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Studies on the Terpenoids and related Alicyclic Compounds. VIII.[1] Chemical Transformation of α-Santonin into Arsantin and Arsanin

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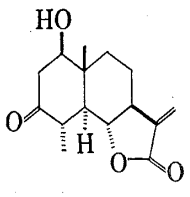
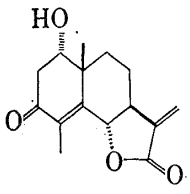
Chemical transformations of α-santonin (V) into arsantin (IIIa) and arsanin (IVa) isolated from *Artemisia santolina* by Sidyakin, *et al.* were described. α-Epoxyketone (IX) was prepared from α-tetrahydrosantonin (VI) *via* three steps. Reductive ring-opening of IX with zinc dust in methanol in the presence of a small amount of acetic acid afforded arsantin (IIIa). IIIa was not coincident with the reported natural atsantin, which was probably identical with a dimorph of arsanin (IVa). β-Epoxy compound (XVI) was prepared from 1-en-3β-ol (XIVa) by Sharpless' procedure. Reductive ring-opening of β-epoxyketone (XVIII) by a method similar to described for arsantin gave 1β-hydroxyketone (IVa). The mp, nuclear magnetic resonance and infrared spectra of IVa were identical with those of natural arsanin.

Some sesquiterpenoid lactones having oxygen functions at 1- and 3-position, for example artecalin (I),[3] ludovicin-C (II),[4] have been reported. Recently Sidyakin, *et al.*[5-7] reported new sesquiterpenoid lactones, arsantin and arsanin isolated from *Artemisia santolina* Schrenk. The structure of arsantin and arsanin was determined to be IIIa and IVa, respectively, from their spectral data and some chemical transformations.

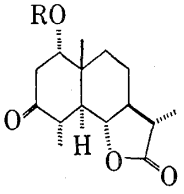
We now report chemical transformation of α-santonin (V), a totally synthesized sesquiterpenoids,[8] into arsantin (IIIa) and arsanin (IVa). α-Tetrahydrosantonin (VI)[9] was chosen as a starting material because of the same absolute configuration as arsantin and arsanin at six chiral centers except C-1 hydroxyl group.



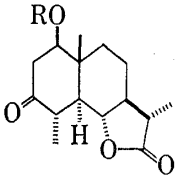
I



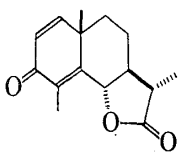
II



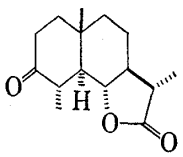
IIIa : R=H
IIIb : R=CH_3CO



IVa : R=H
IVb : R=CH_3CO



V



VI

1) Part VII. K. Yamakawa, K. Nishitani, and A. Yamamoto, *Chem. Lett. Japan*, No. 2, 177 (1976).
2) Location: *12-Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
3) T.A. Geissman, T.S. Griffin, and M.A. Irwin, *Phytochemistry*, **8**, 1297 (1969).
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5) B. Akyev, Sn. Z. Kasymov, and G.P. Sidyakin, *Khim. Prir. Soedin.*, **8**, 461 (1972) [*Chem. Absts.*, **78**, 13748 *k* (1973)].
6) B. Akyev, Sh. Z. Kasymov, and G.P. Sidyakin, *Khim. Prir. Soedin.*, **8**, 730 (1972) [*Chem. Absts.*, **78**, 84565*j* (1973)].
7) G.P. Moiseeva, B. Akyev, Sh. Z. Kasymov, and G.P. Sidyakin, *Khim. Prir. Soedin.*, 167 (1973) [*Chem. Absts.*, 5470*u* (1974)].
8) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956).
9) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).

Chemical Transformation of α-Santonin into Arsantin

Bromination of α-tetrahydrosantonin (VI) gave 2α-bromide (VII)[9,10] and treatment of VII with lithium bromide and lithium carbonate in dimethylformamide afforded an enone (VIII).[11] Epoxidation of the enone (VIII) by 30% hydrogen peroxide in dioxane-sodium hydroxide solution gave stereoselectively an α-epoxide (IX),[12] mp 147—148°, in quantitative yield.

For the purpose of cleavage of the epoxy ring, IX was treated with hydrochloric acid or hydrogen bromide to give no expected halohydrin (Xa or Xb), but dehydrated product chloro-enone (XIa), mp 150—151°, or bromo-enone (XIb), mp 129—130°. XIa and XIb showed a characteristic absorption band of α-halo-enone at 1685 and 1690 cm^{-1} in infrared (IR) and λ_{max} 245 and 254 nm in ultraviolet (UV), which were assigned for stereoformula XIa and XIb, respectively. Then, ketalization of IX with ethylene glycol in the presence of *p*-toluenesulfonic

