893. *Compounds Related to the Steroid Hormones. Part IV.*[1] *Dienone–Phenol Rearrangement of Steroid* $\Delta^{1,4}$-3,11-*Diketones.*

By (Miss) E. J. Bailey, J. Elks, J. F. Oughton, and L. Stephenson.

Prednisone acetate undergoes aromatisation of ring A on treatment with strong acids in acetic anhydride; the reaction is unusual in giving the 3-acetoxy-1-methyl- rather than the 1-acetoxy-4-methyl-$\Delta^{1,3,5(10)}$-compound. Under mild conditions the 17α-hydroxyl group is acetylated, but the 11-oxo-group is unaffected; under more vigorous conditions, the latter group is enol-acetylated, and hydrolysis then gives the 9β-11-ketone as major product. The structures of these compounds were proved by degradation to the known 3-methoxy-1-methylœstra-1,3,5(10)-trien-17-one.

Aromatisation of androsta-1,4-diene-3,11,17-trione also gives the "*meta*-substituted" product, but the 11β-hydroxy-compound, prednisolone acetate, gives the normal "*para*-substituted" product.

The influence of the 11-oxo-group on the direction of rearrangement is discussed.

The nature of the dienone–phenol rearrangement is now well understood, and the influence of a number of structural features upon its direction has been elucidated. With steroid $\Delta^{1,4}$-3-ketones, in particular, rearrangement in acid anhydrides containing a strong-acid catalyst gives exclusively the 1-acyloxy-4-methyl compound; $\Delta^{1,4,6}$-3-ketones, on the other hand, give the 1-methyl-3-acyloxy-compounds (for references, see the preceding paper, where the effect of other reaction conditions is also discussed). There is, however, no record of the acid-catalysed aromatisation of a steroid $\Delta^{1,4}$-3-ketone containing an oxygen group at position 11, and Kirk, Patel, and Petrow [2] failed to aromatise some $\Delta^{1,4}$- and $\Delta^{1,4,6}$-3,11-diketones under the conditions commonly used for analogous compounds having no 11-substituent.

A recent paper by the same authors [3] describes the conversion, under rather vigorous acidic conditions, of a $\Delta^{1,4,6}$-3,11-diketone into a compound that was believed to be the 3-hydroxy-1-methyl-$\Delta^{1,3,5(10),6}$-11-ketone, but the yield was low and the product was inadequately characterised. Analogous 11α- and 11β-acetoxy-compounds, on the other hand, were rearranged smoothly to the usual type of product.

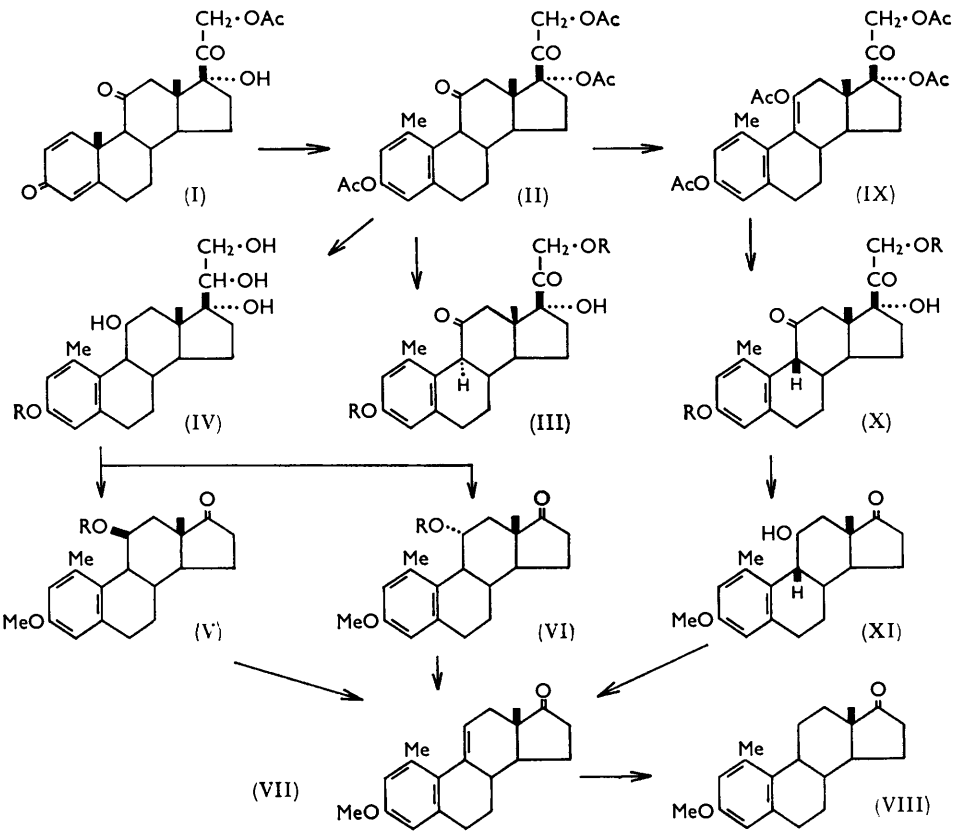
We have now found that the $\Delta^{1,4}$-3,11-diketone, prednisone acetate (I), does in fact undergo aromatisation when treated in acetic anhydride with sulphuric acid, perchloric acid, or toluene-*p*-sulphonic acid. The course of the reaction was followed by examination of the ultraviolet spectrum of material isolated at intervals; the peak at 238 mμ, characteristic of the $\Delta^{1,4}$-3-ketone chromophore, diminished to a minimum value ($E^{1\%}_{1\,cm.}$ 40—50) and was then replaced by a gradually increasing peak at about 240 mμ. We have not found means to stop the reaction precisely at the intermediate stage, but by use of a low concentration (0·05%) of perchloric acid and by careful control of the reaction time, we have isolated the pure intermediate product in 60% yield.

This compound, like its hydrolysis products described below, showed an infrared band close to 850 cm.$^{-1}$, suggestive of a 1,2,3,5- rather than a 1,2,3,4-tetrasubstituted benzene (cf. preceding paper). The other features of the spectrum and the analysis were consistent with the structure (II), which will be shown to represent the compound. Hydrolysis of the triacetate (II), best with only 2 equivs. of sodium hydroxide in methanol,[4] gave the corresponding triol (III; R = H), which showed the expected weak absorption band at ~280 mμ. Acetylation of this compound with acetic anhydride and pyridine at room

[1] Part III, preceding paper.
[2] Kirk, Patel, and Petrow, *J.*, 1957, 1046.
[3] Kirk and Petrow, *J.*, 1960, 4664.
[4] Cf. Ringold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 820.

temperature then gave the 3,21-diacetate (III; R = Ac); this reacted with acetic anhydride in the presence of perchloric acid to yield the original triacetate (II).

That the dihydroxyacetone side-chain had remained intact was shown by a triphenyltetrazolium assay on the diacetate (III; R = Ac). [The triacetate (II) showed only some 26% of the calculated value in this analysis, but we have found similarly low figures to be given by other 17α,21-diacetoxy-20-oxo-steroids.] The triacetate (II) could be converted into an enol acetate (IX) whose ultraviolet spectrum showed the new double bond to be conjugated with the aromatic ring (see below); this suggested that there had been no ring rearrangement.



There were thus left undecided only the positions of the methyl and acetoxy-groups in ring A. Confirmation that they were in the *meta*-relationship was provided by bromination experiments, carried out by Dr. W. C. Taylor at Imperial College and already described by him.[5] Final proof that the aromatic compounds were of the 3-hydroxy-1-methyl type came from the degradation shown in the Chart.

