Preparation and Acid-catalysed Rearrangements of a Steroidal 1,4-Quinol

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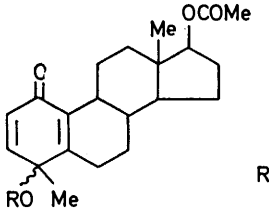
Thallium perchlorate oxidation of 17β-acetoxy-1-hydroxy-4-methylestra-1,3,5(10)-triene (1) was used to prepare the steroidal quinol, 17β-acetoxy-4ξ-hydroxy-4-methylestra-2,5(10)-dien-1-one (2), which could be isolated as a pair of diastereoisomers. Thallium nitrate in methanol yielded the corresponding 4-methoxy-quinol (3). Treatment of the quinol with HBr or HCl rearranged it to the 1,17β-diacetoxy-3-halogeno-4-methylestra-1,3,5(10)-trienes (4) and (5) (after acetylation) while HI expelled the 4-hydroxy-moiety and reduced it to 1,17β-diacetoxy-4-methylestra-1,3,5(10)-triene (6). Hydrogen fluoride failed to effect any reaction. Dienone–phenol type rearrangement, whereby the 4-methyl group migrated to C-3 affording 1,4,17β-triacetoxy-3-methylestra-1,3,5(10)-triene (15), was accomplished with BF_3–ether and subsequent acetylation. Use of $ZnCl_2$–acetic anhydride was found, on the other hand, to bring about migration of the oxygen moiety and give 1,3,17β-triacetoxy-4-methylestra-1,3,5(10)-triene (12). Attempts to rearrange the 4-methoxy-quinol ether (3) by the above methods failed.

In the light of a report by Yamada and co-workers [1] we became interested in thallium triperchlorate oxidation of steroidal *p*-cresol (1) and subsequent rearrangement of any resultant quinol [2] as a potential route to substituted 1-hydroxyestrogens, a class of compounds which has received attention as potential antifertility agents.[3] Thallium perchlorate seemed to offer a more attractive means of forming the quinol than thallium acetate [4] since the indicated yields were much better. Later reports, though, did reveal a major side-reaction during the oxidation of estrone [5] and the formation of 2-alkyl-*p*-quinones from *p*-alkylphenols, probably by rearrangement of an intermediate *p*-alkylquinol.[6]

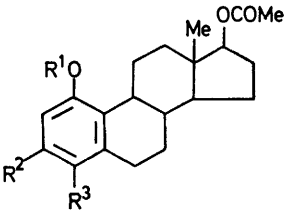
RESULTS AND DISCUSSION

Oxidation of (1) using the reported procedure [1] proceeded easily to afford two quinols (2) in fair yields, which could be separated by repetitive t.l.c. or by medium-pressure liquid chromatography. I.r. and u.v. spectral data were essentially the same for both compounds, indicating that they differed only slightly, most likely in the stereochemistry at C-4. The only distinguishing spectral information was from the ^1H n.m.r. spectra of each, whereby the major and less mobile isomer exhibited doublets (*J* 10 Hz) for the C-2 and C-3 protons at δ 6.55 and 5.9, and the minor isomer had doublets (*J* 10 Hz) for the same protons at δ 6.82 and 6.15. As yet, we have been unable to determine the absolute stereochemistry of each isomer, nor have we observed any differences in their reactivity in the acid-catalysed rearrangements. The corresponding quinol ether (3) was obtained in low yield by treatment with thallium trinitrate in methanol.[7] The product was characterized from its spectral data, particularly the C-2 and C-3 proton doublets (*J* 10 Hz) at δ 6.58 and 6.32 and the three-proton singlet on the methoxy-moiety at δ 2.93. An n.m.r. spectrum of the crude reaction product indicated the presence of a minor amount of another isomer but it could not be readily isolated.