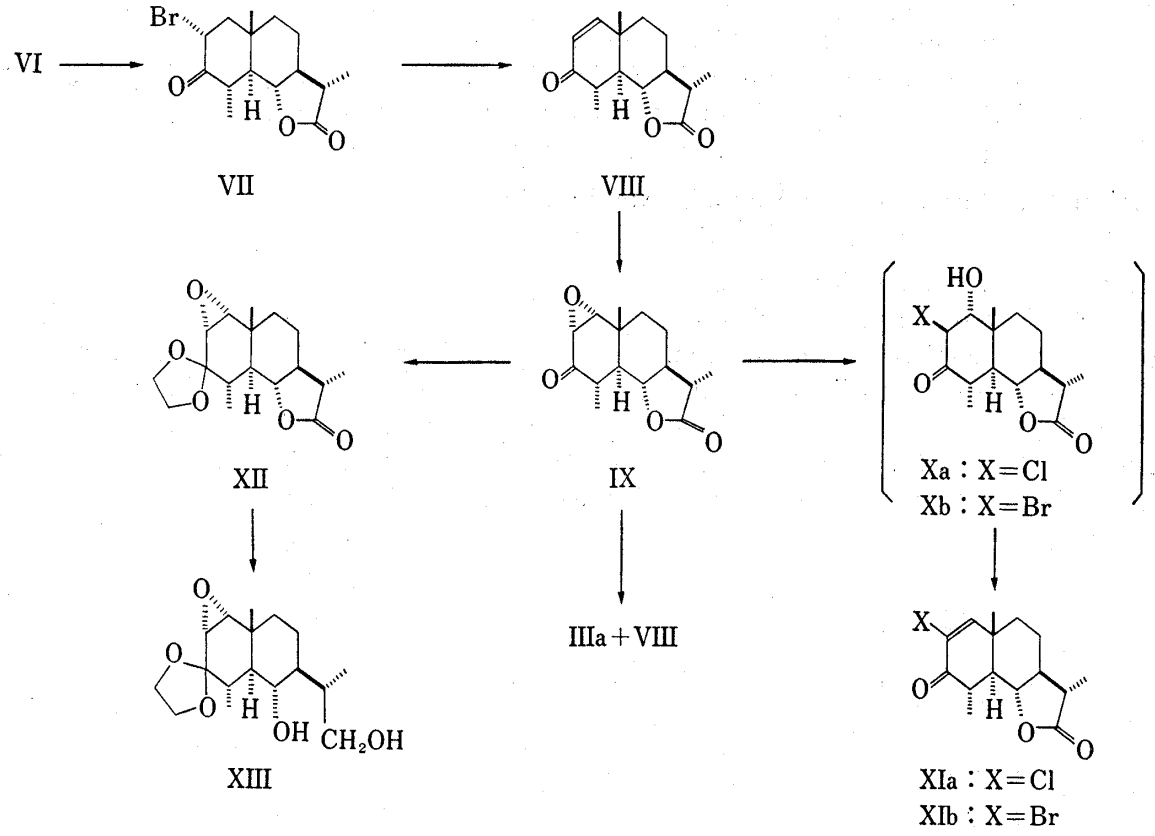

Chart 1

acid gave ketal epoxide (XII), mp 230—231°, whose reductive cleavage with lithium aluminum hydride under several conditions was carried out. However, the γ-lactone was more easily reduced than the epoxy group to give diol (XIII), mp 105—107°.

Schwarz, *et al.*[13] reported reductive cleavage of steroidal epoxyketones using chromous acetate. Therefore, this procedure was applied to the epoxyketone (IX), but a large amount of the starting material recovered together with complex products containing a small amount of the objective compound (IIIa) and the enone (VIII). Reductive cleavage of IX by catalytic reduction with platinum oxide under a hydrogen atmospher, followed by oxidation gave a small amount of arsantin (IIIa) together with major parts of the starting α-epoxyketone (IX).

10) K. Yamakawa, *J. Org. Chem.*, **24**, 897 (1959).
11) E.J. Corey and A.G. Hartmann, *J. Am. Chem. Soc.*, **87**, 5736(1965).
12) V.K. Honwad, E. Siscovic, and A.S. Rao, *Tetrahedron*, **23**, 1273 (1966).
13) V. Schwarz, *Coll. Czech. Chem. Commun.*, **26**, 1207 (1961).

Deacetoxylation of α-ketol acetates with zinc in acetic acid was reported.[14,15] This reductive cleavage reaction was applied to the α-epoxyketone (IX). Treatment of IX with activated zinc dust in ethanol in the presence of a small amount of acetic acid afforded objective (+)-arsantin (IIIa), 1α-hydroxy-α-tetrahydrosantonin (IIIa), mp 183—185°, in 53% yield together with enone (VIII) as a minor product. This 1α-hydroxy-α-tetrahydrosantonin (IIIa) was not coincident with natural arsantin which obtained by Moiseeva, *et al.*[5] in mp (168°) and infrared spectrum. However, the structure of the compound (IIIa) could unequivocally be established to be 1α-hydroxy-α-tetrahydrosantonin on the basis of its nuclear magnetic resonance (NMR) spectrum, showing C-1β H at δ 3.78 (broad t, J=3 Hz), and the IR spectral data and the chemical transformation route from α-santonin. This question could not be cleared without comparing their NMR spectrum with that of the natural arsantin, and unfortunately we could not obtain the NMR data and the sample. On the basis of their IR spectra comparison, we believe that the reported natural arsantin was probably identical with a dimorph of arsanin (IVa), mp 187—188°, which described below.

1α-Hydroxy-α-tetrahydrosantonin (IIIa) was converted to an acetate (IIIb), mp 166—168°, by treatment with acetic anhydride and pyridine. Treatment of IIIa with 50% sulfuric acid afforded the enone (VIII) in quantitative yield. The structure of 1α-hydroxy-α-tetrahydrosantonin (IIIa) was also confirmed from the above facts.

Chemical Transformation of α-Santonin into Arsanin

β-Epoxyketone (XVIII) seems useful as a key intermediate on the transformation to arsanin (IVa) in the similar strategy described above for arsantin (IIIa). Henbest, *et al.*[16] reported the stereoselective β-epoxydation of 3β-hydroxy-cholest-1-ene by perbenzoic acid, and the stereochemistry of the reaction. In order to preparation of 1-en-3β-ol (XIVa), enone (VIII) was reduced with lithium aluminum hydride at room temperature in ether to give a 1-en-3β-ol (XIVa), mp 181—183° in 46% yield together with a triol (XV), mp 144—145°. On the other hand, the reduction of XIVa in tetrahydrofuran at −5∼−10° gave stereoselectively a desired 1-en-3β-ol (XIVa) in high yield. The configuration of 3-hydroxyl group of