Successive treatment of the triacetate (II) with (*a*) lithium aluminium hydride in tetrahydrofuran, (*b*) dimethyl sulphate, and (*c*) sodium metaperiodate gave a mixture of roughly equal amounts of 11β- (V; R = H) and 11α-hydroxy-3-methoxy-1-methyl-œstra-1,3,5(10)-trien-17-one (VI; R = H), each of which formed a methanesulphonate under normal conditions. Treatment of either of these sulphonic esters (V and VI; R = Me·SO_2) with sodium acetate in boiling acetic acid produced 3-methoxy-1-methyl-œstra-1,3,5(10),9(11)-tetraen-17-one (VII), which gave, on hydrogenation with a palladium

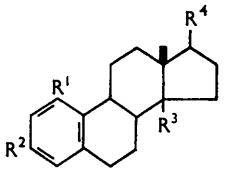
[5] Barton and Taylor, *J.*, 1958, 2500.

catalyst, 3-methoxy-1-methylœstra-1,3,5(10)-trien-17-one (VIII), identical with an authentic sample prepared by the method of Dreiding, Pummer, and Tomasewski.[6]

Certain features of this degradation appear worthy of comment. The formation of similar amounts of 11α- and 11β-hydroxy-compounds by reducing an 11-ketone with lithium aluminium hydride contrasts with the usual preponderance of the 11β-epimer. However, models show that, with the aromatisation of ring A and the concomitant shift of the angular methyl group from $C_{(10)}$ to $C_{(1)}$, the hindrance to approach to $C_{(11)}$ from the β-face is greatly reduced; rather the α-face appears the more hindered.

Again, the ready formation of methanesulphonates by both 11-epimers is unusual, in light of the resistance of normal 11β-hydroxy-groups to acylation. A model of the system shows that, if ring B is in the semi-chair form, the 11β-hydroxy-group is not unduly hindered, but that the 11α-hydroxy-group suffers severe hindrance from the 1-methyl group, to the extent that formation of a methanesulphonate would appear difficult. This could be overcome if ring B were to adopt a semi-boat form.

TABLE 1.



				$[M]_D$ *				$\Delta[M]_D$		
R^1	R^2	R^3	R^4	Parent	11-Oxo	11α-OH	11β-OH	11-Oxo	11α-OH	11β-OH
H	HO	α-H	:O	+440° [a] †			+555° [b] †			+115°
H	AcO	α-H	:O	+431 [a]			+630 [b]			+199
H	HO	α-H	β-OH	+215 [a] †		−181° [c] ‡	+372 [d] †		−396°	+157
H	HO	β-OH	β-CO_2H	+253 [e] §	+770° [e] §			+517°		
H	MeO	β-OH	β-CO_2Me	+334 [e]	+967 [e]			+633		
Me	MeO	α-H	β-COMe	+679 [f]	+1261 [g]	−192 [g]		+582	−871	
Me	HO	α-H	β-OH	+418 [a]			+33 [g]			−385
Me	HO	α-H	:O	+730 [a]	+1269 [h] ‡			+539		
Me	AcO	α-H	:O	+730 [a]	+1274 [h]			+544		
Me	MeO	α-H	:O	+709 [i]		−166 [h]	+754 [h]		−875	+45

[a] Petit and Mathieu, "Pouvoir Rotatoire Naturel, I. Stéroïdes," Masson et Cie., Paris, 1956. [b] Magerlein and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 2220. [c] *Idem, ibid.*, 1957, **79**, 1508. [d] *Idem, ibid.*, 1958, **80**, 2226. [e] Tamm, Volpp, and Baumgartner, *Helv. Chim. Acta*, 1957, **40**, 1469. [f] Djerassi, Lippmann, and Grossman, *J. Amer. Chem. Soc.*, 1956, **78**, 2479. [g] Kirk and Petrow, *J.*, 1960, 4664. [h] This paper. [i] Ringold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 2477.

* In $CHCl_3$ unless otherwise stated. † In dioxan. ‡ In acetone. § In methanol.

In Table 1 there are set out the molecular rotation contributions of 11-oxo- and 11α- and 11β-hydroxy-groups in 3-oxy-$\Delta^{1,3,5}$-steroids; the last three lines refer to the compounds described in this paper. The value for an 11-oxo-group is rather consistent, the presence or absence of a 1-methyl group having no obvious effect; it is, however, very much greater than the standard value (+79°) given for steroids in which ring A is not aromatic (cf. ref. *e*). Agreement is less good among the 11-hydroxy-compounds, but there are too few examples to make an analysis profitable; however, an 11α-hydroxy-group makes a large negative contribution to the molecular rotation and, with one exception, an 11β-hydroxy-group makes a modest positive contribution. It seems justifiable, therefore, to differentiate between our isomeric 11-hydroxy-compounds (V and VI; R = H) on the basis of their widely different rotations, which do, in fact, fit into the general pattern of Table 1 (see last line).

The tetraenone (VII) had its main maximum in the ultraviolet region at a rather lower wavelength (253 mμ) than would be expected; analogous $\Delta^{1,3,5(10),9(11)}$-tetraenones, unmethylated at $C_{(1)}$, absorb, as do $\Delta^{1,3,5(10),6}$-tetraenones, at *ca.* 264 mμ.[7] This hypsochromic

[6] Dreiding, Pummer, and Tomasewski, *J. Amer. Chem. Soc.*, 1953, **75**, 3159.
[7] Dorfman, *Chem. Rev.*, 1953, **53**, 47.

effect presumably arises from the interaction between the 11-hydrogen atom and the 1-methyl group, with a consequent departure from planarity of the styrene chromophore. Dodson and Muir [8] have recently given the $\lambda_{max.}$ for 1-hydroxy-4-methylœstra-1,3,5(10),9(11)-tetraen-17-one as 255·5 mμ and a similar effect is probably operating here.

It will be noted that reduction of the 9,11-double bond in the tetraenone (VII) proceeded mostly by rear-side attack. However, the crude hydrogenation product was clearly a mixture and may well have contained the 9β-epimer of the major product (VIII). The formation of the 8β,9α-compound (VIII) rules out, incidentally, the possibility that the tetraenone had the $\Delta^{1,3,5(10),8(9)}$-structure if *cis*-addition of hydrogen is assumed.

To return to the aromatisation of prednisone acetate (I), prolonged treatment, in acetic anhydride, with sulphuric acid at room temperature or with toluene-*p*-sulphonic acid at 100° gave a non-crystalline material with $\lambda_{max.}$ 242 mμ, $E^{1\%}_{1\,cm.}$ *ca.* 250; the same product was obtained, along with the triacetate (II), when the rearrangement was carried out with *ca.* 0·1% perchloric acid in acetic anhydride. The infrared spectrum suggested that enol acetylation of the 11-ketone group had occurred and this was confirmed by analysis for acetyl, which indicated a tetra-acetoxy-compound. The $\lambda_{max.}$, though apparently low for structure (IX) may, perhaps, be again explained by distortion of the styrene chromophore.

Gentle hydrolysis of the tetra-acetate (IX), with subsequent reacetylation, gave the expected compound (III; R = Ac) as a minor product only, the major product being an isomer thereof. A close structural relationship between the compounds was suggested by their spectra and by the fact that treatment of the triacetate (II) with acetic anhydride containing sulphuric acid gave the enol acetate (IX) and thence the new isomer. These experiments pointed to $C_{(9)}$ as the centre of isomerism, and proof of this came from a degradation of the isomer (X; R = Ac) similar to that applied to the triacetate (II). In this instance, the two 11-hydroxy-17-ketones (XI) could not be completely separated, but successive treatment of the mixture with methanesulphonyl chloride–pyridine and sodium acetate–acetic acid gave 3-methoxy-1-methylœstra-1,3,5(10),9(11)-tetraen-17-one (VII), identical with the material obtained as already described.

