Brominations of Steroidal Hormone Having α,β-Unsaturated Ketone, 17-*O*-Acetyltestosterone, in the Presence of Silver Triflate

Takanobu SHIMIZU, Akihiko TOBARI, Jyunichi KOYANAGI, Masami KAWASE, and Setsuo SAITO*

Faculty of Pharmaceutical Sciences, Josai University, Keyakidai 1–1, Sakado, Saitama 350–0295, Japan.
Received June 27, 2000; accepted September 27, 2000

Bromination of 17-*O*-acetyltestosterone (17β-acetoxyandrost-4-en-3-one) (1) was performed with 1, 5, and 10 eq of Br_2 in AcOH–Et_2O at room temperature. In all cases 2α,6β- (2) and 2α,6α-dibromo-17β-acetoxyandrost-4-en-3-one (3) were obtained, although the yields were dependent upon the conditions used. Bromination of compound 1 with 10 eq of Br_2 in the presence of silver trifluoromethanesulfonate (silver triflate, AgOTf) at room temperature for 12 h gave 2,7α-dibromo- (4) and 2,4,7α-tribromo-17β-acetoxy-3-hydroxy-1-methylestra-1,3,5(10)-triene-6-one (5). The formations of the products were inferred on the basis of products obtained under controlled brominations of 1 in the presence of AgOTf, and of those obtained by the brominations of compounds 9—13 also in the presence of AgOTf.

Key words steroid hormone; α,β-unsaturated ketone; bromination; silver trifluoromethanesulfonate

Brominations of ketones are usually performed using such reagents as bromine[1,2] and *N*-bromosuccinimide.[3—5] α-Bromoketones of steroidal hormones are utilized to lead to various unsaturated ketone derivatives.[3,6—8] Although many investigations involving brominations of steroidal ketones, including kinetically controlled studies,[9—11] have been reported, only a few reports have described the bromination of steroidal hormones having an α,β-unsaturated ketone. Djerassi *et al.*[12] reported that the bromination of 17-*O*-acetyltestosterone (**1**) (17β-acetoxyandrost-4-en-3-one) with bromine in AcOH–Et_2O gave a mixture of 2α,6β- (**2**) and 2α,6α-dibromo-17β-acetoxyandrost-4-en-3-one (**3**) in 80—82% yields. However, during research for the bromination of **1**, we incidentally found that the presence of silver trifluoromethanesulfonate (siver triflate, AgOTf) in benzene led to differently brominated products from those obtained by Djerassi *et al*. This paper describes the brominations of **1** in the presence of AgOTf in benzene under various conditions and analyzes the structure of the products. The formation mechanisms of the products are also considered.

Results and Discussion

Bromination of **1** with 10 eq of Br_2 in AcOH–Et_2O at room temperature for 10 min according to the method reported by Djerassi *et al.*[12] gave 2α,6β- (**2**) and 2α,6α-dibromo-17β-acetoxyandrost-4-en-3-one (**3**) in yields of 37 and 50%, respectively (Table 1, run 1). The reaction of **1** with 1 eq of Br_2 at room temperature for 1 h gave **2** and **3** in yields of 11 and 14%, respectively, together with the recovery (56%) of **1** (run 2). However, when the bromination of **1** was carried out with 5 eq of Br_2 for 10 min, **2** and **3** were obtained in 37 and 44% yields, respectively (run 3).

Brominations of **1** in the presence of AgOTf were carried out with 10, 5, and 1 eq of Br_2. First, compound **1** was reacted with 10 eq of Br_2 in the presence of AgOTf (1.2 eq) in benzene at room temperature for 12 h (run 4) to give dibromide **4** (mp 240—242 °C) and tribromide **5** (amorphous powder) in 48 and 28% yields, respectively. Both compounds **4** and **5** showed bands due to aromatic rings in the UV spectra (see Experimental).[13] The ^{1}H- and ^{13}C-NMR spectral data of **4** and **5** are listed in Tables 2 and 3, respectively. The signal assignments were performed on the bases of ^{1}H–^{1}H and ^{1}H–^{13}C correlated spectroscopys (COSYs), distortionless enhancement by polarizaion transfer (DEPT), and heteronuclear multiple bond connection (HMBC) spectral data. The ^{1}H-NMR spectrum of **5** is similar to that of **4** except for the absence of an aromatic proton at C-4. From the spin–spin coupling constants of the H-7′s of **4** and **5** (2.2 and 1.5 Hz, respectively), it is indicated that the protons are arranged in β. These spectral data suggest that compounds **4** and **5** are 2,7α-dibromo- and 2,4,7α-tribromo-17β-acetoxy-3-hydroxy-1-methylestra-1,3,5(10)-triene-6-one, respectively.