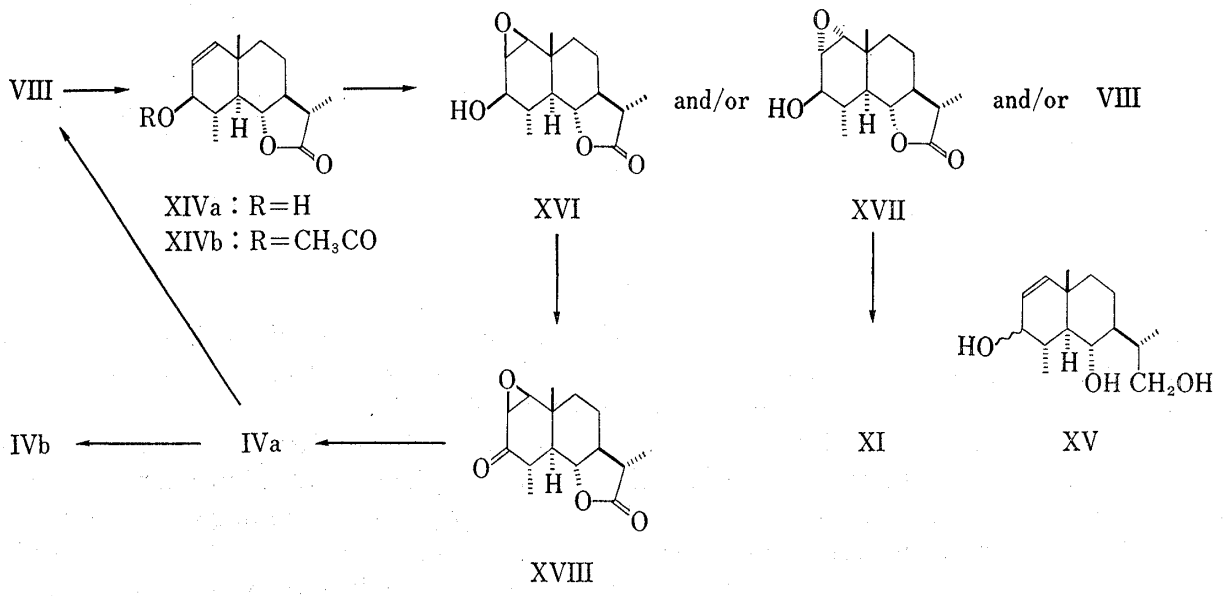

Chart 2

14) R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W.M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
15) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **24**, 903 (1959).
16) H.B. Henbest and R.A.L. Wilson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).

XIVa was confirmed to be β-configuration by means of NMR spectrum, which showed doublet ($J_{3,4}$=9 Hz) at δ 3.76. XIV was converted to an acetate (XIVb), mp 149—150°.

Epoxydation of the 1-en-3β-ol (XIVa) with *m*-chloroperbenzoic acid in methylene chloride, according to modified Henbest procedure,[16] gave a mixture of α- and β-epoxide which was separated by preparative thin-layer chromatography in α-epoxide (XVII; 24% yield), mp 112—113°, and β-epoxide (XVI; 31% yield), mp 210—213°. The structure of α- and β-epoxide was confirmed to be XVII and XVI by means of their NMR spectra, respectively. Recently, Sharpless and Micharlson[17] reported highly stereoselective epoxidation of 1-en-2β-ol derivatives by tert-butyl hydrogen peroxide in the presence of vanadyl acetylacetonate in benzene. The epoxidation of XIVa, according to Sharpless' procedure, gave the β-epoxide (XVI; 20% yield) and together with the enone (VIII; 67% yield), but this reaction carried out in methylene chloride solution to give XVI in 47% yield together with VIII in 39% yield.

Oxidation of the α- and β-epoxide (XVII and XVI) with chromium trioxide-pyridine complex gave α- and β-epoxyketone (IX and XVIII), respectively. Reductive cleavage of the β-epoxyketone (XVIII) with activated zinc dust was carried out by a method similar to described above for arsantin (IIIa). After work-up the desired 1β-hydroxy-α-tetrahydrosantonin (IVa), mp 201.5—202.5°, was isolated in 74% yield from the reduction residure by use of preparative thin-layer chromatography. No depression of the melting point was observed in the mixture of this 1β-hydroxide (IVa) and the natural arsanin. The NMR and IR spectra of IVa were identical with those of natural arsanin which was reported by Sidyakin, *et al.*[3]

IVa was converted to 1β-acetate (IVb), mp 170—171°, which was also identified by IR, NMR and $[\alpha]_D$ comparison with the reported arsanin acetate.[3] Treatment of IVa with 50% sulfuric acid gave an enone, which was identical with an authentic enone (VIII). Recrystallization of arsanin (IVa) from hexane–ethyl acetate gave a dimorph of IVa as colorless plates, mp 187—188°. The IR spectrum of the dimorph of IVa seems to be same as that of arsantin which was already reported by Sidyakin, *et al.*[3]

Experimental

All melting points were determined on Yanagimoto Micro-Melting Points Apparatus and are uncorrected. NMR spectra for solutions in $CDCl_3$ were measured with a Jeol JNM-4H-100 spectrometer at 100 MHz using TMS as internal reference. IR spectra were measured with a Hitachi Perkin-Elmer Model 225 grating spectrophotometer. UV spectra were measured for solutions in ethanol with a Hitachi Model 323 spectrophotometer. Mass spectra were recorded on a Hitachi RMU-7M double forcusing mass spectrometer. High-resolution mass spectral data were determined by a Hitachi datalyzer 002 on-line connected with the mass spectrometer. Specific rotations were measured for solutions in chloroform with a Jasco DIP-SL digital polarimeter. Wako silica gel C-200 (200 mesh) containing 2% fluorescent 254 and quarz column were used in column chromatography. For thin-layer plates were used Merck silica gel HF_{254}.