The material arising *via* the enol acetate is, then, the 9β-epimer (X) of compound (III). Its occurrence as the major product of hydrolysis of the enol acetate shows that this B/C-*cis*-fused compound is of the same order of stability as the *trans*-fused epimer. This contrasts strongly with the situation in steroids (at least in the 5α-series) in which ring A is saturated, when the equilibrium is greatly in favour of the 9α-form.[9] However, it is made less surprising by a number of observations in recent years, that in 1,2,3,4,9,10,11,12-octahydrophenanthrenes, *cis*- and *trans*-fusion of the non-aromatic rings may confer similar stability;[10] the effect of the aromatic ring in increasing the stability of the *cis*-forms has been plausibly explained on conformational grounds.

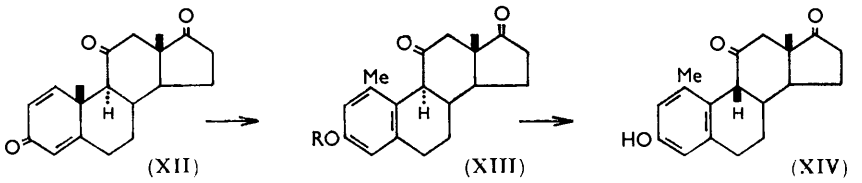
Direct interconversion of compounds (III) and (X) has been tried with perchloric acid in acetic acid. Rotational and paper-chromatographic studies suggested that a mixture of the isomers was obtained from either of them, but an attempt to isolate the 9β-isomer after such treatment of the 9α-compound was only partly successful.

Androsta-1,4-diene-3,11,17-trione [5,11] (XII), on treatment with 0·1% perchloric acid in acetic anhydride for 6 hr., gave 3-acetoxy-1-methylœstra-1,3,5(10)-triene-11,17-dione (XIII; R = Ac); neither the 11- nor the 17-ketone group was enol-acetylated. (With longer reaction times, increasing absorption at 242 mμ indicated enol-acetylation of the

[8] Dodson and Muir, *J. Amer. Chem. Soc.*, 1958, **80**, 5004.
[9] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.
[10] Reusch, Ph.D. Diss., Columbia, 1957; Barltrop and Rogers, *J.*, 1958, 2566; Wenkert and Stevens, *J. Amer. Chem. Soc.*, 1956, **78**, 2318; Johnson, David, Dehm, Highet, Warnhoff, Wood, and Jones, *ibid.*, 1958, **80**, 661; Wenkert and Chamberlin, *ibid.*, 1959, **81**, 688; Saha, Ganguly, and Dutta, *ibid.*, p. 3670; Birch, Smith, and Thornton, *J.*, 1957, 1339.
[11] Herzog, Payne, Jevnik, Gould, Shapiro, Oliveto, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 4781.

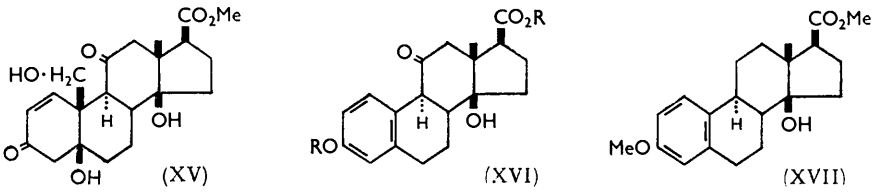
11-oxo-group.) The structure assigned to this compound rests on its infrared spectrum and that of the corresponding 3-hydroxy-compound (XIII; R = H), which were in favour of a " *meta-* " rather than a " *para*-substituted " type.

Treatment of the acetate (XIII; R = Ac) with either acid or base caused changes in the rotation and infrared spectrum suggestive of epimerisation at $C_{(9)}$, but the reactions



were not clean, and it was only with difficulty that a relatively pure specimen of the presumed 9β-compound (XIV) could be isolated.

Tamm, Volpp, and Baumgartner [12] obtained, by the gentle action of alkali upon methyl 5,14,19-trihydroxy-3,11-dioxo-5β,14β-androst-1-ene-17β-carboxylate (XV), with subsequent esterification and 3-*O*-methylation, methyl 14-hydroxy-3-methoxy-11-oxo-14β-œstra-1,3,5(10)-triene-17β-carboxylate (XVI; R = Me); under more vigorous alkaline



conditions an isomer was obtained, and no structure was assigned to it: in the light of our observation of the stability of 9β-11-ketones in the aromatic-A series, a likely structure is that of the 9β-epimer of compound (XVI; R = Me). Again, Wolff–Kishner reduction of the 11-ketone (XVI; R = H) and subsequent treatment with diazomethane gave methyl 14-hydroxy-3-methoxy-14β-œstra-1,3,5(10)-triene-17β-carboxylate (XVII) together with an isomer, which was regarded as the 17α-epimer; since equilibrium could well be established at $C_{(9)}$ before reduction, the isomer may as likely be the 9β-epimer of (XVII). In Table 2 is shown the change in molecular rotation associated with epimerisation at $C_{(9)}$ in our compounds, together with the differences between the isomers described by Tamm *et al.*; [12] though agreement is only partial, the rotation results by no means exclude the above suggestion.

TABLE 2.

Compound	$[M]_D$	$\Delta[M]_D$	Compound	$[M]_D$	$\Delta[M]_D$
(III; R = Ac)	+1184°	−649°	(XVI; R = Me)	+967° [12]	−318°
(X; R = Ac)	+535		Isomer	+649 [12]	
(XIII; R = H)	+1270 *	−549	(XVII)	+334 [12]	−327
(XIV)	+721 *		Isomer	+7 [12]	

* In acetone

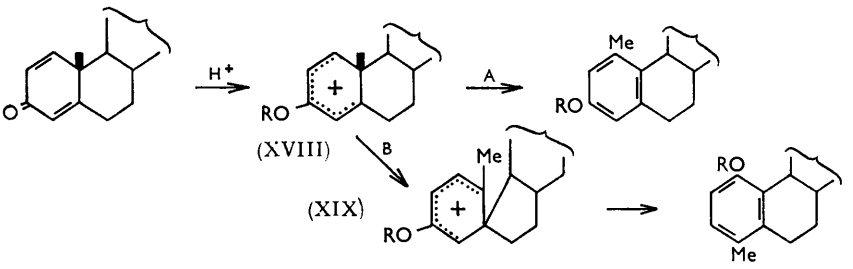
The dienone–phenol rearrangement is considered to proceed as annexed (ref. 13; see also preceding paper).

With a simple 1,4-dien-3-one, saturated and unsubstituted in rings B and C, pathway B, involving migration of a tertiary carbon atom, is preferred to pathway A, in which a methyl group migrates. The effect of a 6,7-double bond in favouring pathway A has

[12] Tamm, Volpp, and Baumgartner, *Helv. Chim. Acta*, 1957, **40**, 1469.

