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# Oxidative Addition of Alkyl Mercaptans to Steroidal $\Delta^{4,6}$-3-Ketones

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Addition of ethyl mercaptan to 6-dehydro-17α-methyltestosterone (I) in the presence of the organic bases afforded two oxidative addition products together with the corresponding 7α-ethylthio derivative (II) in minor yields. Both of them were formulated as 6α-hydroxy-7β-ethylthio- and 6β-hydroxy-7α-ethylthio-17α-methyltestosterone (III and IV) by chemical evidences and the spectral data. Under similar condition, androsta-4,6-diene-3,17-dione (XII) gave an unexpected compound, 4-ethylthio-7β-hydroxyandrost-4-en-3-one (XXIII) accompanied with 7α-ethylthio (XIII), 6α-hydroxy-7β-ethylthio (XIV) and 6β-hydroxy-7α-ethylthio derivative (XV).

It has been reported[2] that a convenient entry of the alkylthio group into C-7 position with the known and readily available 6-dehydro derivatives of appropriate $\Delta^4$-3-ketosteroids is possible *via* the 1,6-addition of various sulfur nucleophiles in the presence of piperidine or hydrochloric acid as the catalyst. In our synthetic program of anabolic steroids, addition of alkyl mercaptans to $\Delta^{4,6}$-3-ketosteroids was reinvestigated. As reported in the previous paper,[3] treatment of ethyl mercaptan with 6-dehydro-17α-methyltestosterone (I) in the presence of sodium methylate or anion exchange resin (Amberlite IRA-411) gave 7α-ethylthio-17α-methyltestosterone (II) in a fairly good yield. However, the reaction using organic bases such as piperidine, triethylamine and/or anion exchange resin (Amberlite IR-45) instead of sodium methylate appeared hardly to proceed without heating. Therefore, under prolonged heating there were unexpectedly observed two additional products along with the 7α-ethylthio steroid (II) on thin-layer chromatography (TLC).

A typical run, treatment of ethyl mercaptan with I[4] in the presence of excess of triethylamine at 40° for 100 hours, afforded a solid, from which after removing of the starting material (I) and 7α-ethylthiosteroid (II) through silica gel chromatography, a less polar crystals, mp 187—190° (III) and a more polar one, mp 198—201° (IV), could be isolated by further elution in 2.8 and 11.5% yields, respectively. Both of them possess same molecular formula $C_{22}H_{34}O_3S$ and have one hydroxy group more than the structure (II) from elementary analysis, in which the former showed absorptions at 1659 and 1617 $cm^{-1}$, and the latter did at 1659 and 1622 $cm^{-1}$ attributable to conjugated ketone and conjugated double bond, respectively in the infrared (IR) spectrum. Mild acetylation of IV with acetic anhydride in pyridine at room temperature gave a monoacetate (VI). Similarly an oily monoacetate (V) was also obtained from III. The ultraviolet (UV) absorption maxima at 240 mμ (ε 14500) for III and at 236 mμ(ε 14100) for IV are good agreement with those of 6α-hydroxy- and 6β-hydroxy-$\Delta^4$-3-ketosteroids,[5] respectively. The 6β-hydroxy compound (IV) was oxidated with activated manganese dioxide or $CrO_3$-pyridine complex to give a $\Delta^4$-3,6-dione (VII). Its UV spectrum,

1) Location: *Kami-Ebie 2, Fukushima-ku, Osaka.*
2) R.E. Schaub and M.J. Weis, *J. Org. Chem.*, **26**, 3915 (1961); J.M. Krämer, K. Brückner, K. Irmscher, and K-H. Bork, *Chem. Ber.*, **96**, 2803 (1963).
3) H. Kaneko, K. Nakamura, Y. Yamato, and M. Kurokawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 11 (1969).
4) J.A. Campbell and J.C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1959).
5) K. Morita, *Nippon Kagaku Zasshi*, **78**, 1581 (1957); Y. Sasaki, Y. Kondo, and T. Miyazima, *Yakugaku Zasshi*, **85**, 377 (1965); J.P. Dusza, J.P. Joseph, and S. Bernstein, *J. Org. Chem.*, **27**, 4046 (1962).

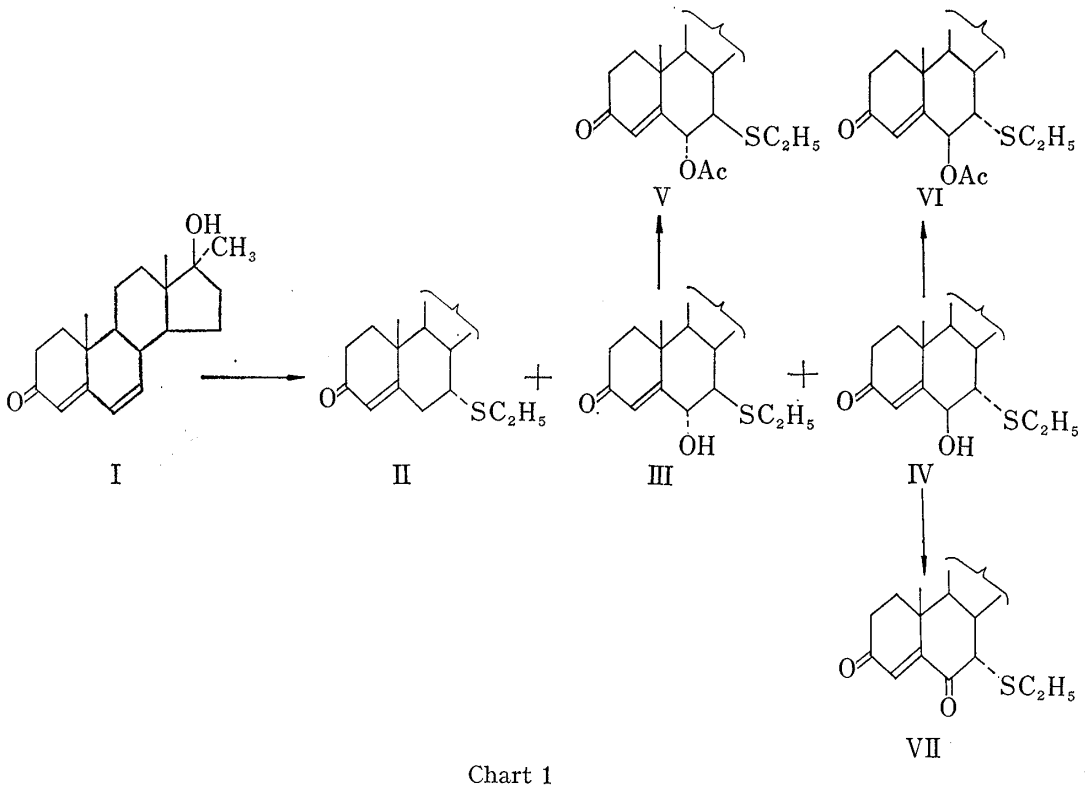



Chart 1

$\lambda_{max}$ 256 m$\mu$, is characteristic for steroidal $\Delta^4$-3,6-dione chromophore.[6] Oxidation of the 6$\alpha$-hydroxy compound (III) in a same manner led to a decomposed material.

