561. *Steroids Containing Ring* A *Aromatic. Part VII.*[1] *Oxidative Cleavage of* 1-*Hydroxy*-4-*methyl*-1,3,5(10)-*triene Steroids*

By E. Caspi, P. K. Grover, D. M. Piatak, and Y. Shimizu

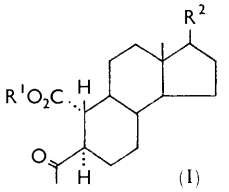
The oxidation of 1-hydroxy-4-methyl-1,3,5(10)-triene steroids by alkaline hydrogen peroxide was investigated. Two major products, 17β-hydroxy-4-methyl-4-oxo-1,4-seco-2,3-bisnorœstr-5(10)-en-1-oic acid and 17β-hydroxy-4-methyl-4-oxo-1,4-seco-2,3-bisnor-5α-œstran-1-oic acid, were isolated. The two acids were interrelated. The saturated acid was degraded by Baeyer–Villiger oxidation to methyl 5,17-dioxo-1,5-seco-2,3,4-trisnorœstra-1-oate, which was synthesised by an alternate route from 19-nortestosterone.

For the past several years, we have been pursuing certain approaches to the degradation of steroids, mainly at ring A. The two primary reasons for undertaking this work were the development of methods for studies on the biosynthesis of steroids [2] and the synthesis of diaza-hormone analogues. The search for intermediates necessary in the synthesis of 2,3-diaza-steroids [3] and 2,4-diaza-steroids [4] (ring A as a pyrimidine) led us to the preparation of compounds (I), (II), and (III). In view of the importance of these substances in the expansion of our synthetic programme of hormone analogues, correlation of these products and the proof of stereochemistry of (I) were deemed necessary.

During studies on the dienone–phenol rearrangement,[1,5] the oxidation of 1,17β-dihydroxy-4-methylœstra-1,3,5(10)-triene (IVa) with alkaline hydrogen peroxide was examined.[3] It was observed that the mixture of acidic products could be differentially partitioned into fractions soluble in sodium hydrogen carbonate and in sodium hydroxide. This separation, however, is not always complete.

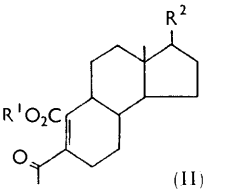
[1] Part VI, Caspi and Grover, *Tetrahedron Letters*, 1963, 591.
[2] Caspi, *Proc. 5th Internat. Congr. of Biochem., Moscow*, 1961, vol. VII, 347.
[3] Caspi, Grover, and Piatak, *Chem. and Ind.*, 1963, 1495; Piatak, Dorfman, Tibbetts, and Caspi, *J. Medicin. Chem.*, 1964, **7**, 590.
[4] Caspi and Piatak, *Experientia*, 1963, **19**, 465; Piatak and Caspi, *Steroids*, 1964, **3**, 631.
[5] Part VIII, Caspi, Grover, and Shimizu, *J. Amer. Chem. Soc.*, 1964, **86**, 2463.

From the fraction soluble in sodium hydroxide, after acidification, the lactol (Va) was isolated in somewhat variable yields. Analysis indicated $C_{17}H_{24}O_4$ and the compound absorbed u.v. light at 215 mμ, indicating either a conjugated carboxylic acid or a strained



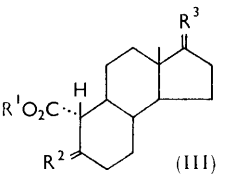
(I)

	R^1	R^2
a:	H	OH
b:	Me	OH
c:	Me	OAc
d:	H	CHMe·OH-β
e:	Me	CHMe·OH-β
f:	Me	Ac
g:	H	Ac



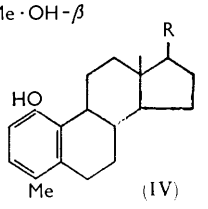
(II)

	R^1	R^2
a:	Me	OH
b:	Me	OAc
c:	Me	CHMe·OH-β
d:	Me	Ac



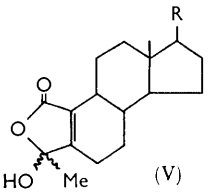
(III)

	R^1	R^2	R^3
a:	Me	O	OAc-β, H
b:	H		OAc-β, H
c:	Me	O	O



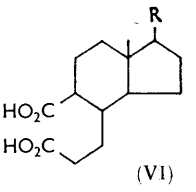
(IV)

a: R = OH
b: R = CHMe·OH-β



(V)

a: R = OH
b: R = CHMe·OH-β
c: R = Ac



(VI)

