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21. Keiji Yoshida and Tokuo Kubota : Studies on A-Norsteroids. II.*1 Reactions of 17β-Hydroxy-A-norandrost-3(5)-ene-1,2-dione with Several Reagents.

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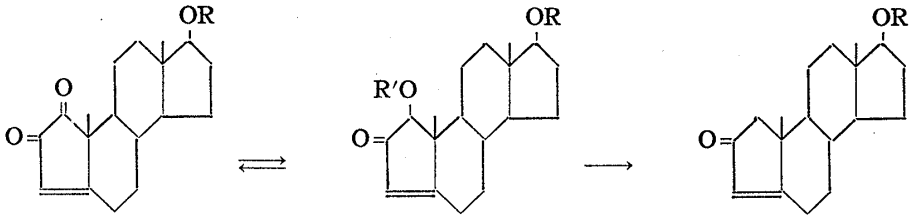
The preceding paper*1 has reported the preparation of several A-norsteroids having the $\Delta^{3(5)}$-ene-1,2-dione moiety (as I) by the oxidation of 1,2-dihydroxy-Δ^4-3-oxosteroids with manganese dioxide. It has previously been found[1] that a derivative of this type, A-nor-25D-spirost-3(5)-ene-1,2-dione, on the treatment with zinc and acetic acid was affected only at the C_1-carbonyl group giving a conjugated ketol, in which configuration of the C_1-hydroxyl group had been undecided. In these connections, our interest was directed to examine the differences in reactivities toward several reagents between the two vicinal carbonyl groups in A-nor-$\Delta^{3(5)}$-1,2-dioxo steroids. The present paper describes the results on the reactions of 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione (Ia) and its 17-propionate (Ib), obtained from testosterone in the earlier paper,*1 with reducing agents such as zinc-acetic acid, lithium-liquid ammonia and metal hydrides and with carbonyl reagents.

Treatment of 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione (Ia) with zinc and glacial acetic acid at room temperature afforded a single product, m.p. 240~243°, in good yield. Similar reduction of the 17-propionate (Ib) of the ene-dione gave the corresponding reduction product, which on hydrolysis of the 17-ester with aqueous hydrochloric acid in methanol was led to the same product as that obtained from the reduction of Ia. This compound can be predicted to be a conjugated ketol based on its ultraviolet absorption maximum at 236 mμ (ε 14,600) and the infrared bands at 1693 and 1620 cm^{-1} due to a five-membered, α,β-unsaturated ketone. In its nuclear magnetic resonance (NMR) spectrum, both the signals at 6.18 τ due to the proton on the hydroxy-bearing carbon atom and at 4.20 τ due to the olefinic proton were singlet as expected for the 1ξ-hydroxy-$\Delta^{3(5)}$-en-2-one structure.



Ia : R=H
b : R=COC_2H_5

IIa : R=R'=H
b : R=COC_2H_5, R'=H
c : R=R'=$COCH_3$

IIIa : R=H
b : R=$COCH_3$

Chart 1.

The following reactions furnished the chemical proof for this structural assignment. The conjugated ketol on treatment with manganese dioxide was easily reoxidized to the original ene-dione (Ia). On the other hand, acetylation of the conjugated ketol with acetic anhydride and pyridine afforded the corresponding diacetate. In order to eliminate its C_1-acetoxyl group, the diacetate was subjected to the reduction with zinc in

*1 Part I : This Bulletin, **13**, 50 (1965).
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1) T. Kubota, K. Takeda : Tetrahedron, **10**, 1 (1960).

refluxing glacial acetic acid and thus the known A-nortestosterone acetate (IIIb) was obtained as expected. This was saponified with methanolic alkali to A-nortestosterone (IIIa). Physical data of these compounds were in good agreement with those previously given in the literatures.[2,3] From these facts, the conjugated ketol can be designated as 1ξ,17β-dihydroxy-A-norandrost-3(5)-en-2-one, that is IIa with reservation on the configuration of the C_1-hydroxyl group, which will be discussed later in this paper. Hence, it has now been elucidated that the treatment of the ene-dione (Ia) with zinc and acetic acid resulted in the reduction of only the keto group at C_1-position to a hydroxyl group.

Reduction of the ene-dione (Ia) with lithium in liquid ammonia also furnished the conjugated ketol (IIa) as in the reduction with zinc-acetic acid, accompanied with a small amount of the unchanged starting material.

Reduction of the ene-dione (Ia) or its 17-propionate (Ib) with lithium alminum hydride in tetrahydrofuran, followed by chromatographic separation over alumina gave two isomeric triols, m.p. 184~186° (A) and m.p. 199~201° (B), in a ratio of 2:3. Acetylation of these triols with acetic anhydride and pyridine afforded the respective triacetates. On treatment with sodium borohydride in methanol, Ia afforded the same two triols, (A) and (B), as those described above, while Ib gave two triol 17-propionates, m.p. 166~167° and m.p, 176~178°, in a ratio of 1:4. The reductive hydrolysis of these two propionates with lithium aluminum hydride showed that the compounds melting at 166~167° and 176~178° correspond to the 17-propionates of the triols, m.p. 184~186° (A) and m.p. 199~201° (B), respectively.

Furthermore, lithium alminum hydride reduction of the above-mentioned 1ξ,17β-dihydroxy-A-norandrost-3(5)-en-2-one yielded the same two triols, (A) and (B), as those obtained from the reduction of the ene-diones (Ia) and (Ib). These two triols, (A) and (B), therefore, must be the epimers with respect to the configuration of the C_2-hydroxyl group.

When the infrared spectra of the two triol 17-propionates were determined in carbon tetrachloride solutions,*3 the propionate of the isomer (A) showed a band at 3549 cm^{-1},

