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Thiosteroids. XXXVI.[1] Synthesis of Some 16-Sulfur-substituted Steroids

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Some estrone and epiandrosterone derivatives having a sulfur function at C_{16} were prepared by substitution reaction of 16α- and 16β-bromo-17-ketosteroids with sulfur nucleophiles. The reaction proceeds with inversion at C_{16}. Equilibration experiments on some of the products indicate that the 16β-substituted steroids are thermodynamically more stable than the corresponding α-isomers and the 16-acetylthiosteroids are epimerized faster than the 16-ethylthiosteroids. The proton signals at C_{16} of the products show characteristic splitting patterns according to their configuration.

Keywords——steroids having 16-sulfur substituent; sulfur nucleophiles; epimerization; equilibration; NMR

An earlier paper[3] of this series reported that the reaction of 16-bromoestrone derivatives with an excess of sulfur nucleophiles gave 16β-sulfur-substituted products irrespective of configuration of the bromine atom. One object of the present paper is to report that the substitution reaction proceeds kinetically with inversion of the configuration at C_{16} and that epimerization at C_{16} of the products is easily caused by basicity of the nucleophile during the reaction.

When 16α- and 16β-bromoestrone methyl ethers were treated with a limited amount of sulfur nucleophiles such as potassium thiolacetate and sodium thioethoxide at low temperature over a short period of time, the corresponding 16β- and 16α-sulfur-substituted estrones with inverted configuration at C_{16} were stereospecifically obtained in high yields. However, only 16β-sulfur-substituted estrones were obtained on treatment at higher temperature because of epimerization at C_{16} of the products (Chart 1).

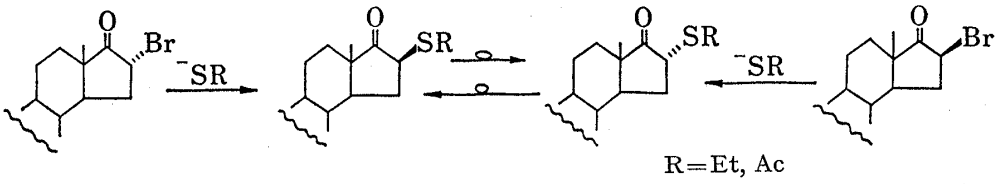

Chart 1

A similar mode of reaction has also been observed in the reaction of 16α- and 16β-bromoepiandrosterone acetates. In these cases, however, the 16α-sulfur-substituted products were prone to be epimerized much more easily than the corresponding estrone derivatives. Particularly, the reaction of 16β-bromoepiandrosterone acetate with sodium thioethoxide in acetone was completed within several minutes under ice-cooling and gave stable 16β-ethylthioepiandrosterone acetate alone. In order to obtain the 16α-counterpart, the reaction had to be conducted at −14° and quenched within four minutes. On the other hand, the reaction of the 16β-bromo derivative with a limited amount of potassium thiolacetate under ice-cooling afforded a 16α-acetylthio derivative in good yield. The

1) Part XXXV: M. Kishi, S. Ishihara, and T. Komeno, *Tetrahedron*, 30, 2135 (1974).
2) Location: *Sagisu, Fukushima-ku, Osaka 553, Japan.*
3) K. Takeda, T. Komeno, N. Tokutake, and Y. Kanematsu, *Chem. Pharm. Bull.* (Tokyo), 12, 905 (1964).

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higher stability of the 16α-sulfur-substituted estrones as compared with that of the corresponding epiandrosterones against epimerization at C_{16} is due to the lower conformational mobility of the former in which the A-ring is aromatic and to the more severe abstraction of the C_{16}-proton, resulting in the occurrence of the following equilibrium to a lesser extent (Chart 2).

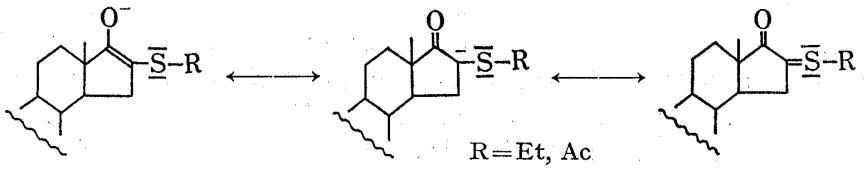

Chart 2

We can not conclude only from the substitution reaction mentioned above whether the more rapid epimerization of the ethylthiosteroids as compared with the acetylthiosteroids is due to easy epimerization of the former or stronger basicity of sodium thioethoxide than potassium thiolacetate. Thus, an equilibration experiment of the two systems was carried out using the following thiosteroids as substrates and sodium acetate as a base (Chart 3).

