

TRANSFORMATIONS OF FUSIDIC ACID—I OXYGENATED-4 α ,8,14-TRIMETHYL-18-NORANDROSTANES

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Abstract—The preparation of the four 9,13-epimeric 11,17-diketones derived from fusidic acid are described. The most stable as determined by both acidic and basic equilibration is the 9 α , 13 β -isomer and this result is discussed in terms of conformational analysis. Equilibration of $\Delta^9(11)$ -17-ketones leads to a 55:45 mixture of the 13 α and 13 β -isomers respectively.

THE structure, relative and absolute configurations of the triterpenoid antibiotic fusidic acid (I) have been presented recently.¹⁻⁴ The unusual substitution pattern and stereochemistry of this compound have stimulated our interest in epimerizations, stabilities and stereochemical relationships of the 18-norandrostanes derived from it. In this paper we would like to present the preparation, structure proof, equilibration and conformational features of some of these derivatives.

Both Godtfredsen and co-workers⁴ and Bucort and co-workers⁵ recently reported the conversion of fusidic acid (I) to the 9 β ,13 α -triketone (IXa) by a series of steps which do not affect the stereochemical integrity of any of the epimeric centers in the molecule. Mild treatment with base isomerized⁴ this triketone to the 9 β ,13 β -triketone (IIIa). The retention of the stereochemical assignment at position 9, was based on the inference that stronger alkaline conditions are necessary to epimerize this position as has been observed¹ with other fusidic acid derivatives. That this inference is correct has now been shown by the base hydrolysis of the 3 α -acetoxy-9 β ,13 β -diketone (IIIc, a compound which has been shown⁵ to have the same stereochemistry at position 9 as fusidic acid) to the 3-ol (IIIb) which could then be oxidized to the triketone (IIIa) and also reacylated to starting material (IIIc). In working with the 3 α -acetoxy-9 β ,13 β -diketone (IIIc), we had occasion to show that both the catalytic reduction and zinc-acetic acid treatment of the 3 α -acetoxy-enedione⁵ (IIc) gave IIIc. The enedione (IIc) could be regenerated from IIIc, albeit in poor yield by DDQ dehydrogenation.

The 9 β ,13 β -triketone (IIIa) could be epimerized to a new triketone (IVa) by refluxing in 5% ethanolic potassium hydroxide with the rigorous exclusion of air. Similarly, the 3 α -acetoxy-9 β ,13 β -diketone (IIIc) under these conditions gave the new 3 α -hydroxy-diketone (IVb) which could be oxidized to the triketone (IVa) or acetylated to a new 3 α -acetoxy-diketone (IVc). This latter compound could also be obtained

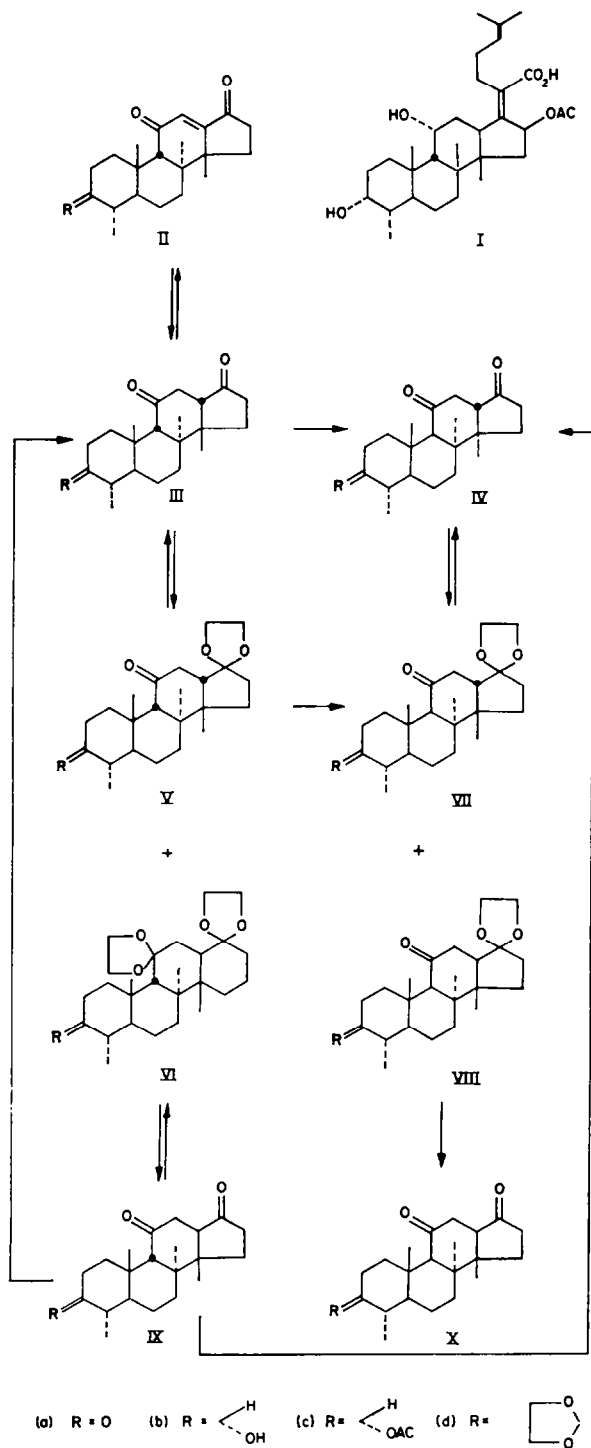
¹ W. O. Godtfredsen and S. Vangedal, *Tetrahedron* **18**, 1029 (1962).

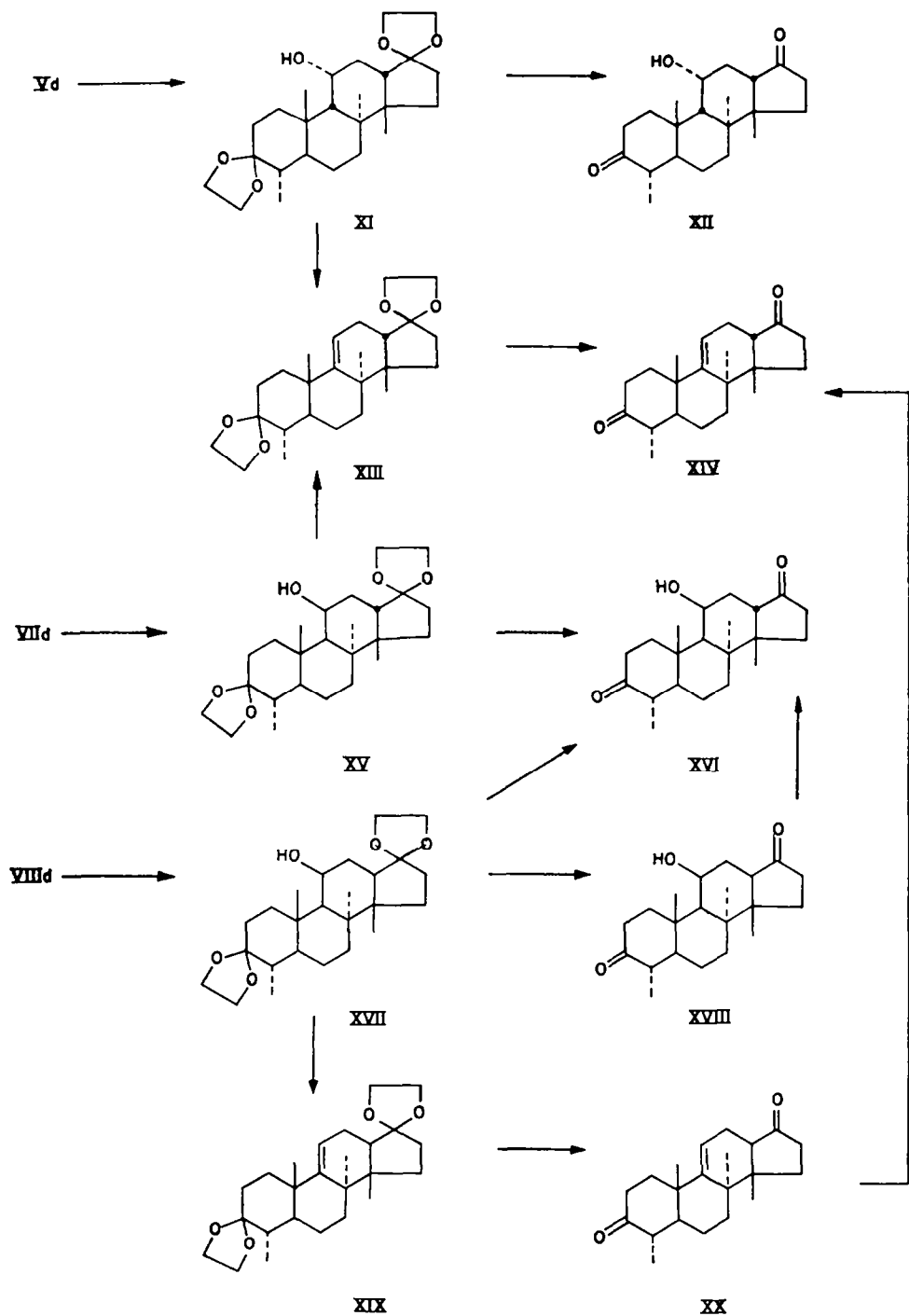
² D. Arigoni, W. von Daehne, W. O. Godtfredsen, A. Marquet and A. Melera, *Experientia* **19**, 521 (1963).

