Ketol Formation by Peracid Oxidation of a Tricyclic Styrene

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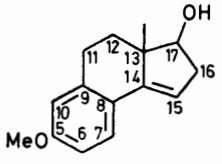
Oxidation of 17β-hydroxy-5-methoxy-de-A-oestra-5,7,9,14-tetraene (1) with *m*-chloroperbenzoic acid or monoperphthalic acid yields the epimeric ketols, 14α- and 14β,17β-dihydroxy-5-methoxy-de-A-oestra-5,7,9-trien-15-one, (2) and (3) in a ratio of 6 : 1. The configurations at C-14 of these ketols were assigned by ^{1}H n.m.r. spectral comparison with AB-aromatic steroids, and the structure of the major product (2) was confirmed by an *X*-ray crystallographic analysis. The 14α-ketol (2) gives the 17β-acetate (14) with acetic anhydride in pyridine, whereas the 14β-ketol (3) gives the 16-en-15-one (15).

INTRODUCTION of an oxygen function at C-15 of the styrene (1) forms an initial stage in a synthetic route to extended quinones based upon the de-A-oestrane ring system.[1] Peracid oxidation [2-7] appeared to be a suitable method for obtaining the 15-oxo-derivative, as the Δ^{14}-bond of the tricyclic styrene (1) is activated towards electrophilic reagents by the electron-releasing effect of the 5-methoxy-group. Acid-catalysed rearrangement of the intermediate epoxide would be expected to give the 15-ketone, since the rearrangement of steroidal 14,15-epoxides with boron trifluoride–diethyl ether is an established route to 15-oxo-steroids.[8,9]



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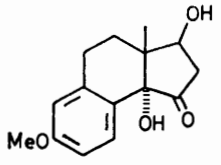

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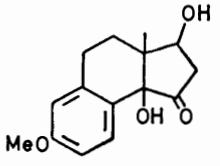
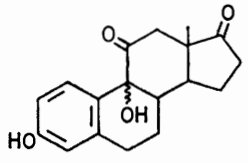


(3)

Reaction of the styrene (1) with an excess of monoperphthalic acid gave the epimeric ketols, (2) and (3), in 63% and 11% yield, respectively. The structures of these two ketols were established from their spectral data. Accurate mass measurement of the molecular ions (*m/e* 262) in the mass spectra gave the molecular formula, $C_{15}H_{18}O_4$, thereby revealing the incorporation of two additional oxygen atoms. The nature of one of these new oxygen atoms was revealed by the i.r. spectra, which showed strong absorption at 1 735 cm^{-1}, characteristic of a carbonyl group in a five-membered ring. The absence of the olefinic proton signal in the n.m.r. spectra indicated that reaction had occurred at the Δ^{14}-bond of the styrene (1), so that the carbonyl group was situated at C-15 and the second oxygen atom was probably incorporated in the form of a tertiary hydroxy-group at C-14. (This was confirmed by the spectral data of acetylation products, discussed later.) The u.v. spectra were typical of 5-methoxy-de-A-oestra-5,7,9-trienes, and showed much reduced intensity compared with that of the starting styrene (1). On the basis of the foregoing evidence, it was concluded that the products were epimeric ketols, differing only in the configuration of the hydroxy-group at C-14.

Hasegawa and Tsuda [6] have shown that the epimeric 9-hydroxy-11-oxo-oestrones (4) can be distinguished on the basis of their i.r. spectra, since only the 9β-hydroxy-11-ketone shows intramolecular hydrogen bonding. The structural similarities between the oestrone ketols (4), obtained in low yield by oxidation of $\Delta^{9(11)}$ oestrone (5) with perbenzoic acid, [6] and the tricyclic ketols (2) and (3)



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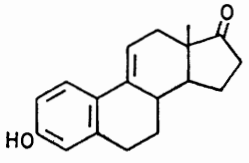
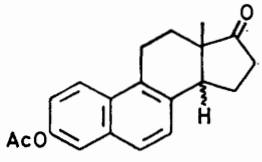
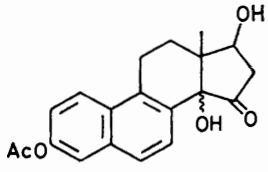


(5)



(6) 14α-H
(7) 14β-H



(8) 14α-OH
(9) 14β-OH

suggested the use of this method for distinguishing between the latter ketols. Unfortunately, no intramolecular hydrogen bonding could be detected since the hydroxy and carbonyl absorption bands in the i.r. spectra of the ketols (2) and (3), in dilute carbon tetrachloride solution, appeared at 3 630, 3 590, and 1 750 cm^{-1} and 3 610, 3 580, and 1 743 cm^{-1}, respectively. Inspection of Dreiding models indicated that the 14α-ketol (Figure 1a) has a rigid structure, the conformation of which precludes intramolecular hydrogen bonding, whereas the 14β-ketol (Figures 1b,c) possesses a more

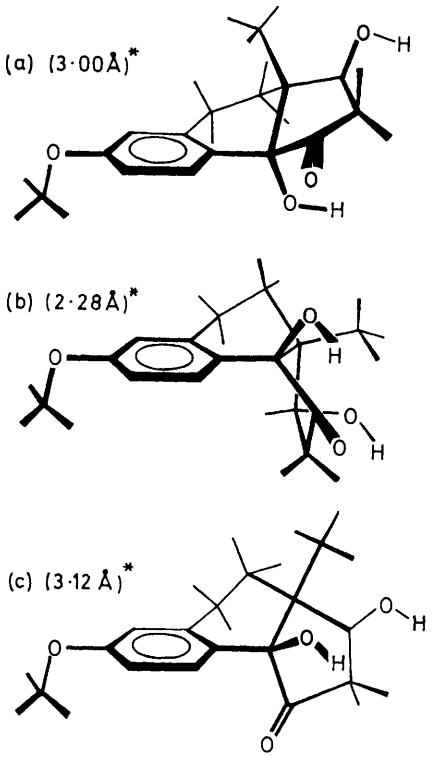


FIGURE 1 Internuclear distance between 14-hydroxy hydrogen atom and 15-carbonyl oxygen atom for possible hydrogen bond formation

flexible structure and hence a range of possible conformations, some of which contain intramolecular hydrogen bonds [*e.g.* (1b)] and some of which do not [*e.g.* (1c)]. Since no intramolecular hydrogen bonding was observed for either ketol, the preferred conformation of the 14β-ketol appeared to be of the latter type, and assignment of the configuration at C-14 is not possible using this method.