As the result of the bromination of **1** with 10 eq of Br_2 in the presence of AgOTf in benzene was different from those of the foregoing brominations without AgOTf in AcOH–Et_2O, further brominations of **1** with 1 and 5 eq of Br_2 in the presence of AgOTf in benzene were investigated. The reaction of **1** with an equivalent of Br_2 in the presence of AgOTf (1.2 eq) in benzene at room temperature for 12 h gave monobromide **6** (mp 157—159 °C, 3%) and dibromide **7** (mp 144—146 °C, 3%), together with the starting material **1** (73 % recovery) and small amounts of unisolated products (run 5). The ^{1}H-NMR spectrum of **6** was similar to that of **1** except for the absence of a proton signal at the 4 position, which suggests that **6** is 4-bromo-17β-acetoxyandrost-4-en-3-one. In the ^{13}C-NMR spectra, the C-6 signal (δ 50.8) of **7** was observed at a lower field by 18.1 ppm than that (δ 32.7) of **6**, indicating a bromine atom linked to C-6 of **7**. The stereochemistry at the 6 position of **7** was revealed by the Karplus rule[14] from the values of dihedral angles of $H_{6\alpha}$-C_6–C_7-$H_{7\beta}$ (58°) and $H_{6\alpha}$-C6–C7-$H_{7\alpha}$ (73°), which corresponds to the spin–spin coupling constants (J=4.6 and 2.3 Hz, respectively) of the α arranged H-6. Therefore, **7** is suggested to be 4,6β-dibromo-17β-acetoxyandrost-4-en-3-one.

The reaction of **1** with 5 eq of Br_2 in the presence of AgOTf (1.2 eq) in benzene at room temperature for 12 h gave six products (run 6): dibromide (**8**) (8%), tribromides (**9**) (20%) and (**10**) (6%), and tetrabromide (**11**) (3%), together with **4** (12%), **5** (14%) and unisolated minor products. In the ^{1}H-NMR spectrum of **8**, two singlet vinyl protons due to H-4 and H-6 were observed at δ 6.39 and 6.56, respectively. The spin–spin coupling constants (J=14.2, 5.6 Hz) of the H-2 of

