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

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Mono- and di-bromination of 2-oxo-5β-santanolide (I), and dehydrobromination of the bromoketones were carried out. Monobromides (II, III, IV, and V) and dibromides (VII and VIII) were obtained. The stereoformulae of these bromides (II—V, and VII—VIII) were determined by infrared, ultraviolet, nuclear magnetic resonance, and circular dichroism spectroscopy. The C-4 axial epimer of I was obtained by hydrogenation of the enone (IX), which was prepared from II. Dehydrobromination of dibromoketones (VII and VIII) under several conditions gave a mixture of XII to XVIII. These structures were confirmed from spectroscopic data. A mechanism of dehydrobromination of VII and VIII is discussed.

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

Since the synthetic studies on 5α- and 5β-2-oxosantan-6,12-olide (A/B ring trans and cis fused) from α-santonin were carried out,[1] the relationship between the conformation and reactivity of 2-oxo-sesquiterpenoids and 2-oxostereroids has become of interest. Recently, Satoh and his coworkers[3] described bromination and related reactions of 2-oxo-5β-steroids, and reported interesting results. Now, we wish to report on the bromination-dehydrobromination of 2-oxo-5β-santanolide (I).

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

Bromination of 2-oxo-5β-steroids gave the 1β(ax)-bromide, which was reported by Satoh, *et al.*[3] In contrast to these results the bromination of 2-oxo-5β-santanolide (I) with a molar equivalent of bromine in chloroform gave a mixture of a major bromide (II), mp 191—192° and three other minor bromides; (III), mp 202—203°; (IV) mp 185—186°; and (V), mp 186—188°, which were isolated by fractional recrystallization and preparative thin-layer chromatography.

The stereoformulae of these bromides (II—V) were determined from the proton magnetic resonance (PMR),[4] infrared (IR),[5] and ultraviolet (UV)[6] spectral data which shown in Table I.

1) Part I: K. Yamakawa, S. Kidokoro, N. Umino, R. Sakaguchi, T. Takakuwa, and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **21**, 296 (1973).
2) Location: *Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan.*
3) Y. Satoh, A. Horiuchi, T. Matsukura, and A. Hagitani, *Bull. Chem. Soc. Japan.*, **41**, 3032 (1968).
4) R.J. Abraham and J.S.E. Holker, *J. Chem. Soc.*, **1963**, 806.
5) R.N. Jones, D.A. Ransay, F. Herling, and K. Dorbriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).
6) R.C. Cookson, *J. Chem. Soc.*, **1954**, 282.

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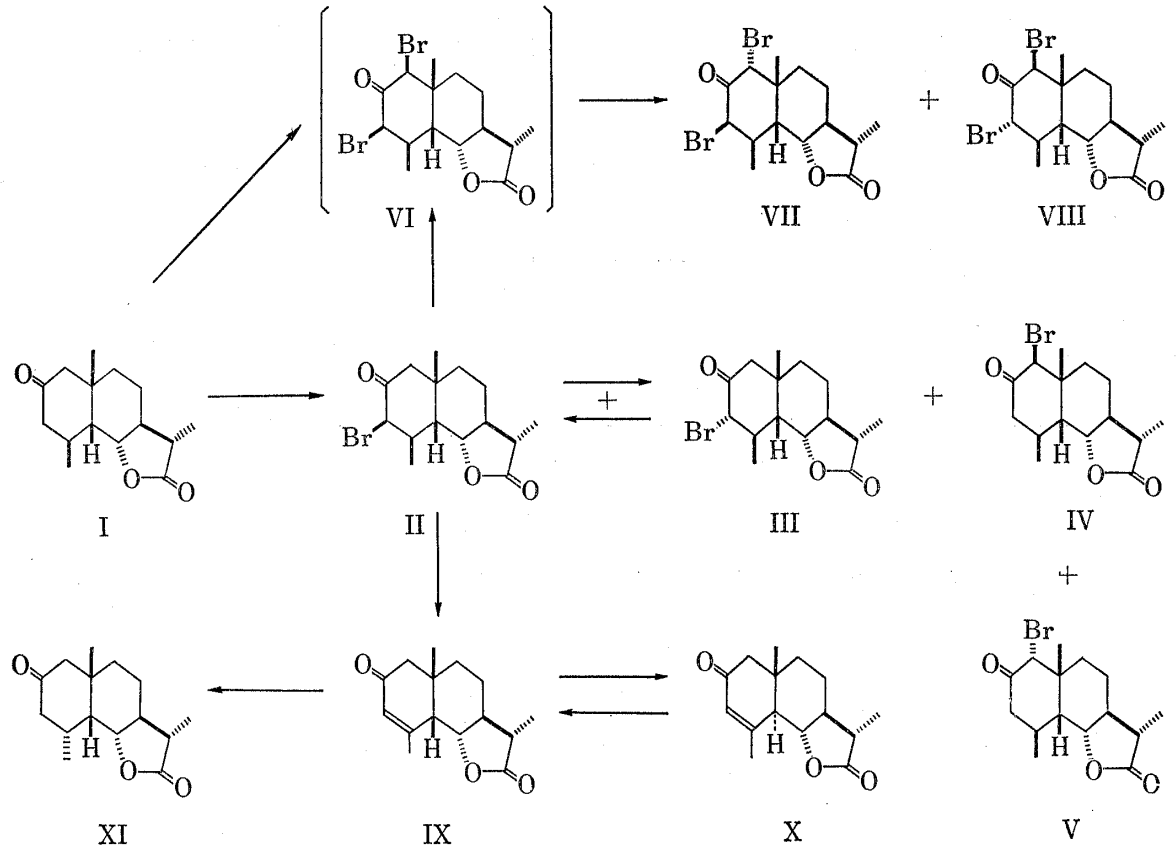

Chart 1

Table I. PMR, UV and CD Data of Monobromides (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	1.20	<2.50[d]	<2.50[d]	—	277	+518°(285)
II	1.23	2.00(dd, J_{1-1}=15, J_{1-3}=2) 3.41(d, J_{1-1}=15)	4.13(1H dd, J_{1-3}=2, J_{3-4}=*ca* 3)	*ca* 60° or 115°	311(+34)	−3900°(308)
III	1.44	2.40, 2.57(1H each, d, J=12)	4.40(1H d, J_{3-4}=10.2)	148° or 25°	284 (+7)	−260°(307)
IV	1.15	3.81(1H, s)	3.21(1H, dd, J_{3-3}=15, J_{3-4}=12.5)	159° or 0°	310(+33)	+23200°(308)
V	1.23	4.74(1H, s)	—[d]	—	279 (+2)	−1320°(280)

a) between 3-H and 4-H
b) using modified Karplus equation[4]; 12.4 $\cos^2\theta$ ($0°\leq\theta\leq90°$), 14.3 $\cos^2\theta$ ($90°\leq\theta\leq180°$)
c) $\Delta\lambda=\lambda$ (bromide)—λ (2-ketone (I))
d) uncleared

Positions of the bromine atom in the two bromides (II and III) were shown to be C-3 from their PMR spectra showing a double doublet signal due to C-3 H at δ 4.13 (II; $J_{1,3}$=2.0, $J_{3,4}$=*ca* 3 Hz) and a doublet signal at δ 4.40 (III; $J_{3,4}$=10.2 Hz), respectively. Other two bromides (IV and V) were also disclosed to be derivatives of C-1 bromide from their PMR spectra showing singlet signals due to C-1 H at δ 3.81 (IV) and δ 4.74 (V), respectively. The coupling constants between C-3 H and C-4α H in these 3-bromides (II and III) were measured and the dihedral angles between these protons were calculated using the modified Karplus equation.[4] The values are listed in Table I.

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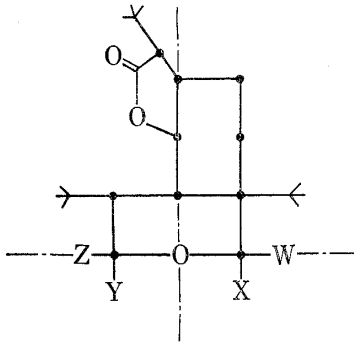
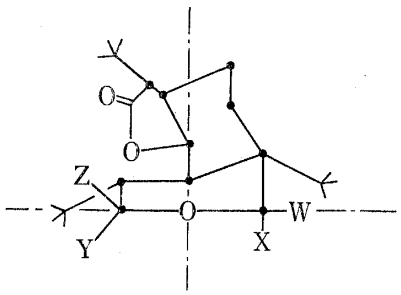
On the basis of these calculated dihedral angles between C-3 H and C-4α H (60° or 117°), the possible stereoformula and their conformation of II should be a ring A chair form (Aa; 3β-bromide) or one of other ring A boat forms [the ring A boat forms with C-3 and C-10 upwards (Ca; 3β-bromide and Cb; 3α-bromide) and a ring A boat form with C-2 and C-5 upwards (Da; 3α-bromide)].

