Tetrahedron, 1966, Vol. 22, pp. 3459 to 3467. Pergamon Press Ltd. Printed in Northern Ireland

TRANSFORMATIONS OF FUSIDIC ACID—II

11-DESOXY-4α,8,14-TRIMETHYL-18-NOR-ANDROSTANES[1]

P. A. DIASSI, I. BACSO, G. W. KRAKOWER and H. ANN VAN DINE
The Squibb Institute for Medical Research, New Brunswick, New Jersey

(*Received* 9 *February* 1966)

Abstract—Ozonolysis of methyl fusidate diacetate or methyl 24,25-dihydrofusidate diacetate followed by reaction with zinc–acetic acid leads to 3α-acetoxy-4α,8,14-trimethyl-18-nor-5α,8α,9β,14β-androst-12-en-17-one (V), 3α-acetoxy-4α,8,14-trimethyl-18-nor-5α,8α,9β,14β-androst-12,15-dien-17-one (VI) and 3α,11α-diacetoxy-4α,8,14-trimethyl-18-nor-5α,8α, 9β,14β-androst-15-en-17-one (VII). The mechanism of formation of these compounds is discussed. Alkaline equilibration of the 13-epimeric 3α-hydroxy-17-ketones XII and XIII gives a 60:40 mixture of the *trans* and *cis* isomers respectively.

FUSIDIC ACID (I) offers a unique stereochemical arrangement for the perhydrocyclopentanophenanthrene ring system in which ring B is forced into a boat conformation by the *trans–syn–trans* arrangement of rings A, B and C and equilibrations in this system have been the subject of a number of recent publications.[1–5] We would like to report the preparation of some 11-desoxy compounds in this series and their equilibration.

The ozonolysis of fusidic acid or its derivatives in which the 11α-hydroxyl group is unprotected results in considerable oxidation of the 11α-hydroxyl group to the 11-ketone.[2,3] In order to avoid this oxidation we have ozonized methyl 24,25-dihydrofusidate diacetate (II) and methyl fusidate diacetate (III). The product obtained from II after mild reductive work-up was the triacetoxy ketone (IV). By refluxing IV in zinc and acetic acid or by direct ozonolysis of III followed by zinc–acetic acid reduction three products could be detected by UV light on TLC. The major product (20% yield) analysed for $C_{23}H_{34}O_3$ corresponding to the reductive removal of one acetoxy group and elimination of the other. The compound had carbonyl bands at 5·82 and 5·85 μ and a strong double bond band at 6·10 μ in the IR and showed a UV maximum at 245 mμ (ε, 9500) indicating a cisoid α,β-unsaturated ketone. The NMR spectrum had chemical shifts for the three tertiary methyl groups at 8·98, 8·95 and 8·83 τ, and the 4α-methyl at 9·15 τ (d, J = 6), the 3α-acetate methyl at 7·93 τ and the 3β-H at 5·09 τ. In addition a single vinyl proton appeared as a multiplet at 3·37 τ and based on these data we have assigned this compound the Δ^{12}-17-ketone[6] structure V.

[1] Paper I in this series, P. A. Diassi, G. W. Krakower, I. Bacso and H. A. Van Dine, *Tetrahedron* **22**, 3443 (1966).

[2] W. O. Godtfredsen and S. Vangedal, *Tetrahedron* **18**, 1029 (1962).

[3] W. O. Godtfredsen, W. von Daehne, S. Vangedal, A. Marquet, D. Arigoni and A. Melera, *Tetrahedron* **21**, 3505 (1965).

[4] D. Arigoni, W. von Daehne, W. O. Godtfredsen, A. Melera and S. Vangedal, *Experientia* **20**, 344 (1964).

[5] R. Bucort and M. Legrand, *C.R. Acad. Sci., Paris* **258**, 3491 (1964).

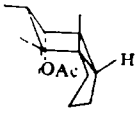
[6] A compound having a similar UV spectrum has been obtained by B. M. Baird, T. G. Halsall, E. R. H. Jones and G. Lowe, *Proc. Chem. Soc.* 257 (1961) on ozonolysis and acid treatment of the dihydromethylester of Cephalosporin P and is assigned a Δ^{13}-17-one structure.

A second slightly more polar band gave a compound which differed from V in that it analysed for $C_{23}H_{32}O_3$. It absorbed at 247 mμ (ε, 9300) and the NMR spectrum showed besides the three tertiary methyls at 9·19, 8·93 and 8·80 τ, the 4α-methyl at 9·14 τ (d, J = 5), the 3-acetate methyl at 7·95 τ, and the 3β-H at 5·08 τ, three vinyl protons; a singlet at 3·50 τ and two doublets at 3·81 (J = 6) and 2·51 τ (J = 6) respectively. The chemical shifts of the three vinyl protons together with the UV spectrum indicated a cross conjugated dienone in which one of the alpha carbons was completely substituted and this was further substantiated by the IR spectrum which showed carbonyl stretching frequencies at 5·80 μ (3-acetate) 5·94 μ (17-carbonyl) and two double bond bands 6·08 and 6·40 μ. On this basis we have assigned structure VI to this compound. Catalytic hydrogenation of V and VI led to the same saturated keto acetate IX which has been assigned the 13β-configuration by analogy with other reductions[5] in this series (see below). Hydrolysis of VI gave the corresponding 3α-ol (X) which could be oxidized with Jones reagent[7] to the diene–dione (XI).

