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The C-1,2 Isomeric Ketols and Diols in 17β-Hydroxy-A-nor-5α-androstane Series

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The possible four isomeric C-1,2 ketols and diols of 17β-hydroxy-A-nor-5α-androstane were prepared. The rearrangements of the four ketol isomers under acidic and basic conditions were examined.

In the previous paper,[2] the four isomeric C-1,2 ketols in the A-nor-5β-androstane series were prepared and their rearrangements under acidic and basic conditions were investigated. In connection with their results, it is of interest to examine the behavior of the C-1,2 ketol isomers in the A-nor-5α-androstane series towards acid and base. This paper is concerned with the preparation of four ketols and four diols of A-nor-5α-androstan-17β-ol, isomeric at C-1,2, and also with the investigation on the ketol rearrangements.

Of the possible four isomeric C-1,2 ketols of A-nor-5α-androstan-17β-ol, the 1β-hydroxy-2-ketone (Ia) has already been prepared.[3] Thus, the remaining three ketol isomers were synthesized by the analogous method to the preparation[4,5] of C-16,17 ketols of the 14α-steroids.

Epoxidation of 2,17β-diacetoxy-A-nor-5α-androst-1-ene[6] (II) with *m*-chloroperbenzoic acid in carbon tetrachloride gave the α-epoxydiacetate (III) which on mild acid treatment afforded a second ketol, mp 211—213°, in 71% yield. Acetylation of this ketol with acetic anhydride and pyridine gave the ketol diacetate which on treatment with zinc and acetic acid afforded the known 2-ketone (V). This showed that the ketol has the 1ξ-hydroxy-2-ketone structure. However, the ketol differed from the previously obtained 1β-hydroxy-2-ketone[3] (Ia) and hence was decided as the 1α-hydroxy-2-ketone (IVa). The α-configuration of the C-1 hydroxyl group was established by the following reactions. Reduction of IVa with lithium aluminum hydride yielded two isomeric triols, mp 187—188° and mp 217—218°, in a ratio of 1:3. In the infrared (IR) spectra,[7] the former triol displays bands at 3539 and 3625 cm^{-1} due to a hydrogen bonded hydroxyl group and a free hydroxyl group and the latter triol lacks band due to an intramolecularly hydrogen bonded hydroxyl group. This suggested that the vicinal glycols at C-1 and C-2 are *cis* in the former and *trans* in the latter. The *cis*-glycol differed from the previously obtained 1β,2β,17β-triol[3] (XVIIIa) and thus was deduced to be the 1α,2α,17β-triol (VIa). The triol (VIa) was acetylated with acetic anhydride in pyridine giving the triacetate (VIc), identical with the material obtained by *cis*-hydroxylation of 17β-acetoxy-A-nor-5α-androst-1-ene[6] (VIII) with osmium tetroxide followed by acetylation. Treatment of VIa with acetone and *p*-toluenesulfonic acid afforded the acetonide (IXa) which on acid hydrolysis regenerated VIa, while the *trans*-glycol gave

1) Location: *Fukushima-ku, Osaka.*
2) K. Yoshida and T. Kubota, *Tetrahedron*, **21**, 759 (1965).
3) K. Yoshida and T. Kubota, *Chem. Pharm. Bull.* (Tokyo), **13**, 165 (1965).
4) N.S. Leeds, D.K. Fukushima and T.F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954); T.R. Rhone and M.N. Huffman, *Tetrahedron Letters*, **1965**, 1395.
5) J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 1478 (1955).
6) K. Yoshida and F. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **15**, 1966 (1967).
7) The infrared spectrum was determined in a carbon tetrachloride solution with a LiF prism and a 20 mm cell by a Nihon Bunko Infrared Spectrophotometer Model DS-402G.

no acetonide as expected. On treatment with digitonin, the *cis*-glycol (VIa) gave no digitonide, whereas the *trans*-glycol afforded the digitonide, indicative of β-configuration[8] of the C-2 hydroxyl group. This fact showed the *trans*-glycol to have the $1\alpha,2\beta,17\beta$-triol structure (VIIa). From the above results, the original ketol was determined to be the structure formulated as IVa.