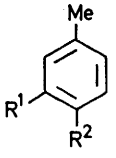
In general, rearrangement of the quinol (2) proceeded easily and in good yield with the various acidic reagents employed. The quinol ether (3), on the other hand, did not undergo any changes when the conditions used for



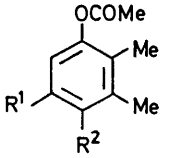
(2) R = H
(3) R = Me
(16) R = MeCO



(1) $R^1 = R^2 = H$, $R^3 = Me$
(4) $R^1 = MeCO$, $R^2 = Cl$, $R^3 = Me$
(5) $R^1 = MeCO$, $R^2 = Br$, $R^3 = Me$
(6) $R^1 = MeCO$, $R^2 = H$, $R^3 = Me$
(12) $R^1 = MeCO$, $R^2 = OCOMe$, $R^3 = Me$
(15) $R^1 = MeCO$, $R^2 = Me$, $R^3 = OCOMe$



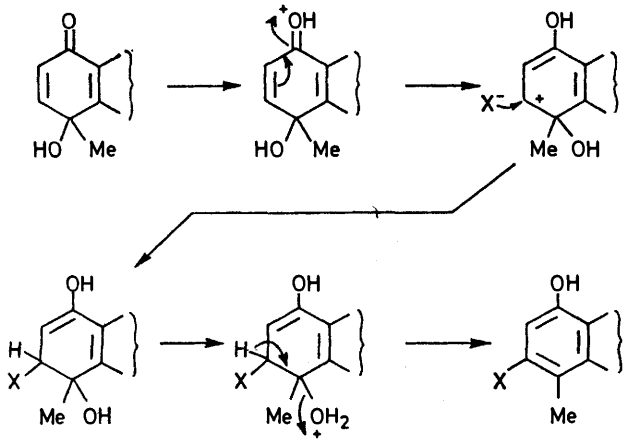
(7) $R^1 = Cl$, $R^2 = Me$
(8) $R^1 = Br$, $R^2 = Me$
(9) $R^1 = I$, $R^2 = Me$
(10) $R^1 = Me$, $R^2 = Br$
(11) $R^1 = Me$, $R^2 = I$



(13) $R^1 = MeCOO$, $R^2 = Me$
(14) $R^1 = Me$, $R^2 = MeCO$

(2) were applied, and gave only intractable mixtures when subjected to more forcing conditions. The most unusual results took place with the hydrohalide acids. By hydrochloric acid or hydrobromic acid treatment, then acetylation, chlorine or bromine was incorporated into ring A to yield 3-halogeno-1-acetoxyestrogens (4)

and (5), respectively. Presence of halogen in both molecules was verified initially by qualitative and quantitative analyses. The halogens were assigned to the C-3 position on the basis of the wide differences (>0.1 p.p.m.) between the chemical shifts of the C-2 protons of (4)—(6). These differences are more consistent with values for the chemical shift [8] of the analogous proton of the halogenated *p*-xylenes (7)—(9), in which the halogen atom is *ortho* to the aromatic proton (>0.1 p.p.m.) than with the same proton in the corresponding halogeno-*m*-xylenes (10) and (11) (<0.1 p.p.m.) in which there is a *meta*-relationship between the C-2 proton and the halogen atom. The rest of the n.m.r. data were consistent with structures (4) and (5). Formation of these