* To whom correspondence should be addressed. e-mail: saitoset@josai.ac.jp

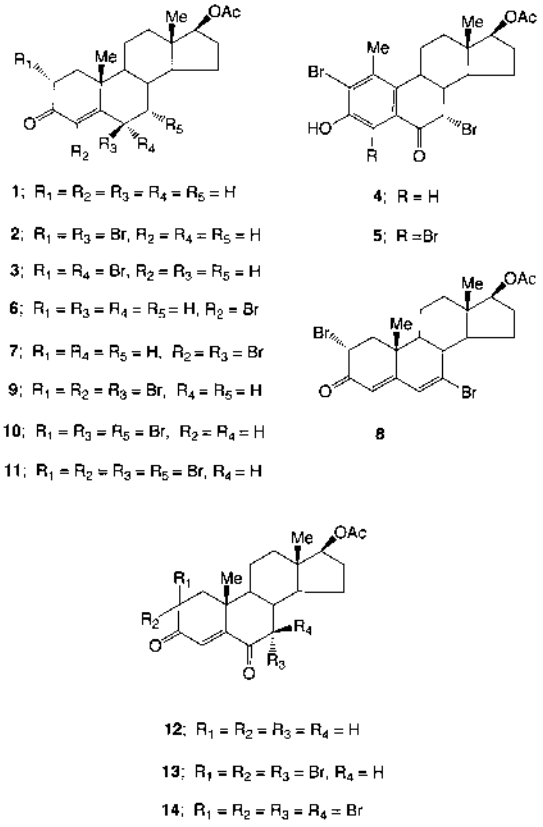

Fig. 1

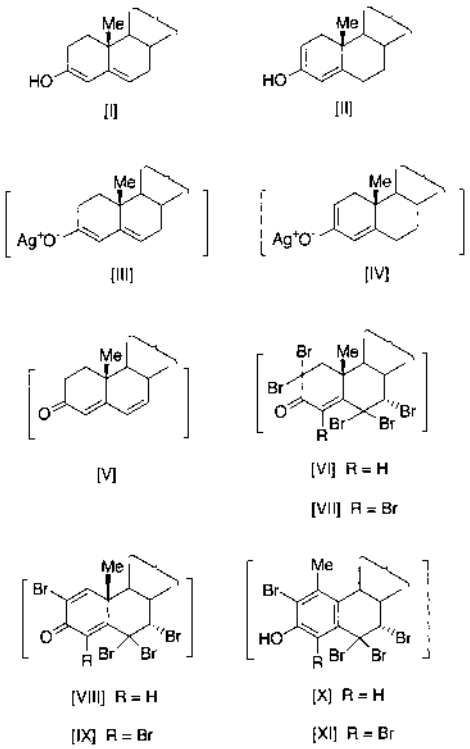

Fig. 2

8 was similar to those of **2** and **3**, which indicates that the H-2 of **8** has the same β configuration as those of **2** and **3**. These spectral data suggest that **8** is 2α,7-dibromo-17β-acetoxyandrost-4,6-dien-3-one. Though compound **9** showed a similar ^{13}C-NMR spectrum to that of **2**, no vinyl proton was observed in the ^{1}H-NMR spectrum, indicating that one bromine atom is substituted at C-4 of **9**. The coupling constants of H-2 (dd, J=14.4, 4.9 Hz) and H-6 (dd, J=4.3, 1.8 Hz) of **9** were similar to the H-2β of **8** and the H-6α of **2**, respectively, indicating that bromine atoms at C-2 and C-6 of **9** are arranged in α and β, respectively. These spectral data suggest that **9** is 2α,4,6β-tribromo-17β-acetoxyandrost-4-en-3-one. In the ^{1}H-NMR spectrum of **10**, the H-2 was observed as a doublet of doublets (J=14.1, 5.0 Hz), which was similar to those of **8** and **9**, suggesting that the bromine atom at C-2 of **10** has an α configuration. The H-6 and H-7 of **10** were observed to be a doublet and a triplet, respectively, having the same coupling constant (J=2.3 Hz). Since the dihedral angles of $H_{6\alpha}$-C_6–C_7-$H_{7\beta}$ in the stereomodel of **10** was nearly 70°, and that of $H_{8\beta}$-C8–C7-$H_{7\beta}$ nearly 80°, the observed spin–spin coupling constants of H-6 and H-7 were in accord with the values estimated by the Karplus rule. These spectral data suggest that **10** is 2α,6β,7α-tribromo-17β-acetoxyandrost-4-en-3-one. Compound **11** exhibited a similar ^{1}H-NMR spectrum to that of **10** except for the lack of a vinyl proton at the 4 position, which indicates, together with FAB-MS spectral data, that **11** is 2α,4,6β,7α-tetrabromo-17β-acetoxyandrost-4-en-3-one.

Compound **10** was further brominated with 3 eq of Br_2 in the presence of AgOTf to afford **4** and **5** in yields of 25 and 56%, respectively (run 8). The same reactions of **9** and **11** gave **5** in yields of 54 and 56 %, respectively (runs 7, 9).

The reaction of 17β-acetoxyandrost-4-en-3,6-dione **12**[15,16] with 3 eq of Br_2 in the presence of AgOTf in benzene gave two unstable products: tribromide **13** (42%) and tetrabromide **14** (17%) (run 10). In the ^{1}H-NMR spectrum of **13** (Table 2), both proton signals at C-2 disappeared and a signal due to H-7β was observed as a doublet (J=3.0 Hz) at δ 4.39, and furthermore, two protons at C-1 were observed as a pair of doublets (J=15.6 Hz) at δ 3.27 and 3.31. The C-2 and C-7 carbon signals of **13** were shifted to lower fields (δ 59.6 and 56.6, respectively), by 25.7 and 10.5 ppm, than C-2 (δ 33.9) and C-7 (δ 46.1), respectively, of **12** in the ^{13}C-NMR spectrum. These spectral data suggest that **13** is 2,2,7α-tribromo-

Table 1. Brominations of Compounds **1** and **9**—**13**

	Starting material	AgOTf	Equivalents of bromine	Reaction times	Products (%)
Run 1[a)]	**1**	−	10	10 min	**2** (37), **3** (50)
Run 2[a)]	**1**	−	1	1 h	**2** (11), **3** (14), **1** (56, recovery)
Run 3[a)]	**1**	−	5	10 min	**2** (37), **3** (44)
Run 4[b)]	**1**	+	10	12 h	**4** (48), **5** (28)
Run 5[b)]	**1**	+	1	12 h	**6** (3), **7** (3), **1** (73, recovery)
Run 6[b)]	**1**	+	5	12 h	**4** (12), **5** (14), **8** (8), **9** (20), **10** (6), **11** (3)
Run 7[b)]	**9**	+	3	10 h	**5** (54)
Run 8[b)]	**10**	+	3	10 h	**4** (25), **5** (56)
Run 9[b)]	**11**	+	3	10 h	**5** (56)
Run 10[b)]	**12**	+	3	10 h	**13** (42), **14** (17)
Run 11[b)]	**13**	+	3	12 h	**4** (42), **5** (22)

All runs were performed at room temperature. Solvent: *a*) AcOH–Et_2O; *b*) benzene. −, absence of AgOTf; +, presence of AgOTf.

Table 2. ^{1}H-NMR Spectral Data for Compounds **1**—**14**[a)]

Proton	**1**	**2**	**3**	**4**	**5**
1	1.70*	2.16 (dd, 14.4, 12.8, Hα)	2.10 (dd, 14.0, 12.8, Hα)	—	—
	2.03*	2.61 (dd, 12.8, 4.9, Hβ)	2.60 (dd, 12.8, 4.9, Hβ)	—	
2	2.32*	4.91 (dd, 14.4, 4.9, Hβ)	4.82 (dd, 14.0, 4.9, Hβ)	—	—
	2.43*	—	—	—	—
4	5.73 (s)	6.01 (s)	6.51 (s)	7.57 (s)	—
6	2.28*	4.98 (dd, 3.7, 1.8, Hα)	—	—	—
	2.40*	-	4.85 (dd, 10.2, 3.6, Hβ)	—	—
7	1.04*	1.64*	1.58*	4.33 (d, 2.2, Hβ)	4.32 (d, 1.5, Hβ)
	1.85*	2.25*	2.30*	—	—
8	1.58*	2.08*	1.83*	2.00*	2.02*
9	0.95*	1.02*	1.55*	2.85*	2.91*
11	1.40*	1.50*	1.45*	1.45*	1.36*
	1.57*	1.61*	1.71*	2.42*	2.29*
12	1.17*	1.20*	1.25*	1.58*	1.58*
	1.80*	1.83*	1.95*	1.83*	1.85*
14	1.06*	1.12*	1.02*	1.78*	1.78*
15	1.36*	1.40*	1.38*	1.45*	1.47*
	1.67*	1.62*	1.89*	1.78*	1.76*
16	1.51*	1.57*	1.62*	1.62*	1.62*
	2.17*	2.27*	2.31*	2.30*	2.34*
17	4.60 (dd, 8.9, 7.9)	4.61 (dd, 8.6, 8.4)	4.62 (dd, 8.6, 8.5)	4.81 (t, 8.5)	4.80 (dd, 8.9, 8.3)
18 (CH_3)	0.84	0.90	0.94	0.89	0.90
19 (CH_3)	1.20	1.63	1.21	2.46	2.43
$COCH_3$	2.05	2.06	2.05	2.08	2.07
OH	—	—	—	6.46 (broad s)	6.60 (broad s)

