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New Synthesis of 16β-Hydroxydehydroepiandrosterone and Related Ketols, with Special Reference to Preparation of Haptens[1]

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A new method for the preparation of 16β-hydroxy-17-keto steroids has been developed. 16β-Hydroxylated dehydroepiandrosterone, epiandrosterone, androsterone and estrone were prepared from the corresponding 3,16-diacetate through the 17-ethylenehemithioketal. 16β-Hydroxydehydroepiandrosterone 3-hemisuccinate for the use of immunoassay as a hapten was prepared from the 3β,16β-dihydroxy-17-ketone ethylenehemithioketal by the sequential reactions: *tert*-butyldimethylsilylation of the hydroxyl functions, selective desilylation followed by hemisuccinylation at C-3, and removal of protecting groups at C-16 and C-17. The synthesis of the related 16,17-ketol derivatives has also been described.

Keywords——16β-hydroxydehydroepiandrosterone; ethylenehemithioketal; 16β-hydroxy-17-keto steroids; hapten; 16β-hydroxydehydroepiandrosterone 3-hemisuccinate; 16,17-ketol derivatives; *tert*-butyldimethylsilylation; 7-(O-carboxymethyl)oxime

A marked increase in the excreted amount of 16β-hydroxydehydroepiandrosterone (**1**) in infancy[3] and pregnancy[4] and during the second half of the menstrual cycle[5] has previously been clarified. Recently, Sennett *et al.* reported that urinary excretion of this steroid was elevated in the patients with low-renin essential hypertension.[6] It is well known that the isomeric ketols, 16α-hydroxydehydroepiandrosterone (**2**) and 3β,17β-dihydroxy-5-androsten-16-one (**3**), are also important from the metabolic and physiological points of view. In order to obtain the more precise knowledge on these problems the development of the radioimmunoassay method for the steroids is required. Among the four isomeric 16,17-ketols **1** is extremely unstable and isomerized readily into **3** even under acidic conditions. Several methods for the preparation of the 16β-hydroxy-17-ketone so far available[3,7] have still inevitable limitations. This paper deals with a new method for the preparation of 16β-hydroxy-17-keto steroids. In addition, the synthesis of 16β-hydroxydehydroepiandrosterone 3-hemisuccinate (**18**) and some related compounds for the use of radioimmunoassay as haptens is also described.

The methods involving hydrolysis of 3β,16β-diacetoxy-5-androsten-17-one (**4**) with acid[3,7a] and enzymes[7b] as well as a route through the 17-semicarbazone[7c] are not suitable for the synthesis of **18**. Therefore, an alternative way leading to the 16β-hydroxy-17-ketone is requisite for this purpose. An initial effort was directed to the introduction of a protect-

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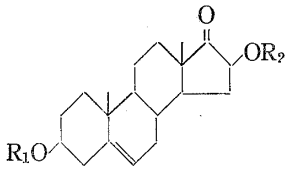
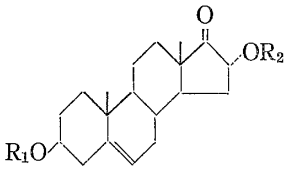
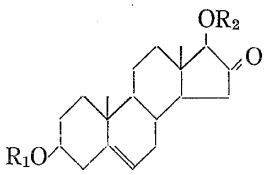


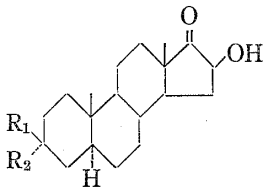
1: $R_1=R_2=H$
4: $R_1=R_2=Ac$
18: $R_1=COCH_2CH_2COOH$, $R_2=H$



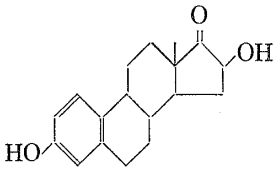
2: $R_1=R_2=H$
7: $R_1=R_2=Ac$
24: $R_1=COCH_2CH_2COOH$, $R_2=H$



3: $R_1=R_2=H$
25: $R_1=R_2=Si(CH_3)_2$-t-Bu
26: $R_1=H$, $R_2=Si(CH_3)_2$-t-Bu
27: $R_1=COCH_2CH_2COOH$, $R_2=Si(CH_3)_2$-t-Bu
28: $R_1=COCH_2CH_2COOH$, $R_2=H$
29: $R_1=R_2=Ac$



11: $R_1=OH$, $R_2=H$
12: $R_1=H$, $R_2=OH$



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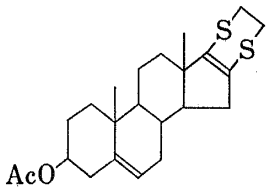

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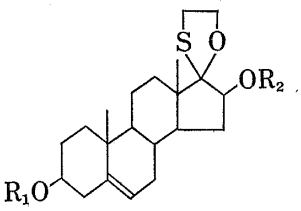
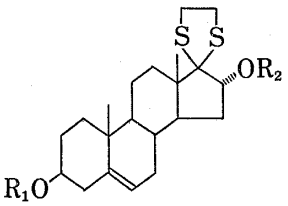


9 : $R_1=R_2=Ac$
10 : $R_1=R_2=H$
14 : $R_1=R_2=Si(CH_3)_2$-t-Bu
15 : $R_1=H$, $R_2=Si(CH_3)_2$-t-Bu
16 : $R_1=COCH_2CH_2COOH$, $R_2=Si(CH_3)_2$-t-Bu
17 : $R_1=COCH_2CH_2COOH$, $R_2=H$



8 : $R_1=R_2=Ac$
19 : $R_1=R_2=H$
20 : $R_1=R_2=Si(CH_3)_2$-t-Bu
21 : $R_1=H$, $R_2=Si(CH_3)_2$-t-Bu
22 : $R_1=COCH_2CH_2COOH$, $R_2=Si(CH_3)_2$-t-Bu
23 : $R_1=COCH_2CH_2COOH$, $R_2=H$

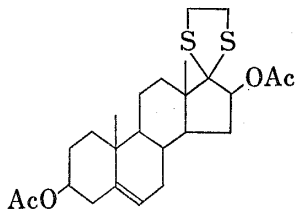


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Chart 1

ing group at the 17-ketone whose removal can be accomplished with ease under mild conditions. The 3β,16β-dihydroxy-17-ketone diacetate (**4**) obtainable from dehydroepiandrosterone was treated with 1,2-ethanedithiol in acetic acid in the presence of boron trifluoride etherate. Contrary to the expectations the product proved to be the dithiane (**5**), but not the 17-ethylenedithioketal (**6**). In contrast, when treated under similar conditions, the isomeric 16α-acetoxy-17-ketone (**7**) was transformed into the expected dithioketal (**8**). The present results, together with previous finding by Baggaley *et al.*[8] implied that the steric factor would favor the formation of the dithiane.

