Applications of High-potential Quinones. Part 13.[1] Dehydrogenation of De-A-estra-5,7,9-trienes to Styrenes

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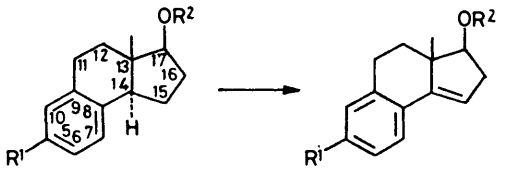
The de-A-estratrienes (1)—(6) yield the corresponding de-A-estra-5,7,9,14-tetraenes (8)—(13) by oxidation with an equimolar amount of dichlorodicyanobenzoquinone in dioxan at room temperature. The rates of dehydrogenation are sensitive to changes in substituents at C-17. Similar rate ratios are observed for the alcohol–acetate pairs (1)–(2) and (3)–(5), indicating a mechanism involving direct attack at the benzylic position in both the phenols and their methyl ethers. Deoxygenation of the phenol (3) was carried out by cleavage of the diethyl phosphate ester with lithium in liquid ammonia, but could not be achieved by cleavage of the phenyltetrazolyl ether.

In continuation of our work on the benzylic oxidation of A- and B-aromatic steroids,[2,3] we have examined the behaviour of some de-A-steroids towards 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).



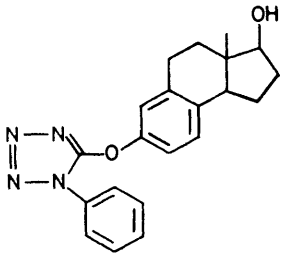
(1) R^1 = OMe, R^2 = H (8)
(2) R^1 = OMe, R^2 = Ac (9)
(3) R^1 = OH, R^2 = H (10)
(4) R^1 = OAc, R^2 = Ac (11)
(5) R^1 = OH, R^2 = Ac (12)
(6) R^1 = R^2 = H (13)
(7) R^1 = H, R^2 = Ac
(14) R^1 = $OPO(OEt)_2$, R^2 = H

The 5-methoxy-de-A-estratriene (1) reacted rapidly with an equimolar amount of DDQ in dioxan at room temperature to give the styrene (8) in 85% yield. The product showed three characteristic changes in the n.m.r. spectrum: the appearance of the olefinic proton as a triplet at δ 5.76, the expected [4] downfield shift of the 13-methyl (Δδ 0.36), and of the aromatic proton in close proximity to the new double bond (Δδ *ca.* 0.7). The alcohol (1) reacted appreciably faster with DDQ than did the derived acetate (2), which gave the styrene (9) in 80% yield.

The phenol (3) was also readily dehydrogenated to the styrene (10) in 90% yield under similar conditions, although the product was rather unstable. Satisfactory spectral data were obtained on the crystalline material from purification using neutral alumina, while all attempts to recrystallise the styrene resulted only in decomposition. The rates of reaction of the phenol (3) and its methyl ether (1) appeared to be quite similar, so it was of interest to establish whether acetylation of the 17β-hydroxy group also led to inhibition of the rate of dehydrogenation of the phenol.

Acetylation of the phenol (3) with excess of acetic anhydride in pyridine gave the diacetate (4) which was converted to the monoacetate (15) by selective hydrolysis of the phenolic ester with potassium carbonate.[5] The monoacetate (5) was dehydrogenated quite rapidly to the styrene (12), whereas the diacetate (4) reacted much more slowly with DDQ but the latter reaction was not reproducible. In some experiments there was good conversion to the styrene (11), but in others less than 50% was formed and appreciable starting diacetate was recovered. These erratic results could be due to partial hydrolysis of the phenolic acetate, perhaps catalysed by $DDQH_2$, and consumption of the quinone by over-oxidation of the phenolic material.

The deoxy compound (6), which was required for rate comparison with neoergosterols,[2] was prepared from the phenol (3) in good yield by the Kenner deoxygenation procedure [6] involving cleavage of the diethyl phosphate ester (14) with lithium in liquid ammonia. It was purified by preparative g.l.c. Attempts to prepare the alcohol (6) by catalytic hydrogenation of the tetrazolyl ether (15) failed, although this method [7] is claimed to afford yields superior to those from metal–ammonia procedures in the reductive cleavage of phenolic ethers. In our hands the method of Musliner and Gates [7] has



(15)

