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Selective Aromatization of Ring B in 19-Norsteroids and Synthesis of Equilenin-type Compounds

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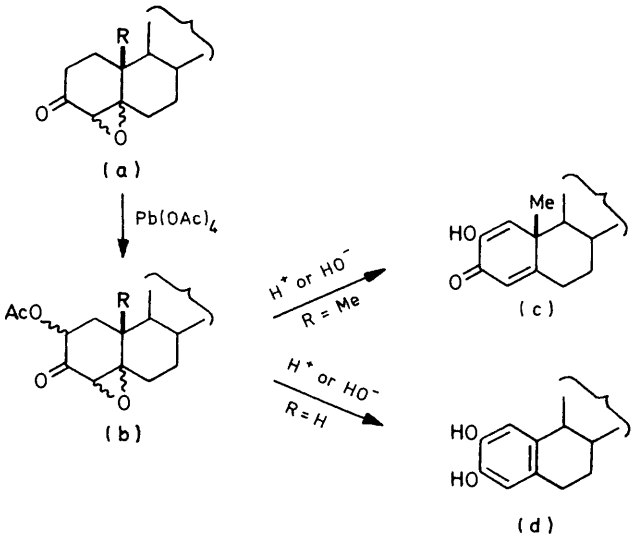
The preparation of 7α-acetoxy-3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-5β,10β-oestran-6-one (4) is described. When heated with alkali it undergoes ring B aromatization to give 3,3:17,17-bis(ethylenedioxy)-oestra-5(10),6,8-triene-6,7-diol (7), without configurational change at C(14). Bis-deacetalization of the corresponding diacetate (8), followed by lead tetra-acetate aromatization of ring A in the resulting diketone (9), produces 6,7-diacetoxyequilenin (10), which is finally converted into its 3-acetate (11). The same ester product (11) could also be obtained by conversion of the diketone (9) into its 3-enol acetate (12), followed by lead tetra-acetate dehydrogenation.

SELECTIVE aromatization of ring B in normal steroid molecules, other than skeletal rearrangements leading to anthrasteroids,[1a] has been realized by way of reactions, involving $CH_3(19)$ group elimination, performed on substrates containing (initially) a 5,7- or 5,8-diene system. Examples are pyrolysis of 7,7′-bis-steroids, produced photochemically from ergosterol and related compounds,[2a] zinc reduction of 3β-acetoxy-lanosta-5,8-dien-7-one [3a] in acetic acid,[3b] lithium aluminium hydride reduction of 4,4-dimethyl-$\Delta^{5,8}$-steroidal azo-esters,[4] and thermal retro-Diels–Alder reaction of the maleic anhydride (or dimethyl maleate) adducts of steroidal 9α-11α-epoxy-5,7-diene derivatives (in the ergostane and pregnane series).[5] On the other hand, the aromatization of ring B in 19-norsteroids has been achieved, so far, by methods (involving dehydrogenation and/or substituent elimination) requiring the substrate to be aromatic in ring A [2b,6,7] or, at least, to contain a 3,5-conjugated double-bond grouping,[7] so that the products obtained were always aromatic in both rings A and B [with, in some cases, the possibility (rarely used) of carrying out selective hydrogenation of ring A [8]].

In a preliminary communication we described briefly a new approach to the aromatization of ring B alone, starting from non-aromatic and non-olefinic 19-norsteroid compounds,[9] and a full description of this work is now given. The procedure is based (Scheme 1) on the lead tetra-acetate α′-acetoxylation of α,β-epoxy-ketones (a) followed by *O*-acetyl and epoxide oxygen elimination [from (b)], reactions which have been successfully applied for the preparation of steroidal 2-hydroxy-1,4-dien-3-ones (c) [10] and for the aromatization of ring A in 19-nortestosterone [partial structure (d)].[11]

A convenient substrate containing the epoxy-oxo-group in the appropriate position to permit aromatization



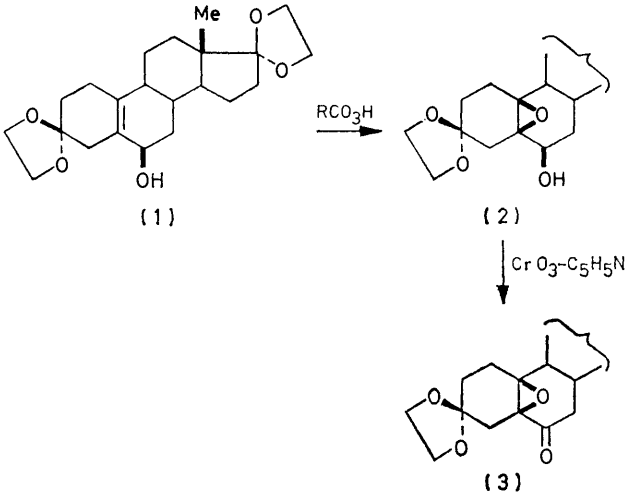
SCHEME 1

of ring B when subjected to similar reactions is 3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-5β,10β-oestran-6-one (3),[12] which was prepared as shown in Scheme 2.

Epoxidation of 3,3:17,17-bis(ethylenedioxy)-oestr-5(10)γ-en-6β-ol (1) [13] with *m*-chloroperbenzoic acid afford-

ed stereoselectively 3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-5β,10β-oestran-6β-ol (2) [12] (in 63% yield).* This compound was then oxidised with chromium trioxide in pyridine to give the epoxy-ketone (3) (in 87—90% yield).

The β-configuration of the oxiran ring in the epoxy-alcohol (2) was assigned mainly on the assumption that, as in most other cases of epoxidation of steroidal allylic



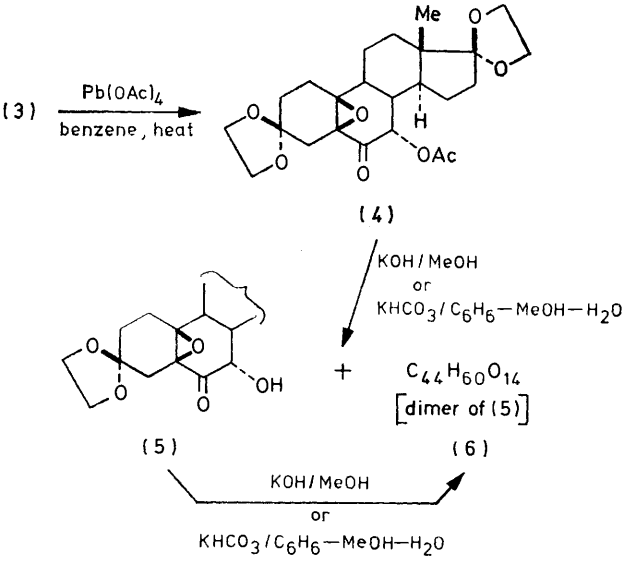
(1) (2) (3)

