

Synthesis of 17 α -Acetoxy-6-chloro-2 α ,3 β -dihydroxy-4,6-pregnadien-20-one, a Metabolite of Chlormadinone Acetate

TATSUYA ABE and AKIRA KAMBEGAWA

Research Division, Teikoku Hormone Mfg. Co., Ltd.¹⁾

(Received November 16, 1972)

For the purpose of identifying a urinary metabolite of 17 α -acetoxy-6-chloro-4,6-pregnadiene-3,20-dione (I, chlormadinone acetate) in the rabbit, 17 α -acetoxy-6-chloro-2 α ,3 β -dihydroxy-4,6-pregnadien-20-one (V), which was found to be identical with the metabolite, was synthesized from I. The starting material (I) was converted to the 2 α - and 2 β -acetoxy compounds (II and III) on heating with lead tetraacetate in acetic acid. When II and III were reduced with sodium borohydride in anhydrous isopropanol, two 2,3-dihydroxy compounds (V and VI) were produced. These two diols were found to be 2 α ,3 β -diol (V) and 2 β ,3 β -diol (VI). It was also found that both diols formed acetonides. 17 β -acetoxy-4-androstene-2 α ,3 β -diol (XIII) could be also transformed into the acetonide.

During the course of studies on the metabolism of 17 α -acetoxy-6-chloro-4,6-pregnadiene-3,20-dione (I, chlormadinone acetate) in the rabbit, 17 α -acetoxy-6-chloro-2,3-dihydroxy-4,6-pregnadien-20-one had been isolated as one of urinary metabolites.²⁾ The configuration of 2- and 3-hydroxyl groups had, however, remained unestablished. In order to determine their configuration two epimeric 2,3-dihydroxy compounds were synthesized, and the metabolite in question was found to be identical with 2 α ,3 β -dihydroxy compound (V). This paper describes the synthesis of the metabolite and related compounds.

TABLE I. ΔM_D Values of Acetoxyl Substitution at C-2

	2 α -Substitution	2 β -Substitution
Testosterone acetate	-53° ^{a)}	-581° ^{a)}
Progesterone	-31° ^{a)}	
Chlormadinone acetate	-95°	-272°

a) reference 3c)

When I was treated with lead tetraacetate in acetic acid³⁾ at 90° for 3 hr, two 2-acetoxy compounds, II, mp 230—232°, and III, mp 238—241°, were obtained in a pure state. III epimerized to II on heating with potassium acetate in acetic acid, which is consistent with the same epimerization reported for 2 β ,17 β -diacetoxy-4-androsten-3-one.^{3b)} Thus III must be considered as the unstable 2 β -acetoxy compound. This conclusion is supported by comparison of ΔM_D values of II and III with those of 2-acetoxy derivatives of testosterone acetate and progesterone, as shown in Table I; more levorotatory epimer III should be considered as 2 β -acetoxy compound. Slightly different ΔM_D values are probably attributed to the difference in the original partial A/B structure (4-en-3-one and 6-chloro-4,6-dien-3-one). Nuclear magnetic resonance (NMR) spectra also support this assignment. The protons at C-2 in II and III appear at 5.63 ppm as a quartet ($J=13.2$, 6 cps) and at 5.33 ppm as a quartet

1) Location: 1604 Shimosakunobe, Kawasaki.

2) T. Abe, "Private communication."

3) a) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944); b) R.L. Clarke, K. Dobriner, A. Mooradian and C.M. Martini, *J. Am. Chem. Soc.*, **77**, 661 (1955); c) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

