Condensation of 1,3,8-Trihydroxynaphthalene with Phenylpropanedione; A Synthesis of Naphthoquinone Methides[1]

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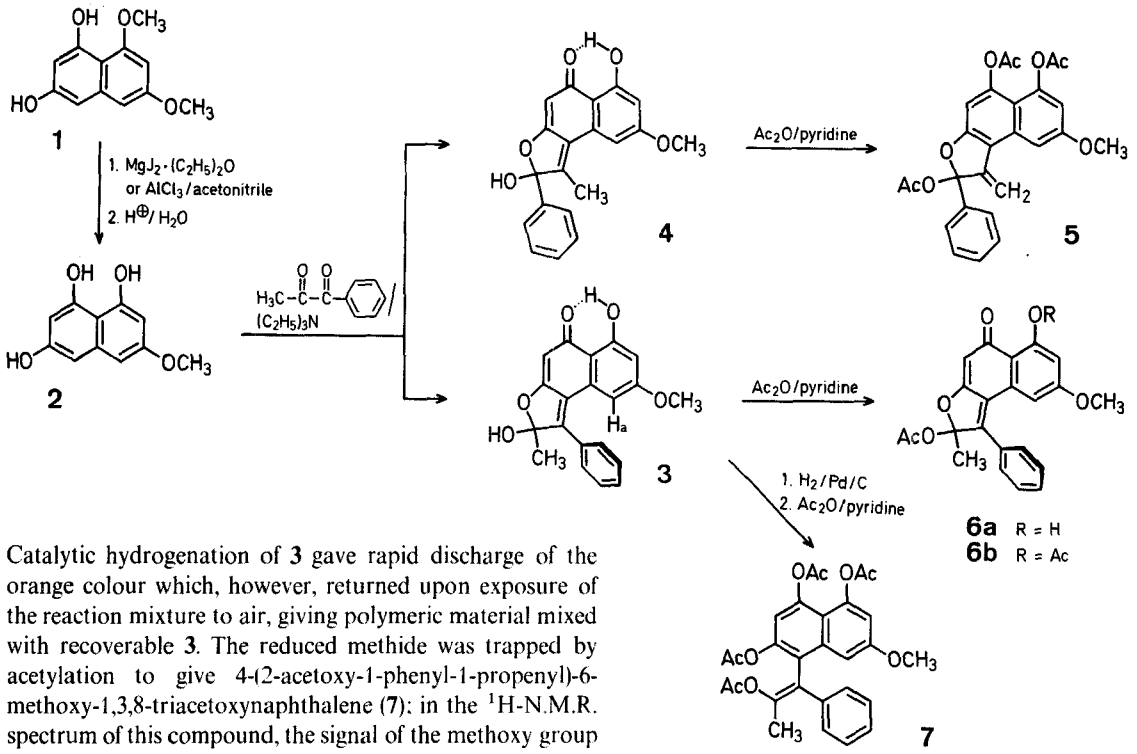
Preliminary communications have reported the isolation[3] and synthesis[4] of stable naphthoquinone methides with structural elements in common with the streptovaricin antibiotics[5]. The compounds possess unusual physical and chemical properties (resistance to nucleophilic addition to the methide system, an acid-stable hemiacetal ring). The structural formulations were suggested primarily on the basis of physical constants and behaviour of the compounds upon acetylation, and were confirmed by model syntheses of homologous methides through condensation of biacetyl or benzil, under weakly basic catalysis (Florisil or triethylamine), with 6-methoxy-1,3,8-trihydroxynaphthalene (**2**). Compound **2** was synthesized from 1,3-dihydroxy-6,8-dimethoxynaphthalene[6] (**1**) by demethylation with magnesium iodide etherate or aluminum chloride/acetonitrile; this represents a significant and useful extension of these reactions, the second of which was far more convenient and clean. They have been previously applied only to methoxy groups *ortho* or *peri* to carbonyl, not to hydroxy groups[7,8].