SCHEME 2

alcohols with peracids,[1b,14] the 6β-hydroxy-group † in olefin (1) exerts a *cis* directive effect on the addition of the peracid oxygen to the 5,10-double bond.‡ Such a 5β,10β-stereochemistry in (2) is in accord with the observation that the n.m.r. signal of the 6α-proton in the *N*-trichloroacetyl carbamate ester of (2)§ is a doublet (at δ 5.27) with a coupling of 6 Hz, this indicating dihedral angles of *ca.* 90° and 30° between the C(6α)–H bond and the β-equatorial and α-axial C(7)–H bonds, respectively, and therefore distortion of ring B as the result of repulsion between the 5β,10β-epoxide oxygen and the 6β-substituent *N*-trichloroacetyl-carbamoyloxy-group.¶

When 3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-5β,-10β-oestran-6-one (3) was treated with 4 mol equiv. of lead tetra-acetate in the presence of anhydrous calcium carbonate in refluxing benzene for several days [*i.e.* until all starting material (3) had been consumed], it underwent acetoxylation (Scheme 3) to give, essentially, as the sole isolable product 7α-acetoxy-3,3:17,17-bis-(ethylenedioxy)-5,10-epoxy-5β,10β-oestran-6-one (4), in *ca.* 54—61% yield. The configuration assigned at C(7) in compound (4), and corresponding to an α-orientation of the 7-acetoxy-group, follows from the 4.5 Hz value (in the ^{1}H n.m.r. spectrum) of the coupling constant $J_{7\text{-H},8\text{-H}}$ for the doublet-signal (at δ 5.14 p.p.m.) of the proton at C(7), this value being compatible with a dihedral angle of *ca.* 40—45° between C(7)–H and C(8)–H(β-axial),** and indicating an equatorial 7β-proton, and therefore an axial 7α-acetoxy-group in compound (4).

Treatment of the 7α-acetoxy-epoxy-ketone (4) with 1% methanolic potassium hydroxide at room temperature, in an attempt to perform aromatization of ring B, resulted only in saponification and conversion of (4) into two non-aromatic products (Scheme 3), one being the expected hydroxy-ketone 3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-7α-hydroxy-5β,10β-oestran-6-one (5) (obtained in 24% yield) and the other, surprisingly, a carbonyl-free dimeric compound (6), m.p. 198—200 °C, $C_{44}H_{60}O_{14}$ (obtained in 42% yield). Similarly, treatment



SCHEME 3

of the epoxy-oxo-acetate (4) with potassium hydrogen carbonate in benzene–methanol–water solution at room temperature also gave only these two products, *i.e.* the oxo-alcohol (5) (in 20% yield) and its dimer (6) (in 35% yield).

The structure of the 7α-hydroxy-ketone (5) was confirmed by reacetylation (with acetic anhydride in pyri-

* Most yields in this part refer to recrystallised and analytically pure compounds. The yields of products isolated and purified only by column chromatography (and which could be used, in most cases, directly for further work) were *ca.* 5—10% (or even) higher (see Experimental section).

† Assignment of the β-stereochemistry to the hydroxy-group at C(6) in (1) was previously achieved by chemical methods.[15]

‡ In 5,10-olefinic 19-norsteroids without an allylic hydroxy-group [such as 6β-OH in (1)], the steric course of epoxidation with peracids may be but is not always selective, and depends on the substitution at C(3) and other structural and stereochemical factors.[16]

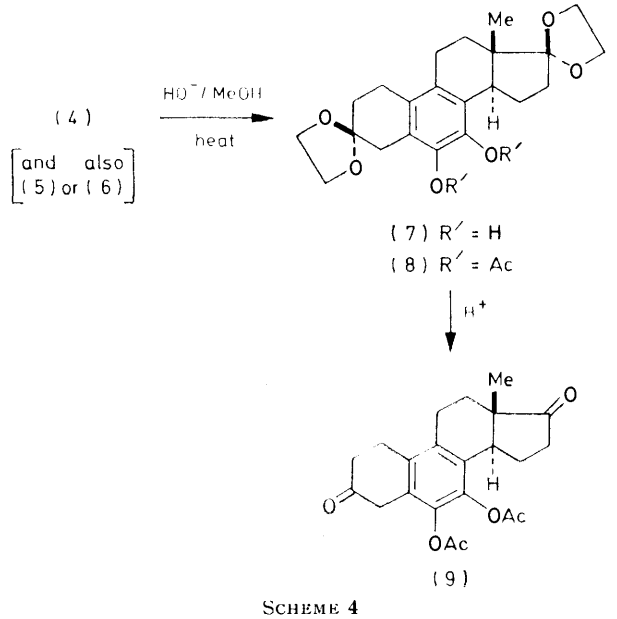
§ This carbamate ester, formed *in situ* by the addition of (2) to deuteriochloroform containing trichloroacetyl isocyanate, had to be used for ^{1}H n.m.r. analysis, since in the spectrum of the unesterified alcohol (2) the 6α-proton resonance coincides and overlaps with that of the methylenic protons of the ethylenedioxy (acetal) groupings.

¶ It appears, according to the absorption OH-bands in its i.r. spectrum, that in the epoxy-alcohol (2) intramolecular hydrogen bonding (in the form of a five-membered chelate ring) is weak, probably because of the unfavourable steric orientation between the lone electron pair of the rigid β-oxiran oxygen and hydrogen of the 6β-hydroxy-group.

** Inspection of molecular models reveals that this dihedral angle in the epoxy-oxo-acetate (4) should actually correspond to 40—45°, because of the deformation of ring B, caused by the strained oxiran system and the oxo-carbonyl group.

dine) to the starting acetate (4),* while the structure of the dimeric product (6) is currently being investigated (and will be discussed elsewhere). Also, it was shown that the hydroxy-ketone (5) could easily undergo conversion into the dimer (6) when subjected to the action of alkali under experimental conditions used for the saponification of the acetate (4) (see above), while the reverse transformation, *i.e.* of (6) into (5), under these conditions, was not possible.