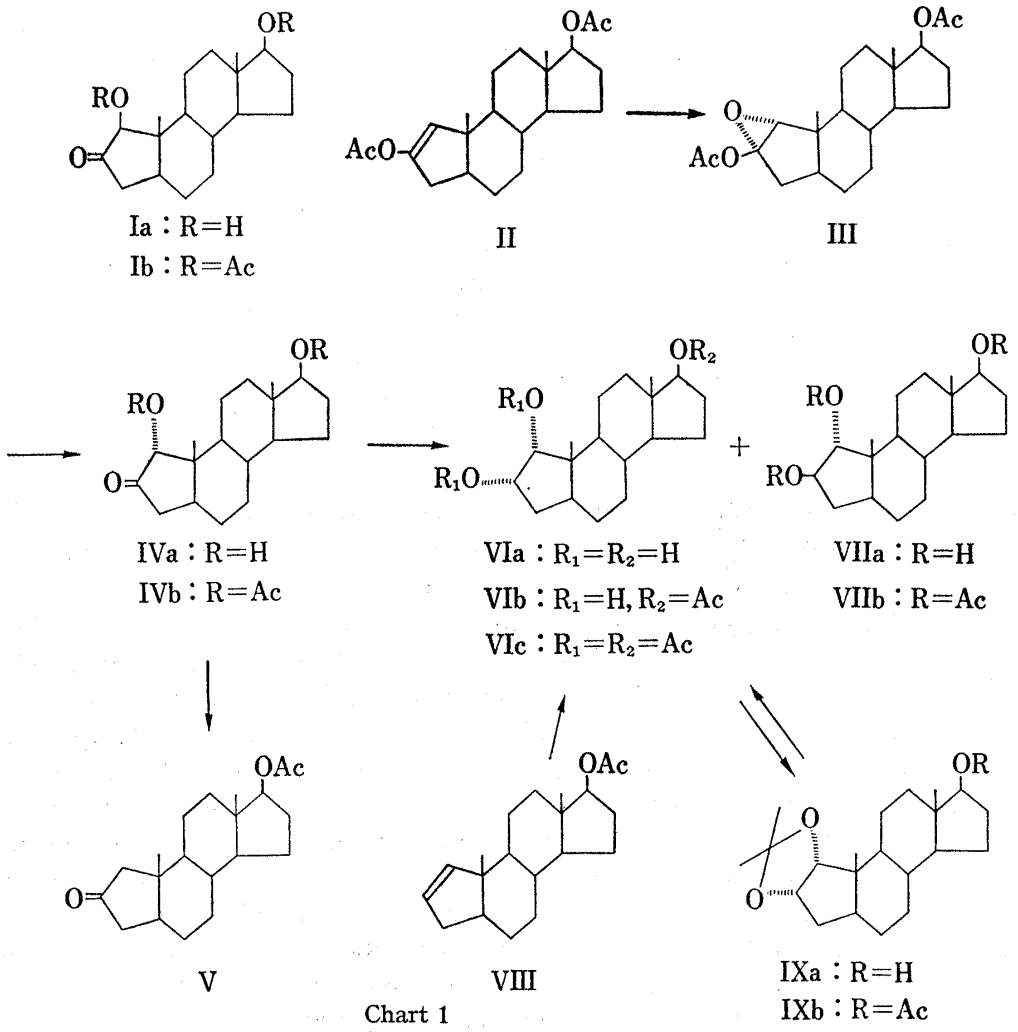

Chart 1

When 17β-acetoxy-A-nor-5α-androstan-1-one[6] (X) was treated with isopropenyl acetate containing a catalytic amount of sulfuric acid, the enol acetate (XI) was obtained in 68% yield with 29% recovery of X. Epoxidation of XI with *m*-chloroperbenzoic acid and subsequent acid treatment of the resultant α-epoxy diacetate (XII) afforded a third ketol, mp 165—166°, in 84% yield, to which the $2\alpha,17\beta$-dihydroxy-A-nor-5α-androstan-1-one structure (XIIIa) was assigned on the basis of the following chemical evidence. Acetylation of XIIIa and subsequent treatment with zinc and acetic acid gave the 1-ketone (X). Reduction of XIIIa with lithium aluminum hydride yielded a mixture of the above-mentioned $1\alpha,2\alpha,17\beta$-triol (VIa) and an unknown triol in 4:5 ratio. The new triol obtained had a *trans*-glycol function at C-1,2, since its IR spectrum[7] showed no absorption due to hydrogen bonded hydroxyl group and treatment with acetone and *p*-toluenesulfonic acid gave no acetonide. Moreover, this *trans*-glycol, different from the above-mentioned $1\alpha,2\beta,17\beta$-triol (VIIa), gave no digitonide on treatment with digitonin and, consequently, was defined as the $1\beta,2\alpha,17\beta$-triol (XIVa).

8) R.E. Marker, O. Kamm, D.M. Jones and L.W. Mixon, *J. Am. Chem. Soc.*, **59**, 1363 (1937); W.G. Dauben, G.A. Boswell and W.H. Templeton, *J. Am. Chem. Soc.*, **83**, 5006 (1961).

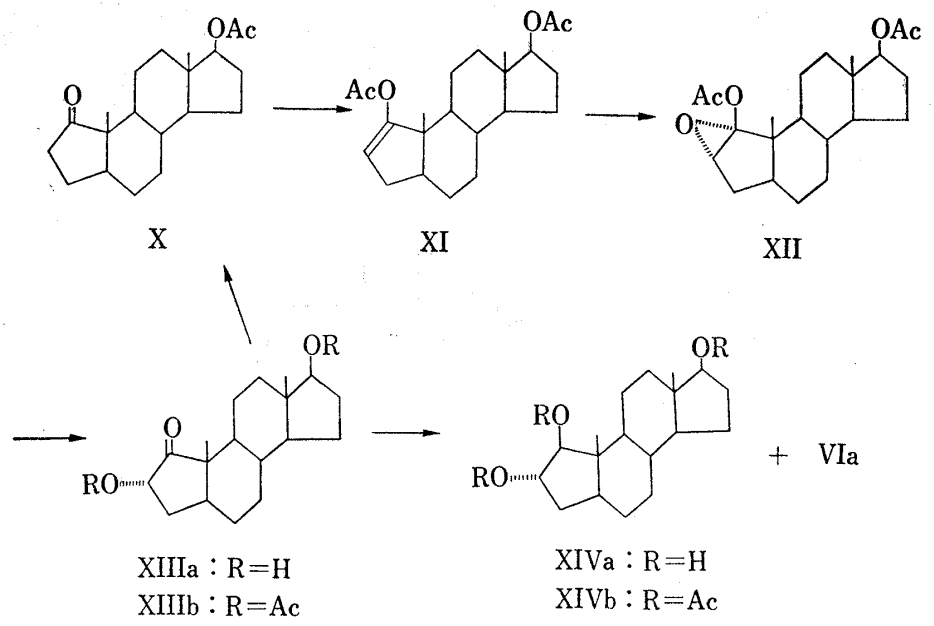

Chart 2

Thus, in connection with the structural elucidation of the above-mentioned ketols, all the four A-nor-5α-androstane-1,2,17β-triols, isomeric at C-1,2, have been prepared.