In the circular dichroism (CD) spectrum of II, negative Cotton effect curve was observed as shown in Fig. 2, although two boat forms (Cb and Da) of 3α-bromide should show a positive

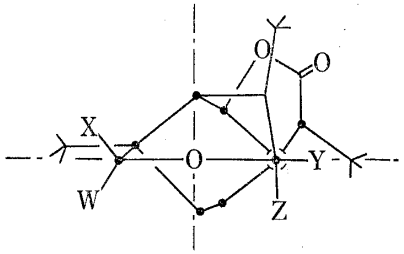
ring A chair form

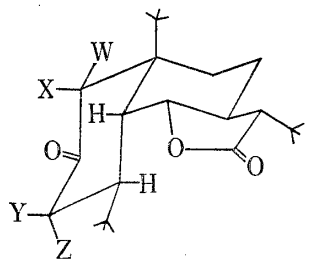


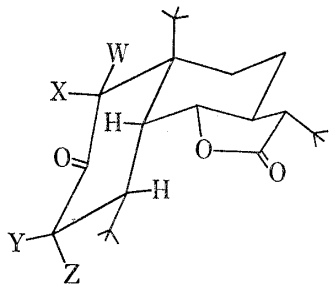
ring A flat chair form

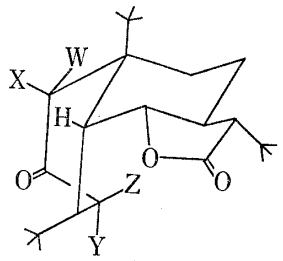


ring A boat form with C-3, C-10 upwarda







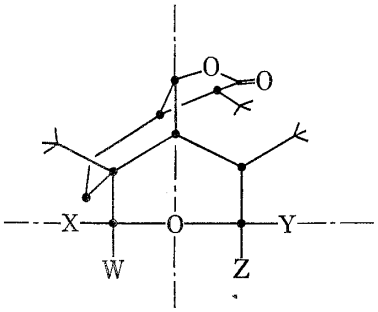


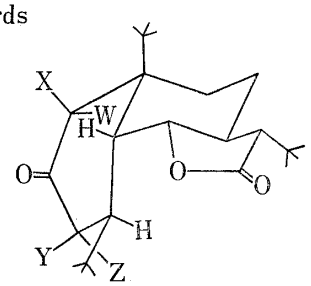
Aa : Y=Br, W=X=Z=H (II, 60°)[a)]
Ab : W=Y=Br, X=Z=H (VII, 59°)[a)]

Ba : Z=Br, W=X=Y=H (III, 148°)[a)]
Bb : X=Br, W=Y=Z=H (IV, 159°)[a)]
Bc : X=Z=Br, W=Y=H (VIII, 150°)[a)]

Ca : Y=Br, W=X=Z=H (II, 60°)[a)]
Cb : Z=Br, W=X=Y=H (II, 60°)[a)]
Cc : X=Z=Br, W=Y=H (VII, 59°)[a)]

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





Da : Z=Br, W=X=Y=H (II, 115°)[a)]
Db : W=Br, X=Y=Z=H (IV, 0°)[a)]
Dc : W=Y=Br, X=Z=H (VIII, 21°)[a)]

Fig. 1

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

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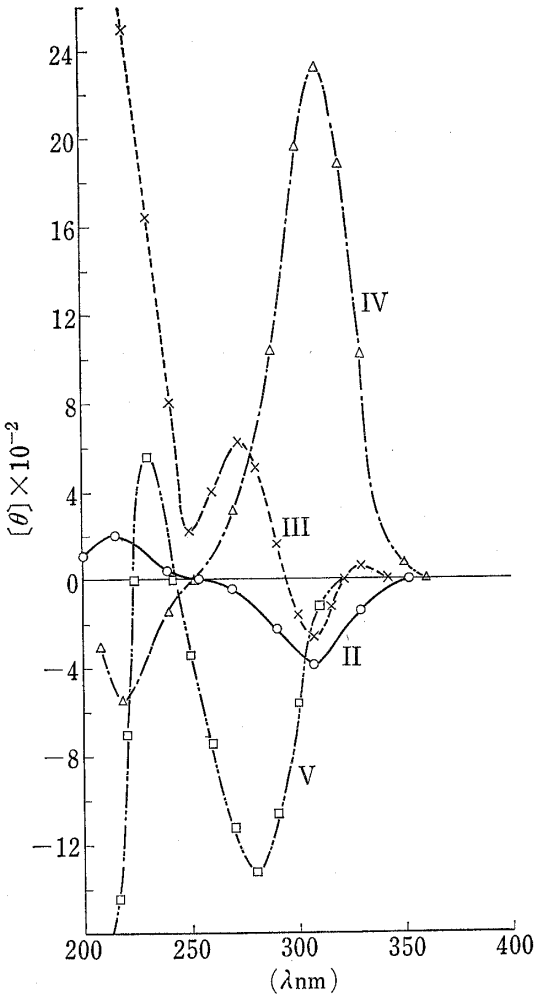

Fig. 2. Circular Dichroism Curves of Monobromides (II, III, IV, and V)

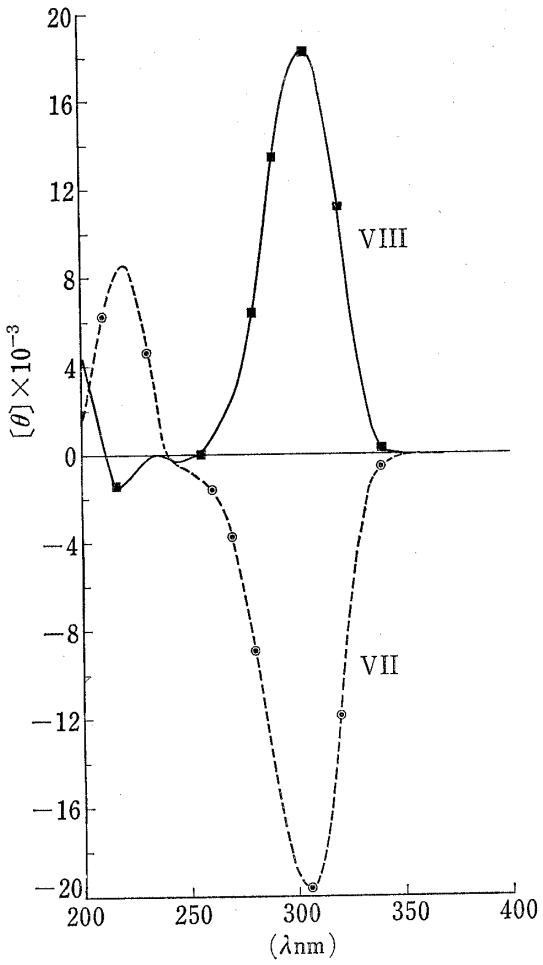

Fig. 3. Circular Dichroism Curves of Dibromides (VII and VIII)

Cotton effect curve in the axial haloketone rule[7] in CD spectrometry. Therefore, these boat forms (Cb and Da) are unsuitable for a stereoformula of II. In the PMR spectrum of II, one of the C-1 H signals was observed at low field δ 3.41 (d, J=15 Hz) than the other C-1 H signal at δ 2.00 (dd, J=15, 2 Hz). This lower field shift of the C-1 H signal should be explained in terms of the spatial proximity of the axial bromine atom at C-3 to C-1 axial H. This interesting behavior of the proton which is effected by the 1,3-diaxial interacting bromine atom, has not been previously reported in steroid chemistry. It seems that this 1,3-diaxial bromine interaction can not be observed in the boat form Ca but in the chair form Aa. From these results, the stereoformula of II is determined to be 3β-bromide and its conformation to be chair form (Aa). This result is also supported by the shift of the carbonyl absorption in UV ($\Delta\lambda$+34 nm) over the parent ketone (I).

Therefore, the stereoformula of the other 3-bromide (III) is shown to be 3α-bromide. The possible conformation of III is a flat chair form (Ba) alone on the basis of the calculated dihedral angle between C-3 H and C-4α H (148° or 25°). This conformation of the 3α-bromide (III) is also supported by the shift of the carbonyl absorption in UV ($\Delta\lambda$+7 nm) over the parent ketone (I) and its CD spectrum.

The stereoformula and its conformation of 1-bromides (IV and V) are also determined by a method similar to that described in II and III. The double doublet signal due to C-3 H was observed at δ 3.21 ($J_{3,3}$=15 Hz, $J_{3,4}$=12.5 Hz) in the PMR spectrum of IV. On the basis of above

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

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PMR spectrum and the calculated dihedral angle between C-3 H and C-4α H (159° or 0°) in IV, possible stereoformula and conformations of IV should be shown to be a ring A flat chair form Bb and a ring A boat form with C-2 and C-5 upwards Db. The signal due to one of the C-3 H's is observed at a low field (δ 3.21) because of the 1,3-diaxial bromine interaction. Therefore the stereoformula of IV in the flat chair form Bb should be 1β (axial)-bromide and that in the boat form Db should be 1α (axial)-bromide. In the CD spectrum of IV, a strong positive Cotton effect is observed as shown in Fig. 2. The boat form Db should show a negative Cotton effect curve. Consequently, the stereoformula of IV is shown to be 1β-bromide and its conformation is flat chair form. These results are also supported by the shift of the carbonyl absorption in UV ($\Delta\lambda$+33 nm) over the parent ketone (I). Thus, the stereoformula of IV is determined to be 1β-bromide, therefore that of the other bromide (V) must be 1α-bromide. The PMR spectrum of V exhibited no low field shifted signal due to C-3 H, and in the UV spectrum of V the shift of the carbonyl absorption ($\Delta\lambda$+2 nm) over the parent ketone (I) was observed. These data suggest that V should have an equatorial bromine atom, therefore the conformation of the 1α-bromide (V) may be a ring A chair form or a ring A flat chair form.

