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TOTALLY SYNTHETIC STEROID HORMONES—XX[1]
NOVEL TOTAL SYNTHESES OF EQUILIN AND EQUILENIN

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Abstract—A series of novel total syntheses of equilin (Ia) and cognate compounds has been developed starting from estra-1,3,5(10),8-tetraenes of the general class II.† The key reactions in these syntheses are oxidation of a tetraene II with *m*-chloroperbenzoic acid, rearrangement of the resulting epoxide III with an acid of p*Ka* 1·42–4·21 to an estra-1,3,5(10),9(11)-tetraen-8α-ol IV, catalytic hydrogenation of the 9(11)-olefinic bond to give an estra-1,3,5(10)-trien-8α-ol V, and dehydration of the latter with methanesulfonyl chloride or phosphorus oxychloride in dimethylformamide to an estra-1,3,5(10),7-tetraene. The most efficient synthesis of equilin so far developed proceeds from 3-methoxyestra-1,3,5(10),8-tetraen-17β-ol IIc to 3-methoxyestra-1,3,5(10),7-tetraen-17β-ol XIIIb (by the above methods) and finally by dimethylation and oxidation to equilin Ia in an overall yield of 37·7%. A novel route to equilenin and its derivatives is provided by the conversion of 8α,9α-epoxy-estra-1,3,5(10)-trienes IIIa-c and estra-1,3,5(10),9(11)-tetraen-8α-ols IVa-c with mineral acid to mixtures of estra-1,3,5(10),6,8-pentaenes of type XIX and estra-1,3,5(10),8,14-pentaenes of type XX. Fused MeMgI constitutes an excellent reagent for demethylating acid-labile steroids such as the estra-1,3,5(10),8-tetraenes II, the estra-1,3,5(10)-trien-8α-ols V and the estra-1,3,5(10),7-tetraenes X. Methanesulfonyl chloride or phosphorus oxychloride in DMF provide useful reagents for the formylation of OH groups under mild conditions, the former being selective for alcoholic over phenolic hydroxyls. Some of these results have already been communicated in preliminary form.[2]

THE female sex hormone equilin (Ia) was first isolated in 1932 from pregnant mares' urine and structurally elucidated between that year and 1939.[3] No synthesis of the compound was described until 1958 when an industrial research group[4] announced a six stage sequence, involving a microbiological dehydrogenation, from 19-nortestosterone acetate, and no claim to its total synthesis by purely chemical means could be asserted until 1964, when a second industrial group[5] disclosed a related reaction sequence from 19-hydroxyandrosta-4,6-dien-3,17-dione which could optionally avoid the use of micro-organisms. More recently, a preliminary note[6] has disclosed the conversion of equilenin methyl ether and its 17β-OH analog to equilin, thereby providing a second formal total synthesis of the hormone. Similarly, the cyclic ethylene ketal of equilenin has been converted[7] by reduction and hydrolysis to equilin. Here we describe what are, to our knowledge, the first total syntheses of equilin using throughout steroid starting materials which have themselves been obtained by chemical total synthesis. Our interest in such a project firstly was derived from the close structural relationship of equilin as an estra-1,3,5(10),7-tetraene to a variety of

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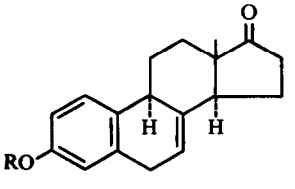
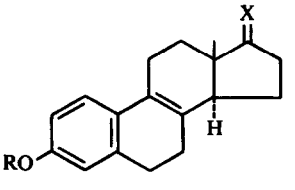
† The graphic formulas correspond to enantiomorphs having the same absolute configuration as the natural steroid hormones, and are employed to denote such enantiomorphs or the corresponding racemates by the use, where necessary, of the prefix *rac-* for the latter compounds in accordance with the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature (see Steroids, 13, 278 [1967]).

estra-1,3,5(10),8-tetraenes which first became available in 1959[8] as intermediates in our total synthesis of estrone[8, 9] (see also [10–13]), and, secondly, was conditioned by the importance of equilin derivatives as biologically active components of a widely used therapeutic estrogen preparation made from pregnant mares' urine.[14, 15] For an estra-1,3,5(10),8-tetraene to serve as a precursor of equilin a method was needed for transposing the olefinic bond at the 8-position to the unconjugated 7-position, and, initially, we envisaged subjecting the tetraene to successive oxidation and reduction steps so as to form an estra-1,3,5(10)-trien-8-ol which would be capable of undergoing dehydration to an estra-1,3,5(10),7-tetraene. The development of such a process, and its incorporation into a number of reaction schemes for the total synthesis of equilin and cognate substances, forms the subject of this paper. The chemistry involved falls into two principal phases which can be conveniently discussed as follows.

Conversion of estra-1,3,5(10),8-tetraenes to estra-1,3,5(10)-trien-8α-ols. Our first oxidative experiments were carried out with the readily available racemic steroid IIa[8, 9] which is produced in four stages from 6-methoxy-1-tetralone.[8–13] Interaction of this substance with *m*-chloroperbenzoic acid for several minutes below room temperature in benzene–hexane followed by the suppression of further reaction with aqueous potassium carbonate, converted IIa to an epoxide formulated as IIIa displaying λ_{max} 235 mμ (ε 11,800). Such light absorption has been found to be typical of an oxiran system conjugated with an aromatic nucleus (Table 2). Under similar conditions IId and IIe were converted to the corresponding epoxides but both IIb and IIc gave mixtures containing, from their UV absorption spectra, the corresponding epoxide and its acid-induced rearrangement product (below). Each epoxide, presumably because of its benzylic character, proved labile to acid. Thus IIIa, IIId and IIIe, and the mixtures obtained by oxidizing IIb and IIc all gave products formulated as the corresponding tetraenols of type IV, on being stirred with benzoic acid in chloroform at room temperature, the first substance undergoing the same rearrangement merely on recrystallization from methanol. The tetraenols IV show the characteristic light absorption λ_{max} 258–259 mμ (ε 16,000–19,000). The tetraenols IVb and c present in the mixtures obtained by oxidizing IIb and IIc presumably result from the rearrangement of the initially produced epoxides by the acid present in the reaction medium. Notably, interaction below room temperature with one equivalent of the

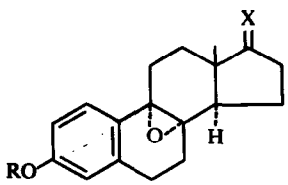




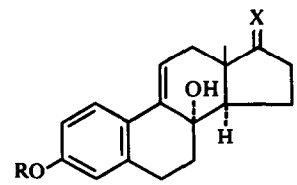
	R
Ia;	H
Ib; *rac*	H
Ic;	CH_3

	X	R
IIa; *rac*	0	CH_3
IIb; *rac*	β-OH; α-H	CH_3
IIc;	β-OH; α-H	CH_3
IId; *rac*	β-$OCOCH_3$; α-H	CH_3
IIe; *rac*	$(OCH_2)_2$	CH_3
IIf; *rac*	β-OH; α-H	H
IIg; *rac*	0	H
IIh; *rac*	0	CH_3CO

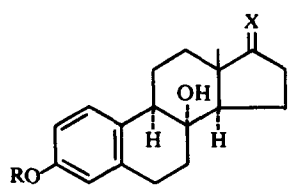
peracid followed, after complete consumption of the reagent, by stirring of the reaction mixture for 1–2 hr at room temperature converted each member of the Series IIa–e directly and efficiently to the respective tetraenol IV.