Proton	**6**	**7**	**8**	**9**	**10**
1	1.79*	1.68	2.17 (dd, 14.2, 12.9, Hα)	2.28 (dd, 14.4 13.1, Hα)	2.20 (dd, 14.1, 12.9, Hα)
	2.02*	2.10	2.59 (dd, 12.9, 5.6, Hβ)	2.65 (dd, 13.1, 4.9, Hβ)	2.66 (dd, 12.9, 5.0, Hβ)
2	2.50—2.70	2.57—2.78	4.93 (dd, 14.2, 5.6, Hβ)	4.97 (dd, 14.4, 4.9, Hβ)	4.97 (dd, 14.1, 5.0, Hβ)
	2.50—2.70	2.57—2.78	—	—	—
4	—	—	6.39 (s)	—	6.08 (s)
6	2.26*	5.70 (dd, 4.6, 2.3, Hα)	6.56 (s)	5.66 (dd, 4.3, 1.8, Hα)	5.10 (d, 2.3, Hα)
	3.27 (ddd, 14.2, 4.0, 2.6)	—	—	—	—
7	1.05*	1.83*	—	1.63*	4.54 (t, 2.3, Hβ)
	1.85	2.28*	—	2.27*	—
8	1.56*	2.05*	2.34 (dd, 9.1, 7.6)	2.07*	2.18*
9	1.00*	0.95*	1.32*	1.03*	1.60*
11	1.30*	1.38*	1.39*	1.48*	1.59*
	1.50*	1.60*	1.60*	1.61*	1.66*
12	1.19*	1.12*	1.25*	1.22*	1.25*
	1.80*	1.80*	1.83*	1.84*	1.84*
14	1.05*	1.00*	1.33*	1.10*	1.42*
15	1.30*	1.30*	1.50*	1.45*	1.36*
	1.60*	1.60*	1.86*	1.66*	1.71*
16	1.48*	1.55*	1.56*	1.56*	1.59*
	2.18*	2.20*	2.23*	2.21*	2.15*
17	4.60 (dd, 8.9, 7.6)	4.63 (dd, 8.9, 7.6)	4.66 (dd, 8.9, 7.3)	4.60 (dd, 8.9, 8.2)	4.69 (dd, 8.3, 7.9)
18 (CH_3)	0.84	0.91	0.88	0.90	0.93
19 (CH_3)	1.24	1.57	1.23	1.64	1.62
$COCH_3$	2.06	2.06	2.10	2.06	2.06
OH	—	—	—	—	—

Proton	**11**	**12**	**13**	**14**
1	2.33 (dd, 14.3, 13.1, Hα)	1.80*	3.27 (d, 15.6)	3.22 (dd, 15.2)
	2.67 (dd, 13.1, 5.2, Hβ)	2.19*	3.31 (d, 15.6)	3.25 (dd, 15.2)
2	4.97 (dd, 14.3, 5.2, Hβ)	2.45*	—	—
	—	2.54*	—	—
4	—	6.16 (s)	6.29 (s)	6.43 (s)
6	5.95 (d, 2.4, Hα)	—	—	—
	—	—	—	—
7	4.54 (t, 2.4, Hβ)	1.95*	4.39 (d, 3.0, Hβ)	—
	—	2.17*	—	—
8	2.15*	1.98*	1.92*	1.76*
9	1.40*	1.40*	1.52*	1.73*
11	1.58*	1.50*	1.57*	1.74*
	1.70*	1.69*	1.72*	1.78*
12	1.26*	1.29*	1.29*	1.30*
	1.83*	1.75*	1.86*	1.87*
14	1.65*	1.26*	1.85*	2.45*
15	1.40*	1.38*	1.33*	2.05*
	1.72*	1.67*	1.75*	2.20*
16	1.57*	1.57*	1.56*	1.60*
	2.26*	2.20*	2.26*	2.25*
17	4.67 (dd, 8.9, 8.2)	4.65 (dd, 8.8, 7.7)	4.68 (dd, 8.8, 8.2)	4.68 (dd, 8.7, 8.0)
18 (CH_3)	0.93	0.86	0.89	0.93
19 (CH_3)	1.62	1.18	1.47	1.40
$COCH_3$	2.06	2.06	2.07	2.10
OH	—	—	—	—

a) Spectra were obtained in $CDCl_3$. Chemical shifts are in ppm from internal Me_4Si. Signal assignments were based on ^{1}H–^{1}H and ^{1}H–^{13}C COSYs, DEPT and HMBC spectral data. Coupling constants (*J* in Hz) are given in parentheses. * These proton signals were overlapped with one or more proton signals.