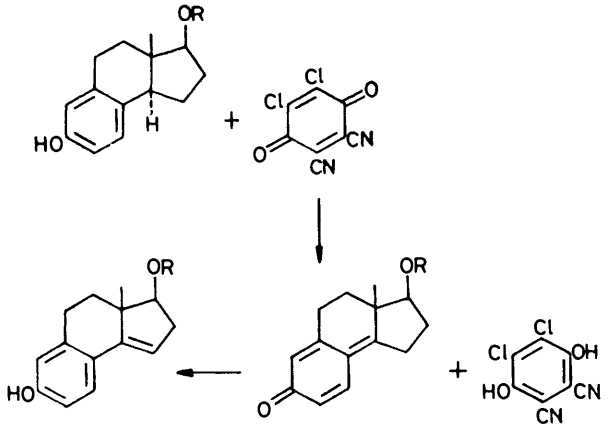
worked well for the deoxygenation of oestrone,[8] although care is required to avoid over-reduction.[9] In the case of the tricyclic phenol, prolonged hydrogenation of the tetrazolyl ether (15) at atmospheric pressure using a platinum catalyst gave traces of a product having a similar retention time to that of the deoxy compound (6), but the product could not be isolated and most of the starting material (15) was recovered unchanged. Our repeated failure to achieve the catalytic cleavage of the tetrazolyl ether (15) of the tricyclic phenol is puzzling,

particularly as those of simple (monocyclic) phenols, naphthols (bicyclic), and steroidal (tetracyclic) phenols are readily cleaved. It may be that the distribution of active sites and binding sites on the surface of the catalyst allows molecules of this particular size and geometry to be adsorbed but not cleaved. If this is so, it implies that the mono- and bi-cyclic phenol derivatives are too small to be strongly adsorbed, and that the steroid derivatives are too large to occupy the stepped surface of the catalyst. In the case of the uncatalysed cleavage of the phosphate ester radical anions in liquid ammonia, no such limitation is apparent. Further investigation of these differences in reactivity is in hand.

The deoxy compound (6) was dehydrogenated to the styrene (13) at room temperature, but the reaction occurred much more slowly than with the original phenol and its methyl ether. The product styrene (13) was unstable on storage in air, giving several polar products. The tetrazolyl ether (15) was resistant to dehydrogenation with DDQ, indicating that approach of the quinone to the α-face of the ether (15) was sterically hindered.

Concerted mechanisms may operate in the dehydrogenation of the above phenols (Scheme 1). The concerted process (Scheme 2) is symmetry allowed,[10] and direct formation of quinone methides from phenols by oxidation with high-potential quinones has been demonstrated by Becker [11,12] in the synthesis of fuchsones. Alternatively, oxidation could occur at the phenolic hydroxy group, rather than at the benzylic position, leading to the quinone methide intermediate. Rate studies were therefore undertaken on the tricyclic compounds in hand, in order to investigate whether the phenols are oxidised by the same mechanism as the other compounds.

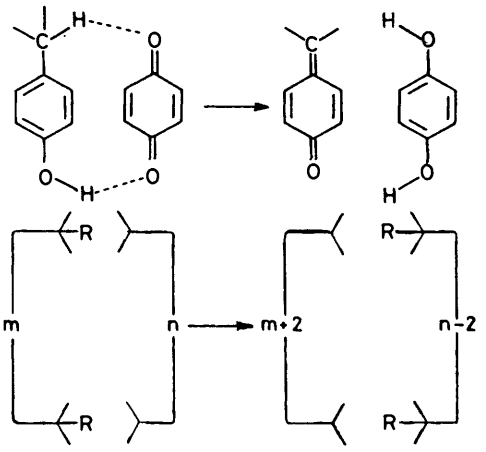
Second order rate constants were determined for the alcohol–acetate pairs (1) and (2), and (3) and (5) by the u.v. method previously employed for steroid oxidations.[2,13] The results (Table) showed that there were similar rate differences between the methyl ether pair



SCHEME 1

and the phenolic pair, indicating that in both series the change in substituent at C-17 produces a similar effect. This, in turn, suggests that the oxidations proceed by attack of the quinone at the benzylic hydrogen atom, as must be the case with the deoxy compound (6).