The configuration of the hydroxy group in III and IV was further confirmed by their nuclear magnetic resonance (NMR) spectra. The down field shift (0.15 ppm) of C-19 methyl protons attributable to a 1,3-diaxial position with the hydroxy group[7] shows the C-6 hydroxy group in IV to be $\beta$-orientation. On the other hand, the fact that the resonance signal of the C-4 proton in the 6$\alpha$-hydroxy compound (III) is observed in the downfield by 0.58 ppm from that usually found for the $\Delta^4$-3-ketosteroids indicates the hydroxy group at C-6 to be $\alpha$-configuration on the basis of the deshielding effect of coplanary hydroxy group.[8]

Furthermore, the configuration of the C-7 ethylthio group in the both hydroxy compounds (III and IV) could be confirmed by the coupling constants of the C-6 proton as well as the C-7 proton signals. The NMR spectrum of III appeared at 5.89 $\tau$ as a quartet ($J$=2.0 and 10.5 cps), in which the smaller splitting pattern ($J$=2.0 cps) was attributable to a long range coupling of the 6$\beta$-proton with the C-4 proton,[9] and from another coupling constant ($J$=10.5 cps) the C-7 proton could unequivocally be assigned to be $\alpha$-orientation. In the NMR spectrum of IV, the signal due to the C-7 proton appeared at 7.06 $\tau$ as a triplet, from whose coupling constant ($J$=3.0 cps) the configuration of the C-7 hydrogen suggests $\beta$-orientation (equatorial). Similar signal pattern of the C-7 proton was observed in the NMR spectrum of the acetate (VI). Moreover, it is evident from the coupling constants of the C-6 and C-7 protons that ring B in IV and VI have normal conformation.

The optical rotatory dispersion (ORD) and circular dichroism (CD) of these compounds were also investigated. The 7$\alpha$-ethylthio (II) and 6$\alpha$-hydroxy-7$\beta$-ethylthio (III) derivatives

6) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).
7) Y. Kawazoe, Y. Sato, M. Nastume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).
8) N.S. Bacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, p. 189.
9) Page 108 in ref. 8.

showed ORD curves similar to that of 17α-methyltestosterone, whereas the 6β-hydroxy-7α-ethylthiosteroid (IV) and its 6β-acetate (VI) exhibited completely different Cotton effects, as shown in Fig. 1 and 2.

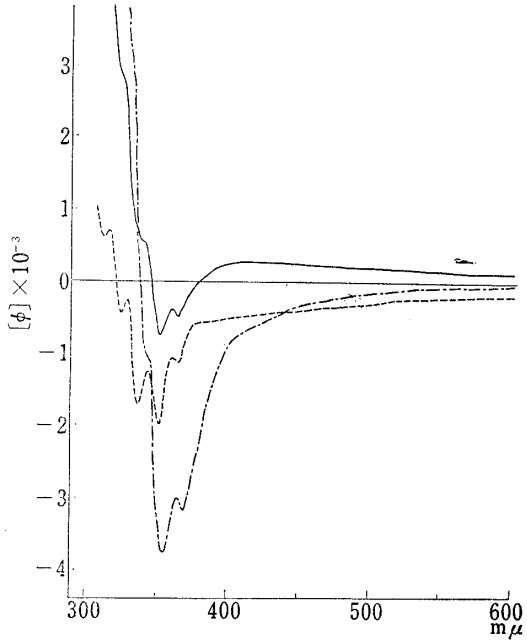



Fig. 1. Optical Rotatory Dispersion Curves of 17α-Methyltestosterone (———), II (--------), and III (———)

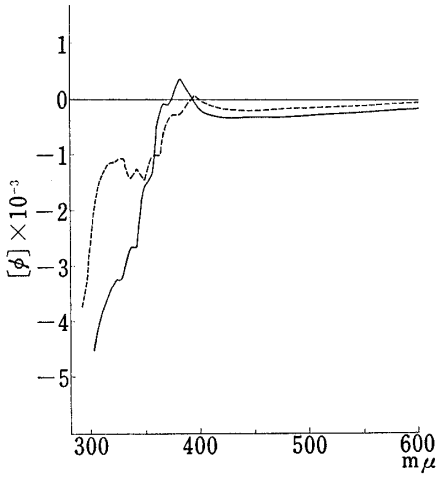



Fig. 2. Optical Rotatory Dispersion Curves of IV (——) and VI (------)

The data on CD maxima associated with n-π* and π-π* transitions of these compounds are listed in Table I. In the 7α-ethylthio derivative (II) and 6α-hydroxy-7β-ethylthiosteroid (III), the signs of the n-π* and π-π* Cotton effects are same to those of 17α-methyltestosterone except the negative maximum of III at 226 mμ. On the other hand, it is of interest that IV and VI have opposite Cotton effects in the K- and R-band regions. In α,β-unsaturated ketones, the signs of the Cotton effects associated with the n-π* and long-wave length π-π* transitions known to reflect the chirality of the C=C–C=O chromophore.[10] If these signs would permit to determine a correct conformation, the 6β-hydroxy compound (IV) and its

Table I. The CD Data of $\Delta^4$-3-Ketosteroids

| Compound | n-π* | | π-π* | | | |
|---|---|---|---|---|---|---|
| | λ (mμ) | [θ] | λ (mμ) | [θ] | λ (mμ) | [θ] |
| 17α-Methyltestosterone | 332 | −4900 | 235[a] | +32700 | 220 | +37900! |
| 7α-Ethylthio-17α-methyl testosterone (II) | 333 | −2300 | 235[a] | +12400 | 220 | +19800! |
| 6α-Hydroxy-7β-ethylthio-17α-methyltestosterone (III) | 334 | −8440 | 245 | +12700 | 226 | −8460 |
| 6β-Hydroxy-7α-ethylthio-17α-methyltestosterone (IV) | 359 | +2290 | 250 | −26900 | 215 | +27800! |
| 6β-Acetoxy-7α-ethylthio-17α-methyltestosterone (VI) | 368 | +1000 | 258 | −15800 | 215 | +29900! |

