[Chem. Pharm. Bull. 25(3) 385—396 (1977)]

UDC 547.597.02.04 : 543.422.25

Studies on Terpenoids and Related Alicyclic Compounds. III.[1] Bromination-Dehydrobromination of 2-Oxo-5α-santanolide

Koji Yamakawa, Kiyoshi Nishitani, Etuko Nagakura, Shinpei Kidokoro, and Reiji Sakaguchi

Faculty of Pharmaceutical Sciences, Science University of Tokyo[2]

(Received August 5, 1975)

Bromination of 2-oxo-5α-santanolide (I) gave a bromide (II) together with III as a minor bromide. This equatorial bromide (III) epimerized into the axial bromide (II). Dibromination of I gave dibromoketones (IV and V). Configuration and conformation of the bromoketones (II-V) were assigned from their infrared, ultraviolet proton magnetic resonance, and circular dichroism spectra. Dehydrobromination of II gave an enone (VI), whose treatment with ethanolic hydrochloric acid afforded an equilibrium mixture of VI and VII. Hydrogenation of VI gave a C-4 axial epimer of I. Dehydrobromination of dibromoketones (IV and V) under several conditions gave a mixture of IX-XII, and XIV-XV, and their structures were confirmed from their spectroscopic data. A mechanism of the bromination of I, and dehydrobromination of IV and V are discussed.

Keywords——2-oxo-5α-santanolide; bromination-dehydrobromination; conformation; dehydrobromination mechanism; Favorsky rearrangement; NMR; CD; NMR shift reagent; haloketone rule; 1,3-diaxial bromine interaction

The preceding paper of this series[1] have described the bromination-dehydrobromination of 2-oxo-5β-santanolide. For the purpose of comparison, a similar sequence of reactions was applied to 2-oxo-5α-santanolide (I),[3] which is a trans-decaline type sesquiterpene.

Bromination of 2-Oxo-5α-santanolide (I)

In the 5β-series,[1] the bromination of 2-oxo-5β-santanolide with bromine in chlotoform gave predominantly 3β(ax)-bromide together with three bromides; 3α-bromide, 1β-bromide and 1α-bromide. In contrast to this result, the bromination of the 2-ketone (I) with a molar equivalent of bromine in chloroform gave a bromide (II), mp 186—187°, in 71% yield, and a small amount of a minor bromide (III), mp 182—184°, which were isolated by fractional recrystallization.

The structures of these bromides (II and III) were determined by means of proton magnetic resonance (PMR),[4] infrared (IR),[5] and ultraviolet (UV)[6] spectral data in the manner similar to that described in the preceding paper.[1] The data are shown in Table I.

Positions of the bromine atom in these bromides (II and III) are established to be C-3 from their PMR spectra showing a double doublet signal at δ 4.22 (J=3, 1.5 Hz) and a doublet signal at δ 4.30 (J=10.5 Hz) due to C-3 H, respectively. Coupling constants between C-3 H and C-4β H in II and III were measured and the dihedral angles between these protons (61° or 117° for II) were calculated using modified Karplus equation.[4] On the basis of these calculated dihedral angles, the possible conformation of II and the orientation of the bromine atom in II should be shown to be a ring A chair form [Aa (3α-bromide)] or one of the ring A boat

1) Part II: K. Yamakawa and K. Nishitani, *Chem. Pharm. Bull.* (Tokyo), **25**, 371 (1977).
2) Location: *Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan.*
3) K. Yamakawa, S. Kidokoro, N. Umino, R. Sakaguchi, T. Takakuwa, and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **21**, 296 (1973).
4) R.J. Abraham and J.S.E. Holker, *J. Chem. Soc.*, **806** (1963).
5) R.N. Jones, D.A. Ransay, F. Herling and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).
6) R.C. Cookson, *J. Chem. Soc.*, **282** (1954).

forms [the ring A boat form with C-3 and C-10 upwards; Da (3α-bromide) and Db (3β-bromide), and a ring A boat form with C-2 and C-5 upwards; Ea (3β-bromide)] in Fig. 1.

Circular dichroism (CD) curve of II showed a strong positive Cotton effect as given in Fig. 2. The boat forms (Db and Ea) should show a negative Cotton effect curve in the axial haloketone rule[7] in CD spectrometry, therefore these boat forms are unsuitable for a conformations of II.

Comparing the PMR spectrum of II with that of 2-ketone (I), one of the C-1 H signals in II was observed at a lower field (δ 3.22) than that of the ketone (*I*; δ 2.42 and 2.28). This 1,3-diaxial bromine interaction[1] can not be observed in the boat form Da but in the chair form Aa. From these results, the stereoformula of II is shown to be 2-oxo-3α-bromo-5α-santanolide, and its conformation is the ring A chair form A. These results are also supported by the shift of the carbonyl absorption in UV ($\Delta\lambda$ +18 nm) over the parent ketone (I) and by the presence of equa-

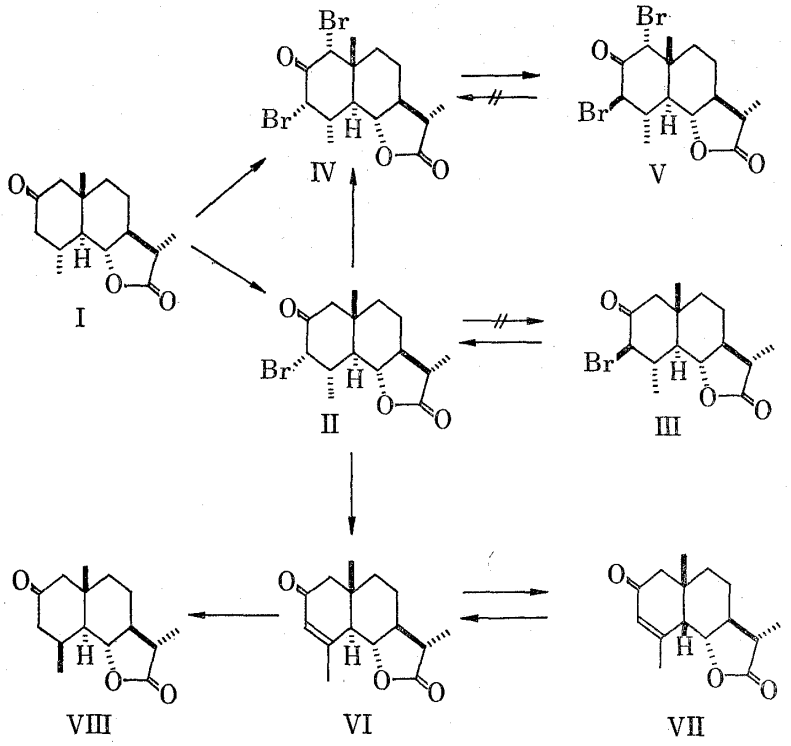


Chart 1

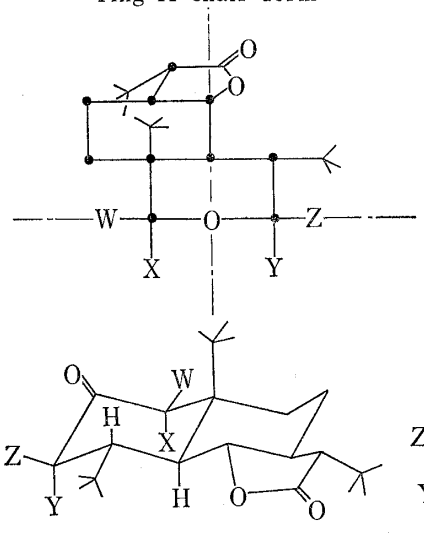
Table I. PMR, UV and CD Data of Bromides (II-V)

