326. *Steroids Containing Ring* A *Aromatic. Part I. The Dienol–Benzene Rearrangement in* C_{19} *Series.*

By E. Caspi, P. K. Grover, (Mrs.) N. Grover, (Miss) E. J. Lynde, and Th. Nussbaumer.

Several deoxy-steroids of the C_{19} series with ring A aromatic have been prepared by the dienol–benzene rearrangement, and the rearrangement is shown to take a uniform course to yield the 4-methyl-substituted compound. Dehydration of 4,17α-dimethylœstra-1,3,5(10)-trien-17β-ol yields the exocyclic-unsaturated 4-methyl-17-methyleneœstra-1,3,5(10),17(20)-tetraene without structural rearrangement. This contrasts with observations reported for other series of steroids. Transesterification resulting from the decomposition of lithium aluminum hydride with ethyl acetate has been observed.

The aromatization of cyclohexa-2,5-dienols was observed [1] as early as 1922, but this rearrangement was little investigated. An analogous reaction was shown to take place in the biosynthesis of aromatic natural products,[2] but only recently was this rearrangement reinvestigated [3] and extended to the field of steroids.[4] A similar reaction occurs

[1] Auwers and Julicher, *Ber.*, 1922, **55**, 2167.

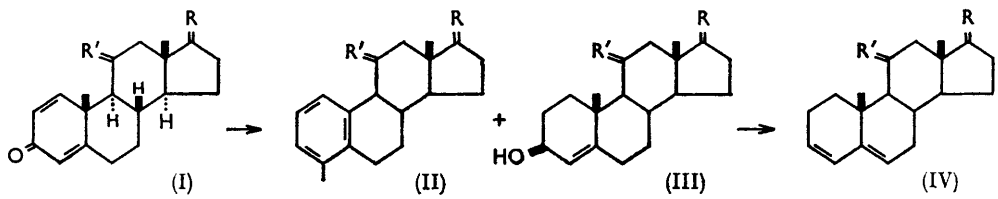
[2] Davis, *Science*, 1953, **118**, 251; Weiss, Gilvarg, Mingoli, and Davis, *Science*, 1954, **119**, 774; Metzenberg and Mitchel, *Arch. Biochem. Biophys.*, 1956, **64**, 51.

[3] Plieninger and Keilich, *Chem. Ber.*, 1958, **91**, 1891.

[4] Dannenberg and Doering, *Z. physiol. Chem.*, 1958, **311**, 84; Dannenberg and Neumann, *Annalen*, 1961, **646**, 148; Gentles, Moss, Herzog, and Hershberg, *J. Amer. Chem. Soc.*, 1958, **86**, 3602.

in the anthrasteroid rearrangement.[5,6] In a programme for the evaluation of the biological activity of deoxy-steroids containing an aromatic ring A we have synthesized several such compounds by the dienol–benzene rearrangement. In this paper we report the synthesis of 4-methyl-deoxy-ring A aromatic steroids of the C_{19} series. Some side reactions observed during the synthesis are also described.

The dihydroxyacetone residue of prednisolone (Ic) was cleaved with sodium bismuthate,[7] and the resulting 11β-hydroxyandrosta-1,4-diene-3,17-dione (Ia) was reduced with lithium aluminium hydride. Chromatography of the resulting mixture on neutral alumina gave several products, three of which were identified. The major product was 4-methylœstra-1,3,5(10)-triene-11β,17β-diol (IIa). Its infrared spectrum had bands at 3030 and 1575 cm.$^{-1}$, characteristic of an aromatic substance, and its nuclear magnetic resonance spectrum had bands at τ 2·88 for protons and 7·79 for a methyl group on an aromatic ring. A small amount of 11β-hydroxy-4-methylœstra-1,3,5(10)-triene-17-one (IIb) was also obtained, and its structure was proved by an independent synthesis from prednisolone (Ic). The products (IIa and b) were oxidized with chromic acid in pyridine to 4-methylœstra-1,3,5(10)-triene-11,17-dione (IIc), and this corroborates the assigned structures. The third compound isolated was the allylic alcohol (IIIa), which on treatment with acid was dehydrated to the expected heteroannular diene (IVa), characterized by its ultraviolet spectrum [8] (bands at 227, 237, and 242 mμ).