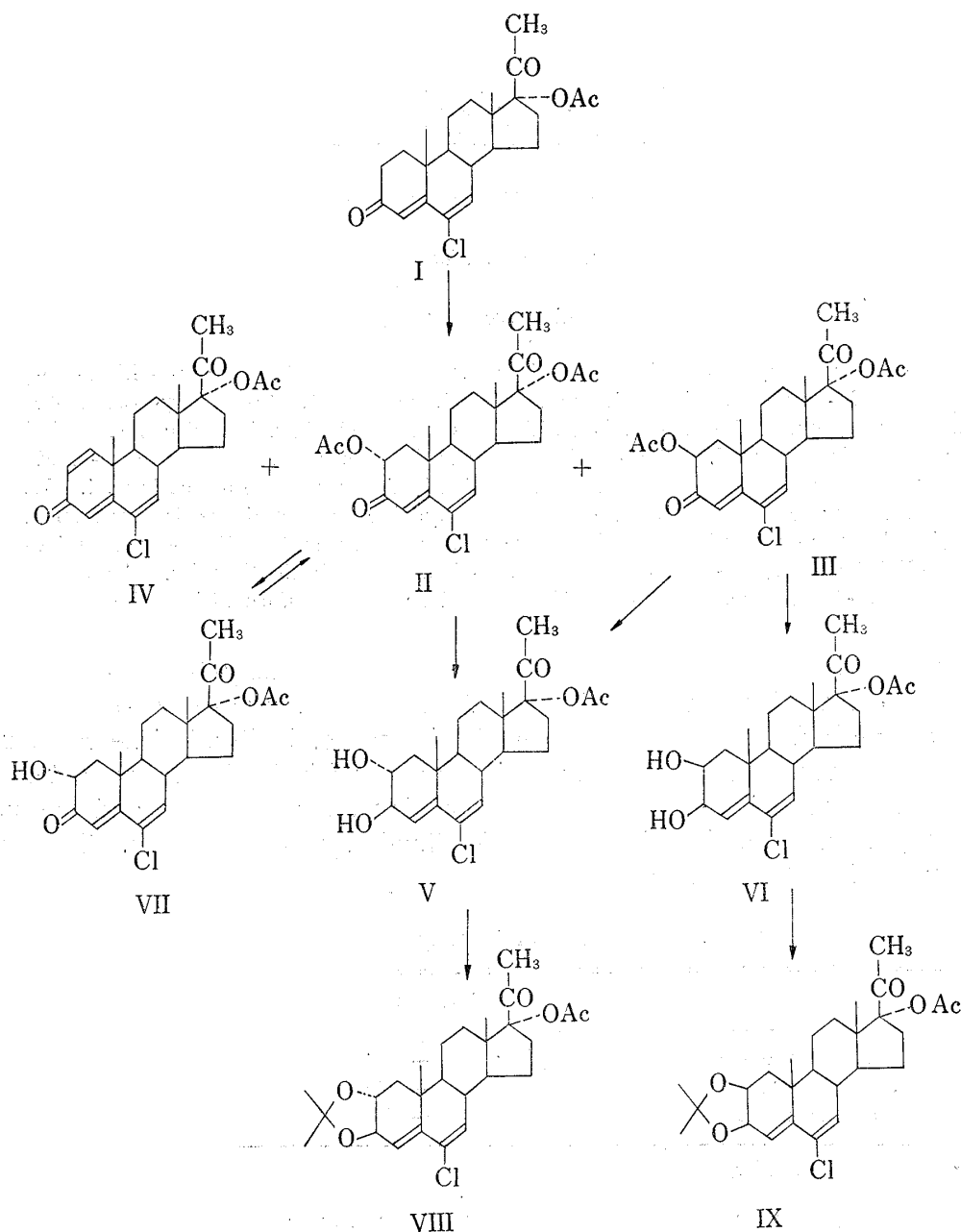


Chart 1

($J=6, 2.2$ cps), respectively. Large coupling constant (13.2 cps) in II is explained smoothly by the fact that the dihedral angle between 2β -proton and 1α -proton is about 180° , while such a large coupling constant is not observed in III, in which the proton at C-2 is equatorially oriented.

Oxidation of I with lead tetraacetate for a prolonged reaction time (24 hr) afforded II in a higher yield (35%), accompanied by 17 α -acetoxy-6-chloro-1,4,6-pregnatriene-3,20-dione (IV), which is consistent with reported data.^{3b)}