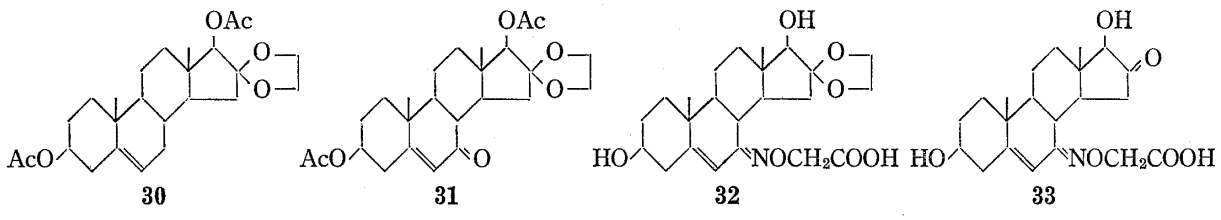
A preliminary experiment by the use of 2-mercaptoethanol instead of 1,2-ethanedithiol indicated that the protection of the carbonyl group in **4** proceeded in the desirable fashion and no rearrangement was accompanied by the subsequent processing under acidic and basic conditions. In actuality, treatment with 2-mercaptoethanol in the presence of

8) K.H. Baggaley, S.G. Brooks, J. Green, and B.T. Redman, *Chem. Commun.*, **1969**, 1458.

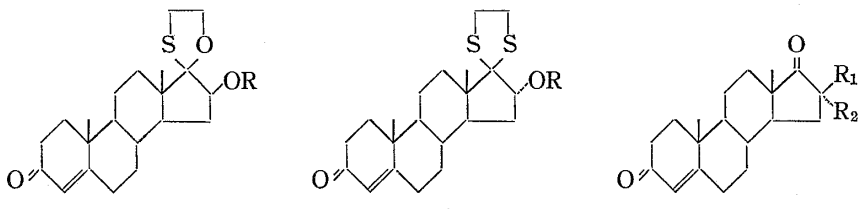
boron trifluoride etherate afforded the hemithioketal (**9**) in 55% yield. Saponification of the diacetate with sodium hydroxide in ethanol-dioxane gave the 3β,16β-dihydroxy derivative (**10**). Being treated with mercuric chloride and calcium carbonate in 80% acetonitrile, **10** was converted into the desired 16β-hydroxy-17-ketone (**1**). The overall yield from **4** to **1** was 27%. Thin-layer chromatography showed that the 16β-hydroxy-17-ketone thus obtained was not contaminated by any detectable amounts of the isomeric ketols. The structure of **1** was confirmed by direct comparison with the authentic sample prepared by the enzymatic method[7b] and by leading to the known diacetate (**4**) by usual acetylation. It is to be noted that the present method is more advantageous than the hitherto known methods since the unstable 16β-hydroxy-17-ketone can be obtained in the pure state by only once recrystallization in a satisfactory yield. In the similar manner 16β-hydroxylated epiandrosterone, androsterone and estrone (**11**, **12**, **13**) were also prepared from the corresponding diacetate.

The synthesis of 16β-hydroxydehydroepiandrosterone 3-hemisuccinate (**18**) was then undertaken. The hemithioketal (**10**) was treated with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide-pyridine to provide the 3,16-disilyl ether (**14**). Selective removal of the silyl group at C-3 in **14** was effected by treatment with hydrogen chloride in acetone to give the 16-monosilyl ether (**15**) in 95% yield. Being refluxed with succinic anhydride in pyridine, **15** was converted into the 3-hemisuccinate-16-silyl ether (**16**). Upon exposure to *p*-toluenesulfonic acid in acetone at 40°, **16** underwent desilylation yielding the 3-hemisuccinate (**17**). Elimination of the protecting group at C-17 with mercuric chloride and calcium carbonate in aqueous acetonitrile furnished the desired **18** in a good yield.

The preparation of the 3-hemisuccinate of the isomeric ketols (**24**, **28**) was also carried out employing *tert*-butyldimethylsilylation. The 3β,16α-dihydroxy derivative (**19**) prepared from **2** by condensation with 1,2-ethanedithiol was transformed into the disilyl ether (**20**), which in turn was led to the 16-monosilyl ether (**21**). Subsequent hemisuccinylation at C-3 and removal of the protecting groups at C-16 and C-17 yielded 16α-hydroxydehydroepiandrosterone 3-hemisuccinate (**24**). The synthesis of 3β,17β-dihydroxy-5-androsten-16-one 3-hemisuccinate (**28**) required no protection of the carbonyl group because of the high stability of this ketol and the excellent selectivity in partial desilylation. Being exposed to hydrochloric acid in acetone, the 3,17-disilyl ether (**25**) derived from **3** was converted into the 17-monosilyl ether (**26**). The structure of **26** was confirmed by inspection of the nuclear magnetic resonance (NMR) spectrum. The two three-proton singlets due to the methyl groups attached to the silyloxy function at C-17 appeared at 0.05 and 0.14 ppm, while a six-proton singlet due to those at C-3 (0.07 ppm in **25**) disappeared. Treatment of **26** with succinic anhydride in pyridine followed by desilylation with acid furnished the desired **28**.



30 **31** **32** **33**



34: R=Si(CH$_3$)$_2$-*t*-Bu
35: R=H

36: R=Si(CH$_3$)$_2$-*t*-Bu
37: R=H

38: R$_1$=OH, R$_2$=H
39: R$_1$=H, R$_2$=OH

Chart 2

The synthesis of another type of hapten, the 7-(O-carboxymethyl)oxime (**33**), was also undertaken. 3β,17β-Dihydroxy-5-androsten-16-one diacetate (**29**) was refluxed with ethylene glycol in toluene in the presence of pyridine hydrochloride as a catalyst to give the 16-ethyleneketal (**30**). Allylic oxidation of **30** with anhydrous sodium chromate in acetic acid–acetic anhydride afforded the 7-ketone (**31**). Condensation with carboxymethoxylamine followed by alkaline hydrolysis yielded the 7-carboxymethyloxime (**32**). Elimination of the protecting group at C-16 with acid provided the desired **33**.

