Tetrahedron, 1965, Vol. 21, pp. 759 to 770. Pergamon Press Ltd. Printed in Northern Ireland

STUDIES ON A-NORSTEROIDS—IV[1]

THE C-1,2 ISOMERIC KETOLS IN 17β-HYDROXY-A-NOR-5β-ANDROSTANE SERIES

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(*Received* 17 *November* 1964)

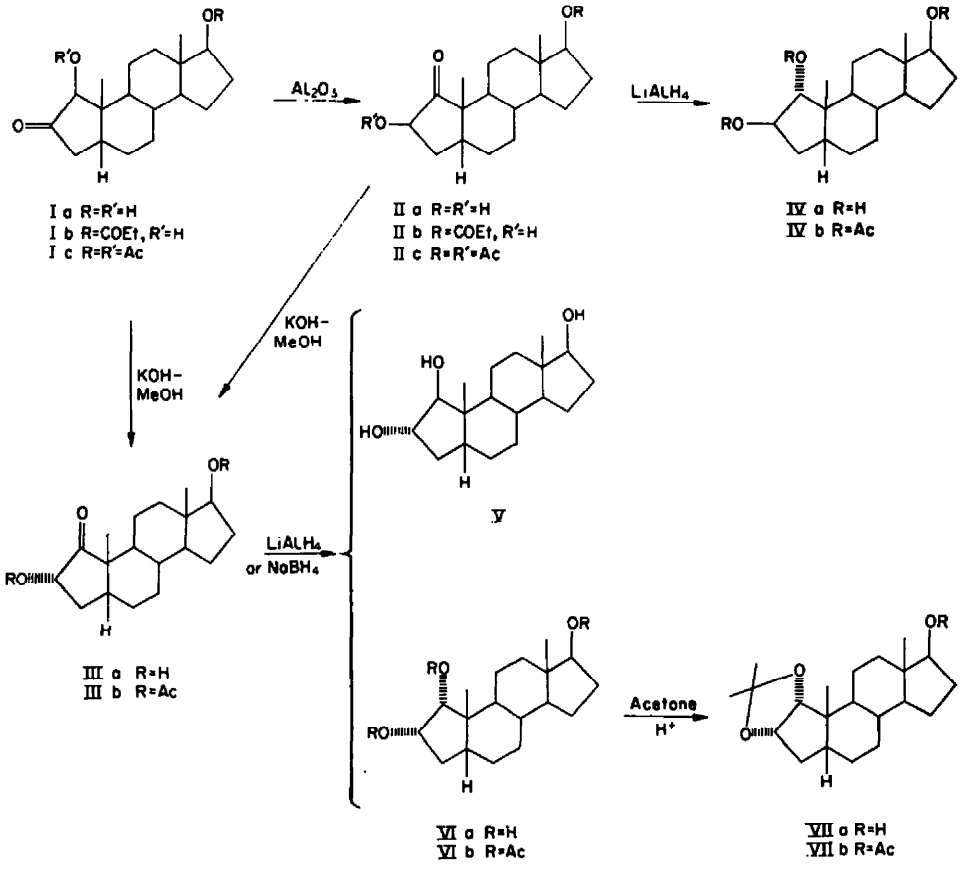
Abstract—The four possible isomers of C-1,2 ketols in the 17β-hydroxy-A-nor-5β-androstane series have been prepared and their rearrangements under various conditions examined. The stabilities are found to be in the order of the 2α-hydroxy-1-ketone (IIIa) > the 2β-hydroxy-1-ketone (IIa) > the 1β-hydroxy-2-ketone (Ia) > the 1α-hydroxy-2-ketone (XIIIa), and the results are discussed. Furthermore, the four A-nor-5β-androstane-1,2,17β-triols, epimeric at C-1,2, have been prepared in connection with the structural elucidation of the ketols.

IN THE preceding paper,[1] 1β,17β-dihydroxy-A-nor-5β-androstan-2-one (Ia) was prepared by hydrogenation of the corresponding A-norandrost-3(5)-ene (IXa) with Pd-C. During further work, it has now been found that this ketol (Ia) isomerizes to the 2β-hydroxy-1-ketone (IIa) with neutral alumina and into the 2α-hydroxy-1-ketone (IIIa) with methanolic sodium hydroxide. Accordingly, the synthesis of the remaining isomer, the 1α-hydroxy-2-ketone (XIIIa), was successfully attempted and ketol rearrangements among the four ketols, isomeric at C-1,2 in the 17β-hydroxy-A-nor-5β-androstane series, were studied.

The crude product from hydrogenation of 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one (IXa) with Pd-C, after chromatography on neutral alumina, affords another isomeric ketol (A), m.p. 210–212°, differing from the product (Ia) on silica gel chromatography. Similar treatment of the unsaturated 17-propionate (IXb) gives the propionate, m.p.131–132°, corresponding to the isomer (A). When the pure 1β-hydroxy-2-ketone (Ia) is adsorbed on a column of alumina and then eluted, it rearranges to give the ketol (A) in 70% yield. On the other hand, the 1β-hydroxy-2-ketone (Ia) on treatment with sodium hydroxide in aqueous methanol at room temperature yields the third isomer (B), m.p. 218–220°, in 60% yield. The same ketol (B) is also obtained from the ketol (A) and its 17-propionate by the same reagent. Both the new compounds (A) and (B) show negative Cotton curves in their optical rotatory dispersions (ORD), as expected[2] for A/B ring *cis*-fusion. In the NMR spectra, the ketol (A) exhibits a doublet signal at 5·71τ (J = 9 c/s); the isomer (B) shows a quartet signal at 6·06τ (J = 8, 5 c/s), attributed to the proton on the hydroxy-bearing carbon atom, besides a second-order quartet signal at 6·41τ due to the proton at C-17. These results are indicative of 2-hydroxy-1-ketone structures for both ketols, which, therefore, should be epimers regarding the configuration of the C-2 hydroxyl group. According to Karplus' correlation,[3] it is expected that the signal arising from

[1] Part III: K. Yoshida and T. Kubota, *Chem. Pharm. Bull.* in press.
[2] W. Klyne, *Tetrahedron* **13**, 29 (1961).
[3] M. Karplus, *J. Phys. Chem.* **31**, 11 (1959); M. Karplus, *J. Amer. Chem. Soc.* **85**, 2870 (1963).

the 2α-proton in the epimeric 2-hydroxy-1-ketones in the A-nor-5β-androstane series should appear as a doublet while the 2β-proton as a quartet, by spin–spin coupling with the protons at C-3. From this assumption, the C-2 hydroxyl groups in the two ketols, (A) and (B), can be deduced to have, β-configuration as shown in IIa and α-configuration as shown in IIIa, respectively. Acetylation of the ketols (IIa and IIIa) affords the corresponding diacetates, (IIc and IIIb), which show a doublet signal at 4·72τ (J = 9 c/s) and a quartet signal at 4·98τ (J = 10, 8 c/s), due to the C-2 proton in the NMR spectra, respectively, as expected.