Satoh and his co-workers[8] reported that 1β-bromo-2-oxo-5β-steroid rearranged to a 3β-bromo-2-one, which easily epimerized into 3α-bromo-2-one in acetic acid containing hydrogen bromide. We tried to treat the bromoketone (II, III, and IV) under the same conditions as that for 5β-steroids. It was found that there is an equilibrium between II and III, and that IV is epimerized into II and V. These results may be due to the facts that in the 2-oxo-3β-bromide (II) C-3β bromine atom has two 1,3-diaxial interactions with C-1β H and C-5β H and in the 2-oxo-3α-bromide (III) C-3α equatorial bromine bond is sterically hindered by C-4β methyl group, and there is a dipole-dipole repulsion between the 2-oxo-group and the bromine atom. It is impossible to show an equivocal difference in the stability between II and III, but it is assumed that equilibrium exists between these bromides. This consideration is supported by the formation ratios of II—V under various bromination conditions, which are shown in Table II. The

Table II. Formation Ratio of II-V under Various Conditions

Reaction time (min)	Product (%)			
	II	III	IV	V
2	61	13	17	9
300	50	22	19	9

ratio of 3α-bromide (III) to the other bromide (II) increased under a prolonged reaction period, and 2-oxo-3-bromides (II and III) and 2-oxo-1-bromides (IV and V) were obtained in a 73: 27 ratio regardless of the reaction time From these results we conclude that in the bromination of I, the ratios of enolization to C-3 and to C-1 orientation are ca 73% and 27% respectively, and the initial products are the bromides (II and IV) which are produced by the axial attack on the enolates.

Recently, Satoh, *et al.*[9] claimed that dibromination of 2-oxo-5β-steroid gave 1β,3β-dibromide and 1β,3α-dibromide, while the former dibromide epimerized into the latter dibromide at room temperature (Chart 2).

The bromination of I with 2 molar equivalents of bromine in chloroform at room temperature gave a mixture of dibromides (VII and VIII) in 2: 5 ratio as evidenced by PMR spectroscopy. This mixture was fractionally recrystallized to give dibromides (VII), mp 198—199°, and (VIII), mp 191—193°. The bromination of the 3β-bromide (II) gave a mixture of the

8) J.Y. Satoh, C.A. Horiuchi, and A. Hagiani, *Chem. Lett.* (Japan), **1972**, 995.
9) Y. Satoh, A. Horiuchi, I. Yoshino, and A. Hagitani, 27th Annual Meeting of the Chemical Society of Japan, Abstract of Papers I-531, Tokyo, 1973.

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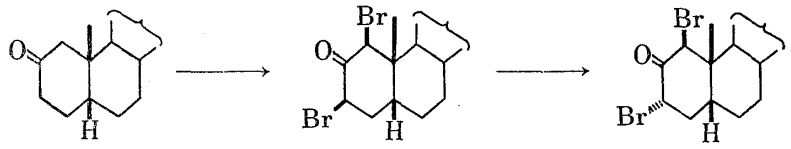

Chart 2

dibromides (VII and VIII) in 4: 3 to 3: 4 ratio as evidenced by PMR spectroscopy. The dibromides (VII and VIII) did not epimerize mutually in acetic acid containing hydrogen bromide at room temperature.

The structure of the dibromides (VII and VIII) was determined from their PMR and UV data, which are listed in Table III. The PMR spectrum of VII exhibited the signals due to

Table III. PMR, UV and CD Data of Dibromides (VII and VIII)

Compd. No.	PMR (δ, $CDCl_3$)			Calcd. Dihedral angle[a,b]	UV; λ_{max}^{EtOH} nm ($\Delta\lambda$)[c]	CD; $[\theta]_{max}^{MeOH}$ (at nm)
	4-CH_3	1-H	3-H (J=Hz)			
I	1.20	<2.50[d]	<2.50[d]	—	277	+518°(285)
VII	1.22	5.68(1H, s)	4.38(1H, d, J=3.3)	59° or 117°	307(+30)	−19800°(305)
VIII	1.45	4.07(1H, s)	5.37(1H, d, J=10.8)	150° or 21°	295(+18)	+18200°(305)

a) between 3-H and 4-H
b) using modified Karplus equation[4]; $12.4\cos^2\theta$ ($0°\leq\theta\leq90°$), $14.3\cos^2\theta$ ($90°\leq\theta\leq180°$)
c) $\Delta\lambda=\lambda$ (dibromide)—λ (2-ketone (I))
d) uncleared

C-1 H and C-3 H at δ 5.68 (s) and 4.38 (d, J=3.3 Hz), respectively, and that of VIII exhibited the signals due to C-3 H and C-1 H at δ 5.37 (d, J=10.8 Hz) and 4.07 (s), respectively. From these data, the dibromide (VII and VIII) are found to be 1,3-dibromides.

In the PMR spectrum of VII, the signal due to C-1 H was observed at a lower field [δ 5.68 (s)] as compared with that of 1-bromides [IV; δ 3.81, V δ 4.74] because of the 1,3-diaxial bromine interaction. Therefore the orientations of both the C-1 hydrogen and the C-3 bromine atom are axial. On the basis of these results and the calculated dihedral angle between C-3 H and C-4α H (59° or 117°) in the PMR spectrum of VII ($J_{3,4}$=3.3 Hz), the possible stereoformulae and their conformations should be a ring A chair form Ab (1α,3β-dibromide) and a ring A boat form with C-3 and C-10 upwards Cc (1β, 3α-dibromide). The boat form Cc must show a positive Cotton effect curve in CD spectrum, but the CD curve of VII shows a strong negative Cotton effect. Therefore this boat form is unsuitable for the conformation of VII. However, the chair form should show a strong negative CD curve. From these results the stereoformula of VII is shown to be 1α,3β-dibromide and its conformation to be the chair form.

In the PMR spectrum of VIII, the signal due to C-3 H was observed at a lower field [δ 5.37 (d)] as compared with that of 3-bromides [II; δ 4.13, III; δ 4.40] because of the 1,3-diaxial bromine interaction. Therefore the C-1 bromine and C-3 hydrogen atom are axially orientated. On the basis of these facts and the calculated dihedral angles between C-3 H and C-4α H (150° or 21°) in the PMR spectrum of VIII ($J_{3,4\alpha}$=10.8 Hz), only ring A flat chair form Bc (1β,3α-dibromide) is possible for the dibromide (VIII). A boat form Dc (1α,3β-dibromide) is also possible but 1α, 3β-dibromide have been determined to be VII. The positive Cotton effect curve in the CD spectrum of VIII also suggests the stereoformula and its conformation to be the flat chair form (Bc) of 1β,3α-dibromide.

The probable dibromination mechanism is proposed in Chart 1. The initial intermediate of the bromination of the II and IV may be assumed to be 1β,3β-dibromide (VI) which can easily epimerize to VII and VIII in the presence of hydrogen bromide.

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Dehydrobromination of Bromides (II, VII, and VIII)

Dehydrobromination of 3β-bromo-2-ketone (II) by the action of lithium bromide and lithium carbonate in dimethylformamide[10] was accomplished by stirring at 130—140° for 80 min under a nitrogen atmosphere to give an enone (IX), mp 208—209°. A presence of an α,β-unsaturated ketone moiety in IX was shown in the IR ($\nu_{C=O}$ 1660 cm^{-1}), the UV (λ_{max}^{EtOH} 237.5 nm), and the PMR spectrum (C-3 H; δ 6.00 (s), C-4 CH_3; δ 1.99). The A/B ring fusion of IX was shown to be *cis* by the coupling constant (J=5 Hz) between C-6 H (δ 4.48, dd, J=5, 10 Hz) and C-5 H. The structure of the enone (IX) was determined to be 2-oxo-3-en-5β(H)-santanolide from the above spectral data. A solution of the enone (IX) in 10% hydrochloric acid–ethanol was refluxed and monitored by gas chromatography. About 1:1 equilibrium mixture of the 5β-enone (IX) and a 5α-enone (X) was obtained through enolization of the 2-oxo-group. The 5α-enone (X)[11] showed a presence of an α,β-unsaturated carbonyl function in the IR and UV spectrum, and its A/B ring *trans*-fusion was manifest in the PMR spectrum, in which C-6 H signal showed as a triplet (J=10 Hz). The structure of X was determined to be 2-oxo-3-en-5α-santanolide.

On the catalytic reduction of the 5β-enone (IX) in the presence of palladium-charcoal, hydrogen atom attacked the double bond from the β-side of IX to give a novel epimer of I, 2-oxo-4,5β(H)-santanolide (XI), mp 139.5—141°. The CD spectrum of XI is shown in Fig. 4.

The dehydrobromination of the dibromides (VII and VIII) was carried out under various conditions as essentially described for the monobromide (II). The reaction products were a complex mixture, and their formation ratios varied depending on reaction conditions. These experimental results are shown in Table IV.