Finally, synthesis of the remaining ketol isomer, 2β-hydroxy-1-ketone (XVIIa), was carried out by using the 1α,2α-epoxide according to the procedure reported[5] for the preparation of the 16β-acetoxy-17-ketone in the 14α-series. When the 1α,2α-epoxide[6] (XV) was refluxed with glacial acetic acid, it afforded a mixture of several products, which was separated by thin-layer chromatography (TLC) on silica gel. The expected 1α,2β,17β-triol 2,17-diacetate (XVI, 15.2%) and the triacetate (VIIb, 6.6%) were as the minor products obtained and the major product in this reaction was a mixture (61.8%) of the unexpected rearranged products. The structures of the rearranged products will be reported in the next paper. Confirmation of the 1α-hydroxy-2β-acetoxy structure of XVI was obtained by acetylation to give the 1α,2β,17β-triacetate (VIIb) and by chromic trioxide oxidation to yield the desired 2β-acetoxy-1-ketone (XVIIb), mp 167—168° in quantitative yield, but not the known 1β-acetoxy-2-ketone (Ib). Expectedly, this acetoxy-ketone (XVIIb) was converted by treatment with zinc and acetic acid into the 1-ketone (X) and by reduction with lithium aluminum hydride into the single 1β,2β,17β-triol[3] (XVIIIa).

Attempts to convert the ketol acetate (XVIIb) into the 2β-hydroxy-1-ketone (XVIIa) by acid hydrolysis were unsuccessful. Treatment of XVIIb with dilute methanolic sulfuric acid at room temperature for 50 hr afforded a ketol which appeared homogenous on thin-layer chromatographic examinations. However, the acetate obtained by acetylation of the ketol exhibited two spots on TLC. Thus separation by TLC afforded the 2β-acetoxy-1-ketone (XVIIb) and the 1β-acetoxy-2-ketone (Ib), arising from isomerization of XVIIa with acid, in approximately 3:2 ratio. Treatment of XVIIb with the same reagents at room temperature for 16 hr followed by separation by TLC gave a ketol, mp 208—213°, and a ketol monoacetate, characterized by the elemental analysis and the IR spectrum. The product prepared by acetylation of this ketol was again found to be a mixture and separation by TLC gave XVIIb and Ib in 8:1 ratio. These facts indicated that the ketol (XVIIa) was partially isomerized into Ia even by such mild acid treatments and XVIIa could not be prepared in pure form.

Incidentally, the 1β-acetoxy-2-ketone (Ib) which resisted to crystallize previously[3] was obtained as crystals, mp 123—124°, which on lithium aluminum hydride reduction afforded two triols, XIVa and XVIIIa, in 1: 5 ratio.

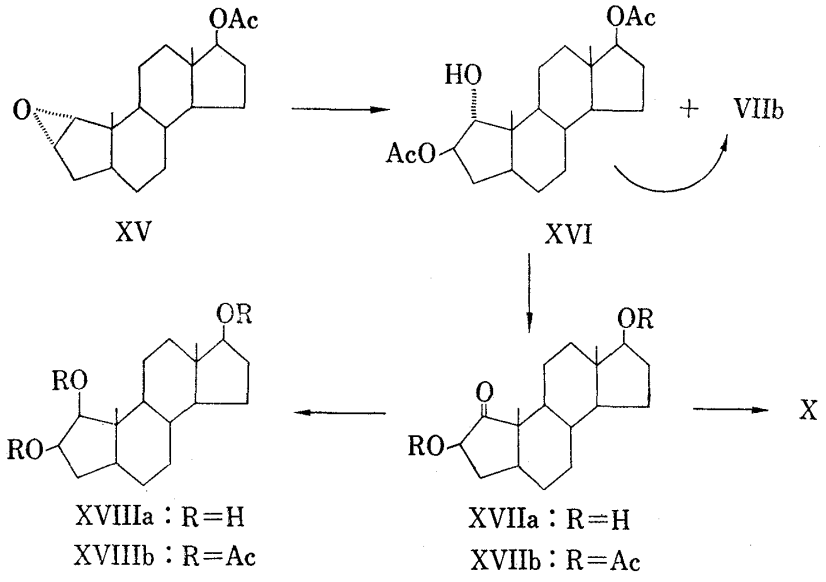

Chart 3

The IR spectra of the 1-acetoxy-2-ketone epimers, Ib and IVb, displayed a methylene absorption adjacent to a carbonyl group at 1416 and 1419 cm^{-1}, respectively, which was lacking in the 2-acetoxy-1-ketone epimers, XIIIb and XVIIb. The optical rotatory dispersion curves showed positive Cotton effect in the 1-acetoxy-2-ketone epimers, Ib (a=+224) and IVb (a= 328) and negative Cotton effect in the 2-acetoxy-1-ketone epimers, XIIIb (a=−118) and XVIIb (a=−46). In the nuclear magnetic resonance (NMR) spectra, the C-1 proton of the epimeric 1-acetoxy-2-ketones appeared as a singlet at 4.89τ in Ib and at 5.18τ in IVb, while the C-2 proton of the epimeric 2-acetoxy-1-ketones appeared as a triplet at 5.03τ in XVIIb and a broad doublet at 4.70τ in XIIIb. On the other hand, the NMR signals of the C-1 proton of four isomeric triol triacetates were observed as a singlet at 5.15τ in VIIb, a broad singlet at 4.97τ in XIVb, a doublet at 4.94τ in VIc and a doublet at 5.38τ in XVIIIb. These spectral data were in good agreement with the structures assigned to the ketol diacetates and triol triacetates.