The correctness of the structures (IIa and IIIa) assigned to the isomeric ketols was elucidated as follows: Reduction of the 2β-hydroxy-1-ketone (IIa) and its 17-propionate (IIb) with LAH gives a triol, m.p. 199–200°, which on acetylation gives the triacetate. The triol has a *trans* glycol function at C-1,2 since its IR spectrum[4] in CCl_4 shows no absorption due to an intramolecularly hydrogen bonded hydroxyl group and treatment with acetone containing *p*-toluenesulphonic acid gives no acetonide. The triol, however, differs from the previously obtained 1β,2α,17β-triol (V)[1] and thus can be defined as the 1α,2β,17β-triol (IVa). On the other hand, reduction

[4] The IR spectra for this purpose were obtained with a LiF prism and a 20 mm cell by a Perkin–Elmer Single-beam IR Spectrophotometer Model 12C.

of the 2α-hydroxy-1-ketone (IIIa) with LAH or $NaBH_4$ results in the formation of a mixture of the known 1β,2α,17β-triol (V)[1] and an unknown triol, m.p. 180–181°. The IR spectrum[4] of the newly obtained triol in CCl_4 shows a band at 3561 cm^{-1} due to intramolecular hydrogen bonding, suggesting a *cis* glycol structure at C-1,2, as well as a free hydroxyl band at 3627 cm^{-1}. This triol, however, differs from the previously obtained 1β,2β,17β-triol[1] and hence should be the 1α,2α,17β-triol (VIa). The triol (VIa) on acetylation gives the triacetate (VIb) and on treatment with acetone and *p*-toluenesulphonic acid affords the 1α,2α-acetonide (VIIa) as an oily substance, which on acetylation with acetic anhydride and pyridine gives the crystalline acetonide acetate (VIIb).

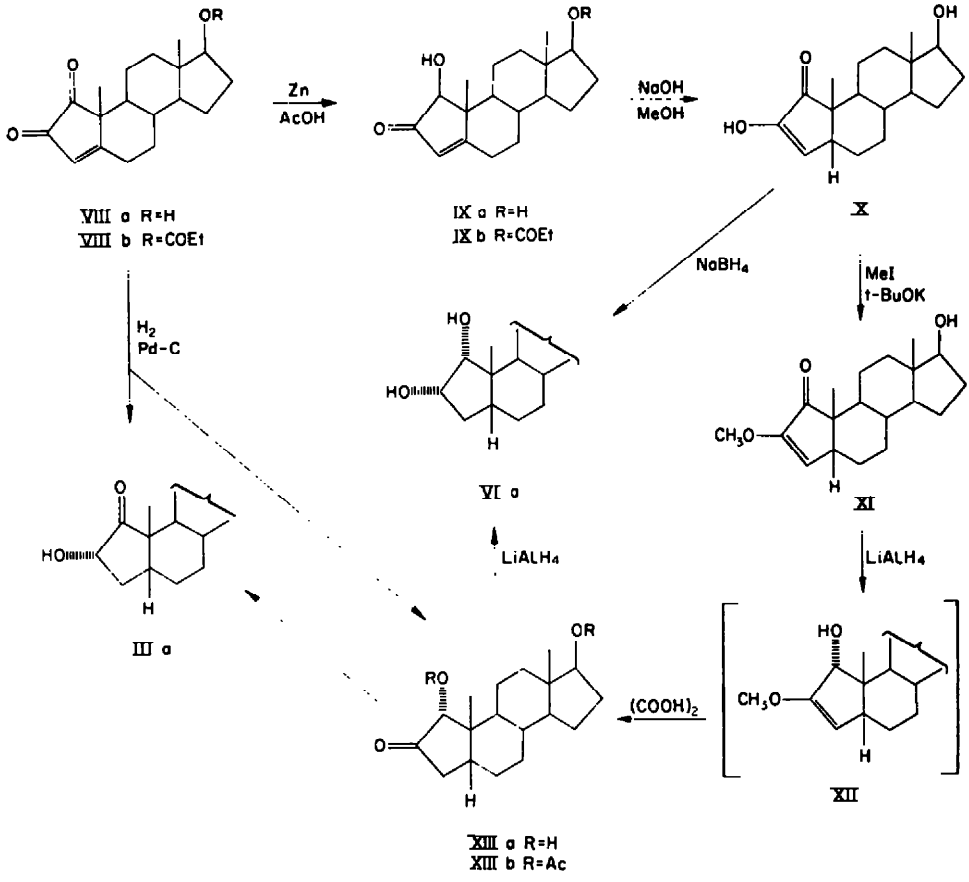
Thus, all the four possible A-nor-5β-androstane-1,2,17β-triols, epimeric at C-1,2 have now been prepared and, accordingly, the structures, IIa and IIIa, assigned to the two isomeric ketols derived from 1β,17β-dihydroxy-A-nor-5β-androstan-2-one (Ia) have been established.

It is of interest to study the ketol rearrangements with completion of the possible four isomers of C-1,2 ketols in the 17β-hydroxy-A-nor-5β-androstane series. Furthermore, a reference sample for identification of an unstable, unknown product in connection with hydrogenation of 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione (VIIIa) was required. In order to meet these demands, the remaining isomer, the 1α-hydroxy-2-ketone (XIIIa), was synthesized using the diosphenol (X) described below as the starting material.

As mentioned in the previous paper,[5] reduction of the enedione (VIIIa) with zinc in acetic acid affords 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one (IXa). This compound on refluxing with methanolic sodium hydroxide in an atmosphere of nitrogen gives an isomer, m.p. 243–245° (dec), which also results from similar treatment of the 17-propionate of IXa, with concomitant hydrolysis of the ester. Its UV spectrum shows a maximum at 262 mμ (ε6,000) and the IR spectrum exhibits bands at 3345, 3055, 1743, 1678, 1643 cm^{-1}. Since this isomer is soluble in dilute sodium hydroxide solution and gives a positive $FeCl_3$ test, it must be a diosphenol. Reduction with $NaBH_4$ gives the above-mentioned A-nor-5β-androstane-1α,2α,17β-triol (VIa) and hence the structure of the diosphenol is confirmed as 2,17β-dihydroxy-A-nor-5β-androst-2-en-1-one (X).