	R	R′
Ia	:O	=OH, ··· H
b	:O	:O
c	··· OH, =CO·CH$_2$·OH	=OH, ··· H
d	=OAc, ··· H	H_2
e	=O·COEt, ··· H	H_2
f	··· Me, =OH	H_2
III a	=OH, ··· H	=OH, ··· H
IV b	=OH, ··· H	H_2

	R	R′
IIa	=OH, ··· H	=OH, ··· H
b	:O	=OH, ··· H
c	:O	:O
d	=OAc, ··· H	H_2
e	=OH, ··· H	H_2
f	:O	H_2
g	=OH, ··· Me	H_2
h	:CH$_2$	H_2
i	H_2	H_2

The configuration of 3-hydroxyl group in compound (IIIa) is tentatively assigned as β, in analogy with the product (IIIb) (see below), as well as on the assumption that the attack of the reducing species proceeded from the more accessible rear side of the molecule,[9] giving rise to the pseudoequatorial hydroxyl group and also on the basis of nuclear magnetic resonance spectroscopy (see Table). The spectrum of compound (IIIa) in deuterated pyridine showed bands at τ 4·50 for the 4-proton, 6·26 for the 17α-proton, and two bands at τ 5·73 and 5·58 for the 3α- and 11α-proton, respectively. The assignment of the bands is based on the spectrum of 17β-hydroxy-5α-androstan-3-one, which had a band at τ 6·18 for the 17α-hydrogen, and that of 11β-hydroxyandrost-4-ene-3,17-dione which had bands at τ 4·17 for the 4-proton and 5·57 for the 11α-proton. Finally, androst-4-ene-3β,17β-diol (IIIb) (see below) had three bands at τ 4·43, 5·79, and 6·22, for the 4, 3α-, and 17α-hydrogen, respectively.

[5] Nes and Mosettig, *J. Amer. Chem. Soc.*, 1954, **76**, 3182; Nes, Steele, and Mosettig, *ibid.*, 1958, **80**, 5233; and references therein.
[6] Bladon, *J.*, 1955, 2176.
[7] Rigby, *J.*, 1950, 1907; Appleby, Gibson, Norymberski, and Stubbs, *Biochem. J.*, 1953, **60**, 453; Caspi, *J. Org. Chem.*, 1959, **24**, 669.
[8] Caspi, *J. Org. Chem.*, 1956, **21**, 729; Dorfman, *Chem. Rev.*, 1953, **53**, 47.
[9] Fieser and Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, p. 268.

Distribution of the hydrogen bands of several steroids in pyridine solutions.

Compound	Proton on carbon (τ units) 4	3	11α	17α
11β-Hydroxyandrost-4-ene-3,17-dione	4·17		5·57	
17β-Hydroxy-5α-androstan-3-one				6·18
Androst-4-ene-3β,17β-diol	4·43	5·79		6·22
Androst-4-ene-3β,11β,17β-triol	4·50	5·73	5·58	6·26

