Chem. Pharm. Bull. 26(6)1718—1728(1978)

UDC 547.92.04.09 : 615.357.011.5.015.11

Synthesis and Antiandrogenic Activity of 16β-Substituted-17β-hydroxysteroids

GIICHI GOTO, KOUICHI YOSHIOKA, KENTARO HIRAGA, MICHIO MASUOKA, RYO NAKAYAMA, and TAKUICHI MIKI

Central Research Division, Takeda Chemical Industries, Ltd.[1]

(Received November 2, 1977)

In order to examine the antiandrogenic activity, a series of 16β-substituted-17β-hydroxysteroids (**9** and **16**) were synthesized by stereoselective introduction of β-substituents at position 16 of steroids. The corresponding 6-chloro-16β-substituted-17β-hydroxysteroids (**20** and **28**) and 1,2α-methylene derivative (**36**) were also prepared.

Among these new steroids synthesized, 17β-hydroxy-16β-ethylestr-4-en-3-one (**9b**: **TSAA-291**) was found to have the most potent antiandrogenic activity with very weak side effects and also found to be useful for a treatment of the benign prostatic hypertrophy.

Keywords——16β-substituted-estrane; 16β-substituted-androstane; 16β-substituted-6-chloroandrostane; antiandrogen; structure-activity relationship; prostatic hypertrophy

During the course of endocrinological studies on synthetic steroids, 17β-hydroxy-13β-isopropylgon-4-en-3-one (**1**)[2] was found to have considerable antiandrogenic activity. The manifestation of the activity appeared to be correlated to a steric interaction between the 13β-isopropyl group and the 17β-hydroxyl group in **1**. As an extention of such steric interaction, we designed a series of 16β-substituted-17β-hydroxysteroids expecting a possible steric interaction between the 17β-hydroxyl group and the 16β-substituents and hence the antiandrogenic activity of these compounds. This paper described synthesis and antiandrogenic activity of 17β-hydroxy-16β-substituted-estr- and androst-4-en-3-ones together with the corresponding $\Delta^{4,6}$-6-chloro and 1,2α-methylene derivatives. These new antiandrogenic steroids might be useful for a treatment of the benign prostatic hypertrophy and prostatic carcinoma.

Preparation of 16β-substituted 17-oxo steroids (**2** and **3**) was achieved by the following methods: a) a kinetically controlled vinyl-dehydration of 16α-substituted-16β,17β-dihydroxysteroids;[3] b) the Serini reaction of 16α-substituted-16β,17β-dihydroxysteroid monoacetates;[4] c) a base catalyzed condensation of aldehydes and ketones with 17-ketosteroids,[5] followed by catalytic hydrogenation. The last one provides a useful method for the introduction of isopropyl and cyclohexyl groups at position 16 of the steroids. Thus aldol condensation of 17-ketosteroids (**4** and **5**) with acetone and cyclohexanone in the presence of potassium hydroxide in methanol afforded 16-isopropylidene-17-oxo steroids (**6a** and **7**) and 16-cyclohexylidene-17-oxo steroid (**6b**), respectively, in 70—85% yields. Catalytic hydrogenation of **6** and **7** over Raney-Ni in ethanol gave stereospecifically 16β-isopropyl-17-oxo steroids (**2e** and **3d**) and 16β-cyclohexyl-17-oxo steroid (**2f**), respectively, in good yields. No trace amount of the 16α-isomers were detected by thin-layer chromatographic analyses and nuclear magnetic resonance (NMR) spectra.[6]

Sodium borohydride reduction of 16β-substituted-17-oxo steroids (**2**) in methanol gave 16β-substituted-17β-hydroxysteroid derivatives (**8**) in 90—96% yields. The configuration of

---

1) Location: *Juso-Honmachi, Yodogawa-ku, Osaka 532, Japan.*
2) K. Hiraga, T. Asako, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **13**, 1294 (1965).
3) G. Goto, K. Yoshioka, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 1393 (1973).
4) G. Goto, K. Yoshioka, and K. Hiraga, *Tetrahedron*, **30**, 2107 (1974).
5) W.C.J. Ross, *J. Chem. Soc.*, **1945**, 25.
6) The C_{13}-methyl proton signals of these 16α-isomers are shifted downfield by *ca.* 0.02—0.03 ppm relative to those of the 16β-isomers.

substituents at positions 16 and 17 in **8** was confirmed by the coupling constant of 17α-proton ($J_{16,17}$) coupled with the chemical shifts of 17α-proton and 13-methyl protons.[7]

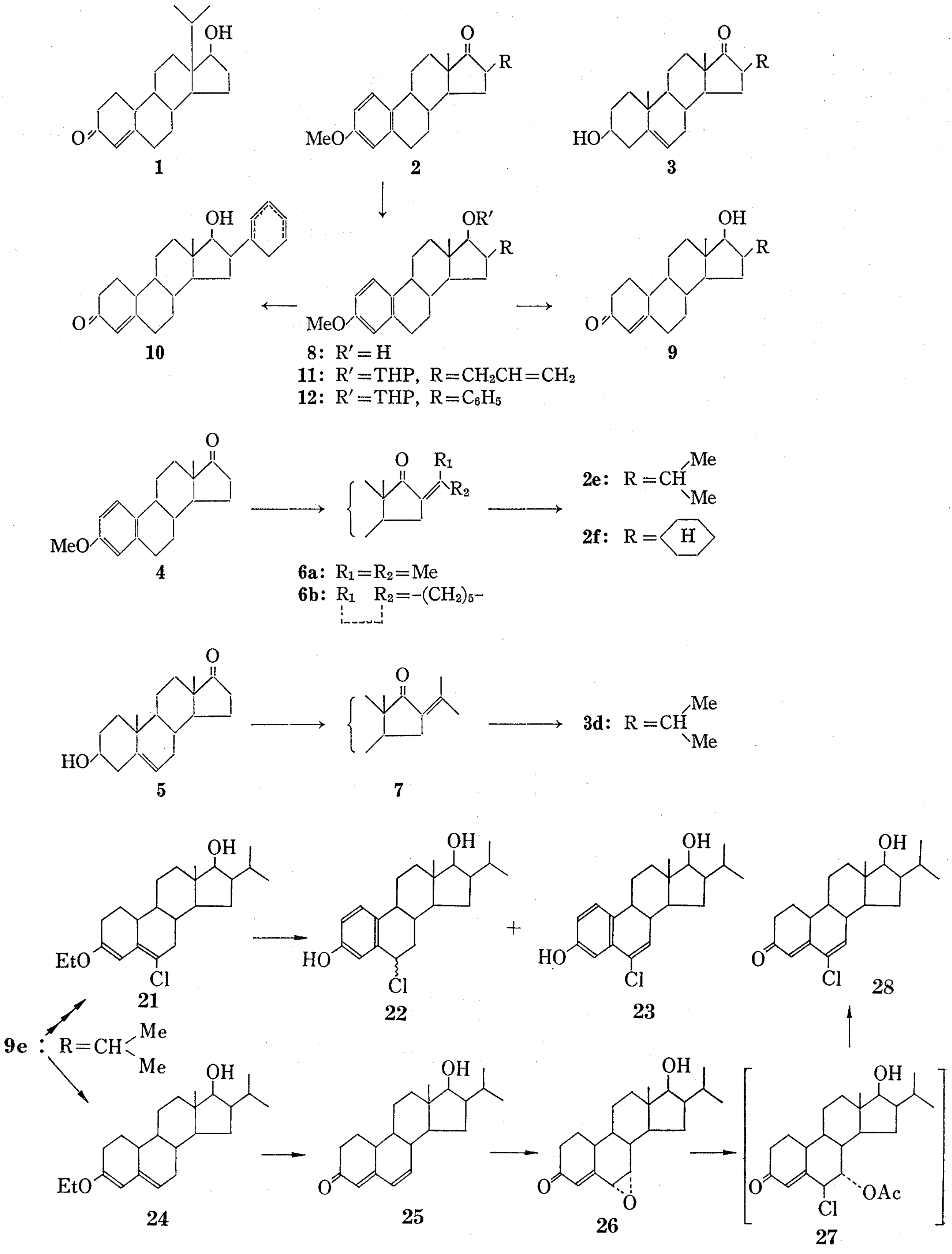


Chart 1

---

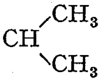
[7] G. Goto, K. Yoshioka, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **25**, 1295 (1977).