	X	R
IIIa; *rac*	0	CH_3
IIIb; *rac*	β-OH; α-H	CH_3
IIIc;	β-OH; α-H	CH_3
IIId; *rac*	β-$OCOCH_3$; α-H	CH_3
IIIe; *rac*	$(OCH_2)_2$	CH_3
IIIf; *rac*	β-OH; α-H	H
IIIg; *rac*	0	H
IIIh; *rac*	0	CH_3CO



	X	R
IVa; *rac*	0	CH_3
IVb; *rac*	β-OH; α-H	CH_3
IVc;	β-OH; α-H	CH_3
IVd; *rac*	β-$OCOCH_3$; α-H	CH_3
IVe; *rac*	$(OCH_2)_2$	CH_3
IVf; *rac*	β-OH; α-H	H
IVg; *rac*	0	H
IVh; *rac*	0	CH_3CO



	X	R
Va; *rac*	0	CH_3
Vb; *rac*	β-OH; α-H	CH_3
Vc;	β-OH; α-H	CH_3
Vd; *rac*	β-$OCOCH_3$; α-H	CH_3
Ve; *rac*	$(OCH_2)_2$	CH_3
Vf; *rac*	β-OH; α-H	H
Vg; *rac*	β-OCHO; α-H	CH_3

Each member of the series IVa–e underwent a stereoselective hydrogenation over palladized charcoal in ethanol to give a product formulated as the respective 9α-estratrienol of general type V. Other possible methods for obtaining trienols of type V from precursors of types III and IV were investigated, but none proved satisfactory. Thus, with lithium in aniline–liquid ammonia, the epoxide IIIb gave a mixture of the tetraenol IIb and *rac*-estradiol-3-methyl ether, the deoxygenation of IIIb to IIb being analogous to the conversion of the epoxides of cholest-6 and 7-en-3-ol back to the corresponding cholestenes with lithium in ethylamine.[16] Also, the tetraenol IVb with the lithium–aniline–liquid ammonia reagent gave only *rac*-estradiol-3-methyl ether, presumably through reductive allylic carbon–oxygen fission of the OH group[17] followed by saturation of the styrenoid bond in the resulting estra-1,3,5(10),8 or 9(11)-tetraene.[18] Notably, the apparently most thermodynamically stable of the possible stereoisomeric products is formed. We did not investigate the direct production of the diol Vb from the epoxides IIIa and b by reduction with LAH in THF,

since unpublished work with the 18-Me homologs of both compounds had shown that, although the reaction was successful, the yields were very low (<12%). Such transformations, apparently involving a *cis*-opening of the oxiran ring, are analogous to the previously observed formation under similar conditions of an 11α-hydroxy-estra-1,3,5(10)-triene from a 9α,11α-epoxyestra-1,3,5(10)-triene.[19]

Satisfactory evidence was obtained to support the structures assigned to the series IV and Va–e. This is exemplified for the diols IVb and Vb as follows. The 9α-configuration of Vb is shown by its subsequent transformation to *rac*-equilin (Ib). The 8α-hydroxy configuration of Vb follows from its proton NMR spectrum which displays the C_1 and C_{18}-proton signals at chemical shifts closely similar in position to those of the analogous protons in authentic *rac*-8α-estradiol-3-methyl ether[20] and appreciably different from those of the analogous protons in estradiol-3-methyl ether. A similar interrelationship obtains between the chemical shifts of the C_1 and C_{18}-protons in the ketol Va, *rac*-8α-estrone-3-methyl ether,[8a, 20] and estrone-3-methyl ether. Data for all six compounds are listed in Table 1. Assuming no inversion of configuration during catalytic hydrogenation, the 8α-OH configuration may be assigned to the diol IVb. This configuration is amply confirmed by comparing the UV and PMR spectra of the substance with those of the corresponding 8α and 8β-hydrogen analogs.

TABLE 1. UV ABSORPTION AND PROTON NMR SPECTRA OF 8α AND 8β-ESTRANE DERIVATIVES

Substance	δ_1[a]	δ_{11}	δ_{18}	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$
Vb	7·01		0·83		
rac-3-Methoxy-8α-estra-1,3,5(10)-trien-17β-ol[b]	7·03		0·83		
3-Methoxyestra-1,3,5(10)-trien-17β-ol	7·17		0·76		
Va	7·03		0·97		
rac-3-Methoxy-8α-estra-1,3,5(10)-trien-17-one[c]	7·03		0·96		
3-Methoxyestra-1,3,5(10)-trien-17-one	7·20		0·89		
IVb	7·40	6·00	0·79	259	18·0
rac-3-Methoxy-8α-estra-1,3,5(10),9(11)-tetraen-17β-ol[d, e]	7·42	6·00	0·78	258	19·8
rac-3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-ol[f]	7·58	6·17	0·78	263	18·5

[a] Chemical shifts in ppm determined in $CDCl_3$ and measured downfield from the signal for tetramethylsilane used as an internal standard.

[b] Ref. 20.

[c] Refs 8a, 20.

[d] Ref. 21.

[e] K. Tsuda, S. Nozoe and Y. Okada, *Chem. Pharm. Bull. Japan* 11, 1271 (1963) give λ_{max} 261·5 mμ (ε 17,300) for 8α-estra-1,3,5(10),9(11)-trien-17-one.

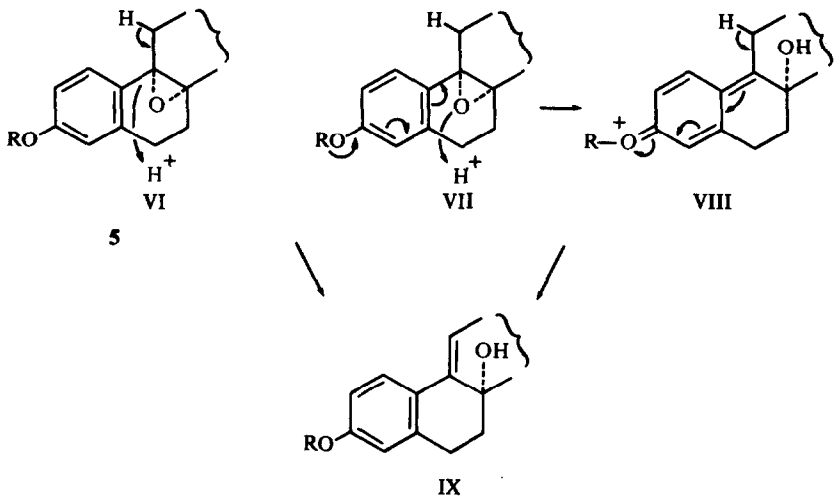
[f] Ref. 9.