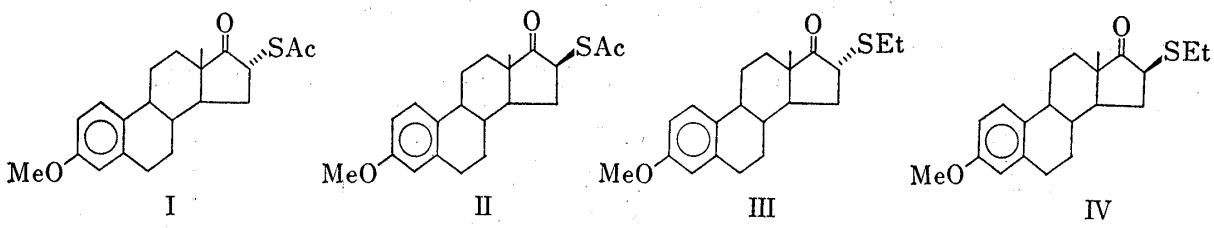

Chart 3

Quantitative Determination of C_{16}-Isomers

NMR spectra of the isomeric mixtures of the acetylthio and ethylthio derivatives exhibited well-resolved C_{18}-methyl singlets assignable to each component. Thus, standard mixtures of I and II or III and IV in various ratios were prepared; 18 mg of the mixture was dissolved in 0.45 ml of chloroform, and C_{18}-methyl singlets of the components were recorded on a Varian A-60A instrument. The error was about 10% when the determination was made with their integral curves, while it was nearly 3% when the area of each C_{18}-methyl singlet was cut out and weighed. By further examination of the experimental conditions, the isomeric mixtures of acetylthiosteroids and of the ethylthiosteroids could be conveniently determined within 0.3% error as follows: the C_{18}-methyl region was scanned 12 times with a sweep width of 100 Hz and a sweep time of 500 seconds; the existing ratio of the 16α-isomer in the mixture was calculated from $\alpha/(\alpha+\beta)$ after cutting out and weighing the singlet areas; then, the arithmetical mean of the ten ratios determined was calculated after the maximum and minimum values had been omitted.

Equilibration Experiment

Though sodium methoxide was at first examined as a base, it was not adopted because the system equilibrated within several minutes and chemical reactions other than epimerization occurred. As a result, sodium acetate was used as an ethanolic solution (0.0454 mol/l). II and IV were dissolved separately in acetone (0.02009 mol/l), and equilibrated at 21.3° by adding a definite amount of the sodium acetate solution. Periodically, aliquots were quenched by adding aqueous sodium chloride solution and analyzed by NMR. Since the base concentration is constant during a run, this reversible system is kinetically treated as pseudo-first order on the substrate using the following equations:

$$16\beta\text{-isomer} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 16\alpha\text{-isomer} \qquad (1)$$

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$$k_1(T^{-1}) = x_e \cdot Z/a \quad (2)$$

$$k_{-1}(T^{-1}) = Z - k_1 \quad (3)$$

$$K = k_1/k_{-1} \quad (4)$$

$$\Delta G(\text{kcal/mol}) = -RT \cdot \ln K \quad (5)$$

where a is the initial mol/l of II and IV, x is the mol/l of I and III at time t, x_e is the x at equilibrium, $Z=(2.303/t)\cdot\log[x_e/(x_e-x)]$, K is the equilibrium constant, and ΔG is the free energy difference. To confirm the values of x_e further, I and III were treated under the same conditions as II and IV, until the values coincided with those from the equilibration of II and IV. These were regarded as the x_e values (Tables II and IV). We confirmed that no side reaction other than the epimerization at C_{16} occurred during the reaction by TLC and NMR.

Results and Discussion

The results of the equilibration experiment are listed in Tables I—IV where $k_{\alpha-SAc}$, $k_{\beta-SAc}$, $k_{\alpha-SEt}$, and $k_{\beta-SEt}$ are the rates of epimerization of compounds I, II, III, and IV, respectively.