As mentioned above, the 2β-hydroxy-1-ketone (XVIIa) was partially isomerized by acid treatment, but the other three ketols gave only starting material under the same acidic condition. This shows that the 2β-hydroxy-1-ketone (XVIIa) is the most unstable isomer under the acidic condition among the four isomeric ketols. In this connection, the ketol rearrangements under basic condition were examined. Treatment of the 2β-acetoxy-1-ketone (XVIIb) with a dilute methanolic sodium hydroxide solution at room temperature for 16 hr caused complete isomerization into the 1β-hydroxy-2-ketone (Ia) which was previously predicted to be the most stable ketol.[2] Under the same condition, the 2α-hydroxy-1-ketone (XIIIa) partially rearranged to the 1β-hydroxy-2-ketone (Ia), but the 1-hydroxy-2-ketone isomers, Ia and IVa, did not react. On refluxing with a dilute methanolic sodium hydroxide solution for 30 min, the 2α-hydroxy-1-ketone (XIIIa) rearranged completely to the most stable 1β-hydroxy-2-ketone (Ia), while the 1α-hydroxy-2-ketone (IVa) partially to Ia. When IVa was refluxed with the same basic solution for 2 hr, it gave a mixture of IVa and Ia in a ratio of 1:9. From the above results, it was concluded that, under the basic conditions, the ease of isomerization in the C-1,2 ketols of the A-nor-5α-steroids is in the following order; the 2β-hydroxy-1-ketone(XVIIa)> the 2α-hydroxy-1-ketone(XIIIa)> the 1α-hydroxy-2-ketone(IVa) > the 1β-hydroxy-2-ketone(Ia).

Fishman has reported[9] the rearrangement of the four isomeric C-16,17 ketols of the 14α-steroids under acidic and basic conditions. From the standpoint that the arrangements

9) J. Fishman, *J. Am. Chem. Soc.*, **82**, 6143 (1960).

about the ketol functions are similar in both the series, the ease of isomerization of the C-1,2 ketols in the A-nor-5α-series is in the same order as that of the C-16,17 ketols in the 14α-series. As described in the previous paper,[2] the ease of isomerization of the C-1,2 ketols in the A-nor-5β-series was in the reverse order to that of the C-16,17 ketols in the 5α,14β-series. In the A-nor-5β-series, the unstability of the 1-hydroxy-2-ketones compared with the 2-hydroxy-1-ketones has been ascribed to the non-bonded interaction between the 1α-H or OH and the 11α-H in the 2-ketone isomers. In the present case, such the non-bonded interaction as above is not observed and the ease of isomerization of the present ketols may be explained in the same way as proposed for that of the C-16,17 ketols in the 14α-series.[9]

Experimental

All melting points were determined in capillary tubes and uncorrected. Optical rotations were measured in dioxane solutions at *ca.* 25° with a Perkin-Elmer Polarimeter type 141. Unless otherwise stated, IR spectra were recorded in Nujol mulls with a Nihon Bunko Infrared Spectrophotometer Model DS-201B. NMR spectra were determined at 60 Mc in $CDCl_3$ solutions containing tetramethylsilane as an internal standard using a Varian A-60 Analytical NMR Spectrometer. ORD curves were run in MeOH solutions at *ca.* 25° on a Nihon Bunko Automatic Recording Spectropolarimeter ORD/UV-5. For thin-layer chromatography, Merck Silica Gel G according to Stahl was used. All solvent extracts were dried over anhydrous Na_2SO_4.

1α,17β-Dihydroxy-A-nor-5α-androstan-2-one (IVa) and the Diacetate (IVb)——To a solution of 2,17β-diacetoxy-A-nor-5α-androst-1-ene[6] (II) (720 mg) in benzene (15 ml), a solution of 0.0024 moles of *m*-chloroperbenzoic acid in benzene (15 ml) was added dropwise with stirring. The solution was stirred at room temperature for an additional 4 hr and diluted with ether. The ethereal solution was washed with 10% $NaHSO_3$, 5% Na_2CO_3 and H_2O, dried and evaporated leaving a crystalline residue (III) (770 mg), mp 160—165°. A solution of the crude product in MeOH (80 ml) containing 6 N H_2SO_4 (20 ml) was allowed to stand at room temperature for 50 hr. After dilution with AcOEt, the organic solution was washed with 5% Na_2CO_3 and H_2O and dried. Evaporation of the solvent gave a crystalline material (581 mg) which was recrystallized from acetone affording plates (241 mg) of the 1α-hydroxy-2-ketone (IVa), mp 211—213°. $[\alpha]_D$ +223° (c=1.04). IR ν_{max} cm^{-1}: 3430, 3330 (OH), 1737 (CO). NMR τ: 6.55 (1H, singlet, C_1-H). *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93: H, 9.65. Found: C, 74.23; H, 9.72.

Concentration of the mother liquor gave the second crop (173 mg), mp 209—212°.

A solution of IVa (100 mg) in Ac_2O (0.5 ml) and pyridine (1 ml) was allowed to stand at room temperature overnight. Working up in the usual manner and recrystallization from acetone-petr. ether gave IVb (108 mg) as needles, mp 194—195°. $[\alpha]_D$ +244.1° (c=0.95). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1764, 1748, 1247, 1222 (OAc), 1419 (CH_2). NMR τ: 5.18 (1H, singlet, C_1-H). ORD (c=0.044) [ϕ] (mμ): +4312 (390), +16814 (344.5) (peak), +14940 (337), +15017 (333), −15966 (292) (trough), −5391 (220). *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.29; H, 8.53.

Treatment of IVb with Zinc and Acetic Acid——To a solution of the diacetate (IVb) (59 mg) in AcOH (10 ml) containing Ac_2O (1 ml) was added Zn dust (3.8 g) with stirring and the mixture was refluxed for 7 hr. After cooling, the Zn dust was filtered off and the filtrate was diluted with AcOEt. The organic solution was washed with 5% Na_2CO_3 and H_2O, dried and evaporated to dryness. Purification of the crude product by preparative TLC (benzene–AcOEt=10:1) gave a crystalline material which on recrystallization from petr. ether yielded the 2-ketone (V) as needles, mp 113—114°. Identity with an authentic specimen[3] was established by the IR comparison and a mixed melting point determination.