A significant difference between the two ketols was apparent in their n.m.r. spectra, in which one angular methyl group resonated at δ 0.74 and the other resonated at δ 1.04. This made possible the assignment of configuration at C-14, since the change in the chemical shift of the angular methyl protons, on going from the 14α-alcohol to the 14β-alcohol, is comparable with that in AB-aromatic steroids possessing identical functional group arrangement. The n.m.r. data recorded for equilenin acetate (**6**; 14α-hydrogen) and isoequilenin acetate (**7**; 14β-hydrogen) showed the angular methyl groups at δ 0.74 and 1.14, respectively.[10] Based on these values, the expected resonance positions for the angular methyl groups of the hypothetical steroid ketols (**8**) and (**9**) were then calculated, using Zürcher's Tables.[11]

Calculated chemical shift for 18-CH_3 in ketol (**8**) = δ 0.740 [observed 18-CH_3 for equilenin acetate (**6**)] − 0.167-(17-oxo) + 0.033(17β-OH) + 0.117(14α-OH) + 0.075-(15-oxo) = 0.798 p.p.m., and for 18-CH_3 in ketol (**9**) = δ 1.140 [observed 18-CH_3 for isoequilenin acetate (**7**)] —

TABLE 1

Fractional atomic co-ordinates (× 10^4) with e.s.d.'s

	x	*y*	*z*
O(1)	−0 005(5)	7 590	2 959(3)
O(2)	2 845(4)	5 222(10)	7 943(3)
O(3)	4 043(6)	9 430(11)	8 339(3)
O(4)	8 160(4)	4 522(11)	9 299(3)
C(5)	1 074(6)	7 229(12)	4 044(4)
C(6)	1 075(6)	8 633(13)	4 798(4)
C(7)	2 043(6)	8 361(12)	5 918(4)
C(8)	3 016(5)	6 706(12)	6 259(4)
C(9)	3 079(6)	5 341(12)	5 477(4)
C(10)	2 070(6)	5 643(12)	4 349(4)
C(11)	4 185(7)	3 582(12)	5 771(4)
C(12)	5 141(7)	3 236(12)	7 027(4)
C(13)	5 618(6)	5 115(11)	7 634(3)
C(14)	3 958(6)	6 251(11)	7 468(3)
C(15)	4 603(6)	7 841(12)	8 367(4)
C(16)	6 042(8)	6 963(12)	9 318(4)
C(17)	6 385(6)	4 969(13)	8 922(4)
C(18)	6 820(6)	6 290(14)	7 211(4)
C(19)	−0 058(7)	6 257(15)	2 124(4)
OW	8 777(7)	1 272(14)	10 477(6)
HO(2)	2 209(138)	6 423(102)	7 726(103)
HO(4)	8 456(61)	3 264(47)	9 592(39)
H(6)	0 311(43)	9 610(49)	4 432(30)
H(7)	2 006(62)	9 299(68)	6 484(37)
H(10)	2 063(60)	4 430(55)	3 944(40)
H(11A)	3 576(57)	2 367(52)	5 431(39)
H(11B)	4 901(107)	3 346(157)	5 278(68)
H(12A)	6 168(54)	2 440(76)	7 052(48)
H(12B)	4 492(64)	2 517(76)	7 424(43)
H(16A)	7 001(78)	7 890(99)	9 430(69)
H(16B)	5 537(62)	6 865(91)	9 910(36)
H(17)	5 834(75)	3 888(70)	9 155(53)
H(18A)	7 806(51)	5 374(57)	7 355(40)
H(18B)	7 134(60)	7 471(48)	7 625(38)
H(18C)	6 342(110)	6 522(109)	6 388(23)
H(19A)	−0 926(66)	6 806(109)	1 444(48)
H(19B)	−0 411(87)	4 979(71)	2 291(74)
H(19C)	1 062(50)	6 145(114)	1 995(60)
HOW(1)	9 656(68)	0 275(79)	10 599(56)
HOW(2)	8 119(108)	0 840(137)	10 968(79)

TABLE 2

Torsion angles (°) with e.s.d.'s

C(19)–O(1)–C(5)–C(6)	178.4(6)
O(1)–C(5)–C(6)–C(7)	176.6(5)
O(1)–C(5)–C(10)–C(9)	−177.4(5)
C(5)–C(6)–C(7)–C(8)	1.2(10)
C(6)–C(7)–C(8)–C(14)	−174.3(6)
C(7)–C(8)–C(9)–C(11)	176.0(6)
C(14)–C(8)–C(9)–C(11)	−7.1(9)
C(7)–C(8)–C(14)–C(13)	−148.3(6)
C(9)–C(8)–C(14)–O(2)	−88.9(6)
C(9)–C(8)–C(14)–C(15)	155.8(6)
C(11)–C(9)–C(10)–C(5)	−178.9(6)
C(10)–C(9)–C(11)–C(12)	−175.0(6)
C(11)–C(12)–C(13)–C(14)	59.7(6)
C(11)–C(12)–C(13)–C(18)	−61.3(7)
C(12)–C(13)–C(14)–C(8)	−62.0(6)
C(17)–C(13)–C(14)–O(2)	−60.1(6)
C(17)–C(13)–C(14)–C(15)	44.1(5)
C(18)–C(13)–C(14)–C(8)	60.5(6)
C(12)–C(13)–C(17)–O(4)	81.8(6)
C(14)–C(13)–C(17)–O(4)	−161.2(5)
C(18)–C(13)–C(17)–O(4)	−45.5(7)
O(2)–C(14)–C(15)–O(3)	−96.1(7)
C(8)–C(14)–C(15)–O(3)	25.0(10)
C(13)–C(14)–C(15)–O(3)	150.6(7)
O(3)–C(15)–C(16)–C(17)	−175.6(7)
C(15)–C(16)–C(17)–O(4)	141.6(6)
C(19)–O(1)–C(5)–C(10)	−0.9(8)
C(10)–C(5)–C(6)–C(7)	−4.1(10)
C(6)–C(5)–C(10)–C(9)	3.5(10)
C(6)–C(7)–C(8)–C(9)	2.4(9)
C(7)–C(8)–C(9)–C(10)	−3.0(9)
C(14)–C(8)–C(9)–C(10)	173.8(5)