3-Oxo-1-en-5α-santanolide (VIII)——According to the procedure described by Corey, *et al.*,[11] to a stirred suspension of LiBr (4.8 g) and Li_2CO_3 (6.4 g) in dry dimethylformamide (100 ml) at 120—125° under N_2 was added 2α-bromide (VII) (11.7 g). Stirring was continued for 100 min at 120—125°. The reaction mixture was concentrated under reduced pressure and diluted with CH_2Cl_2 (400 ml). The resulting solution was washed with successive 10% HCl, $NaHCO_3$ solution and H_2O, dried over Na_2SO_4. Evaporation of the CH_2Cl_2 gave brown brocks, which were recrystallized from ethyl acetate-hexane to give 6.34 g (72%) of 3-oxo-1-en-5α-santanolide (VIII) as colorless needles, mp 141.5—142.5° (lit.[11] mp 141.5—142.5°). IR (KBr, cm^{-1}): 1775, 1670. NMR (δ): 5.88, 6.74 (1H each d, J=10 Hz; C-2,1 H).

1α,2α-Epoxy-3-oxo-5α-santanolide (IX)——This compound was prepared by the procedure similar to that described by Honwad, *et al.*[12] To a stirred solution of VIII (1.27 g) in dioxane (50 ml) was added 35% H_2O_2 (5 ml) and 1N NaOH (12 ml) for 18 min at 0°. The reaction mixture was left another 15 min at 0°, diluted with H_2O (15 ml) and extracted with ether (400 ml). After the extracts had been washed with H_2O, 10% Mohr salt and saturated NaCl, dried over Na_2SO_4, the ether was removed, giving 1.07 g (87%) of 1α,2α-epoxy-3-oxo-5α-santanolide (IX) as colorless plates, mp 122—125° (lit.[12] mp 124—127°). Recrystallization from EtOH gave colorless plates, mp 147—148°, which was a dimorph of the epoxide, mp 124—127°. *Anal.*

17) K.B. Sharpless and R.C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).

Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.12; H, 7.61. Mass Spectrum *m/e* (rel. intensity): 264 (19, M^+), 221 (12), 179 (23), 178 (100). $[\alpha]_D^{27°}$ +120° (*c*, 2.05, $CHCl_3$). UV λ_{max}^{EtOH} 299 nm (ε 32); IR (KBr, cm^{-1}): 1770, 1708; NMR (δ): 0.99 (3H, s; C-10 CH_3), 1.21 (3H, d, *J*=7 Hz; C-11 CH_3), 1.31 (3H, d, *J*=7 Hz; C-4 CH_3), 3.32 (2H, ABq, *J*=4 Hz; C-1,2 H), 3.82 (1H, t, *J*=10 Hz; C-6 H).

Conversion to "Arsantin" (IIIa) from α-Epoxide (IX)——(a) Reduction with Zn Dust: To a stirred solution of IX (445 mg) in MeOH (50 ml) was added, Zn dust (2 g) and glacial acetic acid (0.3 ml). The reaction mixture was refluxed for 1.5 hr, and then cooled and filtered. The filtrate was concentrated under reduced pressure, and diluted with EtOAc (200 ml). The resulting solution was washed with 10% HCl, $NaHCO_3$ solution and H_2O, and dried. The EtOAc was removed under reduced pressure to give crude crystals, which were subjected to preparative thin-layer chromatography. Developing with benzene and EtOAc (3: 1) gave two bands. Band 1 gave 134 mg of a mixture of the enone (VIII) and the starting epoxide(IX) in a 2 to 1 ratio as evidenced by NMR spectrometry. Band 2 gave 245 mg (55%) of 1α-hydroxy-3-oxo-5α-santanolide "Arsantin" (IIIa) as colorless plates, mp 171—175°. Recrystallization from EtOAc–hexane gave colorless plates, mp 183—185° (lit.[7] mp 168°). *Anal.* Calcd. for $C_{15}H_{22}O_4$: 266.1516; C, 67.64; H, 8.33. Found: M^+ 266.1505; C, 67.94; H, 8.13. Mass Spectrum *m/e* (rel. intensity): 266 (13, M^+), 248 (9, $[M-H_2O]^+$), 167 (100). $[\alpha]_D^{26°}$ +31.5° (*c*, 1.78, $CHCl_3$). UV: λ_{max}^{EtOH} 285 nm (ε 23); IR (KBr, cm^{-1}): 3525, 1770, 1710. (lit.[7] λ_{max} 290 nm (ε 18); ν_{max} 3505, 1755, 1715, 1690). NMR (δ): 1.15 (3H, s; C-10 CH_3), 1.18 (3H, d, *J*=7 Hz; C-4 CH_3), 1.21 (3H, d, *J*=7 Hz; C-11 CH_3), 3.05 (1H; OH), 3.78 (1H, t, *J*=3 Hz; C-1 H), 4.00 (1H, t, *J*=10 Hz; C-6 H).

(b) Reduction with Chromous Acetate:——To a stirred solution of IX (50 mg) in 80% acetic acid (6 ml) was added freshly prepared chromous acetate[18] in large excess. The wine red reaction mixture was stirred for 57 hr at room temperature and then poured into H_2O. The resulting mixture was neutralized with $NaHCO_3$ and extracted with EtOAc (200 ml). After the extracts had been washed with H_2O and dried over Na_2SO_4, the EtOAc was removed, giving 50 mg of crystals. The crude product was chromatographed on thin-layer with benzene–EtOAc (2: 1) as a developing solvent. Band 1 gave 32 mg of a mixture of the enone (VIII) and the starting epoxide (IX) as evidenced by NMR spectrometry. Band 2 gave 8.5 mg of "arsantin" (IIIa) as colorless needles, mp 162—165°, which was identified by IR comparison with an authentic sample of IIIa obtained by method (a).