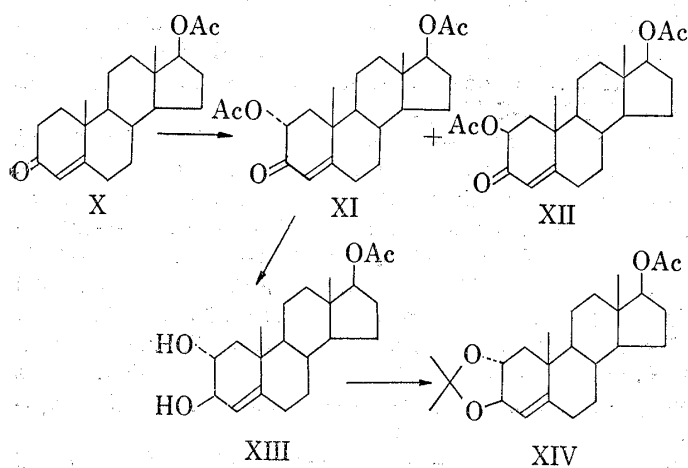
Reduction of II with sodium borohydride in isopropanol⁴⁾ gave a 2,3-dihydroxy compound (V), mp $248-251^\circ$, with high stereospecificity. When V was oxidized with manganese dioxide,⁵⁾ there was obtained 17 α -acetoxy-6-chloro-2-hydroxy-4,6-pregnadiene-3,20-dione

4) D. Kupfer, *Tetrahedron*, **15**, 193 (1961).

5) P. Narashimha Rao and L.R. Axelrod, *J. Am. Chem. Soc.*, **82**, 2830 (1960).

(VII), which was found to be identical with the product obtained by the mild hydrolysis of II with alkali. Since II was recovered on acetylation of VII, the configuration of 2-hydroxy group in V can be considered to be α . Shoppee, *et al.*⁶⁾ have reported that the reduction of 2 α -hydroxy-4-cholesten-3-one under a similar condition yields 4-cholestene-2 α ,3 β -diol. Thus V must be formulated as 17 α -acetoxy-6-chloro-2 α ,3 β -dihydroxy-4,6-pregnadien-20-one (V), and this compound was found to be identical with the metabolite isolated from urine.

Reduction of III under the same condition as in II afforded two epimeric 2,3-dihydroxy compound, VI, mp 229–231°, and V in a ratio of 6:4. The production of V was unexpected but is not surprising, because probably III was partially epimerized to II prior to the reduction and then was reduced by the reagent. The main product VI should be considered as a 2 β ,3 β -dihydroxy compound, because substitution at C-2 in 4-en-3-one system does not produce any change in stereochemical course of reduction of 3-oxo group.^{7,8)}



Treatment of V and VI with acetone in the presence of phosphomolybdic acid⁹⁾ gave the corresponding acetonides, VIII and IX. Although the formation of acetonide of VI, in which two hydroxyl groups at C-2 and C-3 are *cis*-oriented, is acceptable, acetonide formation in *trans* series of V must be considered rather as an exceptional example. Report of such an exceptional is the transformation of 4,4-dimethyl-5 α -cholestane-2 α ,3 β -diol into the acetonide.¹⁰⁾ This finding led us to examine whether acetonide formation of 2 α ,3 β -dihydroxy-4-ene steroid is possible or not.

Reduction of 2 α ,17 β -diacetoxy-4-androsten-3-one (XI) in the same manner as described above gave 17 β -acetoxy-4-androstene-2 α ,3 β -diol (XIII). The acetonide XIV was obtained from the *trans*-diol (XIII) by treatment with acetone in the presence of phosphomolybdic acid.

Experimental¹¹⁾

Oxidation of 17 α -Acetoxy-6-chloro-4,6-pregnadiene-3,20-dione (I) with Lead Tetraacetate—a) A mixture of 17 α -acetoxy-6-chloro-4,6-pregnadiene-3,20-dione (I, 1 g) and lead tetraacetate (1.5 g) in acetic acid (15 ml) was heated on a steam-bath for 3 hr. After addition of cold H₂O and standing for several hours, the precipitate was collected by filtration, washed with H₂O and dried. Repeated crystallizations from EtOH,