The data in Table 1 shows that the UV absorption spectrum and chemical shifts of the C_1, C_{11} and C_{18}-protons are closely similar in IVb and its 8α-H analog,[21] but appreciably different in IVb and its 8β-H analog.[9] Notably, the C_1 and C_{11}-protons apparently are more highly deshielded in *rac*-3-methoxyestra-1,3,5(10)9(11)-tetraen-17β-ol than in the cognate 8α-compounds, presumably because the 8β-stereochemistry of the first compound causes the styrenoid system to assume a more planar configuration and thereby allows a more efficient deshielding by the aromatic nucleus and the 9(11)-olefinic bond, of the C_{11} and C_1-protons, respectively. A Dreiding model indicates the structures of the series IV to be concave at the β-face, which may explain

the observed α-face hydrogenations. We can present no direct experimental evidence for the stereochemistry of the oxiran nucleus in IIIb and its relatives, but assign the 8α,9α-configurations to these substances by analogy with the formation of 6α,7α-epoxides by the peracid oxidation of various 3-methoxy-estra-1,3,5(10),6-tetraenes.[22] On this basis the acid catalyzed transformation of an epoxide of type III to a tetraenol of type IV apparently proceeds with retention of the configuration of the 8-oxy-substituent, and we summarize the mechanism as in the expression VI, (R = alkyl or H) which, for a non-concerted reaction involving participation of the C_3-oxygen electrons, may be expanded to the sequence VII-VIII-IX (Scheme I). The reaction is evidently related to the acid-catalyzed rearrangements of styrenoid epoxides derived from dihydronaphthalene[23] or estra-1,3,5(10),9(11)-tetraene[24] precursors, which can, theoretically, proceed by coordination of the catalyst with the oxide oxygen followed by elimination of a proton β to the aromatic nucleus to give an enol of a ketone[23,24] or, alternatively, by the intramolecular shift of the same proton to the adjacent *cis* α-position to give the ketone directly.[25] With a fully alkylated epoxide of type III no proton is available at the β-position (i.e. at C_8), so that the foregoing reactions are excluded. Deprotonation can, however, occur at the 11-position with formation of a tetraenol of the type IV. From the expressions VI and VII it may be deduced that the ease of the rearrangement reaction will depend upon the electron-donating capacity of the group attached to the 3-position (see also [26]) and, possibly, also upon the acid strength of the catalyzing acid. Evidence to support these contentions may be adduced as follows: The epoxides IIIa–e are all rearranged as noted previously, by treatment overnight at room temperature with benzoic acid (p*Ka* 4·21[27]) in chloroform. The tetraenol IIf (prepared for this work by demethylation of IIb with fused methylmagnesium iodide[28]), on oxidation with *m*-chloroperbenzoic acid in THF below room temperature followed, after consumption of the reagent, by stirring for 1·5 hr at room temperature, gave a quantitative yield of tetraene IVf, indicating that *m*-chlorobenzoic acid (p*Ka* 3·84) has sufficient acid strength to induce a convenient rate of rearrangement under these conditions. However, the acetate IIIh (prepared from IIf by Oppenauer oxidation, acetylation of the resulting IIg, and epoxidation) was converted to the tetraene IVh to the extent of less than 25% and 36% (as judged by the UV absorption spectrum of the product) on stirring overnight at room temperature with benzoic acid and *m*-chlorobenzoic acid, respectively, in chloroform. Notably, the use of acids of increasing acid strengths in the preceding experiment enhanced the rates of conversion to IVh, furoic (p*Ka* 3·16), 2-chloro-5-nitrobenzoic (p*Ka* 2·17) and 2,4-dinitrobenzoic acids (p*Ka* 1·42) giving conversions estimated as 67, 90 and 100% respectively. Mineral acid is to be avoided for conversions of the type III to IV because of the expected tendency of the products to undergo dehydration to estrapentaenes as will be described subsequently.

Conversions of estra-1,3,5(10)-trien-8α-ols to equilins. This conversion requires a selective dehydration of the trienols of type V to related estra-1,3,5(10),7-tetraenes. At the outset it seemed obvious that acidic dehydration would have to be avoided because of the expected tendency of estra-1,3,5(10),7-tetraenes, even if initially formed, to undergo the acid catalyzed rearrangements which are characteristic of equilin.[29,30] However, the dehydration occurred satisfactorily in an exothermic reaction with the ketol Va and methanesulfonyl chloride in pyridine heated to 80–90°, to give a product from which *rac*-equilin methyl ether Xa was obtained in 62% yield. The substance

SCHEME 1

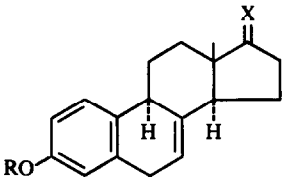


was spectrally identical to equilin methyl ether made by methylating equilin isolated from pregnant mares' urine. With Vd and Ve the same process afforded the corresponding tetraenes Xd and Xe, but the diols Vb and Vc gave the mesylates Xb and Xc through concomitant esterification of the 17-position. No dehydration occurred even with prolonged refluxing of Va in pyridine with *p*-toluenesulfonyl chloride, and it seems possible that the methanesulfonyl chloride induced dehydration involves initial dehydrochlorination to a sulfene,[31] which, being geometrically linear and consequently having a low steric requirement can esterify the hindered 8α-OH group prior to elimination. A significant improvement in the yields of dehydration products from Vb and Vc resulted from conducting the reaction at 80–90° with methanesulfonyl chloride in pyridine-dimethylformamide.[32] Under these conditions the exothermicity of the reaction was easier to control thereby giving a cleaner product from which the highly crystalline formates Xf and g were both obtainable in yields of 74%, after filtration of the crude reaction products in benzene through Florex-alumina impregnated with silver nitrate. With the same reagent at room temperature the sole product from Vb was the monoformate Vg. For reasons to be given later, we gave most attention to the total synthesis of equilin proceeding from the alcohol IIc to the diol Vc. Consequently, we conducted a detailed investigation of the dehydration of the latter and of its racemate Vb, restricting our studies to reagents capable of giving the formates Xf and g because of the high degree of crystallinity of these derivatives and their efficiency of recovery from crystallization solvents. Under the optimum conditions using methanesulfonyl chloride in pyridine-dimethylformamide at ca. 80–90°, Vb gave total products containing the required formate Xf to the extent of 83–88% (74% recovery after the usual column chromatography) together with XIa (10–17%), XIIa (3–5%) and traces of Xb and XIIIa. The foregoing mixtures were analyzed by UV and PMR spectroscopy and GL and TL chromatography using the authentic compounds as standards. In the absence of pyridine, no sulfonate Xb was formed from Vb, the product, obtained in 80% yield after one recrystallization from isopropyl alcohol, containing Vg, Xf, XIIa and XIIIa to the extent of 1·3, 92, 3·8 and 2·4%,

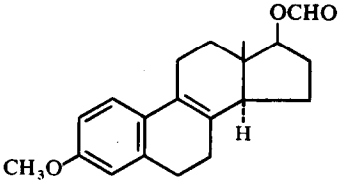
respectively. The presence of the rather insoluble equilenin type impurity XIIa presented a troublesome problem in the purification of the formate Xf, but, fortunately, its formation was suppressed when the dehydration was performed with phosphorus oxychloride in dimethylformamide at or below room temperature, the product, after recrystallization, then affording an 81% yield of the formate Xf of over 99% purity. Application of these conditions, which we currently regard as optimum, in the enantiomorphic series gave a similar result, the recrystallized product, containing 99·2% of Xg and 0·8% of XIIIb, again being obtained in 81% yield from Vc. Dehydration under the same conditions of the triol Vf (made by catalytically hydrogenating IVf or demethylating Vb with fused methylmagnesium iodide), also proceeded efficiently to give the bisformate Xh.