Arsantin Acetate (IIIb)——To a stirred solution of IIIa (50 mg) in pyridine (1 ml) was added acetic anhydried (1 ml) at 0° and stirred for 15 hr at room temperature The reaction mixture was poured into ice-cold water (10 ml) and neutralized with $NaHCO_3$, and then extracted with EtOAc (200 ml). The extracts were washed with successive, 10% HCl, $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. The EtOAc was removed under reduced pressure to afford 55 mg of a mixture of the enone (VIII) and 1α-acetoxy-3-oxo-5α-santanolide "arsantin acetate" (IIIb) in a 8 to 5 ratio as evidenced by NMR spectrometry. Fractional recrystallization from EtOH afforded 14.5 mg of IIIb in 25% yield, as colorless needles, mp 166—168°. Mass Spectrum *m/e* (rel. intensity): 308 (7, M^+), 248 (100, $[M-CH_3CO_2H]^+$), 220 (55), 192 (46). $[\alpha]_D^{28°}$ +53.3° (*c*, 0.60, $CHCl_3$). UV λ_{max}^{EtOH} 283 nm (ε 22). IR (KBr, cm^{-1}): 1777, 1735, 1710, 1238. NMR (δ): 1.22 (3H, d, *J*=7 Hz; C-4 or C-11 CH_3), 1.24 (3H, s; C-10 CH_3), 1.28 (3H, d, *J*=7 Hz, C-4 or C-11 CH_3), 2.04 (3H, s; -$OCOCH_3$), 3.96 (1H, t, *J*=10 Hz; C-6 H), 4.94 (1H, broad t, *J*=3 Hz; C-1 H).

Recrystallization of the residue afforded 5.5 mg of the enone (VIII), mp 141—142°, which was identical in IR spectra and mixed melting point with the authentic sample.

Dehydration of "Arsantin" (IIIa)——To a stirred 50% H_2SO_4 (4 ml) was added IIIa (20 mg), and warmed for 5 min at 65°. The reaction mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (150 ml). The extracts were washed with H_2O and dried over Na_2SO_4. Evaporation of $CHCl_3$ afforded 19 mg of the enone (VIII) as colorless needles, mp 128—135°. Recrystallization from EtOH afforded colorless needles VIII, mp 141.5—142.5°, which was identified by mixed melting point and IR spectra comparison with the authentic sample.

Reaction of the α-Epoxide (IX) with HCl——To a solution of the α-epoxide (IX) (40 mg) in dioxane (5 ml) was added 10% HCl (5 ml). The reaction mixture was stirred for 2 hr at room temperature and then extracted with EtOAc (150 ml). The extracts were washed with $NaHCO_3$ solution and H_2O and dried over Na_2SO_4. Evaporation of the EtOAc afforded 41 mg of colorless crystals, mp 110—115°. Recrystallization from EtOH gave 30 mg (70%) of 2-chloro-3-oxo-1-en-5α-santanolide (Xa) as colorless columns, mp 150—151°. *Anal.* Calcd. for $C_{15}H_{19}O_3Cl$: C, 63.72; H, 6.77. Found: C, 63.60; H, 6.83. Mass Spectrum *m/e* (rel. intensity): 284 (4, $[M+2]^+$), 282 (19, $[M]^+$), 256 (7), 254 (21), 247 (100, $[M-Cl]^+$), 219 (73). $[\alpha]_D^{26}$ +20.3° (*c*, 1.01, $CHCl_3$). UV λ_{max}^{EtOH} 245 nm (ε 7, 160); IR (KBr, cm^{-1}): 1770, 1685, 1610. NMR (δ): 1.21 (3H, d, *J*=6 Hz; C-11 CH_3), 1.22 (3H, s; C-10 CH_3), 1.40 (3H, d, *J*=6 Hz; C-4 CH_3), 3.98 (1H, t, *J*=10 Hz; C-6 H), 6.90 (1H, s; C-1 H).

Reaction of the α-Epoxide (IX) with HBr——To a stirred solution of the α-epoxide (IX) (40 mg) in acetic acid (5 ml) was added 48% HBr in acetic acid solution (0.5 ml). The mixture was stirred for 45 min at room temperature. The reaction mixture was poured into H_2O and extracted with EtOAc (200 ml). The extracts were washed with $NaHCO_3$ solution and H_2O and dried. The EtOAc was removed under reduced pressure to

18) D.H.R. Barton, N.K. Basu, R.H. Hesse, F.S. Morehaouse, and M.M. Pechet, *J. Am. Chem. Soc.*, **83**, 3016 (1966).

give 51 mg of crystals. Recrystallization from EtOH gave 2-bromo-3-oxo-1-en-5α-santanolide (Xb) as colorless prisms, mp 129—130°. Mass Spectrum *m/e* (rel. intensity): 328 and 326 (7; 1: 1, M^+), 300 and 298 (5; 1: 1), 247 (100), 219 (56). UV λ_{max}^{EtOH} 254 nm (ε 6, 720). IR (KBr, cm^{-1}): 1780, 1690, 1608. NMR (δ): 1.21 (3H, d, J=7 Hz; C-11 CH_3), 1.22 (3H, s; C-10 CH_3), 1.41 (3H, d, J=7 Hz; C-4 CH_3), 2.26 (1H, sextet, J=7 Hz; C-4 H), 3.96 (1H, t, J=10 Hz; C-6 H), 7.16 (1H, s; C-1 H).

Ketalization of the α-Epoxide (IX)——To a stirred solution of IX (520 mg) in benzene (50 ml) was added ethylene glycol (4 ml) and *p*-TsOH (50 mg). The resulting solution was refluxed for 12 hr, and then cooled and extracted with benzene (200 ml). The extracts were washed with successive H_2O, $NaHCO_3$ solution and saturated NaCl, and dried over Na_2SO_4. Evaporation of the benzene under reduced pressure afforded yellow brocks. Recrystallization from EtOH gave 296 mg (49%) of the ketal (XII) as colorless columns, mp 230—231°. *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.17; H, 7.92. Mass Spectrum *m/e* (rel. intensity): 308 (40; M^+), 209 (54), 181 (11), 156 (17), 142 (38), 113 (92), 100 (100). $[\alpha]_D^{27°}$ +1.8° (*c*, 1.83, $CHCl_3$). IR (KBr, cm^{-1}): 1767. NMR (δ): 1.01 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 1.08 (3H, s; C-10 CH_3), 1.18 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 2.49 and 3.05 (1H each d, J=3 Hz; C-2, 1H), 4.00 (5H, m; C-6H and ketal CH_2).