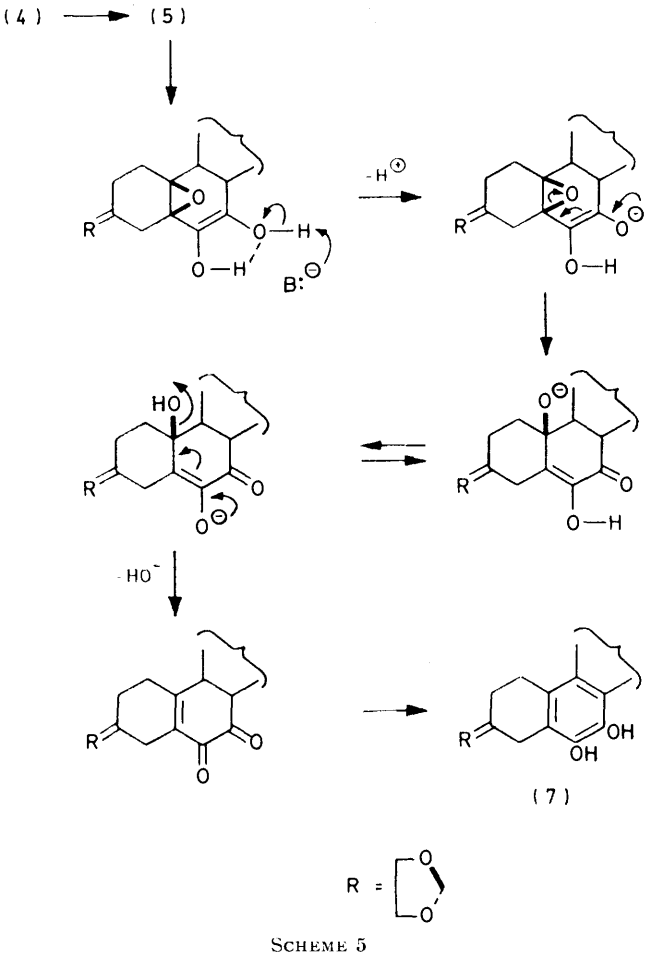
Successful aromatization of ring B was achieved (Scheme 4) when a solution of the acetoxy-epoxy-ketone



SCHEME 4

(4) in 1% methanolic potassium hydroxide was heated at reflux for 1 h under nitrogen; upon column chromatography on silica gel, 3,3:17,17-bis(ethylenedioxy)-oestra-5(10),6,8-triene-6,7-diol (7) was obtained in 80% yield, and converted by acetylation (with acetic anhydride in pyridine) into the corresponding 6,7-diacetate ester (8) (in 83% yield). The same procedure, *i.e.* aromatization (of ring B) under alkaline conditions and acetylation, starting from the 7-hydroxy-compound (5) or from the dimer (6), also afforded the diacetate (8), in 75—90% yield (crude). Bis-deacetalization of this diacetate (8), effected by heating in 85% acetic acid at 100 °C for 2 h, afforded *ca.* 76% of 6,7-diacetoxyoestra-5(10),6,8-triene-3,17-dione (9).

The above transformations of compounds (4), (5) and (6) in alkaline media suggest that aromatization of ring B in (5) possibly follows the mechanistic course shown in Scheme 5.† In connection with this reaction sequence it should be noted that the oxo-epoxide (3) remained unchanged when its solution in 1% methanolic potassium hydroxide was heated to reflux for 8 h, and that aromatization of compounds (5) and (6) did not take place (and they were not altered) in refluxing (3 h) methanol solution in the absence of potassium hydroxide.



SCHEME 5

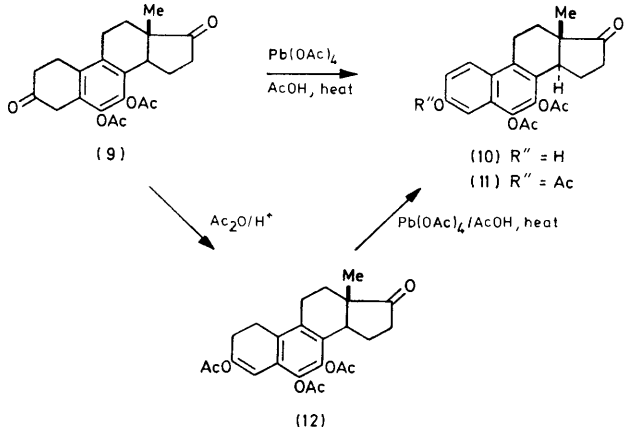
When the diketone (9) was treated, under nitrogen, with 1.35 mol equiv. of lead tetra-acetate in glacial acetic acid at 80 °C for 2 h, it readily underwent aromatization of ring A (Scheme 6) to give 6,7-diacetoxyequilenin (10), which, upon acetylation, afforded the corresponding acetate, *i.e.* 3,6,7-triacetoxyoestra-1,3,5(10),6,8-pentaen-17-one (11) [in 60% yield upon column chromatography and *ca.* 50% yield upon recrystallisation, based on the diketone (9)]. Aromatization of ring A could also be achieved by conversion of the diketone (9) into the corresponding 3-enol acetate (12), followed by lead tetra-acetate dehydrogenation, but in that case the yield of (11) was considerably lower [only *ca.* 10% with respect to the diketone (9)] (Scheme 6).

The structures of all compounds shown in Schemes 4 and 6 were assigned on the basis of their elemental microanalysis and spectral (u.v., i.r. and n.m.r.) data. In addition, by comparison of the ^{13}C n.m.r. spectrum of the triacetoxy-aromatic product (11) with the spectra of

* In the ^1H n.m.r. spectrum of (5), measured in the presence of trichloroacetyl isocyanate, the 7β-proton signal (of the resulting 7α-carbamate ester) appeared as a doublet at δ 5.27 p.p.m., with a coupling (7β-H,8β-H) having a value of *ca.* 5 Hz. [See also discussion above for compound (4).]