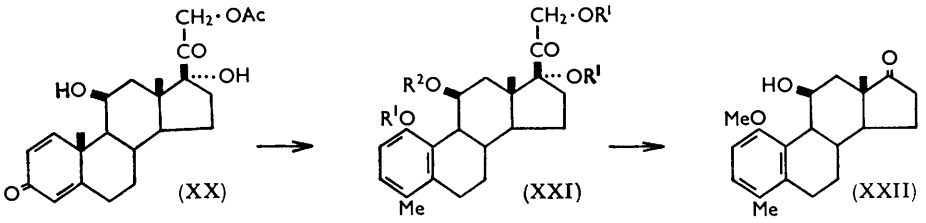
[13] (*a*) Woodward and Singh, *J. Amer. Chem. Soc.*, 1950, **72**, 494; (*b*) Woodward, " Perspectives in Organic Chemistry," ed. Sir Alexander Todd, Interscience Publ. Inc., London, 1956, p. 178; (*c*) Djerassi, Rosenkranz, Romo, Pataki, and Kaufmann, *J. Amer. Chem. Soc.*, 1950, **72**, 4540.

been attributed [13c] to the 5,6-bond in the intermediate ion (XVIII) having some double-bond character, which inhibits formation of the spiro-intermediate (XIX). The effect we have now demonstrated, of an 11-oxo-group in favouring pathway A, presumably results from inhibition of migration of $C_{(9)}$, due to the electron-withdrawing effect of the



neighbouring carbonyl group. Another factor that would tend to the same result and may also be important is the proximity of the negative end of the 11-carbonyl dipole to $C_{(1)}$, which would tend to stabilise the positive charge on that carbon atom in the intermediate (XVIII).

If this is the explanation, then one might expect (*a*) that an 11-oxo-group would make the aromatisation slower, and (*b*) that an 11-hydroxy-group would have little effect on the rate or the outcome of the reaction. A comparison of the rates of disappearance of the $\Delta^{1,4}$-3-ketone chromophore from cholesta-1,4-dien-3-one, prednisone acetate (I), and prednisolone acetate (XX) under identical conditions showed that aromatisation of the cholestane derivative was, in fact, much faster than that of the 11-ketone (I); the rate for prednisolone acetate (XX) was intermediate but closer to that of the former.



The speed of aromatisation of prednisolone acetate (XX) was such that it was not possible to acetylate the 17α-hydroxy-group without concurrent rearrangement in ring A. There was no great tendency towards elimination of the 11β-hydroxy-group, although if reaction was prolonged, a band in the ultraviolet spectrum at *ca.* 250 mμ suggested that dehydration was occurring. The product was a mixture that could not be completely separated into its components, but paper chromatography showed two well-separated spots. The infrared spectrum of the mixture showed a band at 810 $cm.^{-1}$, indicative of "*para*-substitution," but none at 850 $cm.^{-1}$, and was consistent with the mixture's consisting of the fully acetylated compound (XXI; $R^1 = R^2 = Ac$) and the triacetate (XXI; $R^1 = Ac$, $R^2 = H$). Mild alkaline hydrolysis of the mixture gave, in poor yield, a single product, analysing as a tetraol monoacetate (XXI; $R^1 = H$, $R^2 = Ac$). These structures for the partly acetylated products are based on the expectation that the 17-hydroxy-group would be acetylated under the aromatisation conditions and regenerated during the alkaline hydrolysis.[14] The nature of the substitution in ring A is based upon the infrared spectrum, and upon the assumption that the rearrangement will follow pathway

[14] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.

B (see Chart), rather than the less probable one leading to the 4-hydroxy-1-methyl derivative, through migration of $C_{(6)}$ in the intermediate (XIX).

An attempt to prove this last point rigidly has been made, albeit unsuccessfully. The mixture obtained by aromatisation of prednisolone acetate (XX) was treated successively with (*a*) lithium aluminium hydride in tetrahydrofuran, (*b*) dimethyl sulphate, and (*c*) sodium metaperiodate. Chromatography gave a very poor yield of a compound with analysis and infrared spectrum in reasonable agreement with those for the expected 11β-hydroxy-1-methoxy-4-methylœstra-1,3,5(10)-trien-17-one (XXII); an unusual feature of the spectrum was a double band at 812 and 798 $cm.^{-1}$. It was hoped that this compound could be dehydrated to the known 1-methoxy-4-methylœstra-1,3,5(10),9(11)-tetraen-17-one,[8] but neither under the conditions used successfully for the similar compounds (V) and (VI), nor under a variety of other dehydrating conditions, was any material produced showing spectroscopic evidence for the formation of the required tetraenone.

Experimental

Rotations were measured with solutions in chloroform unless otherwise specified. The dihydroxyacetone side-chain was estimated by the method of Mader and Buck,[15] with cortisone acetate as standard. For other general information, see preceding paper.

Aromatisation of Prednisone Acetate.—(a) *With 0·05% perchloric acid in acetic anhydride.* Prednisone acetate (10 g.) was dissolved in warm acetic anhydride (290 ml.) and the solution was cooled to room temperature. 60% w/w Aqueous perchloric acid (0·15 ml.) was added dropwise to ice-cold acetic anhydride (9·85 ml.), and the solution was added to the suspension of the steroid, which was then stirred at room temperature. The mixture became clear after 1½ hr. and was then set aside for a further 3¾ hr.; it was poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to dryness, to give material (14·4 g.) with $\lambda_{max.}$ 240 mμ ($E^{1\%}_{1\,cm.}$ 40·8). This product (10·5 g.) was chromatographed on Florisil (100 g.), the column being eluted with benzene containing increasing amounts of ethyl acetate. Crystallisation from ethanol gave 3,17,21-*triacetoxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione* (II) (5·4 g., 61%), m. p. 198—201°, $[\alpha]_D$ +178° (*c* 1·0). The analytical specimen had m. p. 198—200°, $[\alpha]_D$ +177° (*c* 1·0) (Found: C, 66·85; H, 6·55; Ac, 24·1. $C_{27}H_{32}O_8$ requires C, 66·9; H, 6·7; Ac, 26·6%), $\nu_{max.}$ (in Nujol) 1754 and 1198 (aromatic OAc), 1736 and 1266 (21-OAc), 1724 and 1238 (OAc), 1716 (C=O) and 846 $cm.^{-1}$ (*meta*-type). Side-chain assay, 26%; prednisone 17,21-diacetate also gave a value of 26% in the same assay.

(b) *With 0·1% perchloric acid in acetic anhydride.* Prednisone acetate (12·0 g.) in acetic anhydride (300 ml.) was treated with a mixture of 60% w/w aqueous perchloric acid (0·375 ml.) and acetic anhydride (30 ml.) as described above. The solution was left at room temperature for 5 hr. and was then added slowly to a stirred suspension of sodium hydrogen carbonate (650 g.) in water (3 l.). The crude product (16·02 g.), isolated as described above, had $\lambda_{max.}$ 239·5 mμ ($E^{1\%}_{1\,cm.}$ 135). This product (15 g.), in benzene, was chromatographed on alumina (Grade II—III; 400 g.). Benzene eluted 12·2 g. of material which, on crystallisation from ethanol, gave 3,17,21-triacetoxy-1-methyl-19-norpregna-1,3,5(10)-triene-11,20-dione (II) (2·39 g., 18%), m. p. 190—197°. Evaporation of the ethanol mother-liquors gave 7·8 g. of residue, which was chromatographed on Florisil (300 g.). Benzene containing 5% and then 10% of ethyl acetate eluted 4·75 g. (32%) of 3,11,17,21-tetra-acetoxy-1-methyl-19-norpregna-1,3,5(10),9(11)-tetraen-20-one (IX), $\lambda_{max.}$ 242·5 mμ ($E^{1\%}_{1\,cm.}$ 260). Benzene containing 15% and then 25% of ethyl acetate eluted 2·39 g. of material which, on crystallisation from ethanol, gave a further 1·59 g. (12%) of 3,17,21-triacetoxy-1-methyl-19-norpregna-1,3,5(10)-triene-11,20-dione, m. p. 194—197°.

