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3-HYDROXY-1,4-DIPHENYL-7-OXABICYCLO[4.1.0]HEPT-3-ENE-2,5-DIONE. A MICROBIAL PRODUCT FROM STREPTOMYCES SPECIES (AAA566)

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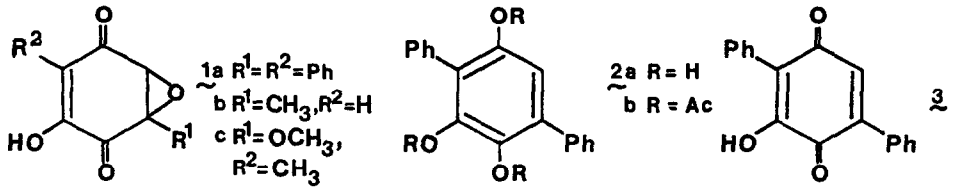
Summary: The epoxyenedione 1a has been isolated from a strain of Streptomyces and its structure has been established by nmr spectroscopy and by its conversion to 2,5-diphenyl-3,4-dihydroxyphenol. Selective hetero J-resolved nmr spectroscopy played a pivotal role in the structure elucidation.

The fermentation broth of a strain of *Streptomyces sp.* designated AAA566, was found to produce an antibiotic possessing weak activity against *B. subtilis* which we have now shown to be 3-hydroxy-1,4-diphenyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione 1a.



The dione 1a was eluted from silica gel with methylene chloride. Further purification by chromatography on sephadex LH-20 and elution with chloroform gave the pure compound as a bright yellow powder; m.p. 162-5°, $[\alpha]_D^{25°}$ = +117° (c, 0.113; $CHCl_3$), which analyzed for $C_{18}H_{12}O_4$. Its u.v. spectra (ethanol) in acid (pH 1), λ_{max} 237(ε6,600) and 337(ε8,400) nm and base (pH 12), λ_{max} 267(ε3,600) and 383(ε4,000)nm indicate the presence of a phenolic or enolic hydroxyl group.

The structure of the compound was established by nmr spectroscopy. The proton spectrum (DMSO-d_6/$CDCl_3$; 360 MHz) exhibits a hydroxyl (exchangeable with D_2O) resonance at δ11.3 and a sharp singlet at δ4.06 ppm. In addition, two very complex multiplets at δ7.605 (2H) and δ7.30 - 7.46 (8H) ppm are observed in the aromatic region and suggest the presence of two phenyl groups, one having somewhat deshielded ortho protons. This conclusion is confirmed by the ^{13}C spectrum (DMSO-d_6, 50.3 MHz) of 1a (see table). The GASPE technique[1] was used to assign the number of attached protons of the carbon atoms associated with each resonance. The relative intensities of the six resonances of the proton bearing carbon atoms in the region δ127 - 131 ppm lead to their assignments to o-, m-, and p-carbon atoms of two phenyl groups. Of the remaining eight resonances two are assigned to the ipso carbons, two to carbonyl groups, two to carbon atoms of an enol double bond and two to sp^3 oxygen bearing carbon atoms one of which carries the proton δ4.06 ppm. The phenyl groups must therefore be attached to a six carbon, monocyclic moiety comprised of the enol double bond, two carbonyl groups and a 1,2-epoxide. This last feature is required to explain the large value of $^1J_{^{13}C,H}$ for the proton bearing sp^3 carbon and is consistent with the i.r. spectrum of 1a (3030, 1250 cm^{-1}). A number of five and six membered ring structures incorporating the above features can be written. A unique structural assignment was possible from a consideration of the precise values of the long range coupling constants between the carbons and the proton absorbing at 4.06 ppm. The determination of the values (table) of the constants with the required accuracy was made possible by selective hetero J-resolved nmr spectroscopy using the recently developed technique of Bax and Feeman.[2] The absence of any coupling to the hydroxyl bearing carbon (154.2 ppm), and large (three-bond) couplings to one carbonyl and one phenyl bearing carbon atom can only be accommodated by 1a.

Confirmation of the structure 1a was obtained by reductive removal of the epoxide oxygen using chromous chloride[3] to yield the trihydroxy derivative 2a characterized as its triacetate (2b), m.p. 188-190°, which is identical with a sample prepared by the Thiele acetylation of 2,5-diphenylquinone.[4]

A cogener of the epoxydione 1 present in a ratio of less than 1:100 proved to be the known hydroxyquinone 3.[5] It also possesses weak antibiotic activity.

Table. ^{13}C Nmr data X or 1a and 3

3-HYDROXY-1,4-DIPHENYL-7-OXABICYCLO-[4.1.0.] HEPT-3-ENE-2,5-DIONE					3-HYDROXY-2,5-DIPHENYL 1,4-BENZOQUINONE	
C()[a]	δ(ppm)	No. H's	Rel. Int.	$J_{^{13}C,^{1}H}$ (Hz)[b]	C()[a]	δ(ppm)
C(2)	190.14	0		3.6	C(1)	186.16
C(5)	188.42	0		0.5	C(4)	182.80
C(3)	154.19	0		0.0	C(3)	153.07
ipso	130.93	0		1.0	C(5)	142.18
ipso	130.86	0		1.7	para	133.54
o/m	130.22	1	2		ipso	132.44
para	128.87	1	1		ipso	130.82
o/m	128.00	1	2		o/m	130.55
para	127.85	1	1		para	129.47
o/m	127.70	1	2		o/m	128.99
o/m	127.49	1	2		o/m	128.20
C(4)	119.66	0	1	5.0	o/m	127.42
C(6)	61.62	1		191.1	C(6)	127.35
C(1)	61.27	0		2.0	C(2)	118.99

[a]The meta(m) and ortho(o) carbons could not be separately assigned. Likewise, it was not possible to make separate assignments of any of the aromatic carbons to a particular phenyl ring.

[b]*coupling to the epoxide proton H(6)*

A number of epoxyquinone antibiotics,[6] including terreic acid 1b[7] and the compound 1c[8] which also possess the enolic hydroxyl group, are known. It is interesting that 1a is more stable to alkali than terreic acid or compound 1c, which decompose in minutes at room temperature, although substantial decomposition of 1a was observed over longer periods.

The CD of terreic acid has been reported and discussed.[9] In cyclohexane it exhibits extrema at 323 ([θ] +11,800) and 374 nm ([θ] -6570). In contrast, 1a in $CHCl_3$ has extrema at 263 ([θ] -70,600) and 340 nm ([θ] +23,900). The sign reversal could well be associated with a change in the preferred conformation rather than absolute configuration.

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