- 6) C.W. Shoppee, D.N. Jones, and G.H.R. Summers, *J. Chem. Soc.*, **1957** 3100.
- 7) J. Herran, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 5531 (1954).
- 8) W.G. Dauben, R.A. Michell, and J.F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).
- 9) H. Mori, K. Tsuneda, K. Shibata, and M. Sawai, *Chem. Pharm. Bull.* (Tokyo), **15**, 466 (1967).
- 10) H. Wada, G. Goto, T. Goto, and Y. Hirota, *Tetrahedron Letters*, **1966**, 3461.
- 11) All melting points were taken on a micro hot-stage apparatus and are uncorrected. All optical rotations were measured in chloroform unless otherwise stated. Ultraviolet (UV) spectra were measured on Hitachi Model EPS-3. Infrared (IR) spectra were run on Hitachi Model EPI-G2 spectrometer. NMR spectra were recorded on Hitachi Model R-20A spectrometer at 60 Mc using tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, q=quartet, m=multiplet. Mass spectra were taken on Hitachi Model RMU-6E. For the preparative TLC Silica gel HF (E. Merck AG) was used as an adsorbent.

AcOEt or MeOH afforded 2 α ,17 α -diacetoxy-6-chloro-4,6-pregnadiene-3,20-dione (II, 120 mg) as colorless prisms. mp 230—232°. $[\alpha]_D^{25} -21.8^\circ$ ($c=1.00$). UV $\lambda_{\max}^{\text{MeOH}}$ $m\mu$ (ϵ): 287 (16450). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1725, 1684 (C=O). Anal. Calcd. for $\text{C}_{25}\text{H}_{31}\text{O}_6\text{Cl}$: C, 64.86; H, 6.75. Found: C, 64.50; H, 6.70. NMR (9% solution in CDCl_3) δ : 0.73 (3H, s, 18- CH_3), 1.31 (3H, s, 19- CH_3), 2.06 (3H, s, 21- CH_3), 2.10 (3H, s, OCOCH_3), 2.20 (3H, s, OCOCH_3), 5.63 (1H, q, $J=13.2$ cps, $J=6$ cps, 2 β -H), 6.37 (2H, 4 and 7-H). Mass Spectrum m/e : 462 (M^+), 420 (M^+-COCH_3), 402 ($\text{M}^+-\text{CH}_3\text{COOH}$), 359 ($\text{M}^+-\text{CH}_3\text{COOH}-\text{COCH}_3$). Repeated crystallizations of the mother liquor from MeOH gave the 2 β -isomer (III, 140 mg) as light yellow needles. mp 238—241°. $[\alpha]_D^{25} -60.0^\circ$ ($c=1.00$). UV $\lambda_{\max}^{\text{MeOH}}$ $m\mu$ (ϵ): 292.5 (20800). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1726, 1665 (C=O). Anal. Calcd. for $\text{C}_{25}\text{H}_{31}\text{ClO}_6$: C, 64.86; H, 6.75. Found: C, 64.88; H, 6.72. NMR (8% solution in CDCl_3) δ : 0.72 (3H, s, 18- CH_3), 1.27 (3H, s, 19- CH_3), 2.06 (3H, s, 21- CH_3), 2.12 (6H, s, OCOCH_3), 5.33 (1H, q, $J=6$ cps, $J=2.2$ cps, 2 α -H), 6.35 (1H, d, $J=2$ cps, 7-H), 6.45 (1H, s, 4-H).

b) A mixture of I (1 g) and lead tetraacetate (1.5 g) in acetic acid (15 ml) was heated for 24 hr and treated by the procedure described above. The product was submitted to preparative thin-layer chromatography (TLC) using benzene-MeOH (9:1) as developing solvent to give mainly two components, less polar compound (601 mg) and more polar compound (168 mg). Recrystallization of the major compound from MeOH yielded II (345 mg). The minor compound was recrystallized from the same solvent to give 17 α -acetoxy-6-chloro-1,4,6-pregnatriene-3,20-dione (IV) as colorless prisms. mp 174—175°. UV $\lambda_{\max}^{\text{MeOH}}$ $m\mu$ (ϵ): 229 (9140), 259 (9060), 299 (9260). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1731, 1654 (C=O). NMR (20% solution in CDCl_3) δ : 0.75 (3H, s, 18- CH_3), 1.25 (3H, s, 19- CH_3), 2.06 (6H, s, 21- CH_3 and OCOCH_3), 6.24 (1H, d, $J=2$ cps, 7-H), 6.31 (1H, d, $J=9.5$ cps, 2-H), 6.62 (1H, s, 4-H), 7.10 (1H, d, $J=9.5$ cps, 1-H). Mass Spectrum m/e : 402 (M^+), 360 (M^+-COCH_3), 342 ($\text{M}^+-\text{CH}_3\text{COOH}$), 299 ($\text{M}^+-\text{CH}_3\text{COOH}-\text{COCH}_3$).