Methylation of the diosphenol (X) with potassium t-butoxide and methyl iodide furnishes the enol methyl ether (XI) in good yield. It was expected that LAH reduction of this compound would probably yield the 1α-hydroxy derivative with the front attack of the reagent toward the C_1-carbonyl group, because in the 5β-structure the A-ring bends backward. Treatment of XI with LAH in dry tetrahydrofuran gives an oily reduction product, of which the IR spectrum shows no absorption due to the original conjugated ketone but a very weak carbonyl absorption at 1744 cm^{-1} suggesting partial hydrolysis of the enol ether group. Without further purification, the substance was subjected to hydrolysis of the enol ether with oxalic acid in aqueous methanol giving a new crystalline ketol, expected to be 1α,17β-dihydroxy-A-nor-5β-androstan-2-one (XIIIa). The m.p. 218–220° of this product coincides with that of the above-mentioned 2α-hydroxy-1-ketone (IIIa) and no depression was observed on admixture of these compounds. However, on thin layer chromatography (TLC) with a silica gel plate using toluene–ethyl acetate (1:3), the newly obtained ketol is

[5] K. Yoshida and T. Kubota, *Chem. Pharm. Bull.* in press.



more mobile (R_f 0·44) than the 2α-hydroxy-1-ketone (IIIa) (R_f 0·37). Furthermore, its IR spectrum exhibits a carbonyl absorption at 1743 cm^{-1}, but clearly differs from those of the known three isomers (Ia, IIa and IIIa) throughout the spectra. Hence, the distinction among these ketols was achieved by thin layer chromatography and the IR spectra.

The new ketol shows a singlet signal at 6·08τ in the NMR spectrum, as anticipated for the C_1-proton in the 1-hydroxy-2-ketone, and a negative Cotton curve in the ORD, as expected[2] for the 2-ketone of the A-nor-5β-structure. Acetylation of the ketol with acetic anhydride and pyridine gives the diacetate, m.p. 178–179°, which shows a clear depression by admixture with the above-mentioned 2α-acetoxy-1-ketone (IIIb), m.p. 204–206°, in spite of an agreement between the m.p.s of these original ketols. The IR spectrum of the new ketol diacetate in CCl_4 exhibits a methylene absorption adjacent to a carbonyl group at 1411 cm^{-1}, which is lacking in the two epimeric 2-acetoxy-1-ketones (IIc and IIIb). The ketol was finally converted into the aforementioned A-nor-5β-androstane-1α,2α,17β-triol (VIa) by reduction with LAH and thus proved to have the desired 1α-hydroxy-2-ketone structure (XIIIa).

With the completion of all the four isomers of C-1,2 ketols in the 17β-hydroxy-A-nor-5β-androstane series, catalytic reduction of the 3(5)-ene-1,2-dione (VIIIa) was examined. Hydrogenation of VIIIa in ethyl acetate–methanol over Pd-C, after uptake

of two molar equivs of hydrogen, affords a mixture showing three spots on TLC. The most mobile is relatively weak and unidentified, but the main two spots appear to correspond with those of the 1α-hydroxy-2-ketone (XIIIa) and the 2α-hydroxy-1-ketone (IIIa). Thus the mixture was subjected to TLC on silica gel with preparative purpose. The 2α-hydroxy-1-ketone (IIIa) could be isolated from the corresponding spots, while the fraction corresponding to XIIIa affords again a mixture showing the two spots of XIIIa and IIIa on TLC. The IR spectrum of the mixture exhibits strong bands observed in that of IIIa, in addition to the bands of XIIIa. From the above result, probably considerable amounts of the 1α-hydroxy-2-ketone (XIIIa) rearrange to the 2α-hydroxy-1-ketone (IIIa) during contact with silica gel and this was actually proved by using a pure sample of XIIIa. Thus, it is concluded that the main products from the hydrogenation of the enedione (VIIIa) over Pd-C are the 2α-hydroxy-1-ketone (IIIa) and the 1α-hydroxy-2-ketone (XIIIa). Hydrogenation of the above-mentioned diosphenol (X) affords a mixture of the two ketols (IIIa and XIIIa), similar to that obtained from the enedione (VIIIa), with absorption of 1 molecular proportion of hydrogen.

The above results suggest that the 1α-hydroxy-2-ketone is the least stable among the four isomeric ketols. The transformation of the ketols was followed by thin layer chromatography and proved by characterization of the isolated products.

The 1α-hydroxy-2-ketone (XIIIa) is affected with silica gel or neutral alumina and, after adsorption on them for 24 hr or 1 hr, respectively, the 2α-hydroxy-1-ketone (IIIa) is isolated. On treatment of XIIIa with dilute sulphuric acid in aqueous methanol, rearrangement is complete at room temperature after 50 hr giving IIIa. Immediate rearrangement to IIIa is observed on addition of dilute sodium hydroxide to a solution of XIIIa in methanol and after treatment for 10 min IIIa is isolated. The rearrangement rate of XIIIa to IIIa in 95% ethanol containing 6% sulphuric acid was determined by using the optical rotatory dispersion method.[6] The isomerization was completed within 23 hr, (Fig. 1), and was shown to be first-order with respect to the ketol (XIIIa).

The 1β-hydroxy-2-ketone (Ia) is converted, on adsorption on neutral alumina for 1 hr, into the 2β-hydroxy-1-ketone (IIa) as mentioned above, but is fairly stable to silica gel chromatography. Treatment of Ia with alkali in aqueous methanol causes complete isomerization to the 2α-hydroxy-1-one (IIIa) at room temperature after 6 hr, while on acid treatment at room temperature no rearrangement occurs.

The 2β-hydroxy-1-ketone (IIa) is practically unchanged by chromatography over silica gel or alumina. On acid treatment at room temperature, IIa is quite stable. Rearrangement of IIa to IIIa in the alkaline medium appears to be slower than that of Ia and is completed after 9 hr.

The 2α-hydroxy-1-ketone (IIIa) is entirely unchanged by treatment with silica gel, alumina, dilute sulphuric acid or even with boiling methanolic sodium hydroxide and is the most stable ketol among the four isomers.

Consequently, it can be concluded that the stability in the C-1,2 ketols of the A-nor-5β-steroids is in the following order; the 2α-hydroxy-1-ketone (IIIa) > the 2β-hydroxy-1-ketone (IIa) > the 1β-hydroxy-2-ketone (Ia) > the 1α-hydroxy-2-ketone (XIIIa). Nambara and Fishman[7] have studied on the stability of the four

[6] The authors are indebted to Dr. K. Kuriyama of this Laboratory for the determination.