† A similar mechanism was previously proposed for 2-hydroxy-1,4-dien-3-one formation in the normal steroid series.[10]

the known 3-hydroxy-14α-oestra-1,3,5(10),6,8-pentaen-17-one (equilenin, 14α-epimer), 3-hydroxy-14β-oestra-1,3,5(10),6,8-pentaen-17-one (isoequilenin, 14β-epimer) and its acetate ester (isoequilenin acetate, also 14β), it could be concluded that in the course of the here outlined aromatization of ring B (and subsequent reactions) the configuration at the benzylic (and therefore easily epimerizable) C(14) remained unchanged. Namely, as shown in the Table, in isoequilenin and its acetate (14β, C/D rings *cis*) the C(18) resonance appears at *ca.* 20 p.p.m.,



SCHEME 6

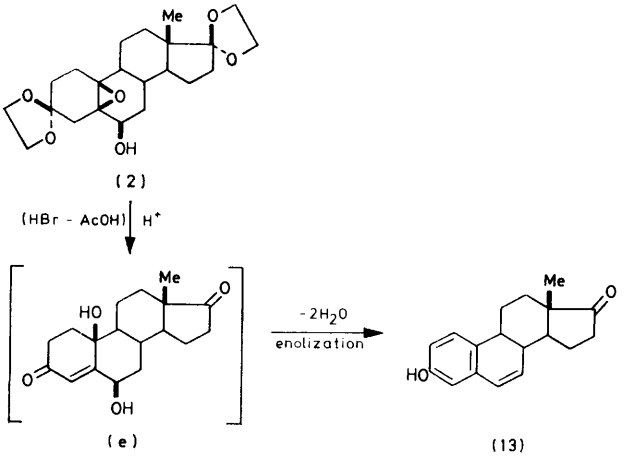
whereas in equilenin (14α, C/D rings *trans*) this signal is shifted upfield to 13.1 p.p.m., due to the two quasi *γ-gauche* interactions [17] [caused by the shielding effect of the C(11)–Hβ and C(15)–Hβ bonds], which are absent in the compounds of the 14β-series. Since the C(18) signal of the triacetoxy-aromatic product (11) is located at 13.9 p.p.m., it follows that this compound has the 14α-configuration (rings C/D *trans*), and that, therefore, the synthetic sequence described above leads exclusively to normal equilenin-type derivatives.

Selected signals from the ^{13}C n.m.r. spectra of 3,6,7-triacetoxy-14α-oestra-1,3,5(10),6,8-pentaen-17-one (11), 3-hydroxy-14α-oestra-1,3,5(10),6,8-pentaen-17-one (equilenin), and 3-hydroxy-14β-oestra-1,3,5(10),6,8-pentaen-17-one (isoquilenin) and its acetate ester [a]

Carbon atom	Compd. (11)	Equilenin	Isoequilenin	Isoequilenin acetate
2	121.7	110.1	110.3	121.2
3	149.2	154.6	155.1	148.1
5	127.1	134.0	134.0	134.8
6	139.8	124.7 [b]	125.2 [b]	124.7 [b]
7	136.4	124.1 [b]	124.5 [b]	*c*
11	24.7	23.9	26.7	26.3
14	45.3	46.7	47.6	47.7
17	218.2	219.8	*d*	222.4
18	13.9	13.1	20.2	19.9

[a] Spectra were measured at 25.15 MHz, in $CDCl_3$ (for compound (11) and isoequilenin acetate) or in $CDCl_3$–$(CD_3)_2SO$ (for equilenin and isoequilenin). Chemical shifts are given in δ p.p.m. values downfield from $SiMe_4$. [b] Assignments uncertain, signals may be interchanged. [c] Not assigned. [d] Not recorded.

Finally, it is of interest to note that the 6β-hydroxy-5β,10β-epoxy-compound (2) was found, in the present study, to be a suitable substrate for selective aromatization of ring A only (Scheme 7). Thus, on treatment with hydrobromic acid in glacial acetic acid,* it underwent bis-deacetalization and cleavage of the oxiran ring (e), followed by water elimination and enolization, to give 6-dehydro-oestrone (13) in 35% yield.



SCHEME 7

As to physiological properties, it was found that 6,7-diacetoxyequilenin acetate (11) was a weak oestrogen. When administered subcutaneously in the Bülbring-Burn test [19] its activity was *ca.* 1/1000 that of oestradiol.

EXPERIMENTAL †

M.p.s are uncorrected. Optical rotations were measured in chloroform, unless stated otherwise. ^1H N.m.r. spectra were obtained at 100 MHz with a Varian HA-100 spectrometer and at 360 MHz with a Bruker HX-360 spectrometer (in deuteriochloroform with tetramethylsilane as internal reference), and noise decoupled ^{13}C n.m.r. spectra were recorded at 25.15 MHz on a Varian XL-100 spectrometer equipped with a Fourier transform accessory (see Table for details); chemical shifts are given in δ p.p.m. values. I.r. spectra were determined on a Perkin-Elmer instrument, model 337. U.v. absorption spectra were recorded in 95% ethanol with a Perkin-Elmer 137 u.v. spectrophotometer. Mass spectra were taken on a Varian-Atlas MAT CH-5 or MAT CH-7 spectrometer. Silica gel (0.05—0.2 mm) was used for preparative column chromatography. The separation of products was monitored by t.l.c., which was carried out on silica gel G (Stahl) with benzene–ethyl acetate (7 : 3 and 4 : 6), detection being effected with 50% aqueous sulphuric acid. Light petroleum refers to the fraction of b.p. 40—60 °C.

3,3:17,17-Bis(ethylenedioxy)oestr-5(10)-en-6β-ol (1) [13] had m.p. 157 °C (from ether–light petroleum) (lit.,[12,13] 157—

* The conversion of steroidal hydroxy-epoxides (5-2,3; 3-4,5; 7-5,6) with 19-methyl group migration,[18a] and of 19-norsteroidal 3-acetoxy-4,5-epoxides [18b] into aromatic ring A 19-norsteroids, by means of hydrobromic acid in refluxing glacial acetic acid, has been extensively studied by Hanson *et al.*

† N.m.r. spectra were recorded at Ciba-Geigy Ltd., Basle, Switzerland. I.r. and mass spectral measurements were performed in the Laboratories for Instrumental Analysis (directed by Prof. D. Jeremić), and elemental microanalyses in the Microanalytical Laboratory (Dr. R. Tasovac) of our Chemistry Department in Belgrade.

