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90. Ken'ichi Takeda, Taichiro Komeno, Norio Tokutake, and Yoshiko Kanematsu: Bile Acids and Steroids. XXXII. Thiosteroids. (17*1). Synthesis of 16β-Acetylthio- and 16β-Alkylthio-estratriene Derivatives.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**2)

In a recent paper of this series,[1] it was reported that the treatment of 16-bromo-17-ketosteroids with sulfur containing nucleophiles such as potassium alkylmercaptides or potassium thiolacetate gave the corresponding 16β-mercaptosteroid derivatives. The ready availability of 4-methylestra-1,3,5(10)-trien-17β-ol[2] (II) and 1-methylestradiol[3] from testosterone prompted us to synthesize additional A-ring aromatic thiosteroids containing a sulfur atom at C-16.

4-Methylestra-1,3,5(10)-trien-17β-ol (II) was prepared from testosterone propionate (I) by three step synthesis; introduction of 1,2-double bond by dichlorodicyano-*p*-benzoquinone-dehydrogenation, reduction with lithium aluminum hydride, and subsequent dienol-benzene rearrangement by treatment with ethanolic hydrochloric acid. By removal of testosterone, the by-product produced by 1,4-addition[4] of lithium aluminum

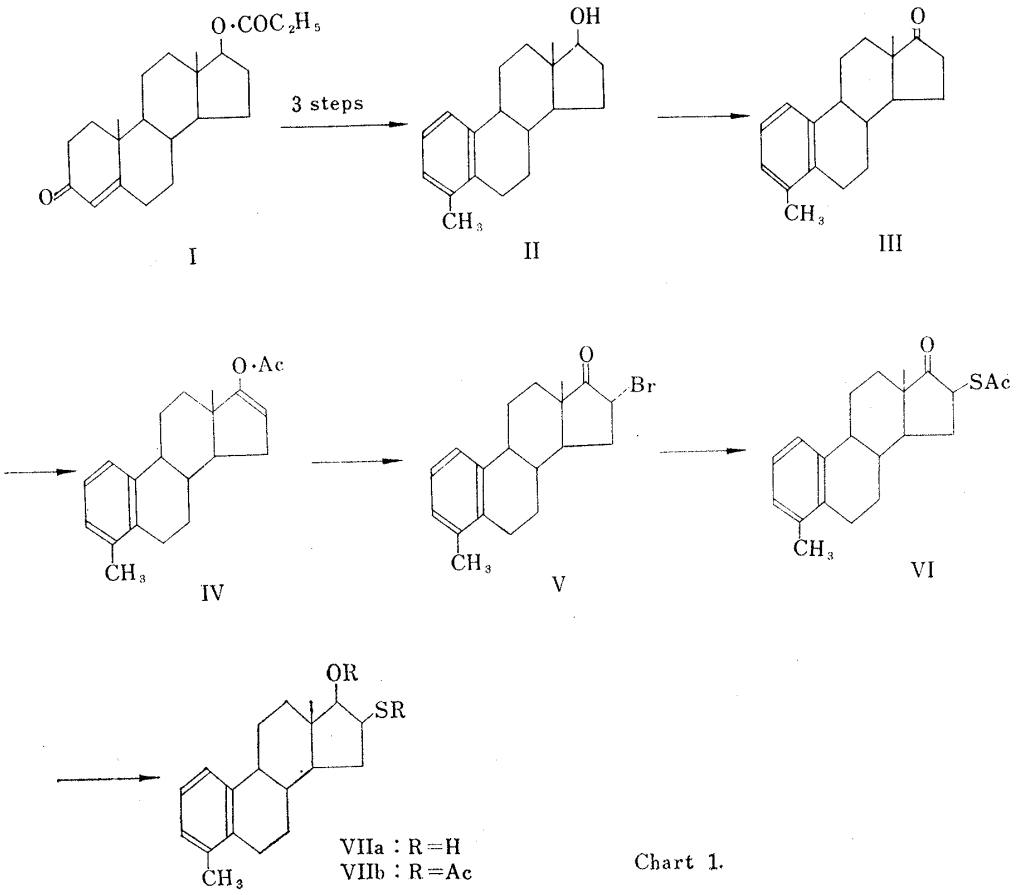

Chart 1.