Since we have shown that migration of the C_7 double bond fails to occur under the conditions used, it follows that the formation of tetraenes of type XI is a direct result of the dehydration of the corresponding 8α-alcohols. The formation of pentaenes of type XII with reagents containing methanesulfonyl chloride is less easy to understand, although we have found that the formate Xf is readily converted by methanesulfonyl chloride at 100° to XIIa. (The latter is more conveniently prepared from Xf by reaction with pyridinium bromide perbromide in pyridine.) Possibly therefore, the reagent (or an entity derived from it), can add to the olefinic bond with subsequent double elimination of the adduct. The production of formates during dehydration is presumably to be attributed to the formation from DMF of intermediates such as XIVa and b of the Vilsmeier type[33] which can yield formates from an alcohol, ROH through the adducts XV. The partial formation of the 17-methanesulfonates Xb and c in the presence of pyridine may be understood in terms of some accompanying competitive formation and reaction of the derived methanesulfene. Conceivably, dehydrations with the methanesulfonyl chloride and phosphorus oxychloride-dimethylform-amide reagents involve the intermediate formation of labile tertiary formates. Incidentally, either reagent provides a ready means for preparing formates of relatively unhindered alcohols under mild conditions, and unpublished results have revealed the methanesulfonyl chloride reagent to be selective for alcoholic, as opposed to phenolic, hydroxyls in several instances. Notably, even with such acidic reagents as methanolic hydrochloric acid at room temperature, acetyl chloride in refluxing methanol, and refluxing acetic anhydride, there is a preponderant tendency for the estra-1,3,5(10),7-tetraene system to be formed, Va and b giving products containing, from spectroscopic and glc analysis, 50% or more of the related estra-1,3,5(10),7-tetraenes together with impurities of the equilenin and estra-1,3,5(10),8 and 9(11)-tetraene types. However, the complexity of these mixtures discouraged attempts at their resolution.

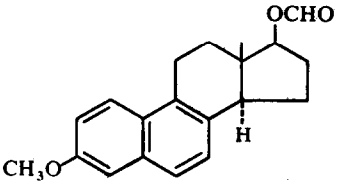
A Dreiding model indicates that, with the flexible B ring in a half chair form, only one H atom (the C_7 β-H) can be in the *trans*-diaxial or pseudo *trans*-diaxial relationship to the 8α-OH group in a structure of the general type V. Possibly therefore, the efficient formation of an estra-1,3,5(10),7-tetraene from such a structure is associated with a kinetically controlled bimolecular elimination mechanism.[34] Interestingly enough, in a 7-hydroxyestra-1,3,5(10)-triene, the OH group, whether α or β, can be accommodated in a pseudo *trans*-diaxial relationship with one hydrogen at the 6-position. When the configuration of the OH group is α, this relation is satisfied if ring B is in the half chair form, and when it is β, the same relationship is met by ring B



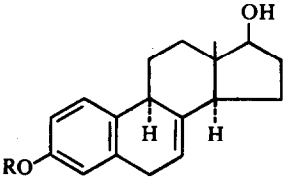
	X	R
Xa; *rac*	0	CH_3
Xb; *rac*	β-CH_3SO_3; α-H	CH_3
Xc;	β-CH_3SO_3; α-H	CH_3
Xd; *rac*	β-$OCOCH_3$; α-H	CH_3
Xe; *rac*	$(OCH_2)_2$	CH_3
Xf; *rac*	β-OCHO; α-H	CH_3
Xg;	β-OCHO; α-H	CH_3
Xh; *rac*	β-OCHO; α-H	CHO



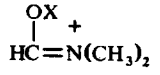
XIa; *rac*
XIb



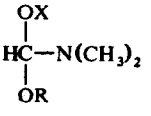
XIIa; *rac*
XIIb



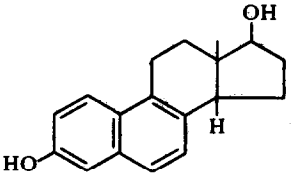
XIIIa; *rac*	CH_3
XIIIb;	CH_3
XIIIc; *rac*	H
XIIId;	H



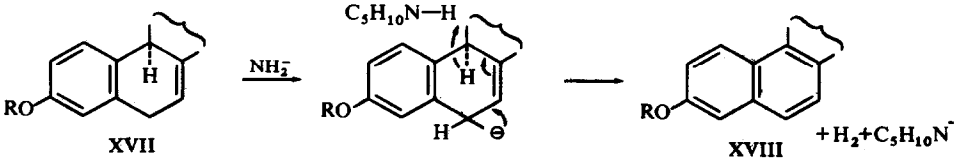
X	
XIVa;	CH_3SO_2
XIVb;	$POCl_2$



XV



XVI



XVII XVIII

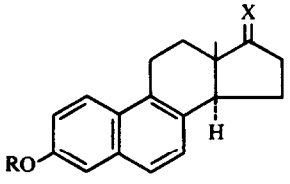
assuming the half-boat form. These observations may be associated with the failure of the previous attempts[22b] to prepare equilin derivatives by the dehydration of 7-hydroxyestra-1,3,5(10)-trienes.

The transformation of the tetraenes Xa-d and Xf-h to equilin or its racemate involved the preliminary formation of the alcohols XIIIa and b and XIIIc and d as appropriate. The reactions involved were the reduction of Xa with sodium borohydride in methanol, and of Xb and c with LAH in THF, and the saponification of Xd and Xf-h with methanolic sodium hydroxide. The oxidation of XIIIb with DMSO acetic anhydride,[35] gave the 17-ketone Ic identical in all respects to authentic equilin-3-methyl ether.[36] Reaction under Oppenauer conditions converted the bis-formate Xh directly to *rac*-equilin (Ib) but the yield (40%) was considerably lower than for the two-stage process. The conversion of XIIIa and b to the corresponding equilin requires a demethylation and an oxidation step. The previously noted propensity of equilin derivatives to undergo acid-catalyzed isomerizations precluded the usual highly acidic reagents in the first step. However, both substances were efficiently demethylated by fusion with methylmagnesium iodide,[28] and the resulting XIIIc and d were thereafter converted by Oppenauer oxidation to *rac*-equilin and equilin, Ib and Ia, the latter proving identical in all respects to the natural hormone. The formates Xf and g were both converted directly to XIIIc and d respectively, by fusion with an excess of methylmagnesium iodide, but this procedure was no more efficient than the foregoing two stage process for the same transformation. Demethylation of XIIIa with sodamide in refluxing piperidine[37,38] was unsatisfactory, since the reaction was accompanied by dehydrogenation and inversion at the 14-position, with formation of the 14β-equilenin derivative XVI. Similar results were obtained with related estra-1,3,5(10),8-tetraenes. We believe these dehydrogenations to be mechanistically similar to previously reported conversions of 1,4-dihydrobenzenes to benzene by potassamide in liquid ammonia,[39] and depict the dehydrogenation of XIIIa as in the sequence XVII-XVIII.