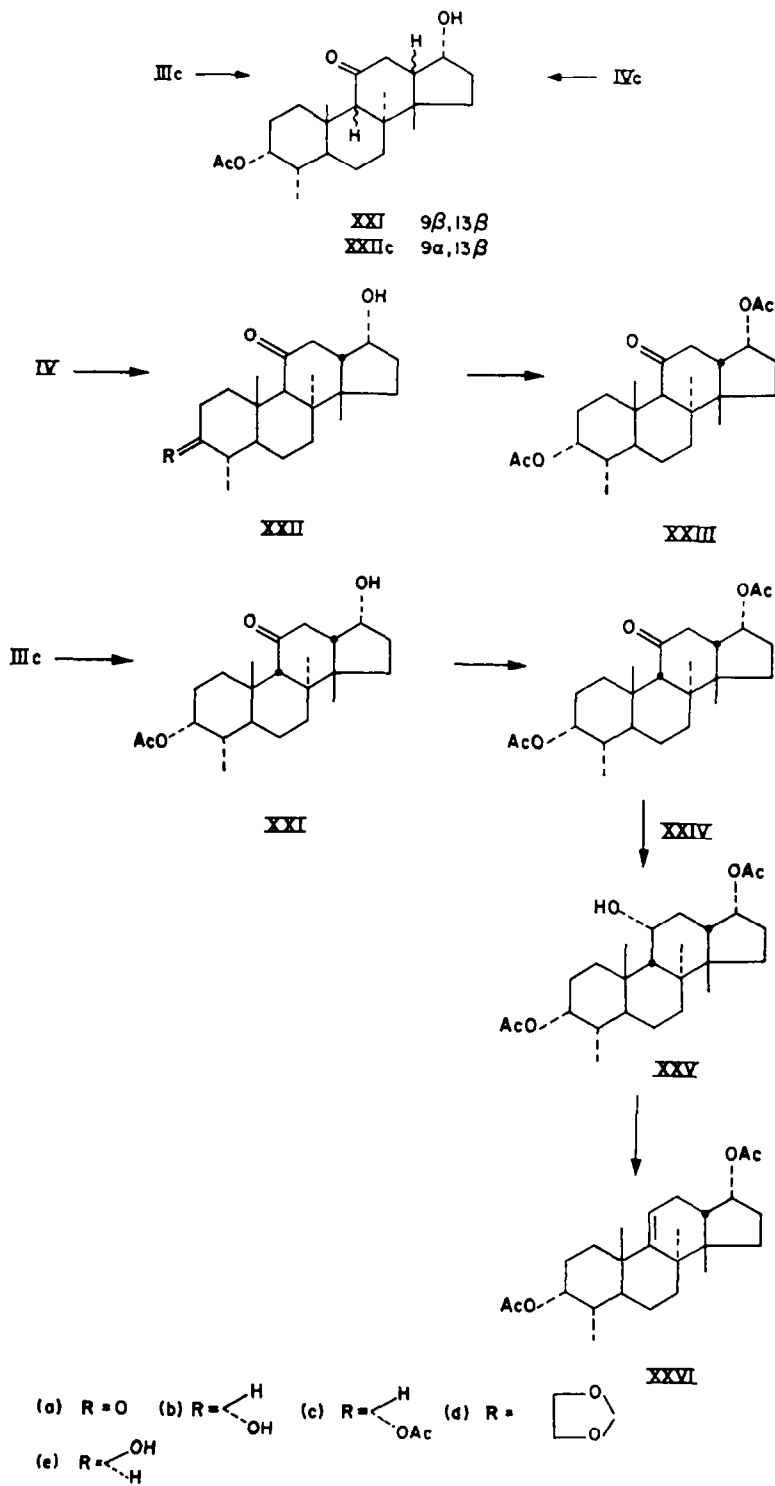
³ D. Arigoni, W. von Daehne, W. O. Godtfredsen, A. Melera and S. Vangedal, *Experientia* **20**, 344 (1964).

⁴ W. O. Godtfredsen, W. von Daehne, S. Vangedal, A. Marquet, D. Arigoni and A. Melera, *Tetrahedron* **21**, 3035 (1965).

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







directly from the 3 α -acetoxy-9 β ,13 β -diketone (IIIc) by acid catalysed epimerization with dioxane saturated with hydrogen chloride. The equilibrium for this epimerization in base has been shown polarimetrically to be 85:15 in favor of the epimerized series. These new epimers have been assigned the 9 α ,13 β -configuration on arguments which follow and unambiguously establish this stereochemistry.

On *p*-toluenesulfonic acid catalysed ketalization of 9 β ,13 β -3,11,17-triketone (IIIa) and 3 α -acetoxy-9 β ,13 β -11,17-diketone (IIIc) in ethylene glycol, the major products isolated from the reaction mixture were the 9 β ,13 β -bisketal (Vd) and the 9 β ,13 β -monoketal (Vc)⁶ respectively. That no epimerization or rearrangement has taken place during this reaction was apparent from the regeneration of the starting materials IIIa and IIIc from the ketals Vd and Vc by the mild room temperature hydrolysis with 80% acetic acid. Similarly the epimeric 3,11,17-triketone (IVa) and 3 α -acetoxy-11,17-diketone (IVc) gave as major products the corresponding epimeric bisketal VIId and monoketal VIIC, and again the ketals VIId and VIIC were converted to the starting ketones on mild hydrolysis. Furthermore, the 9 β ,13 β -bisketal (Vd) was transformed in refluxing base to the epimeric bisketal VIId.

That one of the ketal functions in the pair of bisketals Vd and VIId is at the 3 position, is suggested from the fact that only monoketals (Vc and VIIC) are obtained when the reaction is carried out in the 3 α -acetoxy-series. In addition, the NMR spectra of the bisketals Vd and VIId show the 4 α -methyl doublet shifted to 9.17 τ from 8.95 τ in the starting ketones. Inspection of Dreiding models as well as metal hydride reductions (see below) indicate that the 11 position is more hindered than the 17 position and thus the second ketal grouping of Vd and VIId as well as the ketal group of Vc and VIIC should be at this position. The IR band for the carbonyl of VIId also supports this conclusion since it appears at 1689 cm⁻¹ indicating a 6-membered ring ketone.

Since the ketal functions in Vd and VIId are placed at the 3 and 17 positions, the only center adjacent to a carbonyl that can be epimerized in base is at 9, and this permits the assignment of VII and therefore IV as belonging to the 9 α ,13 β series.

This has been further substantiated as follows: lithium aluminum hydride reduction of the 11-keto-3,17-bisketals (Vd and VIId) led to 11 α -hydroxy-9 β ,13 β -3,17-bisketal (XI) and 11 β -hydroxy-9 α ,13 β -3,17-bisketal (XV), respectively. The stereochemical assignment of the hydroxyl group is based on the fact that in the 9 β -series the 11-ketone is reduced to the axial 11 α -ol by sodium borohydride¹ and in the 9 α -series the 11-carbonyl is even more hindered (inert to sodium borohydride) and would be expected⁶ to give the axial 11 β -hydroxyl. These two hydroxy compounds XI and XV are both converted in good yield to the same olefin, viz. $\Delta^9(11)$ -13 β -3,17-bisketal (XIII).

The ketals XI, XIII and XV when treated with 80% acetic acid are hydrolysed to the 11 α -hydroxy-9 β ,13 β -3,17-diketone (XII) the $\Delta^9(11)$ -13 β -3,17-diketone (XIV) and the 11 β -hydroxy-9 α ,13 β -3,17-diketone (XVI), respectively. The IR spectra of XII, XIV and XVI all show peaks for a 6-membered ring carbonyl (3-ketone) and a 5-membered ring carbonyl (17-ketone) at 1706 cm⁻¹ and 1737 cm⁻¹. This confirms our original placement of the ketal functions at the 3 and 17-positions. The fact that the same olefin XIII is obtained from the epimeric bisketals establishes that position 13 adjacent to the 17-ketal function has the same stereochemistry in XI and XV and therefore in III, IV, V and VII as well.

That the epimers III and IV differ at only one center and this center is at 9 is also

⁶ For leading references see ref. (1) and p. 268, *Steroids*, L. Fieser and M. Fieser. Reinhold, New York.