Compd. No.	PMR (δ, $CDCl_3$) 4-CH_3	1-H (*J*=Hz)	3-H (*J*=Hz)	Calcd. Dihedral angle[a,b]	UV: λ_{max}^{EtOH} nm ($\Delta\lambda$)[c]	CD; $[\theta]_{max}^{MeOH}$ (at nm)
I	1.26	2.28, 2.42 (1H each)	—[d]	—	292	+3400°(288)
II	1.31	3.22[e] (1H, d, *J*=13)	4.22(1H, dd, *J*=1.5, *J*=3.0)	61° or 117°	310(+18)	+19600°(311)
III	1.52	2.44(2H, s)	4.30(1H, d, *J*=10.5)	149° or 23°	284 (−8)	+7600°(292)
IV	1.32	4.02(1H, d, *J*=1.5)	4.34(1H, dd, *J*=1.5, *J*=4.4)	53° or 124°	339(+47)	+1400°(338)
V	1.56	4.18(1H, s)	5.15(1H, d, *J*=10.2)	148° or 24°	309(+17)	−14100°(302)

a) between 3-H and 4-H
b) Using modified Karplus equation[4]; 12.4 $\cos^2\theta$ ($0° \leq \theta \leq 90°$), 14.3 $\cos^2\theta$ ($90° \leq \theta \leq 180°$)
c) $\Delta\lambda$=λ(bromide)-λ(2-ketone(I))
d) uncleared

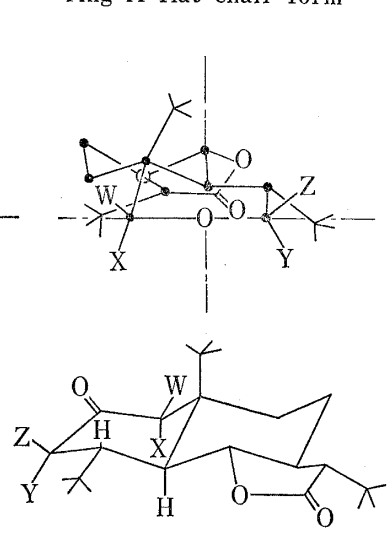
7) C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **78**, 1506 (1957).

ring A chair form



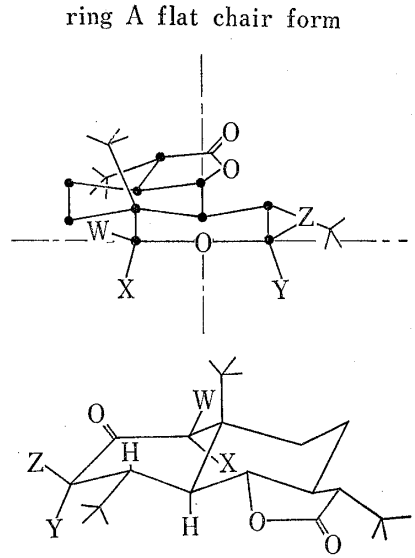
Aa : Y=Br,
W=X=Z=H (II, 61°)[a)]

ring A flat chair form



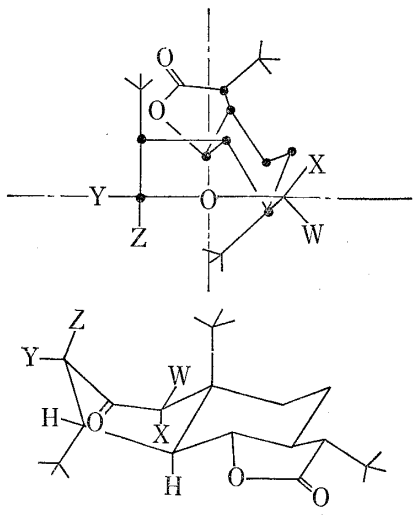
Ba : Z=Br,
W=X=Y=H (III, 149°)[a)]
Bb : X=Z=Br,
W=Y=H (V, 148°)[a)]
Bc : W=Z=Br,
X=Y=H (V, 148°)[a)]

ring A flat chair form



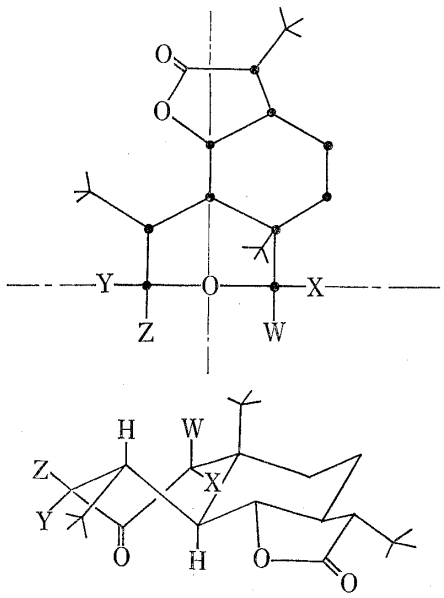
Ca : X=Y=Br,
W=Z=H (IV, 53°)[a)]
Cb : W=Y=Br,
X=Z=H (IV, 53°)[a)]

ring A boat form
with C-3, C-10 upwards



Da : Y=Br, W=X=Z=H (II, 61°)[a)]
Db : Z=Br, W=X=Y=H (II, 61°)[a)]
Dc : X=Y=Br, W=Z=H (IV, 53°)[a)]
Dd : W=Y=Br, X=Z=H (IV, 53°)[a)]

ring A boat form
with C-2, C-5 upwards



Ea : Z=Br, W=X=Y=H (II, 117°)[a)]
Eb : W=Y=Br, X=Z=H (V, 24°)[a)]
Ec : X=Y=Br, W=Z=H (V, 24°)[a)]
Ed : W=Z=Br, X=Y=H (IV, 124°)[a)]

Fig. 1

a) Compound No., and the calculated dihedral angle between C-3 H and C-4 H.

torial-equatorial long range coupling[8] between C-1 H and C-3 H ($J_{1,3}$=1.5 Hz). Consequently the stereoformula of the other 3-bromide (III) is shown to be 2-oxo-3β-bromo-5α-santanolide. On the basis of the calculated dihedral angle between C-3 H and C-4β H (149°) derived from the PMR spectrum of III showing a signal due to C-3 H at δ 4.30 (d, $J_{3,4}$=10.5 Hz), only a ring A flat chair form Ba is possible for the conformation of III. This result is also supported by a weak positive CD curve showing in Fig. 2 and the shift of the carbonyl absorption in UV[6] ($\Delta\lambda$ −8 nm) over the parent ketone (I).

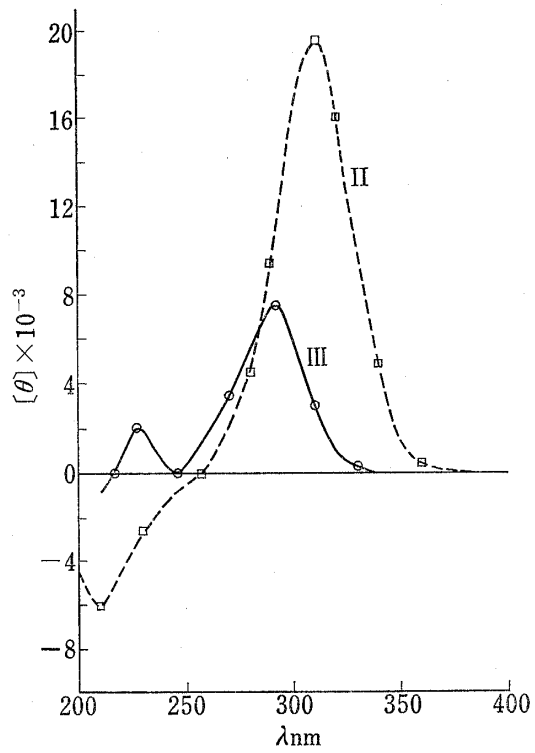


Fig. 2. Circular Dichroism Curves of Monobromides (II and III)