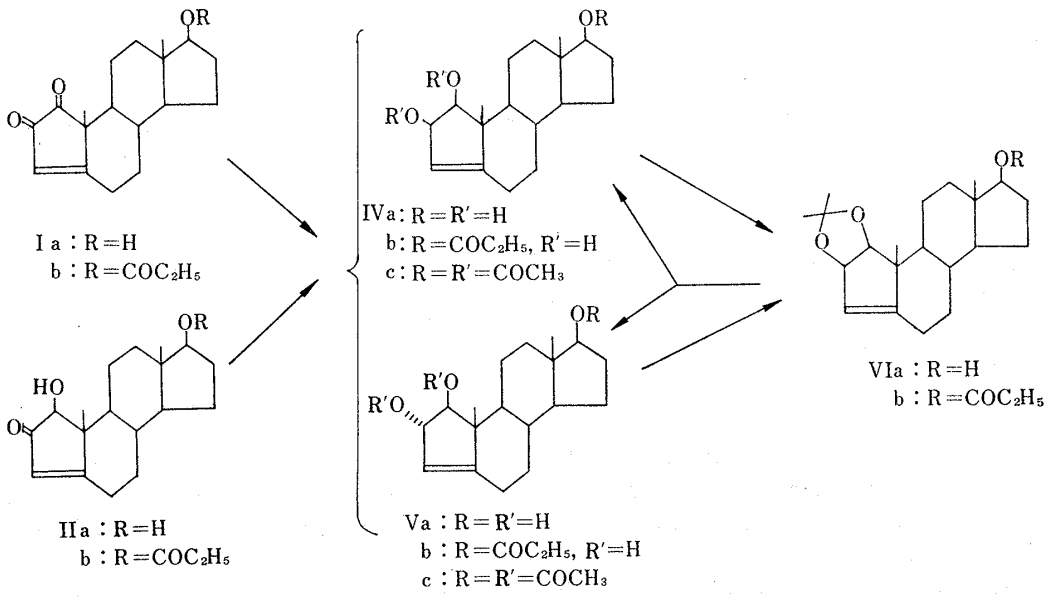

Chart 2.

*3 These infrared spectra were obtained with a LiF prism and a 20 mm. cell by a Perkin-Elmer Single-beam Infrared Spectrophotometer Model 12C.

2) F. L. Weisenborn, H. E. Applegate : J. Am. Chem. Soc., **81**, 1960 (1959).
3) R. Hanna, T. Rüll, G. Ourisson : Bull. soc. chim. France, **1961**, 1209.

indicative of the presence of an intramolecular hydrogen bonding, besides a free hydroxyl band at 3616 cm^{-1}, but the derivative of the isomer (B) showed no absorption except a band at 3623 cm^{-1}. This observation suggested that the vicinal glycols at the C_1- and C_2-positions in the isomeric triols are situated at *cis* in the isomer (A) and at *trans* in (B). Secondly, the two triols were subjected to the digitonide formation. The *cis* glycol (A) was precipitated with digitonin from an ethanol solution while the *trans* glycol (B) gave no precipitate. Although there is no report about precipitation of 2-hydroxy-A-nor-$\Delta^{3(5)}$-steroids with digitonin, Dauben, *et al.*[4] has reconfirmed the former reports[5] that A-nor-5α-steroids with a 2β-hydroxyl group are precipitated by digitonin but the 2α-hydroxy epimers are not. In view of these facts, it can be predicted that the *cis* (A) and *trans* (B) glycols hold the 2β- and 2α-hydroxyl groups in their molecules, respectively. This conclusion was supported by comparison of the molecular rotations of the two triols. In the application of Mills' rule[6,7] for epimeric allylic alcohols to the triols, the more dextrorotatory isomer should be the compound having the 2α-hydroxyl group. The *cis* glycol (A) and its 17-propionate showed levorotations, $[M]_D$ −82° and −112°, and the *trans* glycol (B) and its 17-propionate showed dextrorotations, $[M]_D$ +249° and +251°, respectively. These values brought on the same conclusion as that led from the digitonin test. Hence, one might conclude that the structures of the *cis* (A) and *trans* (B) glycols are A-norandrost-3(5)-ene-1β,2β,17β-triol (Ⅳa) and 1β,2α,17β-triol (Ⅴa), respectively. Consequently, the C_1-hydroxyl group in the above-mentioned, conjugated ketol can be defined as the β-configuration and this ketol has now been described as Ⅱa.

With an attempt to provide a chemical evidence for this assignment, when the isomeric triols (Ⅳa) and (Ⅴa) were treated individually with refluxing acetone containing *p*-toluenesulfonic acid, both the triols were led to an identical acetonide, m.p. 173~174°. Conversely, hydrolysis of this acetonide with 50% acetic acid gave a mixture of the original two triols (Ⅳa) and (Ⅴa). The abnormal consequence that the acetonide was formed not only from the *cis* glycol (Ⅳa) but also from the *trans* glycol (Ⅴa) might be explained in the same manner as a mechanism proposed for the formation of the identical *cis* dioxorane derivative from 1,2-*cis* and *trans* diols of tetrahydronaphthalene by

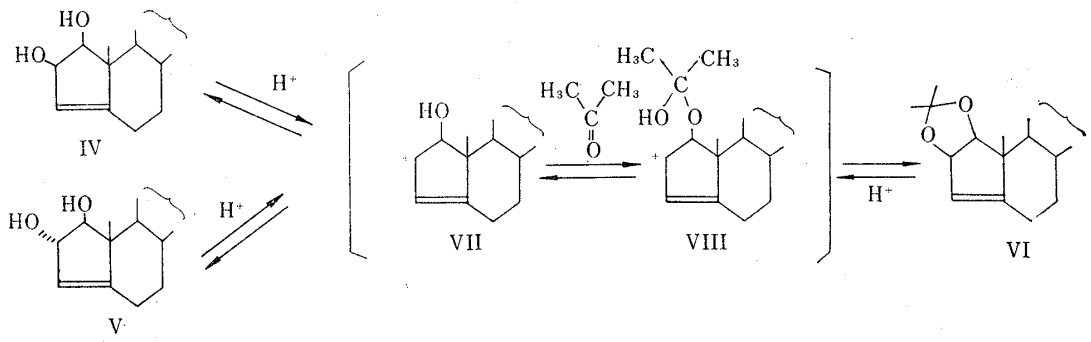

Chart 3.

Nagata, *et al.*[8] Namely, the acetonide formation and cleavage would probably be proceeded through intermediates, Ⅶ or/and Ⅷ, with a stable carbonium ion at the allylic C_2-position and hence this acetonide is described as the 1β,2β-acetonide (Ⅵa).

4) W. G. Dauben, G. A. Boswell, W. H. Templeton : J. Am. Chem. Soc., **83**, 5006 (1961).
5) *a*) R. E. Marker, O. Kamm, D. M. Jones, L. W. Mixon : J. Am. Chem. Soc., **59**, 1362 (1937). *b*) T. Kawasaki : Yakugaku Zasshi, **57**, 1058 (1937). *c*) L. Ruzicka, V. Prelog, P. Meister : Helv. Chim. Acta, **28**, 1651 (1945).
6) J. A. Mills : J. Chem. Soc., **1952**, 4976.
7) J. H. Brewster : J. Am. Chem. Soc., **81**, 5493 (1959).
8) W. Nagata, T. Terasawa : This Bulletin, **9**, 745 (1961).

Treatment of 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione propionate (Ib) with carbonyl reagents such as hydrazine, semicarbazide and hydroxylamine in the usual manner furnished respective products, which were shown to be the derivatives combined with the reagents only at one of the two carbonyl groups in Ib from their analytical results. However, their ultraviolet and infrared spectra provided no information which of the two carbonyl groups was condensed with the reagents.