17 α -Acetoxy-6-chloro-2 α ,3 β -dihydroxy-4,6-pregnadien-20-one (V)—A suspension of II (100 mg) and sodium borohydride (13 mg) in anhydrous isopropanol (25 ml) was stirred for 18 hr at room temperature. After dilution with H_2O the reaction mixture was extracted with ether and the solvent was evaporated *in vacuo* to give colorless oily material. Twice crystallizations from MeOH afforded 17 α -acetoxy-6-chloro-2 α ,3 β -dihydroxy-4,6-pregnadien-20-one (V, 50 mg) as light yellow needles. mp 248—251°. $[\alpha]_D^{25} -104^\circ$ ($c=0.962$, MeOH). UV $\lambda_{\max}^{\text{MeOH}}$ $m\mu$ (ϵ): 236.5 (15370), 244 (17180), 253 (11510). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3540, 3480 (OH), 1715 (C=O). Anal. Calcd. for $\text{C}_{25}\text{H}_{31}\text{O}_5\text{Cl}$: C, 65.31; H, 7.39. Found: C, 65.53; H, 7.36. NMR (4% solution in $\text{C}_5\text{D}_5\text{N}$) δ : 0.65 (3H, s, 18- CH_3), 1.00 (3H, s, 19- CH_3), 2.08 (3H, s, 21- CH_3), 2.19 (3H, s, OCOCH_3), 3.15 (1H, m), 4.28—4.63 (2H, m, 2 and 3-H), 5.90 (1H, m, 4 or 7-H), 6.53 (1H, d, $J=2$ cps, 4 or 7-H). Mass Spectrum m/e : 422 (M^+), 404 ($\text{M}^+-\text{H}_2\text{O}$), 362 ($\text{M}^+-\text{H}_2\text{O}-\text{COCH}_3$), 344 ($\text{M}^+-\text{H}_2\text{O}-\text{CH}_3\text{COOH}$), 319 ($\text{M}^+-\text{H}_2\text{O}-\text{COCH}_2-\text{COCH}_3$), 301 ($\text{M}^+-\text{H}_2\text{O}-\text{CH}_3\text{COOH}-\text{COCH}_3$).

17 α -Acetoxy-6-chloro-2 β ,3 β -dihydroxy-4,6-pregnadien-20-one (VI)—A suspension of III (80 mg) and sodium borohydride (13 mg) in anhydrous isopropanol (20 ml) was stirred overnight at 4°. The product was isolated as described above and submitted to preparative TLC using benzene-AcOEt (2:3) as developing solvent to give two components. Recrystallization of the more polar compound from MeOH yielded V. The less polar compound was recrystallized from the same solvent to give 17 α -acetoxy-6-chloro-2 β ,3 β -dihydroxy-4,6-pregnadien-20-one (VI, 12 mg) as colorless needles. mp 229—231°. UV $\lambda_{\max}^{\text{MeOH}}$ $m\mu$ (ϵ): 236 (17430), 244 (20200), 252 (13690). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3500 (OH), 1728 (C=O). NMR (1.4% solution in CDCl_3) δ : 0.68 (3H, s, 18- CH_3), 1.24 (3H, s, 19- CH_3), 2.03 (3H, s, 21- CH_3), 2.06 (3H, s, OCOCH_3), 3.00 (1H, m), 4.28 (2H, m, 2 and 3-H), 5.88 (1H, m, 4 or 7-H), 5.99 (1H, m, 4 or 7-H). Mass Spectrum m/e : 422 (M^+), 404 ($\text{M}^+-\text{H}_2\text{O}$), 362 ($\text{M}^+-\text{H}_2\text{O}-\text{COCH}_3$), 344 ($\text{M}^+-\text{H}_2\text{O}-\text{CH}_3\text{COOH}$), 319 ($\text{M}^+-\text{H}_2\text{O}-\text{COCH}_2-\text{COCH}_3$), 301 ($\text{M}^+-\text{H}_2\text{O}-\text{CH}_3\text{COOH}-\text{COCH}_3$).