TABLE 2 (*continued*)

C(7)–C(8)–C(14)–O(2)	87.9(7)
C(7)–C(8)–C(14)–C(15)	−27.5(9)
C(9)–C(8)–C(14)–C(13)	34.9(7)
C(8)–C(9)–C(10)–C(5)	0.2(9)
C(8)–C(9)–C(11) C(12)	6.0(9)
C(9) C(11) C(12)–C(13)	−32.8(8)
C(11)–C(12)–C(13)–C(17)	172.8(5)
C(12)–C(13)–C(14)–O(2)	61.8(6)
C(12)–C(13)–C(14)–C(15)	166.0(5)
C(17)–C(13)–C(14)–C(8)	176.1(5)
C(18)–C(13)–C(14)–O(2)	−175.6(5)
C(18)–C(13)–C(14)–C(15)	−71.5(6)
C(12)–C(13)–C(17)–C(16)	−157.4(5)
C(14)–C(13)–C(17)–C(16)	−40.4(6)
C(18)–C(13)–C(17)–C(16)	75.3(6)
O(2)–C(14)–C(15)–C(16)	81.5(5)
C(8)–C(14)–C(15)–C(16)	−157.4(5)
C(13)–C(14)–C(15)–C(16)	−31.8(6)
C(14)–C(15)–C(16)–C(17)	6.7(7)
C(15)–C(16)–C(17)–C(13)	20.8(7)

TABLE 3

Hydrogen bonding in the crystal

D–H · · · A	D · · · A (Å)	D–H (Å)	H · · · A (Å)	D–H · · · A (°)
O(4)–HO(4) · · · OW	2.688(11)	0.96(4)	1.76(4)	161(4)
OW–HOW(2) · · · O(2)[I]	2.889(9)	1.01(11)	1.88(11)	171(8)
OW–HOW(1) · · · O(4)[II]	2.754(8)	0.99(6)	1.85(6)	151(5)

Co-ordinates transformed by: I $1-x, -0.5+y, 2-z$; II $2-x, -0.5+y, 2-z$.

0.083(17-oxo) + 0.025(17β-OH) + (−0.025)(14β-OH) + 0.192(15-oxo) = 1.249 p.p.m. The difference between these two calculated values (0.45 p.p.m.) is comparable with that observed between the tricyclic ketols (0.30 p.p.m.), and it appears that the major ketolic product (2; 18-CH_3 at δ 0.74) from the monoperphthalic acid oxidation of the styrene (1) has the 14α-hydroxy-group, and that the minor ketol (3; 18-CH_3 at δ 1.04) has the 14β-hydroxy-group. However, owing to the uncertainties in these n.m.r. correlations arising from the range of possible conformations available to the 14β-ketol, we regard this as a tentative assignment of configuration.

The substantial downfield shift of the C-7 aromatic proton (δ 8.07) in the n.m.r. spectrum of the 14α-ketol (2), compared with that of the same proton (δ 7.30) in the 14β-ketol (3), can be explained by the close proximity of the C-7 aromatic proton to the carbonyl group at C-15 in the rigid 14α-ketol (2) (Figure 2a). The more flexible 14β-ketol (3) can adopt a conformation in which the carbonyl group is much further away from the C-7 aromatic proton. It is clear that in the 14α-ketol this aromatic proton lies in the deshielding zone of the carbonyl group, whereas in the 14β-ketol the aromatic proton lies in the shielding cone of the carbonyl group (Figure 2b).

The formation of the ketols (2) and (3) may be rationalized (see Scheme) in a manner similar to that employed by Tsuda [6] for the perbenzoic oxidation of $\Delta^{9(11)}$-oestrone (5). Epoxidation initially occurs at the Δ^{14}-bond of the styrene (1) to give the unstable epoxide (10). Cleavage [12,13] of the C(14)–O bond of the epoxide ring, under the influence of electron release from the 5-methoxy-groups, yields the enol (12) *via* the zwitterion

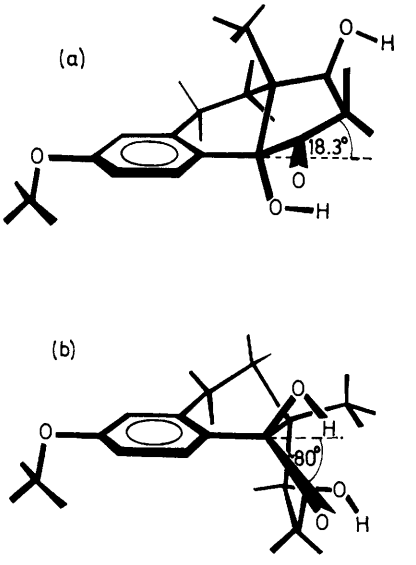
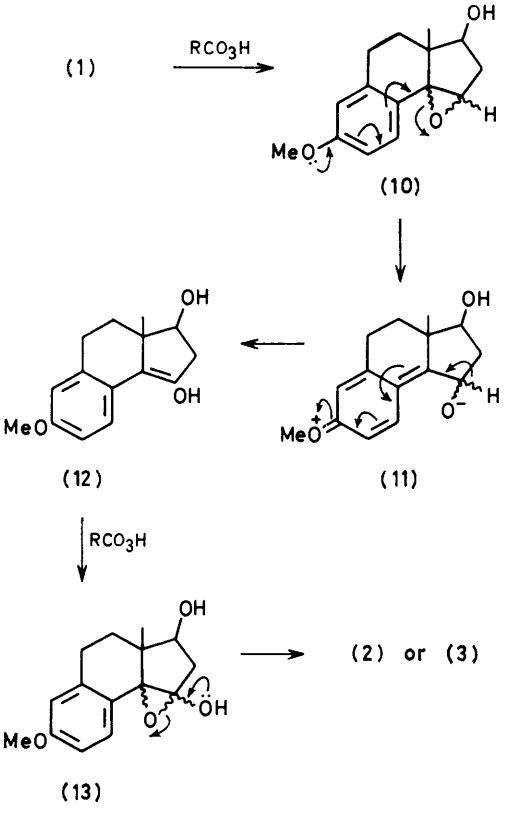