If the carbonyl reagents reacted at the C_1-position in Ib in analogy with the result in the zinc-acetic acid or lithium-liquid ammonia reduction of the ene-dione (I), it might be expected that treatments of the enol acetate (IX), led from Ib as described below, with the carbonyl reagents would give products derived from condensation at the C_1-carbonyl group remaining in IX. Acetylation of the ene-dione (Ib) with refluxing acetic anhydride and pyridine, in the same manner as the example previously reported,[1] furnished the enol acetate (IX) showing the ultraviolet absorption at 297 mμ (ε 9,360) and the infrared bands at 1774, 1723, 1713, and 1603 cm^{-1}. However, treatments of the enol acetate (IX) with hydrazine and semicarbazide resulted in simultaneous hydrolysis of the enol acetate and condensation with the carbonyl reagents yielding the same hydrazone and semicarbazone, respectively, as those obtained from the ene-dione (Ib). On the other hand, acetylation of the hydrazone or the semicarbazone with refluxing acetic anhydride and pyridine resulted in the formation of an identical set of two products from the both. These products were suggested to be mono and diacetates being

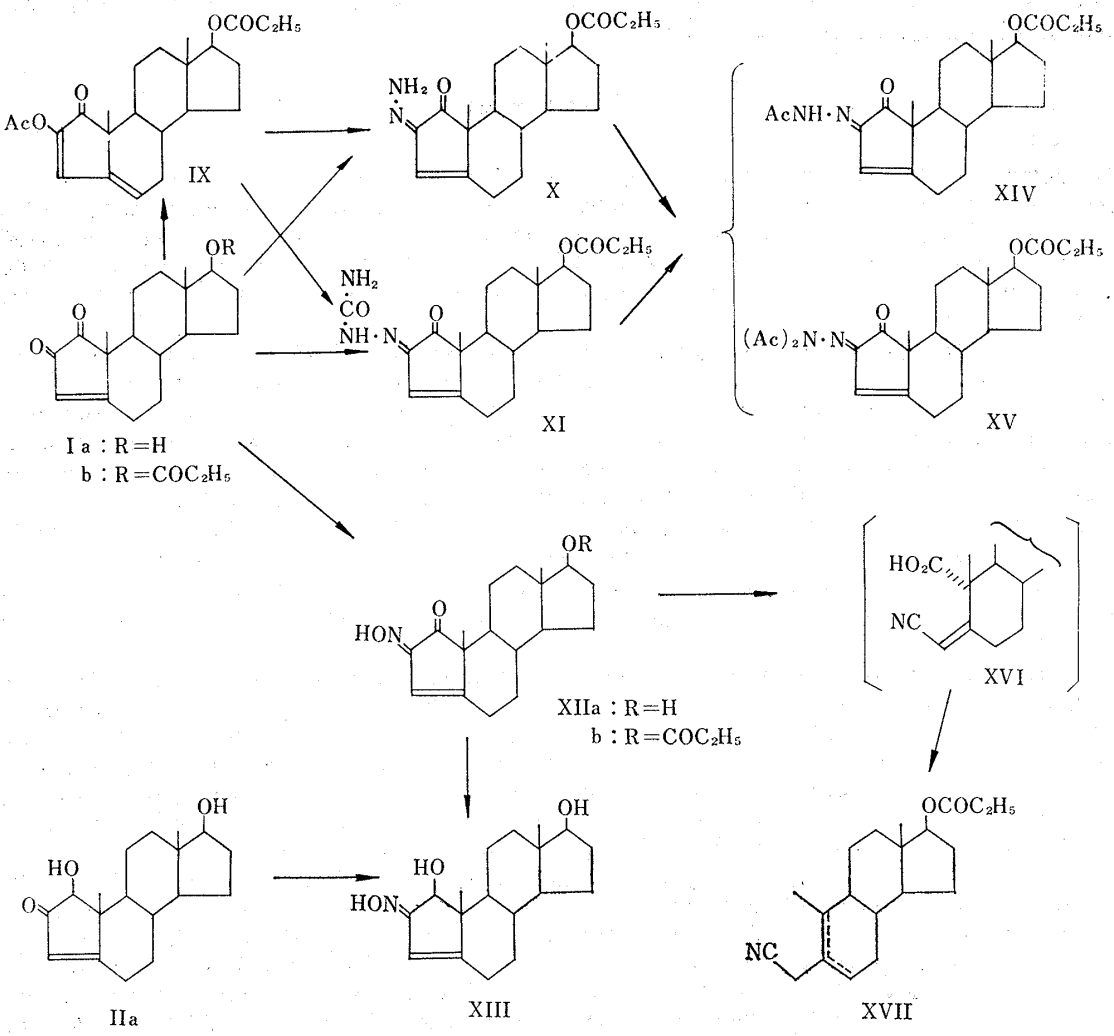

Chart 4.

connected with the amino group in the hydrazone, based on their analytical results and the ultraviolet and infrared spectra.

The above-mentioned oxime, on the same treatment with refluxing acetic anhydride and pyridine, gave a small amount of a crystalline product, $C_{20}H_{29}O_2N$, m.p. 231~233° (decomp.). Its ultraviolet spectrum showed no strong absorption except a maximum at 210 mμ and the infrared spectrum exhibited bands at 2260 and 1653 cm^{-1}, characteristic of an unconjugated nitrile and an isolated double bond, respectively. From these facts, the structure of this compound was deduced to be the nitrile (XVII), which might be arised from abnormal Beckmann rearrangement of the 1-oxo-2-hydroxyimino compound (XIIb) followed by decarboxylation. Depending on the above information that the oxime would probably have the 1-oxo-2-hydroxyimino structure, the above-mentioned 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one (IIa) was treated with hydroxylamine giving the 1β-hydroxy-2-hydroxyimino derivative (XIII), m.p. 235~236° (decomp.). The same compound was obtained, as expected, from sodium borohydride reduction of the oxime (XIIa), derived from the ene-dione (Ia), and identity of these products was established by a mixed melting point determination and infrared comparison.

Thus, it has now been proved that hydroxylamine reacted exclusively at C_2-position of the two carbonyl functions in the ene-dione (I). In analogy, the hydrazone and semicarbazone can probably be assigned as the structures (X) and (XI), respectively. It is noteworthy that the zinc-acetic acid or lithium-liquid ammonia reduction affects only the C_1-carbonyl of the ene-dione (I) while the condensation with carbonyl reagents occurs much easily at the C_2-ketone.

Experimental

All melting points were uncorrected. Optical rotations were determined at ca. 25° with a Rudolf Photoelectric Polarimeter Model 200. UV spectra were taken in 95% EtOH solutions with a Hitachi Recording Spectrophotometer EPS-2. Unless otherwise stated, IR spectra were recorded with a NaCl prism on a Koken Infrared Spectrophotometer Model DS 301. 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.