158 °C); $[\alpha]_D^{20}$ +66° (*c* 0.98); $\nu_{max.}$ (CCl_4) 3 600, 3 440, 1 640, 1 165, 1 102, 1 056, 1 040, 1 015, 945, and 910 cm^{-1}; δ_H ($CDCl_3$, 100 MHz) 0.86 (3 H, s, H_3C-18), 1.88 (1 H, d, J_{gem} 17 Hz, 4-H_{ax}), 2.60 (1 H, broad d, J_{gem} 17 Hz, 4-H_{eq}), *ca.* 3.94 (9 H, m, 6α-H and 2 × OCH_2CH_2O, at C-3 and C-17); δ_H ($CDCl_3$ + trichloroacetyl isocyanate,* 100 MHz) 0.86 (3 H, s, H_3C-18), *ca.* 3.94 (8 H, m, 2 × OCH_2CH_2O, at C-3 and C-17), 5.18 (1 H, broad s, *J ca.* or less than 2 Hz, 6α-H_{eq}) (Found: C, 70.3; H, 8.4. $C_{22}H_{32}O_5$ requires C, 70.2; H, 8.6%).

Epoxidation of 3,3:17,17-*Bis*(*ethylenedioxy*)*oestr*-5(10)-*en*-6β-*ol* (1).—A solution of the allylic alcohol (1) (3.1 g) in methylene chloride (80 ml) (previously filtered through Alox II, neutral) was treated with *m*-chloroperbenzoic acid (1.66 g) at 0 °C and kept 18 h at −8 °C. The reaction mixture was then diluted with ether and the organic layer washed with aqueous sodium hydrogencarbonate, and water; it was then dried (Na_2SO_4) and, after addition of a few drops of anhydrous pyridine, the solvents were evaporated *in vacuo* to dryness. The residue (3.2 g) was chromatographed on silica gel (100 g). Elution with benzene–ether (9 : 1) gave 3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-5β,10β-oestran-6β-ol (2) (2.2 g, 67.4%), which was recrystallised from ether–light petroleum (2.04 g, 63.1%), m.p. 131 °C (lit.,[12] 133 °C); $[\alpha]_D^{20}$ +11° (*c* 0.55); $\nu_{max.}$ (CCl_4) 3 560, 3 480, 1 170, 1 110, 1 050, 1 028, 940, 905, and 850 cm^{-1}; δ_H ($CDCl_3$, 100 MHz) 0.86 (3 H, s, H_3C-18), *ca.* 3.87 (9 H, m, 6α-H and 2 × OCH_2CH_2O, at C-3 and C-17); δ_H ($CDCl_3$ + trichloroacetyl isocyanate,* 100 MHz) 0.86 (3 H, s, H_3C-18), *ca.* 3.88 (8 H, m, 2 × OCH_2CH_2O, at C-3 and C-17), 5.27 (1 H, d, $J_{6.7ax}$ 6 Hz, 6α-H_{eq}) (Found: C, 67.3; H, 8.2. $C_{22}H_{32}O_6$ requires C, 67.3; H, 8.2%).

Oxidation of 3,3:17,17-*Bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,-10β-*oestran*-6β-*ol* (2) *with Chromium Trioxide–Pyridine Complex*.—A solution of the epoxy-alcohol (2) (2 g) in dry pyridine (20 ml) was added to a stirred solution of chromium trioxide (2 g) in dry pyridine (20 ml). The mixture was then stirred at room temperature overnight, diluted with ethyl acetate, filtered through a Celite mat (which was washed thoroughly with the same solvent), washed with water, dried, and evaporated under reduced pressure. The residue (2 g) was dissolved in benzene–ether (95 : 5) and the solution passed through a short SiO_2 column, to give 3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-5β,10β-oestran-6-one (3), which was recrystallised from ether–light petroleum (1.74 g, 87.4%), m.p. 140—141 °C (lit.,[12] 137—138 °C); $[\alpha]_D^{20}$ −93° (*c* 0.99); $\nu_{max.}$ (CCl_4) 1 705, 1 170, 1 110, 1 060, 1 035, 1 010, 990, and 945 cm^{-1}; δ_H ($CDCl_3$, 360 MHz) 0.88 (3 H, s, H_3C-18), 1.91 (1 H, d, J_{gem} 17 Hz, 4-H_{ax}), 1.94 (1 H, d, J_{gem} ~ $J_{7ax,8ax}$ ~ 18 Hz, 7α-H_{ax}), 2.50 (1 H, dd, J_{gem} 18 Hz, $J_{7eq.8ax}$ 5 Hz, 7β-H_{eq}), 2.65 (1 H, dd, J_{gem} 17 Hz, $^4J_{2eq.4eq}$ *ca.* 2 Hz, 4-H_{eq}), *ca.* 3.90 (8 H, m, 2 × OCH_2CH_2O, at C-3 and C-17); δ_C ($CDCl_3$) 204.9 (C-6), 118.8 (C-17), 106.4 (C-3), 66.0 (C-5), 65.2—64.5 (2 × O–C–C–O), 62.9 (C-10), 46.0 (C-13), 41.5 (C-7), 30.4 (C-4), and 14.2 (C-18) (Found: C, 67.8; H, 7.7. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%).

Acetoxylation of 3,3:17,17-*Bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,10β-*oestran*-6-*one* (3) *with Lead Tetra-acetate*. The epoxy-ketone (3) (2.5 g) dissolved in dry benzene (450 ml) was oxidised with a large excess of lead tetra-acetate (11 g, 3.87 mol equiv.) in the presence of anhydrous calcium carbonate (5.5 g) at reflux temperature and with stirring for *ca.* 12 days, *i.e.* until complete disappearance of starting material (3). [Initially the benzene solution of the steroid (3) was treated with 5 g of $Pb(OAc)_4$ and 2.5 g of $CaCO_3$; subsequently, every third day, a 2-g portion of the lead salt and a 1-g portion of the calcium salt were added.] After that time, the mixture was cooled, diluted with ether, filtered through a Celite mat, and the insoluble precipitate thoroughly washed with ether. The combined filtrates were washed with water, aqueous sodium hydrogencarbonate, and water, and then dried (Na_2SO_4) and evaporated under reduced pressure; the residue (2.90 g) was then chromatographed on silica gel (125 g). The benzene and benzene–ether (95 : 5) eluates gave a complex mixture (0.134 g, about 5%) which was not further investigated. The benzene–ether (90 : 10) fractions afforded 7α-*acetoxy*-3,3:17,17-*bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,10β-*oestran*-6-*one* (4) (1.764 g, 61.4%), which was recrystallised from ether–light petroleum (1.544 g, 53.8%), m.p. 126 °C; $[\alpha]_D^{20}$ −159° (*c* 0.92); $\nu_{max.}$ (CCl_4) 1 740, 1 705, 1 210, 1 100, 1 060, 1 040, 995, 965, and 945 cm^{-1}; δ_H ($CDCl_3$, 360 MHz) 0.88 (3 H, s, H_3C-18), 1.95 (1 H, d, J_{gem} 16.5 Hz, 4-H_{ax}), 2.11 (3 H, s, 7α-OAc), 2.64 (1 H, dd, J_{gem} 16.5 Hz, $J_{2eq.4eq}$ *ca.* 2 Hz, 4-H_{eq}), *ca.* 3.91 (8 H, m, 2 × OCH_2CH_2O, at C-3 and C-17), 5.15 (1 H, d, $J_{7eq,8ax}$ 4.5 Hz, 7β-H_{eq}); δ_C ($CDCl_3$) 200.5 (C-6), 118.6 (C-17), 106.2 (C-3), 71.8 (C-7), 66.6 (C-5), 65.2—64.1 (2 × O–C–C–O), 62.7 C-10), 46.2 (C-13), 30.0 (C-4), 14.1 (C-18) [and 169.7 (acetate C=O) and 20.7 (acetate CH_3)] (Found: C, 64.4; H, 7.4. $C_{24}H_{32}O_8$ requires C, 64.3; H, 7.2%).

