[Chem. Pharm. Bull. 21(2) 296—307 (1973)]

UDC 547.597.057 : 581.192

Studies on the Terpenoids and Related Alicyclic Compounds. I. Synthesis of 5α- and 5β-2-Oxosantan-6: 13-olide from Santonin

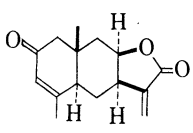
Koji Yamakawa,[1a,b] Shinpei Kidokoro, Norihide Umino, Reiji Sakaguchi,[1b] Takashi Takakuwa,[1c] and Makoto Suzuki[1d]

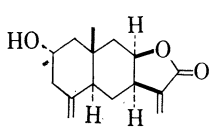
Faculty of Pharmaceutical Sciences, Science University of Tokyo,[1b] Japan Spectroscopic Co., Ltd.,[1c] and Tanabe Seiyaku Co., Ltd.[1d]

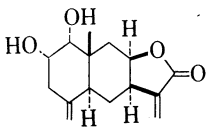
(Received June 22, 1972)

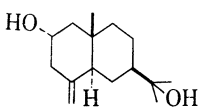
5α- and 5β-2-oxosantanolide (XIII and XXIII) have been synthesized from known 2-acetoxy-α- and γ-tetrahydrosantonin (VIII and XIX), respectively, which has previously been obtained from (−)-santonin. Nuclear magnetic resonance, optical rotatory dispersion and circular dichroism spectra of XIII and XXIII are discussed.

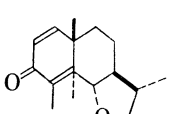
In the family of compositae, two types of sesquiterpenes have been found 2-oxo- or 2-hydroxy-eudesmane; they occur, for example, in pinnatifidin (I),[2] ivarin (II),[3] ivasperin (III),[4] pterocarpol (IV).[5] Synthetic transformations from santonin (V) into these sesquiterpenes have been studied in our laboratory. For these purpose, two transformation methods are nescessary, *i.e.*, one is the transformation of 3-ketone into the isomeric 2-ketone, and the second the transformation of 6: 13-olide into 8: 13-olide.


I


II


III


IV


V

We will report in this paper, the synthesis of 5α- and 5β-2-oxo-santanolide from (−)-santonin (V); this paper is dealing with the exploration of a synthetic route leading to such a system.

α- and γ-tetrahydrosantonin (VI and VII),[6–8] which were already obtained by the reduction of (−)-α-santonin (V), were taken as the starting material of this synthetic method, which has A/B ring *trans* and *cis* fusion.

Syntheses of 5α-2-Oxosantan-6: 13-olide (XIII)

The first synthetic route 2-oxosantanolide involved the desulfurization of the 2-oxo-3-ethylenethioketal (XI) as key intermediate.

2α-Acetoxy-α-tetrahydrosantonin (VIII) and its 3-ethylenethioketal derivative (IXa), which was previously prepared from α-tetrahydrosantonin (VI) by one of the authors (K.Y.)[9]

1) Location: *a*) Address correspondence to this authors; *b*) *12-Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan*; *c*) *Hachioji, Tokyo*; *d*) *Kawaguchi, Toda, Saitama.*
2) W. Herz, R.B. Mitra, K. Rabindran, and N. Viswanathan, *J. Org. Chem.*, **27**, 4041 (1954).
3) W. Herz and G. Hogenawer, *J. Org. Chem.*, **27**, 905 (1962).
4) W. Herz and N. Viswanathan, *J. Org. Chem.*, **29**, 1202 (1964).
5) C.P. Bahl, M.R. Parthasarathy, and T.R. Seshadri, *Tetrahedron*, **24**, 6231 (1968).
6) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).
7) W. Cocker and T.B.H. McMurry, *J. Chem. Soc.*, **1956**, 4549.
8) J.C. Banerji, D.H.R. Barton, and R.C. Cookson, *J. Chem. Soc.*, **1957**, 5041.
9) K. Yamakawa, *J. Org. Chem.*, **24**, 897 (1959).

were chosen as a suitable point of departure. The removal of the keto group, either by Clemmenzen reduction of VIII or by Raney nickel reduction of IXa, was attempted. But, in both cases hydrogenolysis of 2-acetoxyl group occured giving α-desoxytetrahydrosantonin (X); this was reported in a previous paper.[9] Then, hydrolysis of IXa with 5% $NaHCO_3$ gave a hydroxyl derivative (IXb), mp 236—237°, which was oxidized by Kiliani reagent and afforded 2-oxo-3-ethylenethioketal (XI), mp 212.5—214°. Desulfurization of XI by Raney nickel catalyst gave a mixture of the ketone (XIII) and the alcohol (XII), which was immediately oxidized by Kiliani reagent without purifying the product mentioned above gave the expected 2-oxo-5,7α(H)-4,6,11β(H)-santan-6: 13-olide (XIII), mp 150—152°. The nuclear magnetic resonance (NMR) spectrum of XIII is shown on Fig. 1.

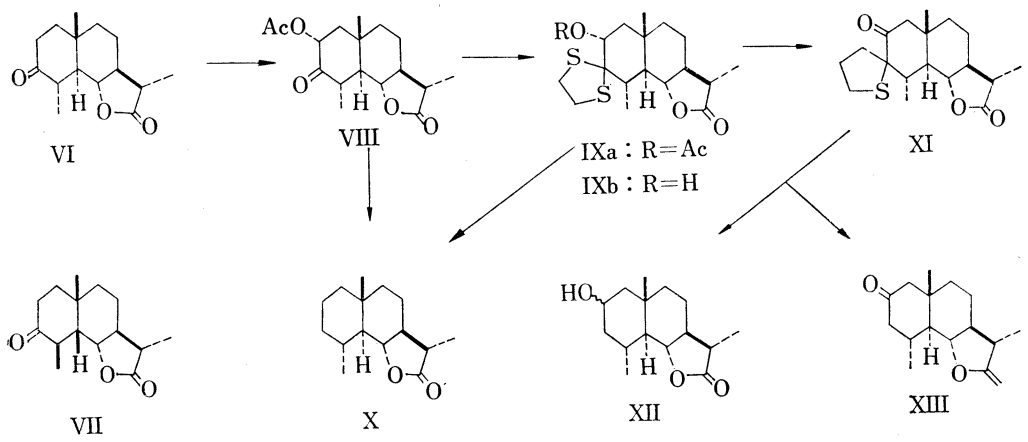


Chart 1

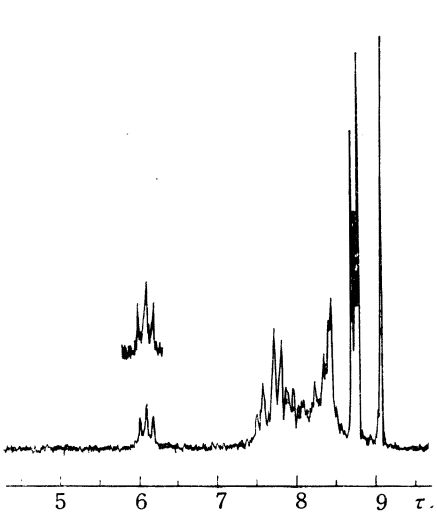


Fig. 1a. NMR Spectrum of 5α-2-Oxosantanolide (XIII)

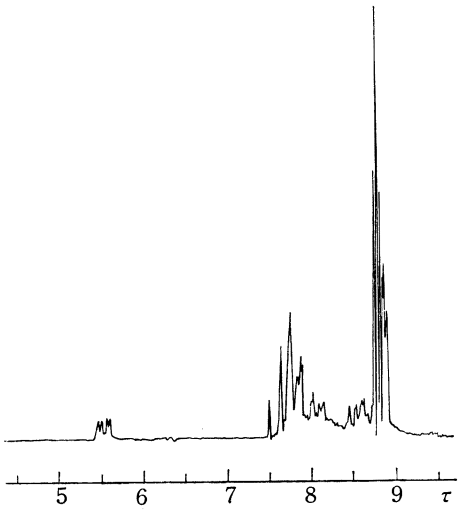


Fig. 1b. NNR Spectrum of 5β-2-Oxosantanolide (XXIII)

Our work[10] had been completed in a similar way as reported by two other groups.[11,12] However, these synthetic methods do not seem suitable to obtain 2-oxo-sesquiterpenes from 3-oxo-sesquiterpenes either the circuitous route or the method using thiol reagents.