Reaction of 17β-Hydroxy-A-norandrost-3(5)-ene-1,2-dione (Ia) with Zinc in Acetic Acid——To a solution of Ia (500 mg.) in AcOH (80 ml.) was added portionwise Zn dust (4 g.) and the mixture was continued to stir at room temperature for 2 hr. The precipitate was filtered off and the filtrate was evaporated *in vacuo*. The residue was taken up with AcOEt and the organic solution was washed with 10% Na_2CO_3 and H_2O, dried over Na_2SO_4 and evaporated leaving a crystalline material (505 mg.). Recrystallization from Me_2CO afforded 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one (IIa) (332 mg.) as needles, m.p. 240~243°. Concentration of the mother liquor gave the second crop (95 mg.), m.p. 235~238°. The first crop showed the following constants : $[\alpha]_D$ −28° (c=1.05, dioxane). UV : λ_{max} 236 mμ (ε 14,600). IR ν_{max}^{Nujol} cm^{-1} : 3544, 3440~3350, 3098, 1693, 1620. NMR (τ) : 4.20 (singlet, C_3-proton), 6.18 (singlet, C_1-proton), 8.91 (singlet, C_{19}-CH_3), 9.20 (singlet, C_{18}-CH_3). *Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44 ; H, 9.03. Found : C, 74.54; H, 9.02.

Reaction of 17β-Hydroxy-A-norandrost-3(5)-ene-1,2-dione Propionate (Ib) with Zinc in Acetic Acid——A mixture consisting of Ib (295 mg.), AcOH (48 ml.) and Zn dust (2.4 g.) was worked up in the same manner as the preceding experiment. Recrystallization of the crude product from Me_2CO furnished 1β, 17β-dihydroxy-A-norandrost-3(5)-en-2-one 17-propionate (IIb) (229 mg.) as plates, m.p. 170~172°, $[\alpha]_D$ −33° (c=1.02, dioxane), UV : λ_{max} 235 mμ (ε 15,100). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3540, 1709, 1613. NMR (τ) : 4.18 (singlet, C_3-proton), 5.42 (second order quartet, C_{17}-proton), 6.18 (singlet, C_1-proton), 8.92 (singlet, C_{19}-CH_3), 9.17 (singlet, C_{18}-CH_3). *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found : C, 72.91; H, 8.80.

Acid Hydrolysis of IIb——To a solution of the foregoing IIb (261 mg.) in MeOH-$CHCl_3$ (3:1) (11 ml.) was added a mixture of conc. HCl (0.55 ml.) and H_2O (1.1 ml.). The mixture was allowed to stand at room temperature for 46 hr., and then diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated *in vacuo*. The crystalline residue was recrystallized from Me_2CO to give needles (180 mg.), m.p. 235~238°, which was identified by comparison of the IR spectra and a mixed melting point determination with a sample of 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one (IIa).

1β,17β-Dihydroxy-A-norandrost-3(5)-en-2-one Diacetate (IIc)——A solution of IIa (120 mg.) in pyridine (1.5 ml.) and Ac_2O (1.2 ml.) was allowed to stand at room temperature overnight. Working up in the usual manner and recrystallization from Me_2CO-hexane afforded the diacetate (IIc) (131 mg.), as needles, m.p. 157~159°, $[\alpha]_D$ −48° (c=0.58, dioxane). UV: λ_{max} 235 mμ (ε 15,100). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1620. *Anal.* Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.70; H, 8.14.

Oxydation of IIa with Manganese Dioxide——A mixture of IIa (200 mg.) and MnO_2 (2 g.) prepared by Mancera's procedure[9] in Me_2CO (20 ml.) was stirred for 30 min. at 30°. The dioxide was filtered off and the filtrate was evaporated to dryness *in vacuo*. The yellow crystalline residue (153 mg.) were recrystallized from Me_2CO-petr. ether giving the ene-dione (Ia) (110 mg.) as yellow needles, m.p. 224~227°. Further recrystallization from the same solvent raised the melting point to 229~230°, identical with an authentic sample of the ene-dione (Ia) in all respects.

A-Nortestosterone Acetate (IIIb)——A mixture of 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one diacetate (IIc) (110 mg.) and Zn dust (880 mg.) in AcOH (17.6 ml.) was refluxed for 2 hr. After cooling, the reaction mixture was filtered and the precipitate was washed with AcOEt. The combined filtrates were evaporated *in vacuo* and extracted with AcOEt. After washing with 5% $NaHCO_3$ and H_2O, the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue (104 mg.) was chromatographed on Al_2O_3 (3 g.). The fractions (81 mg.) eluted with petr. ether-benzene (8:2 to 1:1) afforded, on recrystallization from Me_2CO-hexane, A-nortestosterone acetate (IIIb) (58 mg.) as plates, m.p. 126.5~127.5°, $[\alpha]_D$ −20° (c=0.45, dioxane) (reported[3] m.p. 126~127°, $[\alpha]_D$ −42° (MeOH)). UV: λ_{max} 233 mμ (ε 16,900). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1739, 1714, 1629, 1412, 1247. *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.85; H, 9.12.

A-Nortestosterone (IIIa)——A solution of the acetate (IIIb) (500 mg.) dissolved in MeOH (40 ml.) and 40% NaOH (5 ml.) was refluxed for 30 min. After addition of H_2O and extraction with $CHCl_3$, the $CHCl_3$ layer was washed with H_2O, dried and evaporated to furnish a crystalline material (395 mg.), which was chromatographed on Al_2O_3 (10 g.). The fractions (353 mg.) eluted with benzene-$CHCl_3$ (9:1 to 8:2) afforded, on recrystallization from AcOEt, IIIa (237 mg.) as needles, m.p. 173~175°, $[\alpha]_D$ −22° (c=0.48, dioxane) (reported m.p. 175~176°, $[\alpha]_D$ −22° (EtOH)[2]; m.p. 174~175°, $[\alpha]_D$ −10° (EtOH)[3]). UV: λ_{max} 235 mμ (ε 15,900). IR ν_{max}^{Nujol} cm^{-1}: 3486, 3085, 1684, 1630. *Anal.* Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.97; H, 9.57.

Reduction of Ia with Lithium and Liquid Ammonia——A solution of Ia (100 mg.) in dry tetrahydrofuran (8 ml.) was added dropwise with stirring to a solution of Li (88 mg.) in liquid NH_3 (25 ml.). After 30 min., the blue color of the solution was discharged by addition of NH_4Cl (1.5 g.) and the NH_3 was allowed to evaporate. The residue was distributed between $CHCl_3$ and H_2O and the $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and evaporated leaving a residue (108 mg.), which was chromatographed over silica gel (2 g.). The yellow fractions (22 mg.) eluted with $CHCl_3$-MeOH (100:1) afforded, on recrystallization from Me_2CO, the unchanged starting material (Ia), m.p. 220~225°, as yellow needles. The next fractions (68mg.), eluted with $CHCl_3$-MeOH (100:1 to 50:1), on recrystallization from Me_2CO-petr. ether gave needles (35 mg.), m.p. 240~243°, undepressed by admixture with a sample of the conjugated ketol (IIa) mentioned above and the IR spectra of these two substances were identical.