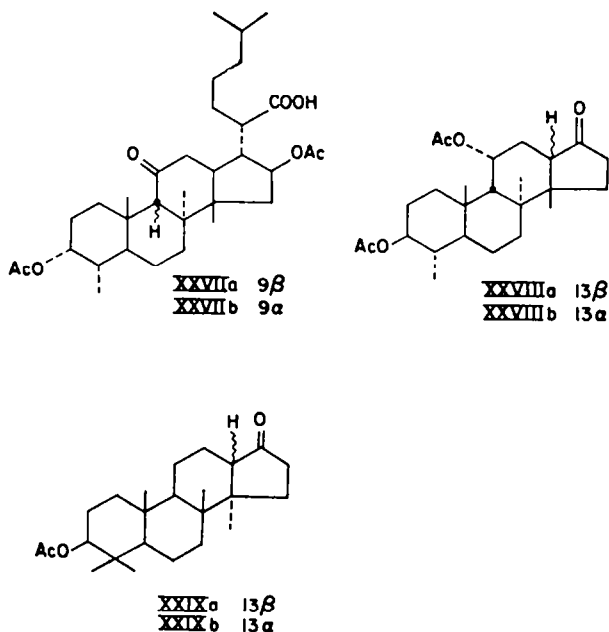
shown by the following experiments. Reduction of the epimeric 3α -acetoxy-11,17-diketones (IIIc and IVc) with lithium tri-*tert*-butoxyaluminum hydride gave the corresponding 17α -ols (XXI and XXIIc). Acid epimerization with hydrogen chloride-dioxane converted the $9\beta,13\beta$ -compound (XXI) to the epimeric XXIIc. This transformation shows that the epimers IIIc and IVc differ at only one center and that the stereochemistry of the hydroxyl produced in the reduction is the same in both cases. That reduction had taken place at position 17 and not 11, is evident from the following: the 11-carbonyl group is more hindered than the 17-carbonyl (see below). The carbonyl that remains after reduction absorbs at 1711 cm^{-1} and 1685 cm^{-1} in XXI and XXIIc, which indicates a 6-membered ring carbonyl. From these facts it is evident that III and IV are 9-epimers and that the assignments we have made are justified.

In the ketalization of the $9\beta,13\beta$ -3,11,17-triketone (IIIa) or the 3α -acetoxy- $9\beta,13\beta$ -11,17-diketone (IIIc) besides the major products Vd and Vc already described a 3,11,17-trisketal (VIId) and a 3α -acetoxy-11,17-bisketal (VIc) were obtained respectively in 15% yield. Hydrolysis of these ketals under non-epimerizing conditions leads to the $9\beta,13\alpha$ -3,11,17-triketone (IXa) previously described^{4,5} and a new 3α -acetoxy- $9\beta,13\alpha$ -11,17-dione (IXc). Re-ketalization of IXa gives the trisketal VIId and treatment with strong base converts IXa to the $9\alpha,13\beta$ -triketone IVa.

The ketalization of the $9\alpha,13\beta$ -3,11,17-triketone (IVa) and the 3α -acetoxy- $9\alpha,13\beta$ -diketone (IVc) also gave as minor components (10–15% yield) the 11-keto-3,17-bisketal VIIIId and the 3α -acetoxy-11-keto-17-ketal VIIIC. When these minor products were hydrolysed with 80% acetic acid, the fourth member of each series, the $9\alpha,13\alpha$ -3,11,17-triketone (Xa) and the 3α -acetoxy- $9\alpha,13\alpha$ -11,17-diketone (Xc) were obtained. The relationship of the bisketal VIIIId to the previously described bisketals Vd and VIIId is apparent from the following experiments.

Reduction of the 11-keto function of VIIIId with lithium aluminum hydride gave the new 11β -hydroxy- $9\alpha,13\alpha$ -3,17-bisketal (XVII). That this compound is the 13α -epimer of XV is evident from the thionyl chloride-pyridine dehydration of it to a new unsaturated bisketal, the $\Delta^{9(11)}$ - 13α -3,17-bisketal (XIX). Compound XIX could in turn be hydrolysed to the new $\Delta^{9(11)}$ - 13α -3,17-diketone (XX). This latter compound on treatment with base equilibrates in the ratio 55:45, *trans*:*cis*, with the previously described $\Delta^{9(11)}$ - 13β -3,17-diketone (XIV). Thus we have established that VIIIId as well as X have the 13α orientation. That VIIIId still retains the 9α -configuration follows from the mild 80% acetic acid hydrolysis of XVII to the 11β -hydroxy- $9\alpha,13\alpha$ -3,17-diketone (XVIII) which is epimeric and converted in 97% yield by base treatment to the previously mentioned 11β -hydroxy- $9\alpha,13\beta$ -3,17-diketone (XVI).

We have referred above to various reduction experiments which exhibited differences in reactivity of the 11 and 17 carbonyl functions. We now wish to present these experiments and show how they tie in with some of the data previously presented. Treatment of the 11,17-diketo- $9\alpha,13\beta$ -3-ketal (IVd) obtained from the $9\alpha,13\beta$ -3,11,17-triketone (IVa) by acid catalysed ketal exchange with the ethylene ketal of 2-butanone, with sodium borohydride gave the 17α -hydroxy-11-keto- $9\alpha,13\beta$ -3-ketal (XXIIId) with IR peak at 1686 cm^{-1} . Hydrolysis of this compound gives the corresponding 17α -hydroxy- $9\alpha,13\beta$ -3,11-diketone (XXIIa) (IR peak at 1706 cm^{-1}) which is stable to refluxing base as expected. Similarly sodium borohydride reduction of the $9\alpha,13\beta$ -3,11,17-triketone (IVa) does not reduce the 11-carbonyl and gives the $3\beta,17\alpha$ -dihydroxy- $9\alpha,13\beta$ -11-ketone (XXIIe) (IR peak at 1685 cm^{-1}).



The reduction of only one carbonyl in 3 α -acetoxy-9 α ,13 β -11,17-diketone (IVc) with lithium-tri-*tert*-butoxyaluminum hydride has been mentioned above. Even when this compound is treated with lithium aluminum hydride, the 11-carbonyl remains unchanged. The resulting 3 α ,17 α -dihydroxy-9 α ,13 β -11-ketone (XXIIb) (IR peak 1675 cm⁻¹) can be acetylated to the same 3 α ,17 α -diacetoxy-9 α ,13 β -11-ketone (XXIII) as the previously obtained XXIIc.

In the 9 β ,13 β -series, the 11-carbonyl is not as hindered as in the 9 α ,13 β -series. The previously described 3 α -acetoxy-17 α -hydroxy-9 β ,13 β -11-ketone (XXI) was readily acetylated (as expected for a 17-hydroxy compound) to 3 α ,17 α -diacetoxy-9 β ,13 β -11-

TABLE 1

Conformer	Ring B	Ring C	Major Interactions	C/D ring junction
9 α ,13 β	Boat	Chair	10-CH ₃ :C-10:C-9:C-11 form <i>cis</i> -butane	<i>cis</i>
9 α ,13 α	Twist	Twist	10-CH ₃ :C-10:C-9:C-11 and C-7:C-8:C-14: 14-CH ₃ form <i>cis</i> -butanes.	<i>trans</i>
9 β ,13 α	Boat	Chair	None	<i>trans</i>
9 β ,13 β	Boat	Chair	14-CH ₃ and C-13:C-17 are 1,3-diaxial	<i>cis</i>

ketone (XXIV). This latter compound could be reduced with sodium borohydride to the 11 α -ol XXV. Treatment of XXV with thionyl chloride-pyridine gave the 3 α ,17 α -diacetoxy- $\Delta^{9(11)}$ -13 β -olefin (XXVI).

The major interactions of the most stable conformations for the four 9,13-isomeric compounds are shown in Table 1.⁷ In considering the relative stabilities in these systems

⁷ Although the all chair conformations can be made for the two 13-epimeric 9 α -compounds these have not been considered further because of the severe interaction of the 10 and 14 methyl groups.

ring A can be disregarded since in all cases it is in the chair conformation with the 4 α -methyl group equatorial. Three principal factors then influence the stability of these isomers. They are: (1) conformations of rings B and C; (2) major interactions between bulky groups; and (3) the inherent stability of a *cis*-hydrindanone (C/D *cis*) over a *trans*-hydrindanone (C/D *trans*).⁸ The most stable by far as indicated in the equilibrium studies described before is the 9 α ,13 β -epimer. This is in agreement with the models since this conformation has the stable *cis* C/D junction and the only destabilizing factors are the ring B boat and *cis*-butane interactions made up by the 10-Me, C-10, C-9 and C-11 bonds. When the 13 α -configuration is fixed isomerization of a 9 β ,13 α -system leads predominately (>90%) to the 9 α ,13 α -isomer. This is evident from the isomerization of a 9 β ,13 α -11-keto derivative (XXVIIa) of fusidic acid to the 9 α ,13 α -epimer (XXVIIb). The 9 α ,13 α -11-ketone-3,17-bisketal (VIIId) is also completely stable to refluxing alkali. The 9 α ,13 α -conformer has a *trans* ring C/D junction with rings B and C in twist conformation and two *cis*-butane interactions involving the 10-Me, C-10, C-9, C-11 bonds and the C-7, C-8, C-14 and 14-Me bonds.

The relative stabilities of the two C-13 epimers are very close in some cases. For example equilibration of $\Delta^{9(11)}$ -13 α -3,17-diketone (XX) with alkali gave a 55:45 mixture of it and the 13 β -isomer XIV. An equivalent mixture of these $\Delta^{9(11)}$ -diketones can be obtained by refluxing acid hydrolysis of $\Delta^{9(11)}$ -13 β -3,17-bisketal XIII. Equilibration of an 11-desoxy-9 β ,13 β -17-one⁹ also gave a 60:40 ratio in favor of the 13 α (*trans*) isomer. Similar ratios have been obtained on basic alumina equilibration⁴ of the 3 β ,11 α -diacetoxy-17-ketones (XXVIIIa and XXVIIIb) and the 17-ketones XXIXa and XXIXb obtained in the dammarane series.¹⁰ The ratio of these products seems reasonable for whereas the 9 β , 13 β -conformation has the stabilizing influence of the C/D *cis* ring fusion it also has the destabilizing factor of the 1,3-diaxial interaction of the 8 α -methyl and 13,17-bond and the *cis* and *trans* isomers would be expected to be about equally stable.