FIGURE 2 Angle between plane of 15-carbonyl group and plane of aromatic ring

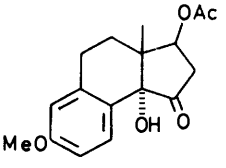
(11). Further epoxidation of the enol (12) by the peracid yields the epoxide (13), which rearranges to the ketol (2) or (3). In both of the epoxidation steps of the Scheme, attack of the peracid would be expected to occur predominantly from the less-hindered α-face of the styrene. Thus both these mechanistic proposals and the n.m.r. spectral correlations already discussed suggest that the



SCHEME

major product is the 14α-ketol. Definitive evidence on the configuration of this ketol is provided by the *X*-ray crystal structure determination reported below.

The two ketols show markedly different behaviour upon acetylation. Oxidation of the styrene (1) with monoperphthalic acid followed by treatment of the crude product, containing mainly the 14α-ketol (2), with acetic anhydride in pyridine, gave the 17β-acetate (14) in an overall yield of 68%. The acetate (14) showed the expected downfield shift of the 17α-hydrogen (0.85 p.p.m.) and of the 18-methyl protons (0.05 p.p.m.). However, treatment of the 14β-ketol (3) with acetic anhydride in pyridine did not give the corresponding 17β-acetate, but instead afforded the α,β-unsaturated ketone (15) in 81% yield. This was identified by the characteristic conjugated cyclopentenone absorption at 1 705 cm^{-1} in its i.r. spectrum, and the olefinic proton signals at δ 7.57 and 6.14 in its n.m.r. spectrum.



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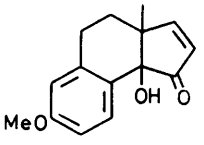
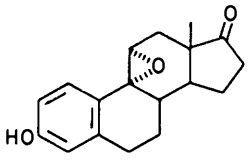


(15)

The elimination of acetic acid across the 16,17-bond of the 14β-ketol (3), but not the 14α-ketol (2), following treatment with an acetylating mixture, may be a consequence of the conformational differences between the two ketols. Using Dreiding models, it is clear that only in the case of the flexible 14β-ketol (3) can a conformation be attained in which the 17β-hydroxy-group and the 16α-hydrogen are pseudo-axial. On acetylation of the 17β-hydroxy-group a better leaving group is obtained, and *trans*-diaxial elimination of acetic acid can occur in the case of the 14β-epimer.

The electron-releasing effect of the 5-methoxy-group, relayed to the benzylic position of the epoxide (10), is responsible for its instability in acidic media,[13] and various devices were employed in an effort to obviate this effect in order to allow the initial epoxide intermediate (10) to be isolated. Oxidation of the styrene (1) with an equimolar amount of *m*-chloroperbenzoic acid gave complex mixtures of products, and even when an excess of this peracid (up to 3 equiv.) was used, we were unable to isolate the pure ketols (2) and (3). Use of a slight excess of monoperphthalic acid, in air or under nitrogen, gave similar product mixtures, as determined by their n.m.r. spectra. The characteristic signals of the angular methyl groups showed that the starting styrene (1) and the ketol (2) were present in a ratio of *ca.* 1 : 2. It thus appears that initial epoxidation of the styrene (1) is the slowest step in the sequence of reactions. Subsequent rearrangements of the epoxide (10) and further oxidation to the ketols must both occur much more rapidly, and hence it is not possible to prepare the epoxide (10) under these conditions.

The preparation of acid-sensitive epoxides under mild conditions using an alkaline biphasic solvent system with *m*-chloroperbenzoic acid has been described by Anderson and Veysoglu.[14] The success of Collins and Sjövall [15] in preparing the labile 9α,11α-epoxyoestrone (16) in 70% yield from $\Delta^{9(11)}$-oestrone (5) using this procedure encouraged us to apply it to the tricyclic styrene (1). However, oxidation of the styrene (1) with *m*-chloroperbenzoic acid (0.88 equiv.) in dichloromethane containing aqueous sodium hydrogen carbonate at room temperature afforded the ketol (2) in an estimated yield of 72%, together with recovered styrene (16%) and a small amount of the ketol (3). When the reaction was repeated under nitrogen, the ketol (2) was formed in 16% yield, along with a trace of the epimeric ketol (3), but the major product was a new compound having the same R_F value as the starting styrene. The n.m.r. spectrum of this compound lacked the C-15 olefinic proton, and showed the C-7 aromatic proton signal at δ 8.01. The angular methyl protons' singlet appeared at δ 0.65, and the triplet for the 17α-proton appeared at δ 4.68. This data, together with i.r. absorptions at 3 450 and 1 740 cm^{-1}, suggested the 15-oxo-structure (17) for the new



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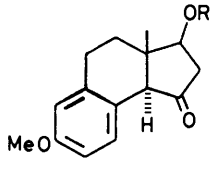
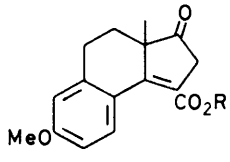
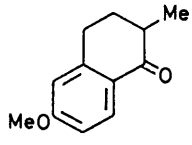


(17) R = H
(18) R = Ac



(19) R = Et
(20) R = H



(21)

product. Treatment with acetic anhydride in pyridine gave the 17β-acetate (18), as shown by the downfield shift (0.84 p.p.m.) of the 17α-proton to δ 5.52 in the n.m.r. spectrum. The i.r. spectrum showed the acetoxy and five-membered ring carbonyl absorptions at 1 745 cm^{-1}, and lacked hydroxy-absorption, showing that the tertiary hydroxy-group of the ketols was not present at C-14. Assignment of the 14α-configuration to the 15-ketones (17) and (18) was made from comparison of the C-7 aromatic proton and 18-methyl protons' resonance positions in the n.m.r. spectra, which corresponded well with those recorded for the 14α-ketol (2). The electron-releasing effect of the 5-methoxy-group in the epoxide (10) is clearly responsible for its ready rearrangement to the 15-ketone (17). This compound (17) is the ketonic form of the intermediate (12) in the Scheme, and it is possible that it is also an intermediate in the formation of the ketols (2) and (3).