Table I. Equilibration of 16β-Acetylthioestrone Methyl Ether (II)
(AcONa–EtOH–acetone, 21.3°, a=0.01116 mol/l)

t (sec)	16α-isomer (%)	$x\times10^3$(mol/l)	$k_{\beta-SAc}\times10^5$(sec^{-1})	$k_{\alpha-SAc}\times10^5$(sec^{-1})
600	4.06	0.453	7.357	20.99
1500	9.02	1.007	7.393	21.10
2700	13.91	1.552	7.380	21.06
4800	19.34	2.158	7.393	21.10
21600	25.95	2.896		
39600	25.94	2.895		

Table II. Equilibration of 16α-Acetylthioestrone Methyl Ether (I)
(AcONa–EtOH–acetone, 21.3°, a=0.01116 mol/l)

t (sec)	16α-isomer (%)	$x\times10^3$(mol/l)
21600	25.94	2.895
39600	25.95	2.896

Table III. Equilibration of 16β-Ethylthioestrone Methyl Ether (IV)
(AcONa–EtOH–acetone, 21.3°, a=0.01116 mol/l)

t (sec)	16α-isomer (%)	$x\times10^3$(mol/l)	$k_{\beta-SEt}\times10^6$(sec^{-1})	$k_{\alpha-SEt}\times10^6$(sec^{-1})
21600	8.94	0.998	4.816	9.504
73800	21.95	2.450	4.823	9.517
157200	30.07	3.356	4.839	9.451
230400	32.41	3.617	4.843	9.557
352800	33.63	3.753		
370800	33.62	3.752		

Table IV. Equilibration of 16α-Ethylthioestrone Methyl Ether (III)
(AcONa–EtOH–acetone, 21.3°, a=0.01116 mol/l)

t (sec)	16α-isomer (%)	$x\times10^3$(mol/l)
352800	33.65	3.755
370800	33.63	3.753

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These tables show that equilibrium in both acetylthio- and ethylthio-estrones involves the predominant formation of isomers of the 16β-configuration (74.1% of 16β-isomer in acetylthioestrone and 66.4% of 16β-isomer in ethylthio-derivatives).

From Tables I and III,

$$k_{\alpha\text{-SAc}} = (21.06 \pm 0.07) \times 10^{-5}\ \text{sec}^{-1}$$
$$k_{\beta\text{-SAc}} = (7.38 \pm 0.02) \times 10^{-5}\ \text{sec}^{-1}$$
$$k_{\alpha\text{-SEt}} = (9.51 \pm 0.06) \times 10^{-6}\ \text{sec}^{-1}$$
$$k_{\beta\text{-SEt}} = (4.83 \pm 0.01) \times 10^{-6}\ \text{sec}^{-1}$$

then,

$$K_{SAc} = 0.35,\ K_{SEt} = 0.51$$
$$\Delta G_{SAc} = +0.614\ \text{kcal/mol}$$
$$\Delta G_{SEt} = +0.396\ \text{kcal/mol}^{4)}$$

These data clearly indicate that in 16-sulfur-substituted steroids, 16β-isomers are more stable than 16α-isomers. Therefore, we conclude that in the reaction of 16β-bromo-17-ketosteroids with sulfur nucleophiles, 16α-sulfur-substituted steroids are primarily formed as kinetically controlled products and isomerized to the more stable 16β-isomers during the reaction owing to the basicity of the nucleophiles.

As mentioned above, ethylthiosteroids were epimerized more easily than acetylthiosteroids during the substitution reaction. However, comparison of the k values of acetylthio- and ethylthio-estrones having the same configuration at C_{16} gave:

$$k_{\alpha\text{-SAc}}/k_{\alpha\text{-SEt}} = 22.1$$
$$k_{\beta\text{-SAc}}/k_{\beta\text{-SEt}} = 15.3$$

Thus, the acetylthiosteroids are epimerized faster than the ethylthiosteroids in both the 16α- and 16β-series. This discrepancy can be explained by noting that sodium thioethoxide is a stronger base than potassium thiolacetate.

The fact that the acetylthiosteroids epimerize faster than the ethylthiosteroids can be explained by the greater contribution of the electron-accepting conjugation[5] involving the sulfur atom which stabilizes the adjacent C_{16} carbanion formed during the isomerization in

TABLE V. NMR Data for 16-Substituted Epiandrosterone Derivatives

Compound	C_{13}–Me		C_{16}–H		
	Chem. shift (δ)	$\Delta^{a)}$ (ppm)	Configuration	Chem. shift (δ)	$\lvert J_{AX}+J_{BX}\rvert$ (Hz)
Epiandrosterone acetate	0.85	—			
16α-Br	0.89	0.04	β	4.51	8.0(dif. q)
16β-Br	1.07	0.22	α	4.13	17.0(t)
16α-SEt	0.88	0.03	β	3.45	9.0(m)
16β-SEt	0.99	0.14	α	2.97	15.5(t)
16α-SAc	0.96	0.11	β	4.29	11.0(q)
16β-SAc	0.86	0.01	α	3.99	17.0(t)

a) down field shift caused by a C_{16}-substituent

4) In sulfur-substituted cyclohexanes, ΔG_{SMe} is 0.7 and ΔG_{SPh} is 0.8 kcal/mol. See E.L. Eliel, N.L. Allinger, S.A. Angyal, and G.A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, 1965, Chapt. 7.

