Syntheses of 2,4-Dihydroxy- and 1,3-Dihydroxy-8-methylphenanthrene-9,10-quinones and their Bearing on the Structure of Denticulatol

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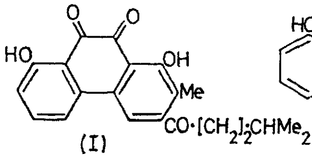
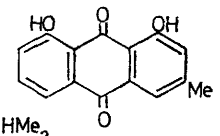
Wittig reaction of (2-methylbenzyl)triphenylphosphonium bromide, 3,5-dimethoxybenzaldehyde, and lithium methoxide gave 3,5-dimethoxy-2′-methylstilbene (V), which on photo-cyclodehydrogenation afforded 2,4-dimethoxy-8-methylphenanthrene (VI). Demethylation of this phenanthrene followed by acetylation furnished 2,4-diacetoxy-8-methylphenanthrene (VII), which on chromium trioxide oxidation and hydrolysis gave 2,4-dihydroxy-8-methylphenanthrene-9,10-quinone (III). A similar route gave 1,3-dihydroxy-8-methylphenanthrene-9,10-quinone. Neither quinone had properties corresponding to those reported for denticulatol.

PHENANTHRENE-9,10-QUINONES are extremely rare in nature. The only examples reported are denticulatol[1] and piloquinone[2] (I). Chi and his co-workers[1] isolated denticulatol, as well as chrysophanol (II), from the root of *Rumex chinensis*[3] (To-Tan-Hwang). They suggested, on the basis of oxidative degradation and zinc dust distillation, that denticulatol possessed either structure (III) or (IV). Birch and Smith,[4] in view of the fact that chrysophanol (II) co-occurs with denticulatol, suggested that both compounds could be derived biogenetically by the acetate pathway, and denticulatol would thus possess structure (III). Since the biogenesis of chrysophanol (II) in *Rumex alpinus* has recently been shown[5] to follow the polyacetate–malonate pathway, we are prompted to report the syntheses of the quinones (III) and (IV).



(I)



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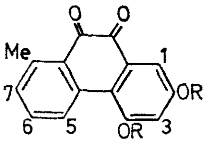
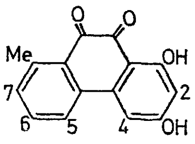


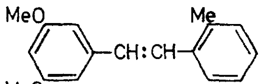
(III) R=H

(VIII)R=Ac

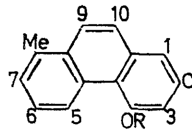


(IV)

Wittig reaction by the ethoxide method between (2-methylbenzyl)triphenylphosphonium bromide and 3,5-dimethoxybenzaldehyde, prepared by a modification of the method of Wenkert and his co-workers,[6] afforded 3,5-dimethoxy-2′-methylstilbene (V) as an oily mixture of isomers. Photocyclodehydrogenation[7] of the stilbene (V) furnished 2,4-dimethoxy-8-methylphenanthrene (VI) (32·5%) as plates, m.p. 95—97°. On demethylation at 210—215° (bath) with pyridine hydrochloride, followed by acetylation, compound (V) afforded 2,4-diacetoxy-8-methylphenanthrene (VII) as rods, m.p. 123—125° (82·3%). Oxidation of this diacetoxyphenanthrene by Fieser's method[8] furnished the diacetoxyphenanthrene-9,10-quinone (VIII) as yellow



(V)



(VI)R=Me

(VII)R=Ac

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[1] J. J. Chi, S. T. Hsu, M. Hu, and S. Wang, *J. Chinese Chem. Soc.*, 1947, **15**, 21.

[2] J. Polonsky, B. C. Johnson, P. Cohen, and E. Lederer, *Bull. Soc. chim. France*, 1963, 1909.

[3] For a discussion of this nomenclature see R. H. Thomson, 'Naturally Occurring Quinones,' Butterworths, London, 1957, p. 259.

[4] A. J. Birch and H. Smith, *Chem. Soc. Special Publ.* no. 12, 1958, p. 1.