Reduction of the Epoxy Ketal (XII)——A solution of XII (50 mg) in tetrahydrofuran at 0° was treated with $LiAlH_4$ (6 mg). The excess $LiAlH_4$ was decomposed with a small amount of H_2O and the resulting solution was extracted with ether. The extracts were washed with 10% HCl and H_2O and dried, the ether was removed to give 47 mg of viscous oil. The product was purified by preparative thin-layer chromatography developing with acetone–hexane (2: 1), affording 35 mg (68%) of diol epoxy ketal (XIII) as prisms, mp 105—107°. Mass Spectrum *m/e* (rel. intensity): 312 (15, M^+), 294 (3, $[M-H_2O]^+$), 253 (10), 237 (7), 142 (19), 126 (9), 113 (100). IR (KBr, cm^{-1}): 3420 (broad). NMR (δ): 0.83 (3H, d, J=7 Hz; C-11 CH_3), 0.95 (3H, s; C-10 CH_3), 1.08 (3H, d, J=7 Hz; C-4 CH_3), 2.44 (2H, OH), 2.82 and 3.06 (1H each d, J=3 Hz; C-2, 1H), 3.42 (1H, t, J=10 Hz; C-6H), 3.49 (2H, d, J=7 Hz; C-12H), 4.50 (4H, m; ethylene ketal).

3β-Hydroxy-1-en-5α-santanolide (XIVa)——(a) A solution of the enone (VIII) (3.0 g; 0.012 mole) in tetrahydrofuran (150 ml) at −5——10° was treated with $LiAlH_4$ (220 mg; 0.0058 mole) in the same solvent (10 ml). The reaction was monitored by TLC and jadged complete after 30 min at the same temperature. The excess reducing agent was decomposed by addition of H_2O. Evaporation of the tetrahydrofuran and extracted with EtOAc (300 ml). The organic layer was washed with 10% HCl and H_2O and dried over Na_2SO_4. Evaporation of the EtOAc afforded colorless crystals (2.94 g). Recrystallization from EtOAc–hexane gave 2.39 g (79%) of 3β-hydroxy-1-en-5α-santanolide (XIVa) as colorless needles, mp 181—183°. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.95; H, 8.95. Mass Spectrum *m/e* (rel. intensity): 250 (50, M^+), 235 (25), 232 (4, $[M-H_2O]^+$), 221 (14), 167 (100). $[\alpha]_D^{27°}$ +65.9° (*c*, 1.72, $CHCl_3$). IR (KBr, cm^{-1}): 3515, 1755, 1650. NMR (δ): 1.06 (3H, s; C-10 CH_3), 1.18 (3H, d, J=7 Hz; C-11 CH_3), 1.23 (3H, d, J=6 Hz; C-4 CH_3), 3.78 (1H, d, J=9 Hz; C-3 H), 3.91 (1H, t, J=10 Hz; C-6 H), 5.50 (2H, s; C-1,2 H), 2.15 (1H; OH).

(b) A solution of the enone (VIII) (250 mg) in ether (40 ml) and benzene (5 ml) at 5° was treated with $LiAlH_4$ (15 mg). The reaction was monitored by TLC and jadged complete after 14 hr at room temperature. The excess reagent was decomposed by addition of H_2O. The reaction mixture was treated in the usual way. Thus obtained crude products (258 mg) were chromatographed on preparative thin-layer with benzene–EtOAc (8: 5) as a developing solvent. Band 1 gave 115 mg (46%) of 1-en-3β-ol (XIVa) as colorless plates which was identical with an authentic sample of XIVa in their IR spectra. Band 2 gave 35 mg of 3ξ,6α,13-trihydroxyeudesm-1-ene (XV). Recrystallization from $CHCl_3$ afforded colorless needles, mp 144—145°. The IR spectrum of the product showed no γ-lactone and α,β-unsaturated carbonyl but hydroxyl absorption at 3330 cm^{-1}. The Mass Spectrum *m/e* (rel. intensity): 252 (24, $[M-H_2]^+$).

Acetylation of 1-En-3β-ol (XIVa)——To a solution of XIVa (80 mg) in pyridine (0.8 ml) was added acetic anhydride (1.2 ml), and the reaction mixture was stirred for 15 hr at room temperature. The reaction mixture was poured into H_2O (10 ml) and neutralized with $NaHCO_3$ and then extracted with EtOAc (200 ml). The extracts were washed with successive 10% HCl, $NaHCO_3$ solution and H_2O and dried over Na_2SO_4. Evaporation of the EtOAc under reduced pressure afforded 91 mg of colorless crystals, mp 143—145°. Recrystallization from EtOH afforded 3β-acetoxy-1-en-5α-santanolide (XIVb) as colorless prisms (59 mg), mp 149—150°. *Anal.* Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.74; H, 8.31. Mass Spectrum *m/e* (rel. intensity): 292 (7, M^+), 277 (5), 250 (100), 232 (63, $[M-CH_3CO_2H]^+$), 217 (43). $[\alpha]_D^{28°}$ +143.1° (*c*, 1.37, $CHCl_3$). IR (KBr, cm^{-1}): 1770, 1722, 1662, 1250. NMR (δ): 1.08 (3H, s; C-10 CH_3), 1.12 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 1.19 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 2.04 (3H, s; CH_3CO_2-), 3.92 (1H, t, J=10 Hz; C-6 H), 5.00 (1H, broad d, J=10 Hz; C-3 H), 5.44 (1H, dd, J=10, 2 Hz; C-1 H), 5.62 (1H, broad d, J=10 Hz; C-2 H).