Table 3. ^{13}C-NMR Spectral Data for **1**—**14**[a)]

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
C-1	35.7	49.7	48.2	138.0	138.1	34.5	36.4	46.4	49.1	48.5	48.2	35.5	56.8	55.9
C-2	33.9	49.6	49.6	136.6	137.3	33.9	34.0	49.5	49.4	48.0	47.5	33.9	59.6	59.4
C-3	199.3	191.2	190.6	151.5	149.1	190.6	190.5	191.1	190.9	184.2	183.9	201.6	183.8	183.8
C-4	123.9	124.6	124.5	112.1	107.4	122.0	126.6	124.7	128.0	123.4	126.0	125.6	123.0	123.0
C-5	170.9	165.5	165.2	129.5	125.9	167.7	162.7	159.9	161.4	163.0	159.4	160.6	158.4	155.9
C-6	32.7	50.5	49.8	191.1	189.9	32.7	50.8	143.5	51.0	49.9	50.2	199.3	193.6	186.7
C-7	31.5	40.0	43.9	50.7	51.6	30.8	39.9	120.5	58.5	39.7	58.3	46.1	56.6	74.4
C-8	35.4	30.0	36.8	41.7	40.9	35.0	30.0	39.9	33.6	29.9	33.5	33.7	37.1	49.1
C-9	53.7	52.3	53.3	41.7	43.2	53.9	52.3	49.8	44.8	52.0	47.5	50.7	45.6	50.0
C-10	38.6	41.5	43.8	122.8	120.6	42.5	42.0	41.3	41.3	42.4	44.0	39.7	42.4	42.6
C-11	20.5	20.3	21.1	22.0	27.5	20.7	20.3	20.1	20.1	20.6	20.3	20.4	20.0	20.9
C-12	36.6	36.1	36.1	37.0	37.0	36.6	36.5	36.1	35.8	36.3	35.9	36.2	35.4	35.9
C-13	42.4	42.5	42.5	43.4	43.6	42.5	42.5	43.5	42.4	44.4	42.4	42.6	43.2	43.7
C-14	50.2	49.3	50.4	45.9	45.9	50.2	49.6	47.5	47.3	49.5	44.6	50.9	46.6	50.4
C-15	23.4	23.2	23.3	23.1	21.9	23.4	23.3	23.0	22.2	23.3	22.2	23.2	22.0	25.6
C-16	27.5	27.2	27.3	27.3	27.3	27.5	27.4	27.4	27.2	27.4	27.2	27.3	27.0	27.5
C-17	82.4	82.0	81.9	82.0	81.6	82.3	82.2	81.6	81.9	82.1	81.8	82.0	81.4	81.6
C-18	12.0	11.9	12.0	13.0	13.1	12.0	12.1	11.9	12.4	12.1	12.4	12.0	12.4	13.0
C-19	17.0	23.1	18.5	21.0	22.8	17.9	21.2	17.0	24.0	21.1	21.1	17.5	18.5	18.6
CO$\underline{C}$H$_3$	21.0	22.7	22.3	21.2	21.1	21.2	22.5	21.1	21.1	23.2	24.5	21.0	21.0	21.1
$\underline{C}$OCH$_3$	171.1	170.9	171.0	171.4	171.0	171.1	171.1	171.0	171.0	171.1	171.0	171.0	171.9	171.0

a) Spectra were obtained in $CDCl_3$. Chemical shifts are in ppm from internal Me_4Si. Signal assignments were based on ^{1}H–^{1}H and ^{1}H–^{13}C COSYs, DEPT, and HMBC spectral data.

17β-acetoxyandrost-4-en-3,6-dione. Compound **14** exhibited a spectrum similar to that of **13** except for the absence of a proton signal at C-7 in the ^{1}H-NMR spectrum. The C-7 carbon signal of **14** in the ^{13}C-NMR spectrum was observed at a lower field (δ 74.4) by 17.8 ppm than that of **13**, which suggests, together with FAB-MS data, that **14** is 2,2,7,7-tetrabromo-17β-acetoxyandrost-4-en-3,6-dione. The reaction of **13** with 3 eq of Br_2 in the presence of AgOTf gave **4** and **5** in yields of 42 and 22%, respectively (run 11). However, **14** was so unstable that it was not further brominated.

The brominations of **1** in AcOH–Et_2O (runs 1—3) gave 2α,6β- (**2**) and 2α,6α-dibromide (**3**), although the yields were dependent upon the amounts of bromine used. In these cases, the substitutions of bromine atoms at the 2- and 6-positions of **1** seemed to occur simultaneously. However, in the controlled bromination in the presence of AgOTf in benzene (run 5), 4-monobromide (**6**) (3%) and 4,6β-dibromide (**7**) (3%), together with the unreacted starting material **1** (73%), were obtained, but no products such as **2** or **3** bearing a bromine atom at the 2 position appeared. These results suggest that AgOTf in the bromination mixture exerts an influence on the reactivity between the 2 position on the one hand and the 4 and 6 positions on the other in the first step of the bromination. Its influence may be explained as follows: It has been thought that brominations of steroidal 4-en-3-ones proceed *via* intermediates such as 3,5-diene-3-ol [I] and 2,4-diene-3-ol [II]. Similarly, in the bromination of **1** in the presence of AgOTf in benzene, it might be thought that silver 3,5-dien-3-olate [III] and silver 2,4-dien-3-olate [IV] are initial intermediates. Breard reported that [I] is more stable than [II].[17)] That 4-monobromide (**6**) and 4,6-dibromide (**7**), but not 2,6-dibromides (**2**, **3**), were obtained in the controlled condition (run 5) suggests that the difference of the stability of [III] over [IV] is much greater than that of [I] over [II]. In the presence of AgOTf, the bromination of **1** may proceed exclusively *via* the intermediate [III] in the first step to give **6** and **7**. When 5 eq of Br_2 were used in the bromination, six products, **4**, **5**, **8**—**11**, were obtained (run 6). All these products were also substituted with bromine at the 2 positions. It seems likely that the bromination at the 2 positions of **1** in the presence of AgOTf occurs after brominations at the 4 and 6 positions. Furthermore, the bromination of **1** with 10 eq of Br_2 in the presence of AgOTf in benzene for 12 h gave only the aromatized products **4** and **5** in good yields. These products might be derived from the products generated in early steps in the bromination.