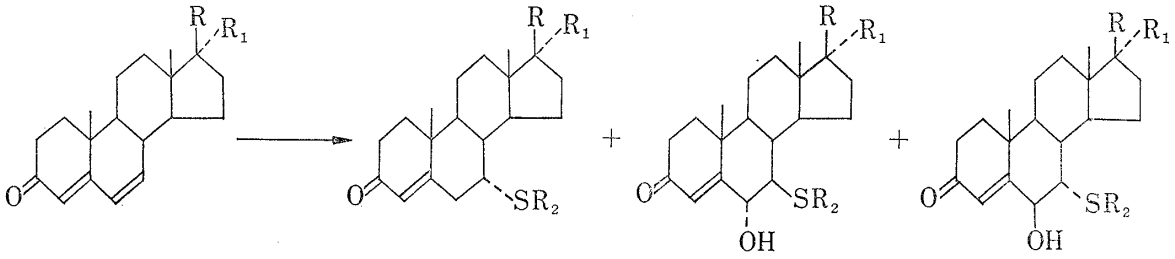
a) inflexion; !: last reading

10) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, 1965, p. 191.

6$\beta$-acetate (VI) should have helicity of the C=C–C=O system opposite to that of 17$\alpha$-methyltestosterone. However, because of no distortion in their B-ring from NMR data of IV and VI as described before, the conformation of the C=C–C=O group in IV and VI is believed to be the same as that in 17$\alpha$-methyltestosterone.

Recently, Kuriyama, *et al.*[11] have reported that the 6$\beta$-hydroxy or 6$\beta$-acetoxy group in the 6-substituted $\Delta^4$-3-ketosteroids has not effect on the CD curve in the R-band region but in the K-band region and this effect is probably due to electronic interaction between the oxygen atom in the 6$\beta$-substituent and the $\Delta^4$-3-keto electrons. From this observation it may be mentioned that the inversion of the n-$\pi^*$ Cotton effects in IV and VI is ascribed to electronic interactions between the sulfur atom in the 7$\alpha$-substituent and $\Delta^4$-3-keto electrons through the 6$\beta$-oxygen atom.

Thus, it is concluded that 6$\alpha$-hydroxy-7$\beta$-ethylthio-17$\alpha$-methyltestosterone (III) and isomeric 6$\beta$-hydroxy-7$\alpha$-ethylthio-17$\alpha$-methyltestosterone (IV) were obtained from the reaction of ethyl mercaptan with 6-dehydro-17$\alpha$-methyltestosterone (I) in the presence of organic bases. Under the similar conditions, 6-dehydrotestosterone (VIII)[12] and androsta-4,6-diene-3,17-dione (XII)[12] also afforded two kinds of oxidative addition products (X), (XI) and (XIV), (XV) respectively together with the corresponding 7$\alpha$-ethylthiosteroids (IX) and (XIII). In addition, the 6-dehydro derivative (I) gave the 6$\alpha$-hydroxy-7$\beta$-*n*-propylthio (XVII) and 6$\beta$-hydroxy-7$\alpha$-*n*-propylthiosteroid (XVIII) along with the 7$\alpha$-*n*-propylthiosteroid (XVI)[3] when *n*-propyl mercaptan was used in place of ethyl mercaptan.



VIII: R=OH, $R_1$=H
XII: R, $R_1$=O
I: R=OH, $R_1$=$CH_3$

IX: R=OH, $R_1$=H, $R_2$=$C_2H_5$
XIII: R,$R_1$=O, $R_2$=$C_2H_5$
XVI: R=OH, $R_1$=$CH_3$, $R_2$=$C_3H_7$

X: R=OH, $R_1$=H, $R_2$=$C_2H_5$
XIV: R,$R_1$=O, $R_2$=$C_2H_5$
XVII: R=OH, $R_1$=$CH_3$, $R_2$=$C_3H_7$

XI: R=OH, $R_1$=H, $R_2$=$C_2H_5$
XV: R,$R_1$=O, $R_2$=$C_2H_5$
XVIII: R=OH, $R_1$=$CH_3$, $R_2$=$C_3H_7$

Chart 2

The mechanism of this reaction seems to be similar to that of co-oxidative addition of indene with thiol acid reported by Readio, *et al.*,[13] that is, a radical addition of ethyl mercaptan may proceed through nonclassical bridged intermediates (XIX) and (XX), and a subsequent rapid addition of oxygen radical may occur *trans* stereospecifically to the bridged radicals. The resulting radicals abstract hydrogens from ethyl mercaptan to yield hydroperoxides (XXI) and (XXII). The hydroperoxides then are reduced by ethyl mercaptan to the corresponding alcohols (III) and (IV). Attempts to prove the above homolytic reaction using UV light or oxygen as reported by the method of Oswald, *et al.*[14] were failed.

Finally, repeating chromatographic separation of the reaction products of androsta-4,6-diene-3,17-dione (XII) with ethyl mercaptan afforded a third oxidative product (XXIII) having melting point at 188—191° in 2% yield. From elemental analysis the compound has

11) K. Kuriyama, M. Moriyama, T. Iwata, and K. Tori, *Tetrahedron Letters*, **1968**, 1661.
12) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufman, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).
13) P.D. Readio and P.S. Skell, *J. Org. Chem.*, **31**, 759 (1966); H.H. Szmant and J.J. Rigau, *Tetrahedron Letters*, **1967**, 3337.
14) A.A. Oswald, K. Giesbaum, and W. Naegele, *J. Am. Chem. Soc.*, **86**, 3791 (1964).