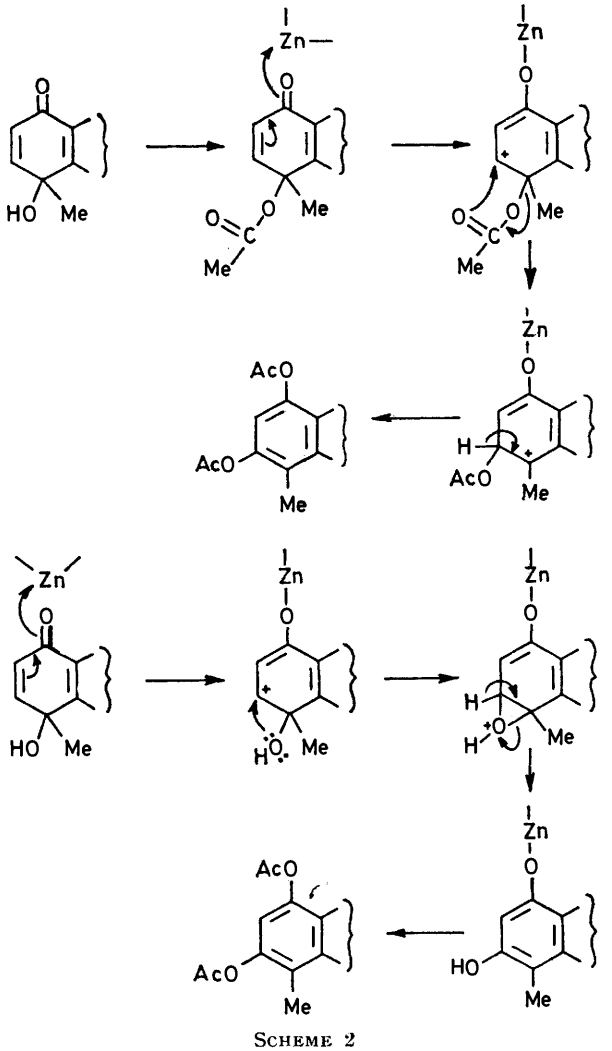
SCHEME 1

molecules can be perceived as proceeding through a 1,4-addition to the quinol, followed by loss of water, as indicated in Scheme 1.

Application of hydriodic acid or hydrofluoric acid did not yield corresponding iodo- or fluoro-estrogens. Instead, HI effected a reduction to give the known dienone–phenol rearrangement product (6).[9] With HF no reaction took place and only starting material resulted.

The next series of experiments examined the effect of the Lewis acid catalysts, zinc chloride–acetic anhydride and boron trifluoride–ether. The former reaction was carried out under the usual dienone–phenol rearrangement conditions [9] by first dissolving (2) in acetic anhydride, adding freshly fused zinc chloride dissolved in acetic acid, and stirring the reaction mixture overnight at ambient temperature. Recovery of the steroids in the usual manner afforded a product with an aromatic ring A having two acetoxy-moieties, a methyl group, and a single aromatic proton as ascertained from the n.m.r. spectra. The structure of the rearranged product was established as (12) from the chemical shift of the C-2 proton, which appeared at δ 6.59. This value is similar to the value [10] of δ 6.56 for the corresponding proton of acetylated resorcinol (13), rather than the δ 6.75 value [10] for the acetylated hydroquinone (14).

With BF_3–ether rearrangement and acetylation of the crude product, a steroid with an aromatic ring possessing two acetoxy-groups, a methyl, and a single aromatic proton was also isolated. However, the aromatic proton occurred at δ 6.72 indicating an *ortho* relationship of the proton with acetoxy and methyl groups as in (14). Therefore, structure (15), which would result by methyl migration in (2), was assigned to the product. Mechanistically, migration of a hydroxy, acetoxy, or methyl group to yield (12) or (15), after acetylation, can take place as indicated in Scheme 2. Formation of (12)



SCHEME 2

could follow either from 1,2-acetoxy-migration of an acetylated quinol (16) as proposed previously,[2] or from migration of the oxygen *via* an epoxide intermediate, then acetylation. Methyl migration, of course, yielding (15), parallels the dienone–phenol rearrangement.

We hope to extend this reaction to other series in the near future in order to prepare additional 1-hydroxy-estrogens substituted at C-4.

EXPERIMENTAL

M.p.s were measured with a Thomas-Hoover apparatus; i.r. spectra were recorded with a Perkin-Elmer 237B spectrometer, n.m.r. spectra with a Varian A-60A spectrometer

(60 MHz; $CDCl_3$ solutions; $SiMe_4$ as an internal standard), and u.v. spectra with a Cary 14 instrument (ethanol solutions). Silica gel HF_{254} plates (0.4 mm) with ethyl acetate–benzene (1 : 4) as the developing solvent were used for t.l.c.

17β-*Acetoxy*-4ξ-*hydroxy*-4-*methylestra*-2,5(10)-*dien*-1-*one* (2).—A solution of thallium triperchlorate in 60% perchloric acid (100 ml) [made [1,5] by dissolving thallium(III) oxide in 60% perchloric acid (100 ml) at 130 °C over 2 h] was added to the triene (1) (2.0 g) in methylene chloride (75 ml) and water (400 ml). The mixture was then vigorously stirred at ambient temperature for 2 d. The layers were separated and the organic portion washed with 5% sodium hydrogen carbonate and water. Preparative t.l.c. afforded two quinols (2) with R_F values of 0.35 (500 mg) and 0.40 (100 mg). The less-mobile material had m.p. 155—156 °C (from acetone–hexane) (Found: C, 73.5; H, 8.15; $C_{21}H_{28}O_4$ requires C, 73.22; H, 8.19%); δ 0.82 (3 H, s), 1.40 (3 H, s, 4-Me), 2.01 (3 H, s, COMe), 5.9 (1 H, d, *J* 10 Hz, 3-H), and 6.55 (1 H, d, *J* 10 Hz, 2-H); $\nu_{max.}$ (KBr) 3 410, 1 730, 1 660, and 1 625 cm^{-1}; $\lambda_{max.}$ 233 and 278 nm.