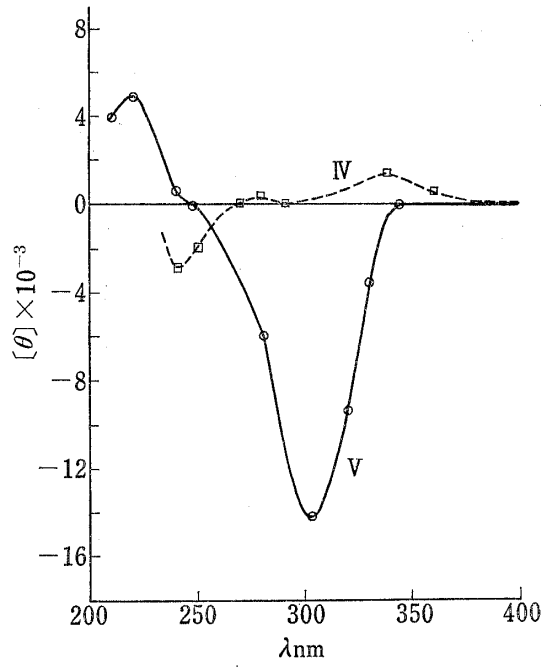


Fig. 3. Circular Dichroism Curves of Dibromides (IV and V)

Djerassi and Nakano[9] and Shoppee, *et al.*[10] reported that halogenation of 2-oxo-5α-steroids afforded 3α(ax)-halo-2-oxo-5α-steroids together with 3β-halo-2-ketones as minor products. The 3α-bromoketone is converted into 3β-bromoketone by equilibriation with hydrogen bromide in acetic acid at 20°. Epimerization of the bromoketones (II and III) with hydrogen bromide saturated in acetic acid at room temperature for 45 hr was attempted, and 3β(eq)-bromoketone (III) epimerized into 3α(ax)-bromoketone (II), while epimerization of II did not occur under the same conditions. These facts suggest that 3β(eq)-bromoketone (III) is less stable than 3α(ax)-bromoketone (II), and the unstability of II is considered to be due to the fact that C-3 equatorial bromine bond is sterically hindered by the C-4 methyl which has a peri interaction with C(6)-O bond in γ-lactone. The three bonds of C=O, C(4)–CH_3, and C(3)–Br are coplanar, and there is the dipole-dipole repulsion between the carbonyl-oxygen and the bromine atom. These results are supported by the conformation of the bromides (II and III). Namely, 3α(ax)-bromide (II) is a ring A chair form, but 3β(eq)-bromide (III) is a ring A flat chair form because of this dipole-dipole repulsion.

8) C. Cuvelie, R. Ottinger, and J. Reisse, *Tetrahedron Letters*, **1972**, 277.
9) C. Djerassi and T. Nakano, *Chem. Ind.* (London), **1960**, 1385; T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. Pharm. Bull.* (Tokyo), **11**, 465 (1963).
10) *a*) C.W. Shoppee and T.E. Bellas, *J. Chem. Soc.*, **1963**, 3366; *b*) C.W. Shoppee and S.C. Sharma, *J. Chem. Soc.*, (*C*), **1967**, 2385.

The bromination of the 2-ketone (I) with two molar equivalents of bromine in chloroform gave a mixture of dibromoketones (IV and V) in 3: 2 ratio as evidenced by PMR spectroscopy, which was fractionally recrystallized to give a dibromide (IV), mp 196—197°, and the other dibromide (V), mp 186—188°. The former dibromide (IV) was also obtained quantitatively on the bromination of the bromide (II). Treatment of IV with hydrogen bromide in acetic acid gave the epimeric dibromide (V) quantitatively.

The PMR spectrum of IV showed a doublet signal at δ 4.02 (J=1.5 Hz) due to C-1 H and a double double signal at δ 4.34 (J=4.4, 1.5 Hz) due to C-3 H which coupled with C-4β H and with C-1 H. The PMR spectrum of V showed a signal at δ 4.18 (s) due to C-1 H and a doublet signal at δ 5.15 (J=10.2 Hz) due to C-3 H which coupled with C-4β H. Consequently, the dibromides (IV and V) are 1,3-dibromides.

On the basis of the calculated dihedral angles between C-3 H and C-4β H (148° or 24°) in the PMR spectrum of V, two ring A flat chair form [Bb (1α,3β-dibromide) and Bc (1β,3β-dibromide)] and two ring A boat forms with C-2 and C-5 upwards [Eb (1β,3α-dibromide) and Ec (1α,3α-dibromide)] are possible for the conformational structure of V. The PMR spectrum of V exhibited a signal due to C-3 H at a lower field (α 5.15, d) than that of 3β-bromide (III; δ 4.30, d) and 3α-bromide (II, δ 4.22, dd) because of the deshielding effect of the C-1 axial bromine atom. This PMR data and the shift of the carbonyl absorption in UV ($\Delta\lambda$ +17 nm) over the parent ketone (I) suggest a presence of an axial bromine atom. These facts suggest that the flat chair form Bc and the boat form Ec should be eliminated for the conformation of V. The strong negative CD curve of V can not explain the boat form Eb but the flat chair form Bb. Therefore, the stereoformula of V is 2-oxo-1α,3β-dibromo-5α-santanolide and its conformation of ring A flat chair form.

On the basis of the calculated dihedral angles between C-3 H and C-4β H (53° or 124°) in the PMR spectrum of IV, two ring A flat chair forms [Ca (1α,3α-dibromide) and Cb (1β,3α-dibromide)], two ring A boat forms with C-3, C-10 upwards [Dc(1α,3α-dibromide) and Dd (1β,3α-dibromide)], and a ring A boat form with C-2, C-5 upwards [Ed (1β,3β-dibromide)] are possible.

In an expected PMR spectrum of the flat chair form Cb a signal due to C-1 H should be observed at a lower field than due to C-3 H because of the 1,3-diaxial interaction between C-3 axial bromine atom and C-1 axial proton, but actually the signals due to C-1 H and C-3 H are observed at δ 4.02 (d, J=1.5 Hz) and δ 4.34 (dd, J=4.4, 1.5 Hz). Therefore, the flat chair form Cb is unsuitable for a conformational structure of IV.

Recently, Cuvelier, *et al.*[8] reported that the long range coupling in some α-halogenocyclohexanones and halogenodecalone derivatives. The W-shaped equatorial-equatorial coupling constant (J_{ee}) and the M-shaped axial-aixal coupling constant (J_{aa}) were 1.0—2.0 and 0.8—1.0 Hz, respectively, and the axial-equatorial coupling (J_{ae}) was never observed. This W-shaped long range coupling (J_{ee}=1.5 Hz) between C-3 (eq) and C-1 (eq) H was observed in the PMR spectrum of IV. These suggest that the conformational structure of IV can not be Dc and Dd but the flat chair form Ca (1α,3α-dibromide) or the boat form Ed (1β,3β-dibromide).

In the UV spectrum of IV, the shift of the carbonyl absorption over the parent ketone (I) ($\Delta\lambda$ +47 nm) suggests the presences of two axial-like bromine atoms, so the flat chair form Ca or the boat form Ed is supported for a conformation IV. The CD spectrum of IV can be explained in terms of the conformation Ca, namely minus and plus signs of the two axial bromine

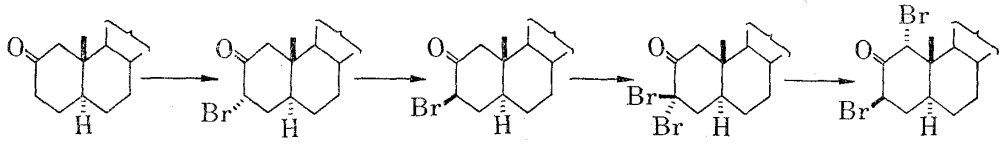


Chart 2

bonds at C-1 and C-3 are compensated each other, and hence IV should show a positive Cotton effect sign. However, the boat form Ed should show a negative Cotton effect sign.

Shopee, *et al*[10a] claimed that initial product on the bromination of 5α-cholestan-2-one was 3,3-dibromide, which rearranged to 1α,3β-dibromo-5α-cholestan-2-one in the presence of hydrogen bromide (Chart 2). But now, we propose a probable mechanism in this bromination, in which 3α(ax)-bromide (II) is the initial product and then further bromination occurs by an α-attack of bromine at C-1 position to give 1α,3α-diaxial dibromide (IV), which is easily epimerized into V in the presence of hydrogen bromide.