17 α -Acetoxy-6-chloro-2 α ,3 β -isopropylidenedioxy-4,6-pregnadiene-20-one (VIII)—A mixture of V (9 mg) in acetone (0.7 ml) and 5% phosphomolybdic acid in acetone (0.14 ml) was stirred for 20 min at room temperature. After adding a few drops of aqueous ammonia, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 -ether. The organic layer was washed with H_2O , dried over anhydrous Na_2SO_4 and condensed to dryness *in vacuo* to give oily residue. Purification on TLC using benzene-MeOH (9:1) as developing solvent gave the corresponding acetonide (VIII, 3 mg) as yellow oily material. An attempt to crystallize was unsuccessful. Mass Spectrum m/e : 462 (M^+), 447 (M^+-CH_3), 404 ($\text{M}^+-\text{CH}_3\text{COCH}_3$), 359 ($\text{M}^+-\text{CH}_3\text{COOH}-\text{COCH}_3$), 344 ($\text{M}^+-\text{CH}_3\text{COCH}_3-\text{CH}_3\text{COOH}$), 301 ($\text{M}^+-\text{CH}_3\text{COCH}_3-\text{CH}_3\text{COOH}-\text{COCH}_3$).

17 α -Acetoxy-6-chloro-2 β ,3 β -isopropylidenedioxy-4,6-pregnadien-20-one (IX)—A mixture of VI (7 mg) in acetone (0.55 ml) and 5% phosphomolybdic acid in acetone (0.11 ml) was handled by the procedure described above. The resultant brown oily material was recrystallized twice from acetone-hexane to give the corresponding acetonide (IX, 5 mg) as colorless prisms. mp 225—227°. UV $\lambda_{\max}^{\text{MeOH}}$ $m\mu$ (ϵ): 237 (19050), 243.5 (21700), 251 (151200). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1734 (C=O). Mass Spectrum m/e : 462 (M^+), 447 (M^+-CH_3), 404 ($\text{M}^+-\text{CH}_3\text{COCH}_3$), 402 ($\text{M}^+-\text{CH}_3\text{COOH}$), 359 ($\text{M}^+-\text{CH}_3\text{COOH}-\text{COCH}_3$), 301 ($\text{M}^+-\text{CH}_3\text{COOH}-\text{COCH}_3-\text{CH}_3\text{COCH}_3$). NMR (1% solution in CDCl_3) δ : 0.70 (3H, s, 18- CH_3), 1.22 (3H, s, 19- CH_3), 1.37 (3H, s, $\text{OC}(\text{CH}_3)_2$), 1.45 (3H, s, $\text{OC}(\text{CH}_3)_2$), 2.23 (3H, s, 21- CH_3), 2.25 (3H, s, OCOCH_3), 4.60 (2H, m, 2 and 3-H), 5.93 (1H, m, 4 or 7-H), 6.26 (1H, q, $J=4.5$ cps, $J=1$ cps, 4 or 7-H).

17 α -Acetoxy-6-chloro-2 α -hydroxy-4,6-pregnadiene-3,20-dione (VII)—a) From II: A suspension of II (40 mg) in MeOH (1.3 ml) and 1M KOH in MeOH (0.1 ml) was stirred for 1.5 hr under nitrogen at room temperature. After the yellow solution turned colorless on acidifying with 1N AcOH (0.17 ml), it was diluted

with H_2O and extracted with ether. The organic layer was washed with H_2O , dried over anhydrous Na_2SO_4 and condensed *in vacuo* to give yellow oily material. Preparative TLC using benzene-MeOH (9:1) as developing solvent afforded oily 17 α -acetoxy-6-chloro-2 α -hydroxy-4,6-pregnadiene-3,20-dione (VII). UV $\lambda_{\text{max}}^{\text{MeOH}}$ $m\mu$ (ϵ): 284 (8090). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1728, 1667 (C=O). NMR (2% solution in CDCl_3) δ : 0.73 (3H, s, 18- CH_3), 1.27 (3H, s, 19- CH_3), 2.05 (3H, s, 21- CH_3), 2.08 (3H, s, OCOCH_3), 4.47 (1H, q, $J=12.9$ cps, $J=5.7$ cps, 2 β -H), 6.34 (1H, m, 4 or 7-H), 6.40 (1H, s, 4 or 7-H). Oily VII was acetylated under the usual conditions to recover the 2-acetoxy compound (II). Recrystallization from MeOH gave colorless prisms, of which IR and UV spectra coincided with those of II.