A third yet more polar compound was obtained in very small yield (<1%). This compound had the empirical formula $C_{25}H_{36}O_5$ and showed a UV maximum at 226 mμ (ε, 8400). The NMR spectrum had the three tertiary methyls at 8·92, 8·88 and 8·78 τ, the 4α-methyl at 9·17 τ (d, J = 6), two acetate methyls which appeared as one band at 8·00 τ, the 3β-hydrogen at 5·10 τ and the 11β-hydrogen at 4·87 τ. In addition two vinyl protons were apparent, both doublets (J = 6) at 3·92 and 2·60 τ. Based on these data the compound has been assigned structure VII and the vinyl protons assigned to positions 16 and 15 respectively.

Catalytic hydrogenation of VII using 5% palladium-on-carbon as catalyst gave the dihydro compound VIII which was shown to have the 13β-configuration since the ORD curve had a positive Cotton effect which corresponds in sign to a 3-keto-5β-A-norsteroid.[3,8] Thus VII must also have the 13β-configuration and the conversion of IV to VII involves inversion at this center as has previously been observed on refluxing 13α-17-ketones in zinc and acetic acid.[1]

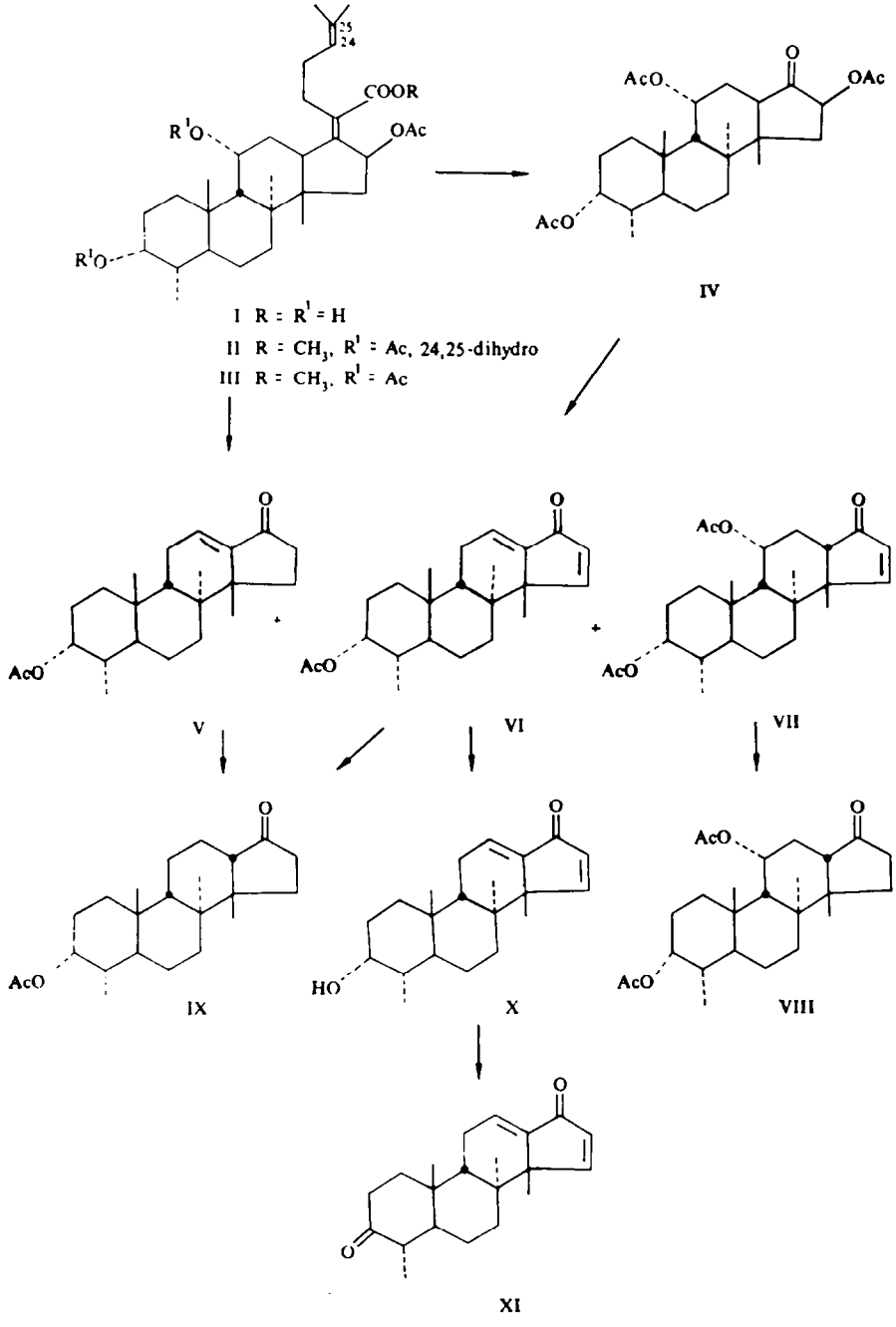
Epimerization at C-13 can be an important factor in the relative ease of elimination of the 11-acetoxy group due to the presence of three 1,3-diaxial interactions (8-CH_3, 11-OAc and C-13:C-17) in the 13β-isomer "i". The pyrolytic cis elimination of the acetoxy group would then give a Δ^{11}-β,γ-unsaturated ketone which on conjugation would give the Δ^{12}-ene-17-one. It would be attractive to suggest that VII is the precurser to VI and that refluxing IV in acetic acid alone would be sufficient to produce these compounds. This hypothesis as yet has not been tested.