ORD results are consistent with the stereochemical assignments for the compounds described. Thus the 13 β -compounds XII, XIV and XVI show positive Cotton effects whereas the epimeric 13 α -compounds XVII and XX have negative curves.

EXPERIMENTAL

M.p.s are uncorrected. UV spectra have been measured with a Cary 11 Spectrometer. The IR spectra were recorded with a Perkin-Elmer Model 237 Spectrophotometer (reported in cm^{-1}) or in 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.

3 α -Acetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androst-12-ene-11,17,dione⁸ (IIc)

A soln of 100 mg of IIc⁸ and 67 mg of 2,3-dichloro-5,6-dicyanobenzoquinone in 5 ml of dioxane was refluxed overnight. The soln was diluted with CHCl_3 and evaporated. The residue was taken up in CHCl_3 and purified by TLC on neutral alumina (Activity V) using CHCl_3 . The UV absorbing band was eluted with AcOEt . It weighed 50 mg, $\lambda_{\text{max}}^{\text{MeOH}}$ 261 μ , $\epsilon = 5000$. Recrystallization from ether gave 13 mg of IIc, m.p. 169-171°. The analytical sample was recrystallized from

⁸ (a) N. L. Allinger, R. B. Hermann and C. Djerassi, *J. Org. Chem.* **25**, 922 (1960). (b) J. F. Biellmann, D. Francetic and G. Ourisson, *Tetrahedron Letters* No. 18, 4 (1960).

⁹ P. A. Diassi, I. Bacso, G. Krakower and H. A. Van Dine, *Tetrahedron* **22**, 3459 (1966).

¹⁰ J. F. Biellmann, P. Crabbe and G. Ourisson, *Tetrahedron* **3**, 303 (1958).

acetone-hexane and had m.p. 167–169°, $[\alpha]_{D589} -211^\circ$, $[\alpha]_{D578} -228^\circ$, $[\alpha]_{D560} -285^\circ$, $[\alpha]_{D536} -279^\circ$, $[\alpha]_{D505} -278^\circ$, $\lambda_{\text{max}}^{\text{OH}}$ 260 m μ , $\epsilon = 7500$. (Found: C, 74.09; H, 8.62. $\text{C}_{28}\text{H}_{44}\text{O}_4$ requires: C, 74.16; H, 8.66%.)

Reduction of IIc to 3 α -acetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-11,17-dione⁴ (IIIc)

(a) *Zinc-acetic acid.* Zinc dust, 100 mg, was added to a refluxing soln of 15 mg of IIc in 5 ml of glacial AcOH. After 30 min, the soln was cooled, filtered and evaporated. The residue was taken up in ether which was washed with water, dried and evaporated. Recrystallization of the residue, 10 mg, gave 3 mg of IIIc whose m.p. 184–185°, and IR spectrum (ν^{OH}) 1736, 1718 cm^{-1}) were identical with those of authentic material.

(b) *Catalytic hydrogenation.* A soln of 100 mg of IIc in 25 ml of 95% EtOH containing 25 mg of 5% Pd-CaCO₃ was hydrogenated at room temp and slight positive press. After uptake of H₂ ceased, the soln was filtered and evaporated to give 97 mg of residue. Recrystallization from MeOH gave authentic IIIc.

3 α -Hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-11,17-dione (IIIb)

A soln of 20 ml of 5% ethanolic KOH was heated to reflux under He, 200 mg of IIIc were added, and reflux was continued for 20 mins. The hot soln was acidified with 20% H₂SO₄ and the solvent evaporated. The aqueous residue was extracted with AcOEt which was washed with saturated NaCl aq until neutral. After drying, the solvent was evaporated, to give 145 mg of material which crystallized from MeOH yielding 75 mg of IIIb, m.p. 152–154°. The analytical sample had m.p. 156–158°, $[\alpha]_{D589} +16^\circ$, $[\alpha]_{D578} +20^\circ$, $[\alpha]_{D560} +29^\circ$, $[\alpha]_{D536} +119^\circ$, $[\alpha]_{D505} +454^\circ$, $\lambda_{\text{max}}^{\text{KBr}}$ 2.90, 5.77, 5.86 μ . (Found: C, 75.82; H, 9.78. $\text{C}_{27}\text{H}_{42}\text{O}_3$ requires: C, 75.86; H, 9.70%.)

Acetylation of 25 mg of this compd (acetic anhydride-pyridine, room temp—overnight) gave back IIIc m.p. 184–186°, IR spectrum identical with that of authentic sample.

4 α ,8,14-Trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-3,11,17-trione^{1,4} (IIIa)

After oxidation of 25 mg of IIIb in 2.5 ml of acetone with Jones reagent, the soln was diluted with water and 16 mg of IIIa, m.p. 164–165° were collected. Recrystallization from MeOH raised the m.p. to 171–174° and gave material whose IR spectrum was identical with that of authentic material.

3 α -Hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11,17-dione (IVb)

A soln of 50 ml of 5% ethanolic KOH was heated to reflux under a blanket of He. To the hot solution was added 483 mg of IIIb and the mixture was refluxed for 92 min under He. The reaction mixture was then acidified with 20% H₂SO₄, cooled and diluted with water. After evaporation of the solvent the aqueous residue was extracted with CH₂Cl₂ and the CH₂Cl₂ soln washed with water until neutral, dried (MgSO₄) and evaporated to give 476 mg of residue. Trituration with ether gave 223 mg of IVb, m.p. 225–230°. Recrystallization from MeOH gave analytically pure material, m.p. 237–239°, $[\alpha]_{D589} -176^\circ$, $[\alpha]_{D578} -186^\circ$, $[\alpha]_{D560} -216^\circ$, $[\alpha]_{D536} -445^\circ$, $[\alpha]_{D505} -1020^\circ$, $\lambda_{\text{max}}^{\text{KBr}}$ 2.90, 5.76, 5.97 μ . (Found: C, 75.80; H, 9.75. $\text{C}_{27}\text{H}_{42}\text{O}_3$ requires: C, 75.86; H, 9.70%.)

3 α -Acetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11,17-dione (IVc)

(a) A soln of 227 mg of IVb in 5 ml of pyridine and 2.5 ml of acetic anhydride was left overnight at room temp. The excess acetic anhydride was decomposed with water and the mixture evaporated. Two crystallizations from MeOH gave 100 mg of IVc, m.p. 202–205°. The analytical sample had m.p. 203–205°, $[\alpha]_{D589} -154^\circ$, $[\alpha]_{D578} -165^\circ$, $[\alpha]_{D560} -191^\circ$, $[\alpha]_{D536} -385^\circ$, $[\alpha]_{D505} -860^\circ$, ν^{OH} 1736, 1689 cm^{-1} . (Found: C, 73.83; H, 9.19. $\text{C}_{28}\text{H}_{44}\text{O}_4$ requires: C, 73.76; H, 9.15%.)

(b) To 160 ml of dioxane saturated with HCl was added 1.00 g of IIIc. After 16 hr at room temp, the reaction mixture was diluted with water and the solution concentrated under red. press. The concentrated residue was extracted with CH₂Cl₂, and the CH₂Cl₂ soln washed with water until neutral, dried and evaporated to give 0.95 g of crude product. Two recrystallizations from MeOH gave 0.60 g of IVc, m.p. 203–205°, whose IR spectrum was identical with that of the material prepared above.

Equilibration studies of IIIb and IVb

Table 2 shows the results of the equilibration of IIIb and IVb. Lines 1 and 5 refer to the rotations of the pure compds IIIb and IVb. Lines 2, 3 and 4 refer to the rotations of the crude material obtained from the refluxing ethanolic KOH treatment of either IIIc or IVc for the length of time given in

Table 2. The conditions are similar to those given above for the preparative experiments. From this data we see that starting with the 9 β isomer IIIc equilibrium is achieved after 3½ hr and starting from the 9 α side, this equilibrium is reached in 1 hr. The equilibrium mixture is approximately 85:15 in favor of the 9 α isomer.

TABLE 2

Reaction time— (starting material)	$[\alpha]_D$	9 α	% 9 β
(1)	+16°	0	100
(2) 1½ hr. (9 β)	-67°	43	57
(3) 3½ hr. (9 β)	-148°	86	14
(4) 1 hr. (9 α)	-153°	88	12
(5)	-176°	100	0

4 α ,8,14-Trimethyl-18-nor-5 α ,8 α ,14 β -androstane-3,11,17-trione (IVa)

(a) To a soln of 400 mg of IIIa in 10 ml of EtOH, 2 ml of 2N NaOH were added and the soln refluxed under He for 1 hr. The soln was cooled, neutralized slowly with 2N HCl and then diluted with water whereupon crystals separated. They were filtered, washed with water and dried to give 309 mg of IVa having a m.p. of 255–257°, $[\alpha]_{589} -154^\circ$, $[\alpha]_{578} -163^\circ$, $[\alpha]_{546} -190^\circ$, $[\alpha]_{438} -380^\circ$, $[\alpha]_{366} -808^\circ$, λ_{max}^{Nujol} 5.77, 5.86, 5.92 μ . (Found: C, 76.24; H, 9.18. C₂₁H₃₀O₃ requires: C, 76.32 H, 9.15%.)