Finally, epimeric 16-hydroxyandrostenediones (**38**, **39**) were prepared from the corresponding hemithioketal and dithioketal, respectively. Oppenauer oxidation of **15** and **21** proceeded without disturbing the ring D structure to afford the Δ^4-3-ketones (**34**, **36**). Removal of the protecting groups at C-16 and C-17 in the manner as described above provided **38** and **39**.

It is hoped that the present methods for the preparation of the 16β-hydroxy-17-ketones and related ketols with the relative ease will serve for the metabolic study of steroids.

Experimental

All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise specified. Infrared (IR) spectra were run on a JASCO Model IRA-1 spectrometer. NMR spectra were recorded on a Hitachi Model R-20A spectrometer at 60 MHz or a JEOL Model PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, t=triplet, and m=multiplet. For preparative TLC silica gel H (E. Merck AG, Darmstadt) was used as an adsorbent.

Reaction of 3β,16β-Dihydroxy-5-androsten-17-one Diacetate (4) with 1,2-Ethanedithiol——To a solution of **4** (100 mg) in AcOH (5 ml) were added 1,2-ethanedithiol (0.4 ml) and BF_3-etherate (0.4 ml), and the resulting solution was allowed to stand at room temperature overnight. The reaction mixture was diluted with ether, washed with 5% NaOH and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene as developing solvent. Recrystallization of the eluate from MeOH gave 3β-acetoxy-5,16-androstadieno[16,17-*b*]dithiane (**5**) (20 mg) as colorless leaflets. mp 193—195°, $[\alpha]_D^{20}$ −120.0° (c=0.17). NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 1.04 (3H, s, 19-CH_3), 2.02 (3H, s, 3-$OCOCH_3$), 3.14 (4H, s, -SCH_2CH_2S-), 4.60 (1H, m, 3α-H), 5.45 (1H, m, 6-H). *Anal.* Calcd. for $C_{23}H_{32}O_2S_2$: C, 68.27; H, 7.97. Found: C, 68.21; H, 7.99.

Reaction of 3β,16α-Dihydroxy-5-androsten-17-one Diacetate (7) with 1,2-Ethanedithiol——Treatment of **7** (120 mg) with 1,2-ethanedithiol was carried out in the manner as described with **4**. The crude product obtained was chromatographed on silica gel (10 g). Elution with benzene–ether (15:1) and recrystallization of the eluate from MeOH gave 3β,16α-diacetoxy-5-androsten-17-one ethylenedithioketal (**8**) as colorless needles. mp 164—165°. $[\alpha]_D^{20}$ −135.6° (c=0.17). NMR ($CDCl_3$) δ: 1.04 (6H, s, 18- and 19-CH_3), 2.02 (3H, s, 3-$OCOCH_3$), 2.10 (3H s, 16-$OCOCH_3$), 3.18 (4H, s, -SCH_2CH_2S-), 4.60 (1H, m, 3α-H), 5.2—5.7 (2H, 6- and 16β-H). *Anal.* Calcd. for $C_{25}H_{36}O_4S_2$: C, 64.61; H, 7.82. Found: C, 64.42; H, 7.76.

3α,16β-Dihydroxy-5α-androstan-17-one Diacetate——To a solution of 3α,17-dihydroxy-5α-androst-16-ene diacetate[9] (2 g) in AcOH (45 ml)–Ac_2O (5 ml) was added $Pb(OAc)_4$ (3.4 g), and the resulting solution was stirred at room temperature for 4 hr. The reaction mixture was diluted with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from MeOH gave 3α,16β-dihydroxy-5α-androstan-17-one diacetate (2 g). mp 169—171°, $[\alpha]_D^{22}$ +79.1° (c=0.18). NMR ($CDCl_3$) δ: 0.82 (3H, s, 19-CH_3), 0.95 (3H, s, 18-CH_3), 2.04 (3H, s, 3-$OCOCH_3$), 2.11 (3H, s, 16-$OCOCH_3$), 4.85—5.15 (2H, 16α- and 3β-H). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.67; H, 8.67.

General Procedure for Preparation of 17-Ethylenehemithioketal——To a solution of 16β-acetoxy-17-ketone (2.6 mmol) in ether (20 ml)–CH_2Cl_2 (3 ml) were added 2-mercaptoethanol (4 ml) and BF_3-etherate (4 ml), and the resulting solution was allowed to stand at room temperature for 4 hr. The reaction mixture was diluted with AcOEt, washed with 5% NaOH and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was chromatographed on silica gel (40 g) (hexane–AcOEt) and recrystallized to give the hemithioketal in *ca.* 55% yield.

3β,16β-Diacetoxy-5-androsten-17-one Ethylenehemithioketal (**9**)——Colorless leaflets (from acetone). mp 238.5—239.5°, $[\alpha]_D^{24}$ −89.0° (c=0.16). *Anal.* Calcd. for $C_{25}H_{36}O_5S$: C, 66.94; H, 8.09. Found; C, 66.77; H, 8.38.

3β,16β-Diacetoxy-5α-androstan-17-one Ethylenehemithioketal——Colorless needles (from MeOH). mp 168—169°, $[\alpha]_D^{27}$ −30.3° (c=0.20). *Anal.* Calcd. for $C_{25}H_{38}O_5S$: C, 66.63; H, 8.50. Found: C, 66.81; H, 8.63.

9) J. Fajkoš and F. Šorm, *Chem. Listy*, **52**, 505 (1958) [*C.A.*, **53**, 4349*c* (1959)].

3α,16β-Diacetoxy-5α-androstan-17-one Ethylenehemithioketal——Colorless needles (from MeOH). mp 108—109.5°, $[\alpha]_D^{23}$ −9.9° (c=0.20). *Anal.* Calcd. for $C_{25}H_{38}O_5S$: C, 66.63; H, 8.50. Found: C, 66.36; H, 8.55.