Reduction of IVa with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (385 mg) in dry tetrahydrofuran (15 ml), a solution of IVa (385 mg) in dry tetrahydrofuran (15 ml) was added dropwise with stirring at room temperature. The reaction mixture was stirred for an additional 1 hr and decomposed by careful addition of a small portion of H_2O and dil. HCl. After extraction with AcOEt, the extract was washed with 5% Na_2CO_3 and H_2O and dried. Evaporation of the solvent gave a residue which was separated into two fractions by preparative TLC (benzene–AcOEt=1:4). The more mobile fraction (82 mg, 21.2%) was recrystallized from acetone-petr. ether yielding A-nor-5α-androstane-1α,2α,17β-triol (VIa) (32 mg) as fine plates, mp 187—188°. $[\alpha]_D$ +39.7° (c=1.03). IR $\nu_{max}^{CCl_4}$ cm^{-1} [7]: 3625 (free OH), 3539 (bonded OH). *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.36; H, 10.27.

The less mobile fraction (270 mg, 69.6%) gave, on recrystallization from acetone, plates (237 mg) of A-nor-5α-androstane-1α,2β,17β-triol (VIIa), mp 217—218.5°. $[\alpha]_D$ +25° (c=0.99). IR $\nu_{max}^{CCl_4}$ cm^{-1} [7]: 3620 (free OH). *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.46; H, 10.33.

To a solution of VIIa (8 mg) in 95% EtOH (0.2 ml) was added a solution of digitonin (40 mg) in 70% EtOH (1 ml). After standing at room temperature for several hr, VIIa gave white precipitate of digitonide. Under the same condition, VIa gave no digitonide.

A-Nor-5α-androstane-1α,2α,17β-triol Triacetate (VIc)——a) From the Triol (VIa): A solution of VIa (45 mg) in Ac_2O (0.5 ml) and pyridine (1 ml) was allowed to stand at room temperature overnight. After working up in the usual way, the product was recrystallized from *n*-hexane affording needles of VIc, mp 132.5—133°. $[\alpha]_D$ +22.2° (c=1.05). IR ν_{max} cm^{-1}: 1741, 1256 (OAc). NMR τ: 4.94 (1H, doublet, J= 5.4 cps, C_1-H). *Anal.* Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.76; H, 8.66.

b) From the 17-Acetate (VIb): Acetylation of VIb with Ac_2O and pyridine in the same manner as above gave needles, mp 132—133°, identical with a sample of the above triacetate (VIc) by the IR comparison and the mixed melting point determination.

A-Nor-5α-androstane-1α,2β,17β-triol Triacetate (VIIb)——A solution of VIIa (80 mg) in pyridine (1 ml) and Ac_2O (0.5 ml) was allowed to stand at room temperature overnight. After working up in the usual manner, recrystallization of the crude product from *n*-hexane afforded plates (97 mg) of VIIb, mp 155—156°, $[\alpha]_D$ −6.8° (c=0.94). IR ν_{max} cm^{-1}: 1740, 1733, 1253, 1230 (OAc). NMR τ: 5.15 (1H, singlet, C_1-H). *Anal.* Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.64; H, 8.77.

Hydroxylation of 17β-Acetoxy-A-nor-5α-androst-1-ene (VIII) with Osmium Tetroxide——To a solution of VIII[6] (450 mg) in ether (60ml) containing pyridine (0.4 ml) was added a solution of OsO_4 (416 mg) in ether (20 ml) and the solution was allowed to stand at room temperature for 20 hr. The precipitated osmate was separated by decantation, washed with petr. ether and dissolved in dioxane. A stream of H_2S was bubbled through the solution kept in an ice bath. After filtration, the filtrate was evaporated leaving a crystalline residue which was chromatographed over silica gel (7 g, Merck Silica gel 0.2—0.5 mm). The eluates (421 mg) with benzene–$CHCl_3$ (1:1) and $CHCl_3$–MeOH (100:1) were recrystallized from acetone yielding the 1α,2α-diol (VIb) (291 mg) as plates, mp 192—193°. Concentration of the mother liquor gave the second crop (74 mg), mp 189—191°. The first crop showed the following constants: $[\alpha]_D$ +32.7° (c=1.14). IR ν_{max} cm^{-1}: 3360 (OH), 1731, 1271, 1252 (OAc). NMR τ: 6.32 (1H, doublet, J=5.0 cps, C_1-H). *Anal.* Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.39; H, 9.39.

A-Nor-5α-androstane-1α,2α,17β-triol 1,2-Acetonide (IXa) and Its Acetate (IXb)——A solution of the 1α,2α,17β-triol (VIa) (72 mg) and *p*-TsOH (7 mg) in acetone (14 ml) was refluxed for 1 hr. After cooling, AcOEt was added and the organic solution was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated to dryness. Recrystallization of the residue from *n*-hexane afforded the acetonide (IXa) (66 mg) as needles, mp 147—148° $[\alpha]_D$ +21.7° (c=1.01). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3490 (OH), 1381, 1373 (*gem.* CH_3). *Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.16; H, 10.07.

Acetylation of IXa with Ac_2O and pyridine in the usual manner gave the acetate (IXb) as plates, mp 114—115°. $[\alpha]_D$ +23° (c=1.13). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1737, 1248 (OAc), 1382, 1374 (*gem.* CH_3). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.39; H, 9.56.

Hydrolysis of the Acetonide (IXb)——The acetonide (IXb) (73 mg) was warmed at 55—60° for 8 hr with 50% AcOH (8 ml). After extraction with AcOEt, the extract was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated leaving an oil which was separated into two fractions by preparative TLC (benzene–AcOEt 3:1). The more mobile fraction (14 mg, 19.2%) was recrystallized from dil. MeOH to give the unchanged starting material (IXb) as plates, mp 113.5—114.5°. The less mobile fraction (45 mg, 69%) gave on recrystallization from acetone plates, mp 192—193°, identical with a sample of the 1α,2α-diol (VIb) by the IR comparison and the mixed mp determination.