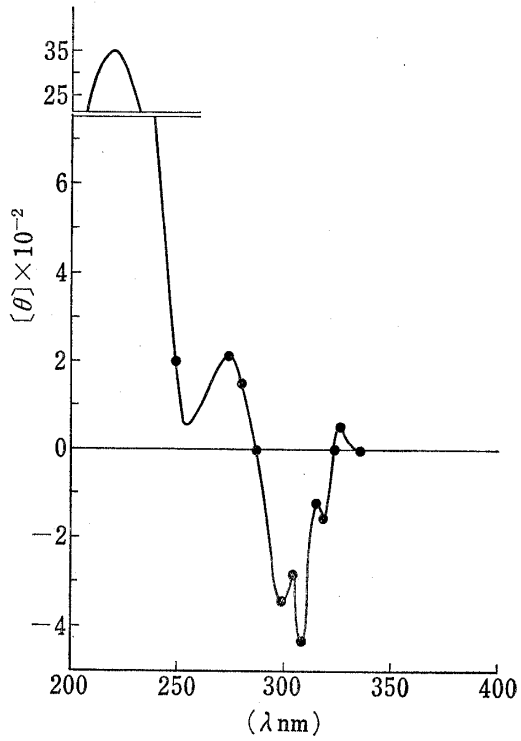

Fig. 4. Circular Dichroism Curve of XI

Table IV. Products Ratio of Dehydrobromination of VII and VIII

Compd. No.	Temp. (°C)	Product (%)							
		XII	XIII	XIV	XV	XVI	XVII	XVIII	Others
VII	120	75	4.8	—	1.5	2.5	3	2.4	5
	130	55	21	3.5	—	8.7	11.5	—	trace
VIII	100	17.5	—	6.8	4.5	4	57	—	11
	120	17.5	trace	12.5	5	3	47.5	—	13
	125	18	4	14	7	13	29	—	9
	135	16	11	11	—	11	31	—	17

The reaction mixture was separated into six neutral products and an acidic product. The neutral products were separated into three bromoenones (XII, mp 143—145°; XIII, mp 139—141°, and XIV, mp 149—150°), a dibromoenone (XV, mp 188—190°) and two Favorsky type rearrangement amides (XVI, mp 145—147° and XVIII, mp 198—199°) by recrystallization

10) E.J. Corey and A.G. Hoffmann, *J. Am. Chem. Soc.*, **87**, 366 (1958).
11) The structure of 5α-enone (X) will be described in detail in a forthcoming paper.

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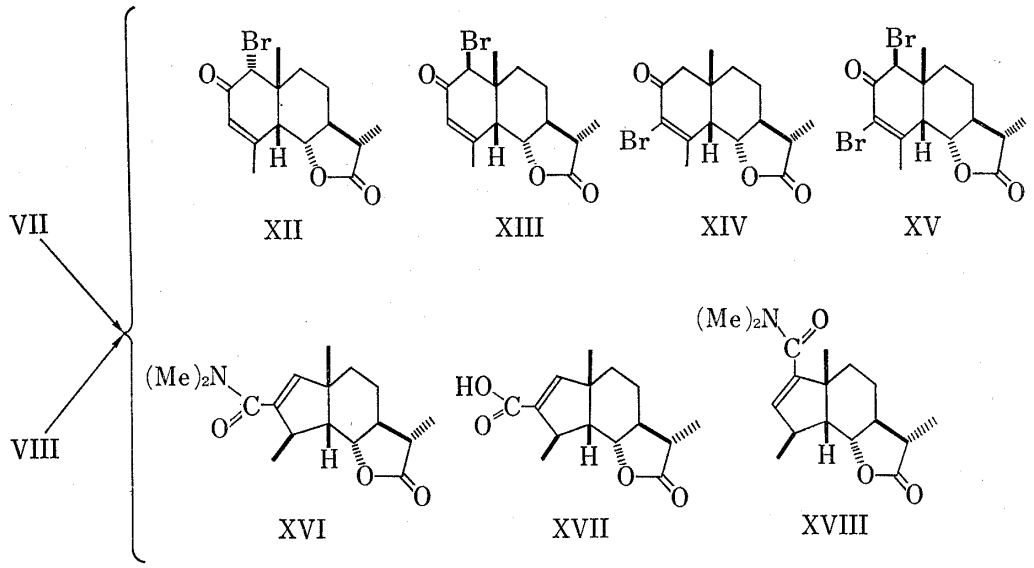

Chart 3

or column chromatography on silica gel. A carboxylic acid derivative (XVII), mp 153—154°, was isolated from the acidic portion.

The structure of XII—XVIII was confirmed from their spectroscopic data. A/B ring *cis*-fusions of these products (XII—XVIII) were manifest in their PMR spectra, in which the C-6 H signals showed as double doublet ($J_{6,7}$=10 Hz, $J_{5,6}$=5 Hz; XII—XV or 4 Hz; XVI and XVIII). The major bromoenone (XII) and another bromoenone (XIII) showed a character of an α,β-unsaturated ketone in their IR [ν_{max}^{KBr} 1678 (XII) and 1672 cm^{-1} (XIII)], UV [λ_{max}^{EtOH} 239.5 (XII) and 248.5 nm (XIII)], and PMR spectra [XII, δ 1.97 (4-CH_3), 6.13 (3-H) and XIII, δ 2.01 (4-CH_3), 6.00 (3-H)], respectively. The positions of the bromine atom in these bromoenones (XII and XIII) were determined to be C-1 from their PMR data [C-1 H: XII, δ 4.77 (s) and XIII, δ 3.88 (s)]. Therefore, these bromoenones are epimers at C-1 mutually. The PMR spectrum of XIII exhibits a C-1 H signal at a higher field (δ 3.88) than that of its epimer XII (δ 4.77). The chemical shifts of C-1 H signals in XII and XIII are similar to those of the 1α-bromide [V; δ 4.74 (s), C-1 H] and the 1β-bromide [IV: δ 3.81 (s), C-1 H], respectively. Consequently the structures of these bromoenones (XII and XIII) were shown to be 2-oxo-1α-bromo-3-en-5β-santanolide (XII) and 2-oxo-1β-bromo-3-en-5β-santanolide (XIII), respectively.

A third bromoenone (XIV) also showed a character of α,β-unsaturated ketone in the IR (ν_{CO} 1679 cm^{-1}) and the UV (λ_{max}^{EtOH} 260 nm) spectra. In the PMR spectrum of XIV, AB-type double doublet signals due to the C-1 H's were observed at δ 2.48 (d, J=16 Hz) and 2.57 (d, J=16 Hz), and no signal due to the C-3 vinylic proton was observed. The shift of the carbonyl absorption of XIV in UV ($\Delta\lambda$ +22 nm) over the 2-oxo-3-ene (IX) is in good agreement with the Woodward-Fieser rule[12] concerning the contribution of α-bromine atom in α,β-unsaturated ketonic absorption. From these data, the structure of this bromoenone (XIV) is shown to be 3-bromo-2-oxo-3-en-5β-santanolide.

Dibromoenone (XV) showed an α,β-unsaturated carbonyl absorption in IR (ν_{CO} 1683 cm^{-1}) and UV (λ_{max}^{EtOH} 273 nm), and the C-1 H signal was observed at δ 4.14 and no signal due to a C-3 vinylic proton was observed in the PMR spectrum of XV. The chemical shift of the C-1 H in XV is similar to that in the 1β-bromoenone (XIII; δ 3.88), and the shift of the carbonyl absorption in UV ($\Delta\lambda$ +35 nm) over the 2-oxo-3-ene (IX) was observed. This shift in UV can be explained in terms of the contributions of the 3-bromine atom in XIV (*ca.* +20 nm) and the 1β-

12) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, p. 15.

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Table V. IR, UV and PMR Data of Bromo-enones (XII—XV)

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
IX	1660	238	2.18, 2.48(1H each)
XII	1678(+18)	240 (+2)	4.77(1H, s)
XIII	1672(+12)	249(+11)	3.88(1H, s)
XIV	1679(+19)	260(+22)	2.48, 2.57(1H each)
XV	1683(+23)	273(+35)	4.14(1H, s)

a) $\Delta\nu=\nu$(bromoenone)-ν(IX)
b) $\Delta\lambda=\lambda$(bromoenone)-λ(IX)

bromine atom in XIII (*ca* +10 nm). From these spectral data, the bromoenone (XV) is shown to be 2-oxo-1β,3-dibromo-3-en-5β-santanolide. These data are listed in Table V.

Novel nitrogen containing compounds (XVI and XVIII) which were probably produced on the Favorsky rearrangement of the dibromides (VII and VIII), were eluted with benzene–ethyl acetate (10: 1) and (5: 1) in column chromatography over silica gel. The ring contracted amide compound (XVI), mp 145—147°, was a major rearrangement product on the dehydrobromination of the 1β,3α-dibromide (VIII). XVI showed an amide absorption band (ν_{CO} 1623 cm^{-1}) in the IR spectrum, and a vinylic proton signal at δ 5.68 (d, J=2 Hz) in the PMR spectrum. The other amide compound (XVIII), mp 198—199°, was formed as a minor rearrangement product on the dehydrobromination of the 1α,3β-dibromide (VII). This amide (XVIII) also showed an amide absorption band (ν_{CO} 1635 cm^{-1}) in the IR spectrum, and a vinylic proton signal at δ 5.55 (d, $W_{1/2}$=3 Hz) in its PMR spectrum. Both amides (XVI and XVIII) are assumed to be positional isomers with respect to the dimethylcarbamoyl group, but their structures can not be determined from their spectral data. In order to determine these structure, PMR spectra of XVI and XVIII were measured in $CDCl_3$ using tris(dipivaloylmethanato) europium (III), $Eu(DPM)_3$, as a shift reagent.[13] The slopes of the δ values for several concentrations of $Eu(DPM)_3$ in solutions of XVI and XVIII are shown in Fig. 5.

