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OXIDATION OF RING A-AROMATIC STEROIDS TO 9,11β-DIOL 11-NITRATES WITH CERIC AMMONIUM NITRATE

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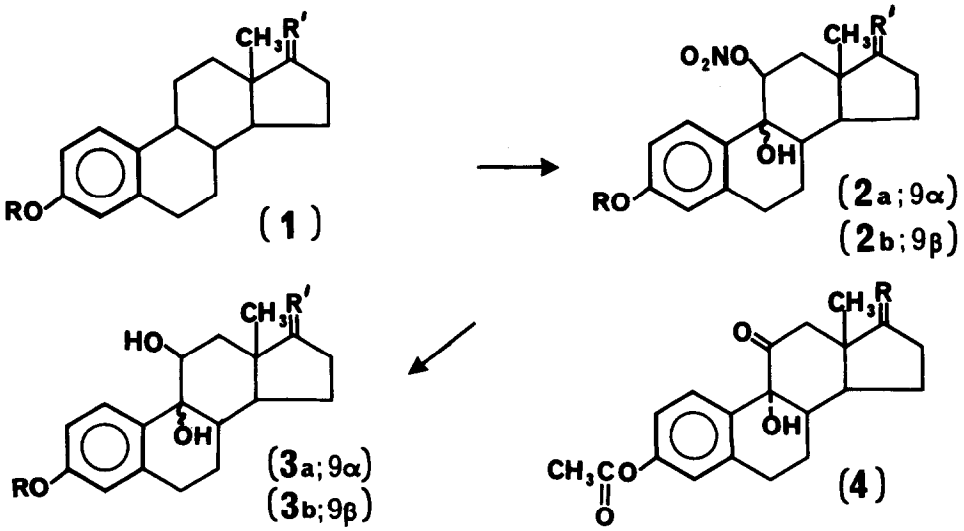
Recently we explored a synthetic route to steroidal oestrogens,[1] the critical stage of which was oxidation by ceric ammonium nitrate of an aromatic 1-methyl group to a 1-formyl group. We now report that in the absence of a 1-substituent oxidation occurs in ring C. Thus, oestrone acetate (1; R=Ac, R'=O) was oxidised in 40 minutes at room temperature by four molar equivalents of ceric ammonium nitrate in aqueous 90% acetic acid to give a readily isolated 69% yield of the corresponding 9α,11β-diol 11-nitrate (2a; R=Ac, R'=O), $\nu_{max.}$ ($CHBr_3$) 1630 and 1270 ($-ONO_2$) and 3570 $cm.^{-1}$(OH). The configuration of the 9-substituent follows from reduction of the nitrate to the 9α,11β-diol (3a; R=Ac, R'=O), by means of zinc or catalytic hydrogenation, and subsequent oxidation to the known 9α-hydroxy-11-ketone (4; R=O)[2] with chromic acid in acetone. The diol (3a; R=Ac,R'=O) could be renitrated to (2a;R=Ac, R'=O) with nitric acid in acetic anhydride.

The configuration of the 11-substituent can be deduced from the nuclear magnetic resonance spectrum (in $CDCl_3$) of the 9α,11β-diol (3a;R=Ac, R'=O), which shows a diffuse apparent triplet (in reality a double double doublet) at τ 5.62 (CHOH, J = ca.2.5 Hz) indicating that the 11-proton is equatorial (α). Further, the signal for the protons of the angular methyl group at τ 8.90, in better agreement with the calculated [3] value (8.82) for the introduction of 9α-hydroxyl (-0.03) and 11β-hydroxyl (-0.25) substituents into oestrone acetate (9.10) than that for the alternative 9α,11α-diol (9.04). The nitrate (2a;R=Ac, R'=O) also exhibits a diffuse triplet (a double doublet) for the equatorial 11α-proton at τ 4.17 (J = ca.3 Hz),the downfield shift relative to the parent alcohol indicating that the 11-hydroxyl carries the nitrate ester. Further, the signal for the angular methyl protons at τ 8.97 is shifted downfield relative to that of oestrone acetate.



In the oxidation of oestrone acetate only a small quantity (ca.5%) of an isomeric diol nitrate was formed. The oxidation of materials with different 17-substituents was less stereospecific; for example, oestradiol diacetate (1;R=Ac, R'=H, β-OAc) gave 46% of one diol nitrate and 17% of a second. The predominant 9α,11β-isomer (2a;R=Ac, R'=H, β-OAc) showed signals at τ 9.06 (13-$C\underline{H}_3$) and 4.26 (multiplet, $C\underline{H}ONO_2$) and on reduction gave the 9α,11β-diol (3a;R=Ac, R'=H, β-OAc), τ 8.95 (calc.from oestradiol diacetate, 8.90) and 5.57 (apparent triplet, J=3 Hz). Oxidation of the diol with chromic acid gave the ketol (4; R=H, β-OAc),which did not show hydrogen bonding in dilute solution in carbon tetrachloride, $\nu_{max.}$ 3600 (OH), further confirming that the 9-hydroxyl is in the α-configuration.[2]

The minor isomer is probably the 9β,11β-diol 11-nitrate (2b; R=Ac, R'=H, β-OAc),for the 11-proton is again equatorial in the nitrate (τ 3.93, J = ca. 3 Hz) and in the diol (3b; R=Ac, R' = H, β-OAc) (τ 5.41, J = ca. 3 Hz) formed from it on reduction. The 13-methyl protons in the nitrate appear at τ 8.95,downfield compared with the 9α-isomer,and on reduction to the diol the same downfield shift (-0.11) to τ 8.84 was observed as in the case of the 9α-isomers.

Oestrone methyl ether (1; $R=CH_3$, R'=O)reacted faster than oestrone acetate to similarly give a mixture of 9α,11β- and 9β,11β-diol 11-nitrates; reaction for a longer time with an excess of oxidant gave a more complex mixture. The effect on the oxidation of other changes in the 3- and 17-substituents is under investigation.

The oxidation of oestrone acetate is envisaged as proceeding first by oxidation at the benzylic 9-hydrogen, to give 9(11)-dehydro-oestrone acetate directly or via dehydration of a 9-hydroxy intermediate. This is supported by the observation that 9β-oestrone

acetate, 9α-hydroxy-oestrone acetate and 9,11-dehydro-oestrone acetate all give the same product (2a; R=Ac, R'=O) with ceric ammonium nitrate, in yields of 44%, 30% and 31% respectively. Further, oxidation does not occur through 9α,11α-epoxy-oestrone acetate or 11-oxo-oestrone acetate for these are not similarly oxidised. We postulate formation of an α-face complex with a ceric ion which allows nucleophilic attack by nitrate anion at the 11β-position to give a free radical at the 9-position which is further oxidised by ceric ion to yield a carbonium ion which then reacts with a water molecule to yield a 9α- or 9β-hydroxyl.

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