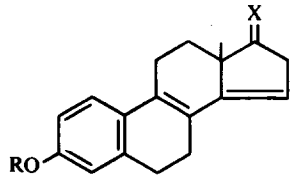
Efficient synthesis of equilin. Using the foregoing reactions, the chemical total synthesis of the natural hormone requires as starting material an enantiomorphic steroid of type II, the most readily available being IIc which we have obtained by the chemical resolution of the racemate IIb and of its chemical precursor, *rac*-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol.[40] Starting with IIc we chose to defer the generation of the 3-OH group until as late as possible in the synthesis, which dictated that demethylation of the 3-OMe group be carried out under conditions incapable of destroying the acid-sensitive estra-1,3,5(10),7-tetraene system, and upon a substrate which would otherwise resist the fused methyl magnesium iodide used as the reagent. Accordingly, our preferred process for the total synthesis of the natural hormone may be defined as in the following sequence, which gives the yields for the most efficient variant at each stage: IIc $\xrightarrow{90\%}$ IVc $\xrightarrow{89\%}$ Vc $\xrightarrow{81\%}$ Xg $\xrightarrow{100\%}$ XIIIb $\xrightarrow{83\%}$ XIIId $\xrightarrow{70\%}$ Ia. The foregoing process makes 17β-dihydroequilin XIIId and equilin Ia available in 53·8 and 37·7% yields, respectively from IIc. Recently, Gibian *et al.*[41] have developed a modification of our estrone syntheses[8,9] which, by incorporating an elegant microbiological asymmetric reduction, led to IIc without formation of any unwanted *ent*-enantiomorph. Since the basic starting material for these syntheses is 6-methoxy-

1-tetralone, the presently described work makes possible an efficient preparation of equilin from that substance.

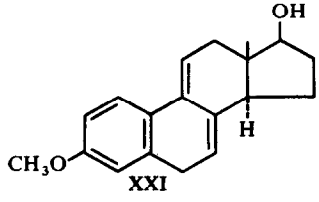
A novel total synthesis of equilenin. During studies on the rearrangements of epoxides of type III with mineral acids it was observed that refluxing methanolic hydrochloric acid converted IIIa to a mixture of approximately equal amounts of *rac*-equilenin-3-methyl ether (XIXa) and the pentaenone XXa. The tetraenol IVa treated similarly, gave the same mixture from which XIXa was readily separated by fractional crystallization. Under the same conditions the alcohols IIIb and IVb gave difficulty separable mixtures of the analogous 17β-ols XIXc and XXc, but oxidation with the Jones reagent[42] destroyed the estra-1,3,5(10),8,14-pentaenol leaving a residue from which XIXa was readily obtained. We believe that the reactions with the expoxides IIIa and b proceed via the corresponding tetraenols IVa or b which undergo dehydration to a mixture of pentaenes, e.g. XXI and XXII, capable of undergoing rearrangement by protonation at the 11-position and deprotonation at the 6- and 15-positions, respectively, to give XIXc and XXc. Since the racemic ketone XIXa has been converted to equilenin XIXe by demethylation and optical resolution,[43] the foregoing transformations represent a novel total synthesis of the hormone from IIa. A simpler, although less efficient, total synthesis of equilenin from the same precursor has been described in earlier papers in this series.[8a, 9] Repetition of the acid treatment with the enantiomorph IVc gave a mixture of the corresponding alcohols XIXd and XXd which was oxidized with DMSO-acetic anhydride[35] and chromatographed to afford XIXb. Demethylation of the latter in refluxing acetic-hydrochloric acids gave, in 9% overall yield from IVc, equilenin (XIXe) identical in all respects to the natural hormone. Since XIXb and d, as previously noted, have been converted to equilin[6, 7] the foregoing studies establish further, but less efficient, totally synthetic routes to equilin from estratetraenes of type II.



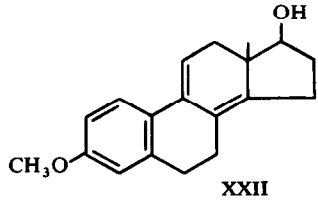
	R	X
XIXa; *rac*	CH_3	0
XIXb;	CH_3	0
XIXc; *rac*	CH_3	β-OH; α-H
XIXd;	CH_3	β-OH; α-H
XIXe	H	0



	R	X
XXa; *rac*	CH_3	0
XXb;	CH_3	0
XXc; *rac*	CH_3	β-OH; α-H
XXd;	CH_3	β-OH; α-H



XXI



XXII

EXPERIMENTAL

All evaporations were under reduced press. All hydrogenations were at atmos press. M.ps were determined in capillary tubes (Thomas–Hoover apparatus) and are uncorrected. UV absorption spectra were measured in 95% EtOH with the Perkin–Elmer 450 spectrophotometer. IR absorption spectra were obtained for all substances as KBr discs using the Perkin–Elmer 21 spectrophotometer and were consistent with the assigned structures. Optical rotations were measured at 25° with the Zeiss 0·005° photoelectric polarimeter and refer to 1% solns in dioxan unless noted otherwise. PMR spectra were recorded with the Varian A-60 spectrometer using 5–10% solns in $CDCl_3$ containing TMS as the internal reference standard. Chemical shifts, δ, are expressed in ppm measured downfield from the reference. GLC was run on a Perkin–Elmer model 881 chromatograph having a 2 m column (0·25 in o.d.) packed with 80–100 mesh Chromsorb G containing 2·5% SE-30 at 220°. Samples were injected in CH_2Cl_2 into the gas chromatograph at 300°. Representative experiments are described for compounds of the natural enantiomorphic series, and where needed to illustrate other procedures, for compounds of the *rac*-series, and it is to be assumed that substances for which no experimental directions are given were prepared as for their closest analogs unless stated otherwise. Physical properties for all of the intermediates and end products of the syntheses covered in this paper are listed in Table 2. All of these substances gave satisfactory elemental analyses and displayed IR absorption and PMR spectra consistent with the assigned structures. *m*-Chloroperbenzoic acid is a grade assayed as of 85% purity supplied by FMC Corporation, Carteret, New Jersey.

rac-17,17-*Ethylenedioxy*-3-*methoxyestra*-1,3,5(10),8-*tetraene* (IIe)

rac-17,17-Ethylenedioxy-3-methoxyestra-1,3,5(10),8,14-pentaene[44] (29·0 g) was shaken with H_2 in benzene (400 ml) containing 2% palladized calcium carbonate (9 g, pre-reduced). After uptake of one equivalent of gas the mixture was filtered (Super Cel) and the filtrate evaporated. The residue was taken up in CH_2Cl_2 treated with Nuchar, filtered and evaporated. The product was recrystallized from EtOH to give IIe (17·0 g) m.p. 130–132°. The analytical sample from EtOH had m.p. 132·5–134·0°.