(b) A soln of 30 mg of IVb in 5 ml of acetone was treated with an excess of Jones reagent. After 15 min at room temp the excess CrO₃ soln was decomposed with MeOH and the soln diluted with water. After evaporation of the solvent the aqueous suspension was extracted with CH₂Cl₂, and the CH₂Cl₂ washed with saturated NaCl aq, dried (MgSO₄) and evaporated. Two recrystallizations from MeOH gave 14 mg of IVa, m.p. 253–257°, IR identical with that of material described above.

3 α -Acetoxy-17-ethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-11-one^b (Vc) and 3 α -acetoxy-11,17-bisethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,13 α ,14 β -androstane (VIc).

A mixture of 1.00 g of IVc, 300 ml of benzene (Na dried) 50 ml of ethylene glycol and 100 mg of *p*-toluenesulfonic acid was refluxed for 70 hr in an apparatus provided with a Dean-Stark water separator and a CaC₂ thimble through which refluxate dripped. After cooling, the reaction mixture was neutralized with 5% NaHCO₃. CHCl₃, 100 ml, was added and the organic layer was separated, washed with water, dried and evaporated to give 1.217 g of crude material. The crude product was triturated with MeOH and 149 mg of VIc were obtained, m.p. 207–213°, $[\alpha]_{589} +2.0$, $[\alpha]_{578} -1.8^\circ$, $[\alpha]_{546} -0.6^\circ$, $[\alpha]_{438} +0.6^\circ$, $[\alpha]_{366} +5.2^\circ$, λ_{max}^{KBr} 5.77, 8.0 μ . After drying the analytical sample had m.p. 212–216°, τ 6.07 (s, 3-OCH₂CH₂O), 6.14 (br, 11-OCH₂CH₂O). (Found: C, 69.71; H, 8.96. C₃₇H₄₈O₆ requires: C, 70.10; H, 9.15%.)

The mother liquors from the above crystallization were thin layer chromatographed on neutral alumina (Activity V) using CHCl₃ as the solvent. The major bands as detected by UV were eluted and the less polar band, *R_f* \approx 0.4–0.6, weighed 733 mg and crystallized on the addition of MeOH to give 296 mg of Vc^b, m.p. 133–138°. Recrystallization from MeOH gave analytically pure material, m.p. 137–139°, $[\alpha]_{589} -14^\circ$, $[\alpha]_{578} -13^\circ$, $[\alpha]_{546} -11^\circ$, $[\alpha]_{438} +30^\circ$, $[\alpha]_{366} +24^\circ$, ν^{CHCl_3} 1712 cm⁻¹ (broad), τ 6.11 (s, 17-OCH₂CH₂O). (Found: C, 72.12; H, 8.74. C₃₅H₄₆O₆ requires: C, 71.74; H, 9.15%.)

Hydrolysis of monoketal Vc. 3 α -Acetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-11,17-dione IIIc

A soln of 21 mg of Vc in 3 ml of 80% AcOH was stirred overnight at room temp. The soln was diluted with water and the resulting precipitate was collected. After drying, this material 12 mg had m.p. 183–187° and its IR spectrum and rotation were identical with that of authentic IIIc.

Hydrolysis of bisketal VIc. 3 α -Acetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,13 α ,14 β -androstane-11,17-dione (IXc)

A soln of 28 mg of VIc in 2.5 ml of 80% AcOH was stirred overnight at room temp. The reaction mixture was diluted with water and the resulting precipitate collected and dried, 7 mg, m.p. 199–205°.

An additional 12 mg of material was obtained from evaporation of the filtrate. The combined material was recrystallized twice from MeOH to give analytically pure IXc, m.p. 199–201°, $[\alpha]_{589} -71^\circ$, $[\alpha]_{578} -77^\circ$, $[\alpha]_{546} -89^\circ$, $[\alpha]_{488} -207^\circ$, $[\alpha]_{365} -538^\circ$, ν^{CHCl_3} 1736, 1725 cm^{-1} . (Found: C, 73.65; H, 9.14. $\text{C}_{28}\text{H}_{38}\text{O}_4$ requires: C, 73.76; H, 9.15%.)

3 α -Acetoxy-17-ethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11-one (VIIc) and 3 α -acetoxy-17-ethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androstane-11-one (VIIIc)

A mixture of 991 mg of IVc, 300 ml of benzene (Na dried), 50 ml of ethylene glycol and 100 mg of *p*-toluenesulfonic acid were refluxed as described above for 70 hr. The reaction mixture was cooled and neutralized with 5% NaHCO_3 and 100 ml of CHCl_3 were added. The CHCl_3 -benzene layer was separated and washed with water, dried and evaporated to give 1.163 g of material. Recrystallization from MeOH gave a first crop of 600 mg having a m.p. of 162–165°. A small portion of this was recrystallized to give analytically pure VIIc, m.p. 165–167°, $[\alpha]_{589} -145^\circ$, $[\alpha]_{578} -153^\circ$, $[\alpha]_{546} -177^\circ$, $[\alpha]_{488} -352^\circ$, $[\alpha]_{365} -765^\circ$, ν^{CHCl_3} 1720, 1686 cm^{-1} , τ 6.13 (br, 17-OCH₂CH₂O). (Found: C, 71.50; H, 9.21. $\text{C}_{28}\text{H}_{38}\text{O}_4$ requires: C, 71.74; H, 9.15%.)

The second and third crops from the crystallization of the crude product weighed 174 mg and had a melting range of 130–150°. Recrystallization of this material gave 168 mg, m.p. 134–148°. A TLC of this material on neutral alumina (Activity V) in CHCl_3 showed the presence of two spots (detection by I₂). The more polar had an $R_f \approx 0.4$ identical to that of VIIc described above and the less polar had an $R_f \approx 0.55$. A preparative TLC showed a wide band, $R_f \approx 0.3$ – 0.6 (detectable by UV) which was cut into two parts and eluted with AcOEt. The more polar part of this band, 27 mg, after recrystallization gave 6 mg of VIIc, m.p. 163–165°. The less polar part of the band on elution gave 94 mg of VIIIc which after three recrystallizations from MeOH weighed 28 mg and had m.p. 185–187°, $[\alpha]_{589} -175^\circ$, $[\alpha]_{578} -184^\circ$, $[\alpha]_{546} -210^\circ$, $[\alpha]_{488} -385^\circ$, $[\alpha]_{365} -717^\circ$, ν^{CHCl_3} 1712, 1693 cm^{-1} , τ 6.16 (br, 17-OCH₂CH₂O). (Found: C, 71.75; H, 9.22. $\text{C}_{29}\text{H}_{38}\text{O}_4$ requires: C, 71.74; H, 9.15%.)

Hydrolysis of monoketal VIIc. 3 α -Acetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11,17-dione (IVc)

A soln of 25 mg of VIIc in 3 ml of 80% AcOH was stirred overnight at room temp. Dilution with water gave a precipitate of IVc which after drying weighed 12 mg and had m.p. 195–198°, $[\alpha]_{589} -162^\circ$, $[\alpha]_{578} -170^\circ$, $[\alpha]_{546} -197^\circ$, $[\alpha]_{488} -385^\circ$, $[\alpha]_{365} -880^\circ$.

Hydrolysis of monoketal VIIIc. 3 α -Acetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androstane-11,17-dione (Xc)

Twelve mg of VIIIc was hydrolyzed (80% AcOH) and worked up as described above. The crude precipitate obtained was recrystallized from acetone-hexane to give 3 mg of Xc, m.p. 158–160°, $[\alpha]_{589} -275^\circ$, $[\alpha]_{578} -288^\circ$, $[\alpha]_{546} -330^\circ$, $[\alpha]_{488} -648^\circ$, $[\alpha]_{365} -1360^\circ$, ν^{KBr} 1742, 1730 (sh), 1705 cm^{-1} . (Found: C, 73.42; H, 9.27. $\text{C}_{29}\text{H}_{38}\text{O}_4$ requires: C, 73.76; H, 9.15%.)

3,17-Bisethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-11-one (Vd) and 3,11,17-trisethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,13 α ,14 β -androstane (VI d)

A mixture of 400 mg of IIIa, 100 ml of dry benzene, 20 ml of ethylene glycol and 40 mg of *p*-toluenesulfonic acid monohydrate was stirred under reflux for 40 hr. The water formed during the reaction was removed by a Dean-Stark moisture trap containing a CaC₂ thimble. The soln was then diluted with CHCl_3 , washed with 5% NaHCO_3 and then with water and evaporated under red. press. This residue was plate chromatographed on neutral alumina (Activity V) using CHCl_3 -hexane (1:1, v:v) as the developing solvent. Two bands both less polar than starting material were detectable by I₂ vapor at $R_f \approx 0.4$ and $R_f \approx 0.5$ respectively. Elution of the less polar band gave 146 mg of material which was re-plate chromatographed using the same system. Crystallization of the less polar material from MeOH gave 37 mg of VI d having a m.p. 235–237°, $[\alpha]_{589} -35^\circ$, $[\alpha]_{578} -39^\circ$, $[\alpha]_{546} -44^\circ$, $[\alpha]_{488} -75^\circ$, $[\alpha]_{365} -120^\circ$, τ 6.12 (s, 3-OCH₂CH₂O), 6.13 (b, 11 + 17-OCH₂CH₂O), 9.17 (d, J = 6, 4 α -CH₃). (Found: C, 70.07; H, 9.13. $\text{C}_{27}\text{H}_{42}\text{O}_6$ requires: C, 70.10; H, 9.15%.)