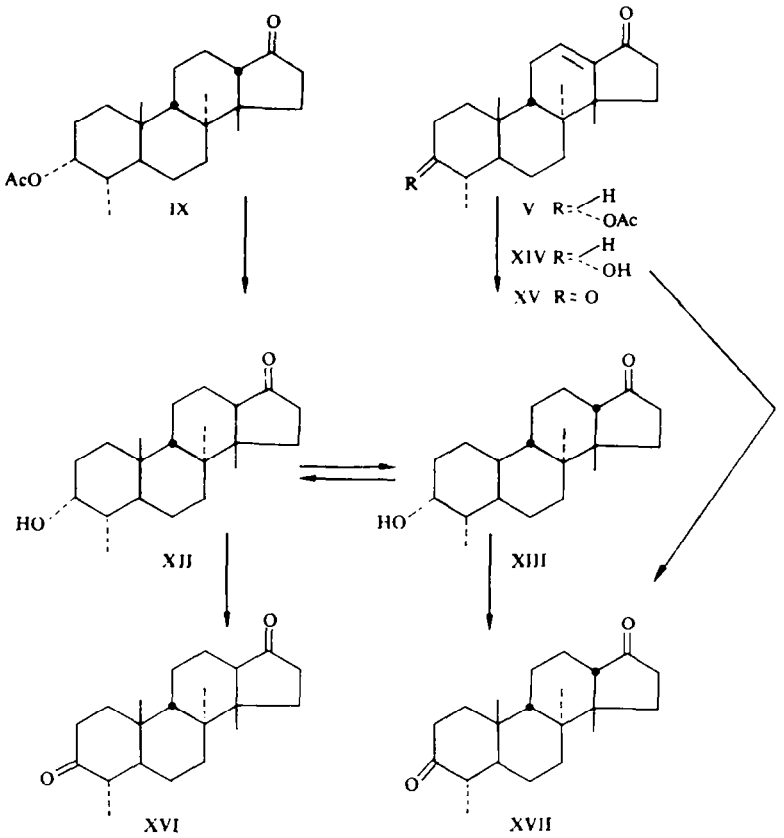
"i"

Formation of V involves both elimination and reduction. At this point it is not possible to say which acetoxy group is eliminated and which is reduced since mechanisms can be written for both cases.

[7] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).
[8] I. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **84**, 4356 (1962).


25
24
COOR
R¹O
OAc
R¹O
AcO
O
OAc
AcO
IV
I R = R¹ = H
II R = CH₃, R¹ = Ac, 24,25-dihydro
III R = CH₃, R¹ = Ac
O
AcO
V
O
AcO
VI
O
AcO
AcO
VII
O
AcO
IX
O
HO
X
O
AcO
AcO
VIII
O
O
XI

Hydrolysis of IX by refluxing in dilute alkali gave two epimeric products in the ratio of 3:2 which were separable by TLC. The less polar and major product XII showed a negative Cotton effect on ORD and has been assigned to 13α (C/D *trans*) structure since it is antipodal to those recorded for C/D *trans* 17-ketosteroids.[8,9] The other product XIII showed a positive Cotton effect and is assigned the 13β (C/D *cis*) structure XIII. Equilibration of XII and XIII was also determined by measuring the

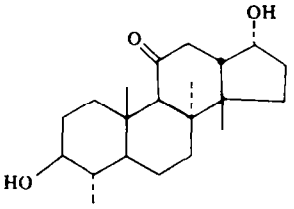


rotation of the optical rotatory dispersion maxima after addition of potassium hydroxide to methanolic solutions of each compound. Equilibration occurred after about three hours at room temperature and indicated a ratio of 40% XIII and 60% XII. Compound XIII alone was obtained when the ene-one V was first hydrolysed and then hydrogenated. Oxidation of XII and XIII with Jones reagent gave the corresponding diketones XVI and XVII. The latter compound could also be obtained by oxidation of XIV to XV followed by catalytic reduction.

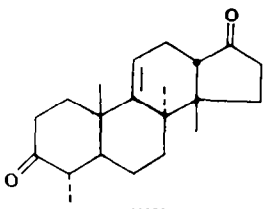
The 9β-configuration in this series of compounds is inferred from the mechanism of formation (see above) which should not involve the 9-position and the position of equilibrium of XII and XIII which corresponds to other 9β- and $\Delta^{9(11)}$-compounds of this series[1,2] as well as similar compounds in the dammarane series.[10] Had these

[9] K. Heusler, J. Kalvoda, Ch. Meyster, G. Anner and K. Wettstein, *Helv. Chim. Acta* **45**, 2161 (1962).
[10] J. F. Biellmann, P. Crabbe and G. Ourisson, *Tetrahedron* **3**, 303 (1958).

