Applications of High-potential Quinones. Part 11.[1] Remote Substituent Effects in the Benzylic Oxidation of Aromatic Steroids

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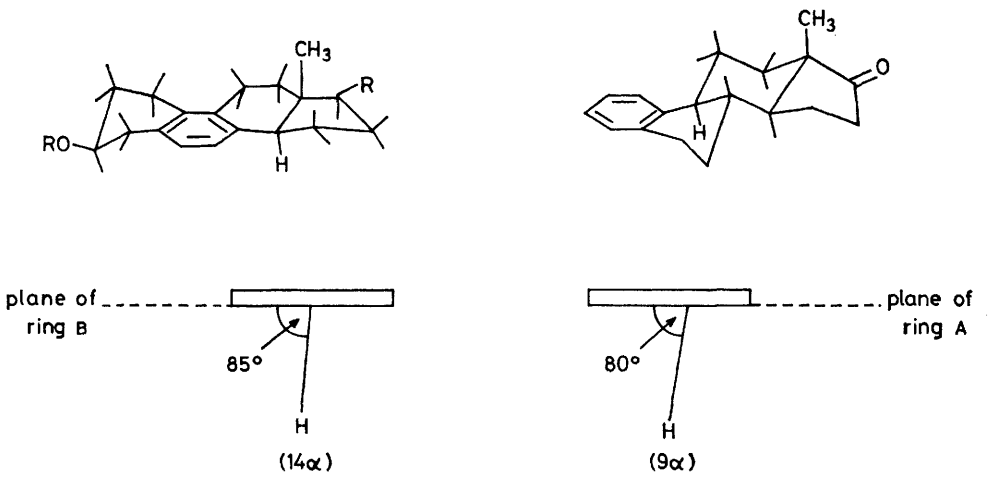
Rates of dehydrogenation of ring A aromatic steroids by dichlorodicyanobenzoquinone are markedly influenced by substituents in ring D. The presence of sp^2-hybridization at C-17 inhibits styrene formation, and a 16α-chloro-group further decreases the rate of oxidation at C-9. Relief of the strain energy in the C/D-*trans*-ring junction does not contribute significantly to the more rapid dehydrogenation of ring B aromatic steroids, judging by the relative rates of oxidation of de-A-oestratrienes and deoxyoestrogens.

RELIEF of the strain energy present in the C/D-*trans* ring junction of the steroid nucleus has been suggested [2] as a possible contributory factor in the highly selective attack of dichlorodicyanobenzoquinone (DDQ) upon the 14α-hydrogen atom of neoergosterol (1). In order to assess the relative importance of this factor, we have compared the rates of dehydrogenation of A- and B-aromatic steroids, both of which possess a tertiary benzylic hydrogen atom which is virtually orthogonal to the plane of the adjacent aromatic ring (9α- and 14α-H, respectively). Measurements on Dreiding models show these dihedral angles (ϕ) to be 80° and 85°, respectively, for typical A- and B-aromatic steroids (Figure), and calculations using the linear relationship recently established [3] between the angle ϕ and the rate of DDQ dehydrogenation predict a three-fold rate enhancement for this angle difference of 5° in favour of the B-aromatic steroid.



FIGURE

The reaction of neoergosterol acetate (2) with DDQ proceeds readily at room temperature to give the styrene (3), and is conveniently followed using a spectrophotometric method involving the quinone absorption maximum.[3,4] Reasonable second-order kinetics (first order in each component) were obtained at 35° in benzene solution (Table 1) over two half-lives. Subsequent deviations, which are probably due to precipitation of hydroquinone, are particularly noticeable in runs involving a low initial steroid concentration. Previous work had shown that reaction of the styrene (3) with DDQ proceeded much more slowly than dehydrogenation of

TABLE 1

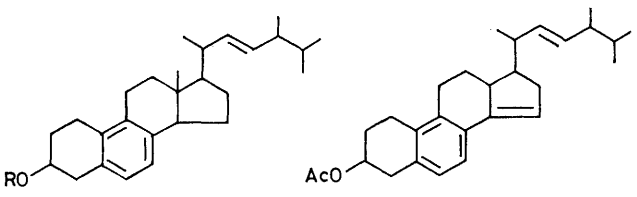
Rates of oxidation of steroids and analogues with DDQ † in benzene at 35°