The reaction of **2** with phenylpropanedione[9] ("acetylbenzoyl") in moist ethyl acetate in the presence of triethylamine gave two products, in a ratio 2.6:1 (^{1}H-N.M.R. spectrum of the purified *p*-methide mixture). These products were separated by column chromatography over oxalated silica gel[10], giving 2,6-dihydroxy-8-methoxy-2-methyl-5-oxo-1-phenyl- (**3**) and 2,6-dihydroxy-8-methoxy-1-methyl-5-oxo-2-phenyl-2,5-dihydronaphtho[2,1-*b*]furan (**4**) (combined yield: 72%). The U.V. and I.R. spectra of **3** and **4** were very similar, though **3**, the principal product, was more strongly orange in colour. The ^{1}H-N.M.R. spectrum of **3** showed a marked upfield displacement of the signals associated with the methoxy group and the proton H_a, with relation to those in the spectrum of **4** (3.84→3.47, 6.59→6.17 ppm), in accord with the location of these protons in **3** over the π-cloud of the benzene ring, which is forced out of the plane of the conjugated methide system by steric compression. In the mass spectrum, only **3** showed a loss of water from the molecular ion and a strong peak for the acetyl group ($m/e=318$ and 43), while only **4** showed fragments corresponding to phenyl ($m/e=77$) and benzoyl ($m/e=105$) groups. These data provide strong support for the structures formulated, analogous to the *p*-methides produced in biacetyl and benzil condensations with **2**[4]. No *o*-methides were detected in the product mixture from the acetylbenzoyl condensation.

Acetylation of **4** gave the triacetate **5**, showing signals for both aromatic and aliphatic acetate groups in the I.R. and ^{1}H-N.M.R. spectra. The exo-methylene group appeared as a singlet in the N.M.R. spectrum, which requires reversal of the published signal assignments in the acetate mixtures from the condensation products with biacetyl[4]. Thus, the acetate having the methylene group conjugated to the aromatic system, as in **5**, is predominant over the isomeric vinylidene ether in mixtures from acetylation of *p*-methides, and exclusive for the *o*-methide nonpolar acetate.

Acetylation of **3** for 2 h gave exclusively the monoacetate **6a**; after 48 h, a mixture of **6a** and the diacetate **6b** was obtained. Both products showed a base peak in the mass spectrum at $m/e=319$ (loss of the aliphatic acetoxy). Both retained the quinone methide system intact, but in the U.V. spectrum of **6b** the longest-wavelength (E.T.)band was lacking. Both were reconverted to **3** in mild aqueous alkali. The stability of the methide system under these conditions, even in the lack of the *peri*-hydroxy group in the case of **6b**, is exceptional and may be attributed to steric hindrance at the carbon end of the system. [Essentially all known natural quinone methides (there are very few exceptions) are stabilized by an *o*- or *peri*-hydroxy group; even these methides readily add nucleophiles at the carbon end of the system][11].



Catalytic hydrogenation of **3** gave rapid discharge of the orange colour which, however, returned upon exposure of the reaction mixture to air, giving polymeric material mixed with recoverable **3**. The reduced methide was trapped by acetylation to give 4-(2-acetoxy-1-phenyl-1-propenyl)-6-methoxy-1,3,8-triacetoxynaphthalene (**7**); in the ^{1}H-N.M.R. spectrum of this compound, the signal of the methoxy group appeared in a normal position at $\delta = 3.88$ ppm, showing the hemiacetal ring to be opened.

The condensation of **2** with methyl pyruvate, pyruvaldehyde, or phenylglyoxal gave no quinone-methide products. Methylation or elimination of any one of the three hydroxy groups in **2** or analogues totally eliminated reactivity with biacetyl. Thus, the scope of the condensation seems limited to 1,3,8-trihydroxynaphthalene systems (which are common natural products, resulting from polyketide cyclizations) and *vic*-diketones, forming a 2-carbonylmethylene-5-hydroxy-2,5-dihydrofuran ring as part of a very stable quinone methide system, of considerable synthetic and biological interest.

Melting points were determined on modified Kofler blocks, and are uncorrected. Visible/U.V. spectra were recorded on a Beckman DB-GT; I.R. spectra on Perkin-Elmer 137B and 257 instruments; ^{1}H-N.M.R. spectra at 60 MHz on Varian T-60 (Instituto Nacional de Tecnologia) and EM-360 spectrometers, at 100 MHz on a Varian XL-100; and M.S. at 70 *e*V on a Varian MAT CH-5-DF.