[5] E. Leistner and M. H. Zenk, *Chem. Comm.*, 1969, 210.

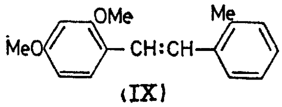
[6] E. Wenkert, E. M. Loeser, S. N. Mahapatra, F. Schenker, and E. M. Wilson, *J. Org. Chem.*, 1964, **29**, 435.

[7] See M. V. Sargent and C. J. Timmons, *J. Chem. Soc.*, 1964, 5544.

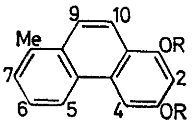
[8] L. F. Fieser, *J. Amer. Chem. Soc.*, 1929, **51**, 1935, 2460, 2471.

laths, m.p. 180—182° (34·4%). Hydrolysis of compound (VIII) gave the required 2,4-dihydroxy-8-methylphenanthrene-9,10-quinone (III) as rosettes of black needles, m.p. >335°, in almost quantitative yield.

An analogous route based on the stilbene (IX), the dimethoxyphenanthrene (X), and the diacetoxyphenanthrene (XI) gave 1,3-dihydroxy-8-methylphenanthrene-9,10-quinone (IV), as dark red prisms, m.p. >335°. Denticulatol is described[1] as dark yellow crystals, m.p. 162·5°. In view of our results, denticulatol can possess neither structure (III) or (IV), and the Chinese work must be viewed with suspicion.



(IX)



(X) R = Me

(XI) R = Ac

Professor Birch has also synthesised the quinones (III) and (IV), and has reached the same conclusion.[9] He has informed us that extraction of a sample of To-Tan-Hwang, obtained in Hong Kong, gave only a complex mixture of hydroxyanthraquinones.[9]

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Silica gel was B.D.H. material. Electronic spectra were determined for solutions in methanol with a Unicam SP 800 spectrophotometer. N.m.r. spectra were determined at 60 MHz for solutions in deuteriochloroform unless stated otherwise. Molecular weights were measured by mass spectrometry with an A.E.I. MS9 spectrometer operating at 70 ev.

3,5-*Dimethoxybenzaldehyde*.—3,5-Dimethoxybenzoic acid (20·0 g.) was esterified with absolute methanol and sulphuric acid. The crude methyl ester (20·7 g.) in absolute ether (100 ml.) was added during 15 min. to a stirred solution of lithium aluminium hydride (4·2 g.) in absolute ether (300 ml.), and the mixture was boiled under reflux for 17 hr., with stirring. It was then cooled to 0° and saturated aqueous sodium sulphate was added until coagulation occurred. The ether was filtered off and the residue was slurried with ethyl acetate (2 × 250 ml.), and filtered. The combined extracts were dried ($MgSO_4$) and evaporated. The crude alcohol (17·6 g.) so obtained was stirred and boiled under reflux for 20 hr. with a suspension of activated manganese dioxide[10] (62 g.) in chloroform (600 ml.). The manganese dioxide was filtered off and washed exhaustively with boiling chloroform. Removal of the chloroform and crystallisation of the residue from cyclohexane afforded the aldehyde (15·3 g., 84% overall) as prisms, m.p. 43·5—45° (lit.,[6] 45—46°), $\nu_{max.}$ (CCl_4) 1701 cm.$^{-1}$, τ (CCl_4) 0·12 (1H, s, CHO), 3·05 (2H, d, 3- and 6-H), 3·38 (1H, t, 4-H), and 6·14 (6H, s, 2 × OMe).

(2-*Methylbenzyl*)*triphenylphosphonium Bromide*.—2-Methylbenzyl bromide, b.p. 94—96°/10 mm. (18·4 g.), and triphenylphosphine (29 g.) in benzene (50 ml.) were boiled under reflux for 2 hr. The *salt* (44 g., 94%) was filtered off, washed with ether, crystallised from ether–methanol, and dried at 90°/0·1 mm., to give plates, m.p. 273—275° (Found: C, 69·6; H, 5·35. $C_{26}H_{24}BrP$ requires C, 69·75; H, 5·4%).