A feature of the u.v. spectral changes which take



SCHEME 2 A double group transfer is symmetry-allowed for ground states when the interacting systems have a total of (4q + 2) π-electrons, where q is an integer.[10] In this case ten interacting π-electrons are involved, *i.e.* m = 4, n = 6, and q = 2

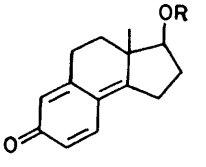
place during the reactions of the free phenols is the appearance of an absorption at 337 nm. This builds up appreciably in the early stages of the dehydrogenation,

Rates of oxidation of de-A-estratrienes with DDQ * in benzene at 25 °C

Compound	Concentration/10^3 M	k_2/l mol^{-1} s^{-1}
(1)	1.59	3.25 ± 0.12
(2)	1.36	0.66 ± 0.03
(3)	1.52	7.31 ± 0.40
(5)	1.37	1.09 ± 0.08

* DDQ concentration 0.493 × 10^{-3} M.

but is not evident in the case of the methyl ethers. It may be due to the quinone methide intermediates (16).



(16)

Similar results have been obtained for other phenols in dioxan.[14] Attempts are being made to use the characteristic change in the ^{1}H n.m.r. signal of the angular methyl group for further kinetic studies on these reactions.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 177 grating spectrophotometer, and u.v. spectra were measured for solutions in ethanol with a Perkin-Elmer 402 spectrophotometer. Analytical gas chromatography was performed on a Perkin-Elmer F-11 instrument, using 2 m × 3 mm (i.d.) glass columns packed with 2.5% silicone gum–rubber E-301

on AW-DMCS Chromosorb G (80—100 mesh) at 220 °C (unless otherwise stated) with a nitrogen flow rate of 33 ml min^{-1}, and preparative g.c. was carried out on a Perkin-Elmer F-21 instrument using two 1 m × 9 mm (i.d.) stainless steel columns packed with 2.5% silicone OV-1 on AW-DMCS Chromasorb G (80—100 mesh) at 180 °C using a nitrogen flow rate of 300 ml min^{-1}. T.l.c. was performed on silica gel (Merck GF_{254}) with location by u.v. illumination or exposure to iodine vapour. N.m.r. spectra were determined for solutions in [^{2}H]chloroform on a Varian HA 100 spectrometer with tetramethylsilane as internal reference. Mass spectra were measured on an A.E.I. MS 30 mass spectrometer at 70 eV. Purified [15] dioxan was stored over molecular sieves.

General Procedure for Dehydrogenation.—A 0.05M-solution of DDQ in dioxan and the de-A-estratriene was left at 20 °C until the orange colour was discharged. The precipitated $DDQH_2$ was collected and washed with a little dioxan. The filtrate and washings were concentrated to a small volume, and then allowed to percolate through a short column of neutral alumina. The column was eluted with ethyl acetate. The residue after evaporation was crystallised directly to give the pure styrene product.

17β-*Hydroxy-5-methoxy-de-A-estra-5,7,9,14-tetraene* (8).—The alcohol (8) was obtained from (−)-17β-hydroxy-5-methoxyde-A-estra-5,7,9-triene (1),[16] with a reaction time of 30 min, in 85% yield as needles, m.p. 172—174° (from EtOH), identical with an authentic sample.[16]

17β-*Acetoxy-5-methoxy-de-A-estra-5,7,9,14-tetraene* (9).—The tetraene (9) was prepared from the triene (2) in 80% yield (reaction time, 15 h) as *needles*, m.p. 89—90.5° (from hexane) (Found: M^+, 272.141 3. $C_{17}H_{20}O_3$ requires M, 272.141 2), $\lambda_{max.}$ 266 (ε 18 700), 297 (3 200), and 308 nm (2 300), $\nu_{max.}$ 1 725, 1 600, 1 315, 1 265, 1 230, 1 215, 1 155, 1 040, 975, 880, 840, 830, and 800 cm^{-1}, δ 1.01 (s, 13-Me), 2.10 (s, OCOMe), 3.77 (s, OMe), 5.07 (t, J 8 Hz, 17-H), 5.76 (t, J 3 Hz, 15-H), 6.70 (m, 6- and 10-H), and 7.45 (d, J 8 Hz, 7-H), R_T 15.1 min, *m/e* 272 (M^+, 5%), 213 (9), 212 (100), 197 (14), 185 (16), and 157 (35).

This compound was also prepared by acetylation (pyridine–Ac_2O) of the alcohol (8), as needles, m.p. 89—90° (from hexene), undepressed by admixture with the above material.

5,17β-*Dihydroxy-de-A-estra-5,7,9,14-tetraene* (10).—The tetraene (10) was prepared from the triene (3) [16] in 90% yield (reaction time, 30 min) as needles, m.p. 161—167° (from ethyl acetate) (Found: M^+, 216.114 9. $C_{14}H_{16}O_2$ requires M, 216.115 0), δ 1.00 (s, 13-Me), 5.75 (t, J 3 Hz, 15-H), 6.65 (m, 6- and 10-H), and 7.43 (d, J 8 Hz, 7-H), *m/e* 216 (M^+, 100%), 201 (25), 188 (16), 187 (23), 185 (13), 183 (14), 173 (35), 172 (14), 160 (15), 159 (25), 158 (15), 157 (20), 146 (14), 145 (33), 144 (14), and 115 (20).