Reduction of Ia with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (100 mg.) in refluxing dry tetrahydrofuran (20 ml.), a solution of Ia (100 mg.) in dry tetrahydrofuran (20 ml.) was added dropwise over a period of 20 min. with stirring. The mixture was refluxed for an additional 2 hr. After cooling, a small portion of H_2O was added carefully to decompose the complex and then the mixture was acidified with dil. HCl to dissolve an amorphous metal hydroxide. The mixture was extracted with AcOEt and the organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue (118 mg.) was chromatographed over silica gel (2 g.). The fractions (40 mg.), eluted with $CHCl_3$-MeOH (100:1), were recrystallized from Me_2CO-hexane to give A-norandrost-3(5)-ene-1β,2β, 17β-triol (IVa) (17 mg.) as plates, m.p. 184~186°, $[\alpha]_D$ −28° (c=1.03, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 3270, 3045, 1658. *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.96; H, 9.77.

To a solution of this triol (IVa) (8 mg.) in 95% EtOH (0.2 ml.) was added digitonin (40 mg.) in 70% EtOH (1 ml.). After standing at room temperature for 1 hr., the white digitonide precipitated.

The next fractions (61 mg.) eluted with $CHCl_3$-MeOH (50:1 to 20:1) afforded, on recrystallization from Me_2CO, A-norandrost-3(5)-ene-1β,2α,17β-triol (Va) (45 mg.) as plates, m.p. 199~201°, $[\alpha]_D$ +85° (c=1.05, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 3638, 3410, 3050, 1666. *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.90; H, 9.67.

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

Reduction of Ib with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (400 mg.) in dry tetrahydrofuran (40 ml.), a solution of the ene-dione 17-propionate (Ib) (400 mg.) in dry tetrahydrofuran (40 ml.) was added dropwise over a period of 20 min. with stirring. The mixture was refluxed for 2 hr.

9) O. Mancera, G. Rosenkranz, F. Sondheimer: J. Chem. Soc., **1953**, 2189.

and processed in the same manner as in the preceding experiment. The crude product (382 mg.) was chromatographed over silica gel (6 g.). The eluate (113 mg.) with $CHCl_3$–MeOH (100:1) on recrystallization from Me_2CO–hexane gave plates (81 mg.), m.p. 176~181°. Further recrystallization from the same solvent afforded the 1β,2β,17β-triol (Ⅳa) as plates, m.p. 184~186°, which showed no depression on admixture with a specimen obtained from the preceding experiment. IR spectra of these samples were identical.

The eluates (184 mg.) of the above chromatography with $CHCl_3$–MeOH (50:1 to 20:1) afforded by recrystallization from Me_2CO the 1β,2α,17β-triol (Va) (141 mg.) as plates, m.p. 199~201°, identical with a sample obtained from the above experiment by comparison of the IR spectra and a mixed melting point.

Reduction of Ia with Sodium Borohydride——To a solution of Ia (200 mg.) in MeOH (40 ml.), $NaBH_4$ (300 mg.) was added and the mixture was refluxed for 3 hr. After cooling, a few drops of dil. HCl were added to decompose the excess reagent. The mixture was extracted with AcOEt and the extract was washed with 5% $NaHCO_3$ and H_2O and dried. Evaporation of the solvent gave a semisolid material (215mg.), which was chromatographed over silica gel (3 g.). The fractions (38 mg.) eluted with $CHCl_3$–MeOH (100:1) afforded, on recrystallization from Me_2CO-petr. ether, plates (24 mg.), m.p. 176~178°. Further recrystallization from the same solvent gave plates, m.p. 184~186°, identical with a sample of the 1β,2β, 17β-triol (Ⅳa) by IR comparison and a mixed melting point.

Further elution of the above chromatography with $CHCl_3$–MeOH (50:1 to 20:1) gave a crystalline material (135 mg.), which was recrystallized from Me_2CO giving plates (93 mg.), m.p. 199~201°. Identity with a sample of the 1β,2α,17β-triol (Va) was established by the IR comparison and a mixed melting point determination.

Reduction of Ib with Sodium Borohydride——A solution of Ib (285 mg.) in MeOH (60 ml.) was treated with $NaBH_4$ (285 mg.) and then processed as described above for the reduction of Ia. The crude product (273 mg.) was chromatographed on silica gel (4 g.). The fractions (49 mg.) eluted with benzene–$CHCl_3$ (1:1) afforded, on recrystallization from MeOH, A-norandrost-3(5)-ene-1β,2β,17β-triol 17-propionate (Ⅳb) (20 mg.) as fine needles, m.p. 166~167°, $[\alpha]_D$ −32° (c=0.95, dioxane). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3526, 3035, 1723, 1651; $\nu_{max}^{CCl_4}$ cm^{-1}*3 : 3616, 3549. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found : C, 72.20; H, 9.27.

To a solution of Ⅳb (40 mg.) in 95% EtOH (7.5 ml.) was added digitonin (200 mg.) in 70% EtOH (10 ml.). After standing at room temperature for several minutes, the white digitonide precipitated.

The second fractions (125 mg.), eluted with $CHCl_3$ and $CHCl_3$–MeOH (100:1), were recrystallized from Me_2CO to give A-norandrost-3(5)-ene-1β,2α,17β-triol 17-propionate (Vb) (82 mg.) as needles, m.p. 176~178°, $[\alpha]_D$ +72° (c=1.00, dioxane). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3590, 3427, 3030, 1723, 1657; $\nu_{max}^{CCl_4}$ cm^{-1}*3 : 3623. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found : C, 72.29; H, 9.34.

This compound (Vb) was not precipitated with digitonin.

The third fractions (36 mg.), eluted with $CHCl_3$–MeOH (20:1) were recrystallized from Me_2CO to give plates (18 mg.), m.p. 199~201°, identical with an authentic sample of the 1β,2α,17β-triol (Va) in all respects.

Reductive Hydrolysis of IVb with Lithium Aluminum Hydride——To a suspension of $LiAlH_4$ (22 mg.) in dry tetrahydrofuran (2 ml.), a solution of Ⅳb (44 mg.) in dry tetrahydrofuran (5 ml.) was added dropwise over a period of 15 min. with stirring. The mixture was refluxed for 2 hr. After cooling, a small portion of H_2O was added carefully to decompose the complex. The product was extracted with AcOEt and the organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue (44 mg.) was chromatographed over silica gel (600 mg.). The fractions (23 mg.), eluted with $CHCl_3$–MeOH (100:1), were recrystallized from Me_2CO-petr. ether giving plates (18 mg.), m.p. 182~184°, identical with an authentic sample of the 1β,2β,17β-triol (Ⅳa) by IR spectra comparison and a mixed melting point determination.

