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GENERATION AND E.S.R. SPECTRUM OF THE 1,8-DIHYDROXY-9-ANTHRON-10-YL RADICAL

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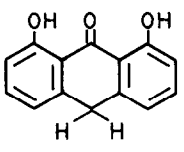
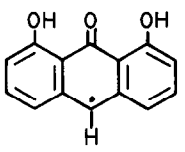
Abstract The e.s.r. spectra are reported of the 1,8-dihydroxy-9-anthron-10-yl radical, and of two of its deuterium isotopomers, and of its spin adduct with 2,4,6-tri-t-butylnitrosobenzene.

1,8-Dihydroxy-9-anthrone (I) (Dithranol, Anthralin) is used for the topical treatment of psoriasis, a proliferative skin disease. Its precise mode of action is uncertain but it is believed that the corresponding 1,8-dihydroxy-9-anthron-10-yl radical (II) is involved directly or indirectly in inhibiting the action of oxidative respiratory enzymes in the mitochondria, thereby slowing down the abnormal proliferation and allowing the epidermal cells to form normal skin tissue.



(I)



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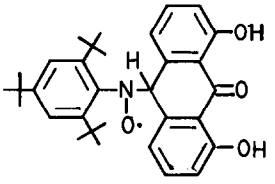

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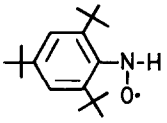

(IV)

The e.s.r. spectrum of a radical derived from dithranol, which appears as a broad triplet with hyperfine coupling *ca.* 2 G, has been published, and a nitroxyl radical obtained by autoxidation of dithranol in pyridine in the presence of 2,4,6-tri-t-butylnitrosobenzene was ascribed the structure (III), a(N) 12.0, a(1H) 13.6, a(2H-*m*) 0.75 G, g 2.007.[1,2] These would be unusual spectral parameters for such a species, and Mottley, Kalyanaraman, and Mason[3] have recently proposed that the spectrum should be ascribed instead to the hydrogen atom adduct (IV), and we agree with this analysis.

We report here the direct observation of what we believe to be the authentic spectrum of the radical (II) and of two of its isotopomers, from different sources, and of the product of spin-trapping by tri-t-butylnitrosobenzene.

If dithranol (V) in xylene is irradiated with U.V. light, alone or in the presence of di-t-butyl peroxide, or is heated above 100 °C in an e.s.r. cavity, it shows a spectrum which can be analysed in terms of the hyperfine coupling constants for the radical (VI), as shown in the Table. Under the same conditions, the same spectrum is obtained from the dehydrodimer