α-Hydroperoxy-ethers and related compounds, generated *in situ*, have recently been employed as mild epoxidising agents for olefins,[16] *e.g.* *trans*-β-methylstyrene, in triethyl orthoacetate, can be epoxidised by treatment with 90% hydrogen peroxide. However, this reagent combination proved ineffective for epoxidation of the styrene (1), as did hydrogen peroxide alone. 6-Methoxy-2-methyl-1-tetralone in small amounts (2—3%) was the only product formed,[17] as determined by g.l.c. analysis.

Having examined possible conditions for suppressing ring-opening and rearrangement of the 14,15-epoxide, we examined the behaviour of the styrene (19) [18] in which the 15-hydrogen is replaced by the ethoxycarbonyl group, thereby precluding the possibility of rearrangement of the derived epoxide to the 15-ketone. Treatment of the ester (19) with *m*-chloroperbenzoic acid (1 equiv.) in dichloromethane at room temperature gave no reaction. Nor was epoxidation achieved when the mixture was heated under reflux for 118 h, when only 33% of the starting ester was recovered. The main product was the carboxylic acid (20). The lack of reactivity of the double bond of the styrenes (19) and (20) is probably due to steric hindrance, or to more extensive delocalization of its π-electrons.

X-Ray Crystal Structure Determination

The molecular structure of the major ketol (2) is shown in Figure 3. Figure 4 shows the bond lengths

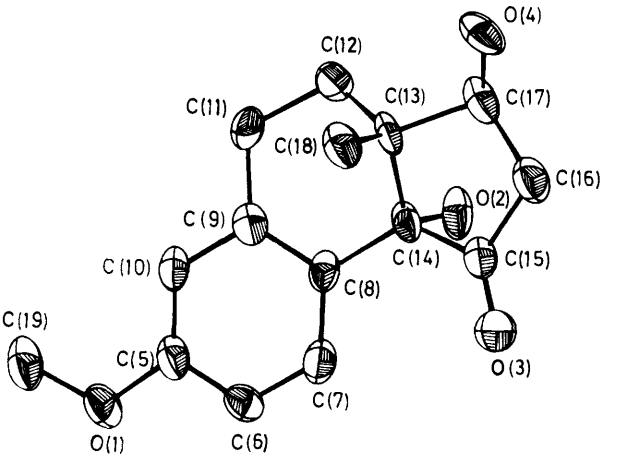


FIGURE 3 The atomic arrangement in the molecule

and valency angles involving non-hydrogen atoms; estimated standard deviations range from 0.006 to 0.012 Å for the bond distances and from 0.4 to 0.7° for the valency angles. A monohydrate is formed in the crystal and the molecules are linked by hydrogen bonding. The C/D ring junction is *trans*: ring C adopts a sofa conformation [$\Delta C_S(9) = 1.9°$] and ring D adopts a conformation midway between the envelope and half-chair forms ($\Delta = 19.0°$, $\phi_m = 44.7°$). Steroids with aromatic B rings and *trans* C/D ring junctions, such as 1(10→6) *abeo*-cholestra-5,7,9-trien-3-yl *p*-bromobenzoate,[19] possess similar conformational properties.

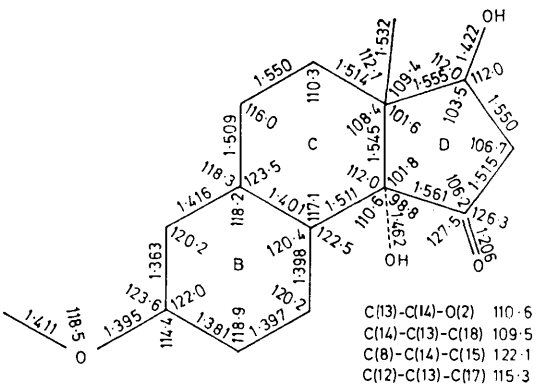


FIGURE 4 Intramolecular bonded distances (Å) and valency angles (°)

There are angular distortions involving C(14), in particular C(8)–C(14)–C(15) 122.1(6)° is larger and C(15)–C(14)–O(2) 98.8(4)° is smaller than the normal tetrahedral value. The O(3) · · · H(7) separation here is 2.40(4) Å and the dihedral angle between the aromatic ring and the carbonyl atoms C(14)C(15)C(16)O(3) is 18.3°.

The crystal structure of 4,6-bis(methoxycarbonyl)-7,8-dimethoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]inden-2-one [20] possesses the same ring nucleus pattern as the ketol (2) but the C/D ring junction of the tricyclic system is *cis*.

EXPERIMENTAL

Gas chromatography was performed on a Perkin-Elmer F-11 instrument equipped for dual-column operation, using 2 m × 3 mm (i.d.) glass columns, packed with 3% silicone OV-1 on Chromosorb W-HP (100—120 mesh) at 175 °C with a nitrogen flow rate of 28 ml min^{-1}. N.m.r. spectra were determined on a Perkin-Elmer R12A (60 MHz) or R34 (220 MHz) spectrometer.

Purified [21] dichloromethane was stored over molecular sieves type 4A. Monoperphthalic and *m*-chloroperbenzoic acids were prepared, and their concentrations were determined by the method of Fieser.[22] For other general directions see ref. 23.