10) N. Umino, Master Thesis, Science University of Tokyo, March 1967.
11) D.L. Robinson and D.W. Theobald, *Tetrahedron*, **24**, 5229 (1968).
12) J.A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).

Consequently, a more convenient method for the synthesis of 2-oxo-santanolide (XIII) from α-tetrahydrosantonin (VI) was investigated as follows. 3-Oxo-2α-acetate (VIII)[9] was treated with hydrazine for the purpose of Wolff-Kishner reduction, but the product obtained was a new α-ketol, mp 148.5—149.5°, instead of the hydrazone derivative of VIII. The structural assignment as 3-oxo-2α-ol (XIV) was confirmed chemically by its conversion with acetic anhydride and pyridine into a 3-oxo-2α-acetate (VIII), and also with 5% KOH–methanol into an α-diketone (XV). These products were identified with authentic specimens of VIII and XV.[9] Consequently, the configuration of the hydroxyl group in the α-ketol (XIV) has an equatorial (2α) orientation.

On the other hand, hydrolysis of VIII with 10% alcoholic HCl or 10% Na_2CO_3 gave a new α-ketol, mp 164—165°. The structure of this α-ketol was shown to be 2-oxo-3β-ol (XVI) from NMR, infrared (IR), and ultraviolet (UV) data. The equatorial orientation of the hydroxyl group in the α-ketol (XVI) was established by the NMR spectrum showing a doublet C_3-hydrogen (τ 6.28; J=10 Hz), and was also supported by the shifts of the carbonyl absorption in the UV ($\Delta\lambda$ +5 nm) and IR ($\Delta\nu$ +13 cm^{-1}) over the parent ketone (VI). Acetylation of XVI with acetic anhydride and pyridine gave a 2-oxo-3β-acetate (XVII), mp 210—211°.

Treatment of VIII with 50—100 times excess of basic alumina in benzene solution for a prolonged period at room temperature resulted in isomerization to 2-oxo-3β-acetate (XVII). A similar isomerization from 2α-acetoxy-cholestanone to 2-oxo-3β-acetoxy-cholestane with basic alumina *via* cyclic intermediate was reported by Fieser, *et al.* and Henbest, *et al.*[13]

The configuration of the α-ketols and α-ketol acetates was determined by physical method: our results agree with those of modified Karplus equation as for the NMR,[14] those of Jones as for the IR,[15] and Cookson's predication as for the UV spectrometry.[16]

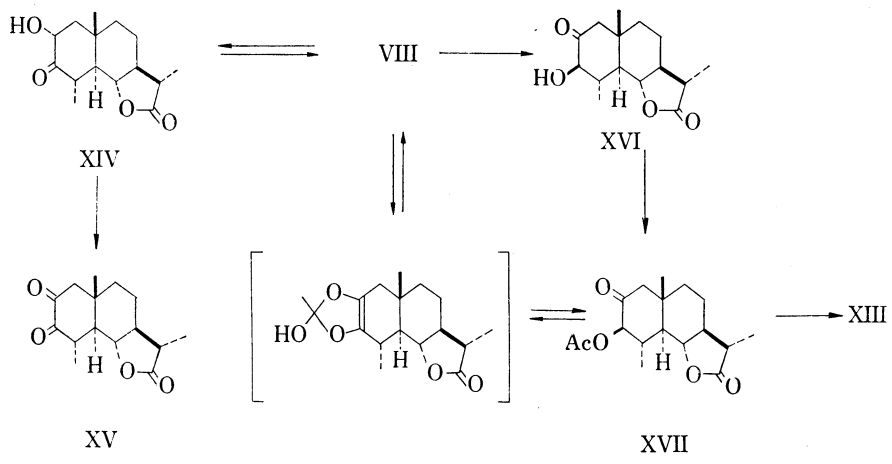


Chart 2

Hydrogenation of XVII by refluxing with zinc and acetic acid[17] for 16 hr afforded the desirable 2-oxo-5α-santanolide (XIII), mp 150—152°, in good yield. The 2-oxo-compound (XIII) was identical to the product of the alternative synthetic route, which is described above

13) *a*) L.F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **76**, 1728 (1954); *b*) H.B. Henbest, D.N. Jones, and G.P. Slater, *J. Chem. Soc.*, **1961**, 4472.
14) *a*) K.L. Williamson and W.S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); *b*) R.J. Abraham and J.S.E. Holker. *J. Chem. Soc.*, **1963**, 806.
15) R.N. Jones, D.A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).
16) R.C. Cookson, *J. Chem. Soc.*, **1954**, 282.
17) *a*) Ref. 9 and 18; *b*) R.B. Woodward, F. Sondeheimer, D. Taub, K. Heusler, and W.M. McLamore, *J. Am. Chem. Soc.*, **74**, 4233 (1952).

including the desulfurization of the 2-oxo-3-ethylenethioketal derivative (XI).

Syntheses of 5β-2-Oxosantan-6: 13-olide (XXIII)

It was previously reported[18] that acetoxylation of γ-tetrahydrosantonin (VII) with lead tetraacetate gave a "2α(axial)-acetoxy-3-ketone" (XVIII). Whereas, in the present investigation the data on the ketol acetate obtained by NMR spectroscopy lead to a correction of its structure as 2β(equatorial)-acetoxy-3-ketone (XIX).[19] The NMR spectrum of XIX shows a proton of C_2–H double doublet (τ 4.66, J=13, 7 Hz)[14a] and singlet C_{10}–CH_3 protons (τ 8.80). The ketol acetate (XIX) was converted to the corresponding 2β(equatorial)-acetoxy-3-ethylenethioketal (XXa), which was previously reported[18] as "2α-acetoxy-3-ethylenethioketal" (XXI). The structural assignment of the acetoxy-ethylenethioketal (XXI) should be corrected to XXa in NMR spectroscopy, which shows a proton of C_2–H double doublet (τ 4.82, J=11, 6 Hz) as similar as XIX. Consequently, previous assigned "2β-acetoxy-3-ketone" and "2β-acetoxy-3-ethylenethioketal" should be corrected to 3α-acetoxy-2-ketone (XXVII) and 3α-acetoxy-2-ethylenethioketal, respectively, as it is described in the following.

