The Transformation of a Methoxy- into a Methylenedioxy-group

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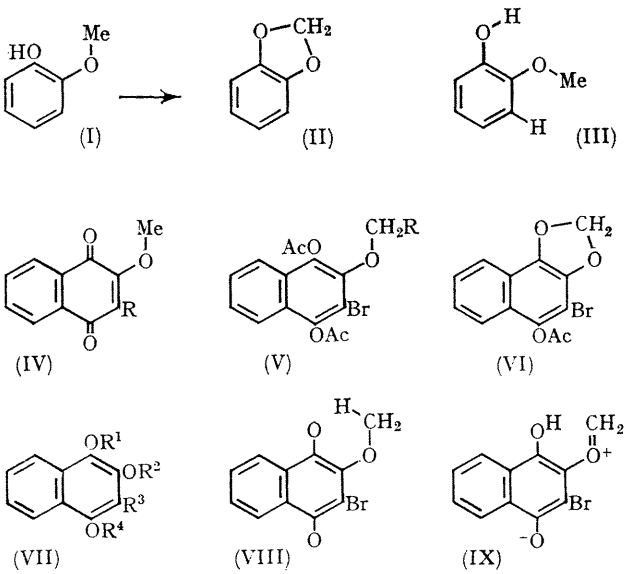
THE suggestion that the methylenedioxy-function of natural products is formed by direct oxidative conversion of the guaicol residue is supported by *in vivo* experiments,[1,2] wherein a suitably labelled methoxy-precursor, as (I), gives the methylenedioxy-product (II) with retention of the methyl carbon atom. An intramolecular hydrogen abstraction, within the guaicol function, might account for this biological conversion[3] and we now report an indirect example of this transformation achieved by photochemical means, and therefore accomplished *in vitro*.

The proximity of the phenolic hydroxy-group to the methyl group of a methoxy-function, in (I), means that a radical at oxygen might be well placed to abstract hydrogen through a six-membered transition state.[4] However chemically-produced phenoxy-radicals, unlike alkoxy-radicals,[5] tend not to abstract hydrogen from saturated carbon,[6] and therefore the radical was activated by photolysis of a quinone.[7] The favoured conformation of a 3-unsubstituted-2-methoxyphenol would be expected to be that described by (III), and this is confirmed, at least in the crystal state, by the recent *X*-ray structure of ochotensine methiodide.[8] Therefore, in order to compress the two functions into the requisite conformation, as (I), we substituted bromine into the 3-position. The model was thus defined as the quinone (IV; R = Br); the low chemical shift (δ 4·32)† of the methoxy-group relative to that (δ 3·94) of the quinone (IV; R = H) indicated population of the required conformation. In the event, irradiation of (IV; R = Br) in acetic anhydride solution‡ with a medium pressure mercury arc, through Pyrex, gave a mixture from which we have isolated, by chromatography over silica gel, two compounds, the triacetate (V; R = OAc) and the methylenedioxy-compound (VI). The triacetate (V; R = OAc), $C_{17}H_{15}O_7Br$,§ m.p. 149°, ν_{max} ($CHCl_3$) 1780 and 1770 cm.$^{-1}$, had a u.v. spectrum λ_{max} (EtOH) 232 mμ (ε 74,000), 285 (5500), 297 (4000), and 326 (450) superimposible on that of (V; R = H), prepared by mild zinc reduction of the starting quinone. The n.m.r. signals ($CDCl_3$) δ 2·10, 2·43, 2·48 (s, 3 × 3H), 5·73 (s, 2H), and 7·68 (sym. m, 4H) were in accord with the formulation except that the shift (5·73) of the methylene group was considerably removed from that expected (6·66).[9] We therefore obtained a chemical proof of the structure by



† All chemical shift data are expressed relative to tetramethylsilane and spectra were obtained at room temperature and 60 MHz, unless otherwise stated.

‡ An acylating solvent is essential in these reactions because in its absence the phenolic intermediates undergo redox processes with the quinone, yielding complex mixtures.

§ All new compounds have given satisfactory analyses (±0·3%) and their formulae have been checked by high resolution mass spectrometry.

acidic hydrolysis to formaldehyde (2,4-dinitrophenylhydrazone) and the phenol (VII; $R^1 = R^2 = R^4 = H$, $R^3 = Br$), characterized as the triacetate (VII; $R^1 = R^2 = R^4 = Ac$, $R^3 = Br$), m.p. 158°, and reduced with zinc in acetic anhydride at reflux to the known triacetate (VII; $R^1 = R^2 = R^4 = Ac$, $R^3 = H$).