5,17β-*Diacetoxy-de-A-estra-5,7,9,14-tetraene* (11).—The diacetate (11) was prepared from the triene (4) in 80% yield, with a reaction time of 50 h, as an oil (Found: M^+, 300.135 9. $C_{18}H_{20}O_4$ requires M, 300.136 1), $\nu_{max.}$ 1 740, 1 240, 1 200, 1 140, 1 030, 975, 925, 890, 805, and 750 cm^{-1}, δ 1.02 (s, 13-Me), 2.07 (s, 17-OCOMe), 2.27 (s, 5-OCOMe), 5.12 (t, J 9 Hz, 17α-H), 5.92 (t, J 3 Hz, 15-H), 6.92 (m, 6- and 10-H), and 7.58 (d, J 10 Hz, 7-H), *m/e* 300 (M^+, 0.2%), 240 (19), 199 (17), 198 (100), and 183 (14).

This compound was also obtained by acetylation (pyridine–Ac_2O) of the diol (10).

17β-*Acetoxy-5-hydroxy-de-A-estra-5,7,9,14-tetraene* (12).—Phenol (12) was obtained from the triene (5) in 86% yield (reaction time 1 h) as an oil, which crystallised to m.p. 122—128°, but which could not be recrystallised, $\nu_{max.}$ 3 350, 1 730, 1 600, 1 230, and 1 035 cm^{-1}, δ 1.01 (s, 13-Me), 2.11 (s, 17-OCOMe), 5.10 (t, J 9 Hz, 17α-H), 5.80 (t, J 3 Hz, 15-H), 6.65 (m, 6- and 10-H), and 7.45 (d, J 8 Hz, 7-H), *m/e* 258 (M^+, 2%), 199 (13), 198 (100), 197 (10), 183 (22), 85 (11), and 83 (18).

17β-*Hydroxy-de-A-estra-5,7,9,14-tetraene* (13).—The alcohol (13) was prepared from the triene (6) in 80% yield (reaction time: 24 h) as *needles*, m.p. 105—107° (from hexane) (Found: M^+, 200.120 0. $C_{14}H_{16}O$ requires M, 200.120 1), $\lambda_{max.}$ 260 (ε 10 600), 289 (1 800), and 300 nm (1 400), $\nu_{max.}$ 3 300, 1 595, 1 250, 1 090, 1 070, 1 030, 975, 770, and 755 cm^{-1}, δ 1.01 (s, 13-Me), 4.14 (t, J 7 Hz, 17α-H), and 5.95 (t, J 3 Hz, 15-H), and 7.1—7.6 (m, ArH), *m/e* 200 (M^+, 100%), 185 (35), 172 (11), 171 (35), 167 (38), 165 (13), 158 (18), 157 (63), 156 (25), 155 (18), 153 (14), 152 (16), 144 (10), 143 (50), 142 (25), 141 (45), 130 (13), 129 (65), 128 (50), 127 (10), 117 (10), 115 (40), and 91 (16).

17β-*Hydroxy-de-A-estra-5,7,9-triene* (6).—A stirred solution of 5,17β-dihydroxyde-A-estra-5,7,9-triene (3) 476 mg) in ethanol (1.6 ml) under nitrogen at 0 °C was treated with 8.5N-aqueous potassium hydroxide (0.27 ml), followed by diethyl chlorophosphate (0.38 ml). After 10 min the resulting light brown suspension was poured onto ether (30 ml) and extracted with water (3 × 5 ml). Evaporation of the dried ($MgSO_4$) solution gave the crude diethyl phosphate (14) as a viscous yellow oil. This was dissolved in ether (1 ml) and diluted with liquid ammonia (5 ml). Lithium (35 mg) was added in 5 mg portions, and the ammonia was allowed to evaporate. The residue was taken up in ether, extracted successively with water (2 ×), dilute H_2SO_4 (2 ×), dilute NaOH (3 ×), and water (2 ×), and dried ($MgSO_4$). Evaporation gave a mobile amber oil, which was purified by p.l.c. (R_F 0.48, 3 : 1 benzene–ethyl acetate) followed by preparative g.c. to give the *alcohol* (6) as a fragrant oil (130 mg; 29%) (Found: M^+, 202.135 8. $C_{14}H_{18}O$ requires M, 202.135 7), $\lambda_{max.}$ 260, 266, and 273 nm (ε 410, 520, and 490), $\nu_{max.}$ 3 340, 1 605, 1 250, 1 115, 1 080, 1 060, 1 015, and 750 cm^{-1}, δ 0.65 (s, 13-Me), 3.90 (t, J 7 Hz, 17α-H), and 7.09 (m, ArH), *m/e* 202 (M^+, 28%), 184 (3), 169 (30), 158 (33), 143 (100), 129 (22), 128 (18), and 115 (10).