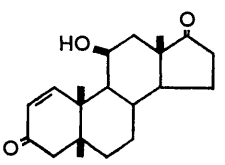
The spectroscopic and analytical data, presented so far, did not provide evidence for the position of the methyl group in ring A. The structures of 4-methylœstra-1,3,5(10)-trien-17β-ol (IIe) and the corresponding 17-ketone (IIf) have been proved previously.[5] We prepared these compounds from 1,2-didehydrotestosterone acetate (Id) and propionate (Ie). When this acetate in ether was reduced with lithium aluminium hydride at 0°, the 3-ketone group was reduced almost selectively, and the 17-acetate (IId) was obtained as the main product. This acetate (IId), on saponification, gave 4-methylœstra-1,3,5(10)-trien-17β-ol (IIe), and this was reacetylated to (IId) and oxidized with chromic acid in pyridine to 4-methylœstra-1,3,5(10)-triene-17-one (IIf). The spectroscopic and physical constants of compounds (IIe and f) were in agreement with those reported.[5] When the reduction was carried out in boiling ether, mainly 4-methylœstra-1,3,5(10)-trien-17β-ol (IIe) was obtained along with a small amount of the corresponding acetate (IId). In the case of 1-dehydrotestosterone propionate (Ie), it was necessary to prolong the reaction in boiling ether to bring it to completion; chromatography of the products on neutral alumina then gave, in addition to 4-methylœstra-1,3,5(10)-trien-17β-ol (IIe), 4-methylœstra-1,3,5(10)-trien-17-one (IIf), 4-methylœstra-1,3,5(10)-trien-17β-yl acetate (IId), and androst-4-ene-3β,17β-diol (IIIb). The 17-acetate (IId) resulted probably from trans-esterification with ethyl acetate, which was used for termination of the reaction.[10] The allylic alcohol (IIIb) was identified by comparison with an authentic sample and by dehydration with acid to the heteroannular conjugated diene (IVb). The mode of formation of the 17-ketone (IIf) from 1-dehydrotestosterone propionate, which obviously could not have occurred during the reduction with lithium aluminum hydride, is obscure and is being investigated. It was expected that aromatization of ring A would make the 11-ketone group accessible for reduction. Indeed, Clemmensen reduction[11] of compound (IIc) gave a hydrocarbon (IIi), in good yield, which was identical with the reduction product of authentic 4-methylœstra-1,3,5(10)-trien-17-one (IIf); this concludes the proof of the assigned structures. The infrared spectrum of the 4-methyl hydrocarbon (IIi) was different from that of 1-methylœstra-1,3,5(10)-triene, the synthesis of which will be reported later.

The preparation of the 17α-methyl compounds started with the 1,2-didehydro-17α-methyltestosterone (If), which on reduction with lithium aluminum hydride in ether at 0°, followed by treatment with aqueous hydrochloric acid in acetone, gave 4,17α-dimethylœstra-1,3,5(10)-trien-17β-ol (IIg). The aromatic 17α-methyl-17β-hydroxy-product (IIg) was dehydrated with phosphorus oxychloride in pyridine[12] to yield the exocyclic-unsaturated methylene-hydrocarbon (IIh) in good yield. The compound showed pronounced infrared bands at 1660 and 890 cm.$^{-1}$ in accordance with the assigned structure.[13] Confirmation of the presence of the exocyclic methylene group was obtained by its cleavage, with sodium metaperiodate in the presence of catalytic amounts of potassium permanganate,[14] to the 17-ketone (IIf) described above, which proves the structures of both compounds (IIg and h). It is of interest that dehydration of the 17β-hydroxy-17α-methyl compound (IIg) proceeded

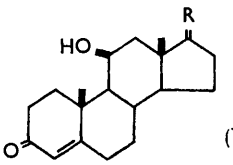
[10] Stap and Rabjohn, *J. Org. Chem.*, 1959, **24**, 1798.
[11] Sigg and Reichstein, *Helv. Chim. Acta*, 1956, **39**, 1507.
[12] Mori and Yasuda, *J. Pharm. Soc. Japan*, 1960, **80**, 330.
[13] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, p. 31.
[14] Lemieux and von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701, 1710; von Rudloff, *ibid.*, p. 1714; Wall and Serota, *J. Org. Chem.*, 1959, **24**, 741.

without structural rearrangement of the steroid nucleus, observed in other cases,[15] and gave almost exclusively the 17-methylene compound (IIh).

The preparation of 11β-hydroxy-4-methylœstra-1,3,5(10)-trien-17-one (IIb) from prednisolone is worthy of note because of the isolation of two by-products which throw additional light on the reduction of cross-conjugated dienones with lithium aluminum hydride. When prednisolone was reduced with lithium aluminum hydride in boiling tetrahydrofuran and the product then treated with sodium bismuthate, chromatography on silica gel then afforded the 11β-hydroxy-17-ketone (IIb) and the 11β-hydroxy-3,17-diketone (VIa) and (V). The last of these products had $\lambda_{max.}$ (in MeOH) 227 mμ (ε 8500)



(V)



(VI) a, R = :O
b, R = ···OH, =CH(OH)·CH$_2$·OH (β)

and $\nu_{max.}$ 3500, 1720, 1665, and 1605 cm.$^{-1}$ and on catalytic hydrogenation (palladium–charcoal in ethyl acetate) gave the known 11β-hydroxy-5β-androstane-3,17-dione. On several occasions, when the crude reduction mixture of prednisolone was chromatographed on silica gel, without prior cleavage of the side chain, 11β,17α,20β,21-tetrahydroxypregn-4-en-3-one was isolated.

Saturation of the 1,2-double bond in a $\Delta^{1,4}$-3-ketone, with metal hydrides, has been previously observed [16] but the reduction of the 4,5-bond had not been reported. In the present investigations, on many occasions, alcohols in which ring A was fully saturated were also isolated, but no efforts were made to identify them. It is of interest that thus far, when the 4,5-bond of a 1,4-dien-3-one was reduced chemically or enzymically [17] the 5β(H)-Δ^1-3-ketone was obtained.

Most frequently the dienone–phenol rearrangement of unsubstituted steroids proceeds with the formation of heterophenols,[18,19] whereas the presence of an 11-oxygen function [19,20] or of unsaturation [20,21] at position 6,7 leads to formation of 1-methyl-3-phenols. However, the conditions, as well as the nature of the catalyst employed for the rearrangement, can profoundly influence the course of the reaction.[18,22] It was suggested by Plieninger and Keilich [3] and by Barton and Cohen [23] that the dienone–phenol and the dienol–benzene rearrangement proceed by the same paths. Should this be the case, analogous alkylated products in the aromatic ring would be expected to arise from the two rearrangements. In the cases investigated so far, in the presence or absence of an 11-oxygen function and regardless of the nature of the 17-substituent, the dienol–benzene rearrangement has taken a uniform course, to yield only 4-methyl compounds. This is at variance with the dienone–phenol rearrangement and may indicate that the two rearrangements are controlled by different factors. The investigation of the influence, on rearrangement, of substituents at other positions of the steroid molecule is in progress.

[15] Julia and Heuser, *Helv. Chim. Acta*, 1952, **35**, 2080; Magrath, Morris, Petrow, and Royer, *J.*, 1950, 2393, and references therein.
[16] Sondheimer, (Miss) Velasco, Batres, and Rosenkranz, *Chem. and Ind.*, 1954, 1482, and references therein.
[17] Caspi and Pechet, *J. Biol. Chem.*, 1958, **230**, 843.
[18] Fieser and Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, p. 327.
[19] Inhoffen and Huang-Minlon, *Naturwiss.*, 1938, **26**, 756; Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1715. Woodward and Singh, *ibid.*, 1950, **72**, 494; Woodward, Inhoffen, Larson, and Menzel, *Chem. Ber.*, 1953, **85**, 594; Djerassi and Grossnickle, *J. Amer. Chem. Soc.*, 1954, **74**, 1741.
[20] Elks, Oughton, and Stephenson, *Proc. Chem. Soc.*, 1959, 6; Bailey, Elks, Oughton, and Stephenson, *J.*, 1961, 4535.
[21] Kirk and Petrow, *J.*, 1960, 4664; 1959, 788; Djerassi, Rosenkranz, Romo, Pataki, and Kaufman, *J. Amer. Chem. Soc.*, 1950, **72**, 4540.
[22] Dreiding, Pummer, and Tomaszewski, *J. Amer. Chem. Soc.*, 1953, **75**, 3159.
[23] Barton and Cohen in "Festschrift Prof. Dr. A. Stoll," Birkenhauser, Basle, 1957, p. 125.

Experimental

Infrared spectra were taken in potassium bromide in paper blotters. Ultraviolet spectra were taken for methanol or " iso-octane " solutions on a Cary spectrophotometer model 11 MS. M. p.s were determined on a hot stage and are corrected. Nuclear magnetic resonance spectra were determined for deuterated chloroform or deuterated pyridine solutions with tetramethylsilane as internal standard, on a Varian high-resolution spectrometer model V4300B. Analyses were made by Schwarzkopf Microanalytical Laboratories, New York, and Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass. Neutral alumina, of activity 1, supplied by Woelm-Eschwege was used for chromatography.

4-Methylœstra-1,3,5(10)-triene-11β,17β-diol (IIa).—To a solution of 11β-hydroxyandrosta-1,4-diene-3,17-dione (Ia) (1 g.) in anhydrous tetrahydrofuran (50 ml.) at 0°, lithium aluminum hydride (2 g.) was added and the mixture was left at 0° for 1 hr. Acetone and water were added and the precipitate filtered off over Celite. The filtrate was concentrated to a small bulk under reduced pressure, and the steroids were recovered with ethyl acetate. The syrup obtained was chromatographed on neutral alumina. The column (A) was percolated with benzene–ethyl acetate. The *product* was eluted with a 3 : 1 mixture as needles, m. p. 184—188°, $[\alpha]_D^{25}$ +125° (in dioxan), $\lambda_{max.}$ (in MeOH) 265 mμ (ε 340), $\nu_{max.}$ 3600, 3030, 1575, 1050 cm.$^{-1}$, τ 2·88, 5·24, 6·27, 7·34, 7·58, 7·79, 7·95, 8·30, 8·69, 8·98 (in $CDCl_3$) (Found: C, 79·4; H, 8·6. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%).

11β-Hydroxy-4-methylœstra-1,3,5(10)-trien-17-one (IIb).—(i) Elution of the chromatographic column from the above experiment with 1 : 4 ethyl acetate–benzene gave compound (IIb) which crystallized from methylene chloride and methanol as prisms, m. p. 244—246°, with a change of structure at 224—226°.

(ii) To a solution of prednisolone (Ic) (3 g.) in anhydrous tetrahydrofuran (50 ml.), a saturated solution of lithium aluminum hydride in tetrahydrofuran (12 ml.) was added and the mixture was boiled for 90 min. The steroids were recovered as described above, and the syrup obtained was oxidized with sodium bismuthate,[7] to yield a colourless glass. The glass crystallized from methylene chloride and methanol as prisms, m. p. 244—246° alone or mixed with the above sample, $[\alpha]_D^{25}$ +95° (in dioxan), $\lambda_{max.}$ (in MeOH) 263 mμ (ε 350), $\nu_{max.}$ 3075, 1720, 1575 cm.$^{-1}$ (Found: C, 80·1; H, 8·7. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%).

Androst-4-ene-3β,11β,17β-triol (IIIa).—Further elution of the column (A above) with 2 : 3 ethyl acetate–benzene gave a solid, which crystallized from ethyl acetate as prisms, m. p. 168—171°, $\nu_{max.}$ 3600, 1660w cm.$^{-1}$, τ 4·50, 5·58, 5·73, 6·26, 8·46, 8·62 (Found: C, 74·7; H, 9·9. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

A sample in acetone was warmed on a water-bath with aqueous 2N-hydrochloric acid. Acetone was distilled off. The product obtained was taken up in ethyl acetate, and the solution was washed with water until neutral, dried (Na_2SO_4), and evaporated. The residue, in methanol, showed ultraviolet bands at 227, 237, 242 mμ characteristic of a heteroannular diene.

4-Methylœstra-1,3,5(10)-triene-11,17-dione (IIc).—(i) 11β-Hydroxy-4-methylœstra-1,3,5(10)-trien-17-one (IIb) (25 mg.) in pyridine (0·5 ml.) was added to a suspension of chromic acid (30 mg.) in pyridine (0·5 ml.), and the mixture left at room temperature for 3 hr. Ethyl acetate was added [24] and the solution filtered through Celite. The filtrate was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to a residue. The syrup obtained crystallized from ethyl acetate as prisms, m. p. 203—205°.

(ii) A solution of 4-methylœstra-1,3,5(10)-triene-11β,17β-diol (IIa) (25 mg.) in pyridine (0·5 ml.) was added to a suspension of chromic acid (50 mg.) in pyridine (0·5 ml.) and kept at room temperature for 3 hr., then was processed as above to give compound (IIc), m. p. and mixed m. p. 203—205°, $[\alpha]_D^{25}$ +386° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 268 mμ (ε 490), $\nu_{max.}$ 3030, 1740, 1710, 1575 cm.$^{-1}$ (Found: C, 80·6; H, 7·8. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%).

4-Methylœstra-1,3,5(10)-triene (IIi).—(i) Hydrogen chloride was bubbled through 4-methylœstra-1,3,5(10)-triene-11,17-dione (IIc) (70 mg.) and zinc amalgam (6 g.) in dioxan (20 ml.) and concentrated hydrochloric acid (14 ml.), at 100°. Portions were taken out at intervals, and the reaction was stopped when the carbonyl bands in the infrared spectrum disappeared (6 hr.). The mixture was filtered, dioxan removed under reduced pressure, water added, and the steroid recovered with ether. The ether solution was washed with water, dried (Na_2SO_4), and concentrated, to yield a brown oil (50 mg.). This was dissolved in hexane and treated with

[24] Vermeulen and Caspi, *J. Biol. Chem.*, 1959, **234**, 2295.

Norite A, and the filtrate chromatographed on neutral alumina. The product (IIi) was eluted with the front, as a colourless oil, which crystallized from ether–methanol as plates, m. p. 101—102°.

(ii) 4-Methylœstra-1,3,5(10)-trien-17-one (IIf) (110 mg.) and zinc amalgam (9 g.) in dioxan (15 ml.) and concentrated hydrochloric acid (17 ml.) gave, as above, the *compound* (IIi), m. p. and mixed m. p. 101—102°, $[\alpha]_D^{25}$ +24° (in $CHCl_3$), $\lambda_{max.}$ (in iso-octane) 265 mμ (ε 240), $\nu_{max.}$ 3030, 1575 cm.$^{-1}$ (Found: C, 89·5; H, 10·1. $C_{19}H_{20}$ requires C, 89·7; H, 10·3%).

4-Methylœstra-1,3,5(10)-trien-17β-ol (IIe).—(i) To a solution of 1,2-didehydrotestosterone propionate (Ie) (3 g.) in anhydrous ether (200 ml.), lithium aluminum hydride (3·5 g.) was added and the mixture was boiled for 3 hr. The product was recovered as previously described, then the syrup obtained was chromatographed in benzene on neutral alumina. The eluates of ethyl acetate–benzene (1 : 19) gave compound (IIe), which crystallized from methylene chloride–methanol as needles, m. p. 113—115°.

(ii) To a solution of 1,2-didehydrotestosterone acetate (Id) (150 mg.) in anhydrous ether (200 ml.) lithium aluminum hydride (300 mg.) was added and the mixture was boiled for 1 hr. The steroids were recovered as previously described, and the syrup obtained was chromatographed on neutral alumina. Elution with ethyl acetate–benzene (1 : 19) gave a colourless solid, which crystallized from methylene chloride–methanol as needles, m. p. 113—115°.

(iii) To a solution of 4-methylœstra-1,3,5(10)-trien-17β-yl acetate (IId) (500 mg.) in benzene (10 ml.) and methanol (30 ml.), 2N-aqueous sodium hydroxide (1 ml.) was added, and the solution boiled for ½ hr. Hydrochloric acid was added, and the steroids were recovered in the usual manner. The *alcohol* obtained crystallized from methylene chloride–methanol as needles, m. p. and mixed m. p. 113—115°, $[\alpha]_D^{25}$ +67° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 265 mμ (ε 440), $\nu_{max.}$ 3500, 3030, 1575 cm.$^{-1}$ (Found: C, 84·0; H, 9·4. $C_{16}H_{26}O$ requires C, 84·4; H, 9·7%).

4-Methylœstra-1,3,5(10)-trien-17-one (IIf).—(i) The eluates of ethyl acetate–benzene (1 : 49) from the column of reduction of 1,2-didehydrotestosterone propionate yielded a colourless solid, which crystallized from methylene chloride–methanol as needles, m. p. 184—186°.

(ii) 4-Methylœstra-1,3,5(10)-trien-17β-ol (IIe) (100 mg.) in pyridine (2 ml.) was added to a suspension of chromic acid (120 mg.) in pyridine (2 ml.), and the solution was kept at room temperature for 3 hr., then was worked up as previously described, to yield the product (IIf), m. p. 184—186°.

(iii) A mixture of 4-methyl-17-methyleneœstra-1,3,5(10),17(20)-tetraene (IIh) (100 mg.), t-butyl alcohol (28 ml.), sodium metaperiodate (640 mg.), potassium permanganate (25 mg.), potassium carbonate (150 mg.), and water (30 ml.) was agitated at room temperature for 2 hr. The excess of potassium permanganate and sodium metaperiodate was reduced with sulphur dioxide, and the tertiary alcohol removed under reduced pressure. Water was added, and the product was recovered with ether. The ether extract was washed with 2N-sodium hydroxide, water, dried (Na_2SO_4), and concentrated under reduced pressure. The oil obtained (70 mg.) crystallized from methylene chloride–methanol, to yield the *compound* (IIf), m. p. 184—186° alone or mixed with the samples obtained as above, $[\alpha]_D^{25}$ +139° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 263 mμ (ε 390), $\nu_{max.}$ 3050, 1720, 1575 cm.$^{-1}$ (Found: C, 85·1; H, 9·0. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0%).

4-Methylœstra-1,3,5(10)-trien-17β-yl Acetate (IId).—(i) Further elution of the chromatographic column from the previous experiment (with 1,2-didehydrotestosterone propionate) with ethyl acetate–benzene (1 : 49) yielded another colourless solid which crystallized from methanol as needles, m. p. 167—169°.

(ii) To a solution 1,2-didehydrotestosterone acetate (Id) (1 g.) in ether (100 ml.), cooled in ice, lithium aluminum hydride (1 g.) was added and the mixture kept for 1 hr. in ice. The steroids were recovered and chromatographed on neutral alumina. Elution of the column with benzene–ethyl acetate (49 : 1) yielded compound (IId) as needles, m. p. 167—169°.

(iii) To a solution of 4-methylœstra-1,3,5(10)-trien-17β-ol (IIe) (75 mg.) in pyridine (1 ml.), acetic anhydride (0·5 ml.) was added and the mixture was kept at room temperature for 16 hr. The product was recovered in the usual manner, to give a colourless *acetate* which crystallized from methanol as needles, m. p. 167—169° alone or mixed with the sample obtained as above, $[\alpha]_D^{25}$ +23° (in $CHCl_3$), $\nu_{max.}$ 3030, 1720, 1575, 1250 cm.$^{-1}$ (Found: C, 80·6; H, 8·9. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

Androst-4-ene-3β,17β-diol (IIIb).—Eluates of ethyl acetate–benzene (3 : 17) from the experiment with 1,2-didehydrotestosterone propionate yielded a colourless solid, m. p. 168—170° with

change of structure at 138°, $\nu_{max.}$ 3500, 1660w cm.$^{-1}$. The infrared spectrum of the product was identical with that of authentic (IIIb).

Androsta-3,5-dien-17β-ol (IVb).—To a solution of androst-4-ene-3β,17β-diol (IIIb) (30 mg.) in acetone (2 ml.), aqueous 2N-hydrochloric acid (0·5 ml.) was added and the whole was warmed on a water-bath for 5 min. The solid that separated was collected and crystallized from aqueous acetone, yielding needles, m. p. 98—100°. The mixed m. p. with a sample obtained from authentic androst-4-ene-3β,17β-diol was undepressed.

17β-*Hydroxy*-17α-*methylandrosta*-1,4-*dien*-3-*one* (If).—To a solution of 17α-methyltestosterone (19·9 g.) in anhydrous dioxan (400 ml.), dichlorodicyanobenzoquinone (19·9 g.) was added, and the solution was boiled for 24 hr. The separated solid was filtered off and washed with methylene chloride. The filtrate was evaporated to dryness, and the residue taken up in methylene chloride–ether (1 : 3), washed with 2N-aqueous sodium hydroxide and water, dried (Na_2SO_4), and evaporated. The oil obtained was crystallized from acetone as tablets of the *hydroxy-ketone*, m. p. 152—154°, $\lambda_{max.}$ (in MeOH) 236 mμ (ε 12,500), $\nu_{max.}$ 3600, 1660, 1610, 1600 cm.$^{-1}$ (Found: C, 80·4; H, 9·55. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

4,17α-*Dimethylœstra*-1,3,5(10)-*trien*-17β-*ol* (IIg).—To a solution of 17β-hydroxy-17α-methylandrosta-1,4-dien-3-one (If) (1 g.) in anhydrous ether (100 ml.), at 0°, lithium aluminum hydride (1 g.) was added, and the solution was kept at 0° for 1 hr., then worked up as previously described, to yield a colourless syrup. The syrup (1·0 g.) was taken up in acetone (10 ml.), 2N-aqueous hydrochloric acid (0·5 ml.) was added, and the solution warmed on a water-bath for 5 min. The separated solid was collected and crystallized from ether–methanol, yielding the *œstratrienol* as prisms, m. p. 153—154°, $[\alpha]_D^{25}$ +27° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 265 mμ (ε 290), $\nu_{max.}$ 3030, 3500, 1575 cm.$^{-1}$ (Found: C, 84·3; H, 9·7. $C_{20}H_{28}O$ requires C, 84·45; H, 9·9%).

4-*Methyl*-17-*methyleneœstra*-1,3,5(10),17(20)-*tetraene* (IIh).—A solution of 4,17α-dimethylœstra-1,3,5(10)-trien-17β-ol (2 g.) (370 mg.) in pyridine (5 ml.) and freshly distilled phosphorus oxychloride (0·9 ml.) was boiled for 3 hr., then poured over ice and hydrochloric acid, and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated under reduced pressure (300 mg.). The solid residue of *methylene derivative* recrystallized from ether–methanol as needles; m. p. 66—67°, $[\alpha]_D^{25}$ +25° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 263 mμ (ε 215), $\nu_{max.}$ 3030, 1660, 1560, and 890 cm.$^{-1}$ (Found: C, 88·3, 88·6; H, 9·7, 10·0. $C_{20}H_{26}.\frac{1}{4}H_2O$ requires C, 88·7; H, 9·9%).

11β-*Hydroxy*-5β-*androst*-1-*ene*-3,17-*dione* (V).—The mother-liquor from the reduction of prednisolone with lithium aluminum hydride and subsequent cleavage of the side chain with sodium bismuthate was chromatographed on silica gel. Elution of the column with benzene–ethyl acetate (3 : 1) yielded a solid, m. p. 224—226°, $\lambda_{max.}$ (in MeOH) 227 mμ (ε 8500), $\nu_{max.}$ 3500, 1720, 1665, and 1605 cm.$^{-1}$. A portion was hydrogenated with 10% palladium–charcoal in ethyl acetate, to give a solid, m. p. 210—213°, whose infrared spectrum was identical with that of 11β-hydroxy-5β-androstane-3,17-dione, and the mixed m. p. with an authentic sample was undepressed.

Further elution of the column with benzene–ethyl acetate (3 : 1) gave compound (VIa), which was identified by comparison of its infrared spectrum with that of authentic 11β-hydroxyandrost-4-ene-3,17-dione.

11β,17α,20β,21-*Tetrahydroxypregn*-4-*en*-3-*one* (VIb).—To a solution of prednisolone (Ic) (10 g.) in tetrahydrofuran (200 ml.) at −70°, lithium aluminum hydride (15 g.) was added and the mixture was kept at −70° for 16 hr. The reaction was terminated with ethyl acetate and water, and the recovered steroids were chromatographed on silica gel. Elution with chloroform–ethyl acetate (1 : 4) yielded compound (VIb), identified by comparison of its infrared spectrum with that of authentic 11β,17α, 20β,21-tetrahydroxypregn-4-en-3-one.

We thank Dr. Marcel Gut from this Foundation for the sample of androst-4-ene-3β,17β-diol. This work was supported by a grant from the U.S. Public Health Service. One of us (T. N.) acknowledges receipt of a Post-doctoral Fellowship, 1959—60.

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, U.S.A.
[Present addresses: (E. J. L.) Glaxo Laboratories, Mddx., U.K.
(T. N.) Robapharm A.G., Basle 6, Switzerland.] [*Received, October 12th*, 1961.]