5) D.P. Craig, A. Maccoll, R.S. Nyholm, L.E. Orgel, and L.E. Sutton, *J. Chem. Soc.* **1954**, 332.

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Table VI. NMR Data for 16-Substituted Estrone Derivatives

Compound	13–Me		C_{16}–H		
	Chem. shift (δ)	$\Delta^{a)}$ (ppm)	Configuration	Chem. shift (δ)	$\lvert J_{AX}+J_{BX}\rvert$ (Hz)
Estrone methyl ether	0.91	—			
16α-Br	0.94	0.03	β	4.58	7.5(q)
16β-Br	1.11	0.20	α	4.15	17.5(t)
16α-SEt	0.95	0.04	β	3.55	8.5(q)
16β-SEt	1.03	0.12	α	3.16	17.0(t)
16α-SAc	1.01	0.10	β	4.38	11.0(q)
16β-SAc	0.92	0.01	α	4.09	17.0(t)

a) down field shift caused by a C_{16}-substituent

the acetylthiosteroids than in the ethylthiosteroids. The electron-withdrawing acetyl group attached to the sulfur atom may assist the effective overlapping of this 2p-3d π bond with electronic advantage for proton removal at C_{16}.

NMR Spectra of 16-Substituted 17-Ketosteroids

The 16-substituted 17-ketosteroids prepared in this study showed characteristic signal patterns without exception in the region of the C_{16} proton and C_{13}-methyl groups according to the configuration at C_{16}. The data obtained are summarized in Tables V and VI.

For the C_{13}-methyl:

i) The 16β-bromine or -ethylthio group shifts the singlet of C_{13}-methyl downfield by 0.12—0.22 ppm, while the corresponding 16α-substituents shift it by 0.04 ppm.

ii) The 16β-acetylthio group shifts the singlet of C_{13}-methyl downfield by only 0.01 ppm owing to an "acetylation shift."[6]

For the C_{16} proton:

i) In epimers of the same substituents at C_{16}, the 16α-H signal is always in higher field than that of 16β-H.

ii) The splitting pattern of 16α-H is apparently a triplet and its $\lvert J_{AX}+J_{BX}\rvert$ is in the range of 15.5—17.5 Hz.

iii) The splitting pattern of 16β-H is apparently a quartet and its $\lvert J_{AX}+J_{BX}\rvert$ is in the range of 7.5—11.0 Hz.

iv) In epimers of the same substituents at C_{16}, $\lvert J_{AX}+J_{BX}\rvert$ of 16α-H is larger than that of 16β-H.

The regularity mentioned is useful for the examination of the configuration at C_{16} of 16-substituted 17-ketosteroids.

Experimental[7]

16α-Acetylthioestrone Methyl Ether (I)——To a solution of 250 mg of 16β-bromoestrone methyl ether in 6 ml of acetone, a solution of 160 mg of AcSK in 0.75 ml of H_2O was added and the mixture was stirred at 40° for 0.5 hr. Water was added and the mixture was extracted with $CHCl_3$. The crude crystals obtained on evaporation of the solvent were recrystallized from acetone–MeOH to give 220 mg (89%) of colorless plates, mp 169—170°. *Anal.* Calcd. for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.41; H, 7.33; S, 8.76.

6) *a*) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962); *b*) Y. Kawazoe, Y. Sato, T. Okamoto, and K. Tsuda, *ibid.*, **11**, 328 (1963); *c*) T. Okamoto and Y. Kawazoe, *ibid.*, **11**, 643 (1963); *d*) K. Tori and T. Komeno, *Tetrahedron*, **21**, 309 (1965); *e*) K. Takeda, T. Komeno, J. Kawanami, S. Ishihara, H. Kadokawa, H. Tokura, and H. Itani, *ibid.*, **21**, 329 (1965).

7) Melting points are uncorrected. IR spectra were taken on a JASCO IR-S spectrometer and NMR spectra on a Varian A-60A instrument in a $CDCl_3$ solution with tetramethylsilane as an internal standard.