[7] T. Nambara and J. Fishman, *J. Org. Chem.* **27**, 2131 (1962).

isomeric C-16,17 ketols of 5α,14β-androstan-3β-ol and demonstrated the sequence; the 17α-hydroxy-16-ketone > the 17β-hydroxy-16-ketone > the 16β-hydroxy-17-ketone > the 16α-hydroxy-17-ketone. From the standpoint that the arrangements about the ketol functions are similar in both the series, the stability sequence in the C-1,2 ketols of A-nor-5β-steroids are in the reverse order to that in the C-16,17 ketols of 5α,14β-steroids.

Greater stability of the 1-ketones than the 2-ketones in the A-nor-5β-steroids may be explained by steric consideration including the C-ring. It is conceivable that a definite non-bonded interaction exists between the 1α-H or OH and the 11α-H in the

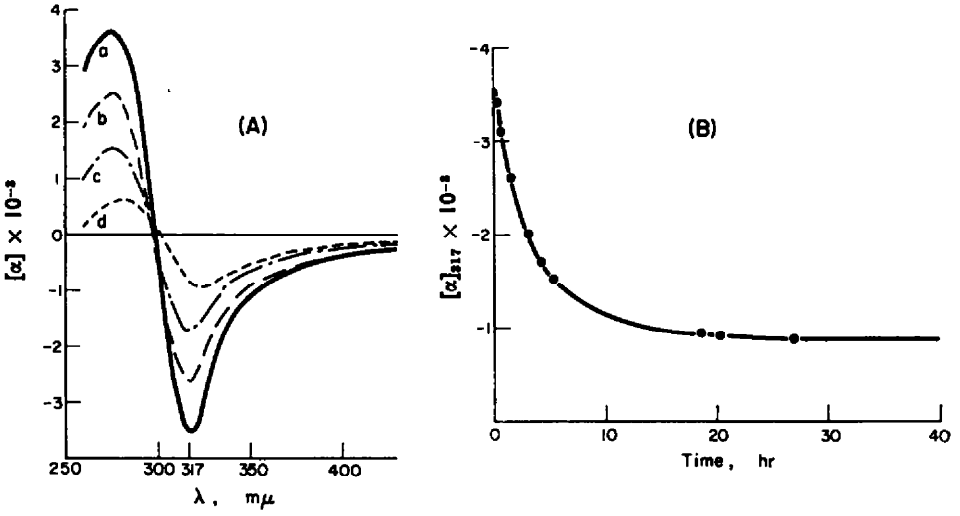


FIG. 1. Change in the ORD curve on treatment of 1α,17β-dihydroxy-A-nor-5β-androstan-2-one (XIIIa) (*c* 0·1908) with 6% sulphuric acid in 95% ethanol at 24 ~ 25°: (A) The ORD curves after the treatment for (a) 5 min, (b) 1 hr 30 min, (c) 4 hr 10 min and (d) 52 hr; and (B) change of the specific rotation at 317 mμ with time of treatment.

2-ketones of A-nor-5β-steroids. Since this interaction must be much relieved by enolization of the C_2-ketones to Δ^1 or by formation of the ketone at C_1, the 1α-hydroxyl or hydrogen in the 2-ketones (XIIIa or Ia) probably provide a driving force in the ketol rearrangements. Accordingly, it is reasonable that XIIIa having the bulkier 1α-hydroxyl group is less stable than the 1β-hydroxy-2-ketone (Ia) having hydrogen at 1α. This is also explained by assuming that the 1β-H in the 1α-hydroxy-2-ketone (XIIIa) can be more easily abstracted or migrated than the more hindered 1α-H in Ia.

The difference in stability between the two epimers (IIa and IIIa) of the 2-hydroxy-1-ketones probably lies in the structural feature of the *cis*-fused A/B ring bending to the α-side, in which protonation of the enol should be favored from the unhindered β-side at C-2 giving the 2α-hydroxy-1-ketone (IIIa). Thus, the treatment of XIIIa with acid and of XIIIa, Ia and IIa with alkali in aqueous methanol, are the conditions leading to enolization of ketones, resulting in conversion into the same most stable ketol (IIIa).

On the other hand, the adsorption of the ketols (XIIIa and Ia) over alumina is a non-enolizable condition, in which alumina ought to serve as a Lewis acid on the

C_2-carbonyl and cause the hydride shift from C-1 to C-2. Hence, the two epimers, (XIIIa and Ia), of the 1-hydroxy-2-ketones rearrange to the respective 1-ketones, (IIIa and IIa), having the same hydroxyl configurations as those in the original compounds.

Regarding the C-1,2 ketols of A-nor-5α-steroids, only 1β,17β-dihydroxy-A-nor-5α-androstan-2-one was obtained in the preceding paper.[1] This 1β-hydroxy-2-ketone, however, is stable even on refluxing in a methanolic sodium hydroxide solution and appears to be the most stable ketol in the A-nor-5α-steroid series. This observation is unlike the result in the A-nor-5β-steroid series mentioned above, but corresponds to the fact[8] that the 17β-hydroxy-16-ketone is the most stable among the C-16,17 ketols of the common 14α-steroid series. Examination of molecular models suggests that the 1α-hydrogen in the 2-ketone of A-nor-5α-steroid considerably recedes from the 11α-hydrogen, compared with that in the 5β-series. It is of interest to establish whether or not the 1α-hydroxy-2-ketone is more stable, regardless of the non-bonded interaction between 1α-OH and 11α-H, than the 2-hydroxy-1-ketones and it is hoped that the three unknown C-1,2 ketols of the A-nor-5α-steroids will be provided in further work.

EXPERIMENTAL

All m.ps. are uncorrected. Optical rotations were measured in dioxan solutions at 25° with a Rudolf Photoelectric Polarimeter Model 200. UV spectra were taken in 95% EtOH using a Hitachi Recording Spectrophotometer EPS-2. Unless otherwise stated, IR spectra were recorded with a NaCl prism on a Koken IR Spectrophotometer Model DS 301. NMR spectra were determined at 60 Mc in $CDCl_3$ containing tetramethylsilane as an internal reference on a Varian A-60 Analytical NMR Spectrometer. ORD curves were run in dioxan with a Rudolf Recording Spectropolarimeter.

Adsorbents. Alumina and silica gel used for column chromatography were Al_2O_3 "Woelm" neutral, activity grade 1 and Tokaigel F-2 mesh 60–200, respectively. For thin layer chromatography, Merck Silica Gel G according to Stahl was used.

General procedure for preparative thin layer chromatography. A solution of material (ca. 20 mg) in $CHCl_3$ (0·5 ml) was spotted in a line at intervals of 3·0 mm on a chromatoplate (20 cm × 20 cm), spread with Merck Silica Gel G in thickness of 0·5 mm. After development with toluene–ethyl acetate (1:3), the chromatoplate was sprayed with a 0·2% solution of morin in MeOH. The lines detected under UV light were separately scraped from the plate and extracted with $CHCl_3$–MeOH and the extracts evaporated.