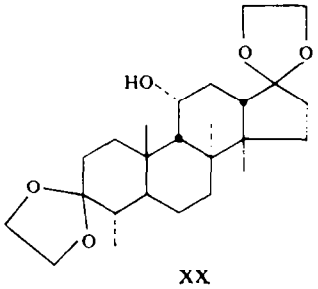
compounds been in the 9α-series the equilibration should lead primarily to the 9α,13β-isomer.[1] Attempts to obtain this series of compounds from the 11-oxygenated compounds previously described failed. Reaction of the 11-keto-3,17-dihyroxy compounds (XVIII) with ethanedithiol failed to give the thioketal. Catalytic hydrogenation of the $\Delta^{9(11)}$-3,17-diketone (XIX) was unsuccessful and attempts to prepare the mesylate of the 11-hydroxy-bisketals (XX) and (XXI) led only to the $\Delta^{9(11)}$-compound (XXII).



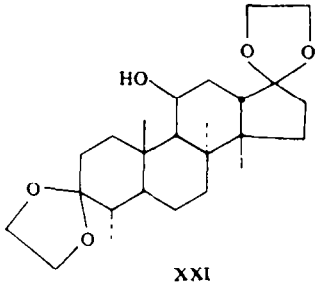
XVIII



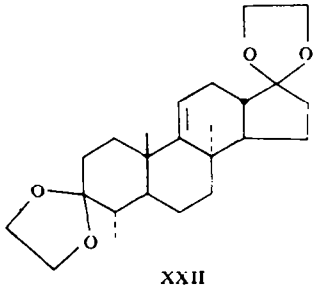
XIX



XX



XXI



XXII

EXPERIMENTAL

M.ps are uncorrected. UV spectra were measured with a Cary 11 Spectrometer. The IR spectra were recorded with a Perkin–Elmer Model 237 Spectrophotometer (reported in cm^{-1}) or with a Perkin–Elmer Model 21 Spectrophotometer (reported in μ). Optical rotations were taken in $CHCl_3$ soln at room temp unless otherwise noted on a Perkin–Elmer Model 141 Polarimeter. NMR spectra were measured in $CDCl_3$ soln using Me_4Si as an internal standard on a Varian Associates A-60. ORD curves were obtained through the courtesy of Prof. Ajay Bose, Stevens Institute of Technology, using a Rudolph Spectropolarimeter.

Methyl 24,25-dihydrofusidate 3,11-*diacetate* (II)

(a) To 20 ml of a soln prepared from 10 g of *p*-toluenesulfonic acid monohydrate in a mixture of 20 ml of acetic anhydride and 40 ml of glacial AcOH, 4·0 g of methyl dihydrofusidate[2] were added and the mixture kept at room temp for 20 min. Water was then added and the oil which separated

was extracted with $CHCl_3$. The $CHCl_3$ was washed several times with water and evaporated under red. press. Crystallization of the residue from MeOH gave 3·5 g of II having a melting point of 159–160° λ_{max}^{Nujol} 5·80–5·84 μ, τ 4·15 (d, J = 8, 16α-H), 4·72 (m, 11β-H), 5·08 (m, 3β-H), 6·35 (s, OCH_3), 7·95 (s, OAc), 7·99 (s, OAc), 8·02 (s, OAc), 8·63 (s, CH_3), 9·00 (s, CH_3), 9·05 (s, CH_3), 9·15 (d, J = 6, 4α-CH_3), $[\alpha]_{589}$ −21°, $[\alpha]_{578}$ −22°, $[\alpha]_{546}$ −24°, $[\alpha]_{436}$ −34°, $[\alpha]_{365}$ −34°. (Found: C, 70·06; H, 9·12. $C_{36}H_{54}O_8$ requires: C, 70·10; H, 9·15%.)

(b) Methyl fusidate,[1] 1·00 g, was added to 5 ml of an acetylating solution (prepared as in a) and kept at room temp for 20 min. Water was added to the mixture and amorphous material separated. The supernatant soln was decanted and the residue taken up in CH_2Cl_2, washed with water, dried and evaporated to give, 1·037 g of substance which could not be induced to crystallize. A preparative TLC of this material was done on neutral alumina (Activity V) using hexane–$CHCl_3$ (2:1) as the developing solvent. Inspection UV light showed two major bands. The less polar band was eluted to give 602 mg of amorphous *methyl fusidate, diacetate*. Analytical TLC of the material as described above showed a single spot.

Six hundred mg of this material and 125 mg of 5% Pd–$CaCO_3$ in 10 ml of absolute EtOH were hydrogenated at room temp for 2 hr at which time the uptake of H_2 had slowed considerably. The soln was filtered and evaporated and 541 mg of material were recovered. Recrystallization from MeOH gave 306 mg of II, m.p. 157–159° and identical in all respects to the material obtained in (a).

3α,11α,16β-*Triacetoxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,13α,14β,*androstan*-17-*one* (IV)

(a) Through a soln of 3·5 g of II in 72 ml of CH_2Cl_2 and 0·7 ml of pyridine cooled in an acetone–dry ice bath 25·4 l. of ozonized oxygen (1·12 mmol O_2/l.) were passed at a rate of 0·25 l. per min. The blue soln was then brought to room temp and 3·5 g of Zn dust and 7·0 ml of glacial AcOH were added and the suspension stirred for 90 min. The mixture was filtered and the filtrate diluted with $CHCl_3$ which was then washed several times with water and evaporated under red. press. to give 2·91 g of a colorless oil.