Oxidation of 17β-*Hydroxy*-5-*methoxy*-*de*-A-*oestra*-5,7,9,14-*tetraene* (1) *with Monoperphthalic Acid.*—(a) *Using* 2.7 *equiv. monoperphthalic acid.* To a solution of the styrene (1) (0.90 g, 3.9 mmol) in a mixture of dry diethyl ether (20 ml) and dichloromethane (30 ml) was added a solution of monoperphthalic acid (1.93 g, 10.6 mmol) in diethyl ether (113 ml), and the mixture was left at 4 °C in the dark. After 17.5 h the solution was decanted and the precipitated phthalic acid was washed with ether. The combined ethereal solutions were washed successively with 5% aqueous sodium hydrogen carbonate (2 × 40 ml) and with water (20 ml) and then dried ($MgSO_4$). Solvent removal gave a colourless oil (1.01 g) which crystallised. Separation by prepared t.l.c. [hexane–diethyl ether (1 : 3)] followed by recrystallisation gave 14α,17β-*dihydroxy*-5-*methoxy*-*de*-A-*oestra*-5,7,9-*trien*-15-*one* (2) as colourless plates (0.65 g, 63%), m.p. 142—144 °C (from hexane–diethyl ether) (Found: C, 68.7; H, 6.7%; M^+, 262.1204; $M^+ - 28$, 234.1251. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%; *M*, 262.1205. $C_{14}H_{18}O_3$ requires *M*, 234.1255); $\lambda_{max.}$ (EtOH) 234 (log ε 3.73), 277—278 (3.10), and 284—285 nm (3.08); $\Delta\varepsilon$ + 4.29 (212 nm),

−8.27 (234 nm), at 1.27×10^{-3} g l^{-1} in MeOH and +0.71(278 nm), +0.87(282 nm), +1.17(320 nm) at 3.8×10^{-3} g l^{-1} in MeOH; $\nu_{max.}$ (KBr) 3 480, 3 350, 1 735, 1 615, 1 575, 1 500, 1 375, 1 275, 1 240, 1 105, 1 090, 1 075, 1 000, 945, 935, 905, and 810 cm^{-1}; δ($CDCl_3$) 0.74 (s, 18-Me), 3.76 (s, 5-OMe), 4.62br (t, *J* 9 Hz, 17-H), 6.64—6.80 (m, 6- and 10-ArH), and 8.07 (d, *J* 9 Hz, 7 ArH); *m/e* 262 (M^+, 0.3%), 246(1), 234(10), 191-(18), 190(100), 175(46) (*M**, 161, calc. 190 ⟶ 175, 161.18), and 14β,17β-*dihydroxy*-5-*methoxy*-*de*-A-*oestra*-5,7,9-*trien*-15-*one* (3) as a colourless oil (0.11 g, 11%), which could not be crystallised (Found: M^+, 262.1199. $C_{15}H_{18}O_4$ requires *M*, 262.1205); $\lambda_{max.}$ (MeOH) 243 (log ε 3.73), 275 (3.37), and 283 nm (3.32); $\nu_{max.}$ 3 420, 1 735, 1 605, 1 500, 1 240, 1 110, 1 050, 1 030, 855, 815, and 755 cm^{-1}; δ^{60} ($CDCl_3$) 1.04 (s, 18-Me), 3.76 (s, 5-OMe), 4.18 (t, *J* 7 Hz, 17α-H), 6.67br (s, 10-ArH), 6.70 (q, $J_{6,7}$ 9 Hz, $J_{6,10}$ 3 Hz, 6-ArH), and 7.30 (d, *J* 9 Hz, 7-ArH); *m/e* 262 (M^+, <0.3%), 244(2), 234(5), 216(17), 201(5), 191(7), 190(100), 189(7), 175(40), and 148(28) (*M**, 161, calc. 190 ⟶ 175, 161.18).

(b) *Using* 1.3 *equiv. monoperphthalic acid.* Reaction of the styrene (1) with monoperphthalic acid (1.3 equiv.) in air and under an atmosphere of nitrogen, was carried out as described above, though when a nitrogen atmosphere was required the system was purged prior to the addition of ethereal peracid solution. Analysis of the product mixture by comparison of the chemical-shift values of the angular methyl group signals in the n.m.r. spectra, indicated the formation of (2) and recovery of (1) in *ca.* 30 and 70% yields respectively.

Equilenin Acetate (6).—To a solution of equilenin (14 mg, 0.053 mol) in a small volume of dry pyridine (0.25 ml) was added redistilled acetic anhydride (0.25 ml) and the mixture was left at room temperature overnight before being hydrolysed with water. The precipitate which formed was filtered off and washed well with water, to give equilenin acetate (16 mg, 98%), as colourless microcrystalline needles, m.p. 151—155 °C (lit.,[24] 156—157 °C), $\nu_{max.}$ (KBr) 1 755, 1 735, 1 600, 1 370, 1 200, 1 150, 1 010, 900, and 820 cm^{-1}; δ($CDCl_3$) 0.74 (s, 18-Me), 2.31 (s, 3-OAc), 7.20—7.33 (m, 2-ArH and 6- or 7-ArH), 7.51 (d, *J* 2 Hz, 4-ArH), 7.66 (d, *J* 9 Hz, 6- or 7-ArH), and 7.94 (d, *J* 9 Hz, 1-ArH).

17β-*Acetoxy*-14α-*hydroxy*-5-*methoxy*-*de*-A-*oestra*-5,7,9-*triene*-15-*one* (14).—The crude ketol (2) (*ca.* 0.65 mmol), prepared from the styrene (1) (150 mg, 0.65 mmol) by treatment with monoperphthalic acid [22] (298 mg; 1.63 mmol) in diethyl ether–dichloromethane at 4 °C in the dark as described previously, was taken up in dry pyridine (5 ml) and redistilled acetic anhydride (4 ml) and the mixture left at room temperature in the dark. After 65 h, the red solution was hydrolysed with water and concentrated under reduced pressure. Separation of the crude acetylated product by preparative layer chromatography [hexane–diethyl ether (1 : 3)] gave 17β-*acetoxy*-14α-*hydroxy*-5-*methoxy*-*de*-A-*oestra*-5,7,9-*trien*-15-*one* (14) (R_F 0.65; 134 mg, overall yield 67.6%), m.p. 101—108 °C, as colourless needles, raised by recrystallisation from hexane–diethyl ether to m.p. 109—110.5 °C (Found: C, 67.3; H, 6.9%; M^+, 304.1309. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%; *M*, 304.1310), $\lambda_{max.}$ (MeOH) 229 (log ε 3.74), 275 (2.99), and 283 nm (2.97); $\nu_{max.}$ (KBr) 3 420, 1 735, 1 605, 1 500, 1 375, 1 360, 1 260, 1 240, 1 085, 1 065, 1 030, 845, and 810 cm^{-1}; δ($CDCl_3$) 0.79 (s, 18-Me), 2.09 (s, 17-OAc), 3.77 (s, 5-OMe), 5.47 (t, *J* 8 Hz, 17-H), 6.68—6.80 (m, 6- and 10-ArH), and 8.08 (d, *J* 9 Hz, 7-Ar H); *m/e* 304 (M^+, 0.6%), 288(2), 276(6), 228(13), 216(16), 201(25), 190(100), 175(16), and 148(11).