2β,17β-Dihydroxy-A-nor-5β-androstan-1-one (IIa)

(a) *Directly from* 1β,17β-*dihydroxy-A-norandrost-3(5)-en-2-one* (IXa). The unsaturated ketol (IXa, 400 mg) in MeOH (20 ml) and ethyl acetate (20 ml) was shaken with 5% Pd-C (1 g) in an H_2 atm. After removal of the catalyst and the solvent, the crude product was dissolved in benzene–$CHCl_3$ (9:1) and adsorbed on a column of Al_2O_3 (15 g). The eluates (320 mg) with $CHCl_3$ and $CHCl_3$–MeOH (100:1) were recrystallized from acetone giving IIa (71 mg) as plates, m.p. 206–208°. Concentration of the mother liquor gave the second crop (125 mg), m.p. 200–204°, which was separated by the preparative thin layer chromatography into the less mobile fraction (86 mg), m.p. 208–210°, and the more mobile fraction (18 mg), m.p. 216–219°. Recrystallization of the major fraction from acetone afforded plates (35 mg) of the pure IIa, m.p. 210–212°, $[\alpha]_D$ −39° (*c* 0·52); $\nu_{max}^{CHCl_3}$ 3605, 1737 cm^{-1}. NMR: 5·71τ (doublet, J = 9 c/s, C-2 proton), 6·42τ (second order quartet, C-17 proton), 8·92τ (singlet, C-19 CH_3) and 9·27τ (singlet, C-18 CH_3). ORD (*c* 0·20): $[\alpha]_{334}$ −854°, $[\alpha]_{288}$ +1183°. (Found: C, 73·70; H, 9·79. $C_{18}H_{28}O_2$ requires: C, 73·93; H, 9·65%.)

Recrystallization of the minor fraction from acetone gave plates (3 mg), m.p. 218–221°, identical with the previously obtained 1β,17β-dihydroxy-A-nor-5α-androstan-2-one[1] by the IR comparison and the mixed m.p. determination.

[8] J. Fishman, *J. Amer. Chem. Soc.* **82**, 6143 (1960).

(b) *From* 1β,17β-*dihydroxy*-A-*nor*-5β-*androstan*-2-*one* (Ia). The pure Ia (54 mg) was dissolved in $CHCl_3$–benzene (1:1) and adsorbed on a column of neutral Al_2O_3 (4 g). The eluates (53 mg) with $CHCl_3$ and with $CHCl_3$–MeOH (100:1) gave on recrystallization from acetone IIa (20 mg), m.p. 207–209°, as plates. Concentration of the mother liquor afforded the second crop (18 mg), m.p. 205–207°. Purification by preparative thin layer chromatography raised the m.p. to 210–212°, identical with that of a sample obtained in (a).

2β,17β-*Dihydroxy*-A-*nor*-5β-*androstan*-1-*one* 17-*propionate* (IIb)

The propionate (IXb, 230 mg) was hydrogenated with 5% Pd-C (570 mg) in MeOH (10 ml) and ethyl acetate (10 ml) at room temp and freed from the catalyst and the solvent. The oily residue was chromatographed on Al_2O_3 (7 g) and the fractions (180 mg), eluted with benzene–$CHCl_3$ (1:1) and $CHCl_3$, were recrystallized from acetone–pet. ether giving needles (103 mg) of IIb, m.p. 122–127°. Further recrystallization from acetone gave the analytical sample as needles, m.p. 131–132°, $[\alpha]_D$ −34° (*c* 0·62); $\nu_{max}^{CHCl_3}$ 3565, 1737, 1730 cm^{-1}. (Found: C, 72·42; H, 9·25. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26%.)

2β,17β-*Dihydroxy*-A-*nor*-5β-*androstan*-1-*one diacetate* (IIc)

A mixture of IIa (75 mg), acetic anhydride (0·6 ml) and pyridine (1 ml) was allowed to stand at room temp overnight. After working up, the product was recrystallized from acetone–n-hexane giving the diacetate (IIc, 62 mg) as plates, m.p. 133–134°, $[\alpha]_D$ −43° (*c* 0·52); $\nu_{max}^{CCl_4}$ 1752, 1744, 1245, 1228 cm^{-1}. NMR: 4·72τ (doublet, J = 9 c/s, C-2 proton), 5·45τ (second order quartet, C-17 proton), 8·92τ (singlet, C-19 CH_3) and 9·23τ (singlet, C-18 CH_3). ORD (*c* 0·39): $[\alpha]_{350}$ −145°, $[\alpha]_{320\cdot5}$ ··625°, $[\alpha]_{282}$ +54°. (Found: C, 70·18; H, 8·64. $C_{22}H_{32}O_5$ requires: C, 70·18; H, 8·57%.)

Alkaline treatment of 1β,17β-*dihydroxy*-A-*nor*-5β-*androstan*-2-*one* (Ia)

A solution of Ia (30 mg) in MeOH (9 ml) and 0·1 N NaOH (6 ml) was allowed to stand at room temp for 6 hr in a N_2 atm. The solution was extracted with ethyl acetate and the organic layer was washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo* leaving a crystalline material (30 mg), which on recrystallization from acetone afforded needles (17 mg), m.p. 214–216°. Further recrystallization from acetone gave an analytical sample of IIIa, m.p. 218–220°, $[\alpha]_D$ - 68° (*c* 0·54); $\nu_{max}^{CHCl_3}$ 3622, 1735 cm^{-1}. NMR: 6·06τ (quartet, J = 8, 5 c/s, C-2 proton), 6·41τ (second order quartet, C-17 proton), 8·91τ (singlet, C-19 CH_3) and 9·25τ (singlet, C-18 CH_3). ORD (*c* 0·22): $[\alpha]_{700}$ −74°, $[\alpha]_{320\text{-}5}$ −1044°, $[\alpha]_{284\text{-}5}$ ÷ 448°, $[\alpha]_{350}$ 222°. (Found: C, 73·98; H, 9·74. $C_{18}H_{28}O_3$ requires: C, 73·93; H, 9·65%.)

Alkaline treatment of 2β,17β-*dihydroxy*-A-*nor*-5β-*androstan*-1-*one* (IIa)

(a) *At room temperature*. A solution of IIa (25 mg) in MeOH (7·5 ml) and 0·1 N NaOH (5 ml) was allowed to stand at room temp for 9 hr in a N_2 atm. The solution was extracted with ethyl acetate and the organic layer washed with water, dried and evaporated. Recrystallization from acetone gave IIIa (15 mg) as needles, m.p. 216–218°.