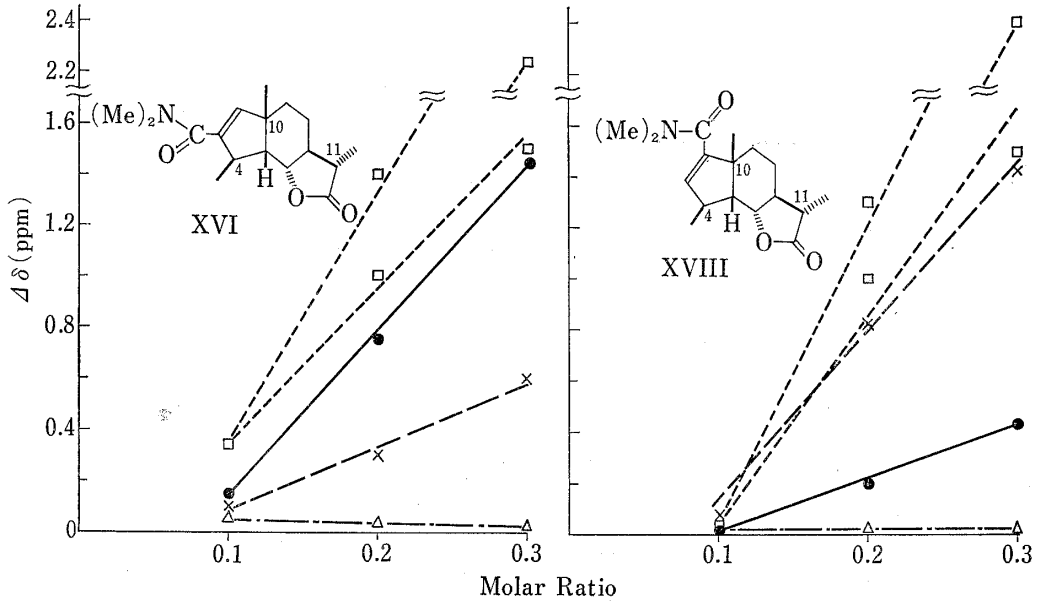

Fig. 5. Shifts of Methyl Protons as a Function of the Molar Ratio $Eu(DPM)_3$/Substrate
□--------□: $N(CH_3)_2$ ×------×: 10-CH_3 ●——●: 4-CH_3 △——△: 11-CH_3

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

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These amides (XVI and XVIII) have two chelation centers, amide and γ-lactone, with Eu $(DPM)_3$. The paramagnetic shift of the signals due to the N,N-dimethyl protons in the amide group are the largest in their PMR spectra. However, the shift of the C-6 H signal and a doublet methyl proton signal are negligible in both PMR spectra.

These facts suggest that $Eu(DPM)_3$ selectively coordinates to the amide group, but not to the γ-lactone group and that the shifted doublet signals are due to the C-4 methyl protons in XVI and XVIII. In the PMR spectrum of the amide (XVI), the paramagnetic shift of the doublet signal due to the C-4 methyl is larger than that of the C-10 methyl proton signal, while in the amide (XVIII), that of the doublet signal due to the C-4 methyl is smaller than that of the C-10 methyl proton signal. Therefore, the C-4 methyl is nearer the amide group than the C-10 methyl group in XVI, while the C-10 methyl group is nearer the amide group than the C-4 methyl group in XVIII. Consequently, the structures of two amides (XVI and XVIII) are shown to be A-2-nor-3-(N,N-dimethylcarbamoyl)-5β-sant-1-enolide and A-2-nor-1-(N,N-dimethylcarbanoyl)-5β-sant-1-enolide, respectively.

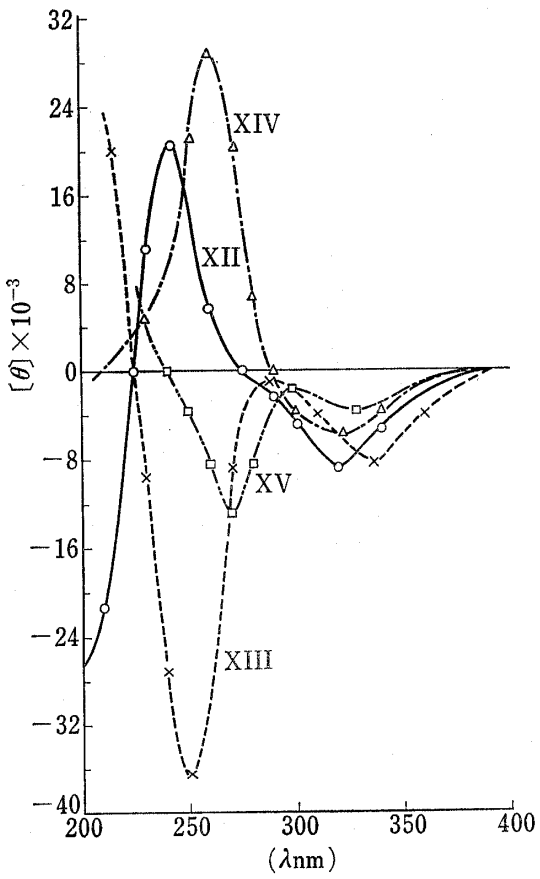

Fig. 6. Circular Dichroism Curves of Bromoenones (XII, XIII, XIV and XV)

A carboxylic acid derivative (XVII), mp 153—154°, was isolated from the acidic part of the dehydrobromination mixture. XVII was treated with thionyl chloride in chloroform and then dry dimethylamine was bubbled in this chloroform solution to afford an amide, mp 145—147°, which was identical with the authentic amide (XVI) as described above. Hydrolysis of XVI with 20% aqueous potassium hydroxide at reflux temperature for 3 hr gave a dicarboxylic acid, mp 146—147°, which was lactonized to the carboxylic acid lactone (XVII). Therefore, the structure of the carboxylic acid (XVII) is A-2-nor-3-carboxy-5β-sant-1-enolide.

The CD spectra of the 1β-bromoenone (XIII) and the 1α-bromoenone (XII) are shown in Fig. 6. It is interesting that these curves have opposite signs to each other. The CD spectra of the 1β,3-dibromoenone (XV) and 3-bromoenone (XIV) are also shown in Fig. 6. The 3-bromoenone (XIV) has a positive CD curve but the 1β,3-dibromoenone (XV) has a negative CD curve. This is explained in terms of the negative contribution of 1β-bromine atom.

Dehydrobromination Mechanisms

For the elucidation of the dehydrobromination mechanisms, the reaction was carried out under several conditions. These experimental results are shown in Table IV.

The experimental results on the 1α,3β-dibromide (VII) may be summarized as follows: (a) The major product from VII is the 1α-bromoenone (XII), and the minor product is the 1β-bromoenone (XIII) which increases with temperature. (*b*) Three ring-contraction products (XVI-XVIII) are obtained on the Favorsky rearrangement, but XVIII is obtained only at a low reaction temperature. The experimental results on the 1β,3α-dibromide (VIII) are summarized as follows: (c) 1-Bromoenones (XII and XIII) are formed in 17—27% yield in these

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reactions, and the 1α-bromoenone (XII) is a major product. The 1β-bromoenone (XIII) is a minor product, and its yield increases with temperature. (d) XVI and XVII are obtained as the Favorsky rearrangement products, but no amide (XVIII) is obtained. (e) The yield of the 3-bromoenone (XIV) is 7-14% which increases with temperature. From these results, we will propose the reaction mechanisms shown in Chart 4.