Dehydrobromination of Bromoketones (II, IV, and V)

Dehydrobromination of 3α-bromo-2-ketone (II) under the same conditions as in the 5β-series[1] gave 5α-2-oxo-3-ene (VI), mp 134—134.5°. This enone (VI) showed a character of an α,β-unsaturated ketone in the IR ($\nu_{C=O}$ 1660, $\nu_{C=C}$ 1613 cm^{-1}), the UV (λ_{max}^{EtOH} 239 nm), and the PMR spectrum (C-3 H, δ 5.95).

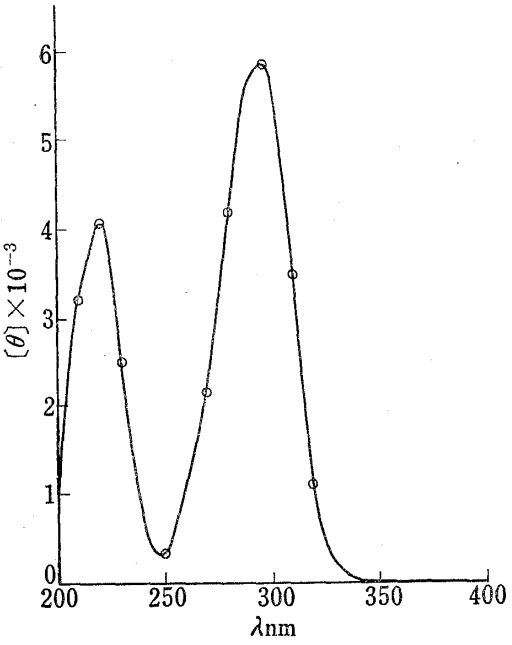


Fig. 4. Circular Dichroism Curve of VIII

The *trans*-configuration of A/B ring in the enone (VI) was manifest in the PMR spectrum, in which C-6 H signal showed as a triplet (J=10 Hz) at δ 4.00. The enone (VI) was refluxed in 10% hydrochloric acid-ethanol to give an equilibrium mixture of the 5α-enone (VI) and a 5β-enone (VII) in a 1:1 ratio as evidenced by PMR spectroscopy.

The 5β-enone (VII), mp 208—209°, was separated from the equilibrium mixture using chromatography or fractional recrystallization. VII was identical with the dehydrobromination product of 5β-2-oxo-3-bromide, which had been reported in the preceding paper.[1]

Reduction of VI catalyzed by palladium-charcoal afforded a novel C-4 epimer of I, 2-oxo-4α,5α(H)-santanolide (VIII), mp 173—174.5°. The CD spectrum of VIII is shown in Fig. 4. Consequently, all four isomers of 2-oxosantanolide were synthesized in our laboratory.[1,3]

The dehydrobromination of the dibromides (IV and V) was carried out in a manner similar to that described for the bromide (II). The reaction products were a complex mixture, and their formation ratios varied depending on reaction conditions. The formation ratios of the products under several conditions are shown in Table II. The reaction mixture was separated into five neutral products and an acidic product. The neutral products were separated into five fractions from 1 to 5 (F1-F5) by chromatography on silica gel, and the structure of each component was confirmed from their spectroscopic data. These neutral products contain three dehydrobromination products (IX, X, and XII), two displacement products (XI and XII), and a rearrangement product (XIV). A/B ring *trans* fusion of these products (IX-XV) were manifest in their PMR spectra, in which the C-6 H signals showed as triplet (IX-XII; J= 10 Hz) and double doublet (XIV, XV; J=9, 10 Hz). Elution with benzene gave two fractions (F1 and F2). F1 gave a bromoenone (X), mp 132—133° and F2 gave another bromoenone (IX), mp 134°. These bromoenones (IX and X) showed a character of an α,β-unsaturated ketone in their IR [$\nu_{C=O}$ 1673 (IX) and 1684 cm^{-1} (X)], UV [λ_{max}^{EtOH} 242 (IX) and 250 nm (X)], and the PMR spectra [IX: δ 2.15 (4-CH_3), 6.08 (3-H); X: δ 2.15 (4-CH_3), 5.95 (3-H)], respectively. The position of the bromine atom in these bromoenones (IX and X) was determined by means

Table II. Product Ratio of Dehydrobromination of IV and V

Compd. No.	Temp. (°C)	Product (%)						
		IX	X	XI	XII	XIV	XV	Others
IV	100	31	—	27.5	0.8	14	3	17.5[a]
	140	32	20	—	4	10.5	3.5	30
V	130	45	trace	7	6.5	20	6	15
	140	51.5	19.5	trace	4	2	3.7	20

a) 3.5% of V was afforded.

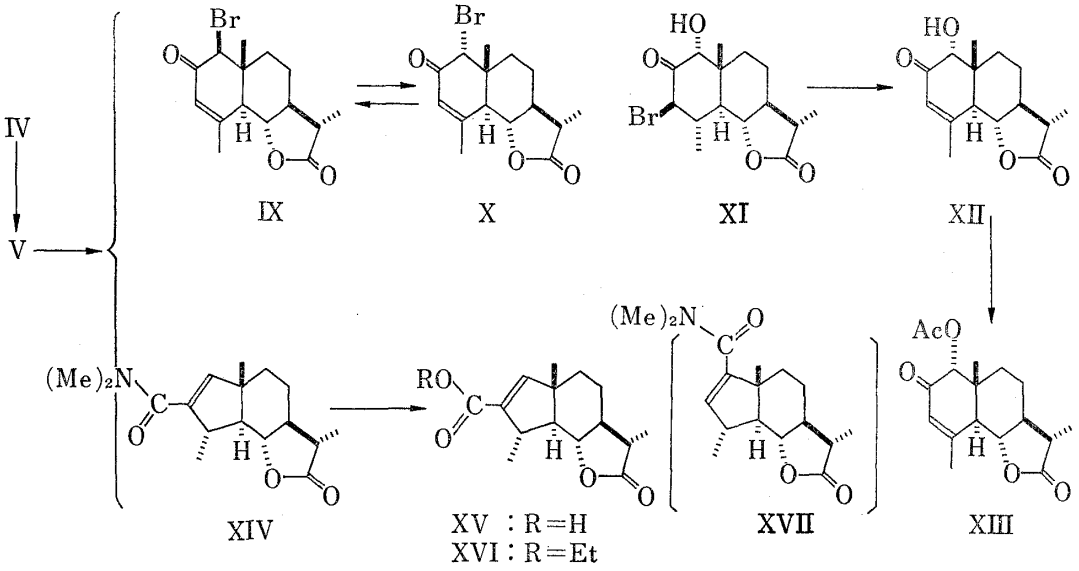


Chart 3

of their PMR spectra, in which their singlet signals due to the C-1 H's were observed at a low field. IX epimerized into an equilibrium mixture of IX and X with lithium bromide and lithium carbonate in dimethyl formamide (DMF) at 120—130°. These facts suggest that these bromoenones (IX and X) are epimers mutually with respect to the C-1 bromine bond. The PMR spectra of IX and X exhibited the singlet signals at δ 4.70 and 4.00 due to the C-1 H's, respectively. These PMR data are similar to those of 2-oxo-1α(ax)-bromo-3-en-5β-santanolide (δ 4.77) and 2-oxo-1β(eq)-bromo-3-en-5β-santanolide (δ 3.88), which described in the preceding paper,[1] respectively. Consequently, the structure of the bromoenones (IX and X) are shown to be 2-oxo-1β-(ax)-bromo-3-en-5α-santanolide and 2-oxo-1α(eq)-bromo-3-en-5α-santanolide, respectively.