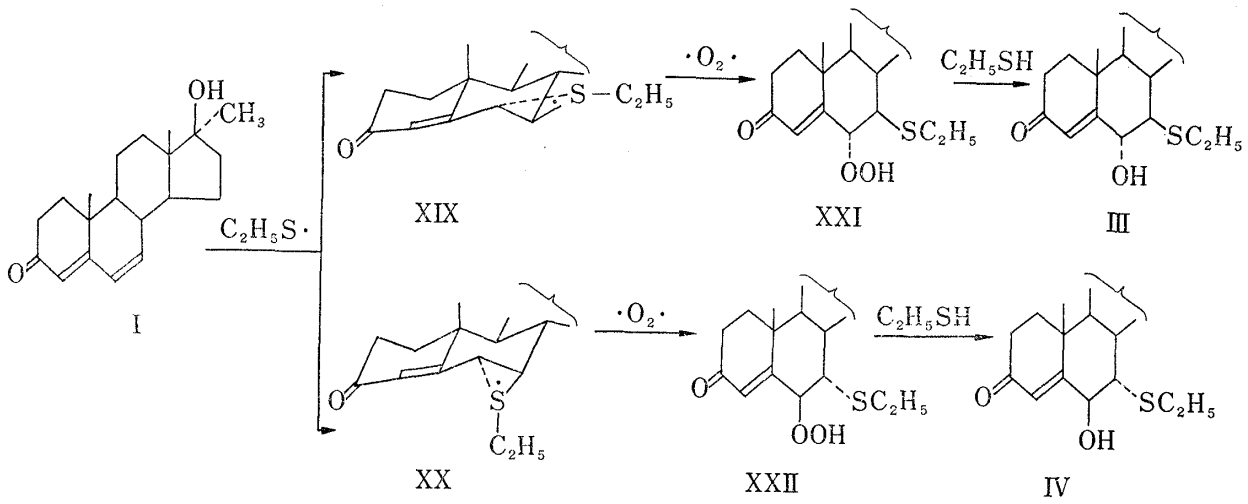


Chart 3

molecular formula $C_{22}H_{34}O_3S$ which is the same formula as the oxidative products (XIV) and (XV) obtained. In the UV spectrum maxima at 248 m$\mu$ ($\varepsilon$ 11200) and 314 m$\mu$ ($\varepsilon$ 2260) are characteristic for the 4-alkylthio-$\Delta^4$-3-ketosteroids.[15] The IR spectrum exhibited absorptions at 3420 and 1673 $cm^{-1}$ due to the hydroxy and $\alpha,\beta$-unsaturated carbonyl groups respectively, and olefinic proton is absent in the NMR spectrum.

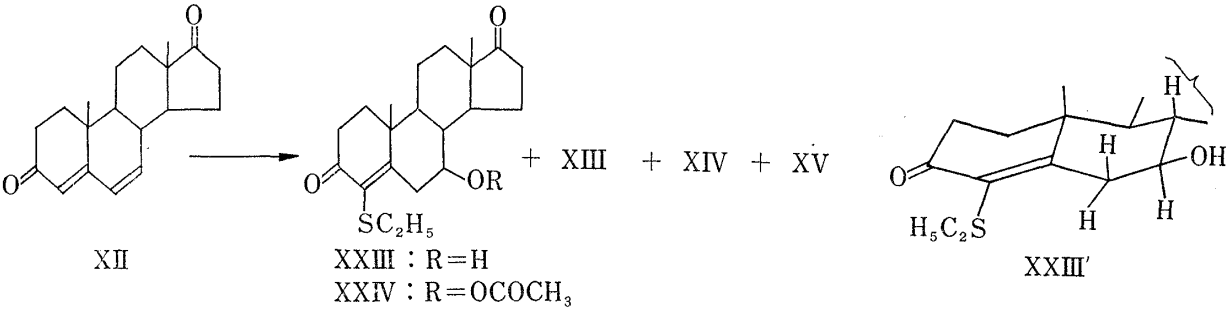


Chart 4

On acetylation of XXIII with acetic anhydride in pyridine gave an acetate (XXIV). From the examination of NMR spectra of XXIII and XXIV, the position and configuration of the hydroxy group in XXIII was suggested to be C-7$\beta$ as follows. The hydroxy derivative (XXIII) showed a quartet ($J$=5.0, 14.0 cps) at 6.00 $\tau$ and a multiplet at 6.48 $\tau$, whereas the acetate (XXIV) exhibited a quartet ($J$=5.0, 14.0 cps) at 5.90 $\tau$ and an octet ($J$=5.0, 10.0, 11.5 cps) at 5.32 $\tau$. According to the observation[16] that the 6$\alpha$-proton in the 4-ethylthio-$\Delta^4$-3-ketosteroids suffers a large deshielding of the 4-ethylthio group and its resonance signal appeared at 6.22 $\tau$ ($J_{6\alpha\cdot6\beta}$=14.5 cps), the signal as a quartet at 6.00 $\tau$ in XXIII and at 5.90 $\tau$ in XXIV are assignable to the 6$\alpha$-hydrogen coupled with the 6$\beta$-($J$=14.0 cps) and C-7 hydrogens ($J$=5.0 cps).

Consequently, above results support that the position of the hydroxy group in the compound is at C-7. Furthermore it was also found that the octet splitting peak at 5.32 $\tau$ in the acetate (XXIV) is due to the proton attached to C-7 having the acetoxy group. From the smallest coupling constant (5.0 cps) resulted from the resonance with the $\alpha$-proton at C-6 and another $J$ values (10.0 and 11.5 cps) coupled with the 6$\beta$- and 8$\beta$-protons the configura-

15) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, and T. Furuta, *Tetrahedron*, **21**, 733 (1965).
16) M. Tomoeda, M. Inuzuka, T. Furuta, and M. Shinozuka, *Tetrahedron*, **24**, 959 (1968).

tion of the acetoxy group at C-7 was found to be $\beta$-orientation (equatorial).[17] Thus the structure of the hydroxy compound (XXIII) represents as 4-ethylthio-7$\beta$-hydroxyandrost-4-en-3,17-dione (XXIII'), as shown in Chart 4. The mechanism of the formation of the 4-ethylthio-7$\beta$-hydroxysteroid (XXIII) is still obscure at present. Similar oxidation product was not isolated from the reaction products of I and VIII with ethyl mercaptan.

## Experimental[18]

**Oxidative Addition of Ethylmercaptan to 6-Dehydro-17$\alpha$-methyltestosterone (I)**——A solution of I (10.0 g) in ethyl mercaptan ($C_2H_5SH$) (150 ml) and triethylamine ($Et_3N$) (30 ml) was stirred at 40° for 100 hr and at room temperature for 80 hr. After evaporation of solvents, the oily residue obtained was dissolved in hexane–benzene (1:1) and chromatographed on silica gel. Fractions eluted with benzene–ether (20:3—5:1) gave a crystalline product (6.5 g) which is a mixture of starting material (I) and 7$\alpha$-ethylthio derivative (II)[3] from their UV and IR spectra.

Elution with benzene–ether (4:1) and recrystallization of the eluate from ether gave 6$\alpha$,17$\alpha$-dihydroxy-7$\beta$-ethylthio-17$\alpha$-methylandrost-4-en-3-one (III) (0.35 g, 2.8%) as colorless needles, mp 187—190°, $[\alpha]_D$ −14.8° ($c$=0.58). UV $\lambda_{max}$ m$\mu$ ($\varepsilon$): 240 (14500). IR $\nu_{max}$ cm$^{-1}$: 1659 (CO), 1617 (C=C). NMR $\tau$: 8.78 (19-H), 5.89 (6$\beta$-H, q, $J_{6\beta\cdot7\alpha}$=10.5, $J_{6\beta\cdot4}$=2.0), 3.65 (4-H, d, $J_{4\cdot6\beta}$=2.0). ORD ($c$=0.12): $[\phi]_{700}$ −31.6°, $[\phi]_{589}$ −63.1°, $[\phi]_{370}$ −3160°, $[\phi]_{365}$ −2950°, $[\phi]_{356}$ −3790°, $[\phi]_{342}$ −946° (inflexion). CD ($c$=0.12, 400—280 m$\mu$): $[\theta]_{380}$ 0, $[\theta]_{346}$ −6560 (inflexion), $[\theta]_{334}$ −8440, $[\theta]_{324}$ −7390 (inflexion), $[\theta]_{290}$ −834; ($c$=0.0177, 280—215 m$\mu$): $[\theta]_{270}$ −7760, $[\theta]_{259}$ 0, $[\theta]_{245}$ +12700, $[\theta]_{235}$ 0, $[\theta]_{226}$ −8460. *Anal.* Calcd. for $C_{22}H_{34}O_3S$: C, 69.80; H, 9.05; S, 8.47. Found: C, 69.71; H, 9.07; S, 8.74.

The Acetate (V) of III: The 6$\alpha$-hydroxysteroid (III) (0.3 g) was acetylated with $Ac_2O$ (0.3 ml) and pyridine (5.0 ml) at room temperature. As usual work up gave an oily material, which was chromatographed on silica gel. Elution with benzene–ether (10:1) afforded the 6$\alpha$-acetate (V) as an oily product (0.2 g). IR $\nu_{max}$ cm$^{-1}$: 1730 ($OCOCH_3$). NMR $\tau$: 8.80 (19-H), 7.83 ($OCOCH_3$), 4.40 (6$\beta$-H, q, $J_{6\beta\cdot7\alpha}$=10.0, $J_{6\beta\cdot4}$=2.0), 4.17 (4-H, d, $J_{4\cdot6\beta}$=2.0).

Further elution with benzene–ether (5:2) and recrystallization of the product from acetone–ether gave 6$\beta$,17$\alpha$-dihydroxy-7$\alpha$-ethylthio-17$\alpha$-methylandrost-4-en-3-one (IV) (1.45 g, 11.5%) as colorless needles, mp 198—201°, $[\alpha]_D$ −43.0° ($c$=0.64). UV $\lambda_{max}$ ($\varepsilon$) m$\mu$: 236 (14100). IR $\nu_{max}$ cm$^{-1}$: 1659 (CO), 1622 (C=C). NMR $\tau$: 8.62 (19-H), 7.06 (7$\alpha$-H, t, $J$=3.0), 5.65 (6$\alpha$-H, d, $J$=3.0), 4.10 (4-H). ORD ($c$=0.12): $[\phi]_{700}$ −158°, $[\phi]_{589}$ −189°, $[\phi]_{381}$ +379°, $[\phi]_{371}$ −94.6°, $[\phi]_{366}$ −82.0°, $[\phi]_{354}$ −1420°, $[\phi]_{340}$ −2690°, $[\phi]_{336}$ −2640°, $[\phi]_{327}$ −3250°, $[\phi]_{322}$ −3220°, $[\phi]_{314}$ −3580° (inflexion). CD ($c$=0.12, 400—280 m$\mu$): $[\theta]_{394}$ 0, $[\theta]_{359}$ +2290, $[\theta]_{352}$ +1670, $[\theta]_{345}$ +1930, $[\theta]_{336}$ +1910, $[\theta]_{333}$ +1120, $[\theta]_{315}$ 0; ($c$=0.018, 280—215 m$\mu$): $[\theta]_{250}$ −26900, $[\theta]_{230}$ 0, $[\theta]_{215}$ +27800. *Anal.* Calcd. for $C_{22}H_{34}O_3S$: C, 69.80; H, 9.05; S, 8.47. Found: C, 69.77; H, 8.86; S, 8.14.

The Acetate (VI) of IV: The 6$\beta$-hydroxysteroid (IV) (0.3 g) was treated with $Ac_2O$ (0.3 ml) and pyridine (4.0 ml) in the similar method as described for V. The reaction product was recrystallized from acetone–hexane to give the 6$\beta$-acetate (VI) (0.23 g) as prisms, mp 160—162°, $[\alpha]_D$ −13.0° ($c$=1.18). UV $\lambda_{max}$ m$\mu$ ($\varepsilon$): 236 (14100). IR $\nu_{max}$ cm$^{-1}$: 1730 ($OCOCH_3$). NMR $\tau$: 8.68 (19-H), 7.92 ($OCOCH_3$), 7.05 (7$\beta$-H, t, $J$=3.0), 4.58 (6$\alpha$-H, d, $J_{6\alpha\cdot7\beta}$=3.0), 3.98 (4-H). ORD ($c$=0.10): $[\phi]_{700}$ −84.1°, $[\phi]_{589}$ −86.0°, $[\phi]_{390}$ +85.0°, $[\phi]_{374}$ −294° (inflexion), $[\phi]_{361}$ −1050°, $[\phi]_{357}$ −1010°, $[\phi]_{348}$ −1520°, $[\phi]_{340}$ −1260°, $[\phi]_{336}$ −1430°, $[\phi]_{327}$ −1050°, $[\phi]_{314}$ −1180° (inflexion). CD ($c$=0.10, 400—280 m$\mu$): $[\theta]_{425}$ 0, $[\theta]_{380}$ +639 (inflexion), $[\theta]_{368}$ +1000, $[\theta]_{360}$ +528, $[\theta]_{351}$ +610, $[\theta]_{344}$ 0; ($c$=0.0176, 280—215 m$\mu$): $[\theta]_{258}$ −15800, $[\theta]_{238}$ 0, $[\theta]_{215}$ +29900. *Anal.* Calcd. for $C_{24}H_{36}O_4S$: C, 68.54; H, 8.63; S, 7.62. Found: C, 68.60; H, 8.61; S, 7.36.

17$\alpha$-Methyltestosterone: ORD ($c$=0.083): $[\phi]_{700}$ +116°, $[\phi]_{589}$ +156°, $[\phi]_{365}$ −499°, $[\phi]_{361}$ −378°, $[\phi]_{353}$ −772°, $[\phi]_{341}$ +570° (inflexion), $[\phi]_{372}$ +2720° (inflexion). CD ($c$=0.083, 400—280 m$\mu$): $[\theta]_{372}$ 0, $[\theta]_{344}$ −3650, $[\theta]_{340}$ −3550, $[\theta]_{332}$ −4900, $[\theta]_{325}$ −3970, $[\theta]_{320}$ −4160, $[\theta]_{270}$ 0; ($c$=0.0171, 280—215 m$\mu$): $[\theta]_{235}$ +32700 (inflexion), $[\theta]_{220}$ +37900.

7$\alpha$-Ethylthio-17$\alpha$-methyltestosterone (II): NMR $\tau$: 8.77 (19-H), 6.92 (7$\beta$-H), 4.23 (4-H). ORD ($c$=0.14): $[\phi]_{700}$ −101.0°, $[\phi]_{589}$ −201°, $[\phi]_{366}$ −117°, $[\phi]_{361}$ −114°, $[\phi]_{353}$ −1990°, $[\phi]_{344}$ −1200°, $[\phi]_{338}$ −1700°, $[\phi]_{329}$ −238°, $[\phi]_{325}$ −435°, $[\phi]_{316}$ +703°, $[\phi]_{311}$ +628°, $[\phi]_{305}$ +1040°. CD ($c$=0.14, 400—280 m$\mu$): $[\theta]_{387}$ 0, $[\theta]_{372}$ +302°, $[\theta]_{360}$ 0, $[\theta]_{346}$ −1050, $[\theta]_{342}$ −956, $[\theta]_{333}$ −2300, $[\theta]_{326}$ −1800, $[\theta]_{310}$ −1550 (inflexion), $[\theta]_{291}$ −835; ($c$=0.026, 280—215 m$\mu$): $[\theta]_{262}$ −9650, $[\theta]_{240}$ 0, $[\theta]_{235}$ +12400 (inflexion), $[\theta]_{220}$ +19800.

17) The definite assignment of the 6$\alpha$- and 7$\alpha$-protons using spin decoupling method was unsuccessful.

18) All melting points are uncorrected. IR spectra were determined in KBr disk and UV spectra in EtOH solution. Specific rotations were measured in $CHCl_3$ solution at 20° and NMR spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ containing tetramethylsilane as internal standard. Following abbreviations are used for the representation of NMR data: s=singlet, d=doublet, t=triplet, q=quartet, o=octet, m=multiplet, and coupling constants are given in cps. ORD and CD spectra were taken in dioxane by use of JASCO/UV-5 spectropolarimeter.

**Oxidation of the 6β-Hydroxysteroid (IV)**——a) With $CrO_3$–Pyridine Complex: To a solution of $CrO_3$ (0.2 g) in pyridine (6.5 ml) was added a solution of IV (0.1 g) in pyridine (2 ml) with stirring and the solution was allowed to stand at room temperature overnight. The mixture was poured into water and extracted with ether. The organic solution was washed with water and dried over $Na_2SO_4$. Evaporation of the solvent yielded a crystalline residue (0.08 g), which was recrystallized from ether to give 7α-ethylthio-17α-methylandrost-4-ene-3,6-dione (VII), mp 210—215°, $[\alpha]_D$ +119° ($c$=0.88). UV $\lambda_{max}$ mμ (ε): 251 (10300), 314 (4000). IR $\nu_{max}$ $cm^{-1}$: 1675 (CO), 1610 (C=C). NMR τ: 6.67 (7β-H, d, $J$=3.2), 3.69 (4-H). *Anal.* Clacd. for $C_{22}H_{32}O_3S$: C, 70.17; H, 8.57; S, 8.52. Found: C, 69.74; H, 8.72; S, 8.35.

b) With $MnO_2$: To a solution of IV (0.2 g) in $CHCl_3$ (100 ml) was added $MnO_2$ (2.0 g) prepared by the method of Attenburrow, *et al.*[19] The reaction mixture was refluxed for 24 hr and filtered off the inorganic material. The mother liquor was evaporated to dryness *in vacuo* and the resulting residue was chromatographed on silica gel. Elution with benzene–ether (5:1) gave a pale yellow compound (0.13 g). Recrystallization from ether afforded a prisms, mp 209—214°, which was identical with VII described above.

Oxidation of the 6α-hydroxysteroid (III) with $CrO_3$–pyridine complex or $MnO_2$ in the similar manner as described above afforded a resinous material.

**7α-Ethylthio-17β-hydroxyandrost-4-en-3-one (IX)**——The 7α-ethylthio derivative (IX) was prepared from 6-dehydrotestosterone (VIII) according to the method of ref. 3. The crude product was recrystallized from acetone to give IX as colorless needles, mp 220—223°, $[\alpha]_D$ −9.5° ($c$=1.06). UV $\lambda_{max}$ mμ (ε): 241 (18100). IR $\nu_{max}$ $cm^{-1}$: 1658 (CO), 1625 (C=C). NMR τ: 8.79 (19-H), 6.93 (7β-H), 4.22 (4-H). *Anal.* Calcd. for $C_{21}H_{32}O_2S$: C, 72.39; H, 9.25; S, 9.20. Found: C, 72.28; H, 9.18; S, 9.15.

**Oxidative Addition of Ethyl Mercaptan to 6-Dehydrotestosterone (VIII)**——A solution of VIII (10.0 g) in $C_2H_5SH$ (50 ml) and $Et_3N$ (10 ml) was stirred at 40° for 50 hr and at room temperature for 30 hr. After evaporation of solvents, the resulting oily residue was chromatographed on silica gel. Elution with benzene–ether (5:1—10:3) gave a mixture of the starting material (VIII) and 7α-ethylthiotestosterone (IX) (1.85 g) from their UV and IR spectra.

Successive elution with benzene–ether (10:1) afforded a oily residue (X) (0.12 g) (IR $\nu_{max}$ $cm^{-1}$: 1665 (CO), 1625 (C=C)), which was chracterized as its acetate. After acetylation with $Ac_2O$ and pyridine in the usual way, the product (0.13 g) obtained was chromatographed on silica gel. Elution with benzene–ether (10:1) gave a crystalline product, which was recrystallized from hexane to yield 6α,17β-dihydroxy-7β-ethylthioandrost-4-en-3-one 6,17-diacetate (0.11 g) as colorless needles, mp 145—147°, $[\alpha]_D$ −7.0 ($c$ =1.00). UV $\lambda_{max}$ (ε): 236.5 (17100). IR $\nu_{max}$ $cm^{-1}$: 1730 ($OCOCH_3$), 1670 (CO), 1625 (C=C). NMR τ: 8.75 (19-H), 4.41 (6β-H, q, $J_{6\beta\cdot7\alpha}$=10.0, $J_{6\beta\cdot4}$=2.0), 4.18 (4-H, d, $J_{4\cdot6\beta}$=2.0). *Anal.* Calcd. for $C_{25}H_{36}O_5S$: C, 66.93; H, 8.09; S, 7.15. Found: C, 67.24; H, 8.01; S, 7.06.

Further elution with benzene–ether (10:9) gave a crystalline residue, which was recrystallized from acetone to yield 6β,17β-dihydroxy-7α-ethylthioandrost-4-en-3-one (XI) (1.15 g, 8.8%) as colorless needles, mp 232—235° (decomp.), $[\alpha]_D$ −30.5° ($c$=1.20). UV $\lambda_{max}$ mμ (ε): 237 (12900). IR $\nu_{max}$ $cm^{-1}$: 1665 (CO), 1620 (C=C). NMR τ: 8.62 (19-H), 7.05 (7β-H, t, $J$=3.0), 5.63 (6α-H, d, $J_{6\alpha\cdot7\beta}$=3.0), 4.12 (4-H). *Anal.* Calcd. for $C_{21}H_{32}O_3S$: C, 69.19; H, 8.85; S, 8.80. Found: C, 68.97; H, 8.97; S, 8.75.

Diacetate of XI: The 6β-hydroxy compound (XI) was treated with $Ac_2O$ and pyridine at room temperature. The product isolated in usual way was recrystallized from hexane to give the 6β,17β-diacetate, mp 166—169°, $[\alpha]_D$ +2.01° ($c$=1.15). UV $\lambda_{max}$ mμ (ε): 235 (17400). IR $\nu_{max}$ $cm^{-1}$: 1730 ($OCOCH_3$), 1670 (CO), 1620 (C=C). *Anal.* Calcd. for $C_{25}H_{36}O_5S$: C, 66.93; H, 8.09; S, 7.15. Found: C, 67.00; H, 8.02; S, 7.13.

**7α-Ethylthioandrost-4-en-3,17-dione (XIII)**——The 7α-ethylthio derivative (XIII) was prepared from androsta-4,6-dione-3,17-diene (XII) accoding to the method of ref. 3. The crude product was recrystallized from acetone to give XIII, mp 205—208°, $[\alpha]_D$ +49.6° ($c$=1.05). UV $\lambda_{max}$ mμ (ε): 240 (16030). IR $\nu_{max}$ $cm^{-1}$: 1739 (17-CO), 1665 (3-CO), 1620 (C=C). NMR τ: 8.77 (19-H), 6.81 (7β-H), 4.20 (4-H). *Anal.* Calcd. for $C_{21}H_{30}O_2S$: C, 72.79; H, 8.73; S, 9.25. Found: C, 72.51; H, 8.70; S, 9.20.

**Oxidative Addition of Ethyl Mercaptan to Androsta-4,6-diene-3,17-dione (XII)**——A solution of the $\Delta^{4,6}$-3-ketosteroid (XII) (5.0 g) in $C_2H_5SH$ (50 ml) and $Et_3N$ (90 ml) was stirred at 40° for 88 hr and at room temperature for 48 hr. After evaporation of the solvents, the oily residue obtained was chromatographed on silica gel. Elution with benzene–ether (5:1—10:3) afforded a crystalline product, which was a mixture of XII and XIII (4.1 g) from UV and IR spectra.

Successive elution with benzene–ether (5:2) gave a crystalline residue which on crystallization from ether–acetone furnished 6α-hydroxy-7β-ethylthioandrost-4-ene-3,17-dione (XIV) (0.28 g, 4.4%) as colorless needles, mp 148—150°, $[\alpha]_D$ +91.1° ($c$=0.76). UVλ$_{max}$ mμ (ε): 240 (15750). IR $\nu_{max}$ $cm^{-1}$: 3450 (OH), 1739 (17-CO), 1670 (3-CO), 1625 (C=C). NMR τ: 8.77 (19-H), 5.82 (6β-H, q, $J_{6\beta\cdot7\alpha}$=10.5, $J_{6\beta\cdot4}$=2.0), 3.66 (4-H, d, $J_{4\cdot6\beta}$=2.0). *Anal.* Calcd. for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.34; S, 8.84. Found: C, 69.40; H, 8.20; S, 8.69.

19) J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, and T. Walker, *J. Chem. Soc.*, **1952**, 1094.

Acetate of XIV: Acetylation of XIV was carried out in the usual way. The crude product was recrystallized from hexane–ether to give the 6α-acetate, mp 114—117°, $[\alpha]_D$ +65.4° ($c$=0.82). UV $\lambda_{max}$ mμ (ε): 236 (14530). *Anal.* Calcd. for $C_{23}H_{32}O_4S$: C, 68.28; H, 7.97; S, 7.93. Found: C, 68.03; H, 7.95; S, 7.96.

Furter elution with benzene–ether (10:7) gave a crystalline product, which was recrystallized from acetone–ether to yield 6β-hydroxy-7α-ethylthioandrost-4-ene-3,17-dione (XV) (1.38 g, 22%) as colorless prisms, mp 184—186°, $[\alpha]_D$ +28.6° ($c$=1.06). UV $\lambda_{max}$ mμ (ε): 237 (14430). IR $\nu_{max}$ cm$^{-1}$: 3430 (OH), 1727 (17-CO), 1665 (3-CO), 1623 (C=C). NMR τ: 8.62 (19-H), 6.92 (7β-H, t, $J$=3.0), 5.57 (6α-H, d, $J_{6\alpha\cdot7\beta}$=3.0), 4.10 (4-H). *Anal.* Calcd. for $C_{21}H_{30}O_3S$: C, 69.59; H, 8.34; S, 8.84. Found: C, 69.74; H, 8.34; S, 8.81.

Acetate of XV: Acetylation of XV was carried out in the usual way. The crude product was recrystallized from acetone–ether to give the 6β-acetate, mp 212—215°, $[\alpha]_D$ +61.0° ($c$=0.93). UV $\lambda_{max}$ mμ (ε): 234 (13260). *Anal.* Calcd. for $C_{23}H_{32}O_4S$: C, 68.28; H, 7.97; S, 7.93. Found: C, 68.14; H, 7.92; S, 7.79.

A solid obtained from the fractions eluted with benzene–ether (10:5—10:6) was chromatographed on silica gel repeatedly. Elution with benzene–ether (10:7) gave a crystalline product, which was recrystallized from hexane–acetone to give 4-ethylthio-7β-hydroxyandrost-4-ene-3,17-dione (XXIII) (0.12 g, 2%) as colorless needles, mp 188—191°, $[\alpha]_D$ +26.6° ($c$=0.55). UV $\lambda_{max}$ mμ (ε): 248 (11200), 314 (2260). IR $\nu_{max}$ cm$^{-1}$: 3240 (OH), 1738 (17-CO), 1673 (3-CO), 1558 (C=C). NMR τ: 8.72 (19-H), 6.46 (7α-H, m, $W_h$=25), 6.00 (6α-H, q, $J_{6\alpha\cdot7\alpha}$=5.0, $J_{6\alpha\cdot6\beta}$=14.0). *Anal.* Calcd. for $C_{21}H_{30}O_3S$: C, 69.59; H, 8.34; S, 8.84. Found: C, 69.67; H, 8.44; S, 8.61.

Acetate (XXIV) of XXIII: Acetylation of XXIII was carried out with $Ac_2O$ and pyridine in the usual way. The reaction product was recrystallized from acetone–hexane to give 4-ethylthio-7β-hydroxyandrost-4-ene-3,17-dione acetate (XXIV), mp 155—158°, $[\alpha]_D$ +173° ($c$=0.52). UV $\lambda_{max}$ mμ (ε): 245.5 (11930), 315 (1890). IR $\nu_{max}$ cm$^{-1}$: 1727 (17-CO, $OCOCH_3$), 1678 (3-CO), 1557 (C=C). NMR τ: 8.70 (19-H), 5.90 (6α-H, q, $J_{6\alpha\cdot7\alpha}$=5.0, $J_{6\alpha\cdot6\beta}$=14.0), 5.32 (7α-H, o, $J_{6\alpha\cdot7\alpha}$=5.0, $J_{6\beta\cdot7\alpha}$, $J_{7\alpha\cdot8\beta}$=10.0 and/or 11.5). *Anal.* Calcd. for $C_{23}H_{32}O_4S$: C, 68.28; H, 7.97; S, 7.97. Found: C, 68.00; H, 8.13; S, 7.86.

**Oxidative Addition of *n*-Propyl Mercaptan to 6-Dehydro-17α-methyltestosterone (I)**——The 6-dehydro compound (I) (10.0 g) was treated with $n$-$C_3H_7SH$ (120 ml) and $Et_3N$ (20 ml) in the similar way as described for the reaction of I and $C_2H_5SH$. The reaction mixture was concentrated *in vacuo* and the oily residue was taken up into benzene (150 ml) and stored in an ice box to separate a crystal, which was collected by filtration. The resulting crude product was recrystallized from hexane–ether to give 6β,17α-dihydroxy-7α-$n$-propylthio-17α-methylandrost-4-en-3-one (XVIII) (1.2 g) as colorless needles, mp 84—87°, $[\alpha]_D$ −48.4° ($c$=1.02). UV $\lambda_{max}$ mμ (ε): 238 (13840). IR $\nu_{max}$ cm$^{-1}$: 3360 (OH), 1658 (CO), 1618 (C=C). NMR τ: 8.63 (19-H), 7.08 (7β-H, t, $J$=3.0), 5.65 (6α-H, d, $J_{6\alpha\cdot7\beta}$=3.0), 4.13 (4-H). *Anal.* Calcd. for $C_{23}H_{36}O_3S$: C, 70.36; H, 9.24; S, 8.17. Found: C, 69.96; H, 9.44; S, 7.82.

Acetate of XVIII: The 6β-hydroxy derivative (XVIII) was acetylated with $Ac_2O$ and pyridine in the usual way. The crude compound was recrystallized from hexane–acetone gave the 6β-acetate, mp 131—135°, $[\alpha]_D$ −9.5° ($c$=1.01). UV $\lambda_{max}$ mμ (ε): 236 (13530). *Anal.* Calcd. for $C_{25}H_{38}O_4S$: C, 69.10; H, 8.81; S, 7.38. Found: C, 68.97; H, 8.76; S, 7.63.

The mother liquor (benzene solution) was evaporated to give an oily residue, which was chromatographed on silica gel. Elution with benzene–ether (10:3—5:2) afforded a crystalline residue (5.6 g) of a mixture of I and 7α-$n$-propylthio-17α-methyltestosterone (XVI) from their UV and IR spectra.

The further elution with benzene–ether (2:1), after evaporation and recrystallization from hexane–acetone, afforded 6α,17α-dihydroxy-7β-$n$-propylthio-17α-methylandrost-4-en-3-one (XVII) (0.25 g, 1.92%) as colorless needles, mp 188—190°, $[\alpha]_D$ −16.5° ($c$=0.95). UV $\lambda_{max}$ mμ (ε): 240 (14460). IR $\nu_{max}$ cm$^{-1}$: 3490 (OH), 1665 (CO), 1623 (C=C). NMR τ: 8.80 (19-H), 5.91 (6β-H, q, $J_{6\beta\cdot7\alpha}$=10.5, $J_{6\beta\cdot4}$=2.0), 3.67 (4-H, d, $J_{4\cdot6\beta}$=2.0). *Anal.* Calcd. for $C_{23}H_{36}O_3S$: C, 70.36; H, 9.24; S, 8.17. Found: C, 70.10; H, 9.03; S, 8.22.

Fractions eluted with benzene–ether (5:4) gave a crystalline product, which was identified by mixed melting point and comparison of the IR spectrum with XVIII (total 1.23 g, 9.5%).

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