck Kieselgel G or GF₃₅₄.

The 1,6-Diketone (4).—(a) Dihydroherqueinone dimethyl ether (70 mg) (containing some dihydroisoherqueinone dimethyl ether), in chloroform (1·5 ml), was added to a suspension of m-chloroperbenzoic acid (36 mg) in wet chloroform (0·5 ml) containing a crystal of toluene-p-sulphonic acid monohydrate. After 18 h the mixture was diluted with chloroform and washed successively with sodium hydrogen sulphite solution, dilute sodium carbonate solution, and water. Removal of solvent in vacuo gave a quantitative yield of the diketone (4), constant-melting at 186—192° after three recrystallisations from ether-light petroleum (b.p. 40—60°) (Found: C, 63·15; H, 6·45%; m/e 418·1624. Calc. for C₂₂H₂₆O₈: C, 63·15; H, 6·25%; M, 418·1628), λ_max. 215, and 247 nm (log ε 4·16 and 4·37); ν_max. (KCl) 1560, 1640, 1662, 1710, and 3400 cm⁻¹; τ 3·84 (1H, q, J 1·5 Hz, -CMe=CH-CO-), 5·51 (1H, s, allylic H), 5·96 (3H, s, OMe), 6·10 (1H, s, OH), 6·13 and 6·15 (each 3H, s, OMe), 6·72 (1H, s, OH), 7·00 [1H, q, J 6·5 Hz, CH(Me)O], 7·85 (3H, d, J 1·5 Hz, -CMe=CH-CO-), 9·01 (3H, s, CMe₂), 9·12 (3H, d, J 6·5 Hz, MeCH·O), and 9·31 (3H, s, CMe₂) [also weak signals attributable to the isomeric diketone, τ 5·77 (s, allylic H), 6·20 (s, OMe), and 9·65 (s, CMe₂)].

(b) Dihydroherqueinone trimethyl ether (100 mg) (containing some dihydroisoherqueinone trimethyl ether), m-chloroperbenzoic acid (51 mg), and toluene-p-sulphonic acid monohydrate (1 mg) were added to wet chloroform (1·5 ml). After 20 h more m-chloroperbenzoic acid (30 mg) was added. After 2 days, the mixture was worked up as described in (a) to give a red gum, which was separated by preparative t.l.c. [20 × 20 cm plate, 0·5 mm coating of Kieselgel GF₂₅₄; ethanol-benzene (5 : 95) as eluant] into two bands. The non-fluorescent band of lower R_F value

gave the diketone (4) (66 mg, 66%) as white crystals, m.p. 186—191° [from ether-light petroleum (b.p. 40—60°)], identical (n.m.r. spectrum) with the product described in (a). The band of higher R_F value gave a yellow gum (19 mg), identical (t.l.c.) with the starting material. By further treatment of this material with m-chloroperbenzoic acid, almost complete conversion into the diketone was achieved.

(c) Dihydroherqueinone trimethyl ether (200 mg) (containing some dihydroisoherqueinone trimethyl ether), in glacial acetic acid (2 ml), was treated with a solution of chromium trioxide (450 mg) in glacial acetic acid (16 ml) and water (4 ml) for 8 min. The deep-red mixture was poured into water (25 ml) and excess of oxidising agent was destroyed with sodium disulphite. The product was extracted with chloroform, and the extract was washed with water, dried (Na₂SO₄), and evaporated in vacuo to give a pale yellow gum, which was chromatographed on a column of Kieselgel H (12 g) and Hyflosupercel (1·3 g) [ethanol-benzene (4 : 96) as eluant] to give the diketone (4) (19 mg, 9%), m.p. 185—191° [from ether-light petroleum (b.p. 40—60°)], identical (u.v., i.r., and n.m.r. spectra) with the products obtained in (a) and (b).

