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SYNTHESIS OF NATURALLY OCCURRING BINAPHTHAQUINONES AND RELATED COMPOUNDS A NOVEL REACTION BETWEEN PLUMBAGIN AND ITS HYDROQUINONE

Akella V.B. Sankaram, Adapa Srinivasa Rao and Gurbachan S. Sidhu

Regional Research Laboratory, Hyderabad - 500009, India.

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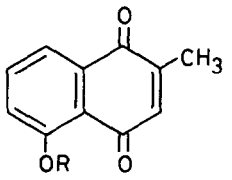
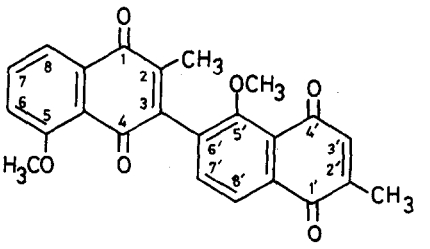
To synthesise naturally occurring 1,4-binaphthaquinones derived from 4,5-dihydroxy-2-methyl-naphthalene[1] under mild conditions, such as may prevail in living plants, plumbagin (I) (94 mg in methanol, 10 ml) and its hydroquinone (190 mg in methanol, 14 ml), buffered in phosphate (140 ml) to pH 6.8, were reacted at ca 30°. After 4 hrs. the reaction mixtures from twenty such experiments were combined, filtered and the precipitate and the mother liquor were separately extracted with chloroform. The extracts were, however, later combined and washed with aqueous sodium bicarbonate to remove 2-methyl-3,5-dihydroxy-1,4-naphthaquinone (droserone) which was recovered by acidification (65 mg). The chloroform extract was washed with water, dried, concentrated and fractionated over a silicagel column with chloroform as the eluent into plumbagin (2.7 g), Mixture 'A' and Mixture 'B'. Mixture 'A' was methylated with methyl iodide and silver oxide in $CHCl_3$ and separated by column chromatography over silicagel with $CHCl_3$ - EtOAc (7:1) into two fractions F_1 and F_2, and two pure compounds A-1 and A-2, F_1 on elution with C_6H_6 - EtOAc (2:1) on a silicagel column separated into compounds A-3 and A-4 and F_2 on elution with EtOAc yielded compounds A-5 and A-6.

Compound A-1, yellow crystals, m.p. 243-44° from CH_2Cl_2 - Petroleum ether, b.p. 40-60° (305 mg); ν_{max}^{KBr} : 1660 cm^{-1}; analyses for $C_{24}H_{18}O_6$; M^+, 402; it is thus a binaphthaquinone derived from plumbagin methylether (M.W. 202); only one allylic proton is seen in its NMR spectrum ($CDCl_3$) at 6.97* (q, J=1.5 Hz) with the corresponding CH_3 doublet at 2.05; the other CH_3 gives a singlet at 1.94. Therefore, the linkage is between the C-3 position of the quinone ring in one moiety and C-6', 7' or 8' position in the benzene ring of the other moiety. Since A-1 is different from chitranone dimethylether (III)[2], the 3,6'-linkage is ruled out; if the linkage were to be 3,7', a meta coupled quartet for 6'-H and 8'-H would be expected, but these two protons appear as a sharp singlet at 7.41, pointing to a 3,8'-linkage. The protons at C-6, C-7 and C-8 give a clear ABX pattern (approximated to AMX, 6-H, 7.28-7.38, q, $J_{6,8}$ = 2 Hz, $J_{6,7}$ = 8 Hz; 7.64-7.80, t, J = 8 Hz;

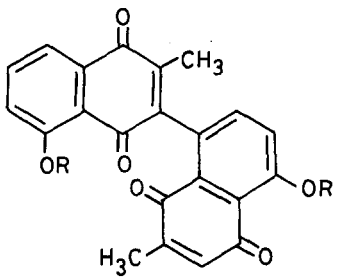
* Chemical shifts are given in δ values with TMS as internal standard.