The more-mobile dienone had m.p. 210—211 °C (from acetone-hexane) (Found: C, 72.95; H, 8.2%); δ 0.82 (3 H, s), 1.40 (3 H, s, 4-Me), 2.01 (3 H, s, COMe), 6.15 (1 H, d, *J* 10 Hz, 3-H), and 6.82 (1 H, d, *J* 10 Hz, 2-H); $\nu_{max.}$ and $\lambda_{max.}$ same as the less-mobile compound.

17β-*Acetoxy*-4ξ-*methoxy*-4-*methylestra*-2,5(10)-*dien*-1-*one* (3).—To a solution of $Tl(NO_3)_3 \cdot 3H_2O$ (0.88 g) in methanol (60 ml) cooled to −20 °C, a solution of triene (1) (1.00 g) in methanol (60 ml) was added.[7] The mixture was stirred until it reached ambient temperature, then the solvent was removed *in vacuo*. Ether (75 ml) and water (75 ml) were added to the residue, the phases separated, and the organic layer washed with water. Chromatography of the steroid gave (3) (320 mg), m.p. 129—131 °C (from methanol) (Found: C, 73.6, 73.85; H, 8.6, 8.45. $C_{22}H_{30}O_4$ requires C, 73.71, H, 8.44%); δ 0.84 (3 H, s), 1.38 (3 H, s, 4-Me), 2.02 (3 H, s, COMe), 2.93 (3 H, s, OMe), 6.32 (1 H, d, *J* 10 Hz), and 6.58 (1 Hz, d, *J* 10 Hz); $\nu_{max.}$ (KBr) 1 730, 1 670, and 1 635 cm^{-1}; $\lambda_{max.}$ 231 and 280 nm.

3-*Chloro*-1,17β-*diacetoxy*-4-*methylestra*-1,3,5(10)-*triene* (4).—(*a*) A solution of the dienone (2) (100 mg) in acetic acid (5 ml), concentrated HCl (5 ml), and water (1 ml) was refluxed for 6 h. The deep red solution was then diluted with water and extracted with methylene chloride. The steroid layer was washed with 5% sodium hydrogen carbonate and water. Removal of the solvent, acetylation of the residue with acetic anhydride–pyridine, and preparative t.l.c. of the acetate yielded 55 mg of colourless prisms, m.p. 191—192 °C (from ethyl acetate–hexane) (Found: C, 68.3; H, 7.3. $C_{23}H_{29}ClO_4$ requires C, 68.22; H, 7.24%); δ 0.83 (3 H, s, 18-Me), 2.0 (3 H, s, COMe), 2.18 (3 H, s, 4-Me), and 2.25 (3 H, s, COMe), and 7.07 (1 H, s, 2-H).

(*b*) To a solution of the dienone (2) (100 mg) in methylene chloride (5 ml) was added concentrated HCl (5 ml). After vigorously stirring the mixture for 2 d, the steroids were isolated, acetylated, and purified as above to afford (4) (70 mg), identical in all respects to the above material.

3-*Bromo*-1,17β-*diacetoxy*-4-*methylestra*-1,3,5(10)-*triene* (5).—A mixture of the dienone (2) (100 mg) in methylene chloride (5 ml) and 35% HBr (5 ml) was vigorously stirred for 2 d. Separation of the layers, then isolation, acetylation, and chromatography of the steroids as above for (4) yielded the bromotriene (5) (80 mg), m.p. 187—188 °C (from ethyl acetate–hexane) (Found: C, 61.2; H, 6.65. $C_{23}H_{29}BrO_4$ requires C, 61.5; H, 6.47%); δ 0.83 (3 H, s, 18-Me), 2.0 (3 H, s, COMe), 2.18 (3 H, s, 4-Me), 2.23 (3 H, s, COMe), and 7.20 (1 H, s, 2-H).

Reaction of the Dienone (2) *with* 35% HI.—Dienone (2) (100 mg) was reacted with 35% HI (5 ml) in methylene chloride (5 ml) as above, then isolated and acetylated to give the diacetate (6) (80 mg), m.p. 131—133 °C, identical in all respects with an authentic specimen.