Hydrolysis of the XXa with 5% $NaHCO_3$ gave an alcohol (XXb), mp 236—237°, which was oxidized by Kiliani reagent giving 2-oxo-3-ethylenethioketal (XXII), mp 212.5—214°. Desulfurization of the ethylenethioketal (XXII) by Raney nickel catalyst gave a mixture of the alcohol and ketone, which was immediately oxidized by Kiliani reagent without purifying the product mentioned above gave the expected 2-oxo-4;7α(H)-5;6;11β(H)-santan-6: 13-olide (XXIII), mp 151—153°.

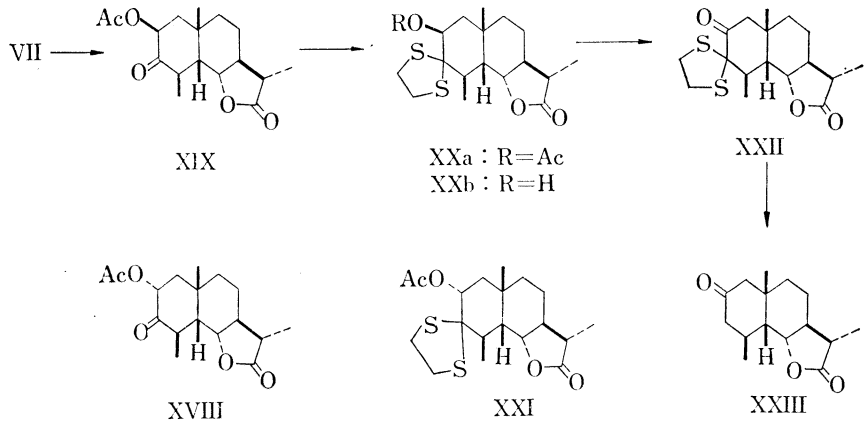


Chart 3

18) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **24**, 903 (1959).

19) On the assumption that the conformation of the ketol acetate takes a boat form in A-ring, the J-values of a proton at C_2-H of the NMR spectrum of XVIII may be interpreted. But the ketol acetate is inert to epimerization under the several conditions in each cases as following: refluxed in acetic acid, acetic acid-potassium acetate, N,N-dimethylaniline for 20 hr, respectively, and warmed on water bath in pyridine for 20 hr, and also refluxed in decaline for 34 hr.

Whereas, in 5β-steroids, Satoh, *et al.* [T. Takahashi, Y. Satoh, A. Hagitani, *Nippon Kagaku Zasshi*, **89**, 974 (1968)] reported that 2α-acetoxy-5β-cholestan-3-one (NMR: C_2-H; τ 4.72, triplet; J= 7.5 Hz) are very easily epimerized in acetic acid and two drops of HBr at room temperature for 3 hr gave 2β-acetoxy-3-ketone (NMR: C_2-H; τ 4.76, double doublet; J=13.8, 6 Hz). And also same authors reported [Y. Satoh, T. Kimura, Y. Tajima, T. Takahashi, A. Hagitani, *Nippon Kagaku Zasshi*, **90**, 500 (1969); J. Y. Satoh and T. T. Takahashi, *Chem. Comm.*, **1970**, 1714] the 2β-acetoxy-3-ketone isomerized with acetic acid-HBr at 55—60° for 18 hr afforded 3α-acetoxy-2-keto-5β-steroid (NMR: C_3-H; double doublet; J=11.3, 7 Hz).

From the above results, it is never considered a boat form of XVIII more stable than a chair form of XIX.

Alternative synthesis of the 5β-2-oxosantanolide (XXIII) from γ-tetrahydrosantonin (VII) was carried out *via* a similar route giving principally a 5α-2-oxo compound, which is described above.

Treatment of 2β-acetoxy-3-ketone (XIX) with hydrazine, according to the method used for the 5α-series, gave 2-hydroxyl-3-ketone (XXIV), mp 160—161°. Acetylation of XXIV gave the starting 2β-acetoxy-3-ketone (XIX).

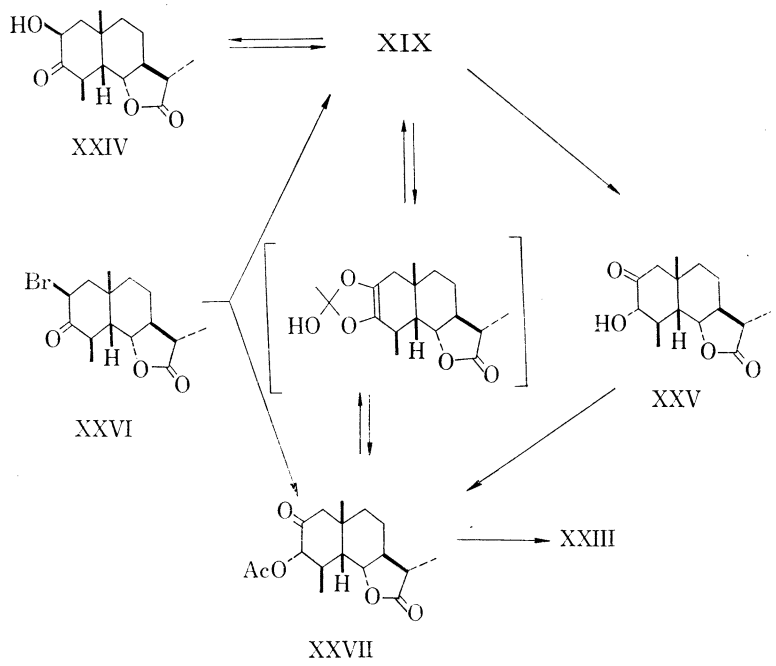


Chart 4

Hydrolysis of the 2β-acetoxy-3-ketone (XIX) with alcoholic HCl gave a new α-ketol, mp 174—175°. The NMR spectrum of the α-ketol, which showed a proton of C_3–H doublet (τ 6.15, J=10 Hz), confirmed the structure to be 2-oxo-3α-ol (XXV). Acetylation of XXV with acetic anhydride and pyridine afforded 2-oxo-3α-acetate (XXVII), mp 245—246°, which was identical with the previously reported[18] "3-oxo-2β-acetate" with mixed mp and IR spectrum. The stereoformula of XXVII is confirmed by NMR spectroscopy, which showed a proton of C_3–H doublet (τ 5.06, J=11 Hz). On the basis of these data the previously described epimerization of 2α(axial)-acetoxy-3-ketone (XVIII) into 2β-(equatorial)-acetoxy-3-ketone (XIX) under reflux for 20 hr in acetic acid should be corrected to the isomerization of 3-oxo-2β-acetate (XIX) into 2-oxo-3α-acetate (XXVII).

This isomerization of 2-acetoxy-3-ketone (XIX) into 2-oxo-3-acetate (XXVII) was successfully carried on by treatment with an excess amount of basic alumina in benzene solution, at room temperature, for a prolonged period. The isomerization results under different conditions are shown in Table I.

Reduction of the 2-oxo-3α-acetate (XXVII) with activated zinc dust and acetic acid under reflux for 12 hr gave the expected 2-oxo-5: 6: 11β(H)-santan-6: 13-olide (XXIII), mp 149—150°. The 2-oxo-compound (XXIII) was identical with the product obtained through the alternative synthetic route, which description given above included the desulfurization of 2-oxo-3-ethylenethioketal derivative (XXII).