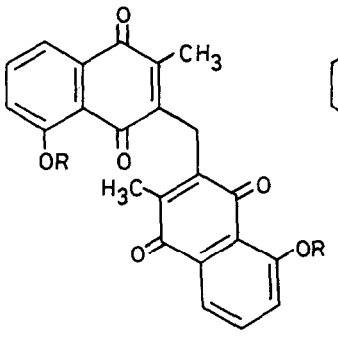
I, R = H
II, R = CH_3



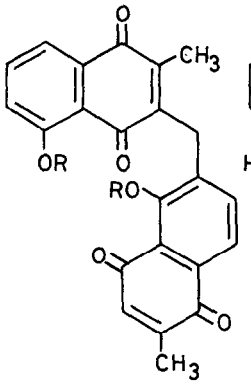
III



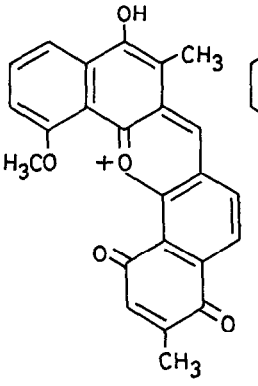
IV, R = H
V, R = CH_3



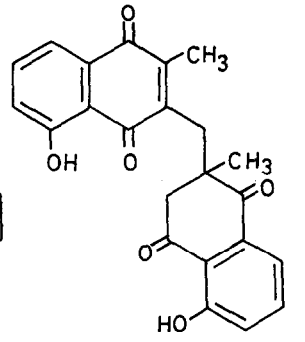
VI, R = H
VII, R = CH_3



VIII, R = H
IX, R = CH_3



X



XI

8-H, 7.83-7.93, q, $J_{8,6}$ = 2 Hz, $J_{7,8}$ = 8 Hz). The methoxyl protons absorb at 4.00 and 4.10. Compound A-1 is, therefore, assigned structure (V) and the parent compound, 3,8'-biplumbagin (IV) is named isochitranone. A comparison of the benzene induced solvent shifts (Δ = δ $CDCl_3$ - δ $CDCl_3$ - C_6H_6 (1:3) of the methyl and methoxyl protons of plumbagin methylether (II) and isochitranone dimethylether also supports structure (V) for the latter. In (II), the ortho positions to methoxyl and methyl groups do not carry a substituent and undergo shifts of + 0.58 and + 0.38 respectively. In isochitranone dimethylether (V) the methoxyl groups and one of the methyl groups undergo shifts of + 0.45 - + 0.63 and + 0.45 respectively. The second methyl group shifts only by + 0.03 as both the ortho positions are substituted. Similarly, in chitranone dimethylether one methoxyl and one methyl group show the ortho effect, while the others undergo the expected shifts (5-OCH_3, + 0.53; 2'-CH_3, + 0.38; 5'-OCH_3, + 0.08; 2-CH_3, + 0.12)[3,4].

Compound A-2, yellow crystals, m.p. 240-1° from $CHCl_3$ (116 mg); ν_{max}^{KBr}: 1660 cm^{-1}; M^+, 416.1257; required for $C_{25}H_{20}O_6$, 416.1260. It has thus an extra CH_2 group when compared to compound A-1.

No allylic proton is seen in its NMR spectrum (CF_3COOH). Singlets at 1.95 (2 x CH_3), 3.58 (2 x OCH_3) and 3.66, bs (CH_2) are seen. The six aromatic protons appear as a multiplet (6.87-7.47) with the splitting pattern as in plumbagin methylether. It thus appears to be a symmetric dimer derived from plumbagin methylether by the loss of two hydrogen atoms but linked by a methylene bridge between the two quinonoid rings. Structure (VII) is, therefore, assigned to this compound. It forms a leucotetra acetate m.p. 241-2°(CH_2Cl_2 - CH_3OH), M^+,588;NMR($CDCl_3$): 2.18, s(4 x $OCOCH_3$); 2.43, s(2 x CH_3); 3.88, s(2 x OCH_3); 4.25, bs(CH_2); 6.78-7.57, m(6 x Ar-H).