Conversion of estra-1,3,5(10),8-*tetraenes* (II) *to* 8α,9α-*epoxyestra*-1,3,5(10)-*trienes* (III) *and* 8α-*hydroxyestra*-1,3,5(10),9(11)-*tetraenes* (IV)

General directions. Oxidations were conducted with one equivalent of *m*-chloroperbenzoic acid using benzene or benzene-hexane mixtures as the solvents for 3-acetoxy or methoxyestra-1,3,5(10),8-tetraenes, and THF for 3-hydroxyestra-1,3,5(10),8-tetraenes. Where the 8,9-epoxyestra-1,3,5(10)-trienes (III) were obtained the oxidation was performed at 10–15° for 4–10 min and then rapidly worked up. Where the 8α-hydroxyestra-1,3,5(10),9(11)-tetraenes (IV) were obtained the oxidation was conducted at 10–15° for 15–45 min and the reaction mixture stirred at room temp for 0·75–2 hr before working up.

rac-8α,9α-*Epoxy*-17,17-*ethylenedioxy*-3-*methoxyestra*-1,3,5(10)-*triene* (IIIe)

Solid K_2CO_3 (6 g) and *m*-chloroperbenzoic acid (4 g) were added with stirring to IIe (6·00 g) in benzene-hexane (175:40 ml) at 0° (bath). After stirring for 4 min 5% K_2CO_3 aq (500 ml) and EtOAc were added and and the organic layer was washed successively with 5% K_2CO_3 aq, H_2O, brine, and dried. Recrystallization of the product from ether gave IIIe (5·00 g), m.p. 127·5–129·5°.

rac-17,17-*Ethylenedioxy*-8α-*hydroxy*-3-*methoxyestra*-1,3,5(10),9 (II)-*tetraene* (IVe)

Compound IIIe (4·00 g) and benzoic acid (3·0 g) were stirred overnight at room temp in $CHCl_3$. After evaporation of the solvent the residue in EtOAc was washed successively with 5% K_2CO_3 aq, H_2O, and brine. Recrystallization of the product from ether gave IVe (2·18 g), m.p. 139–141°. For the conversion of IIIh to IVh 2,4-dinitrobenzoic acid was substituted for benzoic acid.

8α-*Hydroxy*-3-*methoxyestra*-1,3,5(10),9(11)-*tetraen*-17β-*ol* (IVc).

Solid K_2CO_3 (50 g) and *m*-chloroperbenzoic acid (43 g) were added with stirring to IIc[40] (60·0 g) in benzene-hexane (1·2:0·2 l) at 0° (bath). Stirring was continued for 15 min at 0° (negative starchiodide test), and continued at room temp for a further 45 min. 5% K_2CO_3 aq (1 l.) was added and the mixture filtered to give IVc (46·0 g), m.p. 128–131°. The filtrate was extracted with EtOAc and the extract washed successively with 5% K_2CO_3 aq, water, and brine, and dried and evaporated. Recrystallization of the residue from benzene yielded a second crop of IVc (11·5 g), m.p. 125–130°. The analytical sample had m.p. 134–136° (from benzene).

rac-*Estra*-1,3,5(10),9(11)-*tetraen*-3,8α,17β-*triol* (IVf)

m-Chloroperbenzoic acid (1·5 g) was added with stirring to IIf (2.00 g) in THF (75 ml) at 0° (bath) and the stirring continued for several min at 0° and 1·25 hr at room temp. $NaHCO_3$ aq and EtOAc were added and the organic layer was washed, dried, and evaporated to a residue which was recrystallized from CH_2Cl_2 to give IVf as a CH_2Cl_2 solvate (3·46 g), m.p. 160–163°. A sample recrystallized from EtOH-H_2O gave a mixed solvate, m.p. 132–135°.

TABLE 2. ESTRAPOLYENES

Compound	(%) Yield[a]	Precursor	Crystn[b] solvent	Mp, °C[c]	$[\alpha]_D$ (deg.)	λ_{max} (mμ) (10^{-3} ε)
Ia[d]	70	XIIId	F	232–235	+287	222 (inf. 6·1)[e]
Ib	72	XIIIc	F	222–224		222 (inf. 7·3)
	40	Xh				
Ic[f]	56	XIIIb	H	159–161	+277[g]	222 (inf. 8·5)
IId	89	IIb	G	119–121		276 (17·2)
IIe	58	[h]	G	132·5–134·0		276 (17·2)
IIf	86	IIb	E	215–217		275 (16·2)
IIg	63	IIf	D	249–251		272 (14·4)
IIh	66	IIg	G	129–131		263 (13·8)
IIIa	57	IIa	B	142–146		235 (11·8)
IIId	56	IId	C	118–121		235 (13·1)
IIIe	79	IIe	C	127·5–129·5		235 (12·2)
IIIh	47	IIh	G	157–159		227 (9·7)
IVa	63	IIa	C	148–150		259 (17·4)
IVb	84	IIb	C	176–178		259 (18·0)
IVc	90	IIc	B	134–136	−22	258 (16·5)
IVd	84	IIId	C	174–176		258 (17·6)
IVe	55	IIIe	C	139–141		258 (18·9)
IVf	100	IIf	G–I	132–135		266 (12·5)
IVh	100	IIIh		[i]		252 (13·5)
Va	85	IVa	C	136–138		218 (8·7)
Vb	87	IVb	C	179·5–180·5		220 (9·1)
Vc	89	IVc	B	146–148	+32	220 (8·4)
Vd	72	IVd	A–B	140·5–142·5		220 (9·4)
	77	Vb				
Ve	51	IVe	C	131–132		219 (8·7)
Vf	75	IIf[j]	D	254–256		220 (7·3)
	40	Vb				
Vg	68	Vb	B	173–175		
Xa	88	Va	G	130–132		223 (inf. 10·0)
Xb	50	Vb	H	138–140		226 (inf. 12·1)
Xc	69	Vc	H	160–163	+110	222 (inf. 7·7)
Xd	78	Vd	H	115–118		226 (inf. 13·0)
Xe	54	Ve	H	119–121		226 (inf. 9·4)
Xf	81	Vb	F	126–128		223 (inf. 7·1)
Xg	81	Vc	F	154–156	+135	223 (inf. 7·4)
Xh	75	Vf	F	118–120		223 (inf. 6·3)
XIa	64	IIb	H	110–111		276 (16·8)
XIIa	48	Xf	H	193–195		230 (54·0)
XIIIa	96, 69, 61	Xa, Xb, Xd	A–B	126–128		222 (inf. 9·1)
	100	Xf				

Compound	(%) Yield[a]	Precursor	Crystn[b] solvent	Mp, °C[c]	$[\alpha]_D$ (deg.)	λ_{max} (mμ) (10^{-3} ε)
XIIIb	100	Xg	F	136–138	+208	222 (inf. 7·6)
XIIIc	86	XIIIa	E	220–222		222 (inf. 6·8)
	72	Xh				
XIIId[k]	83	XIIIb	F–I	174–175	+211	222 (inf. 8·3)
XVI[l]	69	IIb	F	236–238		228 (40·6)
	69	XIIIa				
XIXa[m]	36	IIIa	G	190–192		230 (49·5)
	36	IVa				
XIXb[n]	13	IVc	F	197–199	+64[g]	231 (60·0)
XIXe[o]	72	XIXb	H	254–256	+100	230 (61·0)

[a] Unless otherwise noted yields refer to crystalline substance sufficiently pure for further chemical reaction.