Table I. Isomerization of 2β-Acetoxy-γ-tetrahydrosantonin (XIX) by Basic Alumina (20°, 24 hr)

XIX	Amount of alumina	Solvent	Isomerization (%)[a]
1	100	MeOH	30—40
1	100	EtOAc	60—70
1	20	benzene	30
1	50	benzene	50
1	100	benzene	80—90

a) Isomerization (%) was determined by gas chromatography (1% SE 30 on Chromosorb-W; column temperature 200°)

Spectra

NMR spectra of 2-oxo derivatives of the 5α-series for XIII, XVI, and XVII, show a singlet peak due to the C_{10}-angular CH_3 group with a field upper than that of isomeric 3-oxo derivatives for VI, XIV, and VIII (see Table IIa). These evidence are due to an anisotropic effect of C_2 or C_3 carbonyl group.[20] While, between the NMR spectra of a singlet C_{10}-angular methyl peak of 3-oxo derivatives of the 5α-series for VII, XXIV, and XIX and corresponding isomeric 2-oxo derivatives for XXIII, XXV, and XXVII show a slightly difference (Table IIb).

Table II. Chemical Shifts of Angular Methyl Group in 2- and 3-Oxosantanolide Derivatives (τ-value)

a) 5α-(A/B ring *trans* fusion) compounds

2-Oxo-	Ketone	α-Ketal	α-Ketol acetate
2-Oxo-compound	XIII; 9.05	XVI; 9.08	XVII; 9.08
3-Oxo-compound	VI; 8.80	XIV; 8.64	VIII; 8.67
$\Delta\tau$[a]	0.25	0.44	0.41

b) 5β-(A/B ring *cis* fusion) compounds

	Ketone	α-Ketol	α-Ketol acetate
2-Oxo-compound	XXIII; 8.78	XXV; 8.75	XXVII; 8.77
3-Oxo-compound	VII; 8.72	XXIV; 8.79	XIX; 8.78
$\Delta\tau$[a]	0.06	−0.04	−0.01

a) $\Delta\tau=\tau_{2\text{-oxo}}-\tau_{3\text{-oxo}}$

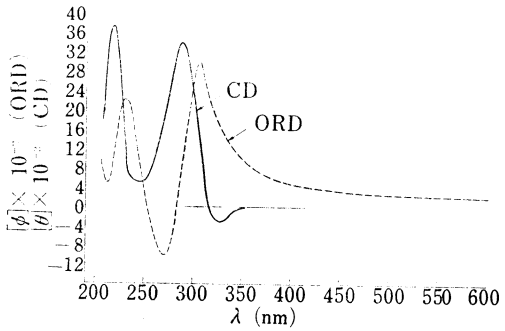


Fig. 2. Optical Rotatory Dispersion and Circular Dichroism Curves of 5α-2-Oxo-santanolide (XIII) (MeOH)

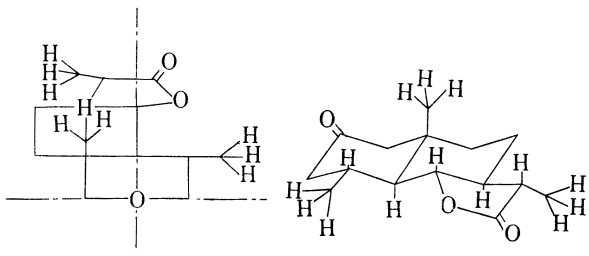


Fig. 3

20) *a*) J.W. ApSimon, W.G. Craig, P.V. Demarco, D.W. Mathieson, A.K.G. Nasser, L. Saunders, and W.B. Whalley, *Chem. Commun.*, **1966**, 754; *b*) G.J. Karabatsos, G.C. Sonnichsen, N. Hsi, and D.J. Fenoglio, *J. Am. Chem. Soc.*, **89**, 5067 (1967).

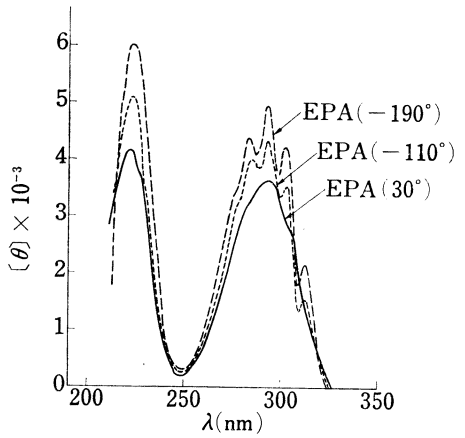


Fig. 4. Circular Dichroism Curves (EPA solvent) of 5α-2-Oxosantanolide (XIII) at 30°, −110°, and −190°

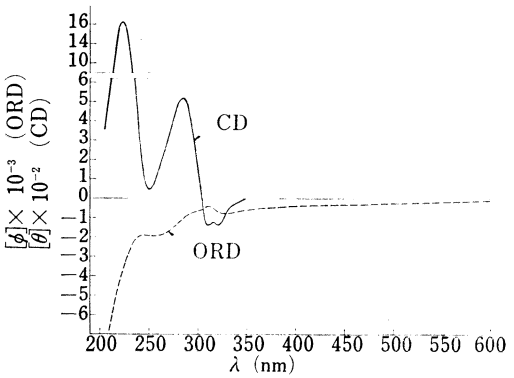


Fig. 5. Optical Rotatory Dispersion and Circular Dichroism Curves of 5β-2-Oxosantanolide (XXIII) (MeOH)

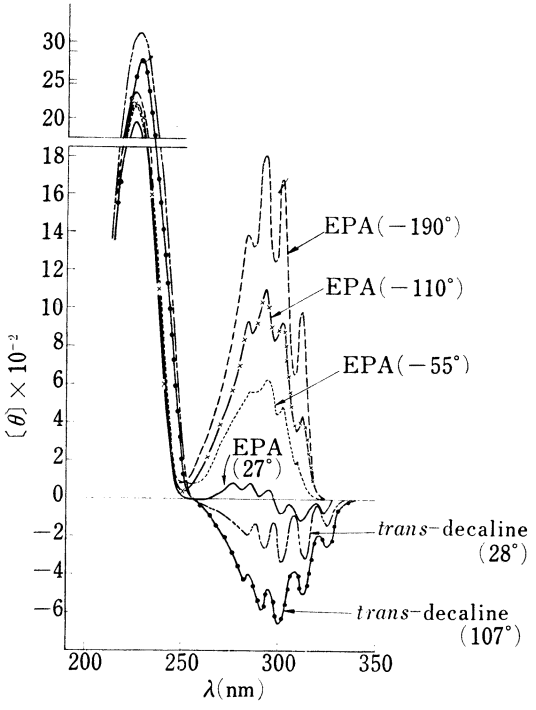


Fig. 6. Circular Dichroism Curves of 5β-2-Oxosantanolide (XXIII) in *trans*-Decaline (28° and 107°) and EPA solvent (27°, −55°, −110°, and −190°)

In optical rotatory dispersion (ORD) and circular dichroism (CD) curves, 5α-2-ketone (XIII) exhibits strong positive Cotton effect at 290 nm region (ketonic carbonyl, n–π^* transition) as shown in Fig. 2. The positive sign of Cotton effect shown by XIII can be understood where applying the Octant rule[21] to the cyclohexanone system of the A ring in the compound, as visualised in the octant projection (Fig. 3).

The splitted negative maximum of CD curve recognized in the longer wave length in methanol solution (Fig. 2) is disappeared in non-polar solvent and low temperature measurement. In latter case, the intensity of positive maximum of XIII does not indicate marked change with decreasing the temperature (Fig. 4).

