

Benzylic Hydroxylation of 11-Oxo-oestrones by Hydration of Quinone Methides. A Novel Demonstration of the Presence of a Reactive Intermediate

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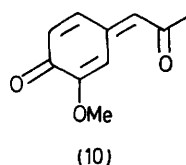
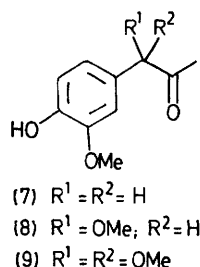
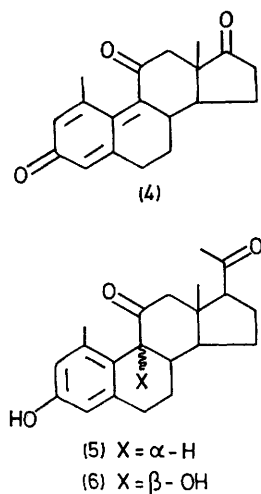
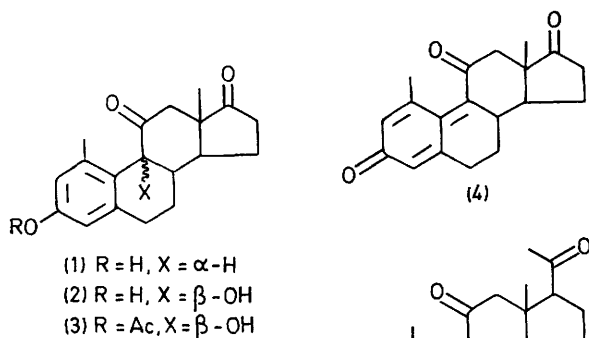
Summary Oxidation of 3-hydroxy-1-methyloestra-1,3,5-(10)-triene-11,17-dione (**1**) with dichlorodicyanobenzoquinone (DDQ) in aqueous dioxan gives the 9 β -hydroxy-derivative (**2**) by a mechanism involving addition of water to the intermediate quinone methide (**4**).

1-METHYL-11-OXO-OESTRONE (**1**) reacts slowly with DDQ in 1% aq. dioxan to give the 9 β -ketol (**2**). A 0.2M solution of steroid (**1**) and of DDQ gradually deposits crystals of dichlorodicyanohydroquinone (5 days; 20°). Evaporation after removal of the hydroquinone, followed by addition of

ethyl acetate, gave the ketol (**2**), m.p. 218—220° (decomp.), † [m/e 314 (M^+ , 16%), 296 (32), 229 (80), and 176 (100)], in 50% yield. Further crystals were obtained from the mother liquors, raising the yield to 65%. The ketol (**2**) gave the monoacetate (**3**), m.p. 191—192° [m/e 356 (M^+ , 18%), 271 (55), 229 (48), and 176 (100)], after acetylation with acetic anhydride in pyridine. The 9 β -configuration of the tertiary hydroxy-group in these compounds was clear from i.r. studies, which showed intramolecular hydrogen bonding in the ketol system.¹ The pregnane (**5**) was similarly oxidised to the ketol (**6**), m.p. 188—191°, in 35% yield.

† Satisfactory analytical and spectral data were obtained for all new compounds.

The hydroxy-group introduced at the 9 β -position was shown to originate from water by labelling experiments.



When the reaction was run in dioxan containing 1% H₂¹⁸O, the first crystals of ketol contained 85% 9 β -¹⁸OH [*m/e* 316 (*M*⁺, 20%), 298 (50), 296 (42), 231 (68), and 178 (100), monoacetate *m/e* 358 (*M*⁺, 13%), 273 (45), 231 (45), and 178 (100)]. Retention of ¹⁸O in the major fragments, apart from that formed by loss of H₂¹⁸O, was established by accurate mass measurements. Further

crystals of ketol, from the mother liquor, unprotected against atmospheric moisture, contained decreasing amounts of ¹⁸O. This suggested that the intermediate quinone methide (4) was present in the mother liquors, and was only slowly hydrated, since no DDQ remained at this stage. This was confirmed by repeating the original reaction in H₂¹⁶O-dioxan and adding H₂¹⁸O to the reaction mixture after all the DDQ had been consumed and after about 50% of the unlabelled ketol had been isolated, when 18% ¹⁸O-incorporation was observed. Attempts to obtain direct spectroscopic evidence for the intermediate (4), particularly from u.v. studies, were hindered by the formation of purple by-products, and no adducts were obtained when simple aliphatic alcohols were used instead of water.

Similar oxidation of guaiacylacetone (7) in 5% methanolic dioxan gave the methoxy-derivative (8) in 50% yield (g.l.c.). It was also formed by oxidation in pure MeOH and characterised as its monoacetate. The product (8) was resistant to DDQ in methanolic dioxan at 20°, but further oxidation occurred in refluxing solution, and the dimethoxy-derivative (9) was formed. Only an intractable mixture was obtained when the phenol (7) was oxidised in aq. dioxan, and in the anhydrous solvent polymeric material was obtained. These results indicate formation of the extended quinone (10), which either polymerises or is trapped by the addition of methanol.²

In these substrates when the carbonyl group is adjacent to the benzylic centre undergoing oxidation the usual hydride abstraction mechanism³ is prevented, so the formation of the intermediate quinone methide may involve a concerted process,^{4,5} leading directly to the quinone methide and dichlorodicyanohydroquinone, or one-electron oxidation to the phenoxyl radical, followed by further oxidation to the phenoxonium cation and subsequent proton loss from the 9 α -position.⁶

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¹ Cf. H. Hasegawa and K. Tsuda, *Chem. Pharm. Bull. (Japan)*, 1964, **12**, 473; H. Hasegawa, S. Nozoe, and K. Tsuda, *ibid.*, 1963, **11**, 1037; P. Crabbé and A. Bowers, *J. Org. Chem.*, 1967, **32**, 2921.

² Cf. H.-D. Becker, *J. Org. Chem.*, 1965, **30**, 982; J. W. A. Findlay and A. B. Turner, *J. Chem. Soc. (C)*, 1971, 23.

³ W. Brown and A. B. Turner, *J. Chem. Soc. (C)*, 1971, 2057.

⁴ R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8**, 837; thermal hydrogen transfer is a symmetry-allowed process for interacting systems of (4*q* + 2) π -electrons (*q* = 2 in this case).

⁵ For studies on other DDQ dehydrogenations which may involve concerted hydrogen transfer, see P. Müller and J. Roček, *J. Amer. Chem. Soc.*, 1972, **94**, 2716; F. Stoos and J. Roček, *ibid.*, 1972, **94**, 2719; P. Müller, *Helv. Chim. Acta*, 1973, **56**, 1243; I. Fleming and E. Wildsmith, *Chem. Comm.*, 1970, 223; cf. also G. B. Gill, S. Hawkins, and P. H. Gore, *ibid.*, 1974, 742.

⁶ H.-D. Becker, 'The Chemistry of the Quinonoid Compounds,' ed. S. Patai, Interscience, New York, 1974, p. 335.