Saponification of 7α-*Acetoxy*-3,3:17,17-*bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,10β-*oestran*-6-*one* (4) *with Potassium Hydrogencarbonate*.—The 7α-acetoxy-epoxy-ketone (4) (300 mg) in benzene (10 ml) and methanol (40 ml) was treated with a solution of potassium hydrogencarbonate (300 ml) in water (5 ml); the mixture was then stirred at room temperature for 36 h. The reaction mixture was diluted with water and extracted with ether; the organic layer was then washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to afford a mixture which was chromatographed on silica gel (12 g) (210 mg, *ca.* 77%). Elution with benzene–ether (80 : 20) gave 7α-*hydroxy*-3,3:17,17-*bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,10β-*oestran*-6-*one* (5) (54 mg, 19.9%), which was recrystallised from ether–light petroleum (38 mg, 14.0%), m.p. 229 °C; $[\alpha]_D^{20}$ −165° (*c* 0.32); $\nu_{max.}$ (KBr) 3 420, 1 706, 1 168, 1 115, 1 100, 1 055, 1 040, 1 020, 985, 965, 950, 940, and 855 cm^{-1}; δ_H ($CDCl_3$, 360 MHz) 0.90 (3 H, s, H_3C-18), 1.91 (1 H, d, J_{gem} 16.5 Hz, 4-H_{ax}), 2.77 (1 H, dd, J_{gem} 16.5 Hz, $^4J_{2eq.4eq}$ *ca.* 2 Hz, 4-H_{eq}), *ca.* 3.90 (9 H, m, 7β-H and 2 × OCH_2CH_2O, at C-3 and C-17); δ_H ($CDCl_3$ + trichloroacetyl isocyanate,* 360 MHz): spectrum unchanged, except that the multiplet signal at 3.90 corresponded now to only 8 H, and that the resonance of 7β-H_{eq} was shifted downfield to 5.28 (1 H, d, $J_{7eq.8ax}$ 5 Hz); δ_C ($CDCl_3$) 206.7 (C-6), 118.8 (C-17), 106.2 (C-3), 70.9 (C-7), 67.5 (C-5), 65.2—64.1 (2 × O–C–C–O), 62.8 (C-10), 46.0 (C-13), 30.0 (C-4), and 14.1 (C-18); *m/e* 406 (M^+), 388 (M − H_2O), 378 (M − CO), 361 (M − CO − OH), 305, 224, 183, and 99 (Found: C, 64.9; H, 7.6. $C_{22}H_{30}O_7$ requires C, 65.0; H, 7.4%).

Benzene–ether (75 : 25 and 70 : 30) eluates gave a mixture (12 mg, *ca.* 4%), which was not further investigated.

Elution with benzene–ether (60 : 40) afforded a product (6) (96 mg, 35.3%), which was recrystallised from ether (84 mg, 30.9%), m.p. 198—200 °C. According to physical measurements, spectral data, and chemical evidence available so far, this compound appears to be a dimer of the 7α-hydroxy-epoxy-ketone (5) described above, but further

* Resulting in esterification of the hydroxy-group, *i.e.* formation of the corresponding *N*-trichloroacetyl-carbamate ester ($CCl_3CO–N{=}C{=}O$ + ROH ⟶ $CCl_3CONHCOOR$).

study is necessary in order to establish its structure with certainty {Found: C, 65.3; H, 7.6. $C_{44}H_{60}O_{14}$ [*i.e.* 2 × ($C_{22}H_{30}O_7$)] requires C, 65.0; H, 7.4%}.

Further benzene–ether (50 : 50) and ether fractions eluted a complex mixture (28 mg, *ca.* 10%), which was not investigated.

Saponification of 7α-*Acetoxy*-3,3:17,17-*bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,10β-*oestran*-6-*one* (4) *with Methanolic Potassium Hydroxide*.—A solution of compound (4) (100 mg) in 1% methanolic potassium hydroxide (5 ml) was left overnight at room temperature. The mixture was then acidified with acetic acid (to pH 6), diluted with water, and extracted with ether. The ethereal layer was washed with aqueous sodium hydrogencarbonate and water, and then dried and evaporated under reduced pressure. The residue (70 mg, 77.2%) was chromatographed on silica gel (5 g) as described above, to give the ketol (5) (22 mg, 24.3%), a complex mixture (9 mg), and the dimer (6) (38 mg, 41.9%).