A small portion of this oil on TLC using neutral aluminum (Activity V) as adsorbent and $CHCl_3$ as the developing solvent on detection with iodine vapor showed several products. The main spot ($R_f \approx 0·5$) on preparative plate chromatography showed a hydroxyl band in the IR and could not be induced to crystallize. A portion (55 mg) of the original oil was therefore dissolved in 2 ml of acetone and treated with a few drops of Jones reagent[7] until it was no longer decolorized. The mixture was then diluted with water and extracted with $CHCl_3$ which was evaporated and the residue plate chromatographed as described above to give 33 mg of IV having a m.p. of 149–151°, λ_{max}^{Nujol} 5·74, 5·84 μ, τ 4·72 (m, *H*COAc), 5·10 (m, *H*COAc), 7·86 (s, OAc), 7·92 (s, OAc), 7·98 (s, OAc), 8·50 (s, CH_3), 9·01 (s, CH_3), 9·03 (s, CH_3), 9·15 (d, J = 6, 4α-CH_3), $[\alpha]_{589}$ −104°, $[\alpha]_{578}$ −112°, $[\alpha]_{546}$ −130°, $[\alpha]_{436}$ −267°, $[\alpha]_{365}$ −611°. A satisfactory analysis could not be obtained for this compd.

(b) A soln of 1·00 g of methyl fusidate[8] in 5 ml of acetylating mixture (prepared from 40 ml glacial AcOH, 10 g of *p*-toluenesulfonic acid and 20 ml of acetic anhydride was kept at room temp for 20 min. Water was then added to the reaction mixture and the amorphous material which separated was taken up in CH_2Cl_2. This soln was washed well with water, dried and evaporated. TLC on neutral alumina (Activity V) using hexane–$CHCl_3$ (2:1) as the developing solvent gave two UV absorbing bands. The less polar band was eluted with AcOEt and on evaporation gave 650 mg of material which was used in the following reaction.

A soln of 650 mg of crude methyl fusidate, diacetate, in 25 ml of CH_2Cl_2 containing 0·25 ml of pyridine was cooled to −70° (acetone–dry ice bath) and treated with 5·5 l. of an ozone–oxygen mixture (1·1 mmole O_2/l.). The soln was allowed to come to room temp and then stirred for 45 min after the addition of 750 mg of Zn dust and 1·25 ml AcOH. The soln was filtered, washed successively with 5% HCl, water, 5% $NaHCO_3$, water, dried and evaporated to give 469 mg of product. TLC of this material on neutral alumina (Activity V) and elution with $CHCl_3$ showed two bands on UV scanning. Elution of the less polar band with AcOEt led to 218 mg of crude IV. Two recrystallizations from MeOH–water gave IV, m.p. 149–151°, $[\alpha]_D$ −104°.

3α-*Acetoxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,14β-*androst*-12-*en*-17-*one* (V), 3α-*Acetoxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9α,14β-*androst*-12,15-*dien*-17-*one* (VI) *and* 3α,11α-*Diacetoxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,14β-*androst*-15-*en*-17-*one* (VII)

(a) To a soln of 5 g of *p*-toluenesulfonic acid monohydrate in 10 ml of acetic anhydride and 20 ml of AcOH 5·6 g of methyl fusidate[8] were added and the soln left at room temp for 20 min. The soln

was then carefully diluted with ice while stirring, th diluted with water and extracted with $CHCl_3$. The $CHCl_3$ was then washed several times with wat nd evaporated to give 6·0 g of crude methyl fusidate 3,11-diacetate (III).

A soln of 6 g of III in a mixture of 122 ml of CH and 1·22 ml of pyridine was cooled in an acetone–dry ice bath and 443 l. of ozone–oxygen (1·1 noles O_3/l.) were slowly passed through. Twelve ml of AcOH and 6 g of Zn dust were then added and the mixture stirred vigorously at room temp for 90 min. It was then filtered and washed with $CHCl_3$. The combined filtrate and washings were then extracted successively with water, 5% $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated to dryness under red. press. The residue was then redissolved in 500 ml of AcOH, 11 g of Zn dust were added and the mixture refluxed for 4 hr. It was then filtered, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ was washed well with water and then evaporated to dryness under red. press. The residue was dissolved in $CHCl_3$-hexane (1:1, v:v) and plate chromatographed using neutral alumina (Activity V) as adsorbent and $CHCl_3$–hexane (1:1, v:v) as developing solvent. The band detectable by UV at $R_f \approx 0{\cdot}3$–$0{\cdot}7$ was eluted by AcOEt, evaporated to dryness and crystallized from acetone–hexane to give 663 mg of V having a m.p. of 138–140°, $[\alpha]_D^{22}$ −260°, λ_{max}^{alc} 245 mμ (ε, 9500), λ_{max}^{Nujol} 5·82, 5·88, 6·10 μ, τ 3·37 (m, 12-H), 5·09 (m, 3β-H), 7·93 (s, 3-OAc), 8·83 (s, CH_3), 8·95 (s, CH_3), 8·98 (s, CH_3), 9·15 (d, J = 6, 4α-CH_3). (Found: C, 77·39; H, 9·29. $C_{32}H_{44}O_8$ requires: C, 77·05; H, 9·56%.)