14β-*Hydroxy*-5-*methoxy*-*de*-A-*oestra*-5,7,9,16-*tetraen*-15-*one* (15).—A solution of the ketol (3) (53 mg, 0.20 mmol) in dry pyridine (2 ml) and redistilled acetic anhydride (0.5 ml was left at room temperature. After 17.5 h, the mixture was hydrolysed with water (10 ml), concentrated under reduced pressure and the resulting oil was separated by preparative layer chromatography [hexane–diethyl ether (1 : 2)] to give the crude ketol (15) (R_F 0.28; 40 mg, 81%), m.p. 138—143 °C. Two recrystallisations from hexane–chloroform gave the *ketol* (15) in 49% yield as prisms, m.p. 143—144 °C (Found: M^+, 244.1101. $C_{15}H_{16}O_3$ requires *M*, 244.1099), $\lambda_{max.}$ (EtOH) 232 (log ε 4.06), 275 (3.36), 284—285 (3.32), and 339 nm (2.78); $\nu_{max.}$ (KBr) 3 480, 1 705, 1 610, 1 500, 1 385, 1 285, 1 255, 1 105, 1 090, 1 065, 1 035, 885, 845, and 810 cm^{-1}; δ($CDCl_3$) 1.2 (s, 18-Me), 3.73 (s, 5-OMe), 6.14 (d, *J* 7 Hz, 16-olefinic H), 6.54 (d, *J* 3 Hz, 10-ArH), 6.82 (q, $J_{6,7}$ 9 Hz, $J_{6,10}$ 3 Hz, 6-ArH), 7.54—7.61 (m, 7-ArH and 17-olefinic H); *m/e* 244 (M^+, 20%), 229(7), 217(8), 216(100), 201(14), 198(18), 175(25), 148(71) (M_1*, 187, calc. 216 ⟶ 201, 187.04; M_2*, 161, calc. 190 ⟶ 175 161.18).

15-*Ethoxycarbonyl*-5-*methoxy*-*de*-A-*oestra*-5,7,9,14-*tetraene*-17-*one* (19).—The synthesis of the ketone (18) was carried out by the route of Banerjee [18] with a slight modification in the final stage. From the Stobbe condensation of crude 2-cyano-6-methoxy-2-methyl-1-tetralone (1.27 g, 5.9 mmol) and redistilled diethyl succinate (6.49 g, 37.2 mmol) in a solution of potassium t-butoxide (from 1.490 g potassium and 45 ml t-butyl alcohol), after 41 h at room temperature an oil was obtained, which, after separation by preparative layer chromatography [hexane–diethyl ether (2 : 1.5)], crystallised from hexane, m.p. 51—57 °C. Repeated recrystallisation gave the *ester* (19) as colourless needles, m.p. 78—79.5 °C (from hexane) (Found: C, 72.3; H, 6.7%; M^+, 300.1362. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%; *M*, 300.1361), $\lambda_{max.}$ (EtOH) 231 (log ε 4.05) and 309 nm (4.09); $\nu_{max.}$ (KBr) 1 745, 1 710, 1 615, 1 585, 1 565, 1 495, 1 275, 1 245, 1 205, 1 075, 1 035, 865, 820, and 775 cm^{-1}; δ($CDCl_3$) 1.11 (s, 18-Me), 1.30 (t, *J* 7 Hz, 15-CH_3′), 1.96 (m, 12-CH_2), 2.96 (m, 11-CH_2), 3.46 (AB-q, *J* 22 Hz, 16-CH_2), 3.82 (s, 5-OMe), 4.24 (q, *J* 7 Hz, 15-CH_2′), 6.69br (s, 10-ArH), 6.79 (q, $J_{6,7}$ 9 Hz, $J_{6,10}$ 3 Hz, 6-ArH), and 8.02 (d, *J* 9 Hz, 7-ArH); *m/e* 300 (M^+, 100%), 273(8), 272(71), 255(9), 199(50), 198(25), 197(10), 183(9), and 172(9) (M_1*, 247, calc. 300 ⟶ 272, 246.61; M_2*, 145, calc. 272 ⟶ 199, 145.59).

Attempted Oxidation of the Ester (19) *with* m-*Chloroperbenzoic Acid.*—(a) *At room temperature.* To a solution of the ester (19) (138 mg, 0.468 mmol) in dichloromethane (5 ml) was added, during 5—10 min, *m*-chloroperbenzoic acid (142 mg of 55.5%; 0.457 mmol) in dichloromethane (4 ml). The mixture was stirred at room temperature for 5 h after which it was diluted with dichloromethane and washed successively with 10% aqueous Na_2SO_3 and 5% aqueous $NaHCO_3$ and then dried ($MgSO_4$). Solvent removal gave a quantitative recovery of the ester (19), identified by t.l.c. and i.r. comparison with that of an authentic sample.

(b) *At* 40 °C. To the ester (19) (99 mg, 0.33 mmol) in dichloromethane (10 ml) was added *m*-chloroperbenzoic acid (154 mg of 55.5%; 0.49 mmol) and the mixture was stirred under reflux with protection from moisture ($CaCl_2$). Dichloromethane was added as required to maintain the solvent level. After 118 h the mixture was cooled and worked up as described in (a) to give an oil, which on separation by preparative layer chromatography gave

unchanged ester (19) (33 mg, 33%) identified by comparison of the i.r. spectrum with that of an authentic sample, together with a polar component (38 mg), which from its mobility on t.l.c. was thought to be the free acid (20) (42%).