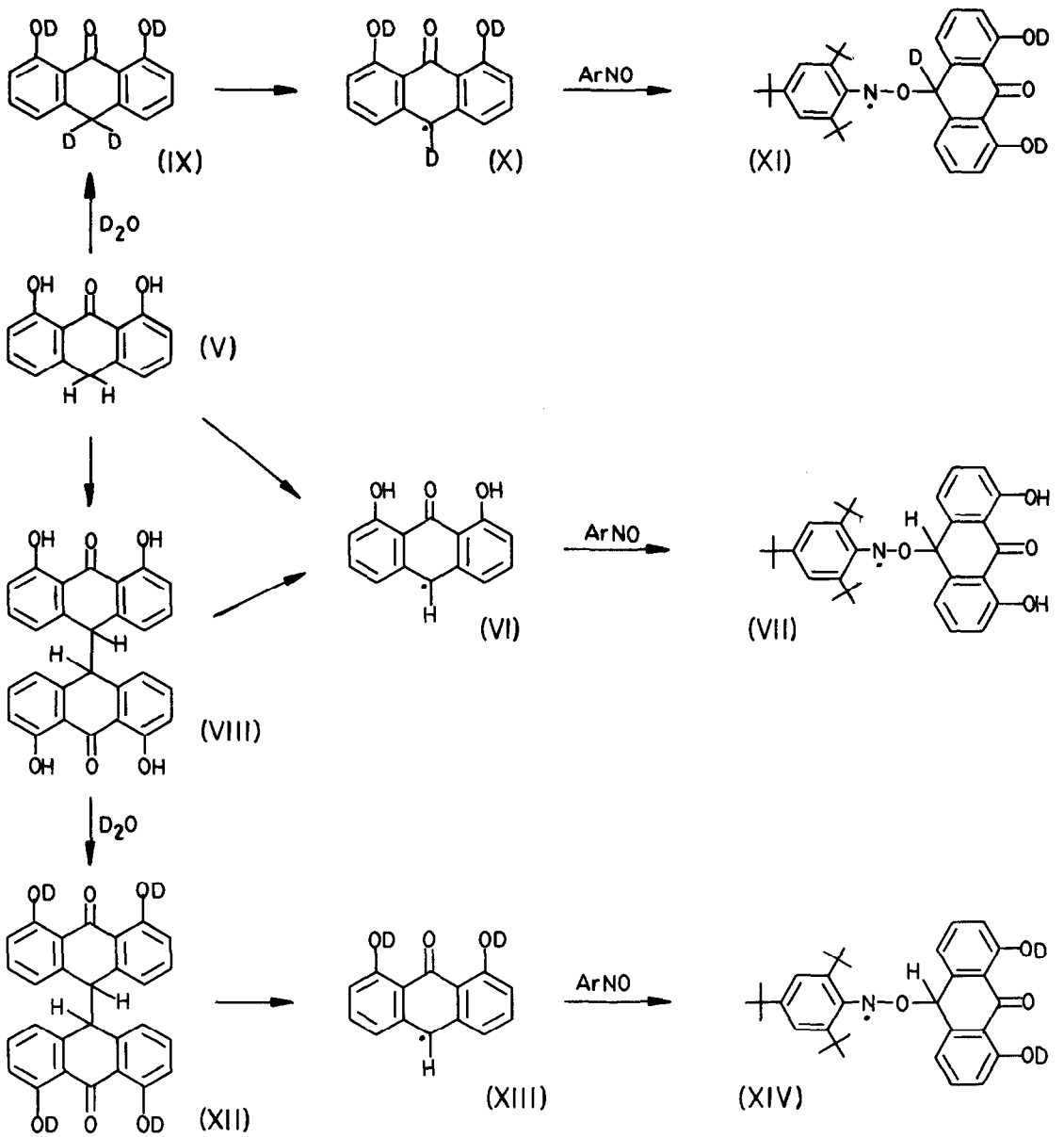

Table E.s.r. Spectra of radicals

Radical	T/°C	a/G H-2,4,5,7	H-3,6	H-10	HO-1,8	N	H-2m	g
VI	121	4.33	1.0	10.4	0.4			2.0029
X	140	4.33	1.05	1.61				2.0029
XIII	118	4.3	1.0	10.45				2.0029
VII	20			1.00		11.25	1.85	2.0047
XI	130					10.2	1.85	2.0041
XIV	150					11.25	1.85	

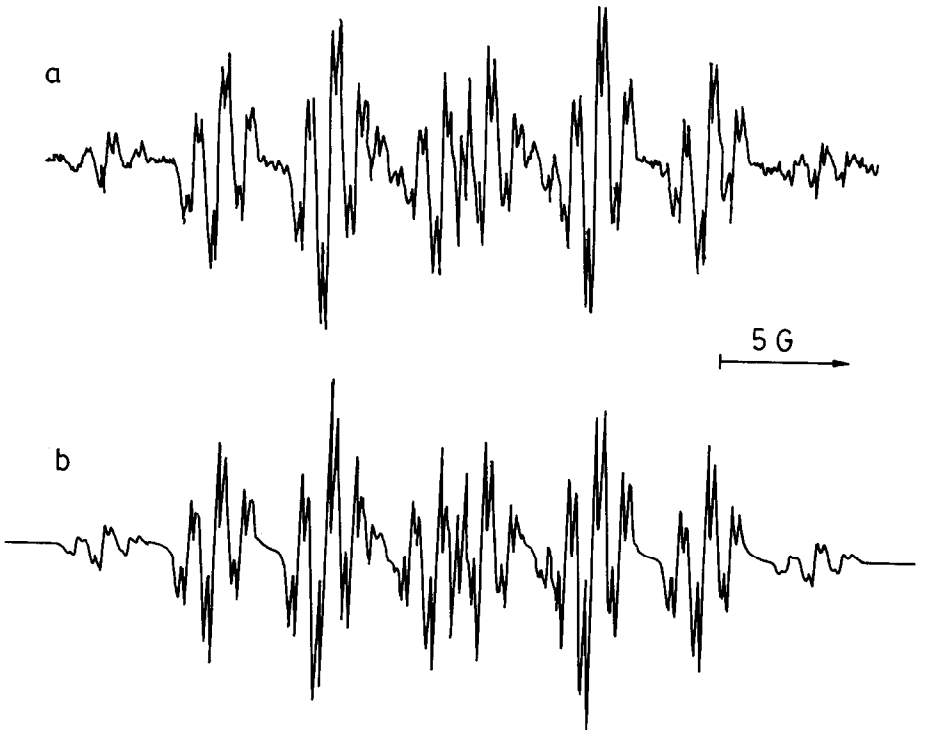

Figure 1 (a) E.s.r. spectrum of the 1,8-dihydroxy-9-anthron-10-yl radical (VI), obtained by the thermolysis of the dehydrodimer (VIII) in xylene at 121 °C.
(b) Computer simulation, using the hyperfine coupling constants given in the Table, and a line width of 0.165 G.