Compound	10^3 Concentration (M)	k/l mol^{-1} s^{-1}
(2)	3.28	0.611 ± 0.007
(4)	4.04	$3.1 \pm 0.3 \times 10^{-2}$
(5)	7.25	$7.1 \pm 0.4 \times 10^{-3}$
(6)	5.88	$1.8 \pm 0.2 \times 10^{-3}$
(7)	1.24	0.5 ± 0.04
(8)	13.9	$9.1 \pm 0.9 \times 10^{-4}$
(9)	4.10	4.12 ± 0.18
(10)	4.15	1.67 ± 0.05
(11)	10.1	$3.2 \pm 0.4 \times 10^{-4}$
(12)	80.0	$8.0 \pm 0.4 \times 10^{-4}$

† DDQ concentration 0.590×10^{-3} M except in the case of oestrone methyl ether (0.564×10^{-3} M)

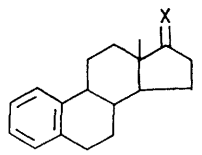
[1] Part 10, S. M. Ali, J. W. A. Findlay, and A. B. Turner, *J.C.S. Perkin I*, 1976, 407.
[2] W. Brown and A. B. Turner, *J. Chem. Soc.* (*C*), 1971, 2057.
[3] D. R. Brown and A. B. Turner, *J.C.S. Perkin II*, 1975, 1307.
[4] S. H. Burstein and H. J. Ringold, *J. Amer. Chem. Soc.*, 1964, **86**, 4952.

neoergosterol acetate (2) itself. Although linear second-order plots were obtained for benzene solutions, this was not the case for dioxan solutions, perhaps owing to

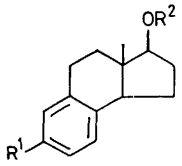


(1) R = H
(2) R = Ac

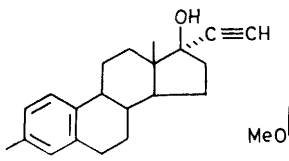
(3)



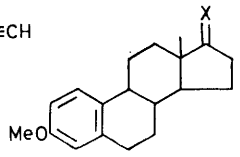
(4) X = β-OH, α-H
(8) X = O



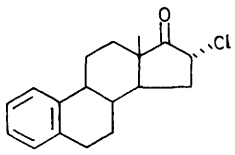
(5) $R^1 = R^2 = H$
(6) R^1 = OAc, R^2 = Ac



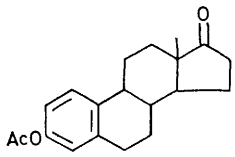
(7)



(9) X = CH_2
(10) X = O



(11)



(12)

slight overlapping of the hydroquinone absorption with the DDQ maximum in the latter solvent.

TABLE 2

Rate constants and activation parameters for the reaction of DDQ with neoergosteryl acetate

Temp. (°C)	k/l mol^{-1} s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
14.95	0.171		
35.0	0.611	45.6	−110

The rate constant for the reaction of neoergosterol acetate (2) with DDQ was measured at 15 and 35° and the activation parameters [5] obtained (Table 2) were found to be similar to those determined [4] for the DDQ oxidation of androst-4-en-3β-ol, indicating energetic and geometric similarity of the respective transition states. In both cases an activated tertiary C–H bond is attacked, and the mechanism is considered to involve rate-determining hydride abstraction at this position by the high-potential quinone.

Neoergosterol acetate (2) was found to react almost 20 times faster than 3-deoxyoestradiol (4) (Table 1). However, the B-aromatic sterol (2) has a tetrasubstituted aromatic ring, whereas in deoxyoestradiol the aromatic ring is only disubstituted, so that the energy of the transition state is lowered by the additional stabilization of the benzylic carbonium ion by the *meta*- and *para*-alkyl substituents (*i.e.* the ring A residues, C-1 and -4) in the case of the sterol (2). An estimate of the magnitude of this additional stabilization was made using the Hammett substituent constants, together with the rate constant for the oxidation of oestrone methyl ether (Table 1). This gave a 36-fold enhancement over the value obtained for the ring A-aromatic compound (4). Taken with the three-fold rate enhancement derived from the angle factor, this gives a rate advantage of about two orders of magnitude for the sterol (2). Since this exceeds the observed rate increase (× 86), we conclude that relief of the strain in the C/D-*trans*-ring junction does not play a significant role in these reactions.

In qualitative agreement with the above calculations, two tricyclic compounds, (5) and (6), having structures related to neoergosterol but possessing only disubstituted aromatic rings, were found to be dehydrogenated at rates very much slower than that of neoergosterol acetate. The fact that both compounds were attacked more slowly than deoxyoestradiol suggests that the proximity of the oxygen functions to the benzylic centre inhibits the oxidation to some extent in the tricyclic compounds.