3,5-*Dimethoxy*-2′-*methylstilbene* (V).—3,5-Dimethoxybenzaldehyde (12·67 g.) and the foregoing phosphonium salt (34·5 g.) in absolute methanol (350 ml.) were stirred and heated under reflux during the addition, during 15 min., of methanolic lithium methoxide [from lithium (0·645 g.) and methanol (180 ml.)]. The solution was heated under reflux for a further 2 hr. and then stirred at room temperature for 15 hr. Methanol (400 ml.) was removed under reduced pressure and the residue was diluted with water (250 ml.). The mixture was exhaustively extracted with light petroleum (b.p. 40—60°), and the extracts were washed with saturated brine and dried ($MgSO_4$). The solvent was removed and the resulting oil was filtered from a little triphenylphosphine oxide. The *stilbene* (18·5 g., 94%), b.p. 175—185° (bath)/0·3 mm., contained *ca.* 75% *trans*- and 25% *cis*-isomer (n.m.r. spectrum) (Found: *M*, 254·135. $C_{17}H_{18}O_2$ requires *M*, 254·131).

2,4-*Dimethoxy*-8-*methylphenanthrene* (VI).—The foregoing stilbene (16·5 g.) was divided into four portions and each was irradiated in hexane (1200 ml.), with stirring, by a Hanovia lamp (Pyrex jacket) as described previously.[7] Removal of the solvent left an oily residue which was crystallised from methanol to give the phenanthrene (2·67 g.). The mother liquors were chromatographed over silica gel with 5—10% ether–pentane as eluant. The *phenanthrene* (total 5·32 g., 32·5%) formed plates from methanol, m.p. 95—97° (Found: C, 81·2; H, 6·3. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%), $\lambda_{max.}$ 256, 294, 307, 327, 343, and 360 nm. (ε 51,200 10,600, 10,600, 800, 1380, and 1560), $\lambda_{infl.}$ 235, 271, and 284 nm. (ε 15,600, 31,200, and 14,900), τ 0·17 (1H, q, $J_{5,6}$ 8 Hz, $J_{5,7}$ 2·5 Hz, 5-H), *ca.* 1·9—2·8 (4H, complex m, 6-, 7-, 9-, and 10-H), 3·08 (1H, d, $J_{1,3}$ 2·5 Hz, 1-H), 3·18 (1H, d, $J_{5,3}$ 2·5 Hz, 3-H), 5·97 (3H, s, OMe), 6·10 (3H, s, OMe), and 7·28 (3H, s, Me).

2,4-*Diacetoxy*-8-*methylphenanthrene* (VII).—The foregoing phenanthrene (4·154 g.) was maintained at 210—215° (bath) with pyridine hydrochloride (65 g.) for 3 hr. The cooled melt was dissolved in water and the resulting suspension was exhaustively extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated and the dark oily residue was acetylated with pyridine–acetic anhydride. The solvents were removed and the crude product was preadsorbed on to silica gel and chromatographed over a column of the same material with 25—40% ether–pentane as eluant. The *phenanthrene* (4·175 g., 82·3%) gave rods, m.p. 123—125° (from methanol) (Found: C, 74·3; H, 5·1. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·25%), $\lambda_{max.}$ 223, 254, 282, 292, 304, 335, and 349 nm. (ε 20,200, 67,100, 12,000, 12,900, 14,700, 330 and 160), τ 0·85 (1H, poorly resolved hump, 5-H), *ca.* 1·75—2·8 (6H, complex, m, 1-, 3-, 6-, 7-, 9-, and 10-H), 7·28 (3H, s, Me), 7·52 (3H, s, OAc), and 7·68 (3H, s, OAc).

2,4-*Diacetoxy*-8-*methylphenanthrene*-9,10-*quinone* (VIII).—The foregoing phenanthrene (0·75 g.) in the minimum of glacial acetic acid was treated, with stirring at 45°, with a solution of chromium trioxide (0·75 g.) in glacial acetic acid (3·75 ml.) and water (2·25 ml.). After 1 hr. at 45° the mixture was allowed to cool to room temperature and stirred for a further 12 hr. The precipitated *quinone* (283·5 mg., 34·4%) was filtered off, washed with water,

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[9] A. J. Birch, personal communication.