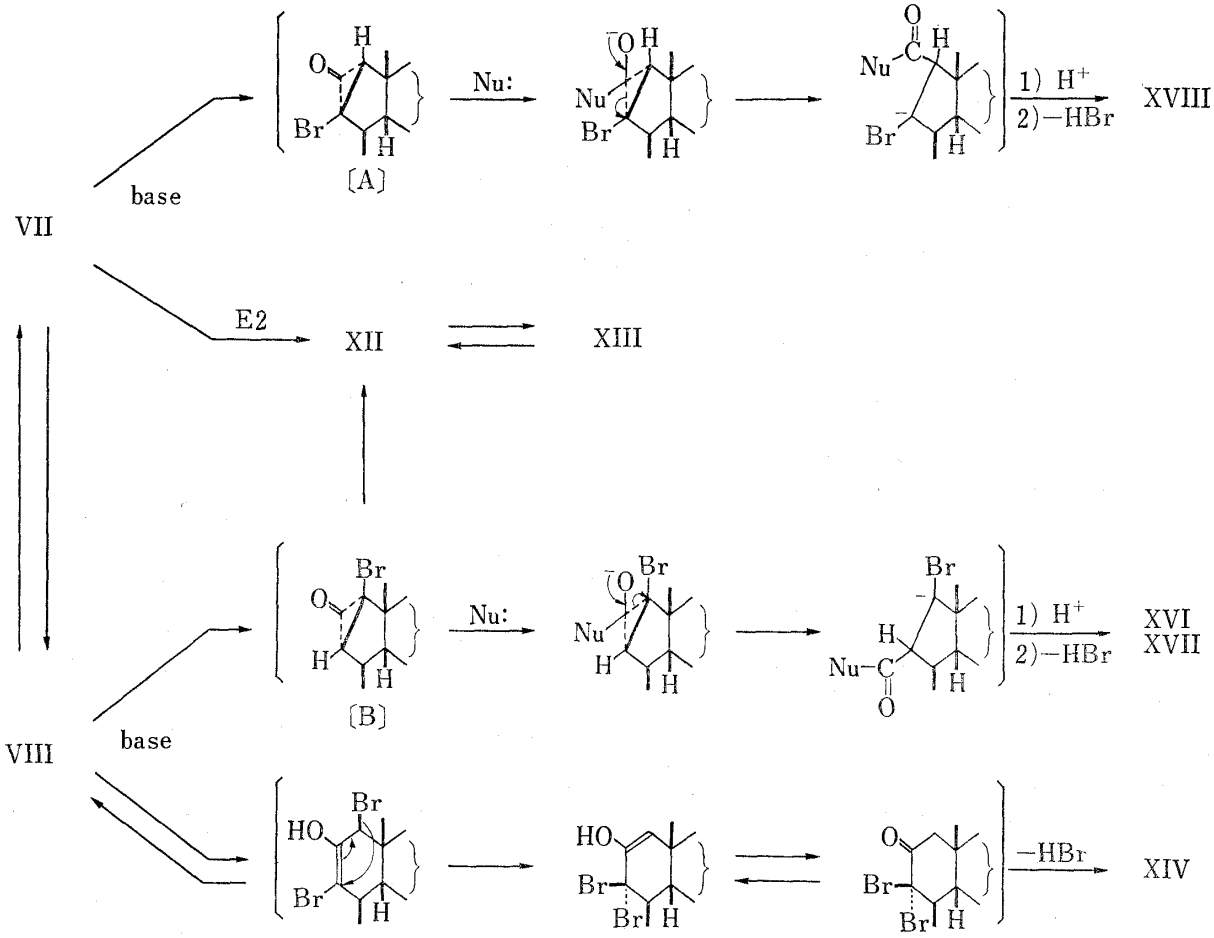

Chart 4

Generally, dehydrobromination is a trans E2 reaction, hence the E2 reaction easily occurs on the 1α,3β-dibromide (VII) giving the 1α-bromoenone (XII) in good yield and then a part of the resulting bromoenone (XII) epimerizes into the 1β-bromoenone (XIII) as described in (a). The other hand, if *cis*-elimination of hydrogen bromide from the 1β,3α-dibromide (VIII) occurs the major product must be the 1β-bromoenone (XIII). However, the 1β-bromoenone is not obtained at low temperature and ratio of XIII to XII increases with temperature as described in (c). These results suggest that the initial dehydrobromination product of the 1β,3α-dibromide (VIII) is the 1α-bromoenone (XII) and that a part of XII epimerizes into the 1β-bromoenone (XIII) at a high temperature.

Therefore, the major bromoenone (XII) is obtained on the dehydrobromination of the 1α, 3β-dibromide (VII) and/or derived from the 1-bromocyclopropanone intermediate [B] which are derived from the 1β,3α-dibromide (VIII).

The conversion of VIII into VII may be explained in terms of the epimerization of VIII under these basic conditions. The ring-contracting products, amides (XVI and XVIII) and a carboxylic acid (XVII) are selectively formed on the Favorsky rearrangement of VII and VIII with a base. Smissman, *et al.*[14] reported that the equatorial bromine atom was the good

14) E.E. Smissman, T.L. Lemke, and O. Kristiansen, *J. Am. Chem. Soc.*, **88**, 334 (1966).

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leaving group in the Favorsky reaction. Therefore, the 1α,3β-dibromide (VII) leads to the bromocyclopropanone intermediate [A] which is attacked by the dimethylformamide used as a solvent. Next, selective ring-opening of the cyclopropanone anion takes place, and the dehydrobromination of the resulting bromide gives the amide (XVIII). The other amide (XVI) is derived from the 1β,3α-dibromide (VIII) *via* the bromocyclopropanone intermediate [B] in a manner similar to that described for XVIII. The formation mechanism of XVI from the 1α, 3β-dibromide (VII) is assumed that VII is epimerized into VIII under these basic conditions and the intermediate VIII is converted to the amide (XVI). The 3-bromo-enone (XIV) is probably formed VIII *via* the 3,3-dibromoketone intermediate which is derived on the allylic rearrangement of the C-1 bromine atom to C-3.

Experimental

All melting points were determined on a Yanagimoto Micro-Melting Point Apparatus and are uncorrected. NMR spectra were measured with a Jeol JNM-4H-100 spectrometer at 100 MHz using TMS as internal reference. IR spectra were measured using a KBr disk with a Hitachi Perkin-Elmer model 225 grating spectrophotometer and UV spectra were measured with a Hitachi model 323 spectrophotometer. ORD and CD curves were measured with a Jasco J-20 and ORD-UV/CD-5 spectropolarimeter; specific rotations were determined with a Jasco DIP-SL digital polarimeter. Gas chromatography was performed on a Shimadzu Gas-Chromatography model GC-3AF equipped with a hydrogen flame detector, using a 1% SE-30 on Chromosorb W column.

Bromination of 2-Oxo-5β-santanolide (I)——A solution of Br_2 (2.6 g) in $CHCl_3$ (20 ml) was added dropwise to a stirred solution of I[4] (4 g) in $CHCl_3$ (250 ml). Br_2 was absorbed for 20 min at room temperature. Evaporation of the solvent under reduced pressure left colorless crystals in a quantitative yield, which were fractionally recrystallized from EtOH to 2-oxo-3β-bromide (II) (0.16 g; 30%) as colorless prisms, mp 191—192°. *Anal.* Calcd. for $C_{15}H_{21}O_3Br$: C, 54.72; H, 6.43; Br, 24.27. Found: C, 54.98; H, 6.34; Br, 24.59. $[\alpha]_D^{26}$ −187.6° ($CHCl_3$, $c=0.58$); IR (cm^{-1}): 1783 (γ-lactone), 1725 (cyclohexanone); UV λ_{max}^{EtOH} 311 nm (ε 120); NMR ($CDCl_3$, δ): 1.22 (3H, d, $J=7$ Hz; C-4 CH_3), 1.23 (3H, d, $J=7$ Hz; C-11 CH_3), 1.24 (3H, s; C-10 CH_3), 3.41 (1H, d, $J=15$ Hz; C-1β H), 4.13 (1H, dd, $J=2$, 3 Hz; C-3 H), 4.45 (1H, dd, $J=5$, 10 Hz; C-6 H).

Recrystallization of the residue gave 2-oxo-1β-bromide (IV) (196 mg; 3.7%) as colorless plates, mp 185—186°. *Anal.* Calcd. for $C_{15}H_{21}O_3Br$: C, 54.72; H, 6.43; Br, 24.27. Found: C, 54.95; H, 6.42; Br, 24.55. $[\alpha]_D^{26}$ +136.8° ($CHCl_3$, $c=0.35$); IR (cm^{-1}): 1772 (γ-lactone), 1706 (cyclohexanone); UV λ_{max}^{EtOH} 310 nm (ε 120); NMR ($CDCl_3$, δ): 1.15 (3H, d, $J=7$ Hz; C-4 CH_3), 1.12 (3H, d, $J=7$ Hz; C-11 CH_3), 1.32 (3H, s; C-10 CH_3), 3.21 (1H, dd, $J=12.5$, 15 Hz; C-3ax H), 3.81 (1H, s; C-1 H), 4.35 (1H, dd, $J=4.11$ Hz; C-6 H).

A residual mixture of 3α- and 1α-bromide (36 mg; 0.7%) was separated by preparative thin-layer chromatography with benzene and EtOAc (4: 6) as a developing solvent. 2-Oxo-3α-bromide (III) as colorless plates, mp 202—203°. *Anal.* Calcd. for $C_{15}H_{21}O_3Br$: C, 54.72; H, 6.43; Br, 24.27. Found: C, 55.25; H, 6.53; Br, 25.74. IR (cm^{-1}): 1782 (γ-lactone), 1722 (cyclohexanone); UV: λ_{max}^{EtOH} 284 nm (ε 29); NMR ($CDCl_3$, δ): 1.21 (3H, d, $J=7$ Hz; C-11 CH_3), 1.22 (3H, s; C-10 CH_3), 1.44 (3H, d, $J=6$ Hz; C-4 CH_3), 2.40 (1H, d, $J=10.2$ Hz; C-3 H), 4.40 (1H, dd, $J=4$, 10 Hz; C-6 H). 2-Oxo-1α-bromide (V) as colorless needles, mp 186—188°. *Anal.* Calcd. for $C_{15}H_{21}O_3Br$: C, 54.72; H, 6.43. Found: C, 54.62; H, 6.52. IR (cm^{-1}): 1780 (γ-lactone), 1715 (cyclohexanone); UV: λ_{max}^{EtOH} 279 nm (ε 26); NMR ($CDCl_3$, δ): 1.23 (3H, d, $J=7$ Hz; C-4 CH_3), 1.23 (3H, d, $J=7$ Hz; C-11 CH_3), 1.46 (3H, s; C-10 CH_3), 4.50 (1H, dd, $J=2$, 10 Hz; C-6 H), and 4.74 (1H, s; C-1 H).