A similar experiment, carried out for 24 hr., gave a crude product with $\lambda_{max.}$ 243 mμ ($E^{1\%}_{1\,cm.}$ 219), enol acetylation of the 11-oxo-group being more or less complete.

(c) *With sulphuric acid and acetic anhydride.* Prednisone acetate (1·5 g.) was dissolved in warm acetic anhydride (40 ml.). The solution was cooled to room temperature and treated with a solution of sulphuric acid (0·1 ml.) in acetic anhydride (3 ml.). After being left at room temperature for 2 hr., the solution was treated with a further quantity of sulphuric acid

[15] Mader and Buck, *Analyt. Chem.*, 1952, **24**, 666.

(0·2 ml.) in acetic anhydride (3 ml.) and left for a further 16 hr. It was worked up as above, to give material (1·52 g.) with $\lambda_{max.}$ 240—242 mμ ($E^{1\%}_{1cm.}$ 225). This product was chromatographed on alumina (Grade II; acid-washed; 70 g.). Benzene eluted 3,11,17,21-*tetra-acetoxy*-1-*methyl*-19-*norpregna*-1,3,5(10),9(11)-*tetraen*-20-*one* (IX) as an oil (0·90 g., 46%), $\lambda_{max.}$ 242 mμ $E^{1\%}_{1cm.}$ 248 (Found: Ac, 33·3. $C_{29}H_{34}O_9$ requires Ac, 32·8%), $\nu_{max.}$ (in Nujol) 1754 and 1210 (aromatic OAc), 1734 and 1234 (OAc) and 840 cm.$^{-1}$ (*meta*-type).

The use of toluene-*p*-sulphonic acid as catalyst is exemplified below.

3,17,21-*Trihydroxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione* (III; R = H).—3,17,21-Triacetoxy-1-methyl-19-norpregna-1,3,5(10)-triene-11,20-dione (2 g.) in methanol (200 ml.) was treated with 2% w/v methanolic potassium hydroxide (23·2 ml.; 2 equiv.) under nitrogen and left at room temperature for ½ hr. Acetic acid was added to neutralise the alkali, followed by water, and the methanol was distilled off under reduced pressure. The white precipitate was filtered off and crystallised from aqueous methanol, giving 3,17,21-*trihydroxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione* (1·0 g., 68%), m. p. 229—232°, $[\alpha]_D$ +282° (*c* 1·0 in acetone) (Found: C, 70·3; H, 7·6. $C_{21}H_{26}O_5$ requires C, 70·4; H, 7·3%), $\lambda_{max.}$ 278—285 mμ ($E^{1\%}_{1cm.}$ 43·7), $\nu_{max.}$ (in Nujol) 3470 and 3300 (OH), 1709 and 1689 (C=O), and 856 cm.$^{-1}$ (*meta*-type). Side-chain, 92%.

3,21-*Diacetoxy*-17-*hydroxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione* (III, R = Ac).—The foregoing triol (0·35 g.) was acetylated overnight at room temperature with pyridine (2·5 ml.) and acetic anhydride (2·5 ml.). The solution was poured into water and the product isolated with ethyl acetate. Crystallisation from ethyl acetate (charcoal) gave the 3,21-*diacetate* (0·25 g., 58%), m. p. 235—236°, $[\alpha]_D$ +268° (*c* 1·0) (Found: C, 67·7; H, 6·7; Ac, 19·9. $C_{25}H_{30}O_7$ requires C, 67·85; H, 6·8; Ac, 19·4%), $\nu_{max.}$ (in Nujol) 3440 (OH), 1744 and 1210 (aromatic OAc), 1744 and 1240 (21-OAc), 1730 (20-C=O), 1690 (11-C=O) and 848 cm.$^{-1}$ (*meta*-type). Side chain 90%.

3,17,21-*Triacetoxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione from the* 3,21-*Di-acetate*.—The foregoing diacetate (0·1 g.) in benzene (2 ml.) was shaken with a 0·125% solution of perchloric acid in acetic anhydride (0·2 ml.) until the solid had dissolved (30 min.) and then for a further ½ hr. It was diluted with benzene and washed successively with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated. Crystallisation of the residue from ethanol gave the triacetoxy-compound (54 mg., 49%), m. p. 193—195°, undepressed on admixture with a sample prepared as described above. The identity of the compounds was also indicated by their infrared spectra.

Degradation of 3,17,21-*Triacetoxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione*.—Lithium aluminium hydride (1·6 g.) was added to tetrahydrofuran (freshly distilled from phenylmagnesium bromide; 60 ml.) and stirred under nitrogen for 1 hr. A solution of the steroid (1·57 g.) in tetrahydrofuran (60 ml.) was added and the mixture was boiled under reflux with stirring for 5 hr., then left overnight at room temperature. The excess of hydride was destroyed by ethyl acetate; water and 2N-sulphuric acid were added and the product was isolated with ethyl acetate. The crude mixture of pentaols (IV; R = H) weighed 1·10 g.

The products (1·90 g.) from two such experiments were dissolved in methanol (125 ml.) and the solution was stirred at 30° while dimethyl sulphate (10 ml.) and 40% aqueous sodium hydroxide (5 ml.) were added, each in 5 equal portions, added alternately. Sufficient of the alkali was added to make the solution permanently alkaline and the treatment with dimethyl sulphate and sodium hydroxide was repeated. The alkaline solution was evaporated to small bulk under reduced pressure, the residue was diluted with water, and the product was isolated with ethyl acetate.

The crude mixture of 3-methoxy-11,17,20,21-tetraols (IV; R = Me) (1·91 g.) in ethanol (140 ml.) and water (210 ml.) was treated with sodium metaperiodate (2·8 g.) and left at room temperature for 24 hr. The solution was diluted with water and extracted with ether. Concentration of the extract and storage at room temperature for a few hours resulted in the separation of 11α-hydroxy-3-methoxy-1-methylœstra-1,3,5(10)-trien-17-one (VI; R = H) (0·45 g., 26%), m. p. 172—178°, $[\alpha]_D$ −38·4° (*c* 0·89). Evaporation of the filtrate left a froth (1·01 g.), which was chromatographed on acid-washed alumina (grade II—III, 30 g.). The first 1 : 1 hexane–benzene eluate contained material whose infrared spectrum indicated the presence of 11-ketone. Subsequent elution with the same mixture and then with pure benzene gave 11β-hydroxy-3-methoxy-1-methylœstra-1,3,5(10)-trien-17-one (V; R = H) (0·583 g.) which, on crystallisation from aqueous methanol, gave 0·361 g. (21%) of material, m. p. 168—173°,

$[\alpha]_D$ +240° (*c* 1·12). Benzene containing 10% and then 25% of ether eluted a further quantity of the 11α-hydroxy-epimer which, on crystallisation from aqueous methanol, gave 0·061 g. (3%) of material, m. p. 174—180°, $[\alpha]_D$ −43° (*c* 1·0).

The analytical specimen of the 11α-*hydroxy-compound* (from aqueous acetone) formed prisms, m. p. 176—177°, $[\alpha]_D$ −53° (*c* 0·99) (Found: C, 76·2; H, 8·5. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%), $\nu_{max.}$ (in CS_2) 3620 (OH), 1745 (17-C=O), 1296, 1142, and 1046 (aromatic ether) and 852 cm.$^{-1}$ (*meta*-type).