[10] O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1953, 2189.

and dried *in vacuo*. It formed yellow laths, m.p. 180—182° (from benzene) (Found: C, 67·15; H, 4·20; *M*, 338. $C_{19}H_{14}O_6$ requires C, 67·45; H, 4·15%; *M*, 338), $\nu_{max.}$ (KCl) 1770 (acetate) and 1688 (quinone) cm.$^{-1}$, τ 1·77 (1H, q, $J_{5,6}$ 1 Hz, $J_{5,7}$ 8 Hz, 5-H), 2·14 (1H, d, $J_{1,3}$ 2·5 Hz, 1-H), 2·37 (1H, t with a broad central signal, $J_{6,5} = J_{6,7} =$ 8 Hz, 6-H); the remaining signals due to the aromatic protons were partially obscured by the chloroform resonance: 7·32 (3H, s, Me), 7·64 (3H, s, OAc), and 7·66 (3H, s, OAc).

2,4-*Dihydroxy*-8-*methylphenanthrene*-9,10-*quinone* (III).—The foregoing diacetoxyquinone was hydrolysed at room temperature under nitrogen, with dilute aqueous methanolic potassium hydroxide. The *quinone* (95%) formed rosettes of black needles from chloroform, m.p. >335° (Found: C, 70·55; H, 3·85. $C_{15}H_{10}O_4$ requires C, 70·85; H, 3·95%), $\lambda_{max.}$ 265, 355, 476, and 517 nm. (ε 14,000, 3500, 1400, and 750), and $\lambda_{infl.}$ 291 nm. (ε 7400), $\nu_{max.}$ (KCl) 1665 and 1653 cm.$^{-1}$, τ [$(CD_3)_2SO$] −0·55br (2H, s, OH), 1·14 (1H, q, $J_{5,6}$ 1 Hz, $J_{5,7}$ 8 Hz, 5-H), 2·38 (1H, t with a broad central signal, $J_{6,5} = J_{6,7} =$ 8 Hz, 6-H), 2·78 (1H, d with broad signals, $J_{7,6} =$ 8 Hz, 7-H), 2·94 (1H, d, $J_{1,3}$ 2·5 Hz, 1-H), 3·09 (1H, d, $J_{3,1}$ 2·5 Hz, 3-H), and 7·43 (3H, s, Me).

2,4-*Dimethoxy*-2′-*methylstilbene* (IX).—(*a*) This was prepared by Wittig reaction between 2,4-dimethoxybenzaldehyde, (2-methylbenzyl)triphenylphosphonium bromide, and lithium methoxide. The crude product was preadsorbed on silica gel and chromatographed over a column of the same material with 5—10% ether–pentane as eluant. The *stilbene* (81%) was an oil, b.p. 160—170° (bath)/0·5 mm., and contained *ca.* 85% *trans*- and 15% *cis*-isomer (n.m.r. spectrum) (Found: *M*, 254·135. $C_{17}H_{18}O_2$ requires *M*, 254·131).

(*b*) The Grignard reagent was prepared from 2-methylbenzyl bromide (14·96 g.), magnesium (2·02 g.), and ether (60 ml.). After the addition of the bromide the mixture was heated under reflux for 3 hr. To the cooled solution was added 2,4-dimethoxybenzaldehyde (12·7 g.) in dry ether (120 ml.), at such a rate that gentle reflux was maintained. The mixture was then heated under reflux for 3 hr., and the complex was decomposed by the addition of chilled dilute hydrochloric acid to the cooled mixture. The aqueous layer was exhaustively extracted with ether, and the extracts were washed with water and saturated brine, and dried (Na_2SO_4). The crude carbinol (21 g.) obtained on removal of the ether was then heated under reflux with acetic anhydride (150 ml.). After 15 min. the source of heat was removed and the acetic anhydride was hydrolysed by the cautious addition of a large excess of water. The crude stilbene was extracted with ether, and the extracts were washed successively with water, saturated sodium hydrogen carbonate solution, water, and saturated brine, and dried ($MgSO_4$). The dark oily residue obtained on removal of the ether was preadsorbed on silica gel and chromatographed over a column of the same material (total 400 g.) with 10—15% ether–pentane as eluant. Early fractions afforded the Wurtz product, 2,2′dimethylbibenzyl (0·74 g.) which formed leaflets from methanol, m.p. 67—67·5° (lit.,[11] 66—67°), τ 2·97 (8H, s, aromatic), 7·20 (4H, s, 2 × CH_2), and 7·77 (6H, s, Me). Later fractions furnished the stilbene (7·94 g., 40·8%) as an oil slightly contaminated with a highly fluorescent impurity; it had the same R_F value on silica plates as that prepared in (*a*).