Elution of the residual mixture with a mixture of benzene and ethyl acetate (50: 1, 20: 1, and 5: 1) gave three fractions (F3—F5). F-3 (50: 1) gave a hydroxy-bromide (XI), mp 211—212° (decomp.). The IR spectrum of XI showed absorption bands at δ 3475 cm^{-1} (OH) and 1728 cm^{-1} (C=O), and its PMR spectrum (measured in pyridine-d_5) showed a singlet signal at δ 3.95 due to the C-1 H and a doublet signal at δ 5.39 (J=10 Hz) due to the C-3 H. The structure of XI was shown to be 2-oxo-1-hydroxy-3-bromide from the above PMR data. The β-orientation of the bromine atom at C-3 was determined on the basis of the coupling constant (J=10 Hz) between the C-3 H and the C-4β H. The axial configuration of the C-1 OH in XI was confirmed by means of the PMR spectrum, in which a doublet signal due to the C-3 H was observed at a lower field (δ 5.39) than that in the 3β-bromoketone (III; δ 4.72, measured in pyridine-d_5). This result is supported by the Kawazoe rule.[11] From these spectral data, the stereoformula of XI is shown to be 1α-hydroxy-3β-bromo-2-oxo-5α-santanolide.

11) Y. Kawazoe, Y. Satoh, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

Table III. IR, UV and PMR Data of Bromoenones (IX, X)

Compd. No.	IR; ν_{max}^{KBr} cm^{-1} cyclohexanone $(\Delta\nu)^{a)}$	UV; λ_{max}^{EtOH} nm $(\Delta\lambda)^{b)}$	PMR (δ, $CDCl_3$) 1-H
VI	1660	239	2.32(2H, s)
IX	1673(+13)	242 (+3)	4.70(1H, s)
X	1684(+24)	250(+11)	4.00(1H, s)

a) $\Delta\nu=\nu$(IX or X)-ν(VI)
b) $\Delta\lambda=\lambda$(IX or X)-λ(VI)

F-4 (20:1) gave a hydroxy-enone (XII), mp 219—222° (decomp.), which was also obtained on the dehydrobromination of XI. The structure was deduced to be 2-oxo-1α-hydroxy-3-en-5α-santanolide from the spectral properties [IR ν_{max}^{KBr} 3410 (OH) and 1665 (enone) cm^{-1}; UV λ_{max}^{EtOH} 242.5 nm; PMR δ 3.47 (C-1 H) and 5.92 (C-3 H)], and the above dehydrobromination result. XII was converted into the ketol acetate (XIII).

F-5 (5:1) gave a novel nitrogen containing compound (XIV), whose compositional formula was $C_{17}H_{25}O_3N$ as evidenced by elemental analysis. The IR spectrum of XIV exhibited an amide absorption band at 1623 cm^{-1}, and the signals appeared at δ 3.04 (s) and 6.02 (d, J=2 Hz) due to the N,N-dimethyl protons and a vinylic proton respectively, in its PMR spectrum. This nitrogen containing compound (XIV) may have been produced on the Favorsky rearrangement of the dibromide (V), in which a cyclopropanone intermediate is attacked by dimethylamine which is generated from dimethylformamide as used solvent under the conditions.

In order to determine whether the structure of this amide is XIV or XVII, its PMR spectrum was measured using tris(dipivaloylmethanato)europium Eu(DPM)$_3$] as a shift reagent.[12] The slope of the values for several concentrations of Eu(DPM)$_3$ in a solution of the amide are shown in Fig. 5. This amide (XIV) have two chelation centers, amide and γ-lactone, with Eu(DPM)$_3$. The paramagnetic shift of the signals due to the amide methyl protons are the largest. However, the shift of the C-6 H signal and a doublet methyl signal are negligible in the PMR spectrum of the amide. These data show that Eu(DPM)$_3$ selectively coordinates to the amide group, not to the γ-lactone group. The paramagnetic shift of the C-4 methyl signal is larger than that of the C-10 methyl signal. Therefore, the C-4 methyl is nearer the amide group than the C-10 methyl group, so the structure of the amide (XIV) is determined to be A-2-nor-3-(N,N-dimethylcarbamoyl)-5α-sant-1-enolide.

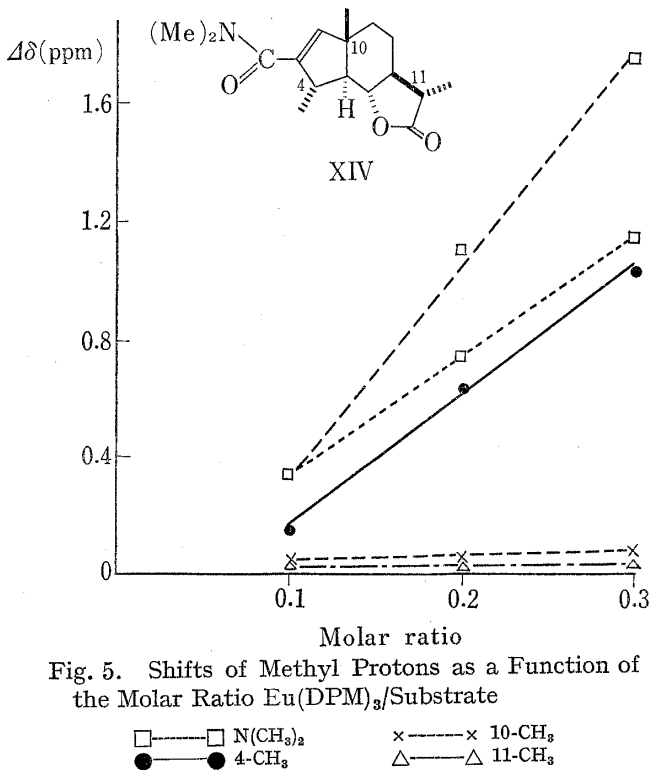


Fig. 5. Shifts of Methyl Protons as a Function of the Molar Ratio Eu(DPM)$_3$/Substrate

A carboxylic acid compound (XV), mp 242—244°, was isolated from the acidic part of the dehydrobromination

12) C.C. Hinkley, *J. Am. Chem. Soc.*, **91**, 5160 (1969); R. von Ammon and R.D. Fischer, *Angew. Chem. Intern. Ed.*, **11**, 675 (1972).

products. It was identical with the carboxylic acid derived from the amide compound (XIV) by hydrolysis. The structure of the carboxylic acid (XV) is shown to be A-2-nor-3-carboxy-5α-sant-1-enolide.

Dehydrobromination Mechanism

For the elucidation of the dehydrobromination mechanisms, the reaction was carried out under several conditions (see Table III). From the Table III, experimental results may be summarized as follows: (a) The 1β,3α-dibromide (V) is obtained at a low temperature on the reaction of the 1α,3α-dibromide (IV). (b) 1α-Bromoenone (X) is not obtained at low temperature, but at a high temperature. (c) The major product is the 1β-bromoenone (IX). (d) Yield of the displacement product, 1α-hydroxy-3β-bromide (XI), and that of the Favorsky rearrangement products, amide (XIV) and acid (XV), increases at low temperature.

The result (a) suggests that the epimerization of diaxial-dibromide (IV) into equatorial-axial dibromide (V) easily occurs in the initial step of this reaction at low temperature. The result (b and c) suggest that the initial dehydrobromination product of IV and V is the 1β-bromoenone (IX) a part of which epimerizes into the 1α-bromoenone (X) with temperature.

However, *cis*-elimination of hydrogen bromide from V should give the 1α-bromoenone (X). Therefore, we consider that the major bromoenone, 1β-bromoenone (IX), is derived from a 1β,3α-dibromide (V′) by *trans* E2 reaction and/or from the 1-bromocyclopropanone intermediate [A], which are derived from 1α,3β-dibromide. The intermediate 1β,3α-dibromide (V′) is probably produced from the 1α,3β-dibromide by epimerization under these basic conditions.

The 1α-hydroxy-enone (XII) is formed on the dehydrobromination of the 1α-hydroxy-3β-bromide (XI) which may be formed from the 1β,3α-dibromide *via* 3-bromocyclopropanone intermediate [B]. The intermediate [B] is attacked by-a hydroxy ion from α-side due-to the steric hindrance.