[b] *A* = hexane, B = benzene, C = ether, D = tetrahydrofuran, E = ethyl acetate, F = isopropyl alcohol, G = ethanol, H = methanol, I = water.

[c] Refers to samples of analytical purity.

[d] The natural hormone described in Ref. 3, p. 463, has m.p. 240° and $[\alpha]_D$ + 308°. Sample Ia was identical in m.p., mixed m.p., PMR and IR spectrum with a sample of the natural product.

[e] Extinction values of 6,000–7,000 are considered to be characteristic of the estra-1,3,5(10,7-tetraene chromophore; larger extinction values are attributed to contributions at 222 mμ from estra-1,3,5(10),6,8-pentaenes present as minor impurities.

[f] Identical in m.p., mixed m.p., $[\alpha]_D$ and IR and PMR spectra with a sample prepared as in Ref. 36 which gives m.p. 161–163°, $[\alpha]_D$ + 290° (*c*, 1% in chloroform).

[g] $CHCl_3$.

[h] Ref. 44.

[i] Oil.

[j] The product Vf is best prepared in high yield from IIf in two steps without purification of the intermediate IVf.

[k] Identical in m.p., mixed m.p., $[\alpha]_D$ and IR spectrum with a sample prepared from authentic Ia by reduction with sodium borohydride. The product is a lower melting polymorph of that described by J. Carol, E. O. Haenni and D. Banes, *J. Biol. Chem.* **185**, 267 (1950).

[l] This substance is distinct from the 14α-epimer, m.p. 239–241°, made by reduction of XIXa with sodium borohydride in MeOH. The PMR spectrum of the epimer displays the 18-Me protons as a singlet at δ 0·57, upfield from the analogous signal in XVI. W. N. Speckamp, H. de-Koning, U. K. Pandit and H. O. Huisman, *Tetrahedron* **21**, 2517 (1965) have cited a similar relationship between the 18-Me signals in the spectra of the corresponding 14α and β-6-azaequilenin derivatives.

[m] Ref. 43 gives m.p. 185–186·5°.

[n] Ref. 43 gives m.p. 193·5–194°.

[o] Ref. 3, p. 463, gives m.p. 259°; $[\alpha]_D$ + 87° (EtOH).

3-*Methoxyestra*-1,3,5(10)-*triene*-8α,17β-*diol* (Vc)

Compound IVc (30·0 g) was shaken with H_2 in EtOH (850 ml) containing 5% Pd-C (10 g, pre-reduced). After uptake of gas was complete the mixture was filtered (Super Cel) and the filtrate evaporated. The residue was taken up in CH_2Cl_2 (Nuchar) and the product recrystallized from benzene to give Vc (26·7 g) m.p. 148–152°. The analytical sample had m.p. 146–148° (from benzene).

rac-17β-*Acetoxy*-3-*methoxyestra*-1,3,5(10)-*trien*-8α-*ol* (Vd)

Compound Vb (3·20 g) was kept overnight at room temp in pyridine-Ac_2O (15:10 ml). The product was charcoaled (Nuchar) in CH_2Cl_2 and recrystallized from benzene-hexane to give Vd (2·71 g), m.p. 140·5–142·5°.

rac-3-*Acetoxyestra*-1,3,5(10),8-*tetraen*-17-*one* (IIh)

Compound IIg (1·00 g) was kept overnight at room temp in pyridine-Ac_2O (10:2 ml). The product was charcoaled (Nuchar) in CH_2Cl_2 to give IIh (0·77 g), m.p. 129–131°.

rac-17β-*Formyloxy*-3-*methoxyestra*-1,3,5(10)-*trien*-8α-*ol* (Vg)

Compound Vb (1·00 g) was added to pyridine-methanesulfonyl chloride (15:3 ml) at 0° (bath). The mixture was kept at room temp for 30 min, and added to water. The ppt was filtered off (Super Cel), and extracted with EtOAc, and the extracts were filtered and evaporated. The residue was recrystallized from benzene to give Vg (0·90 g), m.p. 176–178°. The analytical sample had m.p. 173–175°.

3-*Methoxy*-17β-*methanesulfonyloxyestra*-1,3,5(10),7-*tetraene* (Xc)

Compound Vc (3·50 g) was heated (steam bath) with methanesulfonyl chloride (10 ml) in pyridine (30 ml) until initiation of an exothermic reaction caused the solvent to reflux. The heating was discontinued until the reaction had subsided and then continued for a further 15 min. The cooled mixture was poured into ice-water and the ppt filtered off, dried, charcoaled in CH_2Cl_2 (Nuchar), recrystallized from MeOH, and filtered in benzene through Florex. Recrystallization of the product from MeOH gave Xc (2·90 g) m.p. 160–163°.

17β-*Formyloxy*-3-*methoxyestra*-1,3,5(10),7-*tetraene* (Xg)

(i) Compound Vc (23·5 g) was heated under argon at 85° for 10 min with methanesulfonyl chloride (40 ml) in DMF-pyridine (320:40 ml). The cooled mixture was poured into ice-water and the ppt was filtered off, dried, and percolated in benzene through a column of Florex (upper layer)-Al_2O_3 impregnated with 10% w/w of $AgNO_3$ (lower layer). The product was recrystallized from 95% aqueous EtOH to give crude Xg (18·0 g) estimated by GLC as of 90·2% purity. The analytical sample had m.p. 154–156° (from 95% aqueous EtOH).

(ii) Vc (4·00 g) was added with stirring under N_2 to $POCl_3$ (15 ml) in DMF (80 ml) at 0° (bath), and stirring was continued at room temp for 10 min. The mixture was stirred with water for 2 hr and the ppt was filtered off (Super Cel), dried and extracted with EtOAc. Evaporation gave a residue which was charcoaled (Nuchar) in CH_2Cl_2 and recrystallized from isopropyl alcohol to give Xg (3·35 g), m.p. 154–156°, estimated by GLC as of 99·2% purity.

rac-17β-*Formyloxy*-3-*methoxyestra*-1,3,5(10),8-*tetraene* (XIa)

Compound IIb (2·00 g) was kept for 15 min at room temp in DMF-methanesulfonyl chloride (30:5 ml), and the mixture added to water. After 30 min the resulting ppt was filtered off and dried, and percolated in benzene through a column of Florex (upper layer) Al_2O_3 impregnated with 10% w/w of $AgNO_3$ (lower layer). The product was charcoaled (Nuchar) in CH_2Cl_2 and recrystallized from MeOH to give XIa (1·40 g), m.p. 110–111°.

rac-17β-*Formyloxy*-3-*methoxyestra*-1,3,5(10),6,8-*pentaene* (XIIa)

Compound Xf (1·00 g) was kept for 2 hr at room temp with pyridinium bromide perbromide (1·00 g) in pyridine (20 ml). The mixture was added to water and the ppt was filtered off (Super Cel) and extracted with CH_2Cl_2. The extracts were filtered and evaporated to a residue which was recrystallized from MeOH. The crude XIIa (0·65 g) was charcoaled (CH_2Cl_2), percolated in benzene through anhyd neutral Al_2O_3 and recrystallized from MeOH to give a sample, m.p. 193–195°.

rac-3-*Methoxyestra*-1,3,5(10),7-*tetraen*-17β-*ol* (XIIIa)

(i) Compound Xd (0·70 g) was gently warmed (steam bath) for several min with NaOH (0·50 g) in MeOH (20 ml) and the mixture stirred at room temp for a further 30 min. Water was added dropwise, and the ppt was filtered off, dried, charcoaled (Nuchar) in CH_2Cl_2, and recrystallized from benzene-hexane to give XIIIa (0·37 g) m.p. 126–128°.