Compound A-3,yellow crystals, m.p. 223-4° from CH_2Cl_2(100 mg);ν_{max}^{KBr}: 1655, 1645 cm^{-1}; M^+, 416.1260, $C_{25}H_{20}O_6$ requires 416.1260. It is thus an isomer of A-2. Only one allylic proton is seen in the NMR spectrum ($CDCl_3$ + CF_3CO_2H) at 6.97, q (J = 1.5 Hz), which is coupled to a methyl group at 2.21, d (J = 1.5 Hz); the other methyl group gives a singlet at 2.20. The linkage thus involves the quinone ring of one plumbagin methylether moiety and the benzene ring of the other; the CH_2 bridge protons are seen at 4.23, bs. The two methoxyl groups absorb at 4.02. In the aromatic region there is an AB quartet for two ortho coupled protons at 7.65 and 7.99 (J = 8.5 Hz) which compares well with similar protons in chitranone dimethylether (7.81 and 8.02, q, J = 8 Hz)[2]; the other three aromatic protons give rise to a multiplet (7.45-7.93). A 3-6' linkage through a methylene bridge is, therefore, preferred and the compound is assigned structure (IX).

The expulsion of OCH_3 from the molecular ion of(IX) to give the base peak at m/e 385 appears to be facilitated by the formation of a six membered stable oxonium ion (X). The other major peaks are m/e 418, (20%); 401 (10%); 399 (4%); 384 (70%); 201 (21%).

On reductive acetylation compound A-3 gives a crystalline leucotetra acetate, m.p. 249-50° (CH_2Cl_2 - CH_3OH), M^+, 588; NMR($CDCl_3$):2.15, 2.27, 2.28, 2.38 and 2.43 all singlets for 18 protons, assignable to the 2 x Ar - CH_3 and 4 x $OCOCH_3$ protons; 3.92, s(2 x OCH_3); 4.30, bs(CH_2); 6.88-7.53, m(6 x Ar H) out of which 3'-H gives a singlet at 7.08 and 7'-H gives a doublet in the region 6.98-7.12 (J = 8 Hz).

Compounds A-4 (50 mg), A-5 (35 mg) and A-6 (46 mg) were identified by mixed m.p., TLC, IR, NMR and mass spectral comparison with authentic samples to be the dimethylethers of 6,6'-biplumbagin, (elliptinone), chitranone and 3,3'-biplumbagin respectively[1,2].

Mixture 'A' was subsequently worked up without methylation for separation of some of the parent compounds by silicagel column chromatography and recrystallisation. 3,8'-biplumbagin (IV) (243 mg), orange crystals, m.p. 200-1° from ethylacetate; (VI), red crystals, m.p. 228-9° (218 mg)

from CH_2Cl_2 and 3,3'-biplumbagin (76 mg) could be obtained in a pure state. Their spectral data are consistent with the assigned structures.

Mixture 'B' was chromatographed on a silicagel column with $CHCl_3$-EtOAc (2:1) as the eluent. Elliptinone (31 mg) was eluted first followed by a new compound B-1, orange crystals, m.p. 188-90° from acetone (32 mg); ν_{max}^{KBr} : 1680, 1660, 1640, 1625, 1600 and 1575 cm^{-1}; this light absorption is a summation of the I.R. spectra of plumbagin and β-dihydroplumbagin; M^+, 390.1108, $C_{23}H_{18}O_6$ requires 390.1103; it has thus two hydrogen atoms more than (VI) and (VIII). In its NMR spectrum both the methyl signals (1.38 and 2.18) are singlets; signals for the two methylenes (3.07 and 3.16) are also broad singlets; two perihydroxyl groups absorb at 11.90 and 12.05; there is no signal for an allylic proton and six aromatic protons are seen at 7.15-7.88, m. Structure (XI) can account for this data. In the mass spectrum, the base peak is at m/e 202; other major fragments are m/e 228 (5%), 189 (32%), 121 (10%), 120 (8%) and 92 (10%); M^+ is only 2%.

The formation of the simple dimers appears to proceed through a charge transfer complex and while A-2, A-3 and B-1 involve the possible participation of the solvent methanol (as formaldehyde) in the reaction; the latter is under investigation.

The coupling reaction of juglone and 1,8-dihydroxynaphthalene at pH 6.6 and 80°C was earlier studied[5]. The only isolable product was 4,9-dihydroxyperylene-3,10-quinone; products by attack at C-2, or C-3 of juglone were presumed to be formed but not isolated and identified.

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