The ring-contraction products, amide (XIV) and carboxylic acid (XV), are selectively formed on the Favorsky rearrangement of V with base.

The dibromide (V) produces the bromocyclopropanone intermediate [A], which is attacked by dimethylamine as a nucleophile. The selective ring-opening of the cyclopropanone anion takes place, and the dehydrobromination of the resulting ring-contraction bromide gives the amide (XIV).

These reaction mechanisms are illustrated in Chart 4.

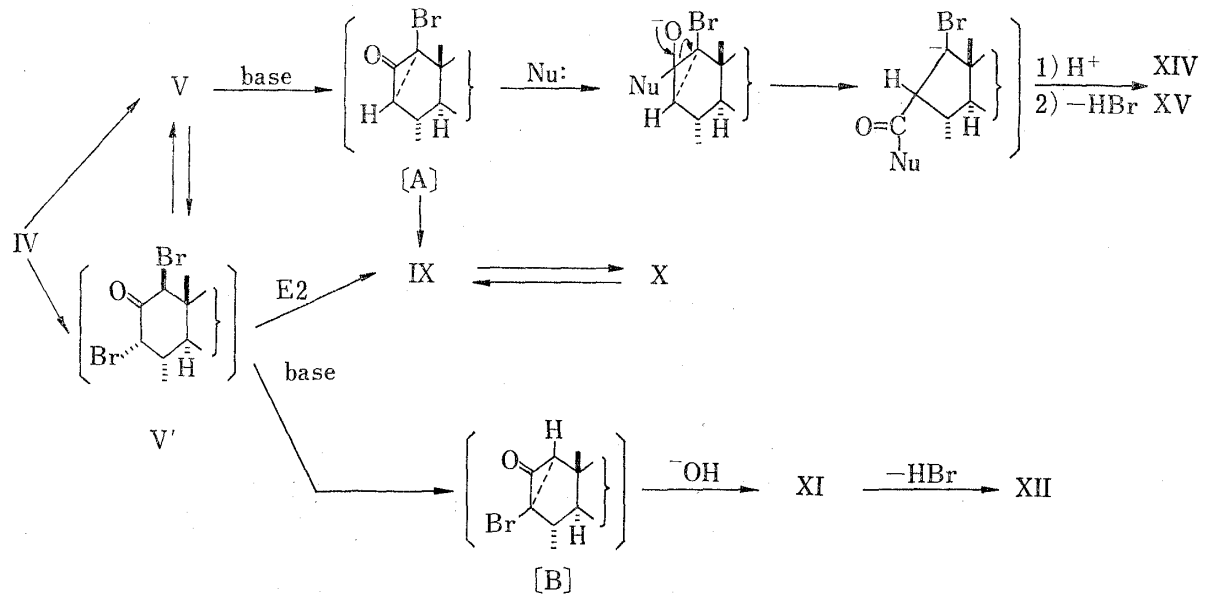


Chart 4

Experimental

Experimental conditions were the same as described in the preceding paper.[1]

Bromination of 2-Oxo-5α-santanolide (I)——To a stirred solution of I[3] (2.0 g) in $CHCl_3$ (200 ml), a solution of Br_2 (1.40 g) in the same solvent (20 ml) was added dropwise. Br_2 was immediately absorbed for 10 min at room temperature. Evaporation of $CHCl_3$ under a reduced pressure left colorless crystals, mp 168—170°, in quantitative yield, which were recrystallized from EtOH to give 2-oxo-3α-bromide (II) as colorless plates, mp 186—187°, in 71% yield. *Anal.* Calcd. for $C_{15}H_{21}O_3Br$: C, 54.72; H, 6.43; Br, 24.27. Found: C, 54.73; H, 6.63; Br, 24.27. $[\alpha]_D^{26}$ +165° ($CHCl_3$, c=0.41); IR (cm^{-1}): 1771 (γ-lactone), 1721 (cyclohexanone); UV λ_{max}^{EtOH} 310 nm (ε 120); NMR ($CDCl_3$ δ): 0.94 (3H, s; C-10 CH_3), 1.25 (3H, d, J=7 Hz; C-11 CH_3), 1.31 (3H, d, J=5 Hz; C-4 CH_3), 3.22 (1H, d, J=13 Hz; C-1α H), 3.90 (1H, t, J=10 Hz; C-6 H), 4.22 (1H, dd, J=3, 1.5 Hz; C-3H).

The above mother liquor was chromatographed over silica gel and gave a small amount of 2-oxo-3β-bromide (III) as colorless plates, mp 182—184°. *Anal.* Calcd. for $C_{15}H_{21}O_3Br$: C, 54.72; H, 6.43; Br, 24.27. Found: C, 54.54; H, 6.53; Br, 24.24. $[\alpha]_D^{27°}$ +138.6° ($CHCl_3$ c=0.54): IR (cm^{-1}): 1768 (γ-lactone), 1730 (cyclohxanone); UV λ_{max}^{EtOH} 284 nm (ε 41); NMR ($CDCl_3$, δ): 0.92 (3H, s; C-10 CH_3), 1.22 (3H, d, J=7 Hz; C-11 CH_3), 1.52 (3H, d, J=7 Hz; C-4 CH_3), 2.44 (2H, s; C-1 H), 3.87 (1H, t, J=10 Hz; C-6 H), 4.30 (1H, d, J=10.5 Hz; C-3 H).

Epimerization of II and III with Hydrogen Bromide in Acetic Acid——To a solution of III (50 mg) in AcOH (5 ml), saturated HBr in AcOH (5 ml) was added, and the whole stirred for 31 hr at room temperature. The reaction mixture was concentrated and was extracted with $CHCl_3$, and then washed and dried. Evaporation of $CHCl_3$ afforded a mixture of II and III in 2: 3 ratio as evidenced by nuclear magnetic resonance (NMR) spectrometry.

II in the same solvent was stirred under same condition, but II was completely recovered. The reaction mixture was stirred for additional 45 hr at room temperature, but the result was not changed.

1α,3α-Dibromo-2-oxo-5α-santanolide (IV)——To a stirred solution of II (2.0 g) in $CHCl_3$ (200 ml), a solution of Br_2 (1.0 g) in the same solvent was added dropwise during 4 hr at room temperature. The reaction mixture was stirred for additional 1 hr at room temperature. The reaction solution was washed with 5% $NaHCO_3$, 10% $Na_2S_2O_3$, and H_2O and dried. Evaporation of the solvent afforded pale yellow dibromide, in a quantitative yield. Recrystallization from EtOH gave 2-oxo-1α,3α-dibromide (IV) as colorless plates, mp 196—197° (decomp.), in 62.5% yield. *Anal.* Calcd. for $C_{15}H_{20}O_3Br$: C, 44.14; H, 4.95; Br, 39.15. Found: C, 44.12; H, 4.95; Br, 39.11. $[\alpha]_D^{27}$+50.4° ($CHCl_3$, c=0.6); IR (cm^{-1}): 1770 (γ-lactone), 1723 (cyclohexanone); UV λ_{max}^{EtOH} 339 nm (ε 187); NMR ($CDCl_3$, δ): 1.10 (3H, s; C-10 CH_3), 1.26 (3H, d, J=7 Hz; C-11 CH_3), 1.32 (3H, d, J=5 Hz; C-4 CH_3), 3.87 (1H, t, J=10 Hz; C-6 H), 4.02 (1H, d, J=1.5 Hz; C-1 H), 4.34 (1H, dd, J=4.4, 1.5 Hz; C-3 H).