1β,2β-Epoxy-3β-hydroxy-5α-santanolide (XVI)——(a) Epoxidation of the 1-En-3β-ol (XIVa) with *m*-Chloroperbenzoic Acid: To a stirred solution of XIVa (1.0 g; 4 mmoles) in dry CH_2Cl_2 (200 ml) was added a solution of *m*-chloroperbenzoic acid (1.02 g, 85% in purity, 5 mmoles) in the same solvent (20 ml). The mixture was stirred for 45 hr at room temperature. The reaction mixture was diluted with CH_2Cl_2 (200 ml) and washed with 1N NaOH, 10% Mohr salt and H_2O and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded 1.17 g of solid. The crude products were subjected to preparative thin-layer chromatography. Twice developments with benzene–EtOAc (8: 5) afforded three bands. Band 1 gave 116 mg of the starting material (XIVa) as colorless plates. It is identified by IR comparison with an authentic sample of XIVa. Band 2 gave 258 mg (24%) of 1α,2α-epoxy-3β-hydoxy-5α-santanolide (XVII) as colorless

crystals. Recrystallization from EtOH gave 237 mg (22%) of colorless plates, mp 113—114°. Mass Spectrum *m/e* (rel. intensity): 266 (0.6, M^+), 248 (27), 217 (26), 93 (100). $[\alpha]_D^{27°}$ +30.1° (*c*, 1.51, $CHCl_3$). IR (KBr, cm^{-1}): 3460, 3250, 1768. NMR (δ): 1.11 (3H, s; C-10 CH_3), 1.13 (3H, d, J=7 Hz; C-4 CH_3), 1.18 (3H, d, J=7 Hz; C-11 CH_3), 2.86 (1H, d, J=3 Hz; C-1 H), 3.15 (1H, d, J=3 Hz; C-2 H), 3.50 (1H, d, J=7 Hz; C-3 H), 3.90 (1H, t, J=10 Hz; C-6 H), 3.00 (1H; OH).

Band 3 gave 503 mg (47.3%) of 1β,2β-epoxy-3β-hydroxy-5α-santanolide (XVI) as colorless crystals. Recrystallization from EtOH gave 330 mg (31%) of colorless columns XVI, mp 206—209°. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.45; H, 8.33. Mass Spectrum *m/e* (rel. intensity): 266 (0.1, M^+), 248 (5, $[M-H_2O]^+$), 219 (8), 206 (9), 68 (100). $[\alpha]_D^{27°}$ +67.9° (*c*, 1.6, $CHCl_3$). IR (KBr, cm^{-1}): 3490, 1763. NMR (δ): 1.09 (3H, s; C-10 CH_3), 1.17 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 1.19 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 3.03 (1H, d, J=3 Hz; C-1 H), 3.33 (1H, dd, J=3,2 Hz; C-2 H), 3.44 (1H, dd, J=10,2 Hz; C-3 H), 3.85 (1H, t, J=10 Hz; C-6 H).

(b) To a solution of XIVa (100 mg; 0.4 mmoles) and vanadyl acetylacetonate, $VO(acac)_2$, (2 mg; 0.0008 mmoles) in refluxing CH_2Cl_2 (10 ml) was added 72% *tert*-butyl hydroperoxide (*t*-BuOOH) (55 mg; 0.44 mmoles). The initial solution of XIVa and $VO(acac)_2$ was bright green, and then turned deep red as the *t*-BuOOH was added. The reaction was monitored by TLC and jadged complete after 50 hr at reflux. The yellow reaction mixture was cooled and diluted with CH_2Cl_2 (150 ml). The resulting solution was washed with 10% Mohr salt and H_2O and dried over Na_2SO_4. Evaporation of the CH_2Cl_2 afforded colorless crystalls, which was chromatographed on thin-layer with benzene–EtOAc (8: 5) as a developing solvent. Band 1 gave 39 mg (39%) of 3-oxo-1-en-5α-santanolide (VIII) as colorless needles, which was identical in their IR spectra with an authentic sample. Band 2 gave 9 mg of the starting material (XIVa), and band 3 gave 50 mg (47.2%) of 1β,2β-epoxy-3β-hydroxy-5α-santanolide (XVI) as colorless plates, which was identical in the IR and NMR spectra with an authentic sample.

(c) According to the procedure described above, 1-en-3β-ol (XIVa) (100 mg) was refluxed with $VO(acac)_2$ (2 mg) and *t*-BuOOH (55 mg) in $CHCl_3$ (10 ml) for 9 hr. The reaction products were separated in the same manner as described above, Band 1 gave 38 mg (38%) of the enone (VIII), and band 2 afforded 39 mg (37%) of the β-epoxide (XVI). They were identified by comparing their IR and NMR spectra with those of authentic specimens, respectively.

(d) According to the procedure described above, 1-en-3β-ol (XIVa) (100 mg) was refluxed with $VO(acac)_2$ (2 mg) and *t*-BuOOH (55 mg) in benzene (10 ml) for 3.5 hr. The reaction products were separated in the same manner as described above. Band 1 afforded 66.5 mg (67%) of the enone (VIII), and band 2 afforded 21.5 mg (20%) of the β-epoxide (XVI). They were identified by IR and NMR spectra comparison with those of authentic specimens[5] respectively.