The 11β-*hydroxy-epimer* (Found: C, 76·1; H, 8·1%) melted at 172—174° after crystallisation from aqueous methanol and had $[\alpha]_D$ +240° (*c* 1·2), $\nu_{max.}$ (in CS_2) 3600 (OH), 1745 (17-C=O), 1295, 1142, and 1062 (aromatic ether) and 852 cm.$^{-1}$ (*meta*-type).

A mixture of the two epimers melted between 150° and 178°.

3-*Methoxy*-1-*methylœstra*-1,3,5(10),9(11)-*tetraen*-17-*one* (VII).—*From* 11β-*hydroxy*-3-*methoxy*-1-*methylœstra*-1,3,5(10)-*trien*-17-*one*. To the steroid (150 mg.), in chloroform (3 ml.) containing pyridine (0·6 ml.), was added methanesulphonyl chloride (0·3 ml.), with shaking at 0° during 5 min. The mixture was left overnight in the refrigerator, treated with ice, and extracted with chloroform, to give the crude 11β-methanesulphonate (218 mg.). This material (207 mg.) was boiled under reflux for ½ hr. with a mixture of freshly fused sodium acetate (600 mg.) and acetic acid (6 ml.). Water was added and the product was isolated with ether. The residual gum (141 mg.), which partly crystallised, was chromatographed on alumina (acid-washed; grade I; 5 g.). Hexane–benzene (1 : 1) and benzene eluted 85 mg. of crystals which crystallised from aqueous methanol to give 71 mg. of material which melted at 94—96°. The analytical specimen of the *tetraenone* had m. p. 95—97°, $[\alpha]_D$ +276° (*c* 1·04), $\lambda_{max.}$ 252·5 mμ ($E^{1\%}_{1cm.}$ 508) (Found: C, 81·2; H, 8·5. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·2%), $\nu_{max.}$ (in CS_2) 1740 (17-C=O), 1298, 1152, and 1062 (OMe), and 856 cm.$^{-1}$ (*meta*-type).

From 11α-*hydroxy*-3-*methoxy*-1-*methylœstra*-1,3,5(10)-*trien*-17-*one*. Treatment of the steroid (250 mg.) with methanesulphonyl chloride as described above gave the crude 11α-methanesulphonyloxy-compound (293 mg.). Treatment of this with sodium acetate and acetic acid as above gave 221 mg. of the crude tetraene which, on chromatography followed by crystallisation from methanol, gave the pure material (125 mg., 53%), m. p. 97—98°, undepressed on admixture with material prepared as described above; it had $\lambda_{max.}$ 253 mμ ($E^{1\%}_{1cm.}$ 494). The specimens had identical infrared spectra.

3-*Methoxy*-1-*methylœstra*-1,3,5(10)-*trien*-17-*one* (VIII).—*By reduction of* 3-*methoxy*-1-*methylœstra*-1,3,5(10),9(11)-*tetraen*-17-*one*. The tetraenone (86 mg.) in ethyl acetate (15 ml.), containing 10% palladised charcoal (43 mg.), was shaken under hydrogen for 1½ hr. The ultraviolet spectrum of the crude material showed that hydrogenation of the 9,11-double bond was complete in this time. The catalyst was filtered off and the filtrate evaporated to give an oil that rapidly solidified (m. p. 110—121° after preliminary softening). Crystallisation from methanol gave 3-methoxy-1-methylœstra-1,3,5(10)-trien-17-one (40 mg., 46%) as prisms, m. p. 125—126°, undepressed on admixture with a sample prepared as described below and having an identical infrared spectrum.

From androsta-1,4-*diene*-3,17-*dione*.[6] Androsta-1,4-diene-3,17-dione (0·78 g.) and 48% hydrobromic acid (11 ml.) were heated together in a Carius tube at 55° for 2 days. The mixture was filtered and the dark solid was washed with water and then heated for 3 hr. on the water bath with 5% aqueous sodium hydroxide (170 ml.). The cooled solution was filtered from a little insoluble material and acidified with hydrochloric acid. The precipitated pink solid (0·56 g.), m. p. 200—225°, was seen from its infrared spectrum to contain both the 3-hydroxy-1-methyl and the 1-hydroxy-4-methyl compound. Crystallisation from methanol gave a first crop (0·178 g., 23%), m. p. 249—251°, consisting substantially of 1-methylœstrone (Djerassi *et al.*[13c] give m. p. 250—252°).

1-Methylœstrone (0·17 g.) was methylated with dimethyl sulphate and sodium hydroxide as described above. The crude product (0·164 g.), isolated with ether, was chromatographed on alumina (grade I; acid–washed; 5 g.). Hexane containing 20% and then 50% of benzene eluted 3-methoxy-1-methylœstra-1,3,5(10)-trien-17-one (75 mg., 42%), m. p. 125—126·5° (from methanol), $[\alpha]_D$ +245° (*c* 1·03), $\nu_{max.}$ (in CS_2) 1744 (17-C=O), 1300, 1145, and 1064 (OMe), and 854 cm.$^{-1}$ (*meta*-type) (Ringold *et al.*[16] give m. p. 129—130°, $[\alpha]_D$ +238°).

3,21-*Diacetoxy*-17-*hydroxy*-1-*methyl*-19-*nor*-9β-*pregna*-1,3,5(10)-*triene*-11,20-*dione* (X; R = Ac) —(a) *From* 3,11,17,21-*tetra-acetoxy*-1-*methyl*-19-*norpregna*-1,3,5(10),9(11)-*tetraen*-20-*one*.

[16] Ringold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 2477.

The steroid (4·75 g.) in dry methanol (160 ml.) was treated with 2·44N-methanolic sodium methoxide (14·9 ml.) in an atmosphere of nitrogen. After 4 min., water (0·6 ml.) was added, followed after a further 5 min. by water (60 ml.) and acetic acid (10 ml.). Most of the methanol was removed under reduced pressure and the residue was diluted with water. The product (3·34 g.) was isolated with ethyl acetate and acetylated overnight at room temperature with pyridine (20 ml.) and acetic anhydride (20 ml.). The solution was poured on ice, and the product was isolated with methylene chloride. Trituration of the recovered gum with ethanol gave crystals (1·34 g., 34%), m. p. 187—189°, after a change of crystal form at 155°. The analytical specimen of 3,21-*diacetoxy*-17-*hydroxy*-1-*methyl*-19-*nor*-9β-*pregna*-1,3,5(10)-*triene*-11,20-*dione* had m. p. 187—189°, $[\alpha]_D$ +121° (*c* 0·7) (Found: C, 67·7; H, 7·0; Ac, 20·6. $C_{25}H_{30}O_7$ requires C, 67·85; H, 6·8; Ac, 19·4%), $\nu_{max.}$ (in Nujol) 3600 and 3400 (OH), 1764 and 1205 (aromatic OAc), 1745 and 1228 (21-OAc), 1728 (20-C=O), 1682 (11-C=O), and 834 cm.$^{-1}$ (*meta*-type). Side-chain assay, 94%.

The alcoholic mother-liquors deposited prisms. Ether was added and the mixture was stored in the refrigerator, to give 3,21-diacetoxy-17-hydroxy-1-methyl-19-norpregna-1,3,5(10)-triene-11,20-dione (0·32 g., 8%), m. p. 232—235°, undepressed on admixture with material prepared as described above and having an identical infrared spectrum and $[\alpha]_D$ +268° (*c* 1·03).