The more polar material on elution with AcOEt, gave 226 mg of Vd which could not be induced to crystallize. It had τ 5.99 (s, OCH₂CH₂O), 6.04 (s, OCH₂CH₂O), 9.17 (d, J = 6, 4 α -CH₃).

Hydrolysis of Vd

A soln of 91 mg of Vd in 4.0 ml of 80% AcOH was kept at room temp for 16 hr then diluted with water. The crystals which separated were filtered, washed with water and dried to give 38 mg of IIIa having m.p. 163–165°, $[\alpha]_{D20} +93^\circ$, $[\alpha]_{D25} +99^\circ$, $[\alpha]_{D40} +120^\circ$, $[\alpha]_{D50} +276^\circ$, $[\alpha]_{D60} +756^\circ$.

Hydrolysis of VIId. 4 α ,8,14-Trimethyl-18-nor-5 α ,8 α ,9 β ,13 α ,14 β -androstane-3,11,17-trione^{4,5} (IXa)

Similarly, hydrolysis of 65 mg of VIId gave 43 mg of IXa^{4,5} having m.p. of 203–205°, $[\alpha]_{D20} +31^\circ$, $[\alpha]_{D25} +32^\circ$, $[\alpha]_{D40} +34^\circ$, $[\alpha]_{D50} +13^\circ$, $[\alpha]_{D60} -146^\circ$.

Ketalization of 100 mg of IXa by the procedure described above gave 33 mg of the trisketal VIId.

IVa from IXa

To a suspension of 50 mg of IXa in 2.0 ml of EtOH, 0.4 ml of 2N NaOH was added and the mixture refluxed under N₂ for 1 hr. The soln was then cooled, neutralized with 2N HCl acid and diluted with water whereupon crystals separated. They were filtered, washed with water and dried to give 42 mg of IVa having m.p. of 256–258°.

3,17-Bisethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11-one (VIId) and 3,17-Bisethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androstane-11-one (VIId)

A mixture of 468 mg of IVa, 117 ml of dry benzene, 23 ml of ethylene glycol and 46 mg of *p*-toluenesulfonic acid monohydrate was stirred under reflux for 40 hr. The water formed during the reaction was removed by a Dean-Stark moisture trap containing a CaC₂ thimble. The yellow soln was then diluted with CHCl₃ and washed with 5% NaHCO₃ and then with water and evaporated under red. press. The residue on crystallization from acetone-hexane gave 302 mg of VIId having m.p. of 182–184°, $[\alpha]_{D20} -132^\circ$, $[\alpha]_{D25} -140^\circ$, $[\alpha]_{D40} -163^\circ$, $[\alpha]_{D50} -334^\circ$, $[\alpha]_{D60} -662^\circ$, $\lambda_{max}^{Nujol} 5.91 \mu$, $\tau 6.07$ (s, 3-OCH₂CH₂O), 6.08, 6.20 (br, 17-OCH₂CH₂O), 9.16 (d, J = 6, 4 α -CH₃). (Found: C, 71.60; H, 9.07. C₂₈H₃₈O₈ requires: C, 71.74; H, 9.15%.)

The mother liquor was evaporated and the residue plate chromatographed on neutral alumina using chloroform-hexane (3:1, v:v) as the developing solvent. Detection by I₂ vapor showed two visible bands at R_f \approx 0.6 and 0.4, respectively. Elution of the latter band with AcOEt, evaporation and crystallization gave an additional 64 mg of VIId. From the less polar band by following the above procedure 72 mg of VIId were obtained having m.p. of 215–216° $[\alpha]_{D20} -160^\circ$, $[\alpha]_{D25} -164^\circ$, $[\alpha]_{D40} -189^\circ$, $[\alpha]_{D50} -349^\circ$, $[\alpha]_{D60} -648^\circ$, $\lambda_{max}^{Nujol} 5.91 \mu$, $\tau 6.06$ (s, 3-OCH₂CH₂O), 6.19 (m, 17-OCH₂CH₂O), 9.17 (d, J = 5.5, 4 α -CH₃). (Found: C, 71.68; H, 9.21. C₂₈H₃₈O₈ requires: C, 71.74; H, 9.15%.)

IVa from VIId

A soln of 50 mg of VIId in 20 ml of MeOH and 0.7 ml of 8% H₂SO₄ was refluxed for 60 min. The MeOH was partially removed by evaporation under red. press. and on dilution with water crystals separated which were filtered, washed with water and dried to give 26 mg of IVa.

Similarly 50 mg of VIId in 4 ml of 80% AcOH on standing at room temp for 16 hr on dilution with water gave 31 mg of IVa.

VIId from Vd

A soln of 161 mg of Vd in a mixture of 3.75 ml of EtOH and 0.75 ml of 2N NaOH was refluxed under He for 60 min. The yellow soln was cooled and on dilution with water crystals separated. They were filtered washed with water and dried to give 102 mg of VIId.

4 α ,8,14-Trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androstane-3,11,17-trione (Xa)

A soln of 50 mg of VIId in 4.0 ml of 80% AcOH was kept at room temp overnight and then diluted with water. The mixture was extracted with CHCl₃ which was washed with water and evaporated under red. press. The residue (41.5) mg on crystallization from acetone-hexane gave 33 mg of Xa having m.p. 170–172°, $[\alpha]_{D20} -275^\circ$. (Found: C, 76.40; H, 9.18. C₂₈H₃₈O₈ requires: C, 76.32; H, 9.15%.)

3,17-Bisethylenedioxy-11 α -hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane (XI)

To a soln of 600 mg of Vd in 48 ml of tetrahydrofuran (freshly distilled from LAH) 600 mg of LAH were added slowly and the mixture stirred at room temp for 1 hr. The excess LAH was decomposed with AcOEt then the mixture was diluted with water and extracted with CHCl_3 . The CHCl_3 was washed with water and evaporated under red. press. Crystallization of the residue from acetone-hexane gave 342 mg of XI having a m.p. of 173–175°, $[\alpha]_{D20}^{25} -82^\circ$, $[\alpha]_{D20}^{17.8} -86^\circ$, $[\alpha]_{D20}^{14.6} -97^\circ$, $[\alpha]_{D20}^{13.4} -164^\circ$, $[\alpha]_{D20}^{10.6} -255^\circ$. (Found: C, 71.61; H, 9.39. $\text{C}_{28}\text{H}_{40}\text{O}_8$ requires: C, 71.39; H, 9.59%.)

3,17-Bisethylenedioxy-11 β -hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane (XV)

To a soln of 600 mg of VIII in 50 ml of tetrahydrofuran (freshly distilled from LAH) 600 mg of LAH were added in portions over a 5-min period and the suspension stirred at room temp for 2.5 hr. The LAH was then decomposed by the dropwise addition of MeOH, the mixture diluted with water and extracted with CHCl_3 . The CHCl_3 was washed with water, evaporated under red. press., and the residue crystallized from acetone-hexane to give 547 mg of XV having a m.p. 202–204°, $[\alpha]_{D20}^{19.9} -60^\circ$, $[\alpha]_{D20}^{17.8} -62^\circ$, $[\alpha]_{D20}^{14.6} -70^\circ$, $[\alpha]_{D20}^{13.6} -117^\circ$, $[\alpha]_{D20}^{10.6} -180^\circ$. (Found: C, 71.25; H, 9.76. $\text{C}_{28}\text{H}_{40}\text{O}_8$ requires: C, 71.39; H, 9.59%.)

3,17-Bisethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androst-9(11)-ene (XIII)

(a) To a soln of 274 mg of XV in 8.1 ml of pyridine cooled to -20° , 2.7 ml of a soln of 100 mg of thionyl chloride per ml of pyridine were added dropwise over a 2-min period. The soln was placed in an ice bath for 30 min and then carefully diluted with water. The crystals which separated were filtered, washed with water and dried to give 250 mg of XIII having a m.p. of 106–108°, $[\alpha]_{D20}^{19.9} -82^\circ$, $[\alpha]_{D20}^{17.8} -86^\circ$, $[\alpha]_{D20}^{14.6} -98^\circ$, $[\alpha]_{D20}^{13.6} -167^\circ$, $[\alpha]_{D20}^{10.6} -263^\circ$, τ 4.52 (m, 11-H), 6.07 (s, 3-OCH₂CH₂O), 6.07 (s, 17-OCH₂CH₂O). (Found: C, 74.67; H, 9.54. $\text{C}_{28}\text{H}_{38}\text{O}_8$ requires: C, 74.59; H, 9.52%.)

(b) Similarly, following the above procedure but substituting the bisketal XI for XV there was obtained XIII.