The methylenedioxy-compound (VI), $C_{13}H_9O_4Br$, m.p. 107°, ν_{max} ($CHCl_3$) 1770 cm.$^{-1}$, had a u.v. absorption expected for a 1,2,4-trioxynaphthalene and similar to that of the accompanying triacetate but exhibiting a bathochromic shift of about 10 mμ, *i.e.* λ_{max} (EtOH) 244 mμ (ε 46,000), 281 (2500), 299 (3500), 312 (3800), and 350 (3600). The n.m.r. ($CDCl_3$) was completely in accord with the formulation (VI) with δ 2·48 (s, 3H), 6·20 (s, 2H),[10] 7·52 (m, 4H), and the mass spectral fragmentation pattern demonstrated, after elimination of the elements of keten, a sequential loss of CH_2O (*m/e* 30) and CO (*m/e* 28) which we have found common to a series of model methylenedioxybenzenes. These two products were not interconvertible under the reaction conditions, and in the present work the yield of methylenedioxy-compound (VI) was 15%, and that of the triacetate (V) 62%, as estimated by n.m.r. spectroscopy on the reaction product.

In keeping with the importance of the conformational relationship between the abstracting atom and the methyl group, we found that the unsubstituted quinone (IV; R = H) gave only the product (VII; $R^1 = R^4 = Ac$, $R^2 = Me$, $R^3 = H$) of hydrogen abstraction from the solvent and its phototransformation product (VII; $R^1 = R^3 = Ac$, $R^2 = Me$, $R^4 = H$).[11] Mechanistically it seems likely that the excited quinone, as (VIII), is transformed by hydrogen abstraction to a diradical. Subsequent to this several possibilities exist but an attractive one is that the intermediate carbon radical undergoes direct electron transfer to the nucleus, yielding a dipole (IX), which could by reaction with solvent or by direct closure give the two products we have encountered.

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[1] D. H. R. Barton, G. W. Kirby, and J. B. Taylor, *Proc. Chem. Soc.*, 1962, 340.

[2] The general area of phenolic oxidation in biosynthesis has recently been reviewed by A. R. Battersby in "Oxidative Coupling of Phenols," ed., W. I. Taylor and A. R. Battersby, Marcel Dekker, New York, 1967, p. 119.

[3] An alternative possibility would involve direct hydroxylation of the methyl group by a mixed function oxidase (*cf.* T. E. Krug, H. S. Mason, and M. Morrison, "Oxidases and Related Redox Systems," Wiley, New York, 1965, vol. I).

[4] D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1961, **83**, 4076.

[5] Reviewed by P. Gray and A. Williams, *Chem. Rev.*, 1959, **59**, 239.

[6] The chemistry of phenoxy-radicals is reviewed by H. Musso in ref. 2.

[7] The intramolecular hydrogen abstraction process of photoexcited quinones is a very widespread phenomenon, *cf.* A. Schonberg and A. Mustafa, *J. Chem. Soc.*, 1944, 67; 1945, 657; G. P. Schenck and G. Koltzenburg, *Naturwiss.*, 1954, **41**, 452; N. K. Bridge and G. Porter, *Proc. Roy. Soc.*, 1958, *A*,**244**, 259, 276; N. K. Bridge, *Trans. Faraday Soc.*, 1960, **56**, 1001; C. A. Parker, N. K. Bridge, and G. Porter, *Nature*, 1958, **182**, 130; C. F. Wells, *Trans. Faraday Soc.*, 1961, **57**, 1703; D. Schulte-Frohlinde and C. V. Sonntag, *Z. phys. Chem.* (*Frankfurt*), 1965, **44**, 314; J. M. Bruce and E. Cutts, *J. Chem. Soc.* (*C*), 1966, 449; J. M. Bruce and J. N. Ellis, *ibid.*, 1966, 1624. Intramolecular abstractions have been noted by A. C. Waiss, jun., and J. Corse, *J. Amer. Chem. Soc.*, 1965, **87**, 2068; J. M. Bruce and P. Knowles, *J. Chem. Soc.* (*C*), 1966, 1627; C. M. Orlando, jun., H. Mark, A. K. Bose and M. S. Manhas, *J. Amer. Chem. Soc.*, 1967, **89**, 6257, and references therein.

[8] A. C. Macdonald and J. Trotter, *J. Chem. Soc.* (*B*), 1966, 929.

[9] *Cf.* R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd edn., Wiley, New York, 1967.

[10] Methylenedioxy-protons in a wide variety of aromatic systems fall in a band between δ5·9 and 6·2, *cf.* N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, NMR Spectra Catalog., vol. 1, Varian Associates, Palo Alto, 1962.

[11] The photochemical Fries rearrangement has many analogies, *cf.* R. A. Finnegan and J. J. Mattice, *Tetrahedron*, 1965, **21**, 1015 and references therein.