6-Methoxy-1,3,8-trihydroxynaphthalene (2):

Method A[7]: All apparatus and reagents require very careful drying before use in this reaction. A solution of magnesium iodide etherate is prepared by adding dried magnesium turnings (4.2 g) and iodine (20 g) to a stirred, ice-cooled mixture of rigorously dried and alcohol-free ether (25 ml) and dry benzene (50 ml) and then stirring the mixture for 2 h at room temperature. This solution of magnesium iodide etherate (10 ml) is added with stirring to a solution of 1,3-dihydroxy-6,8-dimethoxynaphthalene[6] (**1**; 525 mg) in dry benzene (50 ml) under reflux with passage of dry nitrogen. After 3 h at reflux temperature, the reaction is only 50% complete (by T.L.C. analysis on silica H, chloroform/methanol 10:1). More reagent (7 ml) is added and refluxing under nitrogen is continued for 6 h.

The reaction mixture (starting material, tetrahydroxynaphthalene, and trihydroxymethoxynaphthalene, the last greatly predominant by T.L.C.) is recovered by extraction with chloroform/ethyl acetate (10:1) (4 × 50 ml). The combined extracts are washed with 5% aqueous sodium disulfite ($Na_2S_2O_5$) (2 × 50 ml) and water (100 ml), dried with magnesium sulphate, and evaporated at 30° under vacuum to give crude **2**; yield: 385 mg (78%). The product is recrystallized from ethyl acetate (3 ml) to give **2** as brownish clumps; first crop: 80 mg (17%); later crops are less pure and may be directly used in condensations; m.p. 170–174°.

$C_{11}H_{10}O_4$	calc.	$M^{\oplus}$	206.0578
(M.S.)	found		206.0565 (83%),
	cal.	$M^{\oplus} - C_2H_2O$	164.0471
	found		164.0476 (100%);
			no others over 15%.

I.R. (KBr): $\nu_{max} = 2941$, 2703, 1641, 1608, 1587 cm^{-1}.

U.V. (methanol): $\lambda_{max} = 241$ (log $\varepsilon = 4.58$), 300 sh (3.88), 318 (3.95), 327.5 sh (3.97), 332.5 (4.06), 356 sh nm (3.61).

^{1}H-N.M.R. ($CDCl_3$/acetone-d_6): $\delta = 6.32$ (broad s, 4H); 3.84 ppm (s, 3H).

Method B[8]: Anhydrous aluminium chloride (30 mg) is added to a stirred solution of 1,3-dihydroxy-6,8-dimethoxynaphthalene[6] (**1**; 50 mg) in acetonitrile (1.0 ml) and the mixture is set aside for 20 h under dry nitrogen. The complex formed is decomposed with ice (5 g) and 37% hydrochloric acid (1 ml). The solvent is removed under reduced pressure and the aqueous phase extracted with dichloromethane (3 × 10 ml). The extracts are combined, washed with 5% aqueous sodium disulfite (2 × 10 ml) and water (20 ml), dried with magnesium sulphate, and evaporated at 30° under vacuum to give **2**; yield: 25 mg (60%); m.p. 170–174° (from benzene/ethyl acetate).

Condensation of 1,3,8-Trihydronaphthalenes with *vic*-Diketones; General Procedure:

To a solution of 6-methoxy-1,3,8-trihydroxynaphthalene (**2**; 50 mg, 0.24 mmol) or an equivalent amount of another 1,3,8-trihydroxynaphthalene (such as 6-hydroxymusizin or neriaphigenin[3]), in distilled but not dried ethyl acetate (3 ml, ~5% water) is added a two- to threefold excess of phenylpropanedione or other *vic*-diketone (0.5–0.7 mmol) and triethylamine (0.05–0.1 ml). After standing 30 min at room temperature, with occasional agitation, the reaction mixture is evaporated to dryness (or first warmed, if T.L.C. shows less than complete transformation of the yellow-fluorescent starting material into red-fluorescent products), and the residue directly purified using benzene/ethyl acetate gradient mixtures (9:1–2:1) over silica gel (10–50 g).