The band detectable by UV which had an $R_f \approx 0{\cdot}2$ was eluted with AcOEt and the residue, after removal of the solvent, on crystallization from acetone–hexane gave 20 mg of VII having a m.p. of 215–217°, $[\alpha]_{589}$ −82°, $[\alpha]_{578}$ −85°, $[\alpha]_{546}$ −94°, $[\alpha]_{436}$ −121°, $[\alpha]_{365}$ +35°, λ_{max}^{alc} 226 mμ (ε, 8400), λ_{max}^{Nujol} 5·80, 5·90, 6·30 μ, τ 2·60 (d, J = 6, 15-H), 3·92 (d, J = 6, 16-H), 4·87 (m, 11β-H), 5·10 (m, 3β-H), 8·00 (s, 3 and 11-OAc), 8·78 (s, CH_3), 8·88 (s, CH_3), 8·92 (s, CH_3), 9·17 (d, J = 6, 4α-CH_3). (Found: C, 72·33, H, 8·45. $C_{25}H_{36}O_5$ requires: C, 72·08, H, 8·71%.)

By re-plate chromatographing the mother liquors from V several times a second UV detectable band was evident which was slightly more polar than the above compd. Crystallization of the material obtained from this band from acetone–hexane gave 60 mg of VI having a m.p. of 173–175°, $[\alpha]_{589}$ −47°, $[\alpha]_{578}$ −50°, $[\alpha]_{546}$ −48°, $[\alpha]_{436}$ +50°, $[\alpha]_{365}$ +318°, λ_{max}^{alc} 248 mμ (ε, 9300), λ_{max}^{Nujol} 5·81, 5·95, 6·08, 6·30 μ, τ 2·51 (d, J = 6, 15-H), 3·50 (m, 12-H), 3·81 (d, J = 6, 16-H), 5·08 (m, 3β-H), 8·80 (s, CH_3), 8·93 (s, CH_3), 9·14 (d, J = 5, 4α-CH_3), 9·19 (s, CH_3). (Found: C, 77·42; H, 9·13. $C_{23}H_{32}O_5$ requires: C, 77·49; H, 9·05%.)

(b) To a soln of 380 mg of IV in 38 ml of AcOH, 760 mg of Zn dust were added and the mixture refluxed with stirring for 4 hr. It was then cooled, filtered and the filtrate diluted with water and extracted with $CHCl_3$. The $CHCl_3$ was washed several times with water and evaporated under red. press. The residue was adsorbed onto alumina (Activity V) and plate chromatographed using $CHCl_3$–hexane (1:1, v:v) as the developing solvent. The band detectable by UV at $R_f \approx 0{\cdot}5$ gave on elution and crystallization, 63 mg of V. From a more polar band, on elution and crystallization, 5·0 mg of VII were obtained.

3α-*Acetoxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,14β-*androstan*-17-*one* (IX).

(a) *From* V. To a soln of 400 mg of V in 56 ml of abs EtOH 400 mg of 5% Pd–$CaCO_3$ were added and the stirred mixture hydrogenated at room temp under atmospheric press. for 16 hr. The mixture was filtered and evaporated to dryness under red. press. Crystallization of the residue from acetone–hexane gave 331 mg of IX having a m.p. of 143–145°, $[\alpha]_D$ +18°, λ_{max}^{Nujol} 5·78 μ, τ 5·05 (m, 3β-H), 7·96 (s, 3-OAc), 8·71 (s, CH_3), 9·06 (s, CH_3), 9·10 (s, CH_3) and 9·17 (d, J = 6, 4α-CH_3). (Found: C, 76·63; H, 9·82. $C_{32}H_{48}O_8$ requires: C, 76·62; H, 10·07%.)

(b) *From* VI. A soln of 25 mg of VI in 3·5 ml of abs EtOH was hydrogenated at room temp and atmospheric press. using 25 mg of 5% Pd–$CaCO_3$ as catalyst. The mixture was filtered and the solvent evaporated to give a residue which on crystallization from acetone–hexane gave 15·5 mg of IX identical in physical properties with the compd obtained from V.

3α-*Hydroxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,14β-*androsta*-12,15 *dien*-17-*one* (X)

A soln of 107 mg of VI in 10 ml of 1N KOH in 95% EtOH was blanketed with He and left at room temp for 16 hr. The soln was then neutralized with 2N HCl, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ was washed with water and evaporated to dryness under red. press. Crystallization of the residue from acetone–hexane gave 75 mg of X having a m.p. of 184–186°, $[\alpha]_{589}$

$-23°$, $[\alpha]_{578}$ $-24°$, $[\alpha]_{546}$ $-19°$, $[\alpha]_{436}$ $+116°$, $[\alpha]_{365}$ $+379°$, λ_{max}^{alc} 249 mμ (ε, 7500), λ_{max}^{Nujol} 2·90, 5·95, 6·08, 6·30 μ, τ 2·56 (d, J = 6, 15-H), 3·54 (m, 12-H), 3·92 (d, J = 6, 16-H), 6·28 (m, 3β-H), 8·83 (s, CH_3), 8·96 (s, CH_3), 9·06 (d, J = 6, 4α-CH_3), 9·22 (s, CH_3). (Found: C, 79·86; H, 9·54. $C_{31}H_{50}O_3$ requires: C, 80·21; H, 9·62%.)