Acetylation of the alcohol with pyridine and acetic anhydride for 18 h gave 17β-*acetoxy-de-A-estra-5,7,9-triene* (7) as an oil (Found: M^+, 244.146 3. $C_{16}H_{20}O_2$ requires M, 244.146 3), $\nu_{max.}$ 1 735, 1 240, 1 050, 1 025, and 753 cm^{-1}, δ 0.70 (s, 13-Me), 2.07 (s, OAc), 4.85 (t, J 7 Hz, 17α-H), and 7.09 (m, ArH), *m/e* 244 (M^+, 30%), 184 (56), 169 (100), 158 (13), 157 (13), 156 (16), 155 (11), 143 (67), 142 (25), 141 (22), 129 (35), 128 (22), 115 (14), and 91 (10).

17β-*Hydroxy-5-(1-phenyl-1H-tetrazol-5-yloxy)de-A-estra-5,7,9-triene* (15).—To a solution of the diol (3) (305 mg) and 5-chloro-1-phenyl-1*H*-tetrazole (276 mg) in dry acetone was added anhydrous potassium carbonate (1.2 g) and the mixture was heated under reflux for 21 h. Filtration and concentration followed by addition of water and refrigeration gave the *ether* (240 mg, 47%) as needles, m.p. 136—137° (from methanol) (Found: M^+, 362.174 4. $C_{21}H_{22}N_4O_2$ requires M, 362.174 2), $\nu_{max.}$ 3 420, 1 590, 1 540, 1 490, 1 445, 1 290, 1 185, 1 080, 1 010, 910, 880, 765, and 685 cm^{-1}, δ 0.66 (s, 13-Me), 3.91 (t, J 8 Hz, 17α-H), and 7.06—7.86 (m, ArH), *m/e* 362 (M^+, 11%), 334 (63), 275 (22), 218 (10), 217 (13), 201 (16), 173 (22), 146 (25), 118 (75), 117 (100), and 107 (35).

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REFERENCES

[1] Part 12, C. M. Tice and A. B. Turner, *J.C.S. Perkin I*, 1978, 505.
[2] D. R. Brown and A. B. Turner, *J.C.S. Perkin II*, 1978, 165.
[3] W. Brown and A. B. Turner, *J. Chem. Soc.* (*C*), 1971, 2057.
[4] R. F. Zurcher, *Helv. Chim. Acta*, 1961, **44**, 1380; 1963, **46**, 2054.
[5] D. K. Banerjee, B. Sugavanam, and G. Nadamuni, *Proc. Indian Acad. Sci.*, 1969, **69**, 229.
[6] G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 1955, 522; *cf.* R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, 1973, **38**, 2314.
[7] W. J. Musliner and J. W. Gates, *J. Amer. Chem. Soc.*, 1966, **88**, 4271.
[8] T. Nambara, M. Numazawa, and S. Akiyama, *Chem. Pharm. Bull.*, 1969, **17**, 2394; 1971, **19**, 153.
[9] K. I. H. Williams and T. A. Wittstruck, *Steroids*, 1974, **23**, 731.
[10] R. B. Woodward and R. Hoffmann, ' The Conservation of Orbital Symmetry,' Verlag Chemie–AP, 1970, pp. 141—144.
[11] H-D. Becker, *J. Org. Chem.*, 1969, **34**, 1203.
[12] H-D. Becker, ' The Chemistry of Quinonoid Compounds, ed. S. Patai, Wiley–Interscience, 1974, Part I, p. 356.
[13] S. H. Burstein and H. J. Ringold, *J. Amer. Chem. Soc.*, 1964, **86**, 4952.
[14] D. R. Brown, unpublished work.
[15] J. W. A. Findlay and A. B. Turner, *Org. Synth.*, 1969, **49**, 53.
[16] L. Velluz, G. Nomine, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier, and A. Pierdot, *Compt. rend.*, 1960, **250**, 1084.