(ii) Xb (1·00 g) was refluxed for 2·5 hr under N_2 with LAH (1·0 g) in THF (50 ml). EtOAc (15 ml) was added dropwise to the cooled mixture followed by water and dil AcOH, and the mixture was extracted with EtOAc. The product was recrystallized from ether-light petroleum to give XIIIa (0·54 g), m.p. 121–124°.

XIIIa, m.p. 122–124° was also prepared in 96% yield by reduction of Xa with $NaBH_4$ in MeOH, and in 100% yield by hydrolysis of Xf with NaOH in MeOH.

3-*Methoxyestra*-1,3,5(10),7-*tetraen*-17β-*ol* (XIIIb)

Compound Xg (18·0 g) was stirred at room temp for 45 min with NaOH (6·0 g) in MeOH (250 ml). Water (250 ml) was added to the mixture at 0° (bath) and the ppt was filtered off and dried to give XIIIb (16·3 g) m.p. 128–130°. The analytical sample, obtained after recrystallization from isopropyl alcohol (Nuchar), had m.p. 136–138°.

3-*Methoxyestra*-1,3,5(10),7-*tetraen*-17-*one* (*equilin methyl ether*; Ic)

Compound XIIIb (430 mg) was kept overnight at room temp in DMSO-Ac_2O (6:2 ml). The mixture was poured into water and the ppt was filtered off, dried, and percolated in benzene through Al_2O_3 impregnated with 10% w/w of $AgNO_3$. The product was charcoaled (Nuchar) in CH_2Cl_2 and recrystallized successively from EtOH and MeOH to give Ic (200 mg), m.p. 159–161°, and was identical in all respects to a sample made by methylating a sample of equilin obtained from pregnant mares' urine.

Estra-1,3,5(10),7-*tetraen*-3,17β-*diol* (XIIId)

Compound XIIIb (15·7 g) and 3M ethereal MeMgI (200 ml) were heated under argon to 165° (bath) and the bath temp was maintained at 165–170° for a further 3 hr. THF (400 ml) was added to the cooled mixture at −78° (CO_2-acetone bath) followed by EtOAc, and the mixture was stirred at −78° and above until completely decomposed. (The decomposition is violently exothermic at temps above 0°.) Water and sat NH_4Cl aq were added followed by dil AcOH to adjust the equeous layer to pH 7, and the mixture was extracted with EtOAc. The product was charcoaled (Nuchar) in THF and recrystallized from $CHCl_3$ to give XIIId (12·3 g), m.p. 172–173°. The analytical sample had m.p. 174–175° (from isopropyl alcohol-water).

The foregoing method was also used to prepare XIIId directly from Xg.

Equilin (Ia)

Compound XIIId (3·0 g) was refluxed (Dean-Stark water separator) for 2hr with methyl ethyl ketone (40 ml) and aluminum isopropoxide (3·0 g) in benzene (100 ml). Water (200 ml) was added with stirring to the cooled soln, the mixture was filtered, the filtrate diluted with EtOAc, and the organic layer washed, dried and evaporated. The product was charcoaled (Nuchar) in THF and recrystallized from isopropyl alcohol to give equilin, Ia (2·07 g), m.p. 232–235°. The mother liquor yielded further product (0·2 g), m.p. 221–225°.

rac-14β-*Estra*-1,3,5(10),6,8-*pentaene*-3,17β-*diol* (XVI)

Compound IIb (3·00 g) was refluxed for 5 hr under N_2 with sodamide (3·00 g) in piperidine (40 ml). The mixture was decomposed at −78° (bath) with sat NH_4Cl aq and dil HCl was added to pH 7. The product was filtered off (Super Cel), extracted successively with EtOAc and THF and the extracts were filtered and evaporated. The residue was recrystallized from CH_2Cl_2 to give XVI (1·96 g), m.p. 220–223°. The analytical sample had m.p. 236–238° (from isopropyl alcohol).

rac-3-*Methoxyestra*-1,3,5(10),6,8-*pentaen*-17-*one* (XIXa)

(i) Compound IVa (20·0 g) was treated with 3N HCl (20 ml) in boiling MeOH (250 ml) for several min then stirred at room temp for 1 hr. The ppt was filtered off, dried and triturated successively with ether and THF to give XIXa (6·70 g). The pure sample had m.p. 188–190° (from isopropyl alcohol).

(ii) Compound IVb (4·0 g) in hot MeOH (50 ml) was treated with 5N HCl (15 ml) and the mixture refluxed for 5 min. Filtration of the cooled soln gave a 1:1 mixture of XIXc and XXc (1·67 g). The mixture (1·60 g) in acetone (100 ml) containing anhyd Na_2SO_4 was treated with 8N chromic acid[42] dropwise until a permanent red color indicated that excess reagent was present (ca. 3 ml). The excess reagent was destroyed by the addition of isopropyl alcohol and water (400 ml) and the mixture extracted with EtOAc, washed, dried and evaporated. The solid was triturated with 95% aqueous EtOH, filtered and percolated in benzene through Al_2O_3 containing 10% w/w of $AgNO_3$. The product was recrystallized from EtOH to give XIXa (0·35 g), m.p. 190–192°.

3-*Methoxyestra*-1,3,5(10),6,8-*pentaen*-17-*one* (XIXb)

Compound IVc was prepared from IIc (10·0 g) by epoxidation as previously described, and, without purification, was kept with 5N HCl (15 ml) in MeOH (150 ml) at 0° (bath) for 30 min and at room temp for a

further 30 min. Water (500 ml) was added and the mixture extracted with ether, washed, dried and evaporated to give a mixture of XIXd and XXd which was kept overnight at room temp in DMSO-Ac_2O (75:20 ml). The mixture was poured into water and the resulting ppt was filtered off, dried and chromatographed in benzene on neutral Al_2O_3 containing 10% w/w $AgNO_3$. The product was recrystallized from isopropyl alcohol to give XIXb (1·25 g) m.p. 190–194° raised to 197–199° by further recrystallization from isopropyl alcohol.

Equilenin (XIXe)

Compound XIXb (1·25 g) was refluxed under argon overnight in AcOH-11N HCl-H_2O (70:40:12 ml). The cooled solution was diluted with water (250 ml) and the product filtered to give XIXe (0·65 g), m.p. 251–253°. The mother liquors yielded a second crop (0·20 g), m.p. 247–250° raised to 254–256° by further recrystallization from MeOH.

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