a: R = OH-β, H
b: R = O

conjugated carbonyl function. The i.r. spectrum had bands at 3580 and 3350sh cm.$^{-1}$ for hydroxyls; at 1760shoulder, 1740, 1720, and 1700 cm.$^{-1}$ in the carbonyl region; and at 1665 cm.$^{-1}$ probably for a conjugated double bond. Though the compound was soluble in base, its i.r. spectrum was lacking the broad associated hydroxyl bands in the 3200 and 2700 cm.$^{-1}$ regions, characteristic of carboxylic acids. A clue to the structure was provided by n.m.r. spectroscopy which did not show signals for vinylic protons but had, in addition to the resonance for the C-18 methyl (τ 9·22), a signal at τ 8·45, equivalent to three protons on a tertiary carbon. The chemical shift of the 8·45 resonance was consistent with a methyl group on a fully substituted carbon bearing two oxygen atoms. Treatment of lactol (Va) with ethereal diazomethane provided the methyl acetyl-ester (IIa). The esterification was accompanied by a change of the u.v. light absorption to 240 mμ, revealing the formation of a new conjugated system. This assumption was corroborated by a n.m.r. spectrum which had signals for a methoxycarbonyl group (τ 6·23), acetyl (τ 7·76), and 18-methyl (τ 9·22). It was apparent that the group giving the τ 8·45 signal was converted into an acetyl group in the ester (IIa). Since ester (IIa) showed conjugation (240 mμ) in the absence of vinylic protons, the 5(10) location of the double bond was substantiated. Furthermore, oxidation of (Va) with potassium permanganate in acetone gave the dicarboxylic acid (VI).

The product (Va) might be expected to exist as a mixture of lactol, open γ-keto-acid, associated acids, etc.;[6] hence the complexity of carbonyl bands in the infrared spectrum. Unfortunately, its limited solubility in chloroform prevented the recording of a good spectrum in solution. However, the singlets at τ 8·45 for the 4-methyl and τ 9·22 for the 18-methyl in the n.m.r. spectrum in perdeuteromethanol seem to indicate that in methanol the preponderant species is the lactol. On the other hand, the ease by which the acetyl ester (IIa) is formed can be viewed as indicative of the existence of keto-acid–lactol equilibrium sufficient for ready displacement towards IIa by methylation.

[6] Pascual, Wegmann, Graf, Scheffold, Sommer, and Simon, *Helv. Chim. Acta*, 1964, **47**, 213.

Catalytic hydrogenation of (Va) gave the *cis*-acid (VII), which when warmed with base epimerised to (Ia). Acid (Ia) was also isolated * (40—60%) from the fraction soluble in sodium hydrogen carbonate solution. Substance (Ia) exists in two forms, probably as the open acid and the lactol, giving different infrared spectra. Treatment of (Ia) with diazomethane gave the ester (Ib), subsequently acetylated to (Ic).

The problem of the stereochemistry of (I) and (VII) still remained unsolved. We have prepared [4] (IIIa). Conversion of (IIIa) and (Ia) into a common compound of known configuration would provide a sound argument for the stereochemistry.

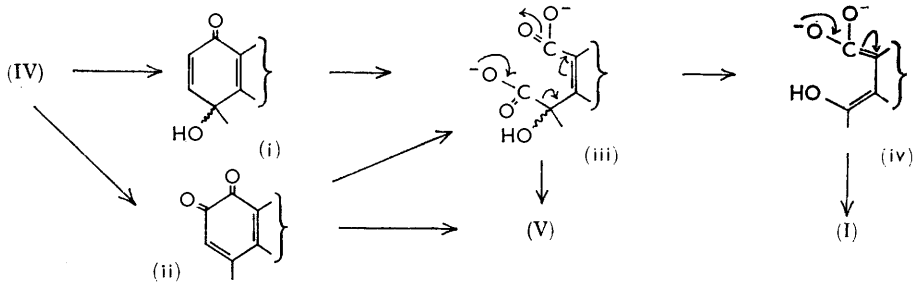
For the synthesis [4] of (IIIa), 19-nortestosterone was condensed with ethyl formate, and the 2-hydroxymethylene compound acetylated to (XI) and ozonised [7] to yield the seco-acid (VIIIa). Esterification with diazomethane provided (VIIIb), which was converted into the 5-ethylene dioxide (VIIIc). Carbon-2 was removed by the Barbier–Wieland degradation procedure. Ester (VIIIc) was treated with phenylmagnesium bromide and the crude product dehydrated to (IXa). After reketalisation, (IXb) was cleaved with ruthenium tetroxide–sodium periodate to (IIIb). The acid (IIIb) was esterified, and the ethylene dioxide part was removed to provide (IIIa).

The 17-keto-analogue (IIIc) was previously prepared by Sondheimer, Mechoulam, and Sprecher.[8] They have proved that this β-keto-ester is rather non-enolic, and the methoxycarbonyl part has the equatorial-1α orientation. To limit the possibility of ring-opening during the hydrolysis of (IIIa), the C-5 ketone was first reduced with sodium borohydride, then the mixture was hydrolysed. The crude product was methylated and oxidised to give (IIIc), whose physical constants were in agreement with those reported.[8]

Baeyer–Villiger oxidation of (Ib) with trifluoroperacetic acid [9] gave (Xa), which was hydrolysed and methylated to (Xb). Oxidation of (Xb) with chromic acid in acetic acid provided (IIIc) in two polymorphic forms, m. p. 128—130° and m. p. 146—148°, identical to the product derived from 19-nortestosterone.