Whereas, 5β-2-ketone (XXIII) shows positive Cotton effect in ketonic carbonyl region as depicted in Fig. 5, however, the splitted negative maximum of CD curve observed in methanol solution is still remained in the measurement using less-polar solvents such as EPA,[22] dioxane and chloroform at room temperature.

21) W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

22) EPA: The mixing solvent for low-temperature CD measurement composed by diethyl ether, *n*-pentane and ethylalcohol (1:1:1/volume).

Moreover, CD positive maximum of XXIII markedly increased by decreasing temperature from −50° to −190°, and on the contrary, the sign of Cotton effect was reversed to negative in non-polar solvent and high-temperature measurement (Fig. 6). These sensitive behaviors of 5β-2-ketone (XXIII) could be explained by subtle conformational change of the A ring, which corresponds to each octant projection shown in Fig. 7.

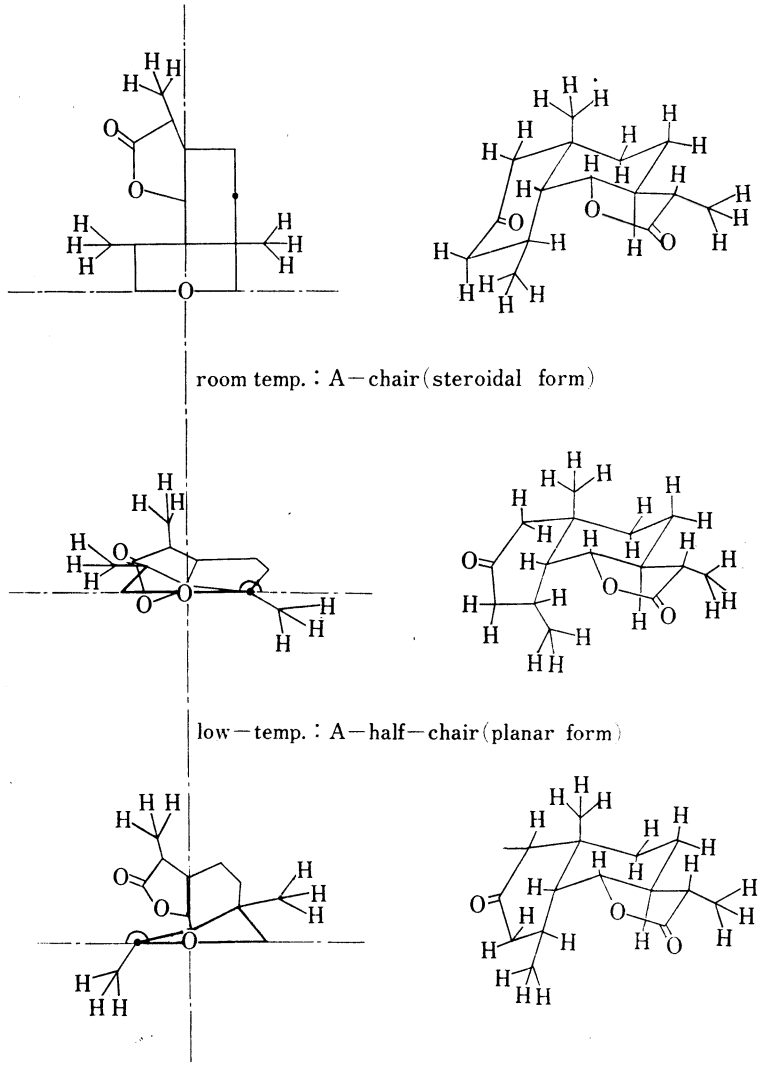


Fig. 7

ORD and CD curves of 2-oxo-5β-steroids exhibit negative Cotton effect, which are normally expected by the octant projection diagram.[23] Experimental results of 5β-2-ketone (XXIII) are quite different from steroid series, and they are finally ascribed to the existence of γ-lactone moiety in the closed ring system.

23) T. Koga and M. Tomoeda, *Tetrahedron*, **26**, 1043 (1970); T. Koga and S. Kawashima, *Chem. Pharm. Bull.* (Tokyo), **20**, 21 (1972).

The conformation of the other compounds, α-ketols and its acetates, and ethylenethioketal derivatives, will be detail discussed in connection with ORD, CD, and NMR spectrometry, which results will be published elsewhere.

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 for KBr disk with a Hitachi EPI-2 and Hitachi Perkin-Elmer 225 greating spectrophotometer; UV spectra were measured with a Hitachi EPU-2 spectrophotometer. ORD and CD curves were measured with a Jasco ORD-CD/UV-5 and J-20 spectropolarimeter; specific rotations were determined with a Jasco-DIP-SL digital spectropolarimeter. Gas-chromatography was performed on a Shimazu Gas-chromatograph Model GC-3AH and 3AF equipped with a thermal conductivity and hydrogen flam detector respectively, using a 1% SE-30 on Chromosorb W column.

5α(H)-Compounds (A/B ring *trans* fusion)

2-Hydroxy-α-tetrahydrosantonin Ethylenethioketal (IXb)——The 2-acetoxy-α-tetrahydrosantonin ethylenethiolketal (IXa)[9] (0.70 g) was treated with ethanolic KOH (KOH 1.5 g in 90% EtOH 70 ml) for 6 hr at room temperature; then ethanol was evaporated under reduced pressure. After acidification of the residue with 10% HCl, it was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried. The $CHCl_3$ solution was evaporated giving 0.63 g of 2-hydroxy-3-ethylenethioketal (IXb) as colorless plates, mp 200—235°. Recrystallization from EtOH gave colorless plates, mp 236—237°. $[\alpha]_D^{24°}$ −53.2° ($CHCl_3$, $c=0.56$). *Anal.* Calcd. for $C_{17}H_{26}O_3S_2$: C, 59.61; H, 7.59. Found: C, 59.86; H, 7.72. IR ν_{max} cm^{-1}: 3440 (OH), 1760 (γ-lactone). NMR ($CDCl_3$, τ): 8.94 (s, 3H, 10-CH_3), 8.78 (d, 3H, $J=7$ Hz) 8.58 (d, 3H, $J=6$ Hz).

2-Oxo-3,3-ethylenethioketal-5α-santan-6:13-olide (XI)——To a solution of 2α-ol (IXb) (30 mg) in acetone (10 ml) Kiliani reagent (0.08 ml) was added, and was allowed to stand for 5 min at room temperature. After addition of water (200 ml) into the reaction mixture, the product was crystallized. Recrystallization from EtOH gave 26 mg of colorless prisms, mp 212.5—214°. $[\alpha]_D^{24°}$ +215.6° ($CHCl_3$, $c=0.59$). *Anal.* Calcd. for $C_{17}H_{24}O_3S_2$: C, 59.99; H, 7.05. Found: C, 60.17; H, 7.23. IR ν_{max} cm^{-1}: 1720 (cyclohexanone), 1770 (γ-lactone); UV λ_{max}^{EtOH} nm (ε): 225 (980), 251 (580), 305 (260). NMR ($CDCl_3$, τ): 9.08 (s, C_{10}-CH_3), 8.78 (d, $J=6$ Hz); 8.46 (d, $J=6$ Hz), 6.16 (t, $J=10$ Hz, C_6-H).

Reduction of IXb with Raney Nickel——A solution of IXb (20 mg) in EtOH (20 ml) was refluxed for 15 hr over W-2 Raney nickel. Filtration and removal of EtOH *in vacuo* gave crystals, and recrystallization from EtOH led to 13 mg of colorless plates, mp 150—152°; this product was identical with mixed mp (150—153°) and IR spectrum of α-desoxytetrahydrosantonin (X).