Bromination of 2-Oxo-3β-bromide (II)——To a stirred solution of 3β-bromoketone (II) (1.63 g) in $CHCl_3$ (150 ml), a solution of Br_2 (1.0 g) in the same solvent (15 ml) was added dropwise during 2 hr at room temperature. The reaction mixture was dissolved in $CHCl_3$ (100 ml), washed with 10% $NaHCO_3$ and H_2O, and dried. Evaporation of the solvent afforded pale yellow dibromide in a quantitative yield. The crude dibromide was a mixture of 2-oxo-1α,3β-dibromide (VII) and 2-oxo-1β,3α-dibromide (VIII) in 4: 3 ratio as evidenced by NMR spectrometry. Fractional recrystallization from EtOH gave VII as colorless plates, mp 198—199° (decomp.) (447 mg; 22%), and VIII as colorless plates, mp 191—193° (decomp.) (315 mg; 16%).

VII: *Anal.* Calcd. for $C_{15}H_{20}O_3Br_2$: C, 44.14; H, 4.95; Br, 39.15. Found: C, 44.16; H, 5.08; Br, 39.18. $[\alpha]_D^{26}$ −114° ($CHCl_3$, $c=0.47$); IR (cm^{-1}): 1775 (γ-lactone) and 1735 (cyclohexanone); UV λ_{max}^{EtOH} 307 nm (ε 150); NMR ($CDCl_3$, δ): 1.22 (3H, d, $J=7$ Hz; C-4 CH_3), 1.22 (3H, d, $J=7$ Hz; C-11 CH_3), 1.46 (3H, s; C-10 CH_3), 2.69 (1H, dd, $J=5$, 12 Hz; C-6 H), 4.38 (1H, d; $J=3$ Hz; C-3 H), 4.48 (1H, dd, $J=5$, 12 Hz; C-6 H), 5.68 (1H, s; C-1 H).

VIII: *Anal.* Calcd. for $C_{15}H_{20}O_3Br_2$: C, 44.14; H, 4.95; Br, 39.15. Found: C, 44.10; H, 4.87; Br, 38.78. $[\alpha]_D^{26}$ +63° ($CHCl_3$, $c=0.41$); IR (cm^{-1}): 1780 (γ-lactone) and 1728 (cyclohexanone); UV λ_{max}^{EtOH} 295 nm (ε 475); NMR ($CDCl_3$, δ): 1.22 (3H, d, $J=7$ Hz; C-11 CH_3), 1.34 (3H, s; C-10 CH_3), 1.45 (3H, d, $J=7$ Hz; 3-4 H), 2.64 (1H, dd, $J=4$, 10 Hz; C-5 H), 4.07 (1H, s; C-1 H), 4.30 (1H, dd, $J=4$, 11 Hz; C-6 H), 5.37 (1H, d, $J=10.8$ Hz; C-3 H).

Dibromination of 2-Oxo-5β-santanolide (I)——To a stirred solution of I (3 g) in $CHCl_3$ (250 ml), a solution of Br_2 (4 g) in the same solvent was added dropwise during 4 hr at room temperature. The reaction mixture

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was treated in the same manner as described above. Evaporation of $CHCl_3$ afforded a crude dibromide as pale yellow crystals in a quantitative yield. The product was a mixture of 1α,3β-dibromide (VII) and 1β,3α-dibromide (VIII) in 2: 5 ratio from NMR spectra. Fractional recrystallization from EtOH gave VIII as colorless plates, mp 191—193° (decomp.), (2.53 g; 52%) and VII as colorless needles, mp 198—199° (decomp.), (636 mg; 13%), which were identical with the authentic samples as described above in mixed mp and IR spectra.

Epimerization of 2-Oxo-3-bromides (II, III, and IV)——(a) Epimerization of 2-oxo-3α-bromide (III): To a solution of 3α-bromide (III) (20 mg) in AcOH (5 ml) a solution of HBr saturated in AcOH (0.5 ml) was added, and the mixture was stirred for 3 hr at room temperature. Evaporation of AcOH and the products neutralized with 5% $NaHCO_3$, and followed by extraction with $CHCl_3$ to produce a pale yellow oil (20 mg). This residue was separated by preparative thin-layer chromatography with benzene–AcOEt (5: 1) as a developing solvent. The main product from band 2, mp 186—187°, was identical with the authentic specimen of 3β-bromide (II), and the minor products from band 4 were found to be a mixture of 1α,3β-dibromide (VIII) and 1β,3α-dibromide (VII) from the NMR spectra.

(b) Epimerization of 2-Oxo-3β-bromide (II): This procedire is the same as described above. To a solution of 3β-bromide (II) (100 mg) in AcOH (10 ml) a solution of HBr saturated in AcOH (0.5 ml) was added and the mixture was refluxed for 1 hr. The reaction mixture was treated and separated in the same manner as above. 3α-Bromide (III) (14 mg), mp 197—198°, and 2-oxo-5β-santanolide (I) (5.5 mg), mp 105—120°, together with the starting material (II) (40 mg) were obtained and were identical with authentic specimens in mixed mp and IR spectra.

(c) Epimerization of 2-Oxo-1β-bromide (IV): This procedure is the same as described above. A solution of 1β-bromide (IV) (63 mg) in HBr saturated in AcOH (5 ml) was stirred at room temperature for 29 hr and work-up the usual manner. The resulting crude crystals were found to be a mixture of 1β-bromide (IV), 1α-bromide (V), and 3β-bromide (II) in 2: 1: 1 ratio from the NMR spectra. When the above reaction mixture was stirred for prolonged period (42 hr) under the same conditions and worked-up in a similar to the above, the ratio of monobromides, IV: V: II, changed to 7: 4: 6 as evidenced by NMR spectrometry.

Dehydrobromination of 2-Oxo-3β-bromide (II)——According to the procedure described by Corey and Hoffmann,[10] 3β-bromide (II) (300 mg) was added to a suspension of LiBr (125 mg) and Li_2CO_3 (166 mg) in dry dimethylformamide (20 ml). The mixture was flushed with N_2 and stirred at 130—140° for 80 min. After the solution had been cooled, it was poured into dil. AcOH (20 ml), and extracted with CH_2Cl_2. The organic layer was washed saturated $NaHCO_3$ and H_2O, and dried. Evaporation of CH_2Cl_2 gave yellowish brown crystals in a quantitative yield. Recrystallization from EtOH afforded 2-oxo-3-ene (IX), mp 208—209°, as colorless needles (169 g; 75%). *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.31; H, 8.23. $[\alpha]_D^{26}$ −165.3° ($CHCl_3$, c=0.79); IR (cm^{-1}): 1776 (γ-lactone), 1660 and 1622 (enone); UV λ_{max}^{EtOH} 237.5 nm (ε 11660); NMR ($CDCl_3$, δ): 1.24 (3H, d, J=7 Hz; C-11 CH_3), 1.28 (3H, s; C-10 CH_3), 1.99 (3H, m, W 1/2= 4 Hz; C-4 CH_3), 1.48 and 2.18 (1H each, AB-type d, J=15 Hz; C-1 H), 3.05 (1H, m, W 1/2=9 Hz; C-5 H), 4.48 (1H, dd, J=5, 10 Hz; C-6 H), 6.00 (1H, m. W 1/2=4 Hz; C-3 H).

Epimerization of 5β-2-Oxo-3-ene (IX)——To a solution of 5β-enone (IX) (57 mg) in EtOH (10 ml), 10% HCl (2.4 ml) was added and the solution was refluxed for 5 hr. The reaction was monitored by gas–chromatography. The reaction mixture was concentrated and neutralized with saturated aqueous $NaHCO_3$, and extraced with benzene. Evaporation of benzene afforded a mixture (54 mg) of 5β-enone (IX) and 5α-enone (X) in 1: 1 ratio, which was identical by the NMR spectrum comparing with those of authentic samples of IX and X.[1]

2-Oxo-7α(H),4,5,6,11β(H)-santan-6,12-olide (XI)——A solution of 5β-enone (IX) (122 mg) in EtOH (15 ml) was catalytically hydrogenated over 10% Pd-C catalyst (27 mg) at ordinary temperature and pressure. Filtration and removal of EtOH produced colorless crystals (110 mg). Fractional recrystallization from EtOH afforded the starting material (IX) (48 mg; 39%), mp 208—209°. The mother liquor of IX deposited 4α-methyl-2-oxo-5β-santanolide (XI) as colorless plates, mp 136—139° (31 mg; 25%); pure sample, mp 139.5—141°. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.94, H, 8.84. $[\alpha]_D^{22}$ 0° ($CHCl_3$, c=0.87); IR (cm^{-1}): 1776 (γ-lactone), 1705 (cyclohexanone); UV: λ_{max}^{EtOH} 283 nm (ε 25); NMR ($CDCl_3$, δ): 1.15 (3H, d, J= 7 Hz; C-4 CH_3), 1.22 (3H, s; C-10 CH_3), 1.23 (3H, d, J=7 Hz; C-11 CH_3), 4.32 (1H, dd, J=6, 11 Hz; C-6 H).

Dehydrobromination of Dibromides (VII and VIII)——General Procedure: This procedure is the same as described for bromide (II). To a suspension of LiBr (205 mg) and Li_2CO_3 (275 mg) in dry dimethylformamide (30 ml), dibromide (613 mg) was added, the mixture was flushed with N_2, and kept between 100 and 140° with stirring. After the solution had been cooled, it was poured into dil. HCl (30—100 ml). The aqueous mixture was extracted with CH_2Cl_2 and the organic layer was washed with H_2O, followed by extraction of acidic products with 5% $NaHCO_3$. The neutral and acidic products were separated into several products by column chromatography and fractional recrystallization. The results are summarized in Table IV.