2,6-Dihydroxy-8-methoxy-1(or 2)-methyl-5-oxo-2(or 1)-phenyl-2,5-dihydronaphtho[2,1-b]furan (**4** and **3**): The reaction mixture from the condensation of **2** with phenylpropanedione[9] is passed through silica gel (50 g) in benzene/ethyl acetate (9:1); the

third coloured band eluted corresponds to a mixture of strongly red-fluorescent *p*-quinone methides (65 mg, 80%), inseparable on T.L.C., containing (by ^{1}H-N.M.R.) **3** and **4** in a ratio of 2.6:1. This mixture is separated in benzene/ethyl acetate (24:1) over silica gel (60 g) previously washed with 3% oxalic acid and dried 2 h at 120°[10]. The first, yellow-coloured band is crystallized from chloroform/cyclohexane to give **4**; yield: 18 mg (22%); m.p. 232–236° (dec.).

$C_{20}H_{16}O_5$	calc.	C 71.42	H 4.76
(336.3)	found	71.39	4.85

M.S.: *m/e* (relative intensity) = 336 ($M^{\oplus}$, 47), 321 (17), 308 (16), 293 (10), 280 (19), 105 (71), 77 (100), no 318 or 43.

I.R. (KBr): ν_{max} = 3360, 1650, 1605, 1590 (these two stronger than 1650), 1379, 1300, 1200, 1169, 838 cm^{-1}.

U.V. (methanol): λ_{max} = 217 (log ε = 4.13), 262 (3.83), 300 (4.05), 391 nm (3.45).

^{1}H-N.M.R. ($CDCl_3$): δ = 13.98 (broad s, 1H, removed by D_2O); 7.40 [broad m, w(1/2) = 6 Hz, 5H]; 6.59, 6.37 (2d, 1H each, J = 2.5 Hz); 5.68 (s, 1H); 3.84 (s, 3H); 2.22 (s, 3H); 1.80 ppm (broad, 1H, removed by D_2O).

The second, orange-coloured band is crystallized from chloroform/cyclohexane to give **3**; yield: 40 mg (50%); m.p. 170–175° (dec.).

$C_{20}H_{16}O_5$	calc.	C 71.42	H 4.76
(336.3)	found	71.52	4.83

M.S. *m/e* (relative intensity) = 336 ($M^{\oplus}$, 100), 321 (33), 318 (5), 308 (45), 293 (25), 43 (14).

I.R. (KBr): ν_{max} = 3280, 1650, 1608, 1587 (these two weaker than 1650), 1365, 1320, 1207, 1160, 837 cm^{-1}.

U.V. (methanol): λ_{max} = 215 (log ε = 4.49), 255 (4.19), 318 (4.39), 400 nm (3.80).

^{1}H-N.M.R. ($CDCl_3$): δ = 13.77 (s, 1H, removed by D_2O); 7.54 [narrow s, w(1/2) = 3 Hz, 5H]; 7.48 (s, 1H, removed by D_2O); 6.30, 6.17 (2d, 1H each, J = 2.5 Hz); 5.58 (s, 1H); 3.47 (s, 3H); 1.58 ppm (s, 3H).

8-Methoxy-1-methylene-2-phenyl-2,5,6-triacetoxy-1,2-dihydronaphtho[2,1-*b*]furan (5):

A mixture of quinone methide **4** (30 mg), acetic anhydride (1 ml), and pyridine (2 ml) is allowed to stand at room temperature for 24 h in the dark. The reagents are then evaporated under reduced pressure. The residue is purified by chromatography over silica gel (5 g). Evaporation of the benzene eluate and recrystallization of the residue from acetone/cyclohexane affords **5**; yield: 26 mg (65%); m.p. 196–198°.

$C_{26}H_{22}O_8$	calc.	C 67.53	H 4.76
(462.5)	found	67.44	4.69

M.S.: *m/e* (relative intensity) = 462 ($M^{\oplus}$, 24), 420 (20), 378 (100), 231 ($M^{\oplus} - 3x\ CH_2CO - C_6H_5CO$, 21), 105 (57), 77 (21), no 402 or 293.