3,16β-Diacetoxy-1,3,5(10)-estratrien-17-one Ethylenehemithioketal——Colorless leaflets (from MeOH). mp 202—204°, $[\alpha]_D^{26}$ +3.6° (c=0.28). *Anal.* Calcd. for $C_{24}H_{30}O_5S$: C, 66.95; H, 7.02. Found: C, 66.61; H, 7.11.

Saponification of 3,16-Diacetoxy-17-ethylenehemithioketal——To a solution of 3,16β-diacetoxy-17-ethylenehemithioketal (500 mg) in dioxane (9 ml)–EtOH (20 ml) was added 10% NaOH (4 ml), and the resulting solution was stirred at room temperature for 5 hr. After neutralization with AcOH the organic solvent was evaporated under reduced pressure. The reaction mixture was evaporated with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was recrystallized from the appropriate solvent to give the 3,16β-dihydroxy-17-ethylenehemithioketal.

3β,16β-Dihydroxy-5-androsten-17-one Ethylenehemithioketal (10)——Colorless needles (from MeOH). mp 184—185°, $[\alpha]_D^{20}$ −103.0° (c=0.17). *Anal.* Calcd. for $C_{21}H_{32}O_3S$: C, 69.19; H, 8.85. Found; C, 69.24; H, 9.12.

3β,16β-Dihydroxy-5α-androstan-17-one Ethylenehemithioketal——Colorless plates (from hexane–acetone). mp 190—193°. $[\alpha]_D^{25}$ −32.0° (c=0.20). *Anal.* Calcd. for $C_{21}H_{34}O_3S$: C, 68.81: H, 9.35. Found: C, 69.12; H, 9.87.

3α,16β-Dihydroxy-5α-androstan-17-one Ethylenehemithioketal——Colorless plates (from hexane–acetone). mp 170—172°, $[\alpha]_D^{22}$ −34.4° (c=0.22). *Anal.* Calcd. for $C_{21}H_{34}O_3S$: C, 68.81; H, 9.35. Found: C, 68.55; H, 9.29.

3,16β-Dihydroxy-1,3,5(10)-estratrien-17-one Ethylenemithioketal——Colorless semicrystal. NMR ($CDCl_3$) δ: 0.92 (3H, s, 18-CH_3), 3.4—4.4 (3H, 16α-H and -OC$\underline{H}_2$CH_2S-), 6.5—6.9 (2H, 2- and 4-H), 7.15 (1H, d, J=8 Hz, 1-H).

Desulfurization of 17-Ethylenehemithioketal——To a solution of 16β-hydroxy-17-ethylenehemithioketal (200 mg) in 80% CH_3CN (12 ml) were added $HgCl_2$ (900 mg) and $CaCO_3$ (350 mg) and the resulting mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with AcOEt, washed with 50% CH_3COONH_4 and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was recrystallized from the appropriate solvent to give the 16β-hydroxy-17-ketone.

16β-Hydroxydehydroepiandrosterone (1)——Colorless needles (from MeOH-AcOEt). mp 192.5—193.5°. IR spectra of **1** and the authentic sample obtained by the method of Wynne and Renwick[7b] were entirely identical in every respect. Usual acetylation of **1** with Ac_2O and pyridine gave **4**.

16β-Hydroxyepiandrosterone (11)——Colorless needles (from aq. MeOH). mp 186—189°, $[\alpha]_D^{22}$ +88.9° (c=0.09, MeOH). NMR ($CDCl_3$–CD_3OD (4:1)) δ: 0.88 (3H, s, 19-CH_3), 0.96 (3H, s, 18-CH_3), 3.65 (1H, m, 3α-H), 3.92 (1H, t, J=8 Hz, 16α-H). *Anal.* Calcd. for $C_{19}H_{30}O_3 \cdot 1/2H_2O$: C, 72.34; H, 9.91. Found: C, 72.26; H, 10.18.

16β-Hydroxyandrosterone (12)——Colorless fine needles (from hexane-acetone). mp 163—166°, $[\alpha]_D^{22}$ +112.0° (c=0.19). NMR ($CDCl_3$) δ: 0.82 (3H, s, 19-CH_3), 0.94 (3H, s, 18-CH_3), 3.92 (1H, t, J=8 Hz, 16α-H), 4.03 (1H, m, 3β-H). *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found; C, 74,64; H, 9.85.

16β-Hydroxyestrone (13)——Colorless fine needles (from MeOH). mp 224—225°. Biggerstaff and Gallagher[10] prepared this compound by the different method (reported: mp 219—221°).

16β-Hydroxydehydroepiandrosterone 3-Hemisuccinate (18)——Colorless granules (from aq. MeOH). mp 216—218°. $[\alpha]_D^{23}$ −7.7° (c=0.13). NMR ($CDCl_3$) δ: 0.93 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 2.63 (4H, s, 3-OCOCH_2CH_2COO-), 4.00 (1H, t, J=8 Hz, 16α-H), 4.80 (1H, m, 3α-H), 5.44 (1H, m, 6-H). *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.05; H, 8.09.

16β-Hydroxy-4-androstene-3,17-dione (38)——Colorless needles (from aq. acetone). mp 129—130°, $[\alpha]_D^{23}$ +183.6° (c=0.21). NMR ($CDCl_3$) δ: 0.97 (3H, s, 18-CH_3), 1.23 (3H, s, 19-CH_3), 3.97 (1H, t, J=8 Hz, 16α-H), 5.75 (1H, s, 4-H). *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.31; H, 8.63. Yamashita *et al.*[11] prepared this compound from dehydroepiandrosterone by microbial oxidation (reported: mp 127—132°).

3β,16β-Bis(*tert*-butyldimethylsilyloxy)-5-androsten-17-one Ethylenehemithioketal (14)——To a solution of **10** (1 g) in dimethylformamide (4 ml)–pyridine (2 ml) were added *tert*-butyldimethylsilyl chloride (3 g) and imidazole (6 g), and the resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product obtained from aq. acetone gave **14** (1.5 g) as colorless fine needles. mp 97—98°. $[\alpha]_D^{24}$ −39.4° (c=0.20). NMR ($CDCl_3$) δ: 0—0.10 (12H, 3, and 16-OSi(CH_3)$_2$), 0.85 (3H, s, 18-CH_3), 0.88 (18H, s, 3- and 16-OSi-*t*-Bu), 1.00 (3H, s, 19-CH_3), 2.8—3.0 (2H, -OCH_2C$\underline{H}_2$S-), 3.52 (1H, m, 3α-H), 3.7—4.1 (2H, -OC$\underline{H}_2$CH_2S-), 4.20 (1H, m, 16α-H), 5.32 (1H, m, 6-H). *Anal.* Calcd. for $C_{33}H_{60}O_3SSi_2$; C, 66.84; H, 10.20. Found: C, 66.87; H, 10.43.

10) W.R. Biggerstaff and T.F. Gallagher, *J. Org. Chem.*, **22**, 1220 (1957).
11) H. Yamashita, K. Shibata, N. Yamakoshi, Y. Kurosawa, and H. Mori, *Agric. Biol. Chem.* (Tokyo), **40**, 505 (1976).

16β-*tert*-Butyldimethylsilyloxy-3β-hydroxy-5-androsten-17-one Ethylenehemithioketal (15)——To a solution of **14** (1.5 g) in acetone (18 ml) was added 5 N HCl (0.5 ml), and the resulting solution was allowed to stand at room temperature for 1 hr. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue obtained was recrystallized from MeOH to give **15** (1 g) as colorless fine needles. mp 186—187°. $[\alpha]_D^{23}$ −54.5° (c=0.20). NMR ($CDCl_3$) δ: 0.04 and 0.08 (each 3H, s, 16-OSi$(CH_3)_2$), 0.90 (12H, s, 18-CH_3 and 16-OSi-*t*-Bu), 1.02 (3H, s, 19-CH_3), 2.8—3.0 (2H, -$OCH_2C\underline{H}_2S$-), 3.52 (1H, m, 3α-H), 3.7—4.1 (2H, -$OC\underline{H}_2$-CH_2S-), 4.20 (1H, m, 16α-H), 5.38 (1H, m, 6-H). *Anal.* Calcd. for $C_{27}H_{46}O_3SSi$: C, 67.73; H, 9.68. Found: C, 67.57; H, 9.92.

16β-*tert*-Butyldimethylsilyloxy-3β-hydroxy-5-androsten-17-one Ethylenehemithioketal Hemisuccinate (16)——To a solution of **15** (500 mg) in pyridine (6 ml) was added succinic anhydride (1.3 g), and the resulting solution was refluxed for 10 hr. After evaporation of pyridine under reduced pressure the residue was diluted with ether and the insoluble material was removed by filtration. The filtrate was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was chromatographed on silica gel (20 g). Elution with hexane–AcOEt (1: 5) gave **16** as colorless oil. NMR ($CDCl_3$) δ: 0.04 and 0.08 (each 3H, s, 16-OSi$(CH_3)_2$), 0.90 (12H, s, 18-CH_3 and 16-OSi-*t*-Bu), 1.04 (3H, s, 19-CH_3), 2.71 (4H, m, 3-$OCOCH_2CH_2$-COO–), 2.8—3.0 (2H, -$OCH_2C\underline{H}_2S$-), 3.7—4.1 (2H, -$OC\underline{H}_2CH_2S$-), 4.20 (1H, m, 16α-H), 4.72 (1H, m, 3α-H), 5.42 (1H, m, 6-H).

3β,16β-Dihydroxy-5-androsten-17-one Ethylenehemithioketal 3-Hemisuccinate (17)——To a solution of **16** (300 mg) in acetone (7 ml) was added anhydrous *p*-TsOH (250 mg), and the resulting solution was stirred at 40° overnight. The reaction mixture was diluted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue obtained was chromatographed on silica gel (10 g). Elution with hexane-AcOEt (1: 5) and recrystallization of the eluate from aq. MeOH gave **17** (206 mg) as colorless plates. mp 178—179°, $[\alpha]_D^{21}$ −80.1° (c=0.12). NMR ($CDCl_3$) δ: 0.91 (3H, s, 18-CH_3), 1.05 (3H, s, 19-CH_3), 2.68 (4H, m, 3-$OCOCH_2CH_2COO$-), 2.8—3.1 (2H, -$OCH_2C\underline{H}_2S$-), 3.6—4.0 (2H, -$OC\underline{H}_2CH_2S$-), 4.24 (1H, m, 16α-H), 4.70 (1H, m, 3α-H), 5.42 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{36}O_6S \cdot 1/4H_2O$: C, 64.00; H, 7.84. Found: C, 64.17; H, 7.83.

3β,16α-Dihydroxy-5-androsten-17-one Ethylenedithioketal (19)——Treatment of **2** (300 mg) with 1,2-ethanedithiol was carried out in the manner as described with **4**. Recrystallization of the crude product obtained from AcOEt gave **19** (240 mg) as colorless fine needles. mp 196—199°. $[\alpha]_D^{16}$ −113.0° (c=0.21). NMR ($CDCl_3$) δ: 1.02 (6H, s, 18- and 19-CH_3), 3.24 (4H, m, -SCH_2CH_2S-), 3.65 (1H, m, 3α-H), 4.53 (1H, m, 16β-H), 5.35 (1H, m, 6-H). *Anal.* Calcd. for $C_{21}H_{32}O_2S_2$: C, 66.27; H, 8.48. Found: C, 66.08; H, 8.33.

3β,16α-Bis(*tert*-butyldimethylsilyloxy)-5-androsten-17-one Ethylenedithioketal (20)——Silylation of **19** (380 mg) with *tert*-butyldimethylsilyl chloride was carried out in the manner as described with **10**. Recrystallization of the crude product from ether–MeOH gave **20** as colorless plates. mp 157—159°. $[\alpha]_D^{16}$ −86.4° (c=0.27). *Anal.* Calcd. for $C_{33}H_{60}O_2S_2Si_2$: C, 65.07; H, 9.93. Found: C, 65.02; H, 9.55.

16α-*tert*-Butyldimethylsilyloxy-3β-hydroxy-5-androsten-17-one Ethylenedithioketal (21)——Selective desilylation of **20** (450 mg) was carried out in the manner as described with **14**. Recrystallization of the crude product from hexane–ether gave **21** (280 mg) as colorless leaflets. mp 173—174°, $[\alpha]_D^{15}$ −108.7° (c=0.25). NMR ($CDCl_3$) δ: 0.08 (6H, s, 16-OSi$(CH_3)_2$), 0.88 (9H, s, 16-OSi-*t*-Bu), 1.00 (6H, s, 18- and 19-CH_3), 3.18 (4H, m, -SCH_2CH_2S-), 3.65 (1H, m, 3α-H), 4.67 (1H, m, 16β-H), 5.40 (1H, m, 6-H). *Anal.* Calcd. for $C_{27}H_{46}O_2S_2Si$: C, 65.53; H, 9.37. Found: C, 65.55; H, 9.45.

16α-*tert*-Butyldimethylsilyloxy-3β-hydroxy-5-androsten-17-one Ethylenedithioketal Hemisuccinate (22)——Treatment of **21** (160 mg) with succinic anhydride was carried out in the manner as described with **15**. The crude product obtained was chromatographed on silica gel (7 g). Elution with hexane–AcOEt (1: 5) and recrystallization of the eluate from aq. MeOH gave **22** (150 mg) as colorless needles. mp 109—112°/120—125°, $[\alpha]_D^{19}$ −97.8° (c=0.23). NMR ($CDCl_3$) δ: 0.08 (6H, s, 16-OSi$(CH_3)_2$), 0.88 (9H. s, 16-OSi-*t*-Bu), 0.97 and 1.00 (each 3H, s, 18- and 19-CH_3), 2.68 (4H, m, 3-$OCOCH_2CH_2COO$-), 2.9—3.1 (4H, -SCH_2CH_2S-), 4.4—4.7 (2H, 3α- and 16β-H), 5.40 (1H, m, 6-H). *Anal.* Calcd. for $C_{31}H_{50}O_5S_2Si$: C, 62.58; H, 8.47. Found: C, 62.49; H, 8.44.

3β,16α-Dihydroxy-5-androsten-17-one Ethylenedithioketal 3-Hemisuccinate (23)——Hydrolysis of **22** (150 mg) with *p*-TsOH was carried out in the manner as described with **16**. Recrystallization of the crude product obtained from MeOH gave **23** (100 mg) as colorless plates. mp 198—200°. $[\alpha]_D^{19}$ −92.3° (c=0.22). NMR ($CDCl_3$) δ: 1.03 (6H, s, 18- and 19-CH_3), 2.67 (4H, m, 3-$OCOCH_2CH_2COO$-), 3.1—3.5 (4H, -SCH_2CH_2S-), 4.4—4.9 (2H, 3α- and 16β-H), 5.37 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{36}O_5S_2 \cdot 1/4H_2O$: C, 61.88; H, 7.58. Found: C, 61.90; H, 7.40.

16α-Dihydroxydehydroepiandrosterone 3-Hemisuccinate (24)——To a solution of **23** (40 mg) in 80% CH_3CN (12 ml) were added $HgCl_2$ (220 mg) and $CaCO_3$ (83 mg), and the mixture was refluxed for 60 hr. The reaction mixture was diluted with AcOEt, washed with 50% CH_3COONH_4 and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue obtained was chromatographed on silica gel (5 g). Elution with

12) K. Furuya, T. Yoshida, S. Takagi, A. Kambegawa, H. Yamashita, and Y. Kurosawa, *Steroids*, **27**, 797 (1976).

AcOEt–MeOH (1:1) and recrystallization of the eluate from acetone–ether gave **24** (10 mg) as colorless fine leaflets. mp 203—208°. NMR ($CDCl_3$) δ: 0.98 (3H, s, 18-CH_3), 1.05 (3H, s, 19-CH_3), 2.64 (4H, s, 3-$OCOCH_2CH_2COO$-), 4.39 (1H, d, d, J=4,7 Hz, 16β-H), 4.63 (1H, m, 3α-H), 5.40 (1H, m, 6-H). Furuya *et al.*[12] prepared this compound from dehydroepiandrosterone hemisuccinate by microbial oxidation (reported: mp 211—218°).

3β,17β-Dihydroxy-5-androsten-16-one Bis(*tert*-butyldimethylsilyl) Ether (25)——Silylation of **3** (230 mg) with *tert*-butyldimethylsilyl chloride was carried out in the manner as described with **10**. Recrystallization of the residue from ether–MeOH gave **25** (380 mg) as colorless needles. mp 131—132°. $[\alpha]_D^{18}$ −124.7° (c=0.20). NMR ($CDCl_3$) δ: 0.07 (9H, s, 3-$OSi(CH_3)_2$ and one of 17-$OSi(CH_3)_2$), 0.14 (3H, s, one of 17-$OSi(CH_3)_2$), 0.74 (3H, s, 18-CH_3), 0.89 (18H, s, 3- and 17-OSi-*t*-Bu), 1.02 (3H, s, 19-CH_3), 3.45 (1H, m, 3α-H), 3.66 (1H, s, 17α-H), 5.30 (1H, m, 6-H). *Anal.* Calcd. for $C_{31}H_{56}O_3Si_2$: C, 69.87; H, 10.59. Found: C, 69.84; H, 10.94.

3β,17β-Dihydroxy-5-androsten-16-one 17-*tert*-Butyldimethylsilyl Ether (26)——Selective desilylation of **25** (350 mg) with 5 N HCl in acetone was carried out in the manner as described with **14**. The crude product obtained was purified by preparative TLC using hexane–AcOEt (3:1) as developing solvent. Recrystallization of the eluate from hexane–ether gave **26** (225 mg) as colorless needles. mp 146.5—148°. $[\alpha]_D^{19}$ −163.0° (c=0.10). NMR ($CDCl_3$) δ: 0.05 and 0.14 (each 3H, s, 17-$OSi(CH_3)_2$) 0.75 (3H, s, 18-CH_3), 0.90 (9H, s, 17-OSi-*t*-Bu), 1.04 (3H, s, 19-CH_3), 3.45 (1H, m, 3α-H), 3.66 (1H, s, 17α-H), 5.30 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{42}O_3Si$: C, 71.72; H, 10.11. Found: C, 71.82; H, 10.27.

17β-*tert*-Butyldimethylsilyloxy-3β-hydroxy-5-androsten-16-one Hemisuccinate (27)——Treatment of **26** (91 mg) with succinic anhydride in pyridine was carried out in the manner as described with **15**. The crude product obtained was purified by preparative TLC using hexane–AcOEt (1:1) as developing solvent. Recrystallization of the eluate from ether–hexane gave **27** (90 mg) as colorless needles, mp 163—165°. $[\alpha]_D^{18}$ −118.6° (c=0.13). NMR ($CDCl_3$) δ: 0.05 and 0.14 (each 3H, s, 17-$OSi(CH_3)_2$), 0.74 (3H, s, 18-CH_3), 0.88 (9H, s, 17-OSi-*t*-Bu), 1.03 (3H, s, 19-CH_3), 2.62 (4H, s, 3-$OCOCH_2CH_2COO$-), 3.67 (1H, s, 17α-H), 4.55 (1H, m, 3α-H), 5.36 (1H, m, 6-H). *Anal.* Calcd. for $C_{29}H_{46}O_6Si$: C, 67.14; H, 8.94. Found: C, 67.49; H, 9.02.

3β,17β-Dihydroxy-5-androsten-16-one 3-Hemisuccinate (28)——To a solution of **27** (50 mg) in acetone (1 ml) was added a solution of HCl (500 mg) in acetone (5 ml), and the resulting solution was allowed to stand at room temperature for 4 hr. The reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$, concentrated under the reduced pressure, then acidified to pH 1 with conc. HCl, and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from aq. MeOH gave **28** (30 mg) as colorless needles. mp 217—220°. $[\alpha]_D^{18}$ −169.7° (c=0.09). NMR ($CDCl_3$–CD_3OD (4:1)) δ: 0.79 (3H, s, 18-CH_3), 1.09 (3H, s, 19-CH_3), 2.64 (4H, s, 3-$OCOCH_2CH_2COO$-), 3.79 (1H, s, 17α-H), 4.60 (1H, m, 3α-H), 5.42 (1H, m, 6-H). *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.24; H, 8.10.

3β,17β-Diacetoxy-5-androsten-16-one Ethyleneketal (30)——To a solution of 3β,17β-dihydroxy-5-androsten-16-one diacetate (**29**) (1g) in toluene (25 ml) were added ethylene glycol (15 ml) and pyridine hydrochloride (800 mg), and the mixture was refluxed azeotropically for 16 hr. The resulting solution was concentrated to its half volume, diluted with benzene, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. To the residue dissolved in tetrahydrofuran (9 ml)–H_2O (1 ml) was added $NaBH_4$ (500 mg) in 90% MeOH (4 ml) and allowed to stand at 0° for 30 min. After addition of AcOH to decompose the excess reagent the resulting solution was diluted with ether, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crystalline residue obtained was chromatographed on Al_2O_3 (80 g). Elution with benzene-ether (5:1) and recrystallization of the eluate from hexane–acetone gave **30** (560 mg) as colorless plates. mp 199—201°, $[\alpha]_D^{16}$ −90.9° (c=0.10). NMR ($CDCl_3$) δ: 0.92 (3H, s, 18-CH_3), 1.04 (3H, s, 19-CH_3), 2.04 (3H, s, 3-$OCOCH_3$), 2.12 (3H, s, 17-$OCOCH_3$), 3.88 (4H, m, -OCH_2CH_2O-), 4.60 (1H, m, 3α-H), 4.73 (1H, s, 17α-H), 5.36 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.47; H, 8.67.

3β,17β-Diacetoxy-5-androstene-7,16-dione 16-Ethyleneketal (31)——To a solution of **30** (300 mg) in AcOH (2.4 ml)–Ac_2O (1.2 ml) was added Na_2CrO_4 (390 mg) and the reaction mixture was stirred at 40° for 5 hr. The resulting solution was poured into ice-water containing $NaHCO_3$ (10 g), extracted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from hexane–acetone gave **31** (180 mg) as colorless plates. mp 205—207°/226—228°, $[\alpha]_D^{15}$ −144.9° (c=0.11). UV λ_{max}^{EtOH} 234 nm (ε 13800). NMR ($CDCl_3$) δ: 0.91 (3H, s, 18-CH_3), 1.21 (3H, s, 19-CH_3), 2.03 (3H, s, 3-$OCOCH_3$), 2.10 (3H, s, 17-$OCOCH_3$), 3.87 (4H, m, -OCH_2CH_2O-), 4.60 (1H m, 3α-H), 4.74 (1H, s, 17α-H), 5.70 (1H, s, 6-H). *Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.36; H, 7.85.

3β,17β-Dihydroxy-5-androstene-7,16-dione 7-(O-Carboxymethyl)oxime 16-Ethyleneketal (32)——To a solution of **31** (100 mg) in EtOH (10 ml) was added carboxymethoxylamine·HCl (200 mg) in 2 N NaOH (0.9 ml), and the reaction mixture was refluxed for 3 hr. After addition of H_2O (10 ml) and 2 N NaOH to adjust to pH 11 the resulting solution was extracted with ether. The aqueous layer was acidified to pH 1 with conc. HCl and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. To the residue dissolved in 90% MeOH (10 ml) was added 2 N NaOH (5 ml) and

allowed to stand at room temperature for 1 hr. The resulting solution was acidified to pH 1 with conc. HCl, extracted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from MeOH-AcOEt gave **32** (50 mg) as colorless needles. mp 206—209° (dec.). $[\alpha]_D^{22}$ −205.4° (c=0.10, MeOH). UV λ_{max}^{EtOH} 241 nm (ε 13600). NMR ($CDCl_3$–CD_3OD (4:1)) δ: 0.85 (3H, s, 18-CH_3), 1.15 (3H, s, 19-CH_3), 3.99 (4H, m, -OCH_2CH_2O-), 4.59 (2H, s, =$NOCH_2CO$-), 6.51 (1H, s, 6-H). *Anal.* Calcd. for $C_{23}H_{33}NO_7 \cdot 1\ 1/4H_2O$: C, 60.31; H, 7.81; N, 3.06. Found: C, 60.52; H, 8.40; N, 3.03.

3β,17β-Dihydroxy-5-androstene-7,16-dione 7-(O-Carboxymethyl)oxime (**33**)——To a solution of **32** (164 mg) in 90% MeOH (11 ml) was added conc. HCl (0.4 ml) and allowed to stand at room temperature for 3 hr. To the reaction mixture was added 1 N NaOH (7 ml) and then allowed to stand at room temperature for 30 min. The resulting solution was diluted with H_2O (20 ml), acidified to pH 1 with conc. HCl, and extracted with AcOEt. The organic phase was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crystalline residue obtained was chromatographed on silica gel (20 g). Elution with $CHCl_3$–MeOH (1:1) and recrystallization of the eluate from aq.MeOH containing one drop of AcOH gave **33** (70 mg) as colorless needles. mp 180° (dec.). $[\alpha]_D^{20}$ −359.6° (c=0.07, MeOH). UV λ_{max}^{EtOH} 243 nm (ε 13100). NMR ($CDCl_3$–CD_3OD (3:1)) δ: 0.77 (3H, s, 18-CH_3), 1.16 (3H, s, 19-CH_3), 3.60 (1H, m, 3α-H), 3.79 (1H, s, 17α-H), 4.53 (2H, s, =$NOCH_2CO$-), 6.53 (1H, s, 6-H). *Anal.* Calcd. for $C_{21}H_{29}NO_6 \cdot 2/3\ H_2O$: C, 62.51: H, 7.58; N, 3.47. Found: C, 62.53; H, 7.99; N, 3.86.

16β-*tert*-Butyldimethylsilyloxy-4-androstene-3,17-dione 17-Ethylenehemithioketal (**34**)——A solution of **15** (250 mg) and Al(iso-Pro)$_3$ (150 mg) in anhydrous benzene (20 ml) was concentrated to its half volume to remove the moisture. After addition of methyl ethyl ketone (3.5 ml) the reaction mixture was refluxed for 4 hr and concentrated. To this solution were added Al(iso-Pro)$_3$ (100 mg) and methyl ethyl ketone (2.5 ml), refluxed for 3 hr, and then concentrated. The resulting solution was diluted with AcOEt, washed with 25% Rochelle salt and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was chromatographed on Al_2O_3 (20 g). Elution with hexane–AcOEt (5:1) and recrystallization of the eluate from MeOH gave **34** (160 mg) as colorless plates. mp 159—160°, $[\alpha]_D^{27}$ +57.8° (c=0.25). NMR ($CDCl_3$) δ: 0.04 and 0.08 (each 3H, s, 16-$OSi(CH_3)_2$), 0.88 (9H, s, 16-OSi-*t*-Bu), 0.90 (3H, s, 18-CH_3), 1.16 (3H, s, 19-CH_3), 2.6—2.9 (2H, -$OCH_2C\underline{H}_2S$-), 3.6—3.9 (2H, -$OC\underline{H}_2CH_2S$-), 4.16 (1H, m, 16α-H), 5.74 (1H, s, 4-H). *Anal.* Calcd. for $C_{27}H_{44}O_3SSi$: C, 68.02; H, 9.30. Found: C, 68.04; H, 9.43.

16β-Hydroxy-4-androstene-3,17-dione 17-Ethylenehemithioketal (**35**)——Hydrolysis of **34** (150 mg) with *p*-TsOH was carried out in the manner as described with **16**. The crude product obtained was chromatographed on silica gel (10 g). Elution with hexane–AcOEt (2:1) and recrystallization of the eluate from hexane–CH_2Cl_2 gave **35** (50 mg) as colorless prisms. mp 210—212°, $[\alpha]_D^{23}$ +43.3° (c=0.15). NMR ($CDCl_3$) δ: 0.88 (3H, s, 18-CH_3), 1.15 (3H, s, 19-CH_3), 2.8—3.1 (2H, -$OCH_2C\underline{H}_2S$-), 3.6—4.1 (2H, -$OC\underline{H}_2CH_2S$-), 4.22 (1H, m, 16α-H), 5.73 (1H, s, 4-H). *Anal.* Calcd. for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.34. Found: C, 69.60; H, 8.56.

16α-*tert*-Butyldimethylsilyloxy-4-androstene-3,17-dione 17-Ethylenedithioketal (**36**)——Oppenauer oxidation of **21** (250 mg) was carried out in the manner as described with **15**. The crude product was chromatographed on silica gel (20 g). Elution with hexane–AcOEt (5:1) and recrystallization of the eluate from MeOH gave **36** (215 mg) as colorless fine needles. mp 180—184°. $[\alpha]_D^{16}$ −18.8° (c=0.21). NMR ($CDCl_3$) δ: 0.09 (6H, s, 16-$OSi(CH_3)_2$), 0.90 (9H, s, 16-OSi-*t*-Bu), 1.00 (3H, s, 18-CH_3), 1.15 (3H, s, 19-CH_3), 3.0—3.4 (4H, -SCH_2CH_2S-), 4.59 (1H, m, 16β-H), 5.70 (1H, s, 4-H). *Anal.* Calcd. for $C_{27}H_{44}O_2S_2Si$: C, 65.80; H, 9.00. Found: C, 65.46; H, 9.30.

16α-Hydroxy-4-androstene-3,17-dione 17-Ethylenedithioketal (**37**)——Hydrolysis of **36** (190 mg) with *p*-TsOH was carried out in the manner as described with **16**. Recrystallization of the product obtained from MeOH gave **37** (140 mg) as colorless needles. mp 183—184°. $[\alpha]_D^{15}$ +17.5° (c=0.23). NMR ($CDCl_3$) δ: 1.06 (3H, s, 18-CH_3), 1.19 (3H, s, 19-CH_3), 2.9—3.4 (4H, -SCH_2CH_2S-), 4.52 (1H, m, 16β-H), 5.72 (1H, s, 4-H). *Anal.* Calcd. for $C_{21}H_{30}O_2S_2 \cdot 1/2H_2O$: C, 65.07; H, 8.06. Found: C, 65.18; H, 8.22.

16α-Hydroxy-4-androstene-3,17-dione (**39**)——Treatment of **37** (60 mg) with $HgCl_2$ and $CaCO_3$ in 80% CH_3CN was carried out in the manner as described with **23**. The crude product obtained was purified by preparative TLC using hexane–AcOEt (1:1) as developing solvent and recrystallized from acetone–ether to give **39** (20 mg) as colorless plates. mp 182—184° (reported: mp 185—186°[13]; 185.5—187.5°[14]). NMR ($CDCl_3$) δ: 1.04 (3H, s, 18-CH_3), 1.14 (3H, s, 19-CH_3), 4.42 (1H, d, d, J=4,7 Hz, 16β-H), 5.76 (1H, s, 4-H).

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