(a) Dehydrobromination of 1α,3β-Dibromide (VII): Acoording to the above general proceduce, the reaction mixture was warmed at 120° for 80 min to allow the reaction to proceed to completion.

Acidic Product: The above alkaline solution was acidified and extracted with AcOEt and the usual work-up produced colorless plates (12 mg). Recrystallization from EtOH gave A-2 nor-3-carboxy-1-en-5β-santanolide (XVII) as colorless plates, mp 153—154°. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found:

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C, 67.99; H, 7.60. $[\alpha]_D^{26}$ −81.1° ($CHCl_3$, c=0.49); IR (cm^{-1}): 1780 (γ-lactone), 1685 (COOH), 1620 (C=C); UV: end absorption; NMR ($CDCl_3$, δ): 1.22 (3H, d, J=7 Hz; C-11 CH_3), 1.25 (3H, s; C-10 CH_3); 1.29 (3H, d, J=7 Hz; C-4 CH_3), 3.00 (1H, m; C-4 H), 4.18 (1H, dd, J=6, 11 Hz; C-6 H), 6.74 (1H, d, J=2 Hz; C-1 H).

Neutral Products: CH_2Cl_2 extract was treated by the standard procedure to give crude brown crystals (458 mg). Recrystallization from EtOH gave 2-oxo-1α-bromo-3-en-5β-santanolide (XII) (283 mg) as colorless needles, mp 143—145°. *Anal.* Calcd. for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.85; Br, 24.42. Found: C, 55.08; H, 5.87; Br, 24.08. $[\alpha]_D^{26}$ −178.6° ($CHCl_3$, c=0.6); IR (cm^{-1}): 1764 (γ-lactone), 1678 and 1632 (enone); UV: λ_{max}^{EtOH} 239.5 nm (ε 10930); NMR ($CDCl_3$, δ): 1.22 (3H, d, J=6 Hz; C-11 CH_3), 1.49 (3H, s; C-10 CH_3), 1.97 (3H, t, J=1 Hz; C-4 CH_3), 3.17 (1H, m; C-5 H), 4.47 (1H, dd, J=5, 10 Hz; C-6 H), 4.77 (1H, s; C-1 H), 6.13 (1H, m, W 1/2=5 Hz; C-3 H).

The residue was chromatographed over silica gel (Wako gel C-200; 12 g). Fraction 1 (benzene elution) gave 2 mg of 2-oxo-1β,3-dibromo-3-en-5β-santanolide (XV) as colorless prisms, mp 188—190°. *Anal.* Calcd. for $C_{15}H_{18}O_3Br_2$: C, 44.36; H, 4.48. Found: C, 44.48; H, 4.51. $[\alpha]_D^{26}$ −71.1° ($CHCl_3$, c=0.59); IR (cm^{-1}): 1782 (γ-lactone), 1682 and 1583 (enone); UV: λ_{max}^{EtOH} 273 nm (ε 7720); NMR ($CDCl_3$, δ): 1.23 (3H, d, J=7 Hz; C-11 CH_3), 1.38 (3H, s; C-10 CH_3), 2.22 (3H, s; C-4 CH_3), 3.28 (1H, d, J=4 Hz; C-5 H), 4.14 (1H, s; C-1 H), 4.38 (1H, dd, J=4, 11 Hz; C-6 H).

Fraction 2 (benzene elution) gave colorless prisms (19.5 mg), 2-oxo-1β-bromo-3-en-5β-santanolide (XIII), mp 139—141° (decomp.). $[\alpha]_D^{26}$ −201.6° ($CHCl_3$, c=0.5); IR (cm^{-1}): 1778 (γ-lactone), 1672 and 1617 (enone); UV; λ_{max}^{EtOH} 248.5 nm (ε 9810); NMR ($CDCl_3$, δ): 1.23 (3H, d, J=7 Hz; C-11 CH_3), 1.37 (3H, s; C-10 CH_3), 2.01 (3H, m, W 1/2=3 Hz; C-4 CH_3), 3.14 (1H, m; C-5 H), 3.88 (1H, s; C-1 H), 4.37 (1H, dd, J=5, 11 Hz; C-6 H), 6.00 (1H, m, W 1/2=4 Hz; C-3 H).

Fraction 4 (benzene elution) gave crystals (23 mg), mp 143—145° (decomp.), which was identical in mixed mp and NMR spectrum with the above authentic sample of XII.

Fraction 5 (benzene: AcOEt=10: 1 elution) gave A-2-nor-1-(N,N-dimethylcarbamoyl)-5β-sant-1-enolide (XVIII) as colorless needles (9.7 mg), mp 198—199°. *Anal.* Calcd. for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.17; H, 8.73; N, 4.64. $[\alpha]_D^{26}$ −34.4° ($CHCl_3$, c=0.44); IR (cm^{-1}): 1768 (γ-lactone), 1635 (amide); UV: end absorption; NMR ($CDCl_3$, δ): 1.18 (3H, d, J=7 Hz; C-4 CH_3), 1.19 (3H, s; C-10 CH_3), 1.23 (3H, d, J=7 Hz; C-11 CH_3), 2.84 (1H, m; C-4 H), 3.02 (6H, s; $N(CH_3)_2$), 4.15 (1H, dd, J=6, 11 Hz; C-6 H), 5.55 (1H, d, W 1/2=3 Hz; C-3 H).

Fraction 6 (benzene: AcOEt=5: 1 elution) gave A-2-nor-3-(N,N-dimethyl-carbamoyl)-5β-sant-1-enolide (XVI) as colorless plates (13.8 mg), mp 145—147°. *Anal.* Calcd. for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.43; H, 8.67; N, 4.73. $[\alpha]_D^{26}$ 0° ($CHCl_3$, c=0.8); IR (cm^{-1}): 1782 (γ-lactone), 1623 (amide); NMR ($CDCl_3$, δ): 1.14 (3H, d, J=7 Hz; C-4 CH_3), 1.23 (3H, d, J=7 Hz; C-11 CH_3), 1.24 (3H, s; C-10 CH_3), 3.02 (1H, m; C-4 H), 3.02 (6H, s; $N(CH_3)_2$), 4.18 (1H, dd, J=6, 11 Hz; C-6 H), 5.68 (1H, d, J=2 Hz; C-1 H).

2-Oxo-3-bromo-3-en-5β-santanolide (XIV)——This compound (XIV) was separated from the benzene fraction 3 of dehydrobromination products of 1β,3α-dibromide (VIII) and 1α,3β-dibromide (VII) at 130°. XIV as colorless needles had mp 149—150° (decomp.). *Anal.* Calcd. for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.85; Br, 24.42. Found: C, 54.85; H, 5.85; Br, 24.84. $[\alpha]_D^{26}$ −87.9° ($CHCl_3$, c=0.48); IR (cm^{-1}): 1772 (γ-lactone), 1679 and 1593 (enone); UV λ_{max}^{EtOH} 260 nm (ε 8860) ; NMR ($CDCl_3$, δ): 1.22 (3H, d, J=7 Hz; C-11 CH_3), 1.27 (3H, s; C-10 CH_3), 2.19 (3H, s; C-4 CH_3), 2.48 and 2.57 (1H each, AB-type d, J=16 Hz; C-1 H), 3.16 (1H, d, J=4 Hz; C-5 H), 4.43 (1H, dd, J=4, 10 Hz; C-6 H).

Hydrolysis of Amide (XVI)——A solution of XVI (100 mg) in 20% KOH solution (32 ml) was refluxed for 3 hr. The alkaline solution was acidified and extracted with AcOEt, the extract was washed with H_2O, and dried. Evaporation of the ester gave a dicarboxylic acid (92 mg), which was recrystallized from EtOH to colorless plates, mp 146—147°. A solution of the diacid (70 mg) in benzene (10 ml) was refluxed for 2 hr in the presence of p-toluenesulfonic acid (40 mg). The reaction mixture was extracted with 5% $NaHCO_3$ and followed by acidification of the alkaline layer with 10% HCl, and the resulting acidic solution extracted with AcOEt. Evaporation of AcOEt gave colorless plates (56 mg/85%). Recrystallization from MeOH gave colorless plates, mp 153—154°, which were identified by mixed mp and IR spectra with authentic acid (XVII).

Dimethylamination of Carboxylic Acid (XVII)——$SOCl_2$ (11 ml) was added to the carboxylic acid (XVII) (60 mg) and the solution was refluxed for 90 min. Evaporation of the solvent under a reduced pressure afforded a pale yellow oily product. The oily acid chloride (40 mg) was dissolved in $CHCl_3$ (18 ml), and dry dimethyl amine was bubbled into the solution. Evaporation of $CHCl_3$ gave a brown oily product (40 mg), which was dissolved in benzene, and then extracted with 5% $NaHCO_3$ as an acid product. Carboxylic acid (XVII) (10 mg) was obtained as colorless plates, which was identified by mixed mp and IR spectra with the authentic samples of the acid (XVII). N,N-Dimethylcarbamoyl derivative (XVI) (15 mg) was obtained as colorless plates, mp 145—147°, which was identified by mixed mp and IR spectra with the authentic sample of XVI.

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