b) From V: A mixture of V (16 mg) and MnO_2 (150 mg) in tetrahydrofuran (2 ml) was stirred for 6 hr at 0° . After removal of inorganic precipitate by filtration the solvent was evaporated *in vacuo* to give oily mixture. Preparative TLC using benzene-AcOEt (1:1) as developing solvent afforded the oily 3-keto compound (VII, 2 mg), IR spectra of which were identical with that of the VII from II. UV $\lambda_{\text{max}}^{\text{MeOH}}$ $m\mu$ (ϵ): 284 (unmeasured). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1728, 1667 (C=O).

2 α ,17 β and 2 β ,17 β -Diacetoxy-4-androsten-3-one (XI and XII)—These compounds were synthesized by the method reported by Sondheimer.³⁰ 2 α -compound (XI). mp 210–212°. $[\alpha]_D^{25} +47^\circ$ ($c=1.00$). UV $\lambda_{\text{max}}^{\text{MeOH}}$ $m\mu$ (ϵ): 241 (14040). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1730, 1683 (C=O). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_5$: C, 71.10; H, 8.30. Found: C, 70.75; H, 8.23. (reported mp 212–213°. $[\alpha]_D +68^\circ$ (CHCl_3). UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ $m\mu$ ($\log \epsilon$): 240 (4.24). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1736, 1684 (C=O). 2 β -Compound (XII). mp 198–201°. $[\alpha]_D^{25} -66^\circ$ ($c=1.00$). UV $\lambda_{\text{max}}^{\text{MeOH}}$ $m\mu$ (ϵ): 242 (15770). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1751, 1730, 1685 (C=O). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_5$: C, 71.10; H, 8.30. Found: C, 71.39; H, 8.31 (reported mp 202–203°. $[\alpha]_D -68^\circ$. UV $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ $m\mu$ ($\log \epsilon$): 242 (4.23). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1736, 1682 (C=O).

17 β -Acetoxy-4-androstene-2 α ,3 β -diol (XIII)—A suspension of XI (11 mg) and NaBH_4 (2 mg) in anhydrous isopropanol (2.7 ml) was stirred overnight at room temperature. After dilution with H_2O , the reaction mixture was extracted with ether and the solvent was evaporated *in vacuo* to give oily residue. Recrystallization from MeOH-AcOEt afforded 17 α -acetoxy-4-androstene-2 α ,3 β -diol (XIII, 5 mg). mp 175–178°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1740 (C=O). Triacetoxy compound. mp 154–157°.

17 β -Acetoxy-2 α ,3 β -isopropylidenedioxy-4-androstene (XIV)—A mixture of XIII (5 mg) in acetone (0.4 ml) and 5% phosphomolybdic acid in acetone (0.08 ml) was handled by the procedure described in the preparation of VIII to give the corresponding acetone (XIV). An attempt to crystallize was unsuccessful. Mass Spectrum m/e : 388 (M^+), 373 (M^+-CH_3), 330 ($\text{M}^+-\text{CH}_3\text{COCH}_3$), 288 ($\text{M}^+-\text{CH}_3\text{COCH}_3-\text{COCH}_2$), 270 ($\text{M}^+-\text{CH}_3\text{COCH}_3-\text{CH}_3\text{COOH}$).

Acknowledgement The authors wish to express their appreciation to Mr. Seiji Homma for his suggestions throughout this work, and Dr. Hiromu Mori and Dr. Kenyu Shibata for their advice in the synthetic techniques. They are indebted to Dr. Ryuta Suzuki, the head of their section, for his understanding and encouragement.