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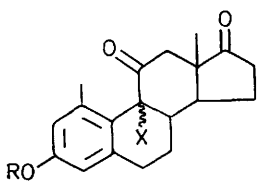
Summary Oxidation of 3-hydroxy-1-methyloestra-1,3,5-(10)-triene-11,17-dione (**1**) with dichlorodicyanobenzoquinone (DDQ) in aqueous dioxan gives the 9β-hydroxy-derivative (**2**) by a mechanism involving addition of water to the intermediate quinone methide (**4**).

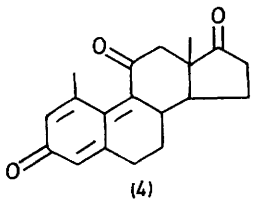
1-METHYL-11-OXO-OESTRONE (**1**) reacts slowly with DDQ in 1% aq. dioxan to give the 9β-ketol (**2**). A 0·2M solution of steroid (**1**) and of DDQ gradually deposits crystals of dichlorodicyanohydroquinone (5 days; 20°). Evaporation after removal of the hydroquinone, followed by addition of ethyl acetate, 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 9β-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.

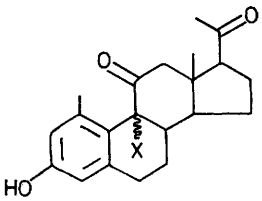
The hydroxy-group introduced at the 9β-position was shown to originate from water by labelling experiments.



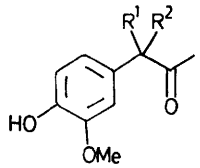
(1) R = H, X = α-H
(2) R = H, X = β-OH
(3) R = Ac, X = β-OH



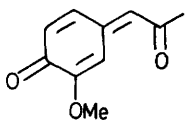
(4)



(5) X = α-H
(6) X = β-OH



(7) $R^1 = R^2 = H$
(8) $R^1 = OMe$; $R^2 = H$
(9) $R^1 = R^2 = OMe$



(10)

When the reaction was run in dioxan containing 1% $H_2{}^{18}O$, the first crystals of ketol contained 85% 9β-^{18}OH [*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 ^{18}O in the major fragments, apart from that formed by loss of $H_2{}^{18}O$, was established by accurate mass measurements. Further crystals of ketol, from the mother liquor, unprotected against atmospheric moisture, contained decreasing amounts of ^{18}O. 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 $H_2{}^{16}O$–dioxan and adding $H_2{}^{18}O$ to the reaction mixture after all the DDQ had been consumed and after about 50% of the unlabelled ketol had been isolated, when 18% ^{18}O-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 mechanism[3] 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 9α-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 $(4q + 2)\pi$-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.