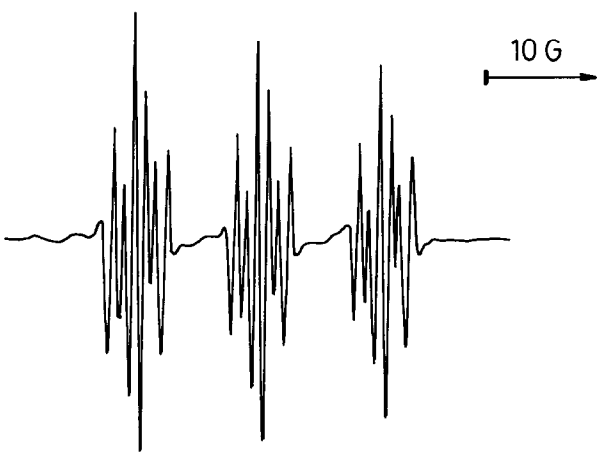

Figure 2 Third derivative e.s.r. spectrum of the radical (VII) obtained from the photolysis of the dehydrodimer (VIII) in xylene in the presence of 2,4,6-tri-t-butylnitrosobenzene at 20 °C.

(VIII), the structure of which has been established by X-ray crystallography[4]. The spectrum of (VI) (from VIII in xylene at 121 °C) is shown in Figure 1, together with a simulated spectrum using the hyperfine coupling constants given in the Table.

To confirm this assignment, dithranol or its dehydrodimer (100 mg) in xylene (0.5 cm^3) was heated under reflux with a few drops of deuterium oxide for 1 hour, and the radicals then generated as before.

The deuteriated dithranol (IX) showed the hyperfine coupling constants for the radical (X) given in the Table, indicating that in (IX) the 1-OH, 2-OH and 10-H_2 atoms had been exchanged, whereas the deuteriated dehydrodimer showed loss of resolvable hyperfine coupling to only the hydroxyl groups in (XIII), demonstrating that only these groups had undergone exchange in (XII).

The consistency of this set of spectra places the identification of the radical (VI) beyond reasonable doubt. The spectrum in the literature[2] must relate to some other species.

When the same reactions were carried out in the presence of 2,4,6-tri-t-butylnitrosobenzene, radicals (VII), (XI) and (XIV), with the spectral characteristics shown in the Table were obtained. The spin-trapped 1,8-dihydroxy-9-anthronyl radical (VI) was best obtained from the dehydrodimer (VIII) and showed the spectrum displayed as the third derivative in Figure 2. Dithranol itself (V) showed a spectrum corresponding to the radical observed by Martinmaa *et al.*[1,2] which we believe to have the structure (IV). However, a clean spectrum of the radical (XI) was obtained from the tetradeuteriated dithranol (IX).

The dideuteriated radical (XIII) reacted to show an indistinguishable spectrum because hyperfine coupling to the hydroxyl groups in the spin adduct cannot be resolved, but the trideuteriated radical (XI) gave a product which showed the loss of the hyperfine coupling to the unique proton. The results are compatible with the formulation of the structures of the spin adducts as shown in (VII), (XI), and (XIV). These are represented as aminyl radicals rather than as nitroxyl radicals because Terabe and Konaka[5,6] showed that primary alkyl radicals reacted with tri-t-butylnitrosobenzene to give nitroxyl radicals with a(N) *ca.* 13 G, g *ca.*2.0060, whereas more bulky radicals reacted to give aminyl radicals with a(N) 10-11 G, g 2.0040.

This work shows that, at least under the conditions of our experiments, the dehydrodimer is equally as good as dithranol itself as a source of the dihydroxyanthronyl radical. If the latter radical is indeed the pharmacologically active species which alleviates psoriasis, then, once absorbed into the tissue, dithranol and the dehydrodimer might be expected to produce the same clinical effects.

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