Since the sequence of reactions described establishes the 1α-equatorial configuration of the carboxylic group in (I), our attention turned to the centre of asymmetry at C-5. In the hydrogenation product (VII), both functional groups at C-1 and C-5 must be *cis*-oriented, *i.e.*, both are either α or β. Considering that an axial acetyl group would be more susceptible to base-catalysed isomerisation than an equatorial carboxylate moiety and that the configuration of the carboxyl group in (I) and (III) is α, the indicated 1α,5α configuration for (VII) is the more likely one. Further support for this assignment is provided by the optical rotatory dispersion curves of (Ia) and (VII). The Cotton effect is essentially related

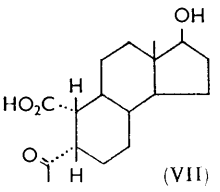
* A possible mechanism for the described oxidation of the phenol can be rationalised by assuming the initial formation of *p*-quinol (i) or *o*-quinone (ii) from (IV). These compounds on further oxidation would yield the products (I) and (V).



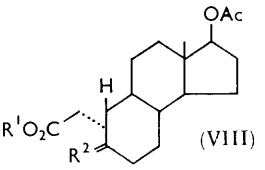
Formation of (V) requires a cleavage of the C—C bond in the α-hydroxy-acid (iii), whereas formation of (I) would proceed by the indicated decarboxylation of C-3 and reprotonation at C-10 and C-5. Obviously, alternative mechanisms can also be written.

[7] Weisenborn, Remy, and Jacobs, *J. Amer. Chem. Soc.*, 1959, **76**, 552.
[8] Sondheimer, Mechoulam, and Sprecher, *Tetrahedron Letters*, 1960, **22**, 38.
[9] Pettit, Green, Kasturi, and Ghatak, *Tetrahedron*, 1962, **18**, 953.

to the carbonyl group, *i.e.*, the acetyl moiety. A change of orientation of the acetyl group or in its immediate environment is usually associated with a pronounced modification of the Cotton effect. In contrast, should the change be associated with the carboxyl group,

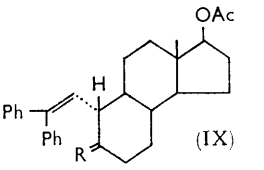


(VII)



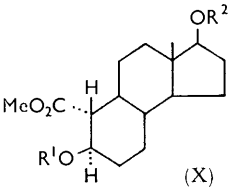
(VIII)

a: R^1 = H, R^2 = O
b: R^1 = Me, R^2 = O
c: R^1 = Me, R^2 = 



(IX)

a: R = O
b: R = 



(X)

a: R^1 = Ac, R^2 = $COCF_3$
b: R^1 = H, R^2 = H

(XI)

little or no change of the Cotton effect should be observed. As expected, the o.r.d. curves of (VII) and (Ia) and of their respective methyl esters differed considerably in shape and in amplitude.

Similar results were obtained when 1,20β-dihydroxy-4-methyl-19-norpregna-1,3,5(10)-triene (IVb) was oxidised with alkaline hydrogen peroxide. The lactol (Vb) was identified as its methyl ester (IIc), which was oxidised to (IId). The hydroxy lactol (Vb) was also oxidised to the keto-lactol (Vc). The saturated acid (Id) was similarly converted into three other compounds, (Ie), (If), and (Ig).

Experimental

Infrared spectra were taken on potassium bromide discs and chloroform solution as indicated. Ultraviolet spectra were obtained with a Cary spectrophotometer, model 14. M. p.s were determined on a hot stage apparatus and are corrected. Nuclear magnetic resonance spectra (n.m.r.) were determined for solutions in deuterochloroform, except when indicated otherwise, with tetramethylsilane as an internal standard on a Varian spectrometer, model V 4300 B. For thin-layer chromatography silica gel HF_{254}, purchased from Merck A. G., Darmstad, Germany, was used.

Oxidation of 1,17β-*Dihydroxyœstra*-1,3,5(10)-*triene* (IVa).—A solution of the phenol [10] (IVa) (16·1 g.) in methanol (330 ml.) and 2N-sodium hydroxide (440 ml.) was heated to reflux on a steam-bath. Hydrogen peroxide (35%; 440 ml.) was added dropwise during 2 hr. More sodium hydroxide (2N; 60 ml.) was added and refluxing was continued for 40 min. The mixture was cooled, water added, and the methanol removed by distillation *in vacuo*.

The basic solution was extracted with ether, then acidified with concentrated hydrochloric acid. After the acidified reaction mixture had been stored for about 30 min., it was thoroughly extracted with ether. The ether solution was first extracted with a saturated sodium hydrogen carbonate solution (3 × 200 ml.), then with 2N-sodium hydroxide (3 × 200 ml.).

Acidification of the sodium hydrogen carbonate solution with concentrated hydrochloric acid and extraction with ether gave a crude mixture (13·1 g.) from which acid (Ia) (6·7 g.) was obtained by crystallisation from methylene chloride.