Treatment of 7α-*Acetoxy*-3,3:17,17-*bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,10β-*oestran*-6-*one* (4) *with Methanolic Potassium Hydroxide at Reflux Temperature* (*Aromatization of Ring* B).—To a solution of the acetoxy-epoxy-ketone (4) (2.24 g) in methanol (40 ml), through which oxygen-free nitrogen was first bubbled for 0.5 h, 5% methanolic potassium hydroxide (10 ml) was added and the mixture refluxed (under nitrogen) for 1 h. The solution was then acidified (to pH 6) with acetic acid, diluted with water, and extracted with ether. The ethereal layer was washed with aqueous sodium hydrogencarbonate and water and then dried (Na_2SO_4) and evaporated under reduced pressure to leave a crystalline solid (*ca.* 2 g, 100%), which was chromatographed on silica gel (65 g). Elution with benzene–ether (95 : 5) gave a complex mixture (210 mg, *ca.* 11%), which was not further investigated. Benzene–ether (90 : 10) eluates afforded 3,3:17,17-*bis*(*ethylenedioxy*)*oestra*-5(10),6,8-*triene*-6,7-*diol* (7) (1.68 g, 86.6%), which was recrystallised from ether–light petroleum (1.54 g, 79.4%), m.p. 195 °C; $[\alpha]_D^{20}$ −48° (*c* 1.0); $\nu_{max.}$ (KBr) 3 450, 1 604, 1 440, 1 148, 1 125, 1 050, 945, 850, and 740 cm^{-1}; $\lambda_{max.}$ 229 (ε 6 830) and 282 nm (2 110); δ_H ($CDCl_3$, 100 MHz), 0.84 (3 H, s, H_3C-18), 3.97 and 4.06 (each 4 H, 2 s, 2 × OCH_2CH_2O, at C-3 and C-17) (Found: C, 68.3; H, 7.3. $C_{22}H_{28}O_6$ requires C, 68.0; H, 7.3%).

Elution with benzene–ether (50 : 50) gave a complex mixture (250 mg, *ca.* 13%), not further investigated.

Acetylation of 3,3:17,17-*Bis*(*ethylenedioxy*)*oestra*-5(10),6,8-*triene*-6,7-*diol* (7).—The diol (7) (1.40 g) was acetylated with acetic anhydride (25 ml) in dry pyridine (25 ml) overnight at room temperature. The reaction mixture was worked up in the usual way and afforded 3,3:17,17-*bis*(*ethylenedioxy*)-*oestra*-5(10),6,8-*triene*-6,7-*diol diacetate* (8) (1.70 g, *ca.* 100%). It was dissolved in benzene and purified by chromatography through a short SiO_2 column, whereby benzene–ether (90 : 10) afforded a sample (1.57 g, 92.2%) which, after crystallisation from ether–light petroleum (1.41 g, 83.0%), melted at 113 °C; $[\alpha]_D^{20}$ −36° (*c* 0.57); $\nu_{max.}$ (CCl_4) 1 770, 1 440, 1 210, 1 180, 1 115, 1 060, 1 030, 1 010, 940, and 875 cm^{-1}; $\lambda_{max.}$ 210 nm (end absorption), 264 nm (ε 650); δ_H ($CDCl_3$, 100 MHz) 0.82 (3 H, s, H_3C-18), 2.12 and 2.15 (each 3 H, 2 s, 6-OAc and 7-OAc), 3.92 and 3.98 (each 4 H, 2 s, 2 × OCH_2CH_2O, at C-3 and C-17) (Found: C, 66.4; H, 7.1. $C_{26}H_{32}O_8$ requires C, 66.1; H, 6.8%).

Treatment of the Hydroxy-ketone (5) *with Base at Room Temperature*.—(a) *With potassium hydrogencarbonate*. A mixture of compound (5) (30 mg) in benzene (1 ml) and methanol (4 ml), and of potassium hydrogencarbonate (30 mg) in water (0.5 ml) was stirred at room temperature for 36 h, and then worked up and chromatographed as described above [for compound (4)], to give 10 mg (33.3%) of starting material (5) and 18 mg (60.0%) of the dimeric compound (6).

(b) *With potassium hydroxide*. A solution of compound (5) (50 mg) in 1% methanolic potassium hydroxide (2 ml) was left at room temperature for 20 h. Work-up and chromatography (see above) afforded starting material (5) (16 mg, 32%) and the corresponding dimer (6) (26 mg, 52%).

Treatment of the Hydroxy-epoxy-ketone (5) *or of the Dimeric Compound* (6) *with Base at Reflux Temperature* (*Aromatization of Ring* B).—When compounds (5) or (6) (30 mg) were treated either with potassium hydrogencarbonate (30 mg) in benzene (1 ml)–methanol (4 ml)–water (0.5 ml), or with 1% methanolic potassium hydroxide (2—3 ml), and the resulting mixture or solution heated at reflux under nitrogen for 45—60 min, aromatization of ring B occurred readily, affording, upon work-up and acetylation [as described above for the sequence (4) ⟶ (7) ⟶ (8)], the 6,7-diacetoxy-5(10),6,8-triene (8) in 75–90% yield (crude).

Deacetalization of 3,3:17,17-*Bis*(*ethylenedioxy*)*oestra*-5(10),6,8-*triene*-6,7-*diol Diacetate* (8).—A solution of the diacetate (8) (1.23 g) in glacial acetic acid (42.5 ml) and water (7.5 ml) was heated on a water-bath with stirring for 1 h; it was then cooled, diluted with water, and extracted with ether–methylene chloride (1 : 1 v/v). The organic layer was neutralized with aqueous sodium hydrogencarbonate, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue (*ca.* 1.0 g, *ca.* 100%) in benzene was purified by passage through a short SiO_2 column, whereby benzene–ether (80 : 20) afforded 6,7-*diacetoxyoestra*-5(10),6,8-*triene*-3,17-*dione* (9) (849 mg, 84.9%), which was recrystallised from ether–light petroleum (759 mg, 75.9%), m.p. 220 °C; $[\alpha]_D^{20}$ +25° (*c* 0.2); $\nu_{max.}$ (KBr) 1 765, 1 738, 1 710, 1 705, 1 205, and 1 180 cm^{-1}; $\lambda_{max.}$ 264 nm (ε 1 300); δ_H ($CDCl_3$, 100 MHz) 0.85 (3 H, s, H_3C-18), 2.28 and 2.30 (3 H each, 2 s, 6-OAc and 7-OAc), 3.40 (2 H, s, H_2C-4) (Found: C, 68.8; H, 6.4. $C_{22}H_{24}O_6$ requires C, 68.7; H, 6.3%).