Reduction of the Diketone (4) with Zinc-Acetic Acid.—(a) The diketone (4) (30 mg), in glacial acetic acid (4 ml), was shaken with zinc dust (300 mg) for 30 s. The mixture was diluted with chloroform and filtered, and the filtrate was washed successively with sodium carbonate solution and water. Removal of solvent in vacuo gave a crystalline residue, which was recrystallised from methanol to give dihydroherqueinone dimethyl ether (15 mg) as yellow crystals, m.p. 188—198°, identical (i.r. and n.m.r. spectra) with an authentic specimen.

(b) The diketone (4) (40 mg) (containing a small amount of the epimer derived from dihydroisoherqueinone dimethyl ether) in glacial acetic acid (2 ml) was shaken with zinc dust (1 g) for 2 h. Work-up as in (a) gave a product shown by t.l.c. to be glycol A, containing a small amount of glycol B as an impurity. Preparative t.l.c. [20 × 20 cm plate, 0·5 mm coating of Kieselgel GF₂₅₄; ethanol-benzene (4 : 96) as eluant] gave glycol A, m.p. 148—149°, identical (i.r. and n.m.r. spectra) with an authentic specimen.

Ketone I (7).—A solution of (+)-glycol C (200 mg) in dry ether (10 ml) was treated with boron trifluoride-ether (200 mg) (freshly distilled from calcium hydride) at 0° for 1 h. The deep-red mixture was poured into water and extracted with chloroform. The extract was washed with water, dried (Na₂SO₄), and evaporated under reduced pressure to give a pale yellow gum, which was chromatographed on a column of Kieselgel H (40 g) and Hyflosupercel (4 g) [ether-benzene (10 : 90) as eluant] to give 3,4-dihydro-6,7,8,9-tetramethoxy-3,4,4,11-tetramethyl-1,5-methanonaphth[1,8-cd]-oxocin-12-one (7) (138 mg, 72%), which crystallised from aqueous methanol as needles, m.p. 159—160°, [α]_D −32° (c 1·13) (Found: C, 68·8; H, 6·95%; m/e, 400·1882. C₂₃H₂₈O₆ requires C, 69·0; H, 7·05%; M, 400·1886), λ_max. 246, 313, and 333infl nm (log ε 4·72, 3·98, and 3·81); ν_max. (KCl) 1576, 1585, 1605, and 1735 cm⁻¹.

Ketone I was recovered unchanged after a solution of it in benzene was heated under reflux with 2,3-dichloro-5,6-dicyano-p-benzoquinone in a nitrogen atmosphere for 2 h. It was also unaffected by treatment with NNN-trimethylanilinium tribromide in peroxide-free tetrahydrofuran at room temperature for 2 days.

Reduction of Ketone I (7) with Lithium Aluminium Hydride.—Ketone I (50 mg), in dry ether (2 ml), was

stirred with a suspension of lithium aluminium hydride (25 mg) in dry ether (4 ml) at room temperature for 1 h. After excess of lithium aluminium hydride had been destroyed with ethyl acetate, water was added followed by enough dilute hydrochloric acid to clarify the aqueous phase; the organic layer was then separated, washed several times with water, dried (Na_2SO_4), and evaporated *in vacuo* to give a gum, which was purified by preparative t.l.c. [20 × 20 cm plate, 0·5 mm coating of Kieselgel GF_{254}; developing twice with ether–benzene (30 : 70)]. The 12-*ol* (8a) (40 mg, 79%) was obtained as needles, m.p. 182—184° [from light petroleum (b.p. 40—60°)] (Found: C, 68·9; H, 7·3%; *m/e*, 402·2046. $C_{23}H_{30}O_6$ requires C, 68·65; H, 7·5%; *M*, 404·2042), $\lambda_{max.}$ 245, 300infl, 310, and 334infl nm (log ε 4·74, 3·90, 3·97, and 3·64); $\nu_{max.}$ (KCl) 1575, 1592, 1610, and 3450 cm^{-1}; τ 3·33 (1H, s, ArH), 5·00 (1H, t, *J* 2 Hz, H_c), 6·00, 6·02, 6·07, and 6·08 (each 3H, s, OMe), 6·50br (1H, t, *J* 2 Hz, H_a); 6·82 [1H, q, *J* 6·5 Hz, C*H*(Me)O], 7·48 (3H, s, ArMe), 8·62 (3H, s, CMe_2), 9·05 (3H, d, *J* 6·5 Hz, *Me*CH·O), and 9·44 (3H, s, CMe_2) (H_b signal obscured by methoxy-absorptions).