The proposed mechanisms for the formation of compounds **4**—**11** are inferred. The bromination at C-4 of [III] gives 4-monobromide (**6**), from which 4,6-dibromide (**7**) is led by further bromination at C-6. The bromination at C-6 of [III] may give a 6-bromo-4-en-3-one intermediate, which was not isolated in this study, from which 4,6-dien-3-one intermediate [V] is probably obtained by dehydrobromination between C-6 and C-7. The addition of bromine on the resulting double bond and bromination at C-2 of [V] may give tribromide 2,6,7-tribromide (**10**), from which 2,7-dibromide (**8**) may be obtained by dehydrobromination between C-6 and C-7. Furthermore, it is thought that the bromination at C-2 of **7** gives 2,4,6-tribromide (**9**), from which 2,4,6,7-tetrabromide (**11**) might be led by dehydrobromination between C-6 and C-7, followed by the addition of bromine on the resulting double bond.

Bromination of **10** with 3 eq of Br_2 gave aromatized 6-oxo products **4** and **5** (run 8), while those of **9** and **11** under the same reaction conditions gave only **5** (runs 7, 9). Bromination of 17β-acetoxyandrost-4-en-3,6-dione (**12**) gave tribromide (**13**) bearing two bromine atoms at the 2 position and tetrabromide (**14**) bearing two bromine atoms, both at the 2 and 7 positions (run 10). Tribromide (**13**) was further reacted with 3 eq of Br_2 in the presence of AgOTf to give **4** (42%) and **5** (22%) (run 11). From these results, mechanisms for the formation of **4** and **5** were presumed to be as follows:

bromination at the C-2 and C-6 of **10** may give an intermediate such as [VI] and those of **9** and **11** give an intermediate such as [VII]. It is thought that such intermediates are unstable because they bear two bulky bromine atoms on both the C-2 and C-6. Dehydrobromination between C-1 and C-2 of the intermediates [VI] and [VII] might give dienone-intermediates [VIII] and [IX], respectively. These dienone intermediates can be easily susceptible to dienone–phenol rearrangement[18,19] to give intermediates [X] and [XI]. The hydrolysis of [X] during the aftertreatment of the reactions may give compound **4** and that of [XI] compound **5**. From the result that the bromination of **10** gave **5** together with **4**, it was thought that **5** was also obtained by further bromination at the C-4 of **4**.

Experimental

General Procedures Dry benzene was obtained by refluxing it with Na, followed by distillation. Other chemicals and solvents were of reagent grade, and were obtained from commercial sources. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The thin-layer chromatography (TLC) utilized a Kieselgel 60 F_{254} (Merck), and spots were detected by spraying the plates with $Ce(SO_4)_2$/10% H_2SO_4 (1 : 9) reagent, followed by heating at 100 °C for 5 min. Column chromatography was carried out on a Wakogel C-200, and the eluates were monitored by TLC. SSC-6300 (Senshu Scientific Co., Ltd.) apparatus equipped with SSC-3000A was employed for analytical HPLC using DOCOSIL (4.6×250 mm), and was further equipped with an SSC autoinjector 6310 and SSC fraction collector 6320 for preparative HPLC using DOCOSIL (10×250 mm; flow rate, 1.0 ml/min, column temp, 40 °C). ^{1}H- and ^{13}C-NMR, ^{1}H–^{1}H and ^{1}H–^{13}C COSY, DEPT, and HMBC spectra were obtained using a JEOL JNM-A500 FT NMR spectrometer at 500 and 125 MHz, respectively. Tetramethylsilane was used as an internal standard, and chemical shifts are given in ppm. Multiplicities of ^{1}H-NMR signals are indicated as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), and m (multiplet). FAB-MS were recorded on a JEOL JMS-DX 300 mass spectrometer. UV spectra of ethanol solutions were recorded on a Hitachi-U-3200 spectrophotometer.

Reactions of 1 with Br_2 in AcOH–Et_2O Compound **1** was reacted with 10, 1, and 5 eq of Br_2 in AcOH–Et_2O according to the procedure described by Djerassi *et al.*[12] These results are listed in Table 1 (runs 1—3).