Reductive Hydrolysis of Vb with Lithium Aluminum Hydride——A solution of Vb (104 mg.) in dry tetrahydrofuran (5 ml.) was treated with $LiAlH_4$ (52 mg.) in dry tetrahydrofuran (5 ml.) as described in the preceding experiment. The crude product (100 mg.) was recrystallized twice from Me_2CO giving plates (66 mg.), m.p. 199~201°, identical with an authentic sample of the 1β,2α,17β-triol (Va) by IR spectra comparison and a mixed melting point determination.

A-Norandrost-3(5)-ene-1β,2β,17β-triol Triacetate (IVc)——The 1β,2β,17β-triol (Ⅳa) (30 mg.) was acetylated with Ac_2O (0.3 ml.) and pyridine (1.5 ml.) by standing at room temperature overnight. The reaction mixture was worked up in the usual manner yielding the crude product (42 mg.). Recrystallization from hexane gave the triacetate (Ⅳc) (19 mg.) as needles, m.p. 129~131°, $[\alpha]_D$ −103° (c=0.89, dioxane). IR $\nu_{max}^{CS_2}$ cm^{-1} : 1738, 1652, 1250~1239. *Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found : C, 68.71; H, 8.16.

A-Norandrost-3(5)-ene-1β,2α,17β-triol Triacetate (Vc)——The 1β,2α,17β-triol (Va) (50 mg.) was acetylated with Ac_2O (0.5 ml.) and pyridine (2 ml.) in the usual manner. Recrystallization of the product (78 mg.) from Me_2CO-petr. ether afforded the triacetate (Vc) (60 mg.) as needles, m.p. 174~175°, $[\alpha]_D$ +80° (c=1.08, dioxane). IR $\nu_{max}^{CS_2}$ cm^{-1} : 1738, 1664, 1244. *Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found : C, 68.95; H, 8.26.

Reduction of 1β,17β-Dihydroxy-A-norandrost-3(5)-en-2-one (IIa) with Lithium Aluminum Hydride——A solution of IIa (72 mg.) in dry tetrahydrofuran (10 ml.) was treated with $LiAlH_4$ (72 mg.) in dry tetrahydrofuran (10 ml.) in the same manner as mentioned for the reduction of the ene-dione (Ia). The product (90 mg.) was separated by the usual method and chromatographed on silica gel (1 g.). The fractions (28 mg.), eluted with $CHCl_3$-MeOH (100:1), were recrystallized from Me_2CO-petr. ether to plates of the 1β,2β,17β-triol (IVa) (10 mg.), m.p. 184~186°. The next fractions (35 mg.) eluted with $CHCl_3$-MeOH (100:1 to 20:1) furnished, on recrystallization from Me_2CO, the 1β,2α,17β-triol (Va) (27 mg.) as plates, m.p. 199~201°. These two triols were identified with samples of the above-mentioned, respective triols by mixed melting points and IR spectral comparisons.

Reduction of 1β,17β-Dihydroxy-A-norandrost-3(5)-en-2-one 17-Propionate (IIb) with Sodium Boro hydride——Reduction of IIb (80 mg.) with $NaBH_4$ (80 mg.) in MeOH (16 ml.) was carried out in the same manner as described above for the reduction of Ib with $NaBH_4$ and the product (90 mg.) was chromatographed over silica gel (1.2 g.). The fractions (23 mg.) eluted with benzene-$CHCl_3$ (1:1) afforded, on recrystallization from MeOH, the 1β,2β,17β-triol 17-propionate (IVb) (12 mg.) as needles, m.p. 166~167°. The next fractions (40 mg.), eluted with $CHCl_3$, were recrystallized from Me_2CO giving the 1β,2α,17β-triol 17-propionate (Vb) (28 mg.) as needles, m.p. 176~178°. The further fraction (12 mg.) eluted with $CHCl_3$-MeOH (20:1) afforded, on recrystallization from Me_2CO, the 1β,2α,17β-triol (Va) (6 mg.) as plates, m.p. 199~201°. These compounds were identified by mixed melting points and the IR spectra with authentic samples of the respective compounds obtained in the above-mentioned experiments.

A-Norandrost-3(5)-ene-1β,2β,17β-triol 1,2-Acetonide (VIa)——A mixture of the 1β,2α,17β-triol (Va) (145 mg.) dissolved in Me_2CO (30 ml.) and *p*-toluenesulfonic acid (15 mg.) was refluxed for 5 hr. After cooling, the solution was neutralized with 5% $NaHCO_3$, evaporated and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried, and the solvent was removed under reduced pressure. The residue was chromatographed over neutral Al_2O_3 (4 g,). The fractions (128 mg.) eluted with petr. ether-benzene (8:2) and benzene furnished, on recrystallization from Me_2CO-petr. ether, the acetonide (VIa) (62 mg.) as plates, m.p. 173~174°, $[\alpha]_D$ −49° (c=1.04, dioxane). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3610, 3446, 1658. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found : C, 75.80; H, 9.84.

A-Norandrost-3(5)-ene-1β,2β,17β-triol 1,2-Acetonide 17-Propionate (VIb)——a) From IVb : The *cis* diol (IVb) (95 mg.) was treated with refluxing Me_2CO (20 ml.) containing *p*-toluenesulfonic acid (10 mg.) for 5 hr. as in the preceding experiment. Chromatographic purification of the crude product (95 mg.) on neutral Al_2O_3 (3 g.) and recrystallization of the eluate (60 mg.) from Me_2CO afforded the corresponding acetonide (VIb) (27 mg.) as scales, m.p. 173~175°, $[\alpha]_D$ −48° (c=1.02, dioxane). IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1737, 1660, 1381, 1372, 1206, 1186. *Anal.* Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found : C, 74.14; H, 9.40.

b) Form Vb : The *trans* diol (Vb) (141 mg.) was treated for 5 hr. with refluxing Me_2CO (28 ml.) containing *p*-toluenesulfonic acid (14 mg.) as in a). Chromatographic purification of the crude product (154 mg.) on neutral Al_2O_3 (4 g.) and recrystallization of the eluate (103 mg.) from Me_2CO afforded VIb (53 mg.) as scales, m.p. 173~175°, identical with a sample of the acetonide (VIb) obtained in a) by IR comparison and a mixed melting point.