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IR ν_{max}^{Nujol} cm^{-1}: 1739 (C=O), 1692 (SAc). NMR δ: 1.01 (3H, s, 13-Me), 2.39 (3H, s, SAc), 3.78 (3H, s, OMe), 4.38 (1H, q, $|J_{AX}+J_{BX}|=11.0$ Hz, 16β-H).

16β-Acetylthioestrone Methyl Ether (II)——To a solution of 121 mg of 16α-bromoestrone methyl ether in 6 ml of acetone, 46 mg of AcSK was added and the suspension was stirred at room temperature for 40 min. Water was added and the mixture was extracted with ether. The solvent was evaporated and the crude crystals were recrystallized from acetone–MeOH giving 105 mg (88%) of colorless prisms, mp 195.5—197°. *Anal.* Calcd. for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.34; H, 7.40; S, 8.94. IR ν_{max}^{Nujol} cm^{-1}: 1738 (C=O), 1689 (SAc). NMR δ: 0.92 (3H, s, 13-Me), 2.39 (3H, s, SAc), 3.78 (3H, s, OMe), 4.09 (1H, t, $|J_{AX}+J_{BX}|=17.0$ Hz, 16α-H).

16α-Ethylthioestrone Methyl Ether (III)——To a solution of 150 mg of 16β-bromoestrone methyl ether in 12.5 ml of acetone, 38 mg of EtSNa was added under ice-cooling and the suspension was stirred for 15 min. The reaction mixture was diluted with water and extracted with ether. The crystals obtained were recrystallized from ether–hexane to give 115 mg (81%) of colorless needles, mp 129.5—130°. *Anal.* Calcd. for $C_{21}H_{28}O_2S$: C, 73.21; H, 8.19; S, 9.31. Found: C, 73.14; H, 8.24; S, 9.05. IR ν_{max}^{Nujol} cm^{-1}: 1727 (C=O). NMR δ: 0.95 (3H, s, 13-Me), 1.29 (3H, t, $J=7.5$ Hz, $SCH_2\underline{CH_3}$), 2.80 (2H, q, $J=7.5$ Hz, $S\underline{CH_2}CH_3$), 3.55 (1H, q, $|J_{AX}+J_{BX}|=8.5$ Hz, 16β-H), 3.78 (3H, s, OMe).

16β-Ethylthioestrone Methyl Ether (IV)——To a solution of 150 mg of 16α-bromoestrone methyl ether in 7 ml of acetone, 42 mg of EtSNa was added and the mixture was stirred at 12° for 0.5 hr. Water was added, then the mixture was extracted with ether. The crystals obtained were recrystallized from ether to give 121 mg (85%) of colorless prisms, mp 128.5—129.5°. *Anal.* Calcd. for $C_{21}H_{28}O_2S$: C, 73.21; H, 8.19; S, 9.31. Found: C, 73.24; H, 8.20; S, 9.17. IR ν_{max}^{Nujol} cm^{-1}: 1726 (C=O). NMR δ: 1.03 (3H, s, 13-Me), 1.29 (3H, t, $J=7.5$ Hz, $SCH_2\underline{CH_3}$), 2.82 (2H, q, $J=7.5$ Hz, $S\underline{CH_2}CH_3$), 3.16 (1H, t, $|J_{AX}+J_{BX}|=17.0$ Hz, 16α-H), 3.76 (3H, s, OMe).

16α-Acetylthioepiandrosterone Acetate——To a solution of 103 mg of 16β-bromoepiandrosterone acetate in 2.5 ml of acetone, 32 mg of AcSK was added and the suspension was stirred under ice-cooling for 40 min, diluted with water, then extracted with ether. The crude product obtained was crystallized from MeOH to afford 84 mg (83%) of colorless prisms. Recrystallization of part of the crystals from hexane gave colorless needles, mp 142—143.5°. *Anal.* Calcd. for $C_{23}H_{34}O_4S$: C, 67.95; H, 8.43; S, 7.87. Found: C, 67.92; H, 8.48; S, 7.74. IR ν_{max}^{Nujol} cm^{-1}: 1742 (C=O), 1730 (OAc), 1690 (SAc). NMR δ: 0.84 (3H, s, 10-Me), 0.96 (3H, s, 13-Me), 1.99 (3H, s, OAc), 2.35 (3H, s, SAc), 4.29 (1H, q, $|J_{AX}+J_{BX}|=11.0$ Hz, 16β-H), 4.70 (1H, br.s, 3α-H).