4α,8,14-*Trimethyl*-18-*nor*-5α,8α,9β,14β-*androsta*-12,15-*diene*-3,17-*dione* (XI)

To a soln of 50 mg of X in 2 ml of reagent grade acetone a soln containing 20 mg/ml of chromic anhydride and 32 mg/ml of H_2SO_4 in acetone–water (9:1, v:v) was added dropwise until the oxidizing agent is no longer decolorized. After 5 min the excess oxidizing agent was decomposed with MeOH and on careful dilution with water, crystals separated. These were filtered, washed with water and dried. Recrystallization from acetone–hexane gave 41 mg of XI having m.p. 174–176°, $[\alpha]_{589}$ $+15°$, $[\alpha]_{578}$ $+20°$, $[\alpha]_{546}$ $+32°$, $[\alpha]_{436}$ $+225°$, $[\alpha]_{365}$ $+577°$, λ_{max}^{alc} 247 mμ (ε, 9200), λ_{max}^{Nujol} 5·90, 6·06, 6·30 μ, τ 2·54 (d, J = 6, 15-H), 3·54 (m, 12-H), 3·88 (d, J = 6, 16-H), 8·72 (s, CH_3), 8·77 (s, CH_3), 8·97 (d, J = 6, 4α-CH_3), 9·23 (s, CH_3). (Found: C, 80·78; H, 9·00. $C_{31}H_{38}O_2$ requires: C, 80·73; H, 9·03%.)

3α,11α-*Diacetoxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,14β-*androstan*-17-*one* (VIII)

A soln of 25 mg of VII in 5 ml of abs EtOH was hydrogenated at room temp and atmospheric press. using 25 mg of 5% Pd–$CaCO_3$ as catalyst. The mixture was then filtered, evaporated, and the residue crystallized from acetone–hexane to give 23 mg of VIII having a m.p. of 186–188° (dec.), ORD (MeOH): $[\alpha]_{600}$ $-114°$, $[\alpha]_{500}$ $-95°$, $[\alpha]_{400}$ $-76°$, $[\alpha]_{389}$ $\pm 0°$, $[\alpha]_{350}$ $+48°$, $[\alpha]_{306}$ $+800°$ (peak), $[\alpha]_{303}$ $\pm 0°$; λ_{max}^{Nujol} 5·78–5·80 μ. (Found: C, 71·87; H, 9·00. $C_{35}H_{48}O_6$ requires: C, 71·74; H, 9·15%).

3α-*Hydroxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,14β-*androstan*-17-*one* (XIII)

A soln of 330 mg of V in 33 ml of 1N KOH in 95% EtOH was left under He at room temp for 16 hr then neutralized with 10% AcOH diluted with water and extracted with $CHCl_3$. The $CHCl_3$ was washed with water and evaporated and the residue plate chromatographed on neutral alumina (Activity V) using $CHCl_3$ as the developing solvent. The principal band detectable by UV at $R_f \approx 0{\cdot}5$ was eluted with AcOEt and evaporated to give 263 mg of XIV which could not be induced to crystallize but was used without further identification.

Hydrogenation of 140 mg of XIV using 140 mg of 5% Pd–$CaCO_3$ and 21 ml of abs EtOH as described above gave 88 mg of XIII having a m.p. of 159–161°, ORD (MeOH): $[\alpha]_{600}$ $+14$, $[\alpha]_{500}$ $+55°$, $[\alpha]_{400}$ $+173°$, $[\alpha]_{350}$ $+522°$, $[\alpha]_{308}$ $+1710°$ (peak), $[\alpha]_{290}$ $\pm 0°$, $[\alpha]_{268}$ $-1640°$; λ_{max}^{Nujol} 2·90, 5·82 μ; τ 6·27 (m, 3-H), 8·72 (s, CH_3), 9·08 (s, CH_3), 9·10 (d, J = 6, 4α-CH_3), 9·11 (s, CH_3). (Found: C, 79·18; H, 10·81. $C_{21}H_{34}O_2$ requires: C, 79·19; H, 10·76%.)

3α-*Hydroxy*-4α,8,14-*trimethyl*-18-*nor*-5α,8α,9β,13α,14β-*androstan*-17-*one* (XII)

A soln of 50 mg of IX in 10 ml of 1N KOH in 95% EtOH was kept at room temp under He for 16 hr. It was then neutralized with 10% AcOH, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with water and evaporated to dryness under red. press. Plate chromatography of the residue using neutral alumina (Activity V) as adsorbent and $CHCl_3$ as the developing solvent gave two bands detectable by iodine vapor at $R_f \approx 0{\cdot}6$ and 0·4 respectively. Elution of the less polar band with AcOEt and crystallization of the residue from acetone–hexane after removal of the solvent gave 16 mg of XII having a m.p. of 215–217°, ORD (MeOH): $[\alpha]_{600}$ $-133°$, $[\alpha]_{500}$ $-193°$, $[\alpha]_{400}$ $-386°$, $[\alpha]_{350}$ $-765°$, $[\alpha]_{311}$ $-2900°$ (trough), $[\alpha]_{292}$ $\pm 0°$, λ_{max}^{Nujol} 2·80, 5·88 μ, τ 6·23 (m, 3-H), 8·76 (s, CH_3), 9·07 (d, J = 6, 4α-CH_3), 9·11 (s, CH_3), 9·13 (s, CH_3). (Found: C, 79·16; H, 10·63. $C_{21}H_{34}O_2$ requires: C, 79·19; H, 10·76%.)