I.R. (KBr): ν_{max} = 1773, 1745, 1635, 1613, 1232, 1205, 1160, 1031, 953, 902, 769 cm^{-1}.

U.V. (methanol): λ_{max} = 229 (log ε = 4.42), 247 (4.52), 325 nm (4.34).

^{1}H-N.M.R. ($CDCl_3$): δ = 7.67, 6.67 (2d, 1H each, J = 2.5 Hz); 7.11 (s, 1H); 7.8–7.3 (m, 5H); 5.54 (s, 2H); 3.86 (s, 3H); 2.28 (s, 6H); 2.10 ppm (s, 3H).

2-Acetoxy-6-hydroxy-8-methoxy-2-methyl-5-oxo-1-phenyl- (6a) and 2,6-Diacetoxy-8-methoxy-2-methyl-5-oxo-1-phenyl-2,5-dihydronaphtho[2,1-*b*]furan (6b):

Acetylation of **3** (25 mg) under the above conditions for 2 h, followed by an identical isolation procedure, gives upon chloroform elution of the column and crystallization from chloroform/cyclohexane the 2-monoacetate **6a**: yield: 17.5 mg (80%); m.p. 146–150° (dec.).

M.S.: *m/e* (relative intensity) = 378 ($M^{\oplus}$, 68), 336 (45), 319 (100), 308 (55), 293 (32).

I.R. (KBr): ν_{max} = 3360, 1754, 1658, 1587, 1370, 1205, 1010, 949, 885, 840 cm^{-1}.

U.V. (methanol): λ_{max} = 221, 265, 314, 407 nm, very similar to spectrum of **3**.

^{1}H-N.M.R. ($CDCl_3$): δ = 13.50 (s, 1H, removed by D_2O); 7.6–7.2 (m, 5H); 6.36, 6.16 (2d, 1H each, J = 2.5 Hz); 5.85 (s, 1H); 3.46 (s, 3H); 2.02 (s, 3H); 1.75 ppm (s, 3H).

Similar acetylation during 48 h, followed by separation of the two products on preparative T.L.C. (silica H, benzene/ethyl acetate 3:1) and elution of each band with chloroform, and crystallization from chloroform/cyclohexane, gives **6a** (11 mg, 39%; m.p. 147–150°, dec.; R_f: 0.74) and the diacetate **6b**; yield: 15 mg (50%); m.p. 130–135° (dec.); R_f: 0.55.

M.S.: *m/e* (relative intensity) = 378 ($M^{\oplus} - CH_2CO$, 55; $M^{\oplus}$ 420 not seen), 361 ($M^{\oplus} - CH_3COO$, 5), 336 (25), 333 (6), 319 (100), 318 (43), 308 (21).

I.R. (KBr): ν_{max} = 1770, 1613, 1330, 1235, 1149, 1080, 1010, 950, 880, 855 cm^{-1}.

U.V. (methanol): λ_{max} = 214 (log ε = 4.71), 265 (4.27), 313 nm (4.39).

^{1}H-N.M.R. ($CDCl_3$): δ = 7.7–7.2 (m, 5H); 6.57 (s, 2H); 5.84 (s, 1H); 3.40 (s, 3H); 2.40 (s, 3H); 2.06 (s, 3H); 1.78 ppm (s, 3H).

Each of the acetates **6a** and **6b** (6 mg) in chloroform (2 ml) is stirred with aqueous 0.2 normal sodium hydroxide (0.3 ml) for 15 min. In each case, the residue from evaporation of the chloroform phase is identical with **3** (by T.L.C. and superimposable I.R. spectra).

4-(2-Acetoxy-1-phenyl-1-propenyl)-6-methoxy-1,3,8-triacetoxynaphthalene (7):

Quinone methide **3** (50 mg) in acetic anhydride (8 ml) is shaken for 2 h under hydrogen (2 atm) in the presence of palladium-on-carbon 10% (10 mg). The hydrogen is eliminated and the solution immediately treated with pyridine (10 ml) and left 48 h in the dark. The catalyst is separated by filtration, and the residue from evaporation of the filtrate (under reduced pressure) is purified by preparative T.L.C. (silica H, benzene/ethyl acetate 3:1), extracting the adsorbent with chloroform. This affords **7** as a non-crystallizable, waxy powder: yield: 32 mg.