Treatment of 6,7-*Diacetoxyoestra*-5(10),6,8-*triene*-3,17-*dione* (9) *with Lead Tetra-acetate* (*Aromatization of Ring* A).—A solution of the triene-diketone (9) (600 mg) and lead tetra-acetate (935 mg, 1.35 mol equiv.) in glacial acetic acid (12 ml), through which a slow stream of dry oxygen-free nitrogen was bubbled, was heated with stirring at 80—85 °C for 2 h. After cooling, the mixture was diluted with water and extracted with ether–methylene chloride (1 : 1 v/v). The organic layer was neutralized with aqueous sodium hydrogencarbonate, washed with water, dried (Na_2SO_4) and evaporated under reduced pressure, to give 17-*oxo*-*oestra*-1,3,5(10),6,8-*pentaene*-3,6,7-*triol* 6,7-*diacetate* (6,7-*diacetoxyequilenin*) (10) (600 mg, *ca.* 100%), m.p. 270—274 °C; $[\alpha]_D^{20}$ +41° (*c* 0.35, CH_3OH); $\nu_{max.}$ (KBr) 3 420, 1 770, 1 740, 1 640, and 1 200 cm^{-1}; $\lambda_{max.}$ 264 (ε 3 800), 275 (4 900), 286 (5 700), 298 (4 400), 325 (2 300), and 339 nm (2 800) (Found: C, 68.8; H, 6.1. $C_{22}H_{22}O_6$ requires C, 69.1; H, 5.8%).

This product, without further purification, was acetylated with acetic anhydride (6 ml) in dry pyridine (6 ml) at room temperature. The residue, obtained after the usual work-up and evaporation of solvents under reduced pressure (665 mg, *ca.* 100%) was chromatographed on silica gel (12 g). Benzene–ether (90 : 10) afforded 3,6,7-*triacetoxyoestra*-1,3,5(10),-

6,8-*pentaen*-17-*one* (*i.e.* 6,7-*diacetoxyequilenin acetate*) (11) (470 mg, 70.6%*), which was further purified by passing a benzene solution of it through a short SiO_2 column (obtained 400 mg, 60.1%*) and by crystallisation (for analytical purposes) from acetone–light petroleum (339 mg, 51.2%*), m.p. 212—214 °C; $[\alpha]_D^{20}$ +35° (*c* 0.20); $\nu_{max.}$ (KBr) 1 790, 1 780, 1 770, 1 750, 1 640, 1 620, and 1 200 cm^{-1}; $\lambda_{max.}$ 282 (ε 5 900), 292 (6 100), and 324 nm (680); δ_H ($CDCl_3$, 100 MHz) 0.87 (3 H, s, H_3C-18), 2.34, 2.37 and 2.43 (3 H each, 3 s, 3-OAc, 6-OAc, and 7-OAc), 7.34 (1 H, dd, aromatic 2-H), 7.53 (1 H, d, aromatic 4-H), 8.06 (1 H, d, aromatic 1-H); these aromatic proton signals (of 1-H, 2-H and 4-H) had *ortho*-coupling $J_{1,2}$ 9 Hz, and *meta*-coupling $J_{2,4}$ 3 Hz; *m/e* 424 (M^+), 382 (M — CH_2=C=O), 340 (M — $2CH_2$=C=O), 298 (M — $3CH_2$=C=O) (Found: C, 68.1; H, 5.9. $C_{24}H_{24}O_7$ requires C, 67.9; H, 5.7%).

Enolization of 6,7-*Diacetoxyoestra*-5(10),6,8-*triene*-3,17-*dione* (9).—A solution of the dione (9) (200 mg) and toluene-*p*-sulphonic acid (6 mg) in acetic anhydride (6 ml) was heated at 125 °C with stirring for 2.5 h. The mixture was poured into ice–water, neutralized with aqueous sodium hydrogencarbonate, and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated *in vacuo*, to give 3,6,7-*triacetoxyoestra*-3,5(10),6,8-*tetraen*-17-*one* (12) (220 mg, *ca.* 100%), which was recrystallised from ether–light petroleum (150 mg, 67.7%), m.p. 195—197 °C; $[\alpha]_D^{20}$ +27° (*c* 0.50); $\nu_{max.}$ (KBr) 1 790, 1 780, 1 750, 1 690, and 1 205 cm^{-1}; $\lambda_{max.}$ 226 (ε 23 400), 266 (11 950), and 272 nm (12 350); δ_H ($CDCl_3$, 100 MHz) 0.82 (3 H, s, H_3C-18), 2.14 (3 H, s, 3-OAc), 2.27 (6 H, s, 6-OAc + 7-OAc), and 6.11 (1 H, m, 4-H) (Found: C, 67.6; H, 6.2. $C_{24}H_{26}O_7$ requires C, 67.6; H, 6.2%).

Treatment of 3,6,7-*Triacetoxyoestra*-3,5(10),6,8-*tetraen*-17-*one* (12) *with Lead Tetra-acetate* (*Aromatization of Ring* A).—A solution of the enol-acetate (12) (100 mg) and lead tetra-acetate (200 mg) in glacial acetic acid (10 ml), through which dry oxygen-free nitrogen was bubbled, was heated with stirring at 80—85 °C for 10 h. Upon cooling, the mixture was worked up as described above, and the residue obtained (68 mg, *ca.* 68%) was chromatographed on silica gel (6 g). Benzene–ether (90 : 10) eluted a crystalline solid (31 mg, *ca.* 31%), which after rechromatography and crystallisation from acetone–light petroleum, afforded 3,6,7-triacetoxyoestra-1,3,5(10),6,8-pentaen-17-one (11) (15 mg, *ca.* 15%), m.p. 208—210 °C [m.p. undepressed by admixture with authentic sample obtained from (9), as described above].

Aromatization of Ring A *in* 3,3:17,17-*Bis*(*ethylenedioxy*)-5,10-*epoxy*-5β,10β-*oestran*-6β-*ol* (2) *by Treatment with Acid*.—The epoxy-alcohol (2) (500 mg) in 48% hydrobromic acid (1 ml) and glacial acetic acid (4 ml) was heated under reflux for 15 min. The mixture was cooled, carefully neutralized with aqueous sodium hydrogencarbonate (with external cooling), extracted with ether, and the ethereal layer worked up in the usual way. Upon evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (20 g), whereby elution with benzene–ether (90 : 10 and 85 : 15) gave 3-hydroxyoestra-1,3,5(10),6-tetraen-17-one (6-dehydro-oestrone) (13) (144 mg, 42%), which was recrystallised from methanol (120 mg, 35%), m.p. 264—265 °C (lit.,[20] 261—263 °C); $[\alpha]_D^{20}$ −125° (*c* 1.0, dioxan) (lit.,[20] −127°); $\nu_{max.}$ (KBr) 3 400, 3 300, 3 050, 1 740, 1 625, 1 590, and 1 505 cm^{-1}; $\lambda_{max.}$ 226 (ε 18 600), 262 (9 250), and 304 nm (2 540) (Found: C, 80.3; H, 7.7. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%).

* Based on compound (9) as starting material.

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