Acidification of the sodium hydroxide solution and extraction with ether yielded crystalline lactol (Va) (0·89 g.).

Chromatography (silica gel) of the mother-liquors from crystallisation of the sodium hydrogen carbonate fraction gave more acid (Ia) and lactol (Va). In the several experiments performed, the overall yield of (Ia) was 40—60% and that of (Va) was 10—20%.

[10] Dreiding and Voltman, *J. Amer. Chem. Soc.*, 1954, **76**, 537.

17β-*Hydroxy*-4-*methyl*-4-*oxo*-1,4-*seco*-2,3-*bisnor*-5α-*œstran*-1-*oic Acid* (Ia).—(*a*) The acid (Ia) was isolated from the sodium hydrogen carbonate extracts of the hydrogen peroxide oxidation (from methylene chloride); it had m. p. 184—186°.

(*b*) A solution of (Va) (30 mg.) in ethyl acetate (10 ml.) containing 10% palladium–carbon (60 mg.) was shaken in an atmosphere of hydrogen for 6 hr. at 22°. The catalyst was removed and the filtrate evaporated *in vacuo*. The *cis*-acid (VII) (20 mg.) crystallised as prisms (from benzene), m. p. 146—149°; R.D. in dioxan (*c* 0·047) $[\phi]^{25}$ (350 mμ) + 21·5°; (325) − 32°; (317) − 52°; (306) + 220·5°; (304·5) + 188°; (296·5) + 342°; (290) + 227°; (288) + 266°; (280) + 78°; $\nu_{max.}$ (in KBr) 3300, 1720, 1680 cm.$^{-1}$ (Found: C, 69·3; H, 9·6. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

The methyl ester was prepared with diazomethane but resisted crystallisation; R.D. in dioxan (*c* 0·056) $[\phi]^{26}$ (450 mμ) + 11°; (400) + 82°; (350) + 202°; (325) + 427°; (301—303) + 1282°; (296) + 1363°; (287·5) + 652°.

A solution of the *cis*-acid (VII) (5 mg.) in 2N-sodium hydroxide (1 ml.) was heated at 70° for 2 hr. The acid (Ia) was recovered from the acidified, diluted solution by extraction with ethyl acetate. The product was identical (i.r. spectrum and mixed m. p.) with the above (Part *a*).

A portion of (Ia), recrystallised from methanol–ethyl acetate, had m. p. 187—189°, $[\alpha]_D^{20}$ 0·0° (in dioxan); R.D. in dioxan (*c* 0·048) $[\phi]^{24}$ (450 mμ) + 81°; (400) + 247°; (350) + 524°; (325) + 995°; (301) + 2585°; (280) − 203°; $\nu_{max.}$ (in KBr) 3440 and 1695 cm.$^{-1}$ (Found: C, 69·2; H, 8·7. $C_{17}H_{26}O_4$ requires C, 69·4; H, 8·9%).

Treatment of (Ia) with ethereal diazomethane gave (Ib) as fine needles (from ethyl acetate–hexane), m. p. 129—130°, $[\alpha]_D^{20}$ +24·0° (in dioxan); R.D. in dioxan (*c* 0·10) $[\phi]^{26}$ (450 mμ) + 103°; (400) + 212°; (350) + 543°; (325) + 1148°; (305) + 2990°; (303·5) + 2980°; (300·5) + 3030°; (275) − 1770°; $\nu_{max.}$ (in KBr) 3400, 1730, 1695, and 1260 cm.$^{-1}$ (Found: C, 69·9; H, 8·9. $C_{18}H_{28}O_4$ requires C, 70·1; H, 9·2%).

The methyl ester (Ib) was acetylated with pyridine–acetic anhydride to (Ic), which crystallised from methylene chloride–hexane as crystals, m. p. 127—129°, $[\alpha]_D^{20}$ +16·4° (in dioxan); τ 6·34, 7·86, 7·96, and 9·18 (Found: C, 68·7; H, 8·2. $C_{20}H_{30}O_5$ requires C, 68·5; H, 8·6%).

17β-*Hydroxy*-4-*methyl*-4-*oxo*-1,4-*seco*-2,3-*bisnorœstra*-5(10)-*en*-1-*oic Acid* (Va).—The lactol (Va), isolated from the acidified sodium hydroxide extracts of the oxidation, crystallised as needles (from ethyl acetate), m. p. 218—220°, $[\alpha]_D^{20}$ +83·5° (in dioxan), $\lambda_{max.}$ (in MeOH) 215 mμ (ε 8000); $\nu_{max.}$ (in KBr) 3580, 3360, 1760, 1740, 1720, and 1665 cm.$^{-1}$; τ (in CD_3·OD) 8·45 (4-Me), 9·22 (18-Me) (Found: C, 69·8, 70·2; H, 8·4, 8·7. $C_{17}H_{24}O_4$ requires C, 69·8; H, 8·3%).