Acid Hydrolysis of the Acetonide (VIa)——The above-mentioned acetonide (VIa) (126 mg.) was warmed at 55~60° for 1.5 hr. with 50% AcOH (4 ml.). A solid precipitated by addition of H_2O was taken up in AcOEt. The extract was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated to dryness. The residue (113 mg.) was chromatographed on silica gel (2 g.). Elution with $CHCl_3$ and $CHCl_3$-MeOH (100:1) afforded an oily material (60 mg.), which was assumed to be an epimeric mixture of A-norandrost-3(5)-ene-1β,2ξ,17β-triol 2-acetates, on account of its IR spectrum ($CHCl_3$ solution) showing bands at 3610, 3450, 1725, 1661 (w) cm^{-1}. The fractions (22 mg.) eluted with $CHCl_3$-MeOH (50:1) on recrystallization from Me_2CO afforded A-norandrost-3(5)-ene-1β,2β,17β-triol (IVa) (5 mg.) as needles, m.p. 183~185°. The fractions (30 mg.), eluted with $CHCl_3$-MeOH (40:1), were recrystallized from Me_2CO yielding A-norandrost-3(5)-ene-1β,2α,17β-triol (Va) (16 mg.) as needles, m.p. 199~201°. These products, (IVa) and (Va), were identified by mixed melting points and the IR spectra with an authentic samples of the respective compounds.

2,17β-Dihydroxy-A-norandrosta-2,5-dien-1-one 2-Acetate 17-Propionate (IX)——A mixture of the ene-dione 17-propinate (Ib) (600 mg.), Ac_2O (13 ml.) and pyridine (13 ml.) was heated under reflux for 2 hr. The product, extracted with Et_2O in the usual manner, was recrystallized from AcOEt-hexane giving plates of the enol acetate (IX) (487 mg.), m.p. 144~146°, $[\alpha]_D$ +136° (c=1.01, $CHCl_3$). UV : λ_{max} 297 mμ (ε 9,360). IR ν_{max}^{Nujol} cm^{-1} : 1774, 1723, 1713, 1603, 1191. *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found : C, 71.27; H, 7.78.

2-Hydrazono-17β-hydroxy-A-norandrost-3(5)-en-1-one 17-Propionate (X)——a) From the ene-dione 17-propionate (Ib) : A mixture of Ib (155 mg.) in EtOH (10 ml.) and 80% hydrazine hydrate (155 mg.) was refluxed for 40 min. The reaction solution was concentrated *in vacuo* to about a half volume. The precipitate separated by addition of H_2O was recrystallized from aq. EtOH giving the hydrazone (X) (125 mg.) as yellow needles, m.p. 172~174° (decomp.). The analytical sample was obtained by further recrystal-

lization from aq. EtOH and showed m.p. 174~176° (decomp)., $[\alpha]_D$ −43° (c=1.04, $CHCl_3$). UV λ_{max} mμ (ε): 253 (14,800), 345 (6,250). IR ν_{max}^{Nujol} cm^{-1}: 3410, 3269, 3180, 3070, 1737, 1692, 1623, 1600, 1544, 1191. *Anal.* Calcd. for $C_{21}H_{30}O_3N_2$: C, 70.36; H, 8.44; N, 7.82. Found: C, 70.17; H, 8.49; N, 7.88. b) From the enol acetate (IX): The enol acetate (IX) (150 mg.) was treated with 80% hydrazine hydrate (150 mg.) in EtOH (10 ml.) as described in a) and furnished the product (92 mg.) as yellow needles, m.p. 170~172° (decomp.). Recrystallization from aq. EtOH afforded the hydrazone (X), m.p. 174~176° (decomp.), which was identified by a mixed melting point and the IR spectrum with a sample obtained in a).

2-Semicarbazono-17β-hydroxy-A-norandrost-3(5)-en-1-one 17-Propionate (XI)——a) From the enedione 17-propionate (Ib): To a solution of Ib (240 mg.) in EtOH (18 ml.) was added a solution of semicarbazide hydrochloride (240 mg.) and AcONa (240 mg.) in H_2O (5 ml.). The mixture was refluxed for 40 min. and concentrated *in vacuo* to about a half volume. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution was washed with H_2O, dried and evaporated to give the semicarbazone (XI) (161 mg.) as needles, m.p. 234~236° (decomp.), which was recrystallized twice from aq. EtOH to afford an analytical sample, m.p. 239~242° (decomp.), $[\alpha]_D$ +153° (c=1.05, $CHCl_3$). UV λ_{max} mμ (ε): 245 (6,950), 322 (21,400). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3190, 3128, 1733, 1697, 1600, 1585, 1533, 1240, 1211. *Anal.* Calcd. for $C_{22}H_{31}O_4N_3$: C, 65.81; H, 7.78, Found: C, 65.89; H, 8.01. b) From the enol acetate (IX): A solution of IX (80 mg.) in EtOH (6 ml.) was treated with a mixture of semicarbazide hydrochloride (75 mg.) and AcONa (90 mg.) in H_2O (2 ml.) as described in a) to give needles (19 mg.), m.p. 218~223° (decomp.). Recrystallization from EtOH afforded the semicarbazone (XI), m.p. 239~242° (decomp.). Identity with a sample prepared in a) was established by a mixed melting point and the IR comparison. Concentration of the mother liquor gave the starting material (IX) (9 mg.) as plates, m.p. 142~144°, identical with an authentic sample of the enol acetate (IX) in all respects.

2-Hydroxyimino-17β-hydroxy-A-norandrost-3(5)-en-1-one (XIIa)——A solution of Ia (200 mg.) in EtOH (10 ml.) was combined with a solution of hydroxylamine hydrochloride (100 mg.) and AcONa (130 mg.) in H_2O (10 ml.). The mixture was refluxed for 40 min. and the product was isolated by extraction with $CHCl_3$ as a crystalline material (153 mg.), m.p. 230~233° (decomp.). Recrystallization from EtOH afforded the oxime (XIIa) as fine prisms, m.p. 236~237° (decomp.), $[\alpha]_D$ +19° (c=1.02, dioxane). UV λ_{max} mμ (ε): 233 (broad) (7,750), 291 (10,400). IR ν_{max}^{Nujol} cm^{-1}: 3525, 3245, 1730, 1617, 1600. *Anal.* Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31; N, 4.62. Found: C, 70.96; H, 8.31; N, 4.51.

2-Hydroxyimino-17β-hydroxy-A-norandrost-3(5)-en-1-one 17-Propionate (XIIb)——A solution of Ib (300 mg.) in EtOH (15 ml.) was treated with a solution of hydroxylamine hydrochloride (150 mg.) and AcONa (200 mg.) in H_2O (15 ml.) as described above for the preparation of XIIa to give the oxime (XIIb) (217 mg.) as needles, m.p. 170~176° (decomp.). The analytical sample was obtained by recrystallization from Et_2O and showed m.p. 189~191° (decomp.), $[\alpha]_D$ +43° (c=0.55, $CHCl_3$). UV λ_{max} mμ (ε): 233 (broad) (7,900), 291 (10,800). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 3272, 1727, 1621, 1603. *Anal.* Calcd. for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.04; H, 8.21; N, 4.01.