1,17β-Diacetoxy-A-nor-5α-androst-1-ene (XI)——To a solution of the 1-ketone[6] (X) (1.7 g) in isopropenyl acetate (26 ml) was added 0.7 ml of a catalyst solution (5 ml of isopropenyl acetate and 0.1 ml of conc. H_2SO_4). Approximately 13 ml of the solvent was distilled over a period of 2 hr. An additional isopropenyl acetate (13 ml) containing the catalyst solution (0.4 ml) was added and the solvent of the reaction mixture was concentrated to one half of its volume by slow distillation over another 2 hr. The solution was extracted with petr. ether and the extract was washed with 5% Na_2CO_3 and H_2O, dried and evaporated. The residue was separated by preparative TLC (benzene–AcOEt 10:1) into two fractions. The less polar fraction (1.305 g, 67.8%) was recrystallized from MeOH yielding the enol acetate (XI) (1.222 g) as plates, mp 82—83°. $[\alpha]_D$ −17.3° (c=0.95). IR ν_{max} cm^{-1}: 1758, 1731, 1617, 1255, 1207. *Anal.* Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.95.

The more polar fraction (492 mg, 28.9%) gave, on recrystallization from MeOH, the starting material (X) (450 mg) as plates, mp 167—168°.

2α,17β-Dihydroxy-A-nor-5α-androstan-1-one (XIIIa) and the Diacetate (XIIIb)——To a solution of the enol acetate (XI) (300 mg) in dry benzene (15 ml), a solution of a 0.001 moles of *m*-chloroperbenzoic acid in dry benzene (15 ml) was added dropwise with stirring and the solution was stirred at room temperature for an additional 4 hr. The solution was diluted with benzene and the benzene solution was washed with 10% $NaHSO_3$, 5% Na_2CO_3 and H_2O. The dried benzene solution was evaporated under reduced pressure to give crystals (320 mg) of the α-epoxydiacetate (XII).

A solution of this crystals in MeOH (30 ml) containing 6 N H_2SO_4 (7.5 ml) was allowed to stand at room temperature for 50 hr. After dilution with AcOEt and washing with 5% Na_2CO_3 and H_2O, the organic layer was dried and evaporated leaving a crystalline material (242 mg). Recrystallization from acetone afforded plates (163 mg) of the 2α-hydroxy-1-ketone (XIIIa), mp 165—166°. Concentration of the mother liquor gave the second crop (40 mg), mp 163—165°. The first crop showed the following constants: $[\alpha]_D$ −20°

(c=0.96). IR ν_{max} cm^{-1}: 3430, 3360 (OH), 1759 (CO). NMR τ: 5.73 (1H, broad doublet, J=7 cps, C_2-H). *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.66; H, 9.70.

Acetylation of XIIIa with Ac_2O and pyridine in the usual manner gave the diacetate (XIIIb) as needles, mp 179—180°. $[\alpha]_D$ −9.3° (c=1.00). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1759, 1745, 1241. NMR τ: 4.70 (1H, broad doublet, J=8.3 cps, C_2-H). ORD (c=0.031) [ϕ] (mμ): −764 (400), −4558 (333), −4706 (328) (trough), +7084 (281) (peak), +4620 (240), +5544 (215). *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.46; H. 8.54.

Treatment of XIIIb with Zinc and Acetic Acid——A mixture of XIIIb (47 mg) in AcOH (9 ml) containing Ac_2O (0.9 ml) and Zn dust (3 g) was refluxed for 18 hr. The product, isolated in the manner described for the same treatment of IVb, was separated into two fractions by preparative TLC (benzene–AcOEt=10:1). The polar fraction (16 mg) was recrystallized from acetone yielding the starting material XIIIb as needles, mp 175—177°. The less polar fraction (24 mg) was recrystallized from MeOH giving needles, mp 165—167°, identical with the 1-ketone[6] (X) by the IR comparison and the mixed melting point determination.

Reduction of XIIIa with Lithium Aluminum Hydride——A solution of XIIIa (200 mg) in dry tetrahydrofuran (10 ml) was added to a suspension of $LiAlH_4$ (200 mg) in dry tetrahydrofurane (10 ml) dropwise with stirring at room temperature and the mixture was stirred for an additional 1 hr. The crude product, isolated in the same manner as in the reduction of IVa, was separated into two fractions by preparative TLC (benzene–AcOEt–MeOH=10:30:1). The less polar fraction (82 mg, 40.8%) was recrystallized from acetone-petr. ether giving plates (67 mg), mp 187—188°, identical with a specimen of the 1α,2α,17β-triol (VIa) by the IR comparison and a mixed melting point determination.

The polar fraction (105 mg, 52.3%) gave, on recrystallization from acetone, A-nor-5α-androstane-1β, 2α,17β-triol (XIVa) (91 mg) as needles, mp 184—186°. $[\alpha]_D$ +5.9° (c=0.99). IR $\nu_{max}^{CCl_4}$ cm^{-1} [7]: 3617 (free OH). *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.15; H, 10.28.

This triol (XIVa) gave no precipitate on treatment with digitonin in the same manner as described for the 1α,2β,17β-triol (VIIa).

A-Nor-5α-androstane-1β,2α,17β-triol Triacetate (XIVb)——Acetylation of XIVa with Ac_2O and pyridine in the usual manner and recrystallization of the product from acetone-petr. ether gave cubic crystals of XIVb, mp 155—155.5°. $[\alpha]_D$ +4.6° (c=0.47). IR ν_{max} cm^{-1}: 1740, 1734, 1268, 1261, 1256 (OAc). NMR τ: 4.97 (1H, broad singlet, C_1–H). *Anal.* Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.65; H, 8.64.