3,17-Bisethylenedioxy-11 β -hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androstane (XVII)

Following the procedure for the preparation of XI 97 mg of VIII_d were reduced with LAH to give 35 mg of XVII having a m.p. of 211–213°, $[\alpha]_{D20}^{19.9} -66^\circ$, $[\alpha]_{D20}^{17.8} -69^\circ$, $[\alpha]_{D20}^{14.6} -79^\circ$, $[\alpha]_{D20}^{13.6} -131^\circ$, $[\alpha]_{D20}^{10.6} -201^\circ$, τ 5.61 (m, 11 α -H), 6.04 (s, 3-OCH₂CH₂O), 6.14 (m, OCH₂CH₂O), 9.16 (d, J = 6, 4 α -CH₂). (Found: C, 71.64; H, 9.59. $\text{C}_{28}\text{H}_{40}\text{O}_8$ requires: C, 71.39; H, 9.59%.)

3,17-Bisethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androst-9(11)-ene (XIX)

Fifty-five mg of XVII were dehydrated with thionyl chloride in pyridine as described for the preparation of XIII to give 38 mg of XIX having a m.p. of 121–123°, $[\alpha]_{D20}^{19.9} -62^\circ$, $[\alpha]_{D20}^{17.8} -66^\circ$, $[\alpha]_{D20}^{14.6} -74^\circ$, $[\alpha]_{D20}^{13.6} -120^\circ$, $[\alpha]_{D20}^{10.6} -177^\circ$, τ 4.54 (m, 11-H), 6.06 (s, 3-OCH₂CH₂O), 6.13 (m, 17-OCH₂CH₂O), 9.16 (d, J = 6, 4 α -CH₂). (Found: C, 74.43; H, 9.26. $\text{C}_{28}\text{H}_{38}\text{O}_8$ requires: C, 74.59; H, 9.52%.)

11 α -Hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-3,17-dione (XII)

A soln of 69 mg of XI in 3.0 ml of 80% AcOH was kept at room temp for 16 hr then diluted with water. The crystals which separated were filtered washed with water and dried to give 47 mg of XII having a m.p. of 181–183°, ORD (MeOH): $[\alpha]_{D20}^{10.6} -69^\circ$, $[\alpha]_{D20}^{10.0} -69^\circ$, $[\alpha]_{D20}^{10.0} -42^\circ$, $[\alpha]_{D20}^{10.0} \pm 0^\circ$, $[\alpha]_{D20}^{10.0} +159^\circ$, $[\alpha]_{D20}^{10.6} +1330^\circ$ (peak), $[\alpha]_{D20}^{10.1} \pm 0^\circ$, $[\alpha]_{D20}^{10.0} -2180^\circ$. (Found: C, 75.86; H, 9.60. $\text{C}_{27}\text{H}_{36}\text{O}_8$ requires: C, 75.86; H, 9.70%.)

11 β -Hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androstane-3,17-dione (XVIII)

Hydrolysis of 60 mg of XVII in 3.0 ml of 80% AcOH was carried out at room temp for 16 hr. On dilution with water, crystals separated which were filtered, washed with water and dried to give 31 mg of XVIII having a m.p. of 206–208°, ORD (MeOH): $[\alpha]_{D20}^{10.0} -238^\circ$, $[\alpha]_{D20}^{10.0} -238^\circ$, $[\alpha]_{D20}^{10.0} -248^\circ$, $[\alpha]_{D20}^{10.0} -570^\circ$, $[\alpha]_{D20}^{10.6} -1980^\circ$ (trough), $[\alpha]_{D20}^{10.0} \pm 0^\circ$, $[\alpha]_{D20}^{10.6} +1760^\circ$. (Found: C, 75.82; H, 9.69. $\text{C}_{27}\text{H}_{36}\text{O}_8$ requires: C, 75.86; H, 9.70%.)

11 β -Hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-3,17-dione (XVI)

(a) A soln of 100 mg of XV in a mixture of 10 ml of MeOH and 0.35 ml of 8% H₂SO₄ was refluxed for 1 hr, then partially evaporated and diluted with water. The crystals which separate were filtered, washed with water and dried to give 74 mg of XVI having a m.p. of 206–208°, ORD (MeOH): [α]₄₀₀ +13°, [α]₅₀₀ +52°, [α]₆₀₀ +171°, [α]₅₀₇ +2050° (peak), [α]₅₈₇ \pm 0°, [α]₅₈₂ –2660°. (Found: C, 75.90; H, 9.75. C₂₁H₃₂O₃ requires: C, 75.86; H, 9.70%.)

(b) From XVII. Compound XVII (30 mg) was hydrolysed with dilute H₂SO₄ as described above and gave 20 mg of XVI.

(c) From XVIII. A soln of 25 mg of XVIII in 2.5 ml of abs EtOH and 0.09 ml of 8% H₂SO₄ was refluxed for 60 min then cooled and diluted with water. The crystals which separated were washed with water and dried to give 20.7 mg of XVI.

4 α ,8,14-Trimethyl-18-nor-5 α ,8 α ,14 β -androst-9(11)-ene-3,17-dione (XIV)

A soln of 51.7 mg of XIII in a mixture of 4 ml of glacial AcOH and 1 ml of water was kept at room temp for 16 hr then slowly diluted with water. The crystals which separate were filtered, washed with water and dried to give 29 mg of XIV having a m.p. of 180–182°, [α]₅₀₀ +44°, [α]₅₇₈ +46°, [α]₅₄₆ +60°, [α]₄₃₈ +176°, [α]₃₈₈ +549°, ORD (MeOH): [α]₄₀₀ +53°, [α]₅₀₀ +505°, [α]₃₀₈ +3120° (peak), [α]₃₉₀ \pm 0°, [α]₂₈₈ –4100°, τ 4.45 (m, 11-H), 9.00 (d, J = 6, 4 α -CH₃). (Found: C, 80.28; H, 9.70. C₂₁H₃₀O₃ requires: C, 80.21; H, 9.62%.)

4 α ,8,14-Trimethyl-18-nor-5 α ,8 α ,13 α ,14 β -androst-9(11)-ene-3,17-dione (XX)

A soln of 21 mg of XIX in 1.0 ml of 80% AcOH was kept at room temp for 16 hr then diluted with water. The crystals which separated were filtered, washed with water and dried to give 11 mg of XX having a m.p. of 156–158°, [α]₅₀₀ –156°, [α]₅₇₈ –164°, [α]₅₄₆ –189°, [α]₄₃₈ –354°, [α]₃₈₈ –692°, τ 4.43 (m, 11-H), 8.93 (d, J = 5, 4 α -CH₃), ORD (MeOH): [α]₆₀₀ –188°, [α]₅₀₀ –241°, [α]₄₀₀ –410°, [α]₃₀₉ –2140° (trough), [α]₃₈₈ \pm 0°, [α]₂₈₈ +1210°. (Found: C, 80.21; H, 10.27. C₂₁H₃₀O₃ requires: C, 80.21; H, 9.62%.)

Equilibration of XX and XIV

(a) A soln of 80 mg of XIX in 8.0 ml of abs EtOH and 0.28 ml of 8% H₂SO₄ was refluxed for 15 min. A sample taken at this time and plate chromatographed using alumina (Activity V) as adsorbent, CHCl₃ as the developing solvent and detection by iodine showed that no starting material was present. The solution was diluted with water and the crystals which separated were recrystallized from acetone-hexane to give 22.0 mg of XIV. From the mother liquor on concentration 20.0 mg of XX were obtained.

(b) A soln of 80.0 mg of XIV in 8.0 ml of abs EtOH and 0.28 ml of 8% H₂SO₄ was refluxed for 60 min then cooled and diluted with water. The crystals which separate were filtered washed with water and dried at 100° under red. press. The rotation of these crystals were [α]₅₀₀ –66°, [α]₅₇₈ –69°, [α]₅₄₆ –76°, [α]₄₃₈ –111°, [α]₃₈₈ –124° indicating a composition of 55% of XX and 45% of XIV.

3 α -Acetoxy-17 α -hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-11-one (XXI)

A soln of 100 mg of IIIc and 275 mg of lithium tri-*tert*-butoxyaluminium hydride in 10 ml of tetrahydrofuran (freshly distilled from LAH) was heated at reflux for 90 min. The mixture was cooled, acidified with glacial AcOH and the solvent evaporated. The residue was extracted with methyl isobutyl ketone which was washed with 5% NaHCO₃ and saturated NaCl aq, dried and evaporated. The crude product was recrystallized from ether-hexane to give 21 mg of XXI having m.p. 165–169°. The analytical sample had m.p. 167–169°, [α]₅₀₀ –17°, [α]₅₇₈ –17°, [α]₅₄₆ –14°, [α]₄₃₈ +33°, [α]₃₈₈ +275°, ν^{CHCl_3} 1722, 1685 cm⁻¹. (Found: C, 73.48; H, 9.66. C₂₃H₃₄O₄ requires: C, 73.36; H, 9.64%.)