Birch reduction of **8** with lithium in liquid ammonia-tetrahydrofuran in the presence of ethanol as a proton donnor afforded, after hydrolysis of the resulting enol ethers with 6 N hydrochloric acid in methanol, 17β-hydroxy-16β-substituted-estr-4-en-3-ones (**9**) in good yields. On Birch reduction of the 16β-allyl derivative (**8d**), a concomitant reduction of the 16β-allyl group occurred to give 17β-hydroxy-16β-propylestr-4-en-3-one (**9c**) in 73% yield. Under the same reduction conditions, the 16β-phenyl derivative (**8g**) was also reduced to 17β-hydroxy-16β-cyclohexenyl-estr-4-en-3-one (**10**) in 77% yield. These greatly facile reduction of 16β-allyl and 16β-phenyl groups may be due to an intramolecular participation by the 17β-hydroxyl group in a reduction intermediate.[8] Investigation of the detailed mechanism is under progress.

In order to avoid these undesirable reduction, the 17β-hydroxyl group in **8d** and **8g** were converted into the tetrahydropyranyl ether.[9] On Birch reduction, followed by acid hydrolysis, **11** and **12** gave 17β-hydroxy-16β-allylestr-4-en-3-one (**9d**) in 50% yield and 17β-hydroxy-16β-phenylestr-4-en-3-one (**9g**) in 56% yield, respectively.

The 17β-hydroxy-16β-substituted-androstane derivatives were also prepared by the following methods. Oppenauer oxidation of **3** gave 16β-substituted-3,17-diones (**13**) in 60—70% yields. Treatment of **13** with ethyl orthoformate afforded the corresponding 3-ethyl enol ethers (**14**). **14** was reduced by sodium borohydride in methanol to give the 17β-hydroxy-16β-substituted derivatives (**15**) in good yields. Acid hydrolysis of the resulting enol ethers (**15**) afforded 17β-hydroxy-16β-substituted-androst-4-en-3-ones (**16**) in good yields. The configurations of C-16 and C-17 of **16** was assigned on the basis of their NMR spectral data[7] together with the analogy with **9**. The physical data of **8**, **9** and **16** are shown in Tables I, II and III.

TABLE I. Physical Data of 17β-Hydroxy-16β-substituted-estrane Derivatives (**8**)

Steroid (**8**)[a]	R	mp (°C)	Formula	Analysis (%) Calcd. (Found)		^{1}H-NMR ($CDCl_3$) δ (ppm)[b,c]		Mass (*m/e*)	
				C	H	O-Me (3H, s)	Others	M+	Others
a[d]	Me	117—118	$C_{20}H_{28}O_2$	79.95 (80.01	9.39 9.26)	3.73	1.07(3H, d, *J*=7 Hz, Me)	300	285, 282
b	Et	97	$C_{21}H_{30}O_2$	80.21 (79.96	9.62 9.83)	3.72	0.96(3H, t, *J*=7 Hz, Me)	314	296, 286
c	$CH_2CH_2CH_3$	76	$C_{22}H_{32}O_2$	80.44 (80.42	9.83 9.86)	3.73	0.92(3H, t, *J*=6 Hz, Me)	328	313, 310
d	$CH_2CH{=}CH_2$	99	$C_{22}H_{30}O_2$	80.93 (80.85	9.26 9.31)	3.72	4.9—5.2(2H, m, =CH_2), 5.6—6.0(1H, m, –CH=)	326	311, 308
e	 $CH(CH_3)_2$	136	$C_{22}H_{32}O_2$	80.44 (80.16	9.83 9.95)	3.70	0.90, 1.03(each 3H, d, *J*=6 Hz, Me)	328	313, 310
f		143—144	$C_{25}H_{36}O_2$	81.47 (81.50	9.85 9.87)	3.74	—	368	350 —
g	C_6H_5	174—176	$C_{25}H_{30}O_2$	82.83 (83.00	8.34 8.28)	3.73	3.52(1H, m, 16α-H), 7.3—7.4(5H, m, Ar)	362	344, 333

a) IR (KBr, cm^{-1}) data are as follows: **8a—e**: ν_{OH} 3450; **8f**: ν_{OH} 3550; **8g**: ν_{OH} 3400.
b) The other NMR data were reported in ref. 7.
c) The signals (3H, m) of aromatic protons appear at 6.6—7.3 ppm for all compounds (**8a—g**).
d) F.A. Kincl and M. Garcia, *Ber.*, **92**, 595 (1959).

---

8) *a*) E. Fujita, M. Shibuya, S. Nakamura, Y. Okada, and T. Fujita, *J. Chem. Soc., Perkin Trans. I*, **1974**, 165; *b*) J. Fried and J.A. Edwards, "Organic Reactions in Steroid Chemistry," Vol. 2, van Nostrand Reinhold Company, New York, 1972.

9) *a*) T.B. Windholz, R.D. Brown, and A.A. Patchett, *Steroids*, **6**, 409 (1965); *b*) K. Yoshioka, G. Goto, T. Asako, K. Hiraga, and T. Miki, *Chem. Commun.*, **1971**, 336; *c*) K. Yoshioka, T. Asako, G. Goto, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 2195 (1973).

TABLE II. Physical Data of 17β-Hydroxy-16β-substituted-estr-4-en-3-ones (**9**)