Reaction of 1 with 10 eq of Br_2 in the Presence of AgOTf To a solution of **1** (2.0 g, 6.06 mmol) in dry benzene (10 ml), Br_2 (3.0 ml, 60 mmol) and AgOTf (1.8 g, 7.0 mmol) were added, and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into cold water (50 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined extracts were successively washed with $Na_2S_2O_3$-saturated water, $NaHCO_3$-saturated water, and water, and were then dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to give a residue, which was subjected to column chromatography (a gradient of 0—15% AcOEt in benzene), followed by the application of preparative HPLC (40% H_2O in acetone), to obtain compounds **4** (1.45 g, 48%; mp 240—244 °C, from ether–petroleum ether) and **5** (980 mg, 28%, amorphous powder). FAB-MS of **4** *m/z*: 521 $[M+Na]^+$, 523 $[M+Na+2]^+$, and 525 $[M+Na+4]^+$ with peak height ratios of 1 : 2 : 1. λ_{max} nm (log ε): 223 (4.19) (B band), 282 (4.04) (P band), and 338 nm (3.59) (R band). Anal. Calcd for $C_{21}H_{24}Br_2O_4 \cdot H_2O$: C, 48.67; H, 5.06. Found: C, 48.55; H, 5.03. FAB-MS of **5** *m/z*: 599 $[M+Na]^+$, 601 $[M+Na+2]^+$, 603 $[M+Na+4]^+$, and 605 $[M+Na+6]^+$ with peak height ratios of 1 : 3 : 3 : 1. λ_{max} nm (log ε): 224 (4.08) (B band), 284 (3.86) (P band), and 339 nm (3.43) (R band). *Anal*. Calcd for $C_{21}H_{23}Br_3O_4$: C, 43.55; H, 4.00. Found: C, 43.28; H, 4.13.

Reaction of 1 with an Equivalent of Br_2 in the Presence of AgOTf The general procedure was employed with **1** (1.0 g, 3.03 mmol), AgOTf (0.9 g, 3.5 mmol), and Br_2 (0.15 ml, 3.0 mmol) in dry benzene (5 ml) at room temperature for 12 h to give products **6** (35 mg, 3%; mp 157—159 °C, from ether–petroleum ether) and **7** (48 mg, 3%; mp 144—146 °C, from ether–petroleum ether), and the starting material **1** (73% recovery). FAB-MS of **6** *m/z*: 431 $[M+Na]^+$ and 433 $[M+Na+2]^+$ with peak height ratios of 1 : 1. λ_{max} nm (log ε): 274 (3.92). *Anal*. Calcd for $C_{21}H_{29}BrO_3$: C, 61.41; H, 7.14. Found: C, 61.29; H, 7.21. FAB-MS of **7** *m/z*: 509 $[M+Na]^+$, 511 $[M+Na+2]^+$, and 513 $[M+Na+4]^+$ with height ratios of 1 : 2 : 1. λ_{max} nm (log ε): 274 (3.84). *Anal*. Calcd for $C_{21}H_{28}Br_2O_3$: C, 51.66; H, 5.78. Found: C, 51.37; H, 5.82.

Reaction of 1 with 5 Eq of Br_2 in the Presence of AgOTf The general procedure was employed with **1** (3.0 g, 9.1 mmol), AgOTf (2.7 g, 10.5 mmol), and Br_2 (2.3 ml, 45 mmol) in dry benzene (10 ml) at room temperature for 12 h to give products **4** (540 mg, 12%), **5** (750 mg, 14.3%), **8** (350 mg, 7.9%; amorphous powder), **9** (1.03 g, 20%; amorphous powder), **10** (310 mg, 6%; amorphous powder), and **11** (153 mg, 3%; amorphous powder). FAB-MS of **8** *m/z*: 507 $[M+Na]^+$, 509 $[M+Na+2]^+$, and 511 $[M+Na+4]^+$ with peak height ratios of 1 : 2 : 1. λ_{max} nm (log ε): 293 (3.82). *Anal*. Calcd for $C_{21}H_{26}Br_2O_3$: C, 51.87; H, 5.39. Found: C, 51.63; H, 5.43. FAB-MS of **9** *m/z*: 587 $[M+Na]^+$, 589 $[M+Na+2]^+$, 591 $[M+Na+4]^+$, and 593 $[M+Na+6]^+$ with peak height ratios of 1 : 3 : 3 : 1. λ_{max} nm (log ε): 275 (4.06). *Anal*. Calcd for $C_{21}H_{27}Br_3O_3$: C, 44.47; H, 4.99. Found: C, 44.23; H, 5.07. FAB-MS of **10** *m/z*: 587 $[M+Na]^+$, 589 $[M+Na+2]^+$, 591 $[M+Na+4]^+$, and 593 $[M+Na+6]^+$ with peak height ratios of 1 : 3 : 3 : 1. λ_{max} nm (log ε): 250 (3.69). *Anal*. Calcd for $C_{21}H_{27}Br_3O_3$: C, 44.47; H, 4.99. Found: C, 44.15; H, 5.13. FAB-MS of **11** *m/z*: 665 $[M+Na]^+$, 667 $[M+Na+2]^+$, 669 $[M+Na+4]^+$, 671 $[M+Na+6]^+$, and 673 $[M+Na+8]^+$ with peak height ratios of 1 : 4 : 6 : 4 : 1. λ_{max} nm (log ε): 273 (4.00). *Anal*. Calcd for $C_{21}H_{26}Br_4O_3$: C, 39.04; H, 4.06. Found: C, 38.89; H, 4.15.