Methylation of (Va) with ethereal diazomethane yielded (IIa) as fine needles (from ethyl acetate–pentane), m. p. 135—137°, $\lambda_{max.}$ (in MeOH) 240 mμ (ε 5500); $\nu_{max.}$ (in KBr) 3540, 1720, and 1620 cm.$^{-1}$; τ 6·23 (O–Me), 7·76 (Me), 9·22 (18-Me) (Found: C, 71·1; H, 8·8. $C_{18}H_{26}O_4$ requires C, 70·6; H, 8·6%).

Acetylation of (IIa) with pyridine–acetic anhydride and crystallisation from methylene chloride–hexane resulted in a sample of (IIb), m. p. 113—114°, $[\alpha]_D^{20}$ +56·6° (in dioxan), $\lambda_{max.}$ (in MeOH) 240 mμ (ε 5300); $\nu_{max.}$ (in KBr) 1730, 1720, 1680, 1610, and 1235 cm.$^{-1}$ (Found: C, 68·8; H, 8·1. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%).

Oxidation of (Va).—To a mixture of potassium permanganate (250 mg.) in acetone (10 ml.) was added (Va) (100 mg.). The mixture was stirred at room temperature for 4 hr. After dilution with water the steroids were dissolved in ether and partitioned with a saturated sodium hydrogen carbonate solution. The acids were recovered with ether and the crude residue was methylated with diazomethane. The mixture was then resolved by thin layer chromatography (ethyl acetate–chloroform; 2 : 3) into two products.

Hydrolysis of the more mobile material gave the *dicarboxylic acid* (VIa) (from ethyl acetate), m. p. 183—185°, $\nu_{max.}$ (in KBr) 1730 and 1700 cm.$^{-1}$ (Found: C, 63·0; H, 7·6. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5%).

The less mobile material was hydrolysed with aqueous methanolic sodium hydroxide to the *dicarboxylic acid* (VIb) (from ethyl acetate), m. p. 168—172° $\nu_{max.}$ (in KBr) 3330, 1715, and 1670 cm.$^{-1}$ (Found: C, 62·3; H, 8·1. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%).

Methyl 5β-*Acetoxy*-17β-*trifluoroacetoxy*-1,5-*seco*-2,3,4-*trisnorœstran*-1-*oate* (Xa).—A solution of trifluoroperacetic acid (prepared from 3·0 ml. of trifluoroacetic anhydride and 0·3 ml. of 90% hydrogen peroxide) in methylene chloride (20 ml.) was added during 15 min. to a stirred, cooled

(ice-bath) mixture of (Ib) (1·00 g.), anhydrous disodium hydrogen phosphate (2·00 g.), and dry methylene chloride (25 ml.). The mixture was then stirred for 3 hr. at room temperature. After termination of the reaction with ice, the product was dissolved in ether, washed with a saturated sodium hydrogen carbonate solution, and water, then dried. Removal of the ether *in vacuo* left an oil (900 mg.), which crystallised from ethyl acetate as crystals, m. p. 154—156°, $[\alpha]_D^{20}$ 0·0° (in dioxan); $\nu_{max.}$ (in KBr) 1780 and 1730 cm.$^{-1}$ (Found: C, 57·5; H, 6·5. $C_{20}H_{27}O_6F_3$ requires C, 57·1; H, 6·3%).

Methyl 5β,17β-*Dihydroxy*-1,5-*seco*-2,3,4-*trisnorœstran*-1-*oate* (Xb).—A solution of (Xa) (612 mg.) in 2N-sodium hydroxide (25 ml.) and methanol (25 ml.) was heated at reflux for 2 hr. The solution was acidified with 2N-hydrochloric acid and diluted with water. Extraction of the mixture with ether gave crystalline acid material (410 mg.) which was methylated with diazomethane to yield fine crystals (from ethyl acetate), m. p. 158—159°, $[\alpha]_D^{20}$ 0·0° (in dioxan); $\nu_{max.}$ (in KBr) 3290 and 1730 cm.$^{-1}$; τ 6·27 (–O–Me) and 9·25 (18-Me) (Found: C, 67·9; H, 9·3. $C_{16}H_{26}O_4$ requires C, 68·1; H, 9·3%).

Methyl 5,17-*Dioxo*-1,5-*seco*-2,3,4-*trisnorœstran*-1-*oate* (IIIc).—(*a*) The diol ester (Xb) (90 mg.) was oxidised by chromium trioxide (200 mg.) in 90% aqueous acetic acid (5·0 ml.) at room temperature for 4 hr. The excess of chromium trioxide was destroyed with methanol, and the mixture was diluted with water. The steroid was recovered in methylene chloride, washed with a saturated sodium hydrogen carbonate solution, and dried. Removal of the methylene chloride *in vacuo* gave flat needles (from ethyl acetate–hexane), m. p. 128—130°, or prisms (from ethyl acetate–heptane), m. p. 146—148°; $\nu_{max.}$ (in $CHCl_3$) 1740 and 1713 cm.$^{-1}$ (Found: C, 68·5; H, 7·7. $C_{16}H_{22}O_4$ requires C, 69·0; H, 7·9%). Infrared spectra of the two forms were identical in solution, but different in potassium bromide discs.