Oxidation of the Styrene (1) *with Hydrogen Peroxide.*—(a) *In dichloromethane.* To the styrene (1) (36 mg, 0.15 mmol) in dichloromethane (3 ml) was added 50% (w/w) hydrogen peroxide solution (1 ml). The mixture was stirred 19 h and then diluted with dichloromethane; it was then washed with water and dried ($MgSO_4$). Solvent removal gave an oil which on g.l.c. comparison with authentic samples indicated the formation of the 6-methoxy-2-methyltetralone (21) [17] (2.5%; R_t 7.8 min) together with recovery of the styrene (1) (92%; R_t 25.2 min).

(b) *In triethyl orthoformate.* The oxidation was carried out and the product mixture analysed as described in (a). The styrene (1) (52 mg, 0.22 mmol) in triethyl orthoformate (6 ml) with 50% (w/w) hydrogen peroxide solution (2 ml) [16] for 3 h gave the tetralone (2) (1.5%) and recovered styrene (1) (93%).

(c) *In triethyl orthoacetate.* The oxidation was carried out and the product mixture analysed as described in (a). The styrene (1) (54 mg, 0.23 mmol) in triethyl orthoacetate (6 ml) with 50% (w/w) hydrogen peroxide solution (2 ml) for 3 h gave the tetralone (21) (3%) and recovered styrene (1) (89%).

Oxidation of the Styrene (1) *with* m-*Chloroperbenzoic Acid under Alkaline Conditions.*—(a) *In air.* To the styrene (1) (101 mg, 0.44 mmol) in dichloromethane (5 ml) containing aqueous sodium hydrogen carbonate (1.32 ml; 0.5M) was added *m*-chloroperbenzoic acid (120 mg of 55.5%; 0.39 mmol) in portions; after the addition of the peracid the mixture was stirred at room temperature for 2.5 h. The two phases were then separated and the organic solution washed successively with dilute NaOH (1N) and water and then dried (Na_2SO_4). Solvent removal under reduced pressure gave an oil which on separation by multiple-development preparative layer chromatography [hexane–diethyl ether (1 : 2 × 4)] gave recovered styrene (1) (*ca.* 1.6%), m.p. 161—170 °C (lit.,[25] 179 °C), the i.r. spectrum of which was identical with that of an authentic sample; the 14α-ketol (2) (*ca.* 72%), m.p. 134—139 °C, identical with an authentic sample [t.l.c. hexane–diethyl ether (1 : 3); hexane–ethyl acetate (1 : 1) and i.r.] and the 14β-ketol (3) as indicated from t.l.c. comparison with an authentic sample [hexane–diethyl ether (1 : 3); hexane–ethyl acetate (1 : 1)].

(b) *Under nitrogen.* The reaction was repeated under conditions identical with those used in part (a) except that the reaction was carried out under nitrogen and further dichloromethane (10 ml) was added to maintain the solvent level. Thus from the styrene (1) (101 mg, 0.44 mmol), *m*-chloroperbenzoic acid (120 mg of 55.5%; 0.39 mmol) and aqueous sodium hydrogen carbonate solution (1.32 ml of 0.5M) was obtained, after separation by preparative layer chromatography [hexane–diethyl ether (1 : 2 × 4)], the 14α-ketol (2) (18 mg, 16%) identical with an authentic sample of both t.l.c. [hexane–diethyl ether (1 : 2)] and its i.r. spectrum; the 14β-ketol (3) as observed from t.l.c. comparison; and the ketone (17) (42 mg, 39%) as an oil [R_F 0.42 in 1 : 2 hexane–diethyl ether], $\nu_{max.}$ 3 450, 1 740, 1 600, and 1 500 cm^{-1}; $\delta(CDCl_3)$ 0.65 (s, 18-Me), 3.77 (s, 5-OMe), 4.68 (t, *J* 7 Hz, 17-H), 6.60—6.91 (m, 6- and 10-ArH), and 8.01 (d, *J* 9 Hz, 7-ArH).

* For details of the Supplementary publications scheme, see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1*, 1981, Index issue.

The ketone (17) (42 mg; 0.17 mmol) in dry pyridine (0.5 ml) was treated with redistilled acetic anhydride. After 2 days the mixture was hydrolysed with water and concentrated under reduced pressure to yield an oil, which on separation by preparative layer chromatography [hexane–diethyl ether (2 : 1)] gave the acetate (18) (20 mg, 41%) as an oil, $\nu_{max.}$ 1 745, 1 610, 1 500, 1 240, 1 060, and 1 040 cm^{-1}; $\delta(CDCl_3)$ 0.70 (s, 18-Me), 2.08 (s, 17β-$OCOCH_3$), 3.78 (s, 5-OMe), 5.52 (t, *J* 7 Hz, 17α-H), 6.72 (m, 6- and 10-ArH), and 8.03 (d, *J* 9 Hz, 7-ArH).

Crystal Data.—$C_{15}H_{18}O_4 \cdot H_2O$, M = 280.2, monoclinic, a = 8.320(8), b = 7.026(11), c = 12.816(12) Å, β = 110.11(8)°, U = 703.5 Å^3, Z = 2, D_c = 1.32 mg m^{-3}, $F(000)$ = 300, Mo-K_α radiation, λ = 0.7107Å, μ = 0.60 cm^{-1}. Space group $P2_1$.

Crystallographic Measurements.—Intensity measurements were obtained from a Nicolet P3 automated diffractometer using monochromatized Mo-K_α radiation. Integrated relative intensities for 1 332 independent reflexions with 2θ < 50° were measured (θ—2θ scan method used); 1 216 reflexions had $I > 2.5\sigma(I)$.

Structure Analysis.—The crystal structure was elucidated by direct methods using the 'Multan' programme.[26] H Atoms were located from electron-density maps calculated at intermediate stages of structure refinement. With anisotropic thermal parameters for the carbon and oxygen atoms and isotropic thermal parameters for the hydrogen atoms, refinement converged at R 6.9%. The weighting scheme used in the final cycles of least-squares refinement was $w = 3.9/(\sigma^2 F_o)$.

Final positional parameters are listed in Table 1, torsion angles in Table 2 and details of the hydrogen bonding in Table 3. Structure amplitudes and thermal parameters are listed in Supplementary Publication No. SUP 23208 (11 pp.).*

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[1/1003 *Received*, 22*nd June*, 1981]

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