(b) *From prednisone acetate, without isolation of intermediates.* Prednisone acetate (2 g.), acetic anhydride (25 ml.), and toluene-*p*-sulphonic acid (0·5 g.) were heated together at 100° for 4 hr. The solution was cooled and poured into aqueous sodium hydrogen carbonate. Isolation with ethyl acetate gave 2·66 g. of material which was hydrolysed and then reacetylated as described in paragraph (a). The product (2·08 g.) was chromatographed on Florisil (100 g.). Benzene containing up to 10% of ethyl acetate eluted material which, on crystallisation from ethyl acetate–hexane, gave 3,21-diacetoxy-17-hydroxy-1-methyl-19-nor-9β-pregna-1,3,5(10)-triene-11,20-dione (0·72 g., 33%), m. p. 180—184°.

(c) *From* 3,17,21-*triacetoxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione*. The triacetate (0·5 g.) in acetic anhydride (12 ml.) was left with sulphuric acid (0·125 ml.) in acetic anhydride (3 ml.) at room temperature for 20 hr. Addition to aqueous sodium hydrogen carbonate and isolation with ethyl acetate gave the tetra-acetoxy-compound (IX) (0·49 g.), $\lambda_{max.}$ 243 mμ ($E^{1\%}_{1\,cm.}$ 233). Hydrolysis, acetylation, and isolation as above gave 3,21-diacetoxy-17-hydroxy-1-methyl-19-nor-9β-pregna-1,3,5(10)-triene-11,20-dione (0·16 g., 35%), m. p. 187—189°, $[\alpha]_D$ +121°.

Degradation of 3,21-*Diacetoxy*-17-*hydroxy*-1-*methyl*-19-*nor*-9β-*pregna*-1,3,5(10)-*triene*-11,20-*dione*.—The steroid (1·81 g.) in tetrahydrofuran (75 ml.) was reduced with lithium aluminium hydride (2·0 g.) in tetrahydrofuran (75 ml.) as described above for the 9α-compound. The crude product (1·49 g.) was methylated as above and the crude monomethyl ether (1·43 g.) was treated with sodium metaperiodate (2·1 g.), to give a mixture containing the epimeric 11-hydroxy-3-methoxy-1-methyl-9β-œstra-1,3,5(10)-trien-17-ones (XI) (1·098 g.). This material, in 1 : 1 hexane–benzene, was chromatographed on alumina (30 g.). The steroids were eluted, without apparent fractionation, by benzene, benzene–ether, and ether. Paper chromatography showed two spots in all the eluates, the slower-running spot becoming relatively more intense in the later fractions. The fractions were combined (0·752 g.), dissolved in chloroform (12 ml.) containing pyridine (2·4 ml.), and treated with methanesulphonyl chloride (1·5 ml.). The mixed methanesulphonates were treated with sodium acetate (2·4 g.) and acetic acid (24 ml.) as described above, and the product (660 mg.) was chromatographed on alumina (grade I; 20 g.). Hexane containing 20% and then 50% of benzene eluted 3-methoxy-1-methylœstra-1,3,5(10), 9(11)-tetraen-17-one which, after crystallisation from aqueous methanol, weighed 301 mg. (25%) and melted at 95—97°; there was no depression of m. p. on admixture with material prepared as described above, and the infrared spectra were identical.

Equilibration of 3,21-*Diacetoxy*-17-*hydroxy*-1-*methyl*-19-*norpregna*-1,3,5(10)-*triene*-11,20-*dione and its* 9β-*Epimer*.—Treatment of the 9α-epimer with a 5% solution of perchloric acid in acetic acid at room temperature resulted in a change of specific rotation from +253° to +162° in *ca.* 56 hr. Under the same conditions, the rotation of the 9β-epimer changed from +116° to +162° in about 16 hr. Reacetylation of the product from the 9α-epimer with acetic anhydride and pyridine gave a mixture whose infrared spectrum was consistent with its containing both epimers; again, paper chromatography of each product suggested that they were similar mixtures of the 9-epimers.

The 9α-epimer (0·5 g.) in acetic acid (75 ml.) was treated with aqueous 60% w/w perchloric

acid (3·75 ml.). After 26 hr. the specific rotation was constant at +163°. After a further 16 hr. the solution was poured into water, and the product was isolated with ethyl acetate and treated overnight at room temperature with acetic anhydride (5 ml.) and pyridine (5 ml.). The product (0·5 g.) had $[\alpha]_D$ +132°. This material (0·42 g.) was chromatographed on Florisil (25 g.). Benzene containing 10—15% of ethyl acetate eluted 0·205 g. of material with m. p. varying from 182° to 220°, and infrared spectra suggestive of 9β-epimer contaminated with some of the 9α-compound. Crystallisation from ethanol gave a first crop of prisms (28 mg.), m. p. 225—233°, $[\alpha]_D$ +269° (*c* 0·9), consisting substantially of the 9α-compound. A second crop consisted of a mixture of prisms and rosettes, which could be largely separated by virtue of their different densities. The prisms (10·5 mg.), m. p. 230—239°, $[\alpha]_D$ +267° (*c* 0·66), again consisted of the 9α-epimer. The needles (62 mg.), m. p. 185—206°, $[\alpha]_D$ +162° (*c* 0·9), appeared to consist chiefly of the 9β-epimer, but an attempt to purify them further by crystallisation was unsuccessful.

3-*Acetoxy*-1-*methylœstra*-1,3,5(10)-*triene*-11,17-*dione* (XIII; R = Ac).—Androsta-1,4-diene-3,11,17-trione [5] (10 g.) in acetic anhydride (280 ml.) was shaken with a mixture of 60% w/w aqueous perchloric acid (0·3 ml.) and acetic anhydride (20 ml.) for 6 hr. at room temperature and poured into aqueous sodium hydrogen carbonate. Isolation with ethyl acetate gave material with $\lambda_{max.}$ 235 mμ ($E^{1\%}_{1\,cm.}$ 86). Chromatography on Florisil (100 g.) gave, in the fractions eluted with benzene and 1 : 1 benzene–ethyl acetate, 3-*acetoxy*-1-*methylœstra*-1,3,5(10)-*triene*-11,17-*dione* (7·8 g., 69%), m. p. 203—208°, $[\alpha]_D$ +375° (*c* 1·0) (Found: C, 74·3; H, 7·3. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1%), $\nu_{max.}$ (in Nujol) 1740 (OAc and 17-C=O), 1710 (11-C=O), 1220 (OAc), and 845 cm.$^{-1}$ (*meta*-type).

3-*Hydroxy*-1-*methylœstra*-1,3,5(10)-*triene*-11,17-*dione* (XIII; R = H).—The foregoing 3-acetoxy-compound (4 g.) in methanol (300 ml.) was treated with potassium hydroxide (1 g.) in methanol (20 ml.) under nitrogen and the solution was stirred at room temperature for 1 hr. Acetic acid was added to neutralise the alkali, followed by water, and the methanol was evaporated under reduced pressure. On being left overnight at 0°, the solution deposited 3-*hydroxy*-1-*methylœstra*-1,3,5(10)-*triene*-11,17-*dione* (2·54 g., 72%), m. p. 230—233° (from methanol), $[\alpha]_D$ +426° (*c* 1·0 in acetone) (Found: C, 76·5; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%), $\nu_{max.}$ (in $CHBr_3$) 3600 (OH), 1742 (17-C=O), 1716 (11-C=O), and 844 cm.$^{-1}$ (*meta*-type).

This material (70 mg.) with pyridine (1 ml.) and acetic anhydride (1 ml.) overnight at room temperature gave the 3-acetoxy-compound, m. p. 203—205°, $[\alpha]_D$ +375° (*c* 1·0), identical with material prepared as described above.