2-Oxo-5,7α(H):4,6,11β(H)-santan-6:13-olide (XIII)——A solution of XI (104 mg) in EtOH (40 ml) was refluxed for 5 hr over W-2 Raney nickel (5 g). The end point of the reaction time was checked by gas chromatography. Filtration and removal of EtOH *in vacuo* gave an oily product (79 mg). To a solution of the product (57 mg) without purification in acetone (18 ml) Kiliani reagent (0.2 ml) was added, and allowed to stand for 5 min at room temperature. 150 ml of water were added to the reaction mixture. A solid product crystallized, which was filtrated, washed and dried. Recrystallization from EtOH gave 51 mg of colorless needles, mp 151—153°. $[\alpha]_D^{20°}$ +70.3° ($CHCl_3$, $c=0.45$). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80. Found: C, 71.85; H, 8.67. IR ν_{max} cm^{-1}: 1718 (cyclohexanone), 1768 (γ-lactone); UV λ_{max}^{EtOH} 292 nm ($\varepsilon=21.4$). NMR ($CDCl_3$, τ): 9.05 (s, 3H, C_{10}-CH_3), 8.77 (3H, d, $J=6$ Hz, C_4-CH_3), 8.74 (3H, d, $J=6$ Hz; C_{11}-CH_3), 6.1 (1H, t, $J=10$ Hz, C_6-H). ORD (MeOH, $c=0.094$) $[\phi]^{23°}$ (nm): +213° (589), +480° (400), +2960° (306) (peak), 0° (284), −986° (272) (trough), 0° (254), +2610° (231) (peak), +906° (213) (trough), +1540° (206). CD (MeOH, $c=0.094$) $[\theta]^{23°}$ (nm): 0° (352), −293° (327) (trough), 0° (318), +933° (310), +3385° (288) (positive maximum), +1730° (270), +500° (241) (trough), +1493° (230), +3700° (218) (positive maximum), +235° (210).

2α-Hydroxy-α-tetrahydrosantonin (XIV)——To a solution of *trans*-α-ketol acetate (VIII)[9] (100 mg) in 90% EtOH (5 ml) 80% hydrazine hydrate (0.1 ml) was added, and was refluxed for 10 min. After acidification, the solution was evaporated under reduced pressure, and the residue was mixed with water and extracted with benzene. Evaporation of the benzene solution gave pale yellow crystals (64 mg), in 74% yield. Recrystallization from hexane–EtOH afforded colorless needles, mp 148.5—149.5°. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.50; H, 8.43. $[\alpha]_D^{20°}$ +26.5° ($CHCl_3$, $c=0.3$). IR ν_{max} cm^{-1}: 1774 (γ-lactone), 1712 (cyclohexanone); UV $\lambda_{max}^{CHCl_3}$ 278 nm (ε 64.5). NMR ($CDCl_3$, τ): 8.68 (3H, d, $J=6$ Hz, C_{11}-CH_3), 8.64 (3H, s, C_{10}-CH_3), 8.64 (3H, d, $J=7.5$ Hz, C_4-CH_3), 6.31 (3H, s, OH), 6.01 (1H, t, $J=10$ Hz, C_6-H), 5.62 (1H, q, $J=10$, 5.7 Hz, C_2-H).

A solution of the α-ketol (XIV) (20 mg) in acetic anhydride (0.3 ml) and pyridine (0.2 ml) was warmed in a water bath for 10 min. The reaction mixture poured into water gave colorless needles (20 mg), mp 199—200°; the product was identical with an authentic specimen of the *trans*-α-ketol acetate (VIII)[9] as confirmed by mixed mp and IR spectrum.

2-Oxo-3β-hydroxy-5α(H)-santan-6:13-olide (XVI)——The α-ketol acetate (VIII)[9] (1.0 g) was treated with 0.25N 20% ethanolic Na_2CO_3 (25 ml), and was refluxed 5 min. After acidification, the solution was evaporated under reduced pressure, and the residue was extracted with $CHCl_3$, washed and dried. Evaporation of the $CHCl_3$ solution gave crystals 0.79 g (92% yield), mp 145—153°. Recrystallization from EtOH furnished colorless plates mp 164—165°. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.15; H, 8.18. $[\alpha]_D^{20°}$ +115° ($CHCl_3$, c=0.41). IR ν_{max} cm^{-1}: 3440 (OH), 1772 (γ-lactone), and 1719 (cyclohexanone); UV λ_{max}^{EtOH} 281 nm (ε 166). NMR ($CDCl_3$; τ): 9.03 (3H, s, C_{10}-CH_3), 8.68 (3H, d, J=7 Hz, C_{11}-CH_3), 8.52 (3H, d, J=7 Hz, C_4-CH_3), 6.31 (1H, s, OH), 6.27 (1H, d, J=10 Hz, C_3-H), 6.1 (1H, t, J=10 Hz).

A solution of the 2-oxo-3β-ol (XVI) (20 mg) in acetic acid (1.0 ml) was refluxed with 1.0 g of acid-washed zinc dust and anhydrous zinc chloride (20 mg) for 2 hr. From the colorless crystals obtained, two compounds were separated which are the 2-oxo-compound (XIII) and α-tetrahydrosantonin (VI) as found by gas chromatography (SE-30, column temperature 200°). The ratio of XIII and VI is 1: 2.

When this reaction was carried on for a prolonged time (8 hr), in the absence of anhydrous zinc chloride, a large amount of starting material was recovered.

2-Oxo-3β-acetoxy-5α(H)-santan-6:13-olide (XVII)——(a) A solution on the α-ketol (XVI) (3.5 g) in acetic anhydride (10.0 ml) and pyridine (10 ml) was warmed in a water bath for 15 min. The reaction mixture was poured into ice water (50 ml), and neutralized with saturated $NaHCO_3$. The above solution was extracted with benzene, it was then washed and dried. Evaporation of the benzene solution gave crude crystals (3.9 g, 97%). Recrystallized from EtOH furnished colorless needles, mp 210—211°. *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.32; H, 7.83. $[\alpha]_D^{20°}$ +110° ($CHCl_3$, c=0.5) IR ν_{max} cm^{-1}: 1782 (γ-lactone), 1760 (acetyl), and 1733 (cyclohexanone); UV λ_{max}^{EtOH} 286 nm (ε 27). NMR ($CDCl_3$, τ) 9.07 (3H, s, C_{10}-CH_3), 8.77 (3H, d, J=7 Hz, C_4-CH_3), 8.73 (3H, d, J=6 Hz, C_{11}-CH_3), 7.82 (3H, s, $COCH_3$), 6.10 (1H, t, J=10 Hz, C_6-H), 5.29 (1H, d, J=11 Hz, C_3-H).

(b) 3-Oxo-2α-acetate (VIII) (20 mg) in benzene (2.5 ml) was absorbed on basic alumina (2.0 g) and allowed to stand overnight. Filtration on alumina and elution with ethyl acetate was carried out. Evaporation of the solvents afforded colorless crystals (16 mg). Recrystallization from EtOH gave 2-oxo-3β-acetate (XVII), mp and mixed mp 209—210°. The IR spectra of the samples were identical.