4-*Methyl*-1,3,17β-*triacetoxyestra*-1,3,5(10)-*triene* (12).—Dienone (2) (50 mg) was dissolved in acetic anhydride (3 ml) containing a trace of zinc chloride. After the solution had been stirred for 16 h, it was decomposed with ice. The steroids were extracted with methylene chloride, and washed with 5% sodium hydrogen carbonate and water. Preparative t.l.c. afforded the resorcinol-type steroid (12) (42 mg), m.p. 187—188 °C (from ethyl acetate–hexane) (Found: C, 70.35; H, 7.55. $C_{25}H_{33}O_6$ requires C, 70.07; H, 7.75%); δ 0.83 (3 H, s, 18-Me), 2.0 (3 H, s, COMe), 2.05 (3 H, s 4-Me), 2.25 (3 H, s, COMe), 2.30 (3 H, s, COMe), and 6.59 (1 H, s, 2-H).

3-*Methyl*-1,4,17β-*triacetoxyestra*-1,3,5(10)-*triene* (15).—(*a*) Boron trifluoride–ether (1.0 ml) was added to a solution of the dienone (2) (100 mg) in ether (10 ml), and the solution then stirred for 24 h in the dark at ambient temperature. The solution was washed with saturated brine and water, and then dried. Acetylation of the recovered steroids, followed by t.l.c., gave the hydroquinone steroid (15) (80 mg), m.p. 95 °C (decomp.) (from ether–hexane) (Found: C, 70.25; H, 7.95. $C_{25}H_{33}O_6$ requires C, 70.07; H, 7.75); δ 0.83 (3 H, s, 18-Me), 2.03 (3 H, s, COMe), 2.10 (3 H, s, 4-Me), 2.25 (3 H, s, CO_2Me), 2.30 (3 H, s, COMe), and 6.72 (1 H, s, 2-H).

(*b*) To the dienone (2) (100 mg) in acetic acid (10 ml), 35% sulphuric acid (5 ml) was added, and the reaction was stirred for 18 h. Recovery and acetylation of the steroids as above yielded a mixture of (15) and starting material (2) in a ratio of 3 : 1, as determined from the n.m.r. spectrum.

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REFERENCES

[1] Y. Yamada, K. Hosaka, H. Sanjoh, and M. Suzuki, *J.C.S. Chem. Comm.*, 1974, 661.

[2] For reviews see A. J. Waring, in 'Advances in Alicyclic Chemistry,' ed. H. Hart and G. J. Karabatsos, Academic Press, New York, 1966, vol. I, p. 129; and B. Miller in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience, New York, 1968, vol. 1, p. 247.

[3] O. Engelfried, H. Gibian, F. Neumann, K. Prezewowsky, G. Schultz, and R. Wiechert, *Arzneim.-Fortsch.*, 1966, **16**, 1518; Y. Nishino, F. Neumann, K. Prezewowsky, and R. Wiechert, *Steroids*, 1976, **28**, 325; Neth. P. 6,606,590/1966; U.S.P. 3,478,019/1969; U.S.P. 4,096,253/1978.

[4] E. Hecker and R. Lattrell, *Annalen*, 1963, **662**, 48; *Angew. Chem.*, 1962, **74**, 652.

[5] Y. Yamada, K. Hosaka, T. Sawahata, Y. Watanabe, and K. Iguchi, *Tetrahedron Letters*, 1977, 2675.

[6] Y. Yamada and K. Hosaka, *Synthesis*, 1977, **1**, 53.

[7] We thank Prof. E. C. Taylor for a preliminary description of this reagent combination prior to publication; A. McKillop, D. H. Percy, M. Edwards, S. Antus, L. Farkas, M. Nógrádi, and E. C. Taylor, *J. Org. Chem.*, 1976, **41**, 283.

[8] 'Sadtler Standard Spectra Index, NMR,' (*a*) 1969, 6402; (*b*) 1974, 18739; (*c*) 1974, 18917; (*d*) 1975, 21869; (*e*) 1974, 18763.

[9] See 'Steroid Reactions,' ed. C. Djerassi, Holden-Day Inc., San Francisco, 1963, pp. 375—377.

[10] H. Budzikiewicz and J. Gunawan, *Monatsh.*, 1973, **104**, 876.