*1 Part XXXI. (16). C. Djerassi, K. Takeda, *et al.*: Tetrahedron, in press.
*2 Fukushima-ku, Osaka, Japan (武田健一, 米野太一郎, 徳竹伯夫, 兼松佳子).
1) Part XXV. Thiosteroids (10).: This Bulletin, **12**, 905 (1964).
2) M. J. Gentles, J. B. Moss, H. L. Herzog, E. B. Hershberg: J. Am. Chem. Soc., **80**, 3702 (1958).
3) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, St. Kaufmann: *Ibid.*, **72**, 4540 (1950).
4) H. Dannenberg, H.-G. Neumann: Ann., **646**, 148 (1961).

hydride to 1-dehydrotestosterone, with alumina chromatography the aimed 4-methylestra-1,3,5(10)-trien-17β-ol (II) was obtained in 69% over-all yield. The ketone (III), obtained by chromic acid oxidation of II in acetone was converted to 4-methylestra-1,3,5(10),16-tetraen-17-ol acetate (IV), m.p. 113~114°, by the action of isopropenyl acetate with a catalytic amount of sulfuric acid. The enol acetate was brominated with bromine to give 4-methyl-16α-bromoestra-1,3,5(10)-trien-17-one (V), m.p. 163~164.5°. Its nuclear magnetic resonance spectrum shows a triplet-like signal of the C-16β hydrogen at 5.43 τ ($J_{AX}+J_{BX}=10.0$ c.p.s.)*3 besides the proton signals of 4-methyl and 18-methyl groups at 7.79 and 9.09 τ, respectively.

Treatment of this bromoketone (V) in acetone with potassium thiolacetate at room temperature afforded the corresponding 16β-acetylthioketone (VI), m.p. 211~213°, in 83% yield. The infrared spectrum of this compound exhibits the characteristic absorptions of thiolacetate at 1693 and 1128 cm^{-1}, while its nuclear magnetic resonance spectrum displays the proton signals of three methyl groups at 9.10 (18-methyl), 7.77 (4-methyl), and 7.61 τ (CH_3CO-S). In addition the proton signal of the C-16α hydrogen shows again a triplet-like pattern ($J_{AX}+J_{BX}=17.0$ c.p.s.) at 5.91 τ.*3

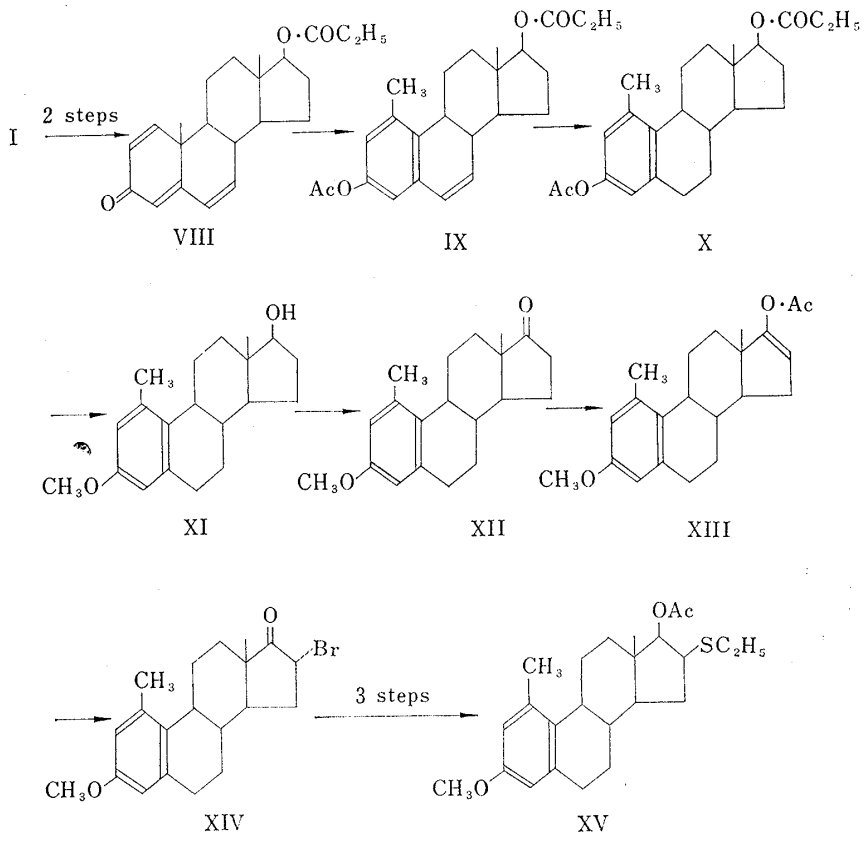

Chart 2.