(b) *On refluxing*. A solution of IIa (40 mg) in MeOH (4 ml) and 40% NaOH (0·5 ml) was refluxed for 20 min in a stream of N_2. After working up as in (a), the crude crystalline product (27 mg) was recrystallized from acetone giving IIIa (12 mg), m.p. 218–220°, as needles. Both the products obtained in (a) and (b) were identical with an authentic sample of IIIa, derived from alkaline treatment of Ia, by mixed m.ps. and IR comparisons.

Alkaline treatment of the propionate (IIb)

A mixture of IIb (80 mg) in MeOH (8 ml) and 40% NaOH (1 ml) was refluxed for 30 min in a N_2 atm. After addition of water and extraction with $CHCl_3$, the $CHCl_3$ solution was washed with water, dried and evaporated giving a crystalline material (47 mg), m.p. 207–211°. In chromatography over silica gel (1 g) it was eluted with $CHCl_3$–MeOH (100:1) and the eluate (44 mg) on recrystallization from acetone afforded IIIa (35 mg) as needles, m.p. 216–218°.

2α,17β-*Dihydroxy*-A-*nor*-5β-*androstan*-1-*one diacetate* (IIIb)

Acetylation of IIIa (50 mg) with acetic anhydride (0·5 ml) and pyridine (0·7 ml) was carried out by standing at room temp overnight. The product was recrystallized from acetone giving the diacetate

(IIIb, 36 mg) as needles, m.p. 204–206°. $[\alpha]_D$ −57° (*c* 0·57); $\nu_{max}^{CCl_4}$ 1743, 1231 cm^{-1}. NMR: 4·98τ (quartet, J = 10, 8 c/s., C-2 proton), 5·46τ (second order quartet, C-17 proton), 8·92τ (singlet, C-19 CH_3) and 9·22τ (singlet, C-18 CH_3). ORD (*c* 0·57): $[\alpha]_{325\cdot5}$ −1012°, $[\alpha]_{332}$ −1004°, $[\alpha]_{337}$ −1021°, $[\alpha]_{285\cdot5}$ +690°. (Found: C, 70·37; H, 8·61. $C_{23}H_{32}O_5$ requires: C, 70·18; H, 8·57%.)

A-*Nor*-5*β*-*androstane*-1α,2*β*,17*β*-*triol* (IVa)

(a) *From* 2*β*,17*β*-*dihydroxy*-A-*nor*-5*β*-*androstan*-1-*one* (IIa). To a suspension of LAH (35 mg) in refluxing dry tetrahydrofuran (5 ml), a solution of IIa (35 mg) in dry tetrahydrofuran (8 ml) was added dropwise over a period of 10 min with stirring and the mixture refluxed for an additional 2 hr. After cooling, a little water was added carefully to decompose the complex and the mixture acidified with dil HCl to dissolve an amorphous metal hydroxide and extracted with ethyl acetate. The organic layer was washed with 5% $NaHCO_3$ and water and dried over Na_2SO_4. After removal of the solvent, the resulting product was chromatographed over silica gel (1 g). The eluates (34 mg) with $CHCl_3$–MeOH (50:1 to 20:1) afforded, on recrystallization from acetone, the 1α,2*β*,17*β*-triol (IVa, 20 mg) as needles, m.p. 196–198°. Further recrystallization from the same solvent gave the analytical sample, m.p. 199–200°, $[\alpha]_D$ −6° (*c* 0·54); ν_{max}^{Nujol} 3352 cm^{-1}; $\nu_{max}^{CCl_4}$ 3625 (free OH) cm^{-1}. (Found: C, 73·50; H, 10·37. $C_{19}H_{30}O_3$ requires: C, 73·43; H, 10·27%.)

(b) *From the* 2*β*,17*β*-*dihydroxy*-1-*ketone* 17-*propionate* (IIb). Treatment of IIb (84 mg) in dry tetrahydrofuran (8 ml) with LAH (84 mg) in refluxing dry tetrahydrofuran (8 ml) was carried out in a manner similar to that described in (a). Recrystallization of the product (75 mg) from acetone–pet. ether gave needles (46 mg), m.p. 195–197°, which was further recrystallized from the same solvent affording the triol (IVa), m.p. 199–200°, identical with a sample obtained in (a).

A-*Nor*-5*β*-androstane-1α,2*β*,17*β*-*triol triacetate* (IVb)

The IVa (20 mg) was acetylated by treatment with acetic anhydride (0·6 ml) and pyridine (0·8 ml) at room temp overnight. The product on recrystallization from n-hexane gave the triacetate (IVb) as prisms, m.p. 138–139°, in nearly quantitative yield. $[\alpha]_D$ −44° (*c* 0·57); ν_{max}^{Nujol} 1740, 1735, 1246 cm^{-1}. (Found: C, 68·84; H, 8·65. $C_{24}H_{36}O_6$ requires: C, 68·54; H, 8·63%.)

Reduction of 2α,17*β*-*dihydroxy*-A-*nor*-5*β*-*androstan*-1-*one* (IIIa)

(a) *With lithium aluminum hydride.* To a suspension of LAH (110 mg) in refluxing dry tetrahydrofuran (12 ml), a solution of IIIa (110 mg) in dry tetrahydrofuran (12 ml) was added dropwise over a period of 10 min with stirring and the mixture refluxed for an additional 2 hr. After cooling, a little water was added carefully to decompose the complex and the mixture acidified with dil HCl and extracted with ethyl acetate. The organic layer was washed with 5% $NaHCO_3$ and water and dried over Na_2SO_4. Removal of the solvent left a semi-solid material (116 mg), which was chromatographed over silica gel (3 g). The fractions (59 mg) eluted with $CHCl_3$–MeOH (100:1) afforded, on recrystallization from acetone, VIa (28 mg) as needles, m.p. 180–181°, $[\alpha]_D$ +9° (*c* 0·53); ν_{max}^{Nujol} 3370–3325 cm^{-1}; $\nu_{max}^{CCl_4}$ 3627 (free OH), 3561 (bonded OH) cm^{-1}. (Found: C, 73·42; H, 10·47. $C_{19}H_{30}O_3$ requires: C, 73·43; H, 10·27%.)

The next fractions (42 mg), eluted with $CHCl_3$–MeOH (50:1 to 20:1), were recrystallized from acetone giving needles (21 mg), m.p. 207–209°, undepressed on admixture with a sample of V mentioned in the preceding paper[1] and the IR spectra of these two substances were identical.