Treatment of 17β-Acetoxy-A-nor-5α-androstan-1α,2α-epoxide (XV) with Glacial Acetic Acid——A solution of XV[6] (4 g) in glacial AcOH (200 ml) was heated to reflux for 7 hr in a N_2 atmosphere. The reaction mixture was evaporated under reduced pressure and the residue was extracted with AcOEt. The extract was washed with 5% Na_2CO_3 and H_2O, dried and evaporated leaving a glassy residue which was chromatographed on silica gel (65 g, Merck Silica Gel 0.2—0.5 mm). The fraction (2.8 g, 61.8%) eluted with benzene and benzene–$CHCl_3$ (8:2) afforded a mixture of rearranged products, the structures of which will be discussed in the next paper.

The next fraction (1.61 g) eluted with benzene–$CHCl_3$ (1:1) and $CHCl_3$–MeOH (50:1) was separated further by preparative TLC (benzene–AcOEt 3:1) into two fractions. The more mobile fraction (349 mg, 6.6%) was recrystallized from n-hexane giving plates, mp 154—156°, identical with a sample of the 1α,2β, 17β-triacetate (VIIb) by the IR comparison and the mixed melting point determination.

The less mobile fraction (725 mg, 15.2%) afforded, on recrystallization from MeOH, A-nor-5α-androstane-1α,2β,17β-triol 2,17-diacetate (XVI) as plates, mp 159—161°. Further recrystallization from the same solvent gave the analytical sample of XVI with the following constants: mp 161—162°. $[\alpha]_D$ +16.6° (c =0.50). IR ν_{max} cm^{-1}: 3460, 3370 (OH), 1732, 1257 (OAc). *Anal.* Calcd. for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.06; H, 8.99.

Acetylation of XVI with Ac_2O and pyridine in the usual manner gave plates, mp 155—156°, identical with a sample of the triacetate (VIIb) by the mixed melting point determination and the IR comparison.

2β,17β-Diacetoxy-A-nor-5α-androstan-1-one (XVIIb)——To a solution of XVI (422 mg) in AcOH (42 ml), a solution of CrO_3 (141 mg) in H_2O (1 ml) was added and the solution was allowed to stand at room temperature for 20 hr. After extraction with AcOEt, the extract was washed with 5% Na_2CO_3 and H_2O, dried and evaporated leaving a crystalline residue. Recrystallization from MeOH yielded XVIIb (384 mg, 91.5%) as plates, mp 167—168°. $[\alpha]_D$ −22.9° (c=1.03). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1757 (shoulder), 1748, 1245, 1229. NMR τ: 5.03 (1H, triplet, C_2–H). ORD (c=0.0528) [ϕ] (mμ): −450 (400), −2230 (337) (trough), +2340 (292.5) (peak), +1400 (250), +2440 (220). *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 69.95; H, 8.44.

Treatment of XVIIb with Zinc and Acetic Acid——A mixture of the diacetate (XVIIb) (30 mg) in AcOH (6 ml) containing Ac_2O (0.6 ml) and Zn dust (2 g) was refluxed for 10 hr. Isolation of the product with AcOEt and recrystallization from MeOH gave the 1-ketone (X) (16 mg) as needles, mp 165—167°. Identity with an authentic sample was established by the IR comparison and the mixed melting point determination.

Reduction of XVIIb with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (100 mg) in dry tetrahydrofuran (5 ml), a solution of XVIIb (35 mg) in dry tetrahydrofurane (3 ml) was added dropwise with stirring at room temperature. The mixture was stirred for an additional 1 hr and decomposed by careful addition of a small portion of H_2O and dil. HCl. After extraction with AcOEt, the extract was washed with 5% Na_2CO_3 and H_2O and dried. Removal of the solvent afforded a crystalline residue which was

recrystallized from acetone to give plates (20 mg), mp 212—213°, identical with an authentic sample of the 1β,2β,17β-triol[3] (XVIIIa) by a mixed melting point determination.

A-Nor-5α-androstane-1β,2β,17β-triol Triacetate (XVIIIb)——Acetylation of XVIIIa with Ac_2O and pyridine in the usual manner and recrystallization of the crude product from *n*-hexane afforded plates of XVIIIb, mp 143—145°. $[\alpha]_D$ −38.3° (c=1.12). IR ν_{max} cm^{-1}: 1740, 1268, 1237 (OAc). NMR τ: 5.38 (1H, doublet, J=7.5 cps, C_1–H). *Anal.* Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.89.

Reduction of the 1β-Acetoxy-2-ketone (Ib) with Lithium Aluminum Hydride——A solution of Ib (90 mg) in dry tetrahydrofuran (5 ml) was added to a suspension of $LiAlH_4$ (90 mg) in dry tetrahydrofuran (10 ml) and the reaction mixture was treated in the same manner as above. The crude product was separated into two fractions by preparative TLC (benzene–AcOEt=1:4). The more mobile fraction (53 mg, 75.2%) was recrystallized from acetone giving the 1β,2β,17β-triol (XVIIIa) as plates, mp 212—213°. The less mobile fraction (11.5 mg, 16.3%) afforded, on recrystallization from acetone, the 1β,2α,17β-triol (XIVa) as needles, mp 183—184°. These two triols were identified with the respective authentic samples by mixed melting points and IR spectral comparisons.

Treatment of XVIIb with Acid——a) On Prolonged Treatment: A solution of the ketol diacetate (XVIIb) (50 mg) in MeOH (8 ml) and 6 N H_2SO_4 (2 ml) was allowed to stand at room temperature (23°) for 50 hr. The solution was extracted with AcOEt and the extract was washed with 5% Na_2CO_3 and H_2O, dried and evaporated to dryness. A solution of the residue in Ac_2O (0.5 ml) and pyridine (1 ml) was allowed to stand at room temperature overnight. The product obtained by the usual treatment showed two spots on TLC and was separated into the respective fraction by preparative TLC (benzene–AcOEt=3:1). The more mobile fraction (28 mg, 56%) was recrystallized from MeOH affording plates (20 mg) of the starting material (XVIIb), mp 166—168°.