*3 Although the proton signals at C_{16} should be observed as X part of ABX type, AB protons could not be fully assigned and hence J_{AB} and δ_{AB} were not obtained in these cases. Since Bhacca and Williams had been mentioned, the observed splittings do not reflect the real J_{AX} and $J_{BX'}$ unless δ_{AB}/J_{AB} was large. (N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry. Illustration from the steroid field," Holden-Day, Inc., 135 (1964)). However, both 16-protons of the epimers of 3β-acetoxy-16-bromo-5α-androstan-17-one show triplet-like patterns (*i. e.* 16β-bromo compound : 5.89 τ, $J_{AX}+J_{BX}=17.5$ c.p.s. 16α-bromo compound : 5.46 τ, $J_{AX}+J_{BX}=7.5$ c.p.s.).

The acetylthioketone (Ⅵ) was reduced with lithium aluminum hydride to give the mercaptol (Ⅶa), which by acetylation with pyridine and acetic anhydride gave 4-methyl-16β-acetylthioestra-1,3,5(10)-trien-17β-ol acetate (Ⅶb), m.p. 178.5~180°.

The synthesis of 1-methyl-3-methoxy-16β-ethylthioestra-1,3,5(10)-trien-17β-ol acetate (XV) was further undertaken. Testosterone propionate (I) was converted to 17β-hydroxyandrosta-1,4,6-trien-3-one propionate (Ⅷ)[4] in two steps. Dienone-phenol rearrangement of this trienone gave 1-methyl-3-acetoxyestra-1,3,5(10),6-tetraen-17β-ol propionate (Ⅸ), which was hydrogenated over palladium-on-charcoal catalyst to afford 1-methyl-3-acetoxyestra-1,3,5(10)-trien-17β-ol propionate (X) in nearly quantitative yield. Alkaline hydrolysis and simultaneous treatment with dimethyl sulfate of X gave 1-methylestradiol 3-methyl ether (Ⅺ) in 91% yield. 1-Methylestrone methyl ether (Ⅻ) was obtained by chromic acid oxidation of Ⅺ and was enol acetylated with isopropenyl acetate to 1-methyl-3-methoxyestra-1,3,5(10),16-tetraen-17-ol acetate (XIII), m.p. 87.5~88.5°. Bromination of this enol acetate with bromine afforded the corresponding bromoketone (XIV), m.p. 152.5~153.5°. The nuclear magnetic resonance spectrum of this compound showed the β-configuration of the C-16 hydrogen (5.45 τ as a triplet-like, $J_{AX}+J_{BX}=8.0$ c.p.s.).*3

The bromoketone (XIV) was converted with potassium ethylmercaptide, as described in the earlier paper[1] to the 16β-ethylthio derivative, which was reduced with lithium alumi-num hydride and acetylated to give 1-methyl-3-methoxy-16β-ethylthioestra-1,3,5(10)-trien-17β-ol acetate (XV), m.p. 86.5~87°.

Experimental*4

4-Methylesta-1,3,5(10)-trien-17β-ol (II)——A solution of 10.0 g. of testosterone propionate (I) in 350 ml. of anhyd. benzene was heated under reflux for 31 hr. with 7.3 g. of dichlorodicyano-*p*-benzoquinone. The resulted hydroquinone was removed by filtration and the filtrate was chromatographed over 120 g. of Al_2O_3 to yield 8.42 g. (84.7%) of 1-dehydrotestosterone propionate, m.p. 134~138°, from the benzene eluates. To a suspension of 2.5 g. of $LiAlH_4$ in 130 ml. of anhyd. ether was added 5.0 g. of this material in 250 ml. of anhyd. ether, and the mixture was heated under reflux for 3.5 hr. After usual treatment of the mixture, the reduction product was heated with a mixture of 130 ml. of 95% EtOH and 5 ml. of concd. HCl for 30 min. on a steam bath. The ethanolic solution was diluted with H_2O and extd. with ether. The ether layer was washed with 5% aq. Na_2CO_3, H_2O, dried over Na_2SO_4, and evaporated to give 4.09 g. of brown oil. The oil was chromatographed over 125 g. of Al_2O_3. The eluates with benzene-ether (95:5~90:10) were crystallized from ether yielding 3.20 g. (68.6% yield based on I) of colorless needles (II), m.p. 112~113°. From the eluates with benzene-ether (85:15) was obtained 1.56 g. of testosterone.

4-Methylestra-1,3,5(10)-trien-17-one (III)——To a solution of 2.77 g. of II in 100 ml. of purified acetone was added 2.57 ml. of Jones' reagent containing 0.66 g. of CrO_3 under ice-cooling. After dilution with H_2O, the precipitate was collected by filtration, washed with H_2O, and recrystallized from acetone to give 1.99 g. of colorless prisms (III), m.p. 183~184.5°. A further 0.11 g. of prism was obtained on Al_2O_3 chromatography of the mother liquor. $[\alpha]_D^{23.5}$ +143.3±2°(c=1.110). UV λ_{max} mμ (ε): 263.5 (300), 270 (270). IR ν_{max}^{Nujol} cm^{-1}: 1732. *Anal.* Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.99; H, 9.03.

4-Methylestra-1,3,5(10),16-tetraen-17-ol Acetate (IV)——A solution of 3.04 g. of III in 25 ml. of isopropenyl acetate and 2 ml. of catalyst solution (5 ml. of isopropenyl acetate and 0.1 ml. of concd. H_2SO_4) was heated under reflux for 1 hr. Approximately 10 ml. of the reagent was slowly distilled over a period of 2 hr., and additional 25 ml. of isopropenyl acetate and 2 ml. of catalyst solution were added to the residue. The solution was concentrated to one-half the volume by slow distillation for 2 hr., chilled, and diluted with ether. The ether solution was washed with 5% aq. $NaHCO_3$, H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed over 125 g. of Al_2O_3. On washing the column with petr. ether 2.61 g. of the enol acetate (IV) was obtained, which was recrystallized from acetone-MeOH (9:1) to give 2.3 g. of colorless prisms, m.p. 113~114°, $[\alpha]_D^{23}$ +81.9±2°(c=1.046). UV λ_{max}

*4 All melting points are uncorrected. IR spectra were measured with a Koken Infrared Spectrophotometer, Model DS-301, and UV spectra were taken in 95% EtOH with a Hitachi Recording Ultraviolet Spectrophotometer, EPS-2. Optical rotations were measured in $CHCl_3$ with a Rudolf photoelectronic Polarimeter, Model 200, and nuclear magnetic resonance spectra were obtained in $CDCl_3$ containing tetramethysilane as an internal reference.

mμ (ε): 262.5 (340), 270 (270). IR ν_{max}^{Nujol} cm^{-1}: 1755, 1206 (enol acetate). *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.13; H, 8.35.

4-Methyl-16α-bromoestra-1,3,5(10)-trien-17-one (V)——A suspension of 1.8 g. of anhyd. K_2CO_3 in a solution of 2.30 g. of IV in 45 ml. of CCl_4 was stirred at −5~0°, while 1.19 g. of bromine in 13.8 ml. of CCl_4 was added over a period of 5 min. Aqueous $NaHSO_3$ solution was added to the light brown solution and the mixture was extd. with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from MeOH to give 2.25 g. of colorless prisms (V), m.p. 163~164.5°, $[\alpha]_D^{23.5}$ +124.0±2° (c=1.103). UV λ_{max} mμ (ε): 263.4 (320), 270 (240), 316 (120). IR ν_{max}^{Nujol} cm^{-1}: 1746. *Anal.* Calcd. for $C_{19}H_{23}OBr$: C, 65.71; H, 6.68; Br, 23.01. Found: C, 65.87; H, 6.70; Br, 23.18.

4-Methyl-16β-acetylthioestra-1,3,5(10)-trien-17-one (VI)——To a solution of 1.99 g. of V in 70 ml. of dried acetone, 1.2 g. of KSAc was added, and the suspension was stirred for 31/3 hr. at room temperature. Approximately 250 ml. of H_2O was added, and the precipitate was collected and recrystallized from acetone to 1.63 g. of colorless prisms (VI), m.p. 211~213°, $[\alpha]_D^{23.5}$ +134.4±2° (c=1.096). UV λ_{max} mμ (ε): 237 (2150), 263.5 (440), 270 (330), 300 (170). IR ν_{max}^{Nujol} cm^{-1}: 1740 (C=O), 1693, 1128 (S-Ac). *Anal.* Calcd. for $C_{21}H_{26}O_2S$: C, 73.64; H, 7.65; S, 9.36. Found: C, 73.69; H, 7.72; S, 9.40.

4-Methyl-16β-acetylthioestra-1,3,5(10)-trien-17β-ol Acetate (VIIb)——A solution of 1.82 g. of VI in 100 ml. of anhyd. tetrahydrofuran was added dropwise to a stirred suspension of 1.1 g. of $LiAlH_4$ in 100 ml. of anhyd. ether. The mixture was heated under reflux for 3.5 hr. and worked up in the usual manner to afford a white powder (VIIa). This material was acetylated without further purification by treating with 30 ml. of pyridine and 15 ml. of Ac_2O for 2.5 hr. on a steam bath. The crude acetate was recrystallized from acetone to give 1.78 g. of colorless needles (VII), m.p. 178.5~180°, $[\alpha]_D^{22.5}$ +78.9±2° (c=0.778). UV λ_{max} mμ (ε): 234 (5290), 263 (420), 270 (280). IR ν_{max}^{Nujol} cm^{-1}: 1747, 1235 (O-Ac), 1687, 1137 (S-Ac). *Anal.* Calcd. for $C_{23}H_{30}O_3S$: C, 71.46; H, 7.82; S, 8.30. Found: C, 71.70; H, 7.84; S, 8.61.

17β-Hydroxyandrosta-1,4,6-trien-3-one Propionate (VIII)——This compound was prepared by the method given in the literature[3] in 62.9% yield from I. Recrystallization from acetone–hexane gave light yellow prisms, m.p. 139.5~141°, $[\alpha]_D^{25}$ −4.3±2° (c=1.015). UV λ_{max} mμ (ε): 223 (11000), 258 (9700), 299~300 (13400). IR ν_{max}^{Nujol} cm^{-1}: 1651, 1622, 1604, 1577 (trienone system). *Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.91; H, 8.44.

1-Methyl-3-acetoxyestra-1,3,5(10),6-tetraen-17β-ol Propionate (IX)——A mixture of 2.1 g. of VIII, 0.5 g. of *p*-TsOH, and 50 ml. of Ac_2O was heated for 5 hr. on a steam bath. The chilled solution was poured into H_2O and swirled. The precipitate was filtered, dried, and chromatographed over Al_2O_3. From the eluates with petr. ether–benzene (75:25) was obtained 2.11 g. of IX, m.p. 105~110°. Recrystallization from hexane gave colorless silky needles, m.p. 117~118°, $[\alpha]_D^{25}$ −141.5±2° (c=1.085). UV λ_{max} mμ (ε): 223.5 (31600), 228.5 (28500), 266.2 (9500). IR ν_{max}^{Nujol} cm^{-1}: 1769 (φ-OAc), 1727 (O-COEt), 1590 (aromatic ring). *Anal.* Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.90. Found: C, 75.08; H, 7.97.

1-Methyl-3-acetoxyestra-1,3,5(10)-trien-17β-ol Propionate (X)——A solution of 10 g. of IX in 150 ml. of EtOAc was shaken in the presence of H_2 with 2 g. of 10% Pd-C catalyst for 2 hr. The reduction product was recrystallized from EtOAc to give 9.73 g. of colorless plates, m.p. 132.5~133°, $[\alpha]_D^{23}$ +104.8±2° (c=1.065). UV λ_{max} mμ (ε): 269.5 (390), 276.5 (340). IR ν_{max}^{Nujol} cm^{-1}: 1762 (φ-OAc), 1731 (O-COEt), 1602, 1588 (aromatic rihg). *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.12; H, 8.41.

1-Methylestradiol 3-Methyl Ether (XI)——To a warm solution of 2 g. of X in 40 ml. of MeOH was added 20 ml. of 40% aq. KOH and the mixture was heated on a steam bath for 20 min. Adding 40% aq. KOH in small portions so as to keep the medium alkaline, 60 ml. of $(MeO)_2SO_2$ was dropped over a period of 2 hr. with heating and stirring. The reaction mixture was chilled and diluted with H_2O. The precipitate was filtered, washed, and dried to give 1.42 g. of XI. Recrystallization from ether–hexane gave colorless prisms, m.p. 119~120°, $[\alpha]_D^{25}$ +151.9±2° (c=1.041). UV λ_{max} mμ (ε): 279.5 (2210), 286 (2200). IR ν_{max}^{Nujol} cm^{-1}: 3360 (OH), 1275, 1265 (anisole ring). *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.11; H, 9.40.

1-Methylestrone Methyl Ether (XII)——By oxidation of 24.4 g. of XI as described above for III, 20.25 g. of XII was obtained as colorless plates, m.p. 128.5~129.5°, $[\alpha]_D^{24.5}$ +237.2±2° (c=1.109). UV λ_{max} mμ (ε): 279.5 (1680), 286.5 (1720). IR ν_{max}^{Nujol} cm^{-1}: 1737 (C=O). *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.69; H, 8.93.

1-Methyl-3-methoxyestra-1,3,5(10),16-tetraen-17-ol Acetate (XIII)——Enol acetylation of XII was carried out in a similar manner as described for IV to give a 62% yield. Recrystallization from MeOH gave colorless plates, m.p. 87.5~88.5°, $[\alpha]_D^{23}$ +176.8±2° (c=1.059). UV λ_{max} mμ (ε): 279.5 (1640), 287 (1670). IR ν_{max}^{Nujol} cm^{-1}: 1748, 1208 (enol acetate). *Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.61; H, 8.40.

1-Methyl-16α-bromoestrone Methyl Ether (XIV)——XIII was brominated as in the foregoing experiment to give 67.3% yield. Recrystallization from benzene gave colorless needles, m.p. 152.5~153.5°, $[\alpha]_D^{23}$ +185.9±2° (c=1.048). UV λ_{max} mμ (ε): 279.5 (1640), 286.5 (1700), 312 (150). IR ν_{max}^{Nujol} cm^{-1}: 1752. *Anal.* Calcd. for $C_{20}H_{25}O_2Br$: C, 63.66; H, 6.68; Br, 21.18. Found: C, 63.87; H, 6.83; Br, 21.05.

1-Methyl-3-methoxy-16β-ethylthioestra-1,3,5(10)-trien-17β-ol Acetate (XV)——Conversion of XIV to the corresponding ethylthio derivative was carried out according to the procedure described in the earlier paper.[1] The product was reduced with $LiAlH_4$ and, without further purification, acetylated by treating with pyridine and Ac_2O to give 2.25 g. of XV. Recrystallization from MeOH yielded colorless plates, m.p. 86.5~87°, $[\alpha]_D^{24}$ +149.9±2° (c=1.030). UV λ_{max} mμ (ε): 226.5 (9650), 279 (1630), 286 (1680). IR ν_{max}^{Nujol} cm^{-1}: 1736, 1237 (O-Ac). *Anal.* Calcd. for $C_{24}H_{34}O_3S$: C, 71.61; H, 8.51; S, 7.95. Found: C, 71.49; H, 8.54; S, 7.68.

Summary

Some estratrienones having a sulfur atom at C-16 were prepared by substitution of 16α-bromo-17-ketosteroids with sulfur nucleophiles.

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91. Ken'ichi Takeda, Ariyoshi Shimaoka, Mitsutaka Iwasaki, and Hitoshi Minato: Studies on the Steroidal Components of Domestic Plants. XLVIII.*1 Components of *Chionographis japonica* Maxim. (1).

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**2)

Chionographis japonica Maxim. is a pernnial herb belonging to Liliaceae and its components have not hitherto been investigated. In this paper, we will report on the steroidal components of this plant. The dried whole plant (1.2 kg.) was extracted with methanol, and the methanol extract was saponified with 5% sulfuric acid in methanol and extracted with benzene. As the thin-layer chromatogram of this extract showed many spots, it was chromatographed on alumina to give the ten-compounds (A~K: except I), shown in Table I.

Table I. Fractions obtained from the Benzene Extract

		Rf value of thin-layer chromatogram[a]	Color test[b]	Yield (mg.)
Compound	A (diosgenin I)	0.93	yellow	560
	B (bethogenin IIa)	0.86	〃	74
	C (β-sitosterol III)	0.80	blue-violet	26
	D (pennogenin IV)	0.75	yellow	130
	E (unknown)	0.73	reddish-purple	50
	F (kryptogenin Va)	0.69	orange-yellow	32
	G (chiogralactone)	0.65	reddish-purple	62
	H (unknown)	0.41	red	85
	J (〃)	0.20	〃	41
	K (〃)	0.15	blue-violet	385

a) solvent system: $CHCl_3$-acetone-acetic acid=27:2:1
b) color test: 5% cinnamic aldehyde in ethanol-sulfuric acid

*1 Part XLVII. T. Okanishi, A. Akahori, F. Yasuda: This Bulletin, 13, 545 (1965).
*2 Fukushima-ku, Osaka (武田健一，島岡有昌，岩崎光隆，湊　均).