1,3-*Dimethoxy*-8-*methylphenanthrene* (X).—This, prepared (44%) by irradiation of the stilbene (IX), formed needles from ethanol, m.p. 100—101° (Found: C, 80·95; H, 6·6. $C_{17}H_{16}O_2$ requires C, 80·95; H, 6·4%), $\lambda_{max.}$ 231, 252, 305, 315, 341, and 359 nm. (ε 19,400, 33,100, 9900, 10,500, 1800, and 1700), $\lambda_{infl.}$ 261 and 278 nm. (ε 28,200 and 8900), τ *ca.* 1·4—2·8 (6H, complex m, 4-, 5-, 6-, 7-, 9-, and 10-H), 3·34 (1H, d, $J_{2,4}$ 2·5 Hz, 2-H), 6·00 (6H, s, OMe), and 7·27 (3H, s, Me).

1,3-*Diacetoxy*-8-*methylphenanthrene* (XI).—The foregoing dimethoxyphenanthrene was demethylated with pyridine hydrochloride, and then the crude product was acetylated. The *phenanthrene* (62·5%) formed rosettes of needles from methanol, m.p. 182—184° (Found: C, 73·85; H, 5·3. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·25%), $\lambda_{max.}$ 267, 279, 291, 303, 337, and 352 nm. (ε 64,500, 14,500, 15,100, 16,300, 1150, and 1050), $\lambda_{infl.}$ 251 nm. (ε 52,900), τ *ca.* 1·0—2·6 (7H, complex m, aromatic), 7·26 (3H, s, Me), 7·51 (3H, s, OAc), and 7·61 (3H, s, OAc).

1,3-*Dihydroxy*-8-*methylphenanthrene*-9,10-*quinone* (IV).—The foregoing diacetoxyphenanthrene (150 mg.) in glacial acetic acid (6 ml.) was treated, at 45° with stirring, with chromium trioxide (150 mg.) in glacial acetic acid (0·75 ml.) and water (0·45 ml.). After 1 hr. the mixture was allowed to cool to room temperature and stirred for a further 12 hr. It was then diluted with water and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and the solvent was removed. The residue was hydrolysed with dilute aqueous methanolic potash at room temperature under nitrogen. The crude product was chromatographed over two layer plates (Kieselgel GF_{254}; 20 × 20 × 0·1 cm.) with 50% ethyl acetate–benzene as eluant. A dark red band which developed was separated and extracted with chloroform. The solvent was removed and the residue crystallised from chloroform to give the *quinone* (15·1 mg., 12%). A sample sublimed at 170°/0·05 mm. formed dark red prisms m.p. >335° (Found: C, 70·6; H, 3·75. $C_{15}H_{10}O_4$ requires C, 70·85; H, 3·95%), $\lambda_{max.}$ 262 and 419 nm. (ε 15,100 and 3400), $\lambda_{infl.}$ 298 nm. (ε 4300), $\nu_{max.}$ (KCl) 1665 and 1628 cm.$^{-1}$, *m*/*e* 254 (M^+), 226 (100%, *M* − CO), and 198 (*M* − 2CO).

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[11] C. S. Rondestvedt, jun., and H. S. Blanchard, *J. Org. Chem.*, 1956, **21**, 229.