Dibromination of I——To a stirred solution of I (2.0 g) in $CHCl_3$ (200 ml), a solution of Br_2 (2.8 g) in the same solvent was added dropwise during 4 hr at room temperature, and the reaction mixture was stirred another 1 hr. The reaction mixture was treated in the usual manner. Evaporation of $CHCl_3$ under reduced pressure left pale yellow crystals in a quantitative yield. This product was a mixture of IV and V in 3: 2 ratio, which was indicated by NMR spectroscopy. Fractional crystallization of the crude crystals from EtOH gave IV (1.19 g; 36.5%), mp 196—197° (decomp), which was identical in the IR and NMR spectrum with an authentic sample of IV, and 1α,3β-dibromide (V) (0.47 g; 14.3%) as colorless plates, mp 186—188°. *Anal.* Calcd. for $C_{15}H_{20}O_3Br_2$: C, 44.14; H, 4.95; Br, 39.15. Found: C, 43.86; H, 4.94; Br, 39.78. $[\alpha]_D^{27}$−15° ($CHCl_3$, c=0.85); IR (cm^{-1}): 1776 (γ-lactone), 1730 (cyclohexanone); UV λ_{max}^{EtOH} 309 nm (ε 191); NMR ($CDCl_3$, δ): 1.10 (3H, s; C-10 CH_3), 1.27 (3H, d, J=7 Hz; C-11 CH_3), 1.56 (3H, d, J=6 Hz; C-4 CH_3), 3.91 (1H, t, J=10 Hz; C-6 H), 4.18 (1H, s; C-1 H), 5.15 (1H, d, J=10.2 Hz; C-3 H).

Epimerization of IV into V——To a solution of IV (50 mg) in AcOH (5 ml), saturated HBr in AcOH (5 ml) was added with stirring during 34 hr at room temperature. After evaporation of AcOH and neutralization with 5% $NaHCO_3$, the resulting mixture was extracted with $CHCl_3$, and the extracts were washed with H_2O and dried. Evaporation of $CHCl_3$ afforded 1α,3β-dibromide (V) (46 mg).

2-Oxosant-3-en-6,12-olide (VI)——According to the procedure described by Corey, *et al.*,[10] to a mixture of LiBr (544 mg), Li_2CO_3 (732 mg), and dimethylformamide (80 ml), 3α-bromide (II) (1.285 g) was added, the mixture was flashed with N_2, and then heated with stirring at 120—130° for 1.4 hr. After the solution was cooled and poured into dil. HCl (50—100 ml), the aqueous mixture was extracted with $CHCl_3$, and then washed with 5% $NaHCO_3$. The neutral extract was washed with H_2O, dried, and $CHCl_3$ was removed. The residue was chromatographed over silica gel. Elution with benzene gave the enone (VI) (540 mg; 56%), which was recrystallized from EtOH to give colorless needles, mp 134—134.5°. *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.43; H, 8.04. $[\alpha]_D^{25}$+178° ($CHCl_3$, c=0.7); IR (cm^{-1}): 1777, 1766 (γ-lactone), 1660 and 1613 (enone); UV λ_{max}^{EtOH} 239 nm (ε 14000); NMR ($CDCl_3$, δ): 1.03 (3H, s; C-10 CH_3), 1.27 (3H, d, J= 7 Hz; C-11 CH_3), 2.13 (3H, m, W 1/2=6 Hz; C-5 H), 4.00 (1H, t, J=10 Hz; C-6 H), 5.95 (1H, m, W 1/2=6 Hz; C-3 H).

Epimerization of Enone (VI) into VII——To a solution of VI (16 mg) in EtOH (10 ml), 10% HCl (2 ml) was added and the solution was refluxed for 3 hr. The reaction was monitored by gas-liquid chromatography.

The reaction mixture was concentrated and neutralized with 5% $NaHCO_3$ and then extracted with benzene. Evaporation of benzene gave a residue (16 mg) which was a mixture of VI and VII, in 1: 1 ratio by NMR spectroscopy. The crystalline residue was separated into VI and VII by silica gel chromatography. The enone (VII), mp 208—209°, was identical with the authentic specimen of 5β-2-oxosant-3-enolide (VII) which was prepared from the corresponding 5β-2-oxo-3-bromide. Treatment of 5β-2-oxosant-3-enolide (VII) under the same condition gave a 1: 1 equilibrium mixture of VI and VII.

2-Oxo-4,5,7α(H),6,11β(H)-satan-6,12-olide (VIII)——A solution of VI (133 mg) in EtOH (18 ml) was hydrogenated over 10% Pd-C catalyst (16 mg) under an ordinary temperature and pressure. Filtration and removal of EtOH *in vacuo* afforded colorless plates in a quantitative yield. Recrystallization from EtOH gave colorless plates, mp 173—174.5°. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.06; H, 9.02. $[\alpha]_D^{26}$ +100° ($CHCl_3$, c=0.7); IR (cm^{-1}): 1766 (γ-lactone), 1720 (cyclohexanone); UV λ_{max}^{EtOH} 289 nm (ε 20); NMR ($CDCl_3$, δ): 1.05 (3H, s; C-10 CH_3), 1.08 (3H, d, J=7 Hz; C-4 CH_3), 1.26 (3H, d, J=7 Hz; C-11 CH_3), 4.02 (1H, dd, J=9, 11 Hz; C-6 H).

Dehydrobromination of Dibromide (V) and (IV)——General Procedure: This procedure is essentially the same as described above for the monobromide (II). To a mixture of LiBr (280 mg), Li_2CO_3 (365 mg) in dimethylformamide (40 ml), the dibromide (V) or (IV) (816 mg) was added, the mixture was flushed with N_2 and then warmed and stirred to keep a constant temperature between 100° and 140° for several hours. After the solution had cooled, it was poured into dil. HCl (50—100 ml). The aqueous mixture was extracted with CH_2Cl_2, the organic layer was washed with H_2O, and then the acidic product was extracted with 5% $NaHCO_3$. The neutral and acidic products were separated into several products by column chromatography and fractional recrystallization. These results are listed in Table III under various conditions.

(a) Neutral Products: According to the above general procedure, the reaction condition at 140° for 80 min was carried out. The CH_2Cl_2 extract was washed with H_2O, dried, and evaporated giving viscous brown oil (630 mg). The neutral oil was chromatographed over silica gel (20 g).

The fractions eluted with below solvents: fractions 1 and 2, benzene; fraction 3, benzene: EtOAc (20: 1); fraction 4, benzene: EtOAc (5: 1). Recrystallization of the fraction residue from EtOH afforded pure samples. Fraction 1 gave 2-oxo-1α-bromo-3-ene (X) (95 mg); analytical sample as colorless needles, mp 132—133°. *Anal.* Calcd. for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.85; Br, 24.42. Found: C, 55.14; H, 5.86; Br, 23.96. $[\alpha]_D^{26}$ +185° ($CHCl_3$, c=0.85); IR (cm^{-1}): 1771 (γ-lactone), 1684 and 1619 (enone); UV λ_{max}^{EtOH} 250 nm (ε 8100); NMR ($CDCl_3$, δ): 1.14 (3H, s; C-10 CH_3), 1.27 (3H, d, J=7 Hz; C-11 CH_3), 2.15 (3H, m, W 1/2=3 Hz; C-4 CH_3), 2.95 (1H, d, J=10 Hz; C-5 H), 4.00 (1H, s; C-1 H), 4.00 (1H, t, J=10 Hz; C-6 H), 5.95 (1H, m, W 1/2=5 Hz; C-3 H).

Fraction 2 gave 2-oxo-1β-bromo-3-ene (IX) (250 mg); analytical sample as colorless plates, mp 134°. *Anal.* Calcd. for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.85; Br, 24.42. Found: C, 55.11; H, 6.00; Br, 23.90. $[\alpha]_D^{26}$ +79.2° ($CHCl_3$, c=0.51); IR (cm^{-1}): 1776 (γ-lactone), 1673 and 1626 (enone); UV λ_{max}^{EtOH} 242 nm (ε 8600); NMR ($CDCl_3$, δ): 1.03 (3H, s; C-10 CH_3), 1.27 (3H, d, J=7 Hz; C-11 CH_3), 2.15 (3H, m, W 1/2=5 Hz; C-4 CH_3), 2.82 (1H, d, J=10 Hz; C-5 H), 4.02 (1H, t, J=10 Hz; C-6 H), 4.70 (1H, s; C-1 H), 6.08 (1H, m, W 1/2=6 Hz; C-3 H).