M.S.: *m/e* (relative intensity) = 506 ($M^{\oplus}$, 11), 464 (10), 446 ($M^{\oplus}$ – HOAc with allene formation, 23), 422 (16), 421 ($M^{\oplus} - 42 - CH_3CO$ from the liberated methyl ketone, 4), 404 (53), 380 (56), 379 (18), 362 (55), 338 (30), 337 (62), 320 (100), 295 (67), 206 (24).

I.R. (KBr): ν_{max} = 1750, 1733, 1624, 1364, 1200, 1150, 1123, 1030, 1005, 895 cm^{-1}.

U.V. (methanol): λ_{max} = 238 (log ε = 4.85), 288 (3.97), 321 (3.57), 335 nm (3.57).

^{1}H-N.M.R. ($CDCl_3$): δ = 7.73, 6.83 (2d, 1H each, J = 2.5 Hz); 7.22 (narrow m, 5H); 6.82 (s, 1H); 3.88 (s, 3H); 2.37; 2.34; 2.14; 2.01, 1.74 ppm (5s, 3H each).

We thank the following agencies for financial support: Conselho Nacional de Desenvolvimento Científico e Tecnológico, Coordenação de Aperfeiçoamento do Pessoal de Ensino Superior, Conselho de Pesquisas e Ensino para Graduados da U.F.R.J., Fundação de Amparo à Pesquisa do Estado de São Paulo, Universidade Federal de Pernambuco, Banco Nacional do Desenvolvimento Econômico (FUNTEC 47 and 101), and Ministério do Planejamento (FINEP/FNDCT, contrato 140/CT).

Received: May 9, 1977

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[1] Stable *ortho*- and *para*-naphthoquinone methides; Part 3. For Parts 1 and 2, see Ref. 3 and 4.

[2] Taken in part from the *Master's dissertation* of A. T. Henriques, Universidade Federal do Rio de Janeiro, 1974.

[3] K. S. Brown, U. Weiss, *Tetrahedron Lett.* **1971**, 3501.

[4] K. S. Brown, Paul M. Baker, *Tetrahedron Lett.* **1971,** 3505.
[5] K. L. Rinehart et al., *J. Am. Chem. Soc.* **93,** 6273 (1971).
[6] P. M. Baker, B. W. Bycroft, *J. Chem. Soc. Chem. Commun.* **1968,** 71.
W. Theilacker, W. Schmid, *Justus Liebigs Ann. Chem.* **570,** 15 (1950).
B. W. Bycroft, J. C. Roberts, *J. Chem. Soc.* **1962,** 2063.
[7] V. Arkley, J. Attenburrow, G. I. Gregory, T. Walker, *J. Chem. Soc.* **1962,** 1260.
[8] L. Fieser, M. Fieser, *Reagents for Organic Synthesis.* John Wiley & Sons, New York, Vol. 1, 1967, p. 31; Vol. 3, 1972, p. 7.
E. Hardegger, E. Widmer, K. Steiner, A. Pfiffner, *Helv. Chim. Acta* **47,** 2027 (1964).
[9] W. A. Noyes, *Org. Synth., Coll. Vol.* II, 108 (1943).
W. H. Hartung, F. Crossley, *Org. Synth., Coll. Vol.* II, 363 (1943).
W. W. Hartman, L. J. Roll, *Org. Synth., Coll. Vol.* III, 20 (1955).
[10] J. W. Mathieson, R. H. Thomson, *J. Chem. Soc.* [C] **1971,** 153.
[11] A. B. Turner, *Quart. Rev.* **18,** 347 (1964); *Fortschr. Chem. Org. Naturst.* **24,** 288 (1966); and recent updatings by various authors in *Annual Reports Progr. Chem. B (Chem. Soc., London)*, **1968–1974.**