(*b*) A solution of (IIIa) (50 mg.) in water (0·3 ml.) and methanol (3·0 ml.) was treated with sodium borohydride (30 mg.), then stored at room temperature for 3 days. The mixture was diluted with water and acidified, and the steroids were isolated by extraction with ethyl acetate. The extract was refluxed for 30 min. in sodium hydroxide (2N; 2 ml.) and methanol (2 ml.). Acidification and extraction with ethyl acetate gave an oil, which failed to crystallise and was methylated with diazomethane. The ester was oxidised with a 4% solution of chromium trioxide in 90% aqueous acetic acid (5·0 ml.). The reaction was terminated and processed as in (*a*) above to give colourless prisms (35 mg.; from ethyl acetate–hexane), m. p. 146—148°, or needles, m. p. 128—130°.

A mixture melting point and infrared spectra (in $CHCl_3$) substantiated that the product was identical to that obtained in (*a*) above.

17β-*Acetoxy*-2-*acetoxymethyleneœstr*-4-*en*-3-*one* (XI).—A mixture of 19-nortestosterone (15·8 g.), sodium hydride (8·0 g.), ethyl formate (37 ml.), and dry benzene (400 ml.) was stirred at room temperature for 4 hr. in an atmosphere of nitrogen, then stored for 20 hr. After the addition of water (about 200 ml.), unchanged starting material was removed by extraction of the basic solution with ether. The basic solution was acidified with 2N-hydrochloric acid, and the 2-hydroxymethylene-19-nortestosterone was isolated by extraction with ether. The crude material was acetylated with pyridine–acetic anhydride [yield of crude diacetate, 23·0 g. (syrup)]. Column chromatography (silica gel) of a portion of the syrup gave colourless crystals (from ethyl acetate–pentane), m. p. 134—137°, $\lambda_{max.}$ (in MeOH) 261 mμ (ε 12,900); $\nu_{max.}$ (in KBr) 1760, 1730, 1670, 1610, 1240, and 1185 cm.$^{-1}$ (Found: C, 71·2; H, 7·9. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8).

Methyl 17β-*Acetoxy*-5-*oxo*-2,5-*seco*-3,4-*bisnorœstran*-2-*oate* (VIIIb).—Crude acetoxymethylene-19-nortestosterone 17-acetate (IX; 13·5 g.) was ozonised for 3 hr. at −70° in methylene chloride (300 ml.). The course of ozonisation was followed by the disappearance of the peak at 260 mμ. The reaction was terminated by adding the mixture to one of zinc dust (24 g.) and glacial acetic acid (250 ml.) and stirring for 16 hr. at room temperature. The excess of zinc dust was collected on Celite by filtration, water was added to the filtrate, and the volume of solution was reduced by distillation *in vacuo*. The steroids were taken up into ether and washed with water.

The crude steroid mixture was then treated in methanol (300 ml.) with a solution of periodic acid (5·0 g.) in water (15 ml.) for 3 hr. The steroids were recovered from the water-diluted mixture with ether. The acid portion (7·5 g.) was isolated *via* a saturated aqueous sodium hydrogen carbonate solution.

The acid fraction was methylated with ethereal diazomethane and reacetylated with

pyridine–acetic anhydride. Chromatography of the methyl ester on silica gel (300 g.) and crystallisation of the fractions eluted with 60% chloroform–benzene from acetone gave crystalline material (970 mg.), m. p. 149—151°, $[\alpha]_D^{20}$ −35·6° (in dioxan); $\nu_{max.}$ (in KBr) 1730 and 1710 cm.$^{-1}$ (Found: C, 68·0; H, 9·1. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·4%).

Methyl 17β-*Acetoxy*-5-*ethylenedioxy*-2,5-*seco*-3,4-*bisnorœstran*-2-*oate* (VIIIc).—A mixture of methyl 17β-acetoxy-5-oxo-2,5-seco-3,4-bisnorœstran-2-oate (VIIIb; 100 mg.), toluene-*p*-sulphonic acid (20 mg.), ethylene glycol (2 ml.), and benzene (50 ml.) was heated at reflux for 18 hr. The water formed during the reaction was collected in a Dean–Stark tube. The cooled reaction mixture was treated with sodium hydrogen carbonate, and the product was isolated by extraction with ether. Chromatography of the ether residue on thin-layer chromatograms (10% ethyl acetate–chloroform) gave colourless crystals (100 mg.) (from benzene–hexane), m. p. 107—109°, $[\alpha]_D^{20}$ 0·0° (in dioxan); $\nu_{max.}$ (in KBr) 1740, 1730, 1265, 1245, and 1060 cm.$^{-1}$ (Found: C, 66·6; H, 8·6. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·5).

17β-*Acetoxy*-2,2-*diphenyl*-2,5-*seco*-3,4-*bisnorœstr*-1-*en*-5-*one* (IXa).—To the phenylmagnesium bromide prepared from magnesium (141 mg.) and bromobenzene (0·5 ml.) in ether (20 ml.) was added a solution of (VIIIc) (100 mg.) in ether (10 ml.). The mixture was heated at reflux for 2 hr., then stirred overnight at ambient temperature. Solid ammonium chloride was introduced to terminate the reaction, and the organic compounds were isolated by extraction with ether. After removal of the by-products by steam distillation, the recovered steroids were dissolved in glacial acetic acid (10 ml.) and heated at reflux for 2 hr. The crude product was recovered from the water-diluted mixture with ether.

Two components were isolated from the mixture on thin-layer chromatography (chloroform). In addition to (IXa), the 17β-hydroxy-compound was obtained, and the products were correlated by acetylation. The combined yield was 96 mg. of fine needles (from methanol), m. p. 156—160°, $\lambda_{max.}$ (in MeOH) 250 mμ (ε 16,100); $\nu_{max.}$ (in KBr) 1730, 1700, 1600, 1490, and 1245 cm.$^{-1}$ (Found: C, 81·6; H, 7·7. $C_{30}H_{34}O_3$ requires C, 81·4; H, 7·7%).

17β-*Acetoxy*-5-*ethylenedioxy*-2,2-*diphenyl*-2,5-*seco*-3,4-*bisnorœstr*-1-*ene* (IXb).—A mixture of (IXa) (100 mg.), toluene-*p*-sulphonic acid (20 mg.), ethylene glycol (2 ml.), and benzene (50 ml.) was heated at reflux, and the water formed was removed with a Dean–Stark tube. The solution was cooled, and sodium hydrogen carbonate added. Isolation of the steroids with ether gave a residue (92 mg.), which crystallised from methanol as crystals, m. p. 117—120°, $[\alpha]_D^{20}$ +114·7° (in dioxan), $\lambda_{max.}$ (in MeOH) 250 mμ (ε 16,500); $\nu_{max.}$ (in KBr) 1735, 1600, 1490, 1250, and 1040 cm.$^{-1}$ (Found: C, 79·2; H, 7·9. $C_{32}H_{38}O_4$ requires C, 79·0; H, 7·9%).

17β-*Acetoxy*-5-*ethylenedioxy*-1,5-*seco*-2,3,4-*trisnorœstran*-1-*oic Acid* (IIIb).—To a solution of (IXb) (100 mg.) in acetone (20 ml.) containing a trace of sodium periodate was added ruthenium tetroxide [11] (prepared from 400 mg. of ruthenium trichloride) in carbon tetrachloride (15 ml.). The mixture was stirred for 2 hr., whilst solid sodium periodate (100 mg.) was added portionwise. The excess of ruthenium tetroxide was decomposed with a little isopropyl alcohol, and the solids were collected on Celite. The filtrate was diluted by extraction with ether, and the steroids were partitioned into neutral and acidic fractions with 2N-sodium carbonate. The carbonate solution was acidified with 2N-hydrochloric acid, and the steroidal acids were isolated with ether.

The acid (IIIb) (68 mg.) was obtained as crystals (from ethyl acetate), m. p. 201—207° (decomp.), $[\alpha]_D^{20}$ +20·6° (in dioxan); $\nu_{max.}$ (in KBr) 3270, 1755, 1730, 1720, 1660, 1245, and 1045 cm.$^{-1}$ (Found: C, 64·9; H, 7·9. $C_{19}H_{28}O_6$ requires C, 64·8; H, 8·0%).

Methyl 17β-*Acetoxy*-5-*oxo*-1,5-*seco*-2,3,4-*trisnorœstran*-1-*oate* (IIIa).—The β-ethylenedioxy-acid (IIIb) (430 mg.) was dissolved in ether and methylated with diazomethane. The crude product was then taken up in methanol (12 ml.) and treated at reflux with 2N-sulphuric acid (4 ml.) for 1 hr. Water was added and the product was isolated with ether. After reacetylation the β-keto-ester (IIIc) (378 mg.) crystallised readily as plates (from ethyl acetate–pentane), m. p. 152—155°, $[\alpha]_D^{20}$ 0·0° (in dioxan), $\nu_{max.}$ (in KBr) 1735, 1700, 1260, and 1250 cm.$^{-1}$ (Found: C, 67·3; H, 8·2. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·1%).

Oxidation of 1,20β-*Dihydroxy*-4-*methyl*-19-*norpregna*-1,3,5(10)-*triene* (IVb).—To a solution of (IVb) (30 g.) in 2N-sodium hydroxide (57 ml.) and methanol (45 ml.) at reflux (steam-bath) 35% hydrogen peroxide (57 ml.) was added during 1 hr. An additional amount of 2N-sodium hydroxide (10 ml.) was introduced, and heating at reflux was continued for 0·5 hr. The mixture

[11] Dean and Knight, *J.*, 1962, 4745.

was then diluted with water, and the methanol was removed *in vacuo*. The basic solution was extracted with ether to remove neutral material. After acidification, the water portion was extracted with ether to recover the acidic steroids. The steroids were then partitioned into sodium hydrogen carbonate and sodium hydroxide soluble portions as previously described for (IVa).

The sodium hydroxide soluble material (2·63 g.) crystallised easily as its methyl ester (IIc).

The material (19·9 g.) soluble in sodium hydrogen carbonate yielded 1·41 g. of crystalline (Id) (from methylene chloride). Chromatography of the mother-liquors on silica gel gave an additional amount of (Id) (5·4 g.).

Methyl 20β-*Hydroxy*-4-*methyl*-4-*oxo*-1,4-*seco*-2,3,19-*trisnorpregn*-5(10)-*en*-1-*oate* (IIc).—The ester (IIc) was obtained crystalline upon methylation of (Vb). The product crystallised from ethyl acetate–pentane as fine needles, m. p. 161—165°, $[\alpha]_D^{20}$ +26·0° (in dioxan), $\lambda_{max.}$ (in MeOH) 240 mμ (ε 5500); $\nu_{max.}$ (in KBr) 3510, 1710, 1685, and 1615 cm.$^{-1}$ (Found: C, 72·0; H, 9·2. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%).

Methyl 4-*Methyl*-4,20-*dioxo*-1,4-*seco*-2,3,19-*trisnorpregn*-5(10)-*en*-1-*oate* (IId).—The 20β-hydroxy-ester (IIc) (200 mg.) was oxidised in pyridine (5 ml.) with a mixture of chromium trioxide (200 mg.) in pyridine (10 ml.). The mixture was stored for 3 hr. at ambient temperature, then diluted with ethyl acetate. The solids were filtered off through Celite and washed with ethyl acetate. The filtrate was washed with 2N-hydrochloric acid and a saturated sodium hydrogen carbonate solution, dried over sodium sulphate, and evaporated *in vacuo*.

Purification of the crude product by thin-layer chromatography (10% ethyl acetate–chloroform) gave crystals (123 mg.) (from ethyl acetate–pentane), m. p. 132—134°, $[\alpha]_D^{20}$ +127·1° (in dioxan), $\lambda_{max.}$ (in MeOH) 240 mμ (ε 6100); $\nu_{max.}$ (in KBr) 1720, 1685, and 1625 cm.$^{-1}$ (Found: C, 72·2; H, 8·5. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%).

4-*Methyl*-4,20-*dioxo*-1,4-*seco*-2,3,19-*trisnorpregn*-5(10)-*en*-1-*oic Acid* (Vc).—A portion of (IIc) (767 mg.) was hydrolysed in methanol (40 ml.) with 2N-sodium hydroxide (10 ml.). The crude product was oxidised directly with chromium trioxide (830 mg.) in pyridine (20 ml.). The oxidation was carried out as described for (IIIc), except for washing with sodium hydrogen carbonate.

The product crystallised from ethyl acetate as fine needles, m. p. 181—183°, $[\alpha]_D^{20}$ +140·2° (in dioxan), $\lambda_{max.}$ (in MeOH) 215 mμ (ε 7050); $\nu_{max.}$ (in KBr) 3390, 1740, and 1680 cm.$^{-1}$ (Found: C, 71·9; H, 8·1. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%).

Methyl 20β-*Hydroxy*-4-*methyl*-4-*oxo*-1,4-*seco*-2,3,19-*trisnor*-5α-*pregnan*-1-*oate* (Ie).—The sodium hydrogen carbonate soluble acid from the oxidation of (IVb) was methylated with diazomethane. Chromatography of the material on silica gel gave (Ie), which was eluted from the column with 50% benzene–chloroform. A portion crystallised from ethyl acetate–pentane as crystals, m. p. 130—133°, $[\alpha]_D^{20}$ 0·0° (in dioxan), $\nu_{max.}$ (in KBr) 3490, 1720, and 1690 cm.$^{-1}$ (Found: C, 71·2; H, 9·4. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%).

Methyl 4-*Methyl*-4,20-*dioxo*-1,4-*seco*-2,3,19-*trisnor*-5α-*pregnan*-1-*oate* (If).—A sample of (Ie) (115 mg.) in pyridine (3 ml.) was oxidised with chromium trioxide (150 mg.) in pyridine (5 ml.). The reaction was performed as previously described. The dioxo-ester crystallised as fine needles (from isopropyl ether–pentane), m. p. 110—111°, $[\alpha]_D^{20}$ +67·9° (in dioxan), $\nu_{max.}$ (in KBr) 1720 and 1690 cm.$^{-1}$ (Found: C, 71·7; H, 8·9. $C_{20}H_{32}O_4$ requires C, 71·8; H, 9·0%).

4-*Methyl*-4,20-*dioxo*-1,4-*seco*-2,3,19-*trisnor*-5α-*pregnan*-1-*oic Acid* (Ig).—A crude sample of (Id) (770 mg.) in pyridine (9·0 ml.) was oxidised by a mixture of chromium trioxide (760 mg.) and pyridine (9·0 ml.). The acid was obtained as flat needles (from ethyl acetate), m. p. 200—205°, $[\alpha]_D^{20}$ +86·4° (in dioxan), $\nu_{max.}$ (in KBr) 3200, 1725, 1690, and 1665 cm.$^{-1}$ (Found: C, 71·1; H, 8·7. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

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