16β-Acetylthioepiandrosterone Acetate——To a solution of 103 mg of 16α-bromoepiandrosterone acetate in 2.5 ml of acetone, 32 mg of AcSK was added and the suspension was stirred under ice-cooling for 1 hr, diluted with water, then extracted with ether. The crude crystals were recrystallized from MeOH to give 75 mg (74%) of colorless prisms, mp 154—156°. *Anal.* Calcd. for $C_{23}H_{34}O_4S$: C, 67.95; H, 8.43; S, 7.87. Found: C, 68.03; H, 8.43; S, 7.87. IR ν_{max}^{Nujol} cm^{-1}: 1740 (C=O), 1732 (OAc), 1696 (SAc). NMR δ: 0.86 (6H, s, 10-Me, 13-Me), 2.00 (3H, s, OAc), 2.38 (3H, s, SAc), 3.99 (1H, t, $|J_{AX}+J_{BX}|=17.0$ Hz, 16α-H), 4.67 (1H, br.s, 3α-H).

16α-Ethylthioepiandrosterone Acetate——A solution of 110 mg of 16β-bromoepiandrosterone acetate in 6 ml of acetone was chilled to −14°, then 27 mg of EtSNa was added. The mixture was stirred 3.5 min, diluted with water, and extracted with ether. Recrystallization of the crude crystals obtained from ether–MeOH gave 73 mg (70%) of colorless plates, mp 107—108°. *Anal.* Calcd. for $C_{23}H_{36}O_3S$: C, 70.37; H, 9.24; S, 8.17. Found: C, 70.20; H, 9.24; S, 8.16. IR ν_{max}^{Nujol} cm^{-1}: 1736 (C=O), 1724 (OAc). NMR δ: 0.84 (3H, s, 10-Me), 0.88 (3H, s, 13-Me), 1.26 (3H, t, $J=7.5$ Hz, $SCH_2\underline{CH_3}$), 2.00 (3H, s, OAc), 2.75 (2H, q, $J=7.5$ Hz, $S\underline{CH_2}CH_3$), 3.45 (1H, m, $|J_{AX}+J_{BX}|=9.0$ Hz, 16β-H), 4.83 (1H, br.s, 3α-H).

16β-Ethylthioepiandrosterone Acetate——To a solution of 110 mg of 16α-bromoepiandrosterone acetate in 6 ml of acetone, 27 mg of EtSNa was added under ice-cooling and the suspension was stirred for 10 min, diluted with water, then extracted with ether. The crude crystals obtained were recrystallized from ether–hexane to give 88 mg (84%) of colorless plates, mp 126—128°. *Anal.* Calcd. for $C_{23}H_{36}O_3S$: C, 70.37; H, 9.24; S, 8.17. Found: C, 70.40; H, 9.22; S, 8.11. IR ν_{max}^{Nujol} cm^{-1}: 1738 (C=O), 1728 (OAc). NMR δ: 0.85 (3H, s, 10-Me), 0.99 (3H, s, 13-Me), 1.28 (3H, t, $J=7.5$ Hz, $SCH_2\underline{CH_3}$), 2.00 (3H, s, OAc), 2.63 (2H, q, $J=7.5$ Hz, $S\underline{CH_2}CH_3$), 2.97 (1H, t, $|J_{AX}+J_{BX}|=15.5$ Hz, 16α-H), 4.70 (1H, br.s, 3α-H).

Equilibration Experiment——Acetone was distilled in the presence of $KMnO_4$ and the distillate was dried over K_2CO_3 and redistilled: bp 56.5°. EtOH, bp 78.5°, was distilled after metallic Na was added to 99.5% EtOH. For the base solution, an appropriate amount of $AcONa\cdot 3H_2O$, recrystallized twice from water, was dissolved at 21.3° in EtOH to give a 0.0454 mol/l solution. For the substrate solution, an appropriate amount of thiosteroid was dissolved at 21.3° in acetone to give a 0.02009 mol/l solution. Base and substrate solutions were immersed in a bath at 21.3° for 0.5 hr, then mixed. The final concentrations were 0.0202 and 0.01116 mol/l, respectively. The mixtures were stirred at 21.3°±0.1° and the reaction was stopped at the time indicated in Tables I—IV by adding aqueous NaCl solution. The mixture was extracted with ether and the ether layer was washed three times with water, dried over Na_2SO_4 and evaporated. The residue was dried *in vacuo* over P_2O_5 to give 17—18 mg of a C_{16}-epimeric mixture, which was submitted to NMR determination.

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