3-Methyl-3-deoxy-17α-ethinyloestradiol (7) [6] showed a rate of dehydrogenation 17 times that of 3-deoxyoestradiol, in keeping with the stabilizing effect of the methyl substituent at the position *para* to the benzylic carbonium ion.

3-Deoxyoestradiol (4) was oxidised much more rapidly (× 34) than 3-deoxyoestrone (8). Changes in hybridization at C-17 are well known to influence the stability of a double bond in ring C of the steroid nucleus,[7] and it is likely that the rate difference between the 17-ketone and the 17β-alcohol is largely derived from conformational transmission effects upon the ease of formation of the planar carbonium ion at C-9. Some confirmation of this hypothesis was obtained from the data on the 17-methylene compound (9) which reacted at almost three times the rate of the corresponding 17-ketone, oestrone methyl ether (10).[8] However, there is

[5] L. L. Schaleges and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.
[6] L. J. Chinn, ' Selection of Oxidants in Synthesis ', Dekker, New York, 1971, p. 78.
[7] R. Bucourt, *Topics Stereochem.*, 1974, **8**, 159, *cf.* M. J. T. Robinson and W. B. Whalley, *Tetrahedron*, 1963, **19**, 2123.
[8] W. Brown, J. W. A. Findlay, and A. B. Turner, *Chem. Comm.*, 1968, 10.

clearly some residual retardation, which can be ascribed to the inductive effect or electrostatic field effect of the carbonyl group.[9] The former effect appears the more likely, although the precise nature of the collision complex will have an important bearing on this. If these reactions involve intermediate π-complexes,[10] they are less likely to be subject to electrostatic field effects since ring A would be the site of complex formation. No effect would be anticipated if, as has been argued,[11] these π-complexes are not part of the main reaction pathway, but are only formed in a rapid pre-equilibrium stage of the reaction.

The three-fold rate retardation noted for 16α-chloro-3-deoxyoestrone (11) relative to (8) appears to support the involvement of inductive effects (both C-16 and -17 are connected to C-9 *via* planar zig-zags of the σ-bond framework, although these zig-zags are not extended by the terminal substituent). Conformational transmission may also be involved in this instance, owing to the flattening of ring C in the region of the B/C-ring junction in the transition state for hydride abstraction. This could lead to a more pseudo-axial orientation of the chloro-substituent, resulting in further destabilization of the carbonium ion.

Oestrone acetate (12) reacted at a rate similar to that of 3-deoxyoestrone (8). The very slow rate for the 16α-chloro-derivative (11) thus indicates that, at these low levels of reactivity, benzylic oxidation is more sensitive to remote substituents than to substituents on the aromatic ring.

[9] *Cf.* D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms', Elsevier, 1968, pp. 16—20 and references therein; P. A. Kollman, D. D. Giannini, W. L. Duax, S. Rothenberg, and M. E. Wolff, *J. Amer. Chem. Soc.*, 1973, **95**, 2869.

[10] J. W. A. Findlay and A. B. Turner, *J. Chem. Soc.* (*C*), 1971, 23; *cf.* A. C. Allison and T. Nash, *Nature*, 1963, **197**, 758.

EXPERIMENTAL

General experimental details are as reported previously,[3] except that an excess of substrate was used in order to minimise the possibility of a competing reaction of the product styrene with the quinone. This was noticed in the cases of the methoxy-substituted steroids by an upward curvature of the kinetic plot at low steroid concentrations. The rate constants were calculated from least squares analysis of the usual second-order plot for unequal concentrations of reactants. A typical set of readings is given in Table 3 below. The reactions of 3-deoxyoestrone and its 16α-chloro-derivative were so slow that the accuracy of the rate constants were lower than for those of the other substrates studied.

TABLE 3

Readings of optical density for the reaction of neoergosterol acetate with DDQ at 35.0°

t/min	O.D.	*t*/min	O.D.
3.92	1.086	11.15	0.500
5.25	0.932	12.38	0.446
6.45	0.829	13.57	0.406
7.65	0.726	14.80	0.351
8.82	0.640	16.00	0.313
10.00	0.563	17.20	0.286

Starting materials were commercial products or gifts, and oxidation products are described elsewhere.[2,6,8,12]

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[7/1002 *Received*, 13th *June*, 1977]

[11] See *e.g.* R. Foster, 'Organic Charge Transfer Complexes', Academic Press, 1969, p. 303.

[12] A. B. Turner, *Chem. and Ind.*, 1976, 1030.