Epimerisation of 3-*Acetoxy*-1-*methylœstra*-1,3,5(10)-*triene*-11,17-*dione*.—The steroid (500 mg.) in acetic acid (50 ml.) was treated with 60% perchloric acid (2·5 ml.) and left under nitrogen, in the dark, for 6 days. Addition to water gave a clear solution, which was extracted with ether (3 × 300 ml.). The extract was washed with aqueous sodium hydrogen carbonate and water. The extracts were dried ($MgSO_4$) and evaporated, to give a blue semi-solid residue (474 mg.), whose infrared spectrum showed that the acetate group had been hydrolysed. Trituration with a little ether gave a solid (342 mg.), which was extracted with boiling ether to leave a residue (62 mg.) of 3-hydroxy-1-methylœstra-1,3,5(10)-triene-11,17-dione, m. p. 226—231°. The ether extracts, on evaporation to small bulk and storage at 0°, gave a solid (158 mg.), m. p. 200—212° (decomp.). Crystallisation from a little methanol gave 46 mg. of a substance, probably essentially 3-*hydroxy*-1-*methyl*-9β-*œstra*-1,3,5(10)-*triene*-11,17-*dione* (XIV), m. p. 195—205° (decomp.), $[\alpha]_D$ +242° (*c* 0·81 in acetone) (Found: C, 75·6; H, 7·6. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%), $\nu_{max.}$ (in $CHBr_3$) 1736 (17-C=O), 1710 (11-C=O), and 842 cm.$^{-1}$ (*meta*-type).

Comparative Rates of Aromatisation of Prednisone Acetate, Prednisolone Acetate, and Cholesta-1,4-*dien*-3-*one*.—Prednisone acetate (0·4 g.), prednisolone acetate (0·4 g.), and cholesta-1,4-dien-3-one (0·38 g.) were separately added to alcohol-free chloroform (10 ml.) and the mixtures were each treated with 2·5 ml. of a 0·125% solution of perchloric acid in acetic anhydride. The prednisolone acetate went into solution only after shaking for ½ hr.; the others dissolved at the outset. At intervals, 1 ml. samples were withdrawn, added to ice and extracted with chloroform. The extracts were washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated. The ultraviolet spectra of the residues were examined, with the results shown in the Table.

Aromatisation of Prednisolone Acetate.—Prednisolone acetate (5 g.), suspended in chloroform (alcohol-free; 80 ml.), was treated with a solution prepared by the addition, at 0°, of 60% w/w aqueous perchloric acid (0·025 ml.) to acetic anhydride (20 ml.), and the mixture was shaken

Time (hr.)	Prednisone acetate $\lambda_{max.}$	Prednisone acetate $E^{1\%}_{1\ cm.}$	Prednisolone acetate $\lambda_{max.}$	Prednisolone acetate $E^{1\%}_{1\ cm.}$	Cholesta-1,4-dien-3-one $\lambda_{max.}$	Cholesta-1,4-dien-3-one $E^{1\%}_{1\ cm.}$
0	238	362	242	378	244	431
1	237	350	242 *	64	243 *	14·4
2·5	237	325	242 *	55	243 *	12
6	236·5	241	242 *	38·4		
24	237	246	242 *	22·9		

* No maximum.

for 3 hr.; after 1 hr. the prednisolone acetate was in solution. Aqueous sodium hydrogen carbonate was added, and the chloroform layer was separated, washed with further sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The crude product, whose spectra indicated the presence of about 20% of unchanged prednisolone acetate, was chromatographed on Florisil (100 g.). Hexane–benzene gave a product (0·1 g.), probably substantially 1,11β,17,21-tetra-acetoxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one (XXI; $R^1 = R^2 = Ac$); $\nu_{max.}$ (in $CHBr_3$) 1745—1735 and 1240—1210 (OAc), and 812 $cm.^{-1}$ (*para*-type) (no hydroxyl bands). Benzene, and benzene containing ethyl acetate, gave material that appeared, from infrared spectra and paper chromatography, to consist chiefly of a triacetate, presumably the 1,17,21-triacetate (XXI; $R^1 = Ac$, $R^2 = H$), $\nu_{max.}$ (in $CHBr_3$) 3580 (OH), 1750 and 1215 (aromatic OAc), 1730 and 1245 (OAc), and 812 $cm.^{-1}$ (*para*-type). This could not be obtained crystalline.

The crude product (4·8 g.), obtained by aromatisation of prednisolone acetate (5·0 g.) as described above and removal of unchanged $\Delta^{1,4}$-3-ketone by chromatography on Florisil, was dissolved in methanol (150 ml.), and 1·4N-methanolic sodium methoxide (23·2 ml.) was added under nitrogen. After 4 min. water (0·6 ml.) was added followed, after a further 5 min., by water (60 ml.) and acetic acid (9 ml.). The methanol was distilled off under reduced pressure and the residue was diluted with water and left overnight at 0°. The resulting white solid (2·5 g.) appeared from paper chromatography to contain two compounds. Crystallisation from aqueous methanol gave 11β-*acetoxy*-1,17,21-*trihydroxy*-4-*methyl*-19-*norpregna*-1,3,5(10)-*trien*-20-*one* (XXI; $R^1 = H$, $R^2 = Ac$) (1·2 g., 24%), m. p. 218—222°. Recrystallisation from aqueous methanol gave material with m. p. 225—227°, $[\alpha]_D$ +175° (*c* 1·0 in acetone), which ran as a single spot on paper (Found: C, 68·1; H, 7·5. $C_{23}H_{30}O_6$ requires C, 68·6; H, 7·5%), $\nu_{max.}$ (in Nujol) 3530 and 3300 (OH), 1730 and 1248 (OAc), 1710 (C=O) and 805 $cm.^{-1}$ (*para*-type).

Degradation of the Aromatisation Product of Prednisolone Acetate.—Material (3·24 g.), obtained as above by aromatisation of prednisolone acetate and removal of $\Delta^{1,4}$-3-ketone and coloured impurities by chromatography on Florisil, was added in tetrahydrofuran (100 ml.) to a stirred solution of lithium aluminium hydride (3 g.) in tetrahydrofuran (100 ml.). The mixture was boiled under reflux under nitrogen, with stirring, for 4 hr. and then left overnight at room temperature. After addition of ethyl acetate and water, 2N-sulphuric acid was added, and the product was isolated with ethyl acetate to give a crude material (2·06 g.), whose infrared spectrum showed the presence of some unreduced ketone. This material, in methanol (100 ml.), was methylated with dimethyl sulphate and alkali as described above. Isolation with ethyl acetate gave the crude monomethyl ether, which was dissolved in ethanol (140 ml.) and water (210 ml.) and treated with sodium metaperiodate (2·8 g.). After 24 hr. at room temperature the mixture was diluted with water, and the product (1·42 g.) was isolated with ether. Chromatography on acid-washed alumina (grade I; 50 g.) gave, first, materials whose infrared spectra showed them to be deficient in hydroxyl. Benzene–ether (1 : 1) eluted material, which, on trituration with a little ether, gave a solid (240 mg.), m. p. 83—87°. Crystallisation from aqueous methanol gave the supposed 11β-*hydroxy*-1-*methoxy*-4-*methylœstra*-1,3,5(10)-*trien*-17-*one* (XXII) as long needles, m. p. 86—87°, $[\alpha]_D$ +80·8° (*c* 0·9) (Found: C, 76·6; H, 9·1. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%), $\nu_{max.}$ (in CS_2) 3620 (OH), 1740 (17-C=O), 1254 and 1046 (OMe), and 812 and 798 $cm.^{-1}$.

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