1β,2β-Epoxy-3-oxo-5α-santanolide (XVIII)——The β-epoxy-3β-ol (XVI) (230 mg; 0.865 mmoles) was added to a stirred pyridine solution of CrO_3–pyridine complex which was prepared from CrO_3 (700 mg; 7 mmoles) and pyridine (10 ml), at 0°. After 14 hr stirring at room temperature, the pyridine was evaporated under reduced pressure. H_2O was added to the residue and extracted with EtOAc (300 ml). The extracts were washed with successive 10% HCl, $NaHCO_3$ solution and H_2O and then dried over Na_2SO_4. Evaporation of the EtOAc afforded 1β,2β-epoxy-3-oxo-5α-santanolide (XVIII) as colorless crystals, mp 150—154°, quantitatively. Recrystallization from EtOAc-ether afforded colorless needles, mp 164—165°. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.84; H, 7.64. Mass Spectrum *m/e* (rel. intensity): 264 (24, M^+), 235 (16), 221 (100). $[\alpha]_D^{27°}$ −23.7° (*c*, 1.83, $CHCl_3$). UV λ_{max}^{EtOH} 296 nm (ε 32). IR (KBr, cm^{-1}): 1760 1710. NMR (δ): 1.12 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 1.19 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 1.26 (3H, s; C-10 CH_3), 2.85 (1H, m, J=7 Hz; C-4 H), 3.28 (2H, ABq, J=4 Hz; C-1,2 H), 3.92 (1H, t, J=10 Hz; C-6 H).

Oxidation of the α-Epoxy-3β-ol (XVII)——According to the usual procedure described above, α-epoxy-3β-ol (XVII) (475 mg) was oxidized by CrO_3–pyridine complex. The resulting reaction mixture was processed in the usual manner, 447 mg of colorless crystals was obtained in 94% yield, mp 125—127°, which was identified by comparing their IR and NMR spectra with those of an authentic sample of IX.

Conversion to Arsanin (IVa) from the β-Epoxide (XVIII)——To a stirred solution of the β-epoxide (XVIII) (150 mg) in EtOH (20 ml) was added Zn dust (1.1 g) and 10 drops of glacial acetic acid. The reaction mixture was heated at reflux temperature for 2.5 hr, and then cooled and filtered. The filtrate was evaporated under reduced pressure and diluted with EtOAc (200 ml). The solution was washed with successive 10% HCl, $NaHCO_3$ solution and H_2O and then dried over Na_2SO_4. The EtOAc was removed under reduced pressure to give 157 mg of 1β-hydroxy-3-oxo-5α-santanolide (Arsanin) (IVa) as colorless plates, mp 198—200°. Recrystallization from EtOAc–hexane gave 111 mg (74%) of colorless plates, mp 201.5—202.5° (lit.[8] mp 193—194°). Additional IVa(23 mg) was obtained from the mother liquor by preparative thin-layer chromatography (total yield 89%). This 1β-hydroxy-3-oxo-5α-santanolide (IVa) was identified by mixed melting point and IR and NMR spectra comparison with those of an authentic specimen of the natural arsanin. *Anal.* Calcd. for $C_{15}H_{22}O_4$: 266.1516; C, 67.64; H, 8.33. Found: M^+ 266.1505; C, 67.34; H, 8.30. Mass Spectrum *m/e* (rel. intensity): 266 (1, M^+), 248 (2, $[M-H_2O]^+$), 167 (100). $[\alpha]_D^{27°}$ +26.0° (*c*, 2.0, $CHCl_3$) (lit.[8] $[\alpha]_D$ +26°). UV λ_{max}^{EtOH} 286.5 nm (ε 32) (lit.[8] λ_{max} 290 nm (log 1.12), IR (KBr, cm^{-1}): 3485, 1773, 1705. (lit.[8] 3490, 1770, 1705 cm^{-1}). NMR (δ): 1.13 (3H, s: C-10 CH_3), 1.22 (3H, J=7 Hz; C-4 or C-11 CH_3), 1.23 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 3.64 (1H, dd, J=10, 6 Hz; C-1 H), 4.00 (1H, t, J=10 Hz; C-6 H): NMR (δ, pyridine-d_5): 1.13

(3H, d, J=7 Hz; C-4 or C-11 CH_3), 1.21 (3H, s; C-10 CH_3), 1.36 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 3.75 (1H, dd, J=6, 10 Hz; C-1 H), 3. 94 (1H, t, J=10 Hz; C-6 H).

Recrystallization from EtOAc-hexane (in large amount) gave a dimorph of the IVa as colorless plates, mp 187—188°. IR (KBr, cm^{-1}): 3500, 1750 (broad), 1695. This dimorph (mp 187—188°) was identified by mixed melting point, NMR and IR (in $CHCl_3$) comparison with an authentic sample of IVa (mp 201.5—202.5°).

Arsanin Acetate (IVb)——To a stirred solution of arsanin (IVa) (30 mg) in pyridine (1 ml) was added acetic anhydride (1 ml), and stirred for 14 hr at room temperature. The reaction mixture was processed in the usual manner to afford the acetate (IVb) quantitatively as colorless needles, mp 164—168°. Recrystallization from EtOH afforded 22 mg of acetate (IVb) as colorless plates, mp 170—171°, whose mp, and IR and NMR spectra were good agreement with arsanin acetate reported by Akev, *et al.*[8] Mass Spectrum *m/e* (rel. intensity): 308 (6, M^+), 293 (5), 266 (16), 248 (100, $[M\text{-}CH_3CO_2H]^+$), 220 (38). $[\alpha]_D^{28°}$ +18.3° (*c*, 1.09, $CHCl_3$). UV λ_{max}^{EtOH} 284 nm (ε 28). IR (KBr, cm^{-1}): 1780, 1735, 1700, 1250. NMR (δ): 1.15 (3H, s; C-10 CH_3), 1.20 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 1.26 (3H, d, J=7 Hz; C-4 or C-11 CH_3), 2.03 (3H, s; $OCOCH_3$), 3.94 (1H, t, J=10 Hz; C-6 H), 4.88 (1H, dd, J=6, 10 Hz; C-1 H).

Dehydration of the Synthetic Arsanin (IVa)——This procedure was reported by Akyev, *et al.*[8] To a stirred 50% H_2SO_4 (4 ml) was added the synthetic arsanin (15 mg) and warmed for 5 min at 65°. The reaction mixture was processed in the usual manner to afford 14 mg of the enone (VIII), mp 132—138°. Recrystallization from EtOH afforded the enone as colorless needles, mp 141.5—142.5°, which was identical in mixed melting point and their IR spectra with the authentic specimen.

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