Fraction 3 gave 2-oxo-1α-hydroxy-3-ene (XII) (20 mg); analytical sample as colorless plates, mp 219—222° (decomp.). *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.63; H, 7.50. $[\alpha]_D^{26}$ +263° ($CHCl_3$, c=0.37); IR (cm^{-1}): 3410 (OH), 1768 (γ-lactone), 1665 and 1609 (enone); UV λ_{max}^{EtOH} 242.5 nm (ε 13290); NMR ($CDCl_3$ δ): 0.95 (3H, s; C-10 CH_3), 1.27 (3H, d, J=7 Hz; C-11 CH_3), 2.15 (3H, dd, W 1/2=3 Hz; C-4 CH_3), 3.12 (1H, d, J=12 Hz; C-5 H), 4.02 (1H, dd, J=10, 12 Hz; C-6 H), 3.47 (1H, s: C-1 H), 5.92 (1H, m, W 1/2=5 Hz; C-3 H).

Fraction 4 gave A-2-nor-3-(N,N-dimethylcarbamoyl)-5α-sant-1-en olide (XIV) (10 mg); analytical sample as colorless needles, mp 182—184°. *Anal.* Calcd. for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.00; H, 8.52; N, 4.75. $[\alpha]_D^{26}$ −14.4° ($CHCl_3$, c=0.5); IR (cm^{-1}): 1772 (γ-lactone), 1623 (amide), 1595 (C=C); NMR ($CDCl_3$, δ): 0.97 (3H, s; C-10 CH_3), 1.18 (3H, d, J=7 Hz; C-4 CH_3), 1.23 (3H, d, J=7 Hz; C-11 CH_3), 3.04 (6H, s; $N(CH_3)_2$), 4.10 (1H, dd, J=9, 11 Hz; C-6 H), 6.02 (1H, d, J=2 Hz; C-1 H).

(b) Acidic Product: The above alkaline solution was acidified and extracted with EtOAc. The extract was washed with H_2O and dried. Evaporation of the EtOAc left pale yellow crystals (18 mg). Recrystallization from EtOH gave A-2-nor-1-ene-3-carboxylic acid (XV) as colorless prisms, mp 242—244°. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.70; H, 7.55. $[\alpha]_D^{26}$ +67.7 ($CHCl_3$, c=0.44); IR (cm^{-1}): 3180 (COOH), 1768 (γ-lactone), 1700 (COOH), 1582 (C=C); NMR ($CDCl_3$, δ): 0.94 (3H, s; C-10 CH_3), 1.22 (3H, d, J=7 Hz; C-11 CH_3), 1.33 (3H, d, J=7 Hz; C-4 CH_3), 2.95 (1H, m; C-4 H), 4.10 (1H, t, J=10 Hz; C-6 H), 7.00 (1H, d, J=2 Hz; C-1 H).

Dehydrobromination of 1α,3α-Dibromide (IV)——The conditions described above were used. To a mixture of LiBr (272 mg), Li_2CO_3 (365 mg), in dimethylformamide (40 ml), 1α,3α-dibromide (IV) (816 mg) was added, and the mixture was warmed at 100° for 80 min. The reaction products were separated in the same manner as above.

(a) The neutral products (671 mg) were separated into bromides V (17 mg) and IX (156 mg), XII (4 mg), and XIV (68 mg), which were identical in mixed mp, and IR, UV, and NMR spectra with respective authentic samples. The structure of a new compound XI (121 mg) was found to be 2-oxo-1α-hydroxy-3β-bromo-5α-santanolide obtained as colorless needles, mp 211—212°. *Anal.* Calcd. for $C_{15}H_{21}O_4Br$: C, 52.19; H, 6.13; Br

23.15. Found: C, 51.84; H, 6.29; Br, 22.68. $[\alpha]_D^{26}+88°$ (EtOH, $c=0.34$); IR (cm^{-1}): 3475 (OH), 1770 (γ-lactone), 1728 (cyclohexanone); UV λ_{max}^{EtOH} 266 nm (ε 140); NMR (pyridine-d_5, δ): 0.82 (3H, s; C-10-CH_3), 1.17 (3H, d, $J=7$ Hz; C-11 CH_3), 1.61 (3H, d, $J=6$ Hz; C-4 CH_3), 3.90 (1H, t, $J=10$ Hz; C-6 H), 3.95 (1H, s; C-1 H), 5.39 (1H, d, $J=10$ Hz; C-3 H).

(b) Acidic product gave XV (15 mg) which was identical with the authentic sample of XV.

Epimerization of IX into X——A solution of IX (230 mg) was added to a mixture of LiBr (100 mg) and Li_2CO_3 (150 mg) in dimethylformamide (20 ml) and heated with stirring at 130—135° for 100 min. The solution was cooled and poured into dil. HCl (60 ml). The aqueous mixture was extracted with CH_2Cl_2 and gave a dark brown viscous oil, which was chromatographed over silica gel. Fraction 1 (from benzene elution) gave X (26 mg) and fraction 2 (from benzene elution) gave IX (62 mg), which were identical with authentic samples of X and IX, respectively.

Dehydrobromination of XI——This procedure is essentially the same as described above. To a mixture of LiBr (50 mg) and Li_2CO_3 (68 mg) in dimethylformamide (20 ml), XI (150 mg) was added, and the mixture was heated at 130—150° with stirring for 80 min. The reaction mixture was treated as described above, and a crude brown oily product (72 mg) was obtained. The products were chromatographed over silica gel. Elution with benzene–EtOAc (10: 1) gave 2-oxo-1α-hydroxy-3-en-5α-santanolide (XII), mp 216—219°, (11 mg) which was identical with the authentic sample of XII. The starting material XI was recovered in a trace amount.

Hydrolysis of Amide (XIV)——A solution of XIV (100 mg) in 20% KOH solution (32 ml) was refluxed for 3 hr. After the alkaline solution had been cooled it was acidified and extracted with EtOAc. The extract was washed with H_2O and dried. Evaporation of EtOAc gave a dicarboxylic acid in a quantitative yield. The crude acid without purification was dissolved in a mixture of EtOH (10 ml) and 10% HCl (10 ml). After the mixture had been refluxed for 110 min, EtOH was evaporated. The residue was neutralized with $NaHCO_3$ and extracted with EtOAc. The extract was washed with H_2O and dried. Evaporation of EtOAc gave a brown oil (90 mg), which was chromatographed over silica gel. Carboxylic acid ethyl ester (XVI) (24.5 mg; 25% yield), mp 110—120°, was obtained from the first benzene eluate. Recrystallization from aq. EtOH gave colorless prisms, mp 120—121°. *Anal.* Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.28; H, 8.36. $[\alpha]_D^{26}+64.1°$ ($CHCl_3$, $c=0.44$); IR (cm^{-1}): 1778 (γ-lactone), 1710 (ester); NMR ($CDCl_3$, δ): 0.93 (3H, s; C-10 CH_3), 1.22 (3H, d, $J=7$ Hz), 1.33 (3H, d, $J=7$ Hz), 1.28 (3H, t, $J=7$ Hz; ester CH_3), 2.95 (1H, m; C-4 H), 4.08 (1H, t, $J=10$ Hz; C-6 H), 4.21 (2H, q, $J=7$ Hz; ester CH_3), 6.81 (1H, d, $J=2$ Hz; C-1 H).

Carboxylic acid (XV) (33 mg, 35% yield) was obtained from the second benzene eluate, which was recrystallized from EtOH to colorless prisms, mp 242—244°, which was identical with the authentic sample of XV.

Acknowledgements (−)-α- Santonin was kindly supplied by Dr. Ohara of Fujisawa Pharmaceutical Co., Ltd. The authors are indebted to Mr. Takakuwa, Nippon Bunko Co., Ltd., for ORD and CD spectral measurement, to Dr. Suzuki, Tanabe Seiyaku Co., Ltd., for microanalyses, and to Mrs. Sanada in this laboratory for NMR spectral measurement.