Reduction of the 2-Oxo-3β-acetate (XVII) with Zinc "Dust" and Acetic Acid——A solution of the 2-oxo-3β-acetate (XVII) (3.0 g) in acetic acid (40 ml) was refluxed with acid-washed zinc dust (25 g) for 8 hr. After removal of zinc by filtration, and evaporation of the acetic acid under reduced pressure, the residue was dissolved in benzene. The benzene layer was washed with 10% Na_2CO_3, then with water, and dried. Evaporation of the benzene solution gave crude crystals (2.6 g), mp 122—131°. Recrystallization from EtOH afforded colorless needles, mp 150—152°. It showed no depression of the melting point on admixture with the 2-oxo-5α-santan-6:13-olide (XIII) described in the above procedure.

5α(H)-Compounds (A/B ring *cis* fusion)

Acetoxylation of γ-Tetrahydrosantonin (VII) with Lead Tetraacetate——According to the procedure described in a previous paper,[18] γ-tetrahydrosantonin (VII) (5.0 g) was heated 6 hr with lead tetraacetate (10.0 g) in glacial acetic acid (200 ml) in a boiling water bath. Crude crystals were obtained (5.9 g) from which fractional recrystallization from EtOH afforded a small amounts of 3α-acetoxy-2-ketone (XXVII), mp and mixed mp 246—247° of "2β-acetoxy-3-ketone" as it was reported in a previous paper.[18] $[\alpha]_D^{24°}$ −124° ($CHCl_3$, 0.6) (reported[18] mp 246—248°, $[\alpha]_D^{26°}$ −36°) NMR ($CDCl_3$, τ): 8.79 (3H, d, J=6 Hz, C_4-CH_3), 8.78 (3H, d, J=7 Hz, C_{11}-CH_3), 8.77 (3H, s, C_{10}-CH_3), 7.83 (3H, s, $COCH_3$), 5.55 (1H, dd, J=10, 3 Hz, C_6-H), 5.05, d, J=11, C_3H).

On standing for a few hours the mother liquor gave a deposit of 2β-acetoxy-3-ketone (XIX) (2.2 g), mp and mixed mp 190—191°. $[\alpha]_D^{24°}$ −55° ($CHCl_3$, c=0.6) (reported,[18] mp 187—188.5°, $[\alpha]_D^{26°}$ −24.3°). NMR ($CDCl_3$, τ): 8.78 (3H, s, C_{10}-CH_3), 8.83 (3H, d, J=7 Hz, C_{11}-CH_3), 8.74 (3H, d, J=7 Hz, C_4-CH_3), 7.85 (3H, s, $COCH_3$), 5.65 (1H, dd, J=10, 4 Hz, C_6-H), 4.65 (1H, q, J=12, 7 Hz, C_2-H). The ratio of crude α-ketol acetate of 2-ketone (XXVII) and 3-ketone (XIX) was 1: 50 as indicated by NMR spectrometry.

Acetolysis of 2β-Bromo-γ-tetrahydrosantonin (XXVI)——Employing the conditions described in a previous paper,[18] acetolysis of the α-bromoketone (XXIV), mp 145—146° (decomp.),[18] (2.0 g) and anhydrous potassium acetate (3.0 g) in glacial acetic acid (25 ml) was refluxed for 10 hr, crude pale-yellow brown crystals (1.8 g) were obtained, from which fractional recrystallization from EtOH afforded 3α-acetoxy-2-ketone (XXVII) (321 mg) as colorless needles, mp 245—246°. (reported[18] as "2β-acetoxy-3-ketone," 246—248°).

The mother liquor being allowed to stand for a few hours, deposites as colorless prisms of 2β-acetoxy-3-ketone (XIX) (710 mg), mp 190—191° (reported[18] as "2α-acetoxy-3-ketone," mp 187—188.5°). The ratio of 2-ketone (XXVI) and 3-ketone (XIX) in the crude α-ketol acetates was 1: 6 as indicated by NMR spectrometry.

2β-Hydroxy-γ-tetrahydrosantonin Ethylenethioketal (XXb)——This procedure is essentially the same as described above for the 5α-series (Xa). 2β-Acetoxy-3-ethylenethioketal (XXa)[18] (1.50 g) was treated with ethanolic KOH (KOH 3.0 g in 90% EtOH 200 ml) and allowed to stand overnight at room temperature. The product obtained as colorless crystals (958 mg) was hydroxy-carboxylic acid. Recrystallization from EtOH afforded cololess needles, mp 194—196°. *Anal.* Calcd. for $C_{17}H_{28}O_4S_2$: C, 56.67; H, 7.78. Found: C, 56.55; H, 7.62. $[\alpha]_D^{22°}$ −23.3° (CH_3OH, c=0.52).

This acid (XXI) (850 mg) was refluxed 2 hr in benzene (60 ml) with *p*-toluene sulfonic acid (200 mg). The reaction mixture was washed with $NaHCO_3$ and water, and after drying, evaporated to leave 800 mg of 2β-hydroxy-3-ethylenethioketal (XXb), melting in the range 187—195°. Recrystallization from EtOH gave colorless needles, mp 191—193.5°. *Anal.* Calcd. for $C_{17}H_{26}O_3S_2$: C, 59.61; H, 7.59. Found: C, 60.07; H, 7.32. $[\alpha]_D^{24°}$ −23.3° ($CHCl_3$, c=0.6). IR ν_{max} cm^{-1}: 3520 (OH), 1764 (γ-lactone). NMR ($CDCl_3$, τ): 8.88 (3H, s, C_{10}-CH_3), 8.75 (3H, d, J=7 Hz, C_{11}-CH_3), 8.69 (3H, d, J=6 Hz, C_4-CH_3), 7.45 (1H, s, OH), 6.73 (4H, broad s, $\langle \begin{matrix} S\text{-}CH_2 \\ | \\ S\text{-}CH_2 \end{matrix}$), 6.18 (1H, dd, J=12, 5 Hz, C_2-H), 5.61 (1H, dd, J=11, 4 Hz, C_6-H).

2-Oxo-5β(H)-santan-6:13-olide-3-ethylenethioketal (XXII)——This compound was synthesized according to the procedure described above for 2-hydroxy-3-ethylenethioketal (IXb) in the 5α-series. To a solution of the 2β-hydroxy-3-ethylenethioketal (XXb) (1.76 g) in acetone (200 ml) Kiliani reagent (5.8 ml) was added drop by drop, and stirred for 1 hr at room temperature. Addition of aqueous $NaHSO_3$ into the reaction mixture by indicating KI-starch test paper. Evaporation of acetone under reduced pressure was done, and the residue was poured into ice-water (200 ml). Colorless crystals (0.83 g; 47.5% yield) of 2-oxo-3-ethylenethioketal (XXII) were obtained. Recrystallization from EtOH afforded colorless plates, mp 175—177°. *Anal.* Calcd. for $C_{17}H_{24}O_3S_2$: C, 59.97; H, 7.10. Found: C, 59.71; H, 7.29. $[\alpha]_D^{22°}$ −182.5° ($CHCl_3$, c=0.55) IR ν_{max} cm^{-1}: 1770 (γ-lactone), 1714 (cyclohexanone); UV λ_{max}^{EtOH} nm (ε): 225.5 (1090), 248.5 (730), 307 (300). NMR ($CDCl_3$; τ): 8.80 (3H, s, C_{10}-CH_3), 8.77 (3H, d, J=7 Hz, C_{11}-CH_3), 8.58 (3H, d, J=6 Hz, C_4-CH_3), 6.76 (4H, s, $\langle \begin{matrix} S\text{-}CH_2 \\ | \\ S\text{-}CH_2 \end{matrix}$), 5.44 (1H, dd, J=10, 4 Hz, C_6-H).