(b) *With sodium borohydride.* To a solution of IIIa (86 mg) in MeOH (17 ml) was added $NaBH_4$ (86 mg) and the mixture refluxed for 3 hr. After cooling, a few drops of dil HCl were added to decompose the unreacted hydride. The mixture was extracted with ethyl acetate and the organic layer washed with 5% Na_2CO_3 and water and dried over Na_2SO_4. After removal of the solvent, the residue (87 mg) was chromatographed on silica gel (2 g). The fractions (72 mg) eluted with $CHCl_3$–MeOH (100:1) afforded, on recrystallization from acetone, the 1α,2α,17*β*-triol (VIa, 52 mg) as needles, m.p. 179–181°.

The eluates (14 mg) with $CHCl_3$–MeOH (50:1 to 20:1) were recrystallized from acetone giving the 1*β*,2α,17*β*-triol (V, 7 mg) as needles, m.p. 207–209°. These two triols were identified with samples of the respective triols by mixed m.ps. and IR comparisons.

A-*Nor*-5*β*-*androstane*-1α,2α,17*β*-*triol triacetate* (VIb)

The VIa (33 mg) was treated with pyridine (1 ml) and acetic anhydride (0·6 ml) at room temp overnight. The product was recrystallized from n-hexane giving the triacetate (VIb, 32 mg) as needles,

m.p. 109–110°, $[\alpha]_D$ −19° (*c* 1·06); ν_{max}^{Nujol} 1738, 1241 cm^{-1}. (Found: C, 68·80; H, 8·68. $C_{26}H_{36}O_6$ requires: C, 68·54; H, 8·63%.)

A-*Nor*-5*β*-*androstane*-1*α*,2*α*,17*β*-*triol* 1,2-*acetonide* 17-*acetate* (VIIb)

A solution of VIa (100 mg) in acetone (20 ml) containing *p*-toluenesulphonic acid (10 mg) was refluxed for 5 hr. The solution was neutralized with 5% $NaHCO_3$, concentrated under red. press. and extracted with ether. The ether layer was washed with water, dried and evaporated leaving the acetonide (VIIa, 116 mg) as an oil. Attempts to crystallize this oil were unsuccessful. $\nu_{max}^{CCl_4}$ 3635, 3510, 1382, 1374 cm^{-1}.

A mixture of VIIa (104 mg) in acetic anhydride (1 ml) and pyridine (1·2 ml) was allowed to stand at room temp overnight. The product was recrystallized from n-hexane giving the acetonide acetate (VIIb, 56 mg) as plates, m.p. 120–121°, $[\alpha]_D$ +41° (*c* 0·58); $\nu_{max}^{CCl_4}$ 1738, 1382, 1374, 1250 cm^{-1}. (Found: C, 73·14; H, 9·62. $C_{28}H_{36}O_4$ requires: C, 73·36; H, 9·64%.)

2,17*β*-*Dihydroxy*-A-*nor*-5*β*-*androst*-2-*en*-1-*one* (X)

(a) *From* 1*β*,17*β*-*dihydroxy*-A-*norandrost*-3(5)-*en*-2-*one* (IXa). A solution of the unsaturated ketol (IXa, 600 mg) in MeOH (24 ml) and 40% NaOH (3 ml) was refluxed for 30 min in a stream of N_2. After dilution with water and washing with ether, the alkaline layer was acidified with 10% HCl and extracted thoroughly with ether containing a small amount of MeOH. The ether extract was washed with 5% Na_2CO_3 and water, dried over Na_2SO_4 and evaporated under red. press. leaving a crystalline material (497 mg). Recrystallization from acetone gave the diosphenol (X, 436 mg) as scales, m.p. 243–245° (dec), $[\alpha]_D$ −96° (*c* 0·57). λ_{max} 262 mμ (*ε* 6,000). ν_{max}^{Nujol} 3345, 3055, 1743, 1678, 1643 cm^{-1}. NMR: 3·82*τ* (doublet, J = 2 c/s., C-3 proton), 8·87*τ* (singlet, C-19 CH_3) and 9·23*τ* (singlet, C-18 CH_3). $FeCl_3$ test: positive. (Found: C, 74·43; H, 9·03. $C_{18}H_{26}O_3$ requires: C, 74·44; H, 9·02%.)

(b) *From* 1*β*,17*β*-*dihydroxy*-A-*norandrost*-3(5)-*en*-2-*one* 17-*propionate* (IXb). A mixture of IXb (335 mg) in MeOH (12 ml) and 40% NaOH (1·5 ml) was refluxed for 30 min in a N_2 atm. The product was recrystallized from acetone giving scales (188 mg), m.p. 243–245° (dec), identical with a sample of the diosphenol (X) obtained in (a).

Reduction of 2,17*β*-*dihydroxy*-A-*nor*-5*β*-*androst*-2-*en*-1-*one* (X) *with sodium borohydride*

To a solution of X (84 mg) in MeOH (17 ml), $NaBH_4$ (84 mg) was added and the mixture refluxed for 3 hr. After cooling, a little 5% HCl was added to decompose the unreacted hydride. The product (85 mg) isolated was chromatographed on silica gel (2 g). The early fractions (12 mg), eluted with $CHCl_3$–MeOH (100:1), were recrystallized from acetone to recover the starting material (X), m.p. 238–240° (dec). The further eluate (53 mg) with $CHCl_3$–MeOH (100:1) was recrystallized from acetone giving needles (22 mg), m.p. 175–177°. Further recrystallization from the same solvent afforded needles, m.p. 180–181°, which were identified with an authentic sample of the 1*α*,2*α*,17*β*-triol (VIa) by comparison of their IR spectra and mixed m.p.

17*β*-*Hydroxy*-2-*methoxy*-A-*nor*-5*β*-*androst*-2-*en*-1-*one* (XI)

The diosphenol (X, 422 mg) and methyl iodide (3 ml) was added to a solution of K (64 mg) dissolved in t-butyl alcohol (80 ml). The mixture was refluxed for 45 min, then concentrated *in vacuo* and extracted with ether. The ether solution was washed with 5% NaOH and water, dried and evaporated leaving a crystalline residue (434 mg). Recrystallization from acetone–n-hexane gave needles (336 mg) of the enol methyl ether (XI), m.p. 191–193°, $[\alpha]_D$ −65° (*c* 0·48). λ_{max} 258 mμ (*ε* 5,900), $\nu_{max}^{CHCl_3}$ 3615, 1707, 1630 cm^{-1}. (Found: C, 74·87; H, 9·46. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%.)

1*α*,17*β*-*Dihydroxy*-A-*nor*-5*β*-*androstan*-2-*one* (XIIIa)

A suspension of LAH (205 mg) in dry tetrahydrofuran (20 ml) was stirred at room temp and a solution of XI (205 mg) in dry tetrahydrofuran (20 ml) was added dropwise over a period of 10 min. The mixture was refluxed for 1·5 hr and after cooling the excess reagent was decomposed by careful additions of water and dil HCl. The mixture was extracted with ethyl acetate and the organic solution was washed with 5% $NaHCO_3$ and water, dried and evaporated *in vacuo* leaving a glassy oil (218 mg)

expected as the crude XII. The residue was dissolved in MeOH (30 ml) and a solution of oxalic acid (454 mg) in water (6 ml) added. The mixture was allowed to stand at room temp for 40 min and then extracted with ethyl acetate. The organic layer was washed with 5% $NaHCO_3$ and water, dried and evaporated *in vacuo* leaving a crystalline material (187 mg). Recrystallization from acetone furnished XIIIa (131 mg) as plates, m.p. 218–220°, $[\alpha]_D$ −83° (*c* 0·54). $\nu_{max}^{CHCl_3}$ 3613, 3518, 1743 cm^{-1}. NMR: 6·08τ (singlet, C-1 proton), 6·40τ (second order quartet, C-17 proton), 8·71τ (singlet, C-19 CH_3) and 9·27τ (singlet, C-18 CH_3). ORD (*c* 0·23): $[\alpha]_{316}$ −2649°, $[\alpha]_{275\cdot5}$ +2710°. (Found: C, 74·08; H, 9·65. $C_{18}H_{28}O_3$ requires: C, 73·93; H, 9·65%.) Although admixture with a sample of IIIa, m.p. 218–220°, did not depress the m.p., the IR spectra of these compounds determined in $CHCl_3$ were quite different from each other.

1α,17β-*Dihydroxy*-A-*nor*-5β-*androstan*-2-*one diacetate* (XIIIb)

The XIIIa (70 mg) in acetic anhydride (0·7 ml) and pyridine (1 ml) was allowed to stand at room temp overnight to afford a crystalline material (90 mg). Recrystallization from acetone–n-hexane gave the diacetate (XIIIb, 70 mg) as plates, m.p. 178–179°, $[\alpha]_D$ −72° (*c* 0·57). $\nu_{max}^{CCl_4}$ 1766, 1742, 1411, 1243, 1230 cm^{-1}. NMR: 4·82τ (singlet, C-1 proton), 5·45τ (second order quartet, C-17 proton), 8·81τ (singlet, C-19 CH_3) and 9·23τ (singlet, C-18 CH_3). ORD (*c* 0·21): $[\alpha]_{316}$ −2051°, $[\alpha]_{275\cdot5}$ +1895°. (Found: C, 70·14; H, 8·54. $C_{22}H_{32}O_5$ requires: C, 70·18; H, 8·57%.)

Reduction of 1α,17β-*dihydroxy*-A-*nor*-5β-*androstan*-1-*one* (XIIIa) *with lithium aluminum hydride*

The XIIIa (50 mg) in dry tetrahydrofuran (10 ml) was treated with LAH (50 mg) in refluxing dry tetrahydrofuran (10 ml) as described for the reduction of IIa. The product was chromatographed over silica gel (1 g) and the eluate (42 mg) with $CHCl_3$–MeOH (100:1) gave, on recrystallization from acetone, needles (28 mg), m.p. 179–180°, identical with a sample of the above-mentioned VIa by the IR and mixed m.p. determinations.

Rearrangement of 1α,17β-*dihydroxy*-A-*nor*-5β-*androstan*-2-*one* (XIIIa)

(a) *With alumina.* A solution of XIIIa (30 mg) dissolved in $CHCl_3$–benzene (1:1) was adsorbed on a column of neutral Al_2O_3 (2 g) and allowed to stand for 1 hr. Elution with $CHCl_3$–MeOH (100:1) gave a crystalline material (25 mg), which was recrystallized from acetone yielding IIIa (14 mg) as needles, m.p. 218–220°.

(b) *With acid.* A solution of XIIIa (50 mg) in MeOH (8 ml) and 6 N H_2SO_4 (2 ml) was allowed to stand at room temp for 48 hr and extracted with ethyl acetate. The organic layer was washed with 5% Na_2CO_3 and water, dried and evaporated giving the crystalline residue (46 mg). Recrystallization from acetone gave needles (27 mg) of IIIa, m.p. 216–218°.

(c) *With alkali.* To a solution of XIIIa (30 mg) in MeOH (9 ml), 0·1 N NaOH (6 ml) was added in a stream of N_2 and the mixture allowed to stand at room temp for 10 min. The crude product (32 mg) was recrystallized from acetone giving IIIa (17 mg) as needles, m.p. 217–219°.

The products obtained by the above 3 methods were identified with an authentic sample of IIIa by mixed m.p. determinations, comparisons of the IR spectra and by thin layer chromatography.

Hydrogenation of 17β-*hydroxy*-A-*norandrost*-3(5)-*ene*-1,2-*dione* (VIIIa) *with palladium-charcoal*

A solution of VIIIa (75 mg) in MeOH (2·5 ml) and ethyl acetate (2·5 ml) was hydrogenated over 5% Pd-C (185 mg) at room temp. Absorption of 2 molar equiv H_2 was completed within 30 min. The catalyst was filtered off and the filtrate evaporated *in vacuo*. The residue was separated into 3 fractions by the preparative thin layer chromatography described above. The easily moved fraction (11 mg) resisted crystallization and was unidentified. The middle crystalline fraction (21 mg) showed 2 spots corresponding to IIIa and XIIIa on the thin layer chromatography. The less mobile fraction (33 mg) on recrystallization from acetone gave the pure IIIa (19 mg), m.p. 217–219°. Identity with an authentic sample was established by the thin layer chromatography and the IR spectra.

Hydrogenation of 2,17β-*dihydroxy*-A-*nor*-5β-*androst*-2-*en*-1-*one* (X) *over palladium-charcoal*

A mixture of X (40 mg) and 5% Pd-C (100 mg) in MeOH (5 ml) and ethyl acetate (5 ml) was shaken in an H_2 atm. at room temp. The H_2 absorption ceased with uptake of 1·18 molar equiv

(3·9 ml) after 20 min and no more observed for an additional 1 hr. The product, isolated by removal of the catalyst and the solvent, was chromatographed over silica gel (4 g). The eluates (39 mg) with $CHCl_3$ and $CHCl_3$–MeOH (100:1) were recrystallized from acetone giving plates (30 mg), m.p. 214–216°. This product on thin layer chromatography showed the 2 spots corresponding to IIIa and XIIIa. The IR spectrum of the crystals in Nujol was superimposable to that of a synthetic mixture in 3:2 ratio of IIIa to XIIIa.

Acknowledgement—The authors express their deep gratitude to Dr. Ken'ichi Takeda, Director of this Laboratory, for his helpful guidance throughout the course of this work.