Acetylation of 2-Hydrazono-17β-hydroxy-A-norandrost-3(5)-en-1-one 17-Propionate (X)——A mixture of X (130 mg.), Ac_2O (3 ml.) and pyridne (3 ml.) was refluxed for 40 min. The product, extracted with Et_2O in the usual manner, was chromatographed on Al_2O_3 (4.5 g.). Elution with petr. ether–benzene (9:1 to 1:1) and recrystallization of the eluate (49 mg.) from Me_2CO–petr. ether furnished the diacetate (XV) (24 mg.) as needles, m.p. 183~185°, $[\alpha]_D$ −37° (c=1.06, $CHCl_3$). UV: λ_{max} 243 mμ (ε 9,550). IR ν_{max}^{Nujol} cm^{-1}: 1759, 1731, 1669, 1661, 1270, 1191. *Anal.* Calcd. for $C_{25}H_{34}O_5N_2$: C, 67.85; H, 7.75; N, 6.33. Found: C, 68.01; H, 7.93; N, 6.13.

Further elution of the above chromatography with benzene–$CHCl_3$ (1:1) and $CHCl_3$ gave a crystalline material (26 mg.). Recrystallization from Me_2CO–petr. ether afforded the monoacetate (XIV) (12 mg.) as yellow needles, m.p. 207~209°. UV λ_{max} mμ (ε): 245 (broad) (7,500), 322 (21,000). IR ν_{max}^{Nujol} cm^{-1}: 3186, 3125, 1737, 1687, 1611, 1591, 1211, 1186. *Anal.* Calcd. for $C_{23}H_{32}O_4N_2$: C, 68.97; H, 8.05; N, 7.00. Found: C, 68.89; H, 7.95; N, 7.11.

Treatment of the Semicarbazone (XI) with Acetic Anhydride and Pyridine——A mixture of XI (160 mg.), Ac_2O (5 ml.) and pyridine (5 ml.) was refluxed for 1.5 hr. The product, extracted with Et_2O in the usual manner, was chromatographed on Al_2O_3 (6 g.). Elution with petr. ether–benzene (9:1 to 1:1) and recrystallization of the eluate (42 mg.) from Me_2CO–petr. ether afforded needles (28 mg.), m.p. 183~185°, which was identical with the diacetate (XV) derived from acetylation of the hydrazone (X), by a mixed melting point and the IR comparison. Further elution with benzene–$CHCl_3$ (1:1) and $CHCl_3$ afforded crystalline eluate (29 mg.). Recrystallization from Me_2CO–petr. ether gave yellow needles, m.p. 207~209°. This compound was identical with the monoacetate (XIV) derived from acetylation of the hydrazone (X), in all respects.

Treatment of the Oxime (XIIb) with Acetic Anhydride and Pyridine——A mixture of XIIb (240 mg.), Ac_2O (5 ml.) and pyridine (5 ml.) was refluxed for 1.5 hr. The product (230 mg.), extracted with Et_2O in the usual manner, was chromatographed on Al_2O_3 (7 g.). The fractions (28 mg.) eluted with benzene furnished, on recrystallization from Me_2CO, plates, m.p. 231~233° (decomp.). The structure of this compound was assumed to be the nitril (XVII) based on the following constants; UV: λ_{max} 210 mμ. IR ν_{max}^{Nujol} cm^{-1}:

2260, 1731, 1653, 1196. *Anal.* Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27. Found : C, 76.38; H, 9.02.

2-Hydroxyimino-A-norandrost-3(5)-ene-1β,17β-diol (XIII)——a) By reduction of XIIa with $NaBH_4$: To a solution of the oxime (XIIa) (151 mg.) in EtOH (40 ml.), $NaBH_4$ (75 mg.) was added and the mixture was refluxed for 2 hr. After cooling, a few drops of dil. HCl were added to decompose the excess reagent. The reaction mixture was diluted with H_2O and concentrated *in vacuo* to about a half volume. The precipitated crystals were collected by filtration, washed with H_2O and dried (84 mg.). Recrystallization from EtOH gave fine needles (46 mg.) of XIII, m.p. 235~236° (decomp.), which was identified by a mixed melting point and by comparison of the IR spectra with an authentic sample prepared by the method b) described below.

b) By treatment of IIa with hydroxylamine : To a solution of the ketol (IIa) (60 mg.) dissolved in EtOH (4 ml.) was added a solution of hydroxylamine hydrochloride (30 mg.) and AcONa (40 mg.) in H_2O (2 ml.). The mixture was refluxed for 40 min. and evaporated *in vacuo*. Addition of H_2O afforded a crystalline material (40 mg.), m.p. 224~230° (decomp.). Recrystallization from EtOH gave XIII (17 mg.) as fine needles, m.p. 235~236° (decomp.), $[\alpha]_D$ −42° (c=0.53, dioxane). UV : λ_{max} 252 mμ (ε 13,600). IR ν_{max}^{Nujol} cm^{-1} : 3260, 1642, 1625. *Anal.* Calcd. for $C_{18}H_{27}O_3N$: C, 70.79; H, 8.91; N, 4.59. Found : C, 70.78; H, 8.93; N, 4.73.

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Summary

Reactions of 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione (Ia) and its 17-propionate (Ib) with several reagents have been examined. Treatment of I with zinc-acetic acid or lithium-liquid ammonia resulted in the reduction of only the C_1-carbonyl group giving 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one (II). On the contrary, reaction of I with carbonyl reagents in the usual condition afforded the corresponding derivatives which were condensed at only the C_2-carbonyl group with the reagents. Lithium aluminum hydride or sodium borohydride reduction of I gave the glycols, (IV) and (V), epimeric at C-2 with the 1β-hydroxyl group.

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22. Keiji Yoshida and Tokuo Kubota : Studies on A-Norsteroids. III.*1 Hydrogenations of A-Nor-$\Delta^{3(5)}$-steroids Substituted at C_1 and C_2-Positions.

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It has been described, in the preceding paper,*1 that the treatment of 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione with zinc and acetic acid resulted in the formation of 1β,17β-dihydroxy-A-norandrost-3(5)-en-2-one (VIIa) which on the reduction with metal hydrides afforded the unsaturated 1β,2β,17β- and 1β,2α,17β-triols, (I) and (II). The present report deals with an interesting result from catalytic hydrogenations of the $\Delta^{3(5)}$ double bond in the A-norsteroids, (I), (II) and (VIIa), bearing substituents at the C_1- and C_2-positions.

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