Elution of the more polar band and crystallization gave 14 mg of XIII.

Equilibration of XII *and* XIII

A drop of methanolic KOH was added to each of two solns containing 2·725 mg of XIII in 5 ml of MeOH and 3·056 mg of XII in 5 ml of MeOH and the ORD curves recorded until each soln had reached equilibrium which took about 3 hr in each case. The equilibrium specific rotations obtained at 307 mμ $-136°$ in the case of XIII and $-146°$ for XII indicating an equilibrium ratio of 40% XIII and 60% XII.

4α,8,14-*Trimethyl*-18-*nor*-5α,8α,9β,14β-*androst*-12-*ene*-3,17-*dione* (XV)

To a soln of 319 mg of XIV in 22 ml of reagent grade acetone, was added dropwise a soln, containing 20 mg of chromic anhydride and 32 mg of H_2SO_4 per ml of acetone–water (1:1, v:v) until the chromic acid was no longer decolorized. The excess oxidizing agent was decomposed with a few drops of MeOH and on dilution with water crystals separated which were filtered washed with water and dried to give 239 mg of XV having a m.p. of 153–155°; $[\alpha]_{589}$ −219°, $[\alpha]_{578}$ −221°, $[\alpha]_{546}$ −253°, $[\alpha]_{436}$ −470°, $[\alpha]_{365}$ −856°; λ_{max}^{alc} 246 mμ (ε, 8300), λ_{max}^{Nujol} 5·88, 6·04 μ; τ 3·38 (m, 12-H), 8·73 (s, CH_3), 8·80 (s, CH_3), 8·97 (d, J = 6, 4α-CH_3), 9·05 (s, CH_3). (Found: C, 80·15; H, 9·66. $C_{21}H_{30}O_2$ requires: C, 80·21; H, 9·62%.)

4α,8,14-*Trimethyl*-18-*nor*-5α,8α,9β,14β-*androsta*-3,17-*dione* (XVII)

(a) *From* XV. A soln of 50 mg of XV in 7·0 ml of abs EtOH was hydrogenated at room temp at atmospheric press. using 50 mg of 5% Pd–$CaCO_3$ until 1 mole equivalent of H_2 had been absorbed. The mixture was filtered and the filtrate evaporated under red. press. Crystallization of the residue from acetone–hexane gave 34 mg of XVII having a m.p. of 182–184°; $[\alpha]_{589}$ +117°, $[\alpha]_{578}$ +125°, $[\alpha]_{546}$ +185°, $[\alpha]_{436}$ +304°, $[\alpha]_{365}$ +679°; λ_{max}^{Nujol} 5·77, 5·80 μ, τ 8·68 (s, CH_2), 8·93 (s, CH_3), 8·98 (d, J = 6, 4α-CH_3), 9·13 (s, CH_3). (Found: C, 79·79; H, 10·14. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%.)

(b) *From* XIII. To a soln of 435 mg of XIII in 20 ml of reagent grade acetone a soln containing 20 mg of chromic anhydride and 32 mg of H_2SO_4 per ml of acetone–water (9:1, v:v) was added dropwise until the chromic acid was no longer decolorized. After 5 min the excess oxidizing agent was decomposed by the addition of a few drops of MeOH. On dilution with water crystals separated which were filtered, washed with water and dried to give 312 mg of XVII.

4α,8,14-*Trimethyl*-18-*nor*-5α,8α,9β,13α,14β-*androstan*-3,17-*dione* (XVI)

A soln of 50 mg of XII in 2·5 ml of reagent grade acetone was oxidized with Jones reagent[7] as described above to give 40 mg of XVI having a m.p. of 166–168°, $[\alpha]_{589}$ +1°, $[\alpha]_{578}$ ±0°, $[\alpha]_{546}$ −3°, $[\alpha]_{436}$ −39°, $[\alpha]_{365}$ −194°; λ_{max}^{Nujol} 5·78, 5·90 μ; τ 8·81 (s, CH_2), 8·96 (d, J = 6, 4α-CH_3), 9·11 (s, CH_3). (Found: C, 79·67; H, 10·24. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%.)

3,17-*Bisethylenedioxy*-4α,8,14-*trimethyl*-5α,8α,14β-*androst*-9(11)-*ene* (XXII)

(a) *From* XX. To a soln of 100 mg of XX[1] in 1·5 ml of pyridine cooled to 0°, 0·15 ml of methanesulfonyl chloride was added and the resulting yellow solution kept at 0° for 16 hr. Ice water was then added and the mixture extracted with $CHCl_3$, which was washed well with water and evaporated under red. press. The residue was plate chromatographed on neutral alumina (Activity V) using $CHCl_3$–hexane (1:1, v:v) as the developing solvent. A band at $R_f \approx 0·7$ detectable by iodine vapor was eluted with AcOEt, evaporated and the residue crystallized to give 67 mg of XXII.[1]

(b) A similar reaction utilizing XXI[1] as starting material yielded only XXII.

Acknowledgement—We are grateful to Mr. Joseph Alicino and staff for micro-analyses, Miss Barbara Keeler for IR determinations and Dr. A. I. Cohen for NMR determinations.