The Acetate (8b).—The alcohol (8a) (25 mg) was treated overnight at room temperature with acetic anhydride (0·5 ml) and pyridine (1 ml). Excess of acetic anhydride was destroyed with methanol, and the mixture was poured into dilute hydrochloric acid and extracted with chloroform. The extract was washed successively with dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated *in vacuo* to give a pale yellow gum. Preparative t.l.c. [20 × 20 cm plate, 0·5 mm coating of Kieselgel GF_{254}; developing four times with ether–benzene (15 : 85)] gave the *acetate* (8b) (24 mg) as a gum, which slowly crystallised (Found: *m/e* 444·2136. $C_{25}H_{32}O_7$ requires *M*, 444·2148), $\lambda_{max.}$ 246, 300infl, 311, and 334infl nm (log ε 4·72, 3·89, 3·95, and 3·58); $\nu_{max.}$ (8% in CHCl$_3$) 1578, 1618, and 1728 cm^{-1}; τ 3·33 (1H, s, ArH), 4·87 (1H, t, collapses to doublets, *J* 2 and 2·5 Hz, on irradiation at τ 6·40 and 5·04,

respectively, H_c), 5·04 (1H, dd, collapses to doublets, *J* 2 and 3 Hz, on irradiation at τ 6·40 and 4·87, respectively, H_b), 6·00, 6·03, 6·07, and 6·08 (each 3H, s, OMe), 6·40 (1H, t, collapses to doublets, *J* 3 and 2·5 Hz, on irradiation at τ 4·87 and 5·04 respectively, H_a), 6·84 [1H, q, *J* 6·5 Hz, C*H*(Me)O], 7·50 (3H, s, ArMe), 7·81 (3H, s, OAc), 8·69 (3H, s, CMe_2), 9·05 (3H, d, *J* 6·5 Hz, *Me*·CH·O), and 9·39 (3H, s, CMe_2).

Ketone II (7).—(+)-Glycol D (52 mg), in dry ether (6 ml), was treated with boron trifluoride–ether (50 mg) (freshly distilled from calcium hydride) at 0° for 1 h. The red mixture was worked up as in the preparation of ketone I. Preparative t.l.c. [20 × 20 cm plate, 0·5 mm coating of Kieselgel GF_{254}; chloroform as eluant] gave *ketone II* (44 mg, 88%), m.p. 133—134: (from light petroleum) $[\alpha]_D$ +91° (*c* 1·04) (Found: C, 69·4; H, 7·2%; *m/e*, 400·1887), $\lambda_{max.}$ 247, 313, and 333infl nm (log ε 4·69, 3·87, and 3·65); $\nu_{max.}$ (Nujol) 1580, 1610, and 1735 cm^{-1}.

Ketone III [*De-O-methyl-*(7)].—(+)-Glycol C (73 mg), in dioxan (3 ml), was stirred at room temperature for 2·25 h with 6N-hydrochloric acid (1 ml). The red mixture was diluted with water, neutralised with dilute sodium carbonate solution, and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give a gum, which was chromatographed on a column of Kieselgel H (20 g) and Hyflosupercel (2 g) [ether–benzene (5 : 95) as eluant]. The major fraction afforded *ketone III*, m.p. 202—206° after three recrystallisations from aqueous methanol, $[\alpha]_D$ −59° (*c* 1·15) (Found: C, 68·05; H, 6·7. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%), $\lambda_{max.}$ 246, 314, 326, and 342 nm (log ε 4·61, 3·78, 3·76, and 3·72); $\nu_{max.}$ (Nujol) 1578, 1608, 1620, 1733, and 3400 cm^{-1}.