3 α -Acetoxy-17 α -hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11-one (XXIc)

(a) A soln of 316 mg of IVc and 875 mg of lithium tri-*tert*-butoxyaluminium hydride in 30 ml of tetrahydrofuran (freshly distilled from LAH) was heated at reflux temp for 2 hr. After addition of water and acidification with glacial AcOH the solvent was evaporated. The residue was taken up in AcOEt which was washed with saturated NaCl aq, dried and evaporated to give 295 mg of crude product. Recrystallization from MeOH gave 218 mg of XXIc having m.p. 241–243°. The analytical

sample had m.p. 245–247°, $[\alpha]_{D20} -176^\circ$, $[\alpha]_{D17.5} -185^\circ$, $[\alpha]_{D14.6} -215^\circ$, $[\alpha]_{D10.6} -420^\circ$, $[\alpha]_{D8.6} -875^\circ$, $\nu^{OHCl_3} 3589, 1722, 1685 \text{ cm}^{-1}$. (Found: C, 73.39; H, 9.69. $C_{22}H_{36}O_4$ requires: C, 73.36; H, 9.64%.)

(b) A soln of 37 mg of XXI in 5 ml of dioxane saturated with HCl was kept overnight at room temp. The soln was diluted with water and concentrated under red. press. Extraction of the residue with AcOEt and washing of the resulting soln with water, drying and evaporation gave 21 mg of crude material. Recrystallization from MeOH gave 9 mg of XXIIc having m.p. 243–245° and IR spectrum identical with that of material described above.

3-Ethylenedioxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11,17-dione (IVd)

A soln of 100 mg of IVa in 10 ml of 2-methyl-2-ethyl-1,3-dioxolane containing 50 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 25 min. The slightly yellow soln was cooled, diluted with ether and 0.2 ml of pyridine were added. The soln was then extracted with water, dried (Na_2SO_4) and evaporated under red. press. The residue on crystallization from acetone-hexane gave 70 mg of IVd having a m.p. of 203–205°, $[\alpha]_{D20} -137^\circ$, $[\alpha]_{D17.5} -144^\circ$, $[\alpha]_{D14.6} -167^\circ$, $[\alpha]_{D10.6} -348^\circ$, $[\alpha]_{D8.6} -792^\circ$. (Found: C, 73.85; H, 9.19. $C_{22}H_{34}O_4$ requires: C, 73.76; H, 9.15%.)

3-Ethylenedioxy-17 α -hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11-one (XXIIId)

To a soln of 77 mg of IVd in 10 ml of abs EtOH 77 mg of $NaBH_4$ were added and the mixture stirred at room temp for 90 min. The soln was acidified with 10% AcOH then diluted with water. The crystals which separated were filtered, washed with water and dried to give 50 mg of XXIIId having a m.p. of 253–255°, $[\alpha]_{D20} -148^\circ$, $[\alpha]_{D17.5} -157^\circ$, $[\alpha]_{D14.6} -183^\circ$, $[\alpha]_{D10.6} -375^\circ$, $[\alpha]_{D8.6} -798^\circ$, ORD (MeOH): $[\alpha]_{D600} -125^\circ$, $[\alpha]_{D500} -176^\circ$, $[\alpha]_{D400} -364^\circ$, $[\alpha]_{D300} -840^\circ$, $[\alpha]_{D271} -2260^\circ$ (trough), $[\alpha]_{D258} \pm 0^\circ$, $[\alpha]_{D271} +2050^\circ$. (Found: C, 73.54; H, 9.49. $C_{22}H_{36}O_4$ requires C, 73.36; H, 9.64%.)

17 α -Hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-3,11-dione (XXIIA)

A soln of 50 mg of XXIIId in 10 ml of MeOH containing 0.35 ml of 8% H_2SO_4 was refluxed for 1 hr. The soln was then partially evaporated, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ was washed with water, evaporated and the residue crystallized from acetone-hexane to give 31 mg of XXIIA having a m.p. of 222–224°, $[\alpha]_{D20} -157^\circ$, $[\alpha]_{D17.5} -165^\circ$, $[\alpha]_{D14.6} -191^\circ$, $[\alpha]_{D10.6} -371^\circ$, $[\alpha]_{D8.6} -766^\circ$. (Found: C, 75.94; H, 9.75. $C_{21}H_{32}O_3$ requires: C, 75.86; H, 9.70%.)

A soln of XXIIA in 5.0 ml of abs EtOH and 0.18 ml of 8% H_2SO_4 was refluxed for 60 min under N_2 . On dilution with water 45 mg of XXIIA were recovered.

3 β ,17 α -Dihydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11-one (XXIIe)

To a suspension of 100 mg of IVa in 10 ml of EtOH 100 mg of $NaBH_4$ were added and the mixture stirred at room temp for 60 min. The solution was acidified with 10% AcOH then diluted with water and extracted with $CHCl_3$. The $CHCl_3$ was washed with water and evaporated to dryness under red. press. The residue on crystallization from acetone-hexane gave XIV having a m.p. of 250–252°, $[\alpha]_{D20} -143^\circ$, $[\alpha]_{D17.5} -146^\circ$, $[\alpha]_{D14.6} -171^\circ$, $[\alpha]_{D10.6} -345^\circ$, $[\alpha]_{D8.6} -959^\circ$ (abs EtOH). (Found: C, 75.39; H, 10.30. $C_{21}H_{34}O_3$ requires: C, 75.40; H, 10.25%.)

3 α ,17 α -Dihydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11-one (XXIIb)

A suspension of 100 mg of LAH in 5 ml of tetrahydrofuran was added to a soln of 92 mg of IVc in 5 ml of tetrahydrofuran and the mixture was heated at reflux for 1 hr. The reaction mixture was cooled and a saturated Na_2SO_4 aq was added slowly until two layers formed. The organic layer was decanted, washed with saturated NaCl aq, dried and evaporated to give 86 mg of crude product. Two recrystallizations from ether-hexane gave 22 mg of XXIIb having m.p. 205–207°, $[\alpha]_{D20} -165^\circ$, $[\alpha]_{D17.5} -175^\circ$, $[\alpha]_{D14.6} -208^\circ$, $[\alpha]_{D10.6} -402^\circ$, $[\alpha]_{D8.6} -865^\circ$, $\nu^{KBr} 3350, 1675 \text{ cm}^{-1}$. The analytical sample had m.p. 207–208°. (Found: C, 75.37; H, 10.30. $C_{21}H_{34}O_3$ requires C, 75.40; H, 10.25%.)

3 α ,17 α -Diacetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androstane-11-one (XXIII)

(a) A soln of 70 mg of XXIIc in 2 ml of pyridine and 1 ml of acetic anhydride was kept at room temp. After 17 hr the reaction mixture was diluted with water and evaporated. Crystallization from MeOH gave 40 mg of XXIII having m.p. 154–156°, $[\alpha]_{D20} -107^\circ$, $[\alpha]_{D17.5} -114^\circ$, $[\alpha]_{D14.6} -132^\circ$, $[\alpha]_{D10.6} -271^\circ$, $[\alpha]_{D8.6} -618^\circ$, $\nu^{OHCl_3} 1731, 1689 \text{ cm}^{-1}$. (Found: C, 71.82; H, 9.21. $C_{20}H_{30}O_6$ requires: C, 71.74; H, 9.15%.)

(b) When XXIIb was treated with pyridine and acetic anhydride as described above XXIII was obtained, m.p. 155–157°, and identical in all respects with the material described in (a).

3 α ,17 α -Diacetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane-11-one (XXIV)

A soln of 170 mg of XXI in 2 ml of pyridine and 7 ml of acetic anhydride was kept at room temp overnight. The reaction mixture was diluted with water and evaporated to dryness. The resulting oil could not be crystallized but showed a single spot when analysed by TLC on neutral alumina (Activity V) with various solvent systems.

3 α ,17 α -Diacetoxy-11 α -hydroxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,9 β ,14 β -androstane (XXV)

A soln of 116 mg of non-crystalline XXIV and 90 mg of NaBH₄ in 10 ml of abs EtOH was stirred at room temp for 1 hr. The reaction mixture was acidified with glacial AcOH and the solvent evaporated. The residue was extracted with AcOEt, washed with saturated NaCl aq, dried and evaporated to give 119 mg of crude product. Two recrystallizations from MeOH gave 42 mg of XXV having m.p. 177–179°. The analytical sample had m.p. 178–180°, [α]_{D²⁰} –102°, [α]_{D¹⁷} –106°, [α]_{D¹⁴} –120°, [α]_{D¹³} –201°, [α]_{D¹¹} –306°. (Found: C, 71.30; H, 9.58. C₂₈H₄₆O₆ requires: C, 71.39; H, 9.59%.)

3 α ,17 α -Diacetoxy-4 α ,8,14-trimethyl-18-nor-5 α ,8 α ,14 β -androst-9(11)-ene (XXVI)

A soln of 100 mg of thionyl chloride in 1 ml of pyridine was added over a period of 1 min to a soln of 100 mg of XVI in 3.0 ml of pyridine at –20°. The mixture was then kept at 0° for 20 min and diluted with water. Extraction with AcOEt was followed by washing the organic phase with 5% HCl saturated NaCl aq, and evaporation of the AcOEt. The resulting viscous oil could not be crystallized. Distillation at 180° and 0.001 mm press. gave XXVI as a clear, colorless gum, [α]_{D²⁰} –83°, [α]_{D¹⁷} –87°, [α]_{D¹⁴} –98°, [α]_{D¹³} –188°, [α]_{D¹¹} –258°, τ 4.48 (br, 11-H), 4.77 (br, 17 β -H), 5.08 (br, 3 β -H). (Found: C, 74.38; H, 9.19. C₂₈H₄₆O₄ requires: C, 74.59; H, 9.52%.)

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