2-Oxo-4;7α(H)-5;6;11β(H)-santan-6:13-olide (XXIII)——This procedure was carried out as described above for 2-oxo-3-ethylenethioketal (XI) in the 5α-series. A solution of XXII (1.96 g) in EtOH (500 ml) was refluxed for 8 hr over W-2 Raney nickel (35.5 g). Filtration and removal of EtOH *in vacuo* gave a pale yellow oily product (1.31 g), which could not be crystallized. The oily product, without purified, was dissolved in acetone (350 ml), and added with Kiliani reagent (11 ml) under continuous stirring for 1 hr, at room temperature. After addition of aqueous $NaHSO_3$ and it was poured into ice water (200 ml). A colorless product was obtained (1.12 g; 86% yield). Recrystallization from EtOH furnished colorless plates, mp 152—153°. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80. Found: C, 71.84; H, 8.55. $[\alpha]_D^{25°}$ −82.0° ($CHCl_3$, c=0.46). IR ν_{max} cm^{-1}: 1775 (γ-lactone), 1709 (cyclohexanone); UV λ_{max}^{EtOH} 277 nm (ε 68). NMR ($CDCl_3$, τ): 8.81 (3H, d, J=6 Hz, C_{11}-CH_3), 8.78 (3H, s, C_{10}-CH_3), 8.75 (3H, d, J=6 Hz, C_4-CH_3), 5.50 (1H, q, J=10, 4 Hz, C_6-H). ORD (MeOH, c=0.084) $[\phi]^{24°}$ (nm): −120° (589), −445° (400), −800° (325) (trough), −595° (305) (peak), −193° (250), −1900° (242) (shoulder), −6850° (210). CD (MeOH, c=0.084) $[\theta]^{24°}$ (nm): 0° (360), −135° (320) (trough), −125° (318) (maximum), −135° (312) (trough), 0° (306), +149° (300), +518° (285) (positive maximum), +480° (280), +42° (251) (trough), +360° (240), +1640° (222) (positive maximum), +357° (205).

2β-Hydroxy-γ-tetrahydrosantonin (XXIV)——As it has been described above for the 2α-acetoxy-α-tetrahydrosantonin (VIII), a solution of 2β-acetoxy-3-ketone (XIX) (200 mg) and anhydrous hydrazine (0.2 ml) in EtOH (10 ml) was refluxed for 10 hr. After acidification, the solution was evaporated and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ solution gave pale yellow crystals (155 mg, 90% yield), mp 150—155°. Recrystallization from EtOH afforded colorless prisms of 2β-hydroxy-3-ketone (XXIV), mp 159—160.5°. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.36; H, 8.15. $[\alpha]_D^{24°}$ −14.6° ($CHCl_3$, c=0.4). IR ν_{max} cm^{-1}: 3460 (OH), 1770 (γ-lactone), 1710 (cyclohexanone); UV $\lambda_{max}^{CHCl_3}$ 274 nm (ε 36.2). NMR ($CDCl_3$, τ): 8.79 (3H, s, C_{10}-CH_3), 8.74 (3H, d, J=7 Hz, C_4-CH_3), 8.68 (3H, d, J=7 Hz, C_{11}-CH_3), 6.62 (1H, broad s, OH), 5.59 (1H, dd, J=13, 7 Hz; C_2-H), 5.59 (1H, dd, J=11, 5 Hz, C_6-H).

As described above for the 5α-series, a solution of the α-ketol (XXIV) (20 mg) in acetic anhydride (0.2 ml) and pyridine (0.1 ml) was warmed in a water bath for 1 hr. The reaction mixture pourded into ice-water gave crystals, which were recrystallized from EtOH to give colorless prisms, mp 189—190°. It did not show any depression mixed mp of 2β-acetoxy-3-ketone (XIX), and IR spectra were identical.

Hydrolysis of 2β-Acetoxy-3-ketone (XIX) with dil. HCl——A solution of the 2β-acetoxy-3-ketone (XIX) (200 mg) in EtOH (5 ml) and 10% HCl (5 ml) was refluxed for 30 min. After neutralization with saturated $NaHCO_3$, the solution was evaporated *in vacuo*, the residue was extracted with benzene. Evaporation of the benzene solution gave crude crystals (178 mg) of 2-oxo-3α-hydroxy derivative (XXV). Recrystallization from EtOH afforded colorless plates, mp 174—175°. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.51; H, 8.32. $[\alpha]_D^{24°}$ −41.4° ($CHCl_3$, c=0.6). IR ν_{max} cm^{-1}: 3440 (OH), 1780 (γ-lactone), 1715 (cyclohexanone); UV $\lambda_{max}^{CHCl_3}$ 282 nm (ε 120). NMR ($CDCl_3$, τ): 8.78 (3H, d, J=6 Hz, C_4-CH_3), 8.75 (3H, s, C_{10}-CH_3), 8.67 (3H, d, J=6 Hz, C_{11}-CH_3), 6.48 (1H, broad s, OH), 6.15 (broad d, J=10 Hz, C_3-H), 5.58 (1H, dd, J=10, 4 Hz, C_6-H).

A solution of the α-ketol (XXV) (170 mg) in acetic anhydride (1.3 ml) and pyridine (1.0 ml) was warmed in a boiling water bath for 1 hr. After treatment by the usual way, colorless crystals were obtained (175 mg), which were recrystallized from EtOH giving colorless needles, mp 245—246°. It did not show any depression mixed mp of 2-oxo-3α-acetate (XXVII), and IR spectra were identical.

Isomerization of 2β-Acetoxy-3-ketone (XIX) into 3-Acetoxy-2-ketone (XXVII)——The procedure is essentially the same as the described for the 5α-series; basic alumina (2.0 g) was added to a solution of 2-acetoxy-3-ketone (XVIII) (20 mg) in benzene (2.5 ml) and allowed to stand overnight at room temperature. After filtration and elution with ethyl acetate, evaporation of the filtrate under reduced pressure afforded colorless crystals (15 mg). Recrystallization from EtOH gave colorless prisms of 2-oxo-3α-acetate (XXVII), mp and mixed mp 244—245°.

Reduction of 2-Oxo-3α-acetate (XXVII) with Zinc Dust and Acetic Acid——As descirbed above for the 5α-series, a solution of the 2-oxo-3α-acetate (XXVII) (100 mg) in glacial acetic acid (5.0 ml) was refluxed with acid-washed zinc dust (1.0 g) for 26 hr. After removal of zinc by filtration, it was treated according to the usual way. Colorless crystals were obtained mp 142—145° (85 mg). This crude product contained 9% of γ-tetrahydrosantonin (VII) as it was demonstrated by the gas chromatography (SE-30, column temperature 200°). Recrystallization from EtOH afforded colorless plates, mp 149—150°. This substance was identical with an authentic specimen of 2-oxo-4;7α(H)-5;6;11β(H)-santan-6:13-olide (XXIII) which was prepared by the above alternative method by mixed mp and their IR spectra were similar.

Acknowledgement The authors wish to thank Professor M. Yanagita of the Keio University for his interest and encorragement. *l*-Santonin was kindly supplied by Dr. Ohara of Fujisawa Pharmaceutical Industry Ltd. The authors are also indebted to Mr. Nishitani in this laboratory for technical assistance and Mrs. Hirose of the Keio University for microanalyses. This work was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowleged.