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1,4-Addition of Vinylmagnesium Bromide to α,β-Unsaturated Steroidal Ketones. II.[1] Reaction of 1-En-3-oxo Steroids

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The reaction of 1-en-3-oxo A/B *trans* steroid with vinylmagnesium bromide in the presence of cupric acetate afforded 1α-vinyl-3-oxo steroid. The configuration of the vinyl group introduced by the reaction was found to be α-oriented by the transformation of II into the lactone (VIII). The stereochemistry of the reduction of 1α-alkyl-3-oxo steroids and 5β-alkyl-3-oxo steroids with complex metal hydride was also studied.

The Grignard reaction of 17β-hydroxy-5α-androst-1-en-3-one (I) with vinylmagnesium bromide in the presence of cupric acetate gave a saturated ketone (II). Infrared (IR) and nuclear magnetic resonance (NMR) spectra, and optical rotatory dispersion showed that the product is a 1,4-addition product, 1-vinyl-3-oxo compound. The configuration of vinyl group introduced by this reaction was confirmed by chemical means. The reduction of II with lithium aluminum hydride gave a mixture of epimers at C-3. The epimer with a higher melting point (185—186°) was acetylated and ozonized to give the aldehyde (V). Hydrolysis of V afforded the hemiacetal (VIa) instead of a hydroxyaldehyde, IR spectrum of which showed no aldehyde carbonyl group. Such a hemiacetal formation is possible only when both aldehyde at C-1 and the hydroxyl group at C-3 are α-oriented (*cis* and axial). The aldehyde (V) was oxidized with the Jones reagent to the carboxylic acid (VIIa). Hydrolysis followed by treatment with acid gave the lactone (VIII), showing that both substituents are *cis* and axial.

Although an unequivocal proof was given by the observations described above, the conclusion was also supported by the transformation of V into 1α-methyl compound. The thioketal (IX) was obtained by treatment of the aldehyde (V) with ethanedithiol and boron trifluoride etherate in acetic acid. Hydrolysis of IX revived the aldehyde (V), showing that no isomerization had occurred in the thioketal formation reaction. The reduction with Raney nickel and then hydrolysis afforded the 1-methyl compound (Xb). Oxidation of Xb with the Jones reagent gave the dione (XI), which was also obtained from the known 1α-methyl compound (XII)[3] by oxidation.

The 1,4-addition of ethylmagnesium bromide to I gave the ethyl compound (XIII). This compound was also obtained by the hydrogenation of II over palladium-charcoal, indicating the same configuration of the substituent at C-1 in both II and XIII.

As described above it is pointed out that the alkyl group introduced by the 1,4-addition of a Grignard reagent in cyclic α,β-unsaturated ketone is axial, where such a bond formation is more effective in overlapping with orbital of α,β-unsaturated ketone.[4,5] It was recently reported however that this generalization does not always apply when a more bulky Grignard

1) Part I: H. Mori and R. Oh-uchi, *Chem. Pharm. Bull.* (Tokyo), **23**, 559 (1975).
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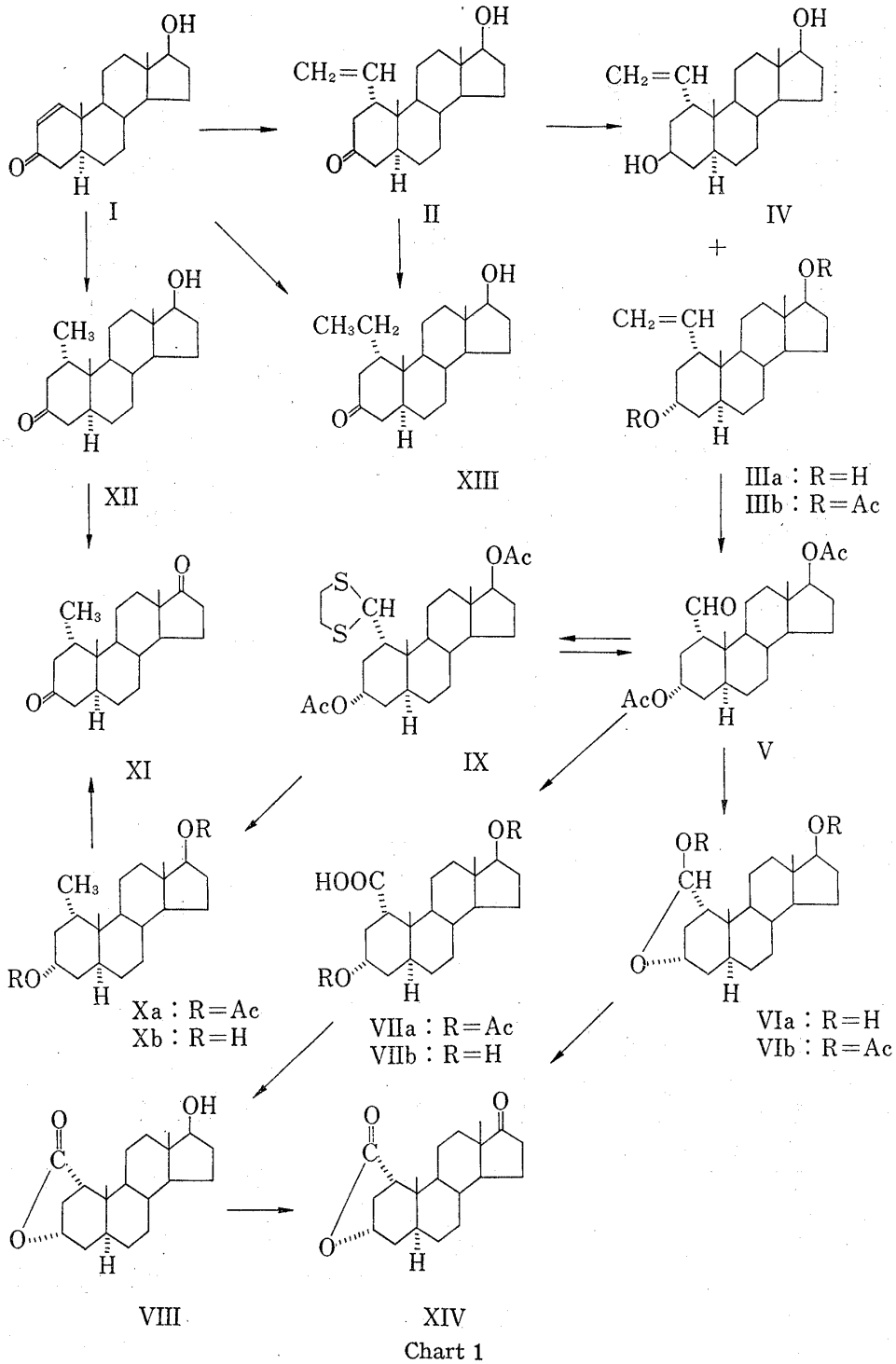
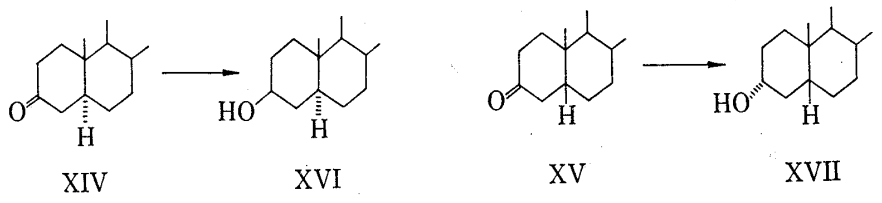


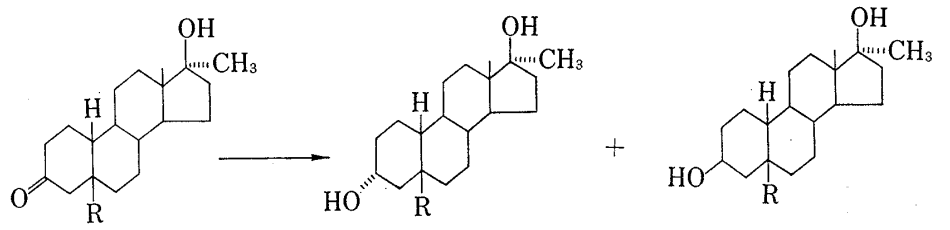
Chart 1

TABLE I. Ratio of Epimers on Reduction of 5β-Alkyl-17β-hydroxy-17-methylestran-3-ones with Lithium Aluminum Hydride and Sodium Borohydride

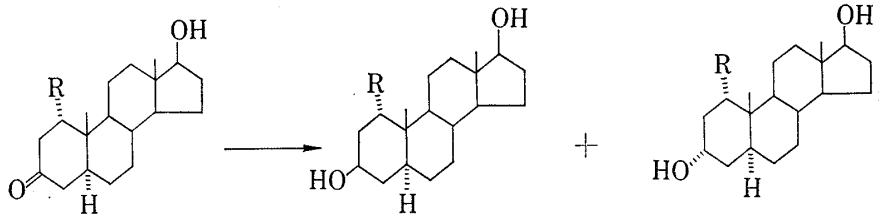
Compound	$LiAlH_4$		$NaBH_4$	
	3α-OH	3β-OH	3α-OH	3β-OH
17β-Hydroxy-17-methyl-5β-estran-3-one (XVIIId)	76	24	76	24
17β-Hydroxy-17-methyl-5β-vinylestran-3-one (XVIIIa)	43	57	43	57
17β-Hydroxy-5β-ethyl-17-methylestran-3-one (XVIIIb)	33	67	44	56
17β-Hydroxy-5β,17-dimethylestran-3-one (XVIIIc)	33	67	48	52



XIV XVI XV XVII



XVIIIa : R=−CH=CH$_2$ XIXa : R=−CH=CH$_2$ XXa : R=−CH=CH$_2$
XVIIIb : R=−C$_2$H$_5$ XIXb : R=−C$_2$H$_5$ XXb : R=−C$_2$H$_5$
XVIIIc : R=−CH$_3$ XIXc : R=−CH$_3$ XXc : R=−CH$_3$
XVIIId : R=−H XIXd : R=−H XXd : R=−H



II : R=−CH=CH$_2$ IIIa : R=−CH=CH$_2$ IV : R=−CH=CH$_2$
XIII : R=−C$_2$H$_5$ XXIa : R=−C$_2$H$_5$ XXIIa : R=−C$_2$H$_5$
XII : R=−CH$_3$ XXIb : R=−CH$_3$ Xb : R=−CH$_3$
XXIII : R=−H XXIc : R=−H XXIIc : R=−H

Chart 2

reagent such as phenylmagnesium bromide is used.[6] Apparently in such a case stereochemical factor is more seriously affected than electrochemical factor. In the cases described in this and the preceding paper, apparently the former generalization can be satisfactorily applied. It should be noted that the double bond in vinylmagnesium bromide does not change stereochemical course of the reactions.

As mentioned in this and the preceding paper, the reduction of II and XVIIIa with lithium aluminum hydride was not stereospecific. This finding seems to be of interest from stereochemical point of view, because the reduction of unsubstituted A/B-*trans* and A/B-*cis*-3-oxo steroids was found to be very stereospecific[7]; A/B-*trans*-3β-hydroxy and A/B-*cis*-3α-hydroxy compounds were obtained in a high yield. This prompted us to study the reduction of 1α- and 5β-substituted 3-oxo steroids. 5β-Substituted 19-nor-3-oxo steroids (XVIIIa, XVIIIb, and XVIIIc) were reduced with lithium aluminum hydride to give mixtures of epimeric 3-hydroxyl compounds. Both epimers were isolated in each case by a preparative thin-layer chromatography (TLC), and the configuration at C-3 was determined by the measurement of half-band width obtained from the signal of C-3 proton in their NMR spectra. The reaction mixture was treated with hexamethyldisilazane and trimethylchlorosilane in pyridine and ratio of two epimers was determined by gas chromatography, the result of which is summarized in Table I. Although the difference of ratio according to substituents was not clear, the substitution at C-5 with alkyl or alkenyl group produced a serious effect in

6) J.A. Marshall and N.H. Andersen, *J. Org. Chem.*, 31, 667 (1966).
7) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1965, p. 268.

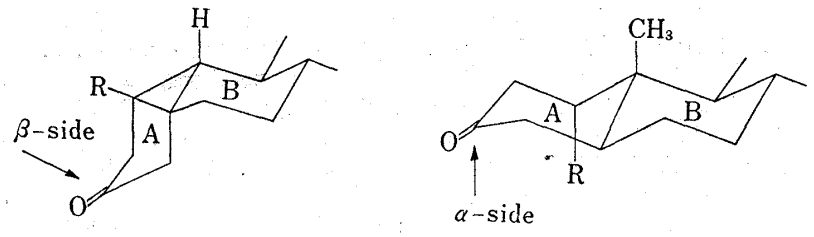


Fig. 1

stereochemistry of reduction. This fact was explained very rationally by the consideration that β-side attack of the reagent was disturbed by 5β-substituents (1,3-diaxial relationship

TABLE II. Ratio of Epimers on Reduction of 1α-Alkyl-17β-hydroxy-5α-androstan-3-ones with Lithium Aluminum Hydride and Sodium Borohydride

Compound	$LiAlH_4$		$NaBH_4$	
	3β-OH	3α-OH	3β-OH	3α-OH
17β-Hydroxy-5α-androstan-3-one (XXIII)	91	9	83	17
17β-Hydroxy-1α-vinyl-5α-androstan-3-one (II)	42	58	58	42
17β-Hydroxy-1α-ethyl-5α-androstan-3-one (XIII)	44	56	52	48
17β-Hydroxy-1α-methyl-5α-androstan-3-one (XII)	45	55	48	52

as shown in Fig. 1). Similar experiments were made on 1α-substituted compounds, II, XIII and XII, and similar results were obtained (Table II). The stereochemistry can also be rationalized by the same explanation as shown in Fig. 1.

Experimental

Melting points were taken on a melting point apparatus Mettler EP21. Optical rotations were measured in chloroform solution unless otherwise stated. Infrared spectra were measured with a spectrometer Hitachi EPI G_2 in a KBr disk. Nuclear magnetic resonance spectra were determined at 60 MHz with a spectrometer Hitachi R-20A in deuteriochloroform solution unless otherwise stated with tetramethylsilane (TMS) as an internal standard.

17β-Hydroxy-1α-vinyl-5α-androstan-3-one (II)——A solution of 17β-hydroxy-5α-androst-1-en-3-one (I, 4.0 g) and cupric acetate (0.7 g) in tetrahydrofuran (THF) (80 ml) was added to a Grignard reagent prepared from Mg (4.0 g), vinyl bromide (12 g) and THF (100 ml). After stirring for 1 hr at 0°, vessel temperature was raised gradually to room temperature and stirring was continued for another 2 hr. The excess Grignard reagent was decomposed by addition of ice, the product was extracted with ether and the organic layer was washed with 10% NH_4Cl, 5% Na_2CO_3 and water. After drying over Na_2SO_4, the solvent was evaporated and the oily residue (4.87 g) was submitted to preparative TLC (silica gel, $CHCl_3$–acetone 9:1) to give 17β-hydroxy-1α-vinyl-5α-androstan-3-one (II). Recrystallization from petrolium ether–*n*-hexane gave colorless needles, mp 148—149°, $[\alpha]_D^{23}$ +70° (c=1.01). IR cm^{-1}: 3450 (–OH), 3040, 1630 (–CH=CH_2), 1700 (C=O). NMR δ: 0.77 (3H, s, 18-CH_3), 1.12 (3H, s, 19-CH_3), 3.61 (1H, t, J=7 Hz, 17α-H), 4.75—6.20 (3H, m, 1α-CH=CH_2). ORD (c=0.286, EtOH): $[\alpha]_{700}$+52° $[\alpha]_{589}$+66°, $[\alpha]_{312}$+886° (peak), $[\alpha]_{290}$+226°, $[\alpha]_{280}$ −28° (trough), $[\alpha]_{260}$ +298°. *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.67; H, 10.91.

1α-Ethyl-17β-hydroxy-5α-androstan-3-one (XIII)——a) From 17β-Hydroxy-5α-androst-1-en-3-one (I): The Grignard reagent prepared from Mg (1.34 g), C_2H_5Br (5.98 g) and THF (30 ml) was added to a solution of I (1.0 g) and cupric acetate (1.0 g) in THF (10 ml) with stirring at 0°. The mixture was stirred for 3 hr at room temperature and worked up as described above to give crude oily product. The product was purified by preparative TLC (silica gel, $CHCl_3$–acetone 9:1) to give 1α-ethyl-17β-hydroxy-5α-androstan-3-one (XIII, 0.53 g) as colorless prisms from ether, mp 145—148°, $[\alpha]_D^{23}$ +18° (c=1.01). IR cm^{-1} ($CHCl_3$ solution): 3450 (–OH), 1700 (C=O). NMR δ: 0.75 (3H, s, 18-CH_3), 1.21 (3H, s, 19-CH_3), 3.42—3.78 (1H, 17α-H). ORD (c=0.282, EtOH): $[\alpha]_{700}$ +18°, $[\alpha]_{589}$ +19°, $[\alpha]_{312}$ +768° (peak), $[\alpha]_{300}$ +391°, $[\alpha]_{280}$ −883°, $[\alpha]_{275}$ −1120° (trough), $[\alpha]_{260}$ −880°. *Anal.* Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.89; H, 10.68.

b) From 17β-Hydroxy-1α-vinyl-5α-androstan-3-one (II): A mixture of II (0.015 g), 5% Pd-C (0.013 g) and EtOH (20 ml) was hydrogenated in the usual manner as described in the preceding paper. There was obtained XIII, the IR spectrum of which was the same as that of the compound obtained above.

1α-Vinyl-5α-androstane-3α,17β-diol (IIIa) and 1α-Vinyl-5α-androstane-3β,17β-diol (IV)——$LiAlH_4$ (2.0 g) was added to a solution of 17β-hydroxy-1α-vinyl-5α-androstan-3-one (II, 2.5 g) in THF (200 ml) at 0°. The mixture was stirred for 2 hr at 0—10° and the excess $LiAlH_4$ was decomposed by addition of ice. After addition of 10% HCl, the product was extracted with ether, and the organic layer was washed with water, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give oily product (2.24 g), which was submitted to preparative TLC (silica gel, $CHCl_3$–acetone 19: 1). The product having higher *Rf* value (0.935 g) was recrystallized from acetone to give 1α-vinyl-5α-androstane-3α,17β-diol (IIIa) as colorless needles, mp 185—186°, $[\alpha]_D^{25}$ +67° (c=1.01, MeOH). IR cm^{-1}: 3400 (–OH), 3050, 1630 (–CH=CH_2). NMR δ: 0.72 (3H, s, 18-CH_3), 0.88 (3H, s, 19-CH_3), 3.30—3.80 (1H, 17α-H), 3.90—4.20 (1H, m, 3β-H), 4.80—6.80 (3H, m, 1α-CH=CH_2). *Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 79.11; H, 10.76. Found: C, 78.83; H, 10.76.

The other product with lower *Rf* value (0.726 g) was recrystallized from ether to give 1α-vinyl-5α-androstane-3β,17β-diol (IV) as colorless prisms, mp 101—102°, $[\alpha]_D^{25}$ +49° (c=1.01, MeOH). IR cm^{-1}: 3400 (–OH), 3050, 1630 (–CH=CH_2). NMR δ: 0.72 (3H, s, 18-CH_3), 0.92 (3H, s, 19-CH_3), 3.40—4.22 (2H, m, 17α-H and 3α-H), 4.84—6.42 (3H, m, 1α-CH=CH_2). *Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 79.11; H, 10.76. Found: C, 79.06; H, 10.70.

1α-Methyl-5α-androstane-3α,17β-diol (Xb)——1α-Vinyl-5α-androstane-3α,17β-diol (IIIa, 0.935 g) was treated with pyridine (10 ml) and Ac_2O (5 ml) at room temperature to give 3α,17β-diacetoxy-1α-vinyl-5α-androstane (IIIb, 1.13 g) as colorless prisms from ether–*n*-hexane, mp 105—107°. IR cm^{-1}: 3050, 1630 (–CH=CH_2), 1730 (C=O). NMR δ: 0.78 (3H, s, 18-CH_3), 0.88 (3H, s, 19-CH_3), 2.01 (6H, s, 3α- and 17β-OAc), 4.38—6.63 (5H, m, 1α-CH=CH_2, 3β-H and 17α-H).

A solution of IIIb (0.30 g) in CH_2Cl_2 (20 ml) and pyridine (0.06 ml) was ozonized at −78° until the peak of 910 cm^{-1} on IR spectrum was disappeared. AcOH (0.51 ml) and zinc powder (0.46 g) were added and the suspension was stirred for 1 hr. Znic was filtered off and the filtrate was washed with 5% Na_2CO_3 and water, and dried over Na_2SO_4. Evaporation of the solvent gave 3α,17β-diacetoxy-1α-formyl-5α-androstane (V, 0.285 g) as oily material. IR cm^{-1}: 1735, 1715 (C=O). NMR δ: 0.78 (3H, s, 18-CH_3), 0.92 (3H, s, 19-CH_3), 1.98, 2.02 (6H, s, 3α- and 17β-OAc), 4.36—4.72 (1H, m, 17α-H), 4.92—5.18 (1H, m, 3β-H), 10.02 (1H, d, J=4 Hz, 1α-CHO).

To a solution of V (0.254 g) in AcOH (5 ml) was added ethanedithiol (0.5 ml) and boron trifluoride etherate (0.5 ml) and the solution was allowed to stand overnight at room temperature. The reaction mixture was poured into water and the product was extracted with ether. The organic layer was washed with 10% NaOH and water, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give thioketal (IX, 0.285 g) as oily material. NMR δ: 0.82 (3H, s, 18-CH_3), 0.92 (3H, s, 19-CH_3), 2.02, 2.06 (6H, s, 3α- and 17β-OAc), 2.60—3.58 (4H, m, 1α-SCH_2CH_2S), 4.48—5.10 (2H, m, 3β- and 17α-H).

A mixture of IX (0.285 g), dioxane (50 ml) and Raney nickel (6 g) was refluxed for 2 hr with vigorous stirring. After removal of the catalyst by filtration, the solution was evaporated *in vacuo* to give 3α,17β-diacetoxy-1α-methyl-5α-androstane (Xa, 0.234 g) as oily material. IR cm^{-1} (CH_2Cl_2 solution): 1720 (C=O). NMR δ: 0.79 (3H, s, 18-CH_3), 0.87 (3H, s, 19-CH_3), 2.03 (6H, s, 3α- and 17β-OAc), 4.45—4.77 (1H, m, 17α-H), 4.88—5.10 (1H, m, 1β-H).

A solution of Xa (0.234 g) in 10% KOH–EtOH (20 ml) was heated on a steam bath for 1 hr and poured into 10% HCl. The product was extracted with ether–CH_2Cl_2 and the organic layer was washed with water, and dried over Na_2SO_4. The solvent was evaporated to dryness, and the residue was recrystallized from acetone to give 1α-methyl-5α-androstane-3α,17β-diol (Xb, 0.185 g) as colorless needles, mp 171—172°, $[\alpha]_D^{23}$ +35° (c=1.01). (lit.[8] mp 177—179°, $[\alpha]_D$ +47° (MeOH)) IR cm^{-1}: 3350 (–OH). NMR (in C_5D_5N) δ: 0.94 (3H, s, 18-CH_3 or 19-CH_3), 0.96 (3H, d, J=4.5 Hz, 1α-CH_3), 0.97 (3H, s, 18-CH_3 or 19-CH_3), 3.72—4.48 (2H, m, 3β- and 17α-H). *Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.20; H, 11.01.

Hydrolysis of 3α,17β-Diacetoxy-1α-formyl-5α-androstane Ethylene Thioketal (IX)——A suspension of IX (0.10 g), mercuric chloride (0.30 g) and yellow mercuric oxide (0.30 g) in acetone (10 ml) was refluxed for 15 min. After removal of the precipitates by filtration, pyridine (3 ml) was added and the solution was allowed to stand overnight at room temperature. The resulting precipitates were filtered off and the filtrate was condensed to dryness to give oily material. This compound was identified with an authentic sample of V in IR spectra.

1α-Methyl-5α-androstane-3,17-dione (XI)——a) From 1α-Methyl-5α-androstane-3α,17β-diol (Xb): Jones reagent (0.2 ml) was added dropwise to an ice-cold solution of Xb (0.50 g) in acetone (5 ml) with stirring and the resulting suspension was stirred for 5 min, and poured into water. The product was extracted with ether, and the organic layer was washed with water, and dried over Na_2SO_4. The solvent removed by evaporation, and the residue was recrystallized from ether to give 1α-methyl-5α-androstane-3,17-dione (XI, 0.041 g) as colorless needles, mp 141—141.5°, $[\alpha]_D^{23}$ +100° (c=1.07). IR cm^{-1}: 1740, 1700 (C=O). NMR δ: 0.85 (3H, d, J=7 Hz, 1α-CH_3), 0.89 (3H, s, 18-CH_3) 1.14 (3H, s, 19-CH_3). *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.14; H, 10.24.

8) B. Pelc, *Collection Czech. Chem. Commun.*, **30**, 3468 (1965).

b) From 17β-Hydroxy-1α-methyl-5α-androstan-3-one (XII): A solution of XII (0.10 g) in acetone (10 ml) was treated with Jones reagent (0.5 ml) in the same manner as described above to give XI (0.083 g), the IR spectrum of which was identical with that of the compound derived above.

3α,17β-Dihydroxy-5α-androstane-1α-carboxylic Acid 1→3-Lactone (VIII)——Jones reagent (1.0 ml) was added to a solution of 3α,17β-diacetoxy-1α-formyl-5α-androstane (V, 0.28 g) in acetone (10 ml) at 0° and the suspension was stirred for 10 min. After addition of water, the product was extracted with ether, and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated to give 3α,17β-diacetoxy-5α-androstane-1α-carboxylic acid (VIIa, 0.25 g) as oily material. NMR δ: 0.78 (3H, s, 18-CH_3), 0.92 (3H, s, 19-CH_3), 4.38—4.80 (1H, m, 17α-H), 4.90—5.18 (1H, m, 3β-H).

A solution of VIIa (0.25 g) in 5% KOH–EtOH (10 ml) was warmed at 70° for 1 hr. 10% HCl was added and the product was extracted with ether. The organic layer was washed with water, and dried over Na_2SO_4. The solvent was evaporated and recrystallization from acetone–MeOH gave 3α,17β-dihydroxy-5α-androstane-1α-carboxylic acid 1→3-lactone (VIII, 0.21 g) as colorless needles, mp 245—246°, $[\alpha]_D^{26.5}$ +54° (c=1.01, DMSO). IR cm^{-1}: 3300 (–OH), 1680 (C=O). NMR δ: 0.73 (3H, s, 18-CH_3), 0.97 (3H, s, 19-CH_3), 3.20—4.90 (2H, m, 3β- and 17α-H). Mass Spectrum m/e: 318 (M^+). *Anal.* Calcd. for $C_{20}H_{30}O_3 \cdot H_2O$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.65.

1α-Formyl-5α-androstane-3α,17β-diol 3→1-lactol Diacetate (VIb)——A solution of 3α,17β-diacetoxy-1α-formyl-5α-androstane (V, 0.242 g) in 5% KOH–EtOH (10 ml) was warmed at 70° for 30 min. The reaction mixture was neutralized with 2% HCl and the product was extracted with ether. The organic layer was washed with water, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give 1α-formyl-5α-androstane-3α,17β-diol 3→1-lactol (VIa, 0.242 g). Recrystallization from acetone–MeOH gave colorless needles, mp 185—186°, $[\alpha]_D^{25.5}$ −14° (c=1.01). IR cm^{-1}: 3300 (–OH). Mass Spectrum m/e: 320 (M^+).

VIa (0.03 g) was acetylated with pyridine (5 ml) and Ac_2O (2.5 ml) by usual method to give 1α-formyl-5α-androstane-3α,17β-diol 3→1 lactol diacetate (VIb, 0.035 g). Recrystallization from ether gave colorless prisms, mp 157—158°, $[\alpha]_D^{25.5}$ −15° (c=1.01). IR cm^{-1}: 1730 (C=O). NMR δ: 0.79 (3H, s, 18-CH_3), 0.87 (3H, s, 19-CH_3), 2.02 (6H, s, –OAc), 4.34—4.80 (2H, m, 3β- and 17α-H). Mass Spectrum m/e: 404 (M^+). *Anal.* Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 70.95; H, 8.82.

3α-Hydroxy-17-oxo-5α-androstane-1α-carboxylic Acid 1→3-lactone (XIV)——a) From 3α,17β-Dihydroxy-5α-androstane-1α-carboxylic Acid 1→3-lactone (VIII): Jones reagent (0.5 ml) was added to a solution of VIII (0.10 g) in acetone (10 ml) at 0°. Stirring was continued for 10 min, and the resulting suspension was treated as described above to give 3α-hydroxy-17-oxo-5α-androstane-1α-carboxylic acid 1→3-lactone (XIV, 0.083 g) as colorless prisms from acetone–ether, mp 221—222°, $[\alpha]_D^{25.5}$ +97° (c=1.01). IR cm^{-1}: 1755, 1730 (C=O). NMR δ: 0.86 (3H, s, 18-CH_3), 0.98 (3H, s, 19-CH_3), 4.59—4.88 (1H, m, 3β-H). Mass Spectrum m/e: 316 (M^+). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.84; H, 8.31.

b) From 1α-Formyl-5α-androstane-3α,17β-diol 1→3-lactol (VIa): Jones reagent (0.3 ml) was added to a solution of VIa (0.05 g) in acetone (10 ml) at 0°. Stirring was continued for 10 min and resulting suspension was treated as described above to give XIV (0.042 g), which was identical with the compound desdcribed above in their IR spectra.

General Procedures of Reduction of Substituted 3-Oxo Steroids——a) By $LiAlH_4$: $LiAlH_4$ (0.10 g) was added to a solution of a 3-oxo steroid (0.10 g) in THF (10 ml) at 0°. The mixture was stirred for 1 hr at 0—10° and worked up in usual manner to give a mixture of epimeric isomers at C-3. The ratio of the products was determined by GLC (silicone SE-30), which was summarized in Table I and II. The compounds which have not been reported in literature were separated by preparative TLC (silica gel Merck GF_{254}: developing solvent, $CHCl_3$–acetone 9: 1) and were recrystallized from suitable solvent.

b) By $NaBH_4$: $NaBH_4$ (0.005 g) was added to a solution of a 3-oxo steroid (0.005 g) in EtOH (3 ml) at 0°, and the solution was stirred at 0 —10° for 1 hr. After addition of a few drops of AcOH, the resulting solution was poured into water, and the product was extracted wth ether–CH_2Cl_2. The organic layer was washed with 5% Na_2CO_3 and water, and dried over Na_2SO_4. Evaporation of the solvent afforded an epimeric mixture, the ratio of which was determined by GLC and was summarized in Table I and II.

5β-Ethyl-17α-methylestrane-3,17-diols (XIXb and XXb)——The reduction product of 5β-ethyl-17β-hydroxy-17-methylestran-3-one (XVIIIb) with $LiAlH_4$ was submitted to preparative TLC. The product having lower Rf value was recrystallized from acetone–ether to give 5β-ethyl-17α-methylestrane-3α,17β-diol (XIXb), mp 103—104°, $[\alpha]_D^{28.5}$ +21° (c=1.03). IR cm^{-1}: 3350 (–OH). NMR δ: 0.84 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 3.50—4.20 (1H, m, 3β-H). *Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.53; H, 11.42.

The product having higher Rf value was recrystallized from acetone–ether to give 5β-ethyl-17α-methylestrane-3β,17-diol (XXb) as colorless prisms, mp 105—107°, $[\alpha]_D^{28.5}$ +33° (c=1.01). IR cm^{-1}: 3350 (–OH). NMR δ: 0.84 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 4.00—4.24 (1H, m, 3α-H). *Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.71; H, 11.47.

5β,17α-Dimethylestrane-3,17-diols (XIXc and XXc)——The reduction product of 5β,17α-dimethyl-17-hydroxyestran-3-one (XVIIIc) with $LiAlH_4$ was submitted to preparative TLC. The product having lower Rf value was recrystallized from acetone to give 5β,17α-dimethylestrane-3α,17-diol (XIXc) as

colorless prisms, mp 189—189.5°, $[\alpha]_D^{28.5}$ +40° (c=1.00). IR cm^{-1}: 3380 (–OH). NMR δ: 0.82 (3H, s, 18-CH_3), 1.20 (3H, s, 17α-CH_3), 0.92 (3H, s, 5β-CH_3), 3.50—4.10 (1H, m, 3β-H). *Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.37; H, 11.18. Found: C, 78.25; H, 11.40.

The product having higher *Rf* value was recrystallized from acetone–ether to give 5β,17α-dimethylestrane-3β,17-diol (XXc) as colorless prisms, mp 179—179.5°, $[\alpha]_D^{28.5}$ +36° (c=1.07).

1α-Ethyl-5α-androstane-3,17β-diols (XXIa and XXIIa)——The reduction product of 1α-ethyl-17β-hydroxy-5α-androstan-3-one (XIII) with $LiAlH_4$ was submitted to preparative TLC. The product having lower *Rf* value was recrystallized from ether–petrolium ether to give 1α-ethyl-5α-androstane-3β,17β-diol (XXIa) as colorless needles, mp 87—88°, $[\alpha]_D^{29}$ +17° (c=1.01). IR cm^{-1}: 3350 (–OH). NMR δ: 0.73 (3H, s, 18-CH_3). 0.92 (3H, s, 19-CH_3), 3.38—4.15 (2H, m, 3α- and 17α-H). *Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69: H, 11.32. Found: C, 78.24; H, 11.41.

The product having higher *Rf* value was recrystallized from ether petrolium ether to give 1α-ethyl-androstane-3α,17β-diol (XXIIa) as colorless needles, mp 78—79°, $[\alpha]_D^{29}$ +16° (c=1.11). IR cm^{-1}: 3400 (–OH). NMR δ: 0.73 (3H, s, 18-CH_3), 0.87 (3H, s, 19-CH_3), 3.89 (1H, m, 3β-H), 3.42—3.82 (1H, m, 17α-H). *Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.33; H, 11.22.

1α-Methyl-5α-androstane-3,17β-diols (XXIb and Xb)——The reduction product of 17β-hydroxy-1α-methyl-5α-androstan-3-one (XII) with $LiAlH_4$ was submitted to preparative TLC. The product having lower *Rf* value was recrystallized from ether–petrolium ether to give 1α-methyl-5α-androstane-3β,17β-diol (XXIb) as colorless prisms, mp 80—81°, $[\alpha]_D^{29}$ +18° (c=1.00). IR cm^{-1}: 3400 (–OH). NMR δ: 0.72 (3H, s, 18-CH_3), 0.85 (3H, s, 19-CH_3), 0.92 (3H, d, J=6 Hz, 1α-CH_3), 3.42—4.20 (2H, m, 3α- and 17α-H). *Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.37; H, 11.18. Found: C, 78.02; H, 11.37.

The product having higher *Rf* value was recrystallized from acetone to give 1α-methyl-5α-androstane-3α,17β-diol, mp 184—185°, $[\alpha]_D^{23}$ +35° (c=1.01).

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