Steroid (**9**)[a,b]	R	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	^{1}H-NMR (CDCl$_3$) δ (ppm)[c] 4-H (1H, s)	Others	Mass (m/e) M+	Others
a[d]	Me	228—229	$C_{19}H_{28}O_2$	79.12 (79.17	9.79 9.77)	5.80	1.10(3H, d, J=6 Hz, Me)	288	273, 270
b	Et	152—153	$C_{20}H_{30}O_2$	79.42 (79.53	10.00 10.01)	5.80	0.88(3H, t, J=7 Hz, Me)	302	287, 284
c	$CH_2CH_2CH_3$	149—151	$C_{21}H_{32}O_2$	79.70 (79.80	10.19 10.03)	5.81	0.89(3H, t, J=7 Hz, Me)	316	301, 298
d	$CH_2CH{=}CH_2$	137—138	$C_{21}H_{30}O_2$	80.21 (80.01	9.62 9.69)	5.80	4.8—5.2(2H, m, =CH$_2$), 5.6—5.9(1H, m, –CH=)	314	299, 296
e	$CH{<}^{CH_3}_{CH_3}$	145—147	$C_{21}H_{32}O_2$	79.70 (79.80	10.19 10.34)	5.80	0.88, 1.03(each 3H, d, J=7 Hz, Me)	316	301, 298
f		148—151	$C_{24}H_{36}O_2$	80.85 (80.72	10.18 10.05)	5.80	—	356	341, 338
g	C_6H_5	160	$C_{24}H_{30}O_2$	82.24 (82.19	8.63 8.64)	5.84	3.50(1H, q, J_1=19 Hz, J_2=10 Hz, 16α-H), 7.29(5H, m, Ar)	350	332, 321

a) IR (KBr, cm^{-1}) data are as follows: **9a**—**e**,**g**: ν_{OH} 3450, $\nu_{\Delta^4\text{-}3\text{-one}}$ 1660; **9f**: ν_{OH} 3400, $\nu_{\Delta^4\text{-}3\text{-one}}$ 1670.
b) UV [EtOH, nm (ε)] data are as follows: **9a**—**c**: λ_{max} 240 (16800); **9d**—**g**: λ_{max} 240 (17000).
c) The other NMR data were reported in ref. 7.
d) F.A. Kincl and M. Garcia, *Ber.*, **92**, 595 (1959).

TABLE III. Physical Data of 17β-Hydroxy-16β-substituted-androst-4-en-3-ones (**16**)

Steroid (**16**)[a,b]	R	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	^{1}H-NMR (CDCl$_3$) δ (ppm)[c] 19-H (3H, s)	4-H (1H, s)	Others	Mass (m/e) M+	Others
a[d]	Me	183—185	$C_{20}H_{30}O_2$	79.42 (79.38	10.00 10.03)	1.21	5.71	1.10(3H, d, J=6 Hz, Me)	302	284, 260
b	Et	165—166	$C_{21}H_{32}O_2$	79.70 (79.78	10.19 10.07)	1.18	5.71	0.89(3H, t, J=6 Hz, Me)	316	298, 274
c	$CH_2CH_2CH_3$	165—167	$C_{22}H_{34}O_2$	79.95 (79.77	10.37 10.66)	1.17	5.70	0.89(3H, t, J=6 Hz, Me)	330	312, 288
d	$CH{<}^{CH_3}_{CH_3}$	144—145	$C_{22}H_{34}O_2$	79.95 (79.94	10.37 10.32)	1.18	5.74	0.89, 1.03 (each 3H, d, J=6 Hz, Me)	330	312, 288
e	C_6H_5	176—177	$C_{25}H_{32}O_2$	82.37 (82.53	8.85 9.01)	1.21	5.72	3.48(1H, q, J_1=19 Hz, J_2=9 Hz, 16α-H)	364	346, 305

a) IR (KBr, cm^{-1}) data are as follows: **16a**—**c**: ν_{OH} 3450, $\nu_{\Delta^4\text{-}3\text{-one}}$ 1660; **16d**,**e**: ν_{OH} 3500, $\nu_{\Delta^4\text{-}3\text{-one}}$ 1670.
b) UV [EtOH, nm (ε)] data are as follows: **16a**—**e**: λ_{max} 240 (17000).
c) The other NMR data were reported in ref. 7.
d) F. Neumann, O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 5657 (1955).

On the other hand, cyproterone acetate (**17**),[10] known as a strong antiandrogenic steroid, has a unique structural moiety such as 6-chloro-1,2α-methylene-$\Delta^{4,6}$-3-one. In order to investigate the antiandrogenic activity of the 16β-substituted-17β-hydroxysteroids having such a moiety of cyproterone acetate (**17**), 17β-hydroxy-6-chloro-16β-substituted-$\Delta^{4,6}$-3-ones and the corresponding 1,2α-methylene derivative were synthesized. The 3-ethyl enol ethers (**15**) were treated with N-chlorosuccinimide in aqueous acetone in the presence of 10% sodium acetate

---

[10] R. Wiechert, *Angew. Chem.*, **82**, 331 (1970) and references cited therein.

to yield the 6β-chloro-Δ^4-3-one derivatives (**18**) in 70—75% yield. Since **18** was easily isomerized to thermodynamically more stable 6α-isomers, **18** was converted to the corresponding 3-ethyl enol ethers (**19**) without purification. Dehydrogenation of **19** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)$^{11)}$ in aqueous acetone afforded 17β-hydroxy-6-chloro-16β-substituted-androsta-4,6-dien-3-ones (**20**) in 40% yields. The physical data of **20** are shown in Table IV.

Table IV. Physical Data of 17β-Hydroxy-6-chloro-16β-substituted-androsta-4,6-dien-3-ones (**20**)

Steroid (**20**)$^{a,b)}$	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	Cl	(Found) C	H	Cl
a	Me	162—165	$C_{20}H_{27}ClO_2$	71.73	8.13	10.59	71.23	8.37	10.42
b	Et	173—176	$C_{21}H_{29}ClO_2$	72.41	8.33	10.21	72.43	8.36	10.07
c	$\mathrm{CH}\begin{array}{l}\diagup \mathrm{CH_3}\\ \diagdown \mathrm{CH_3}\end{array}$	167—170	$C_{22}H_{31}ClO_2$	72.93	8.56	9.68	72.81	8.71	9.43
d	C_6H_5	258—260	$C_{25}H_{29}ClO_2$	75.76	7.32	8.96	75.90	7.45	9.45

Steroid (**20**)$^{a,b)}$	^{1}H-NMR (CDCl$_3$) δ (ppm) 19-H (3H, s)	4-H (1H, s)	7-H (1H, d, J=2 Hz)	Others	Mass (m/e) M$^+$ (^{37}Cl)	M$^+$ (^{35}Cl)	Others
a	1.12	6.25	6.29	1.01(3H, d, J=7 Hz, Me)	336	334	318, 316, 211, 209, 191
b	1.11	6.26	6.29	0.90(3H, t, J=6 Hz, Me)	350	348	332, 330, 315, 313, 295
c	1.14	6.30	6.35	0.92, 1.05(each 3H, d, J=6 Hz, Me)	364	362	346, 344, 329, 327, 309
d	1.16	6.30	6.36	3.52(1H, q, J_1=16 Hz, J_2=10 Hz, 16α-H), 7.27(5H, m, Ar)	398	396	380, 378, 363, 361, 343

a) IR (KBr, cm^{-1}) data are as follows: **20a—c**: ν_{OH} 3500, $\nu_{\Delta^{4,6}\text{-3-one}}$ 1650; **20d**: ν_{OH} 3550, $\nu_{\Delta^{4,6}\text{-3-one}}$ 1650.

b) UV [EtOH, nm (ε)] data are as follows: **20a,b**: λ_{max} 285 (21000); **20c,d**: λ_{max} 286 (21000).

In the same way, 17β-hydroxy-16β-isopropylestr-4-en-3-one (**9e**) was converted to 6-chloro 3-ethyl enol ether (**21**). When **21** was treated with DDQ in aqueous acetone, phenol derivatives (**22** and **23**) were obtained instead of the desired 6-chloro-$\Delta^{4,6}$-3-one (**28**). On the other hand, the 3-ethyl enol ether (**24**), prepared from **9d** and ethyl orthoformate, was dehydrogenated with DDQ$^{11)}$ to give the corresponding $\Delta^{4,6}$-3-one (**25**) in 15% yield. Epoxidation of **25** with *m*-chloroperbenzoic acid$^{12)}$ in dichloromethane proceeded from less hindered α-side to give the 6α,7α-epoxy derivative (**26**) in 84% yield. Treatment of **26** with anhydrous hydrogen chloride in acetic acid$^{13)}$ afforded, through the 6β-chloro-7α-acetoxy intermediate (**27**), the desired 17β-hydroxy-6-chloro-16β-isopropylestra-4,6-dien-3-one (**28**) in 13% yield.

The 1,2α-methylene derivative of **20c** was also synthesized by the followings. Treatment of the acetate (**29**) of **16d** with chloranil$^{14)}$ in *t*-butanol gave the corresponding $\Delta^{4,6}$-3-one (**30**) in 92% yield. Subsequent dehydrogenation of **30** with DDQ$^{15)}$ in dioxane gave the $\Delta^{1,4,6}$-3-one derivative (**31**) in 91% yield. The direct dehydrogenation of **29** to **31** by DDQ proceeded in

---

11) S.K. Pradhan and H.J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).
12) N.N. Schwartz and J.H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).
13) L.H. Knox, J.A. Zderic, J.P. Ruelas, C. Djerassi, and H.J. Ringold, *J. Am. Chem. Soc.*, **82**, 1230 (1960).
14) E. J. Agnello and G.D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).
15) D. Burn, V. Petrow, and G. Weston, *J. Chem. Soc.*, **1962**, 29.

only low yield. Treatment of **31** with dimethylsulfoxonium methylide in dimethyl sulfoxide[16] gave the 1,2α-methylene derivative (**32**) in 86% yield. The α-configuration of 1,2-methylene group of **32** derives from the analogy with cyproterone acetate (**17**).[10] Epoxidation of **32** with *m*-chloroperbenzoic acid[12] in dichloromethane afforded the 6α,7α-epoxy compound (**33**) in good yield. The α-epoxidation of **33** was established by the NMR spectral data. Reaction of **33** with anhydrous hydrogen chloride in acetic acid induced ring-opening reaction[10] of the 1,2α-methylene moiety to give the 1α-chloromethyl-6-chloro-$\Delta^{4,6}$-3-one derivative (**34**) in good yield. In order to reproduce the 1,2α-methylene ring, **34** was treated with γ-collidine[10] under nitrogen to yield desired the 1,2α-methylene-6-chloro derivative (**35**) in 67% yield. **35** was hydrolyzed under the mild conditions to give **36** in good yield.

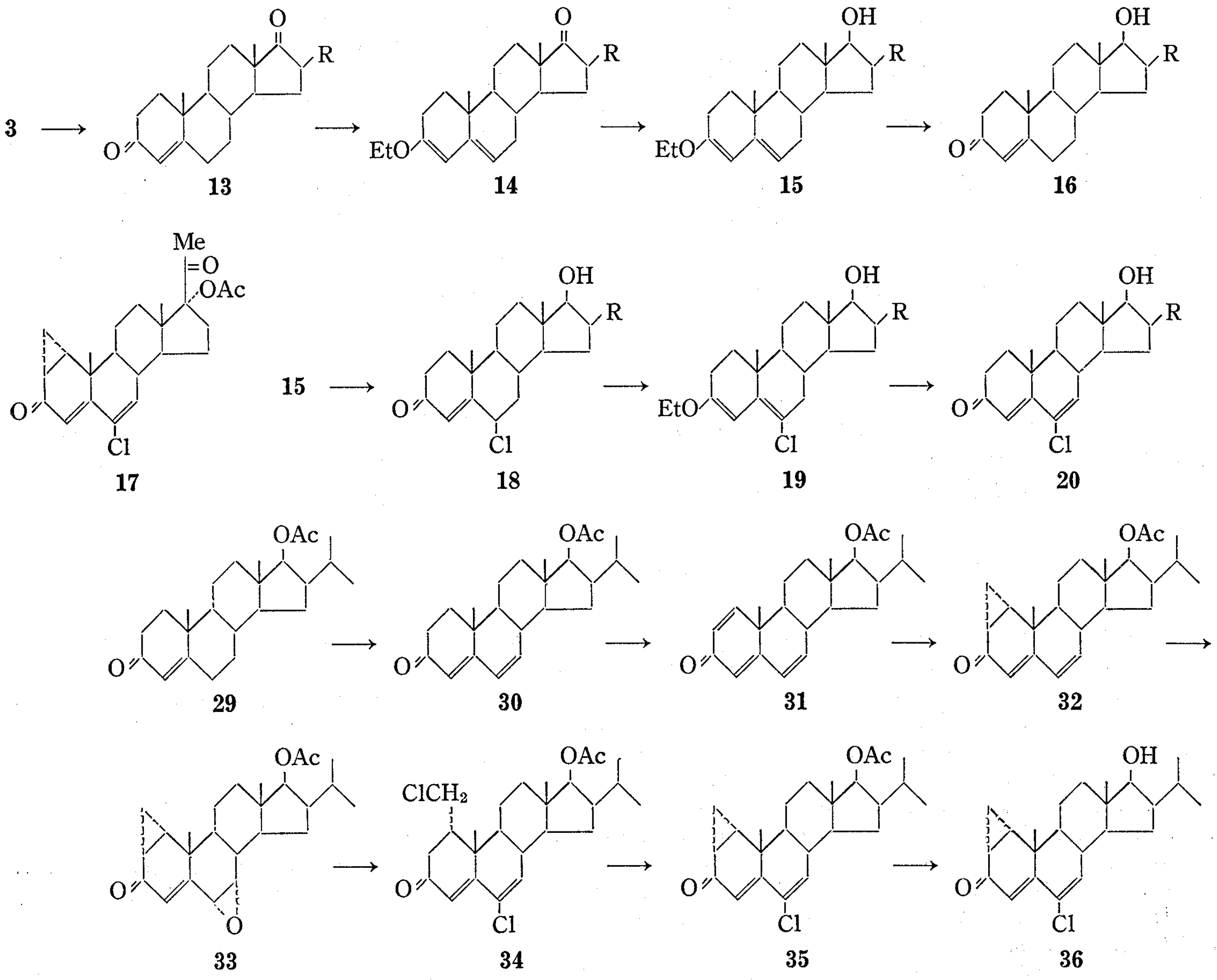


Chart 2

The antiandrogenic activity of these new steroids (**9**, **16**, **20** and **36**) synthesized as above was assessed in the immature castrated male rat.[17] Weight increase of the seminal vesicle, one of the androgen-target organs, caused by a given daily subcutaneous dose (0.15 mg) of testosterone propionate for 12 days was suppressed by the daily subcutaneous treatment with

---

16) *a*) R. Kuhn and H. Trischmann, *Ann. Chem.*, **611**, 117 (1958); *b*) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962); *c*) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

17) *a*) M. Masuoka, T. Masaki, and R. Nakayama, *Folia Endocrinologica Japonica*, **47**, 753 (1972); *b*) I. Yamazaki, T. Hori, Y. Kimura, and R. Nakayama, *ibid.*, **47**, 754 (1974).

these test steroids (2.4 mg) and rates of the inhibition (%) were used as indices of the antiandrogenic activity. The results are shown in Table V.

Table V. Antiandrogenic Activity of 16β-Substituted-17β-hydroxysteroids (**9**, **16**, **20** and **36**)

Steroids	R	Antiandrogenic activity inhibition rate (%)	Steroid	R	Antiandrogenic activity inhibition rate (%)
9a[a]	Me	18.3	**16c**	$CH_2CH_2CH_3$	5.1
9b	Et	58.5	**16d**	$\mathrm{CH}\begin{matrix}\diagup \mathrm{CH_3}\\ \diagdown \mathrm{CH_3}\end{matrix}$	23.0
9c	$CH_2CH_2CH_3$	18.3	**16e**	C_6H_5	8.6
9d	$CH_2CH{=}CH_2$	45.1	**20a**	Me	38.2
9e	$\mathrm{CH}\begin{matrix}\diagup \mathrm{CH_3}\\ \diagdown \mathrm{CH_3}\end{matrix}$	58.5	**20b**[b]	Et	31.2
9f[a]		3.1	**20c**	$\mathrm{CH}\begin{matrix}\diagup \mathrm{CH_3}\\ \diagdown \mathrm{CH_3}\end{matrix}$	25.9
9g	C_6H_5	N.D.	**20d**	C_6H_5	36.9
16a[a]	Me	N.D.	**36**[a,c]	—	22.7
16b	Et	37.8			

N.D.: Not detectable.

[a] Suspended in hydrophilic vehicle. The other steroids were dissolved in sesame oil containing 20% benzyl benzoate.

[b] 1.2 mg/rat daily dose.

[c] Oral administration of 4.8 mg/rat daily dose.

Among these steroids examined, 17β-hydroxy-16β-ethyl-estr-4-en-3-one (**9b**: **TSAA-291**) was found to have the most potent antiandrogenic activity in the detailed evaluations and also found to provide a useful remedy for the treatment of the benign prostatic hypertrophy.[18]

Experimental[19]

16-Isopropylidene-3-methoxyestra-1,3,5(10)-trien-17-one (**6a**)——To a solution of **4** (10 g) in MeOH (200 ml) was added KOH (2.0 g) and acetone (200 ml). After refluxing for 3 hr, the reaction mixture was poured into water and the resulting crystals were recrystallized from MeOH to give **6a** (9.6 g)[5] as colorless needles, mp 155°. *Anal.* Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.64; H, 8.95. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700, 1640, 1610. NMR δ ppm: 0.87 (3H, s, 13-Me), 1.87, 2.23 (each 3H, s, CH(Me)$_2$), 3.68 (3H, s, OMe), 6.5—7.3 (3H, m, Ar). MS *m/e*: 324 (M$^+$), 309.

16-Cyclohexylidene-3-methoxyestra-1,3,5(10)-trien-17-one (**6b**)——To a solution of **4** (2.5 g) in MeOH (100 ml) was added KOH (2.0 g) and cyclohexanone (8 g). After refluxing for 3 hr, the reaction mixture was poured into water and the resulting crystals were recrystallized from MeOH to give **6b** (2.0 g) as colorless needles, mp 127—129°. *Anal.* Calcd. for $C_{25}H_{32}O_2$: C, 82.37; H, 8.85. Found: C, 82.23; H, 8.85. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1710, 1630. NMR δ ppm: 0.91 (3H, s, 13-Me), 3.73 (3H, s, OMe), 6.6—7.3 (3H, m, Ar). MS *m/e*: 364 (M$^+$), 349, 336.

3β-Hydroxy-16-isopropylidene-androst-5-en-17-one (**7**)——**7**[5] (14.6 g) was obtained from **5** (18 g) by the same procedure as used in **6a**.

16β-Isopropyl-3-methoxyestra-1,3,5(10)-trien-17-one (**2e**)——**6a** (4.5 g) in EtOH (300 ml) was hydrogenated over Raney-Ni catalyst (W-3, 1.4 g) at room temperature under atmospheric pressure. After H_2 absorption ceased, the catalyst was filtered off and the filtrates were evaporated to give crystals. Recry-

---

[18] Details of the antiandrogenic activity and effects on the benign prostatic hypertrophy of TSAA-291 will be reported elsewhere.

[19] All melting points were determined on a micro hot stage apparatus and uncorrected. Ultraviolet (UV) spectra were measured in EtOH on a Hitachi EPS-3T spectrophotometer. Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. NMR spectra were recorded on a Varian HA-100 (100 MHz) spectrometer using $CDCl_3$ as a solvent; chemical shifts (δ) are given in ppm relative to internal tetramethylsilane (TMS). The mass spectra (MS) were determined on a Hitachi RMU-6D mass spectrometer equipped with a direct inlet system.

stallization from ether afforded **2e** (4.23 g) as colorless needles, mp 109—111°. *Anal.* Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.70; H, 9.28. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1740. NMR δ ppm: 0.76 (3H, s, 13-Me), 0.83, 0.99 (each 3H, d, $J=7$ Hz, CH(Me)$_2$), 3.66 (3H, s, OMe), 6.5—7.3 (3H, m, Ar). MS *m/e*: 326 (M$^+$), 311, 298.

The other compounds (**2f** and **3d**) were similarly obtained from **6b** and **7**, respectively, by the same hydrogenation procedure described above. The physical data of **2f** and **3d** are as follows.

16β-Cyclohexyl-3-methoxyestra-1,3,5(10)-trien-17-one (2f)——Colorless needles, mp 117—119°. *Anal.* Calcd. for $C_{25}H_{34}O_2$: C, 81.92; H, 9.35. Found: C, 81.65; H, 9.24. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1740. NMR δ ppm: 0.81 (3H, s, 13-Me), 3.74 (3H, s, OMe), 6.5—7.3 (3H, m, Ar). MS *m/e*: 366 (M$^+$), 338.

3β-Hydroxy-16β-isopropylandrost-5-en-17-one (3d)——Colorless needles, mp 140—145°. *Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.96; H, 10.21. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3300, 1740. NMR δ ppm: 0.87 (3H, s, 13-Me), 0.84, 1.01 (each 3H, d, $J=6$ Hz, CH(Me)$_2$), 1.02 (3H, s, 10-Me), 3.2—3.6 (1H, m, 3α-H), 5.30 (1H, d, $J=6$ Hz, 6-H). MS *m/e*: 330 (M$^+$), 315, 312.

16β-Methyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (8a)——To a solution of **2a** (5.8 g) in MeOH (120 ml) was added $NaBH_4$ (1.2 g). After stirring at room temperature for 1 hr, the reaction mixture was poured into water and the resulting crystals were recrystallized from ether–hexane (1: 1) to give **8a** (5.4 g) as colorless needles.

The other compounds (**8b**—**g**) were similarly obtained by the reaction of **2b**—**g** with $NaBH_4$. The physical data of **8a**—**g** are given in Table I.

17β-Hydroxy-16β-methylestr-4-en-3-one (9a)——A solution of **8a** (1.2 g) in EtOH (5 ml), tetrahydrofuran (50 ml) was cooled at $-50°$ by dry ice-acetone. To this solution was added liq. NH_3 (300 ml) at the same temperature. Li ribbon (2.3 g) in *ca.* 0.3 g portion was added dropwise at $-50°$ during 2 hr with stirring. After stirring an additional 1 hr, NH_3 was evaporated in a slow stream of N_2 and the residue was extracted with ether. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to give crude crystals (1.13 g). To a stirred solution of this material (1.13 g) in MeOH (25 ml) was added 6 N HCl solution (3 ml). After stirring at room temperature for 30 min, the reaction mixture was extracted with ether. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to give crude crystals. Recrystallization from ether–hexane (1: 1) gave **9a** (0.98 g) as colorless needles.

The other compounds (**9b**—**g**) were similarly obtained by the Birch reduction of **8b**—**g**. The physical data of **9a**—**g** are given in Table II.

17β-Tetrahydropyranyloxy-16β-allyl-3-methoxyestra-1,3,5(10)-triene (11)——To a solution of **8d** (3.0 g) in CH_2Cl_2 (50 ml) was added dihydropyran (5 ml) and *p*-TsOH (0.2 g). After stirring at room temperature for 30 min, the reaction mixture was poured into 10% $NaHCO_3$ solution and the product was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and dried over Na_2SO_4. The solvent was evaporated to give **11** (2.9 g) as a colorless oil. IR $\nu_{\max}^{\text{Neat}}$ cm^{-1}: 1635, no OH band. MS *m/e*: 410 (M$^+$), 325.

17β-Tetrahydropyranyloxy-16β-phenyl-3-methoxyestra-1,3,5(10)-triene (12)——Treatment of **8g** (1.03 g) with dihydropyran (2 ml) by the same procedure as used in **11** gave, after recrystallization from ether–hexane (1: 1), **12** (1.0 g) colorless plates, mp 123—125°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1610, no OH band. NMR δ ppm: 0.98 (3H, s, 13-Me), 3.75 (3H, s, OMe), 4.05 (1H, d, $J=10$ Hz, 17α-H), 4.74 (1H, s, pyran α-H), 6.5—7.5 (8H, m, Ar). MS *m/e*: 446 (M$^+$), 361.

Birch reduction of 11 and 12: Birch reduction of **11** and **12** were carried out by the same procedure as used in **9** to give **9d** (50%) and **9g** (56%), respectively.

16β-Ethylandrost-4-ene-3,17-dione (13b)——To a solution of **3b** (2.3 g) in dry benzene (100 ml) was added cyclohexanone (20 ml) and aluminum isopropoxide (5.0 g). The reaction mixture was refluxed for 1 hr. After cooling, the reaction mixture was extracted with ether. The ether layer was successively washed with 10% sodium potassium tartrate solution, water and saturated NaCl solution, followed by drying over Na_2SO_4 and then the solvent was evaporated to give crude crystals. Recrystallization from ether–hexane (1: 1) afforded **13b** (1.47 g) as colorless needles, mp 163—164°. *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.92; H, 9.71. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1720, 1650, 1630. NMR δ ppm: 0.87 (3H, s, 13-Me), 0.96 (3H, t, $J=6$ Hz, Me), 1.21 (3H, s, 10-Me), 5.74 (1H, s, 4-H). MS *m/e*: 314 (M$^+$).

The other compounds (**13c**—**e**) were similarly obtained by the same Oppenauer oxidation of **3c**—**e**. The physical data of **13c**—**e** were as follows.

16β-Propylandrost-4-ene-3,17-dione (13c)——Colorless needles, mp 140—142°. *Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.55; H, 9.94. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1720, 1650, 1630. NMR δ ppm: 0.87 (3H, s, 13-Me), 1.21 (3H, s, 10-Me), 5.37 (1H, s, 4-H). MS *m/e*: 328 (M$^+$).

16β-Isopropylandrost-4-ene-3,17-dione (13d)——Colorless needles, mp 152—153°. *Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.66; H, 9.80. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1730, 1660, 1630. NMR δ ppm: 0.80 (3H, s, 13-Me), 0.86, 1.01 (each 3H, d, $J=6$ Hz, CH(Me)$_2$), 1.20 (3H, s, 10-Me), 5.58 (1H, s, 4-H). MS *m/e*: 328 (M$^+$).

16β-Phenylandrost-4-ene-3,17-dione (13e)——Colorless needles, mp 225—230°. *Anal.* Calcd. for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34. Found: C, 82.88; H, 8.14. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1730, 1660, 1630. NMR δ ppm: 0.96 (3H, s, 13-Me), 1.24 (3H, s, 10-Me), 3.38 (1H, q, $J_1=11$ Hz, $J_2=8$ Hz, 16α-H), 5.76 (1H, s, 4-H). MS *m/e*: 362 (M$^+$).

17β-Hydroxy-16β-methylandrost-4-en-3-one (16a)——To a solution of **13a** (2.1 g) in dioxane (100 ml) was added ethyl orthoformate (5 g) and *p*-TsOH (0.1 g). After stirring at room temperature for 2 hr, the reaction mixture was poured into 5% $NaHCO_3$ solution and the product was extracted with ether. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to give **14a** (2.1 g) as crude crystals. **14a** (2.1 g) was dissolved in MeOH (40 ml) without purification. To this solution was added $NaBH_4$ (1.6 g). After stirring at room temperature for 1 hr, the reaction mixture was extracted with ether. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to give **15a** (2.0 g) as an oil. To a solution of **15a** (2.0 g) in MeOH (20 ml) was added 6 N HCl solution (1 ml). After stirring at room temperature for 15 min, the reaction mixture was poured into water and the resulting crystals were recrystallized from ether-hexane (1: 1) to give **16a** (1.48 g) as colorless needles.

The other compounds (**16b**—**e**) were obtained from **13b**—**e** by the same procedure described above. The physical data of **16a**—**e** are given in Table III.

17β-Hydroxy-6β-chloro-16β-methylandrost-4-en-3-one (18a)——To a solution of **15a** (1.0 g) in acetone (34 ml) was added 10% sodium acetate solution (5.7 ml). Under ice cooling, N-chlorosuccinimide (0.5 g) and AcOH (0.57 ml) were added to this solution. After stirring at 5° for 5 min, the reaction mixture was extracted with ether. The extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent gave **18a** (0.87 g) as crude crystals. The analytical sample of **18a** was recrystallized from ether. Colorless needles, mp 125—128°. *Anal.* Calcd. for $C_{20}H_{29}ClO_2$: C, 71.30; H, 8.68; Cl, 10.53. Found: C, 71.22; H, 8.47; Cl, 10.64. IR ν_{max}^{KBr} cm^{-1}: 1690, 1640. UV λ_{max} nm (ε): 239 (16500). NMR δ ppm: 0.82 (3H, s, 13-Me), 1.10 (3H, d, $J=6$ Hz, Me), 1.44 (3H, s, 10-Me), 3.65 (1H, d, $J=10$ Hz, 17α-H), 4.71 (1H, m, 6α-H), 5.82 (1H, s, 4-H). MS *m/e*: 338 and 336 (M^+), 320, 318.

The other compounds (**18b**—**d**) were similarly obtained by the reaction of **15b**—**d** with N-chlorosuccinimide. The physical data of **18b**—**d** are as follows.

17β-Hydroxy-6β-chloro-16β-ethylandrost-4-en-3-one (18b)——Colorless plates, mp 167—169°. *Anal.* Calcd. for $C_{21}H_{31}ClO_2$: C, 72.00; H, 8.85; Cl, 10.14. Found: C, 71.99; H, 8.87; Cl, 10.81. IR ν_{max}^{KBr} cm^{-1}: 1670, 1635. UV λ_{max} nm (ε): 240 (16600). NMR δ ppm: 0.82 (3H, s, 13-Me), 0.90 (3H, t, $J=6$ Hz, Me), 1.45 (3H, s, 10-Me), 3.66 (1H, d, $J=10$ Hz, 17α-H), 4.72 (1H, m, 6α-H), 5.84 (1H, s, 4-H). MS *m/e*: 352 and 350 (M^+), 334, 332.

17β-Hydroxy-6β-chloro-16β-isopropylandrost-4-en-3-one (18c)——Colorless needles, mp 185—188°. *Anal.* Calcd. for $C_{22}H_{33}ClO_2$: C, 72.55; H, 9.07; Cl, 9.62. Found: C, 72.79; H, 9.15; Cl, 9.90. IR ν_{max}^{KBr} cm^{-1}: 1690, 1630. UV λ_{max} nm (ε): 240 (16800). NMR δ ppm: 0.84 (3H, s, 13-Me), 0.90, 1.07 (each 3H, d, $J=6$ Hz, $CH(Me)_2$), 1.47 (3H, s, 10-Me), 3.78 (1H, d, $J=9$ Hz, 17α-H), 4.74 (1H, m, 6α-H), 5.86 (1H, s, 4-H). MS *m/e*: 366 and 364 (M^+), 348, 346.

17β-Hydroxy-6β-chloro-16β-phenylandrost-4-en-3-one (18d)——Colorless needles, mp 180—185°. *Anal.* Calcd. for $C_{25}H_{31}ClO_2$: C, 75.38; H, 7.79; Cl, 8.92. Found: C, 75.62; H, 7.85; Cl, 8.73. IR ν_{max}^{KBr} cm^{-1}: 1680, 1630. UV λ_{max} nm (ε): 240 (16700). NMR δ ppm: 0.88 (3H, s, 13-Me), 1.48 (3H, s, 10-Me), 3.50 (1H, q, $J_1=10$ Hz, $J_2=8$ Hz, 16α-H), 3.87 (1H, d, $J=10$ Hz, 17α-H), 4.74 (1H, m, 6α-H), 5.86 (1H, s, 4-H), 7.28 (5H, m, Ar). MS *m/e*: 400 and 398 (M^+), 382, 380.

17β-Hydroxy-6-chloro-16β-methylandrosta-4,6-dien-3-one (20a)——To a solution of **18a** (1.0 g) in dioxane (20 ml) was added ethyl orthoformate (3 ml) and *p*-TsOH (50 mg). After stirring at room temperature for 2 hr, the reaction mixture was worked up by the usual way to afford **19a** (1.02 g). The crude **19a** (1.02 g) was dissolved in 95% aqueous acetone (100 ml). To this solution was added DDQ (0.8 g) and the mixture was stirred at room temperature for 10 min. After standing at room temperature for additional 1 hr, the reaction mixture was extracted with CH_2Cl_2. The extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent gave crude crystals. Recrystallization from ether-hexane (1: 1) afforded **20a** (0.74 g) as colorless needles.

The other compounds (**20b**—**d**) were similarly obtained from **18b**—**d** by the same procedure described above. The physical data of **20a**—**d** are given in Table IV.

3-Ethoxy-16β-isopropylestra-3,5-dien-17β-ol (24)——To a solution of **9e** (1.5 g) in dioxane (50 ml) was added ethyl orthoformate (2 ml) and *p*-TsOH (0.1 g). After stirring at room temperature for 1 hr, the reaction mixture was poured into 5% $NaHCO_3$ solution and the product was extracted with ether. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to give crude crystals. Recrystallization from MeOH gave **24** (1.4 g) as colorless needles, mp 100—105°. *Anal.* Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.07; H, 10.49. IR ν_{max}^{KBr} cm^{-1}: 3500, 1640, 1620. MS *m/e*: 344 (M^+), 326, 309.

17β-Hydroxy-16β-isopropylestra-4,6-dien-3-one (25)——To a solution of **24** (1.5 g) in 95% aqueous acetone (30 ml) was added DDQ (1.0 g). After stirring at room temperature for 10 min, the reaction mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to give crude crystals. Recrystallization from ether afforded **25** (0.17 g) as colorless needles, mp 170—172°. *Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.13; H, 9.70. IR ν_{max}^{KBr} cm^{-1}: 3550, 1670, 1620, 1600. UV λ_{max} nm (ε): 281 (26800). NMR δ ppm: 0.79 (3H, s, 13-Me), 0.89, 1.02 (each 3H, d, $J=6$ Hz, $CH(Me)_2$), 3.75 (1H, d, $J=10$ Hz, 17α-H), 5.68 (1H, s, 4-H), 6.14 (2H, m, 6-H and 7-H). MS *m/e*: 314 (M^+), 299, 296.

17β-Hydroxy-6α,7α-epoxy-16β-isopropylestr-4-en-3-one (26)——To a solution of **25** (170 mg) in CH_2Cl_2 (10 ml) was added *m*-chloroperbenzoic acid (110 mg). After standing at room temperature for 2 days, the reaction mixture was poured into 5% Na_2CO_3 solution and the product was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to yield **26** (150 mg) as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3450, 1660, 1620. UV λ_{max} nm (ε): 235 (17000). MS *m/e*: 330 (M^+), 315, 314, 312.

17β-Hydroxy-6-chloro-16β-isopropylestra-4,6-dien-3-one (28)——A solution of **26** (150 mg) in glacial acetic acid (10 ml) was saturated with anhydrous hydrogen chloride and the reaction mixture was allowed to stand at room temperature for 4 hr. The solution was poured into ice-water and the product was extracted with ether. The extracts were washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4 and the solvent was evaporated to give an oil (147 mg). The product was purified by chromatography on silica gel (15 g). The benzene–ether (5: 1) fractions were concentrated to yield, after recrystallization from ether, **28** (21 mg) as colorless plates, mp 161—163°. *Anal.* Calcd. for $C_{21}H_{29}ClO_2$: C, 72.29; H, 8.38; Cl, 10.16. Found: C, 72.41; H, 8.21; Cl, 10.04. IR ν_{max}^{KBr} cm^{-1}: 3500, 1650, 1600. UV λ_{max} nm (ε): 284 (21400). NMR δ ppm: 0.80 (3H, s, 13-Me), 0.90, 1.02 (each 3H, d, J=6 Hz, CH(Me)$_2$), 3.79 (1H, d, J=10 Hz, 17α-H), 6.37 (2H, m, 4-H and 7-H). MS *m/e*: 350 and 348 (M^+), 335, 333, 332, 330.

17β-Acetoxy-16β-isopropylandrost-4-en-3-one (29)——Acetylation of **16d** (13.5 g) was performed by the usual way to afford **29** (13.1 g) as colorless needles (from ether), mp 128°. *Anal.* Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.55; H, 9.66. IR ν_{max}^{KBr} cm^{-1}: 1730, 1670, 1610. UV λ_{max} nm (ε): 239 (17000). NMR δ ppm: 0.79 (3H, s, 13-Me), 0.84, 0.87 (each 3H, d, J=6 Hz, CH(Me)$_2$), 1.17 (3H, s, 10-Me), 2.06 (3H, s, OAc), 4.92 (1H, d, J=10 Hz, 17α-H), 5.72 (1H, s, 4-H). MS *m/e*: 372 (M^+), 330.

17β-Acetoxy-16β-isopropylandrosta-4,6-dien-3-one (30)——To a solution of **29** (5.0 g) in *t*-BuOH (50 ml) was added chloranil (4.0 g) and the reaction mixture was heated to 80° for 4 hr. After cooling, the reaction mixture was poured into 10% Na_2CO_3 solution and the products were extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4 and the solvent was evaporated to afford crude crystals. Recrystallization from ether gave **30** (4.6 g) as colorless needles, mp 101—103°. *Anal.* Calcd. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.58; H, 9.41. IR ν_{max}^{KBr} cm^{-1}: 1715, 1650, 1615, 1580. UV λ_{max} nm (ε): 282 (23500). NMR δ ppm: 0.85 (3H, s, 13-Me), 0.89, 0.91 (each 3H, d, J=6 Hz, CH(Me)$_2$), 1.13 (3H, s, 10-Me), 2.07 (3H, s, OAc), 3.98 (1H, d, J=10 Hz, 17α-H), 4.67 (1H, s, 4-H), 5.12 (2H, m, 6-H and 7-H). MS *m/e*: 370 (M^+), 328.

17β-Acetoxy-16β-isopropylandrosta-1,4,6-trien-3-one (31)——To a solution of **30** (3.5 g) in dioxane (40 ml) was added DDQ (2.8 g) and the reaction mixture was refluxed for 5 hr. After cooling, the solution was treated in the same manner as used in **29**. Recrystallization from ether gave **31** (3.2 g) as colorless needles, mp 163—165°. *Anal.* Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.03; H, 8.86. IR ν_{max}^{KBr} cm^{-1}: 1710, 1650, 1600, 1580. UV λ_{max} nm (ε): 222 (9800), 252 (9500), 296 (10500). NMR δ ppm: 0.86, 0.91 (each 3H, d, J=6 Hz, CH(Me)$_2$), 0.88 (3H, s, 13-Me), 1.20 (3H, s, 10-Me), 2.07 (3H, s, OAc), 4.95 (1H, d, J=10 Hz, 17α-H), 5.99 (1H, d, J=2 Hz, 4-H), 6.09 (1H, q, J=2 Hz, 6-H), 6.24 (1H, q, J_1=10 Hz, J_2=2 Hz, 2-H), 7.25 (1H, d, J=10 Hz, 1-H). MS *m/e*: 368 (M^+), 353, 326.

17β-Acetoxy-1,2α-methylene-16β-isopropylandrosta-4,6-dien-3-one (32)——To a solution of trimethylsulfoxonium iodide[16a)] (7.0 g) in dry dimethylsulfoxide (DMSO) (10 ml) was added NaH (700 mg, oil free) at 5° under N_2 and the solution was stirred at the same temperature for 30 min. To this solution was added **31** (3.0 g) in dry DMSO (15 ml) at 5—10°. After stirring at 5—10° for 12 hr under N_2, the reaction mixture was poured into 1 N HCl solution and the resulting crystals were recrystallized from ether to give **32** (2.7 g) as colorless plates, mp 155—159°. *Anal.* Calcd. for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.58; H, 9.24. IR ν_{max}^{KBr} cm^{-1}: 1730, 1640, 1620. UV λ_{max} nm (ε): 280 (18000). NMR δ ppm: 0.85 (3H, s, 13-Me), 0.88, 0.89 (each 3H, d, J=6 Hz, CH(Me)$_2$), 1.19 (3H, s, 10-Me), 2.06 (3H, s, OAc), 4.95 (1H, d, J=10 Hz, 17α-H), 5.51 (1H, s, 4-H), 6.01 (2H, m, 6-H and 7-H). MS *m/e*: 382 (M^+), 329.

17β-Acetoxy-1,2α-methylene-6α,7α-epoxy-16β-isopropylandrost-4-en-3-one (33)——To a solution of **32** (1.5 g) in CH_2Cl_2 (30 ml) was added *m*-chloroperbenzoic acid (0.9 g) and the solution was allowed to stand at room temperature for 24 hr. The reaction mixture was treated in the same manner as used in **26** to yield **33** (1.4 g) as an oil. IR ν_{max}^{KBr} cm^{-1}: 1720, 1660, 1610. UV λ_{max} nm (ε): 233 (16500). NMR δ ppm: 0.80 (3H, s, 13-Me), 0.86, 0.90 (each 3H, d, J=6 Hz, CH(Me)$_2$), 1.14 (3H, s, 10-Me), 2.03 (3H, s, OAc), 3.28 (1H, d, J=4 Hz, 7β-H), 3.36 (1H, d, J=4 Hz, 6β-H), 4.96 (1H, d, J=10 Hz, 17α-H), 5.89 (1H, s, 4-H). MS *m/e*: 398 (M^+), 355.

17β-Acetoxy-6-chloro-1,2α-methylene-16β-isopropylandrosta-4,6-dien-3-one (35)——A solution of **33** (2.0 g) in glacial acetic acid (20 ml) was saturated with anhydrous hydrogen chloride. After standing at room temperature for 20 hr, the reaction mixture was poured into ice-water and the product was extracted with CH_2Cl_2. The extracts were worked up in the usual manner to give **34** (1.79 g) as an oil. Without purification, **34** (1.74 g) was dissolved in γ-collidine (15 ml) and refluxed under N_2 for 30 min. After cooling, the reaction mixture was extracted with CH_2Cl_2. The extracts were washed with 5% HCl solution, water and dried over Na_2SO_4. Evaporation of the solvent gave crude crystals. Recrystallization from ether gave **35** (1.4 g) as colorless needles, mp 168—169°. *Anal.* Calcd. for $C_{25}H_{33}ClO_3$: C, 72.01; H, 7.98; Cl, 8.50. Found: C, 72.30; H, 7.81; Cl, 8.43. IR ν_{max}^{KBr} cm^{-1}: 1720, 1660, 1630, 1605. UV λ_{max} nm (ε): 283 (18100).

NMR δ ppm: 0.83 (3H, s, 13-Me), 1.07 (3H, s, 10-Me), 2.05 (3H, s, OAc), 4.90 (1H, d, J=9 Hz, 17α-H), 5.98 (1H, s, 4-H), 6.16 (1H, d, J=2 Hz, 7-H). MS *m/e*: 418 and 416 (M^+), 403, 401.

17β-Hydroxy-6-chloro-1,2α-methylene-16β-isopropylandrosta-4,6-dien-3-one (**36**)——To a solution of **35** (600 mg) in EtOH (30 ml) was added 1 N KOH–EtOH solution (5 ml) and the solution was heated to 60° under N_2 for 30 min. After cooling, the reaction mixture was poured into water and the resulting crystals were recrystallized from ether to give **36** (520 mg) as colorless needles, mp 177—178°. *Anal.* Calcd. for $C_{23}H_{31}ClO_2$: C, 73.67; H, 8.33; Cl, 9.46. Found: C, 73.61; H, 8.47; Cl, 9.44. IR ν_{max}^{KBr} cm^{-1}: 3400, 1640, 1620, 1605. UV λ_{max} nm (ε): 283 (18000). NMR δ ppm: 0.84 (3H, s, 13-Me), 0.92, 1.05 (each 3H, d, J=6 Hz, CH(Me)$_2$), 1.23 (3H, s, 10-Me), 3.80 (1H, d, J=9 Hz, 17α-H), 6.13 (1H, s, 4-H), 6.26 (1H, d, J=2 Hz, 7-H). MS *m/e*: 376 and 374 (M^+), 361, 359, 358, 357.

Acknowledgement The authors would like to thank Dr. E. Ohmura of this division for his advice and encouragement.