Reactions of 9, 10, and 11 with 3 Eq of Br_2 in the Presence of AgOTf Brominations of **9** and **11** with 3 eq of Br_2 in the presence of AgOTf in benzene at room temperature for 10 h according to the general procedure gave **5** in 54 and 56% yields, respectively. Bromination of **10** under the same reaction condition gave **4** and **5** in yields of 25 and 56%, respectively.

Reaction of 12 with 3 Eq of Br_2 in the Presence of AgOTf The general procedure was employed with **12** (300 mg, 0.87 mmol), AgOTf (200 mg, 0.78 mmol), and Br_2 (0.14 ml, 2.68 mmol) in dry benzene (2 ml) at room temperature for 10 h to give products **13** (210 mg, 41.5%) and **14** (110 mg, 16.7%). FAB-MS of **13** *m/z*: 601 $[M+Na]^+$, 603 $[M+Na+2]^+$, 605 $[M+Na+4]^+$, and 607 $[M+Na+6]^+$ with peak height ratios of 1 : 3 : 3 : 1. λ_{max} nm (log ε): 257 (3.76). *Anal*. Calcd for $C_{21}H_{25}Br_3O_4$: C, 43.40; H, 4.34. Found: C, 43.09; H, 4.55. FAB-MS of **14** *m/z*: 679 $[M+Na]^+$, 681 $[M+Na+2]^+$,683 $[M+Na+4]^+$, 685 $[M+Na+6]^+$, and 687 $[M+Na+8]^+$ with peak height ratio of 1 : 4 : 6 : 4 : 1. This compound was so unstable that the elemental analysis was not obtained.

Reaction of 13 with 3 eq of Br_2 in the Presence of AgOTf The general procedure was employed with **13** (200 mg, 0.344 mmol), AgOTf (90 mg, 0.346 mmol), and Br_2 (0.053 ml, 1.03 mmol) in dry benzene (2 ml) at room temperature for 12 h to give **4** (73 mg, 42.2%) and **5** (50 mg, 21.5%).

References

1) Crowne C. W. P., Evans R. M., Green G. F. H., Long A. G., *J. Chem. Soc*., **1956**, 4351—4356.
2) Zurfluh R., Tamm C., *Helv. Chim. Acta*, **55**, 2495—2517 (1972).
3) Kaufmann S., Pataki J., Rosenkranz G., Romo J., Djerassi C., *J. Am. Chem. Soc*., **72**, 4531—4534 (1950).
4) Velluz L., Nomine G., Joly R., Petit A., *Bull. Soc. Chim. Fr.*, **1953**, 905.
5) Solo A. J., Singh B., *J. Org. Chem*., **30**, 1658—1659 (1965).
6) Mattox V. R., Woroch E. L., Fleisher G. A., Kendall E. C., *J. Biol. Chem*., **197**, 261—270 (1952).
7) Evans R. M., Hamlet J. C., Hunt J. S., Jones P. G., Long A. G., Oughton J. F., L. Stephenson L., Walker T., Wilson B. M., *J. Chem. Soc*., **1956**, 4356—4368.
8) Gould D., Shapiro E. L., Herzog H. L., Gentles M. J., Hershberg E. B., Charney W., Gilmore M., Tolksdorf S., Eisler M., Perlman P. L., Pechet M. M., *J. Am. Chem. Soc*., **79**, 502—503 (1957).
9) Djerassi C., Finch N., Cookson R. C., Bird C. W., *J. Am. Chem. Soc.*, **82**, 5488—5493 (1960).
10) Mauli R., Ringold H. J., Djerassi C., *J. Am. Chem. Soc*., **82**, 5494—5500 (1960).
11) Villotti R., Ringold H. J., Djerassi C., *J. Am. Chem. Soc*., **82**, 5693—5700 (1960).
12) Djerassi C., Rosenkranz G., Romo J., Kaufmann S., Pataki J., *J. Am. Chem. Soc*., **72**, 4534—4540 (1950).
13) Burawoy A., *Ber. Dtsch. Chem. Ges*., **63**, 3155—3172 (1930).
14) Jackman L. M., Sternhell S., " Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," ed. by Barton D. H., Doering W. R., Pergamon Press, Oxford, London, Edinburgh, New York, Toronto, Sydney, Paris, Braunschweig, 1969, pp. 280—356.
15) Holland H. L., Riemaland E., Daum U., *Can. J. Chem*., **60**, 1919—1923 (1982).
16) Cooper A., Roberts A. D., "Dictionary of Steroids," ed. by Hill R. A., Makin H. L. J., Chapman and Hall, Ltd., London, New York, Tokyo,

Melbourne, Madras, 1991, p. 513.
17) Breard C. C., "Organic reactions in steroid chemistry," ed. by Fried J., Edwards J. A., Van Nostrand Reinhokd Co., New York, Cincinnati, Toronto, London, Melbourne, 1972, Vol. I, pp. 265—374.
18) Auwers K., Ziegler K., *Justis Liebigs Ann. Chem.*, **425**, 217—226 (1921).
19) Djerassi C., Rosenkranz G., Romo J., Pataki J., Kaufmann S., *J. Am. Chem. Soc*., **72**, 4540—4544 (1950).