The less mobile fraction (19 mg, 38%) gave, on recrystallization from acetone-petr. ether, 1β,17β-diacetoxy-A-nor-5α-androstan-2-one[3] (Ib) (11 mg) as plates, mp 123—124°. $[\alpha]_D$ +68.1° (c=1.02). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1766 (CO), 1744, 1240 (OAC), 1416 (CH_2). NMR τ: 4.89 (1H, singlet, C_1–H). ORD (c=0.039) [ϕ] (mμ): +900 (400), +9919 (321) (peak), −12521 (278) (trough), −7043 (232.5), −17216 (210). *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.36; H, 8.66.

b) On Brief Treatment: A solution of XVIIb (250 mg) in MeOH (40 ml) was treated with 6 N H_2SO_4 (10 ml) at room temperature for 16 hr. The product (210 mg), isolated in the same procedure as above, was separated into two fractions by preparative TLC (benzene–AcOEt 1:1). The less polar fraction (46 mg, 20.7%) was recrystallized from acetone-petr. ether yielding needles (26 mg) of a ketol monoacetate, mp 137—139°, IR ν_{max} cm^{-1}: 3440, 1755, 1746, 1730, 1258, 1248, 1224. *Anal.* Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.81; H, 9.08.

The more polar fraction (145 mg, 74.7%) was recrystallized from acetone to give plates (120 mg) of a ketol moiety, mp 208—213°, $[\alpha]_D$ −1.4° (c=0.99). IR ν_{max} cm^{-1}: 3468 (shoulder), 3400 (OH), 1733 (CO). *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.78; H, 9.64. This ketol (50 mg) was acetylated with Ac_2O and pyridine and the crude product, isolated in the usual way, showed two spots on TLC. Separation by preparative TLC gave the 2β-acetoxy-1-ketone (XVIIb) (55 mg, 85.5%) and the 1β-acetoxy-2-ketone (Ib) (7 mg, 10.9%).

Rearrangement of the 2β-Acetoxy-1-ketone (XVIIb) with Base——A solution of XVIIb (60 mg) in MeOH (18 ml) and 0.1 N NaOH (12 ml) was allowed to stand at room temperature (23°) for 16 hr. After extraction with AcOEt and washing with H_2O, the organic solution was dried and evaporated leaving a crystalline material (48 mg). Acetylation of the crude product with Ac_2O (0.5 ml) and pyridine (1 ml) at room temperature overnight yielded, following the usual work-up, a crystalline material (60 mg) which showed a single spot on TLC. Recrystallization from acetone-petr. ether afforded needles (44 mg), mp 122—124°, identical with a sample of the 1β-acetoxy-2-ketone (Ib) prepared in the above-mentioned experiment by comparison of the IR spectra and a mixed melting point determination.

Rearrangement of the 2α-Hydroxy-1-ketone (XIIIa) with Base——a) At Room Temperature: A solution of XIIIa (60 mg) in MeOH (18 ml) and 0.1 N NaOH (12 ml) was allowed to stand at room temperature (23°) for 16 hr. The solution was extracted with AcOEt and the extract was washed with H_2O and dried. Removal of the solvent gave a crude product which was acetylated with Ac_2O (0.5 ml) and pyridine (1 ml) by standing at room temperature overnight. The crude product (75 mg), isolated in the usual manner, was separated into two fractions by preparative TLC (benzene: AcOEt=10:1). The more mobile fraction (37 mg, 47.9%) was recrystallized from MeOH giving the 2α-acetoxy-1-ketone (XIIIb) (29 mg) as needles, mp 178—180°. The less mobile fraction (28 mg, 36.2%) was recrystallized from acetone-petr. ether affording the 1β-acetoxy-2-ketone (Ib) (21 mg) as plates, mp 122—124°.

b) On Refluxing: A solution of XIIIa (100 mg) in MeOH (8 ml) and 40% NaOH (1 ml) was refluxed for 30 min. The product, obtained in the usual way, was acetylated with Ac_2O (0.5 ml) and pyridine (1 ml) yielding a crystalline single product (122 mg). Recrystallization from acetone–petr. ether afforded plates (86 mg) of the 1β-acetoxy-2-ketone (Ib), mp 123—124°. Identity of Ib obtained in a) and b) with an authentic sample was established by the IR comparison and a mixed melting point determination.

Rearrangement of the 1α-Hydroxy-2-ketone (IVa) with Base——a) At Room Temperature: Under the same condition as in a) of the preceing experiment, the ketol (IVa) did not rearranged and gave the 1α-acetoxy-

2-ketone (IVb) as sole product.

b) On Brief Refluxing: A solution of IVa (100 mg) in MeOH (8 ml) and 40% NaOH (1 ml) was refluxed for 30 min. The product, isolated in the usual way, was acetylated with Ac_2O (0.5 ml) and pyridine (1 ml) to give a crude material (124 mg), showing two spots on TLC. Separation of the product by preparative TLC (benzene: AcOEt=10:1) afforded the more mobile fraction (58 mg, 45.1%) and the less mobile fraction (53 mg, 41.2%). The former was recrystallized from MeOH giving the 1α-acetoxy-2-ketone (IVb) (48 mg) as plates, mp 192—194°. The latter afforded, on recrystallization from acetone–petr. ether, plates (41 mg) of the 1β-acetoxy-2-ketone (Ib), mp 122—123°.

c) On Prolonged Refluxing: A solution of IVa (100 mg) in MeOH (8 ml) and 40% NaOH (1 ml) was refluxed for 2 hr.

Working up in the usual way and acetylation of the crude product in the same manner as in b) gave a crude acetate (125 mg), indicating two spots on TLC. Separation by preparative TLC in the same manner as in b) gave the fraction (11 mg, 8.6%) of the 1α-acetoxy-2-ketone (IVb) and the fraction (94 mg, 73%) of the 1β-acetoxy-2-ketone (Ib). The ketol diacetates, IVb and Ib, were isolated from the respective fractions and identified with the respective authentic samples by the IR comparisons and mixed melting point determinations.

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