BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 2453—2457 (1968)

Further Studies on Acetoxylation of Isodihydro-*O*-acetylisophotosantonic Lactone

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(Received January 25, 1968)

Acetoxylation of *O*-acetylisophotosantonic lactone (I) and its isodihydro derivative (III) with lead tetraacetate was reinvestigated. The reaction of III in refluxing benzene afforded the known 2-acetoxy derivative (V) as the main product and α-diketone as the minor product which was isolated in its 2-keto-3-ol form (VII). The use of boron trifluoride - etherate as a catalyst in this acetoxylation, however, did not give good results. The ORD curves of dihydro-*O*-acetylisophotosantonic lactone (II), III, 2-bromo-isodihydro-*O*-acetylisophotosantonic lactone (IV), V and one of the hydrogenolysis product of I (X) were measured and some stereochemical problems of these compounds were discussed.

Acetoxylation of *O*-acetylisophotosantonic lactone (I) and its isodihydro derivative (III) by the oxidation with lead tetraacetate has been reported by White and his coworkers;[1] they isolated the corresponding 2-acetoxyl derivative XI and V, respectively in low yields but did not describe the stereochemistry of the 2-acetoxyl group, although the stereochemistry of several derivatives of *O*-acetylisophotosantonic lactone have been established, in particular, that of its 2-bromo derivative IV by X-ray analysis.[3]

In the present paper, acetoxylation of I and III has been studied and compound VII, one of the by-products, has been isolated from III in addition to the normal acetoxylation product V.

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[1] a) E. H. White, J. N. Marx, F. Bacheler and S. Eguchi, submitted to *Tetrahedron;* b) E. H. White and J. N. Marx, *J. Am. Chem. Soc.*, **89**, 5511 (1967).

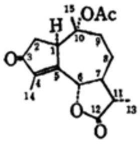
[2] J. D. Asher and G. A. Sin, a) *Proc. Chem. Soc.*, **1962**, 111; b) *J. Chem. Soc.*, **1965**, 1584.

[3] a) D. H. R. Barton, P. de Mayo and M. Shafiq, *ibid.*, **1957**, 929; b) D. Arigoni, H. Boshard, H. Bruderer, G. Büchi, O. Jeger and L. J. Krebaum, *Helv. Chim. Acta*, **40**, 1732 (1957).

The optical rotatory dispersion (ORD) curves of dihydro derivatives of I (II and III), 2-bromo derivative of III (IV), V and one of the hydrogenolysis products of I (X) have been measured and their stereochemical correlations are discussed.

Results and Discussions

Acetoxylations. *O*-Acetylisophotosantonic lactone (I)[3] was hydrogenated by the known method to give the unstable dihydro derivative II which was easily converted to its C-4 epimer by treatment with alumina.[1] Hydrogenation of I afforded X, one of the hydrogenolysis products which has also been reported.[1a]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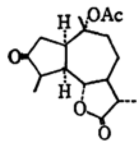
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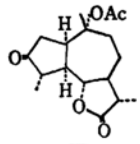
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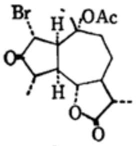
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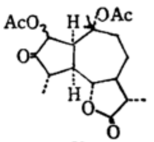
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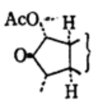
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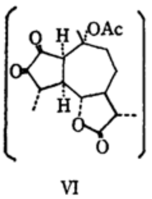
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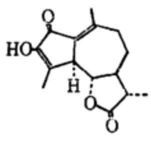
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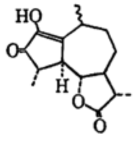
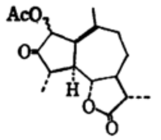

VIII

Oxidation of III with lead tetraacetate in refluxing benzene afforded the reported acetoxyl compound V[1] with a melting point of 166—168°C in a 38% yield. This yield was more or less similar to those reported.[1a] However, a new compound with a melting point of 207—210°C was isolated in a 10% yield upon alkaline hydrolysis of the residue. This compound was shown to be VII by the following evidence; the elemental analysis and the high resolution mass spectrum (M^+ at *m/e* 262.121) indicated a molecular formula $C_{15}H_{18}O_4$. The infrared spectrum which exhibited absorption bands at 3320 (OH), 1770 (γ-lactone), 1675 (cross conjugated cyclopentadienone), 1654 and 1610 (double bonds) cm^{-1}, was very similar to those of achillin[4] and desacetoxy matricarin[5] except for the presence of hydroxyl bands. The ultraviolet spectrum had maxima at 265 mμ (ε 9570) and 294 (7279) in ethanol, and at 270.5 mμ (ε 6836) and 352 (5912) in 1 N ethanolic potassium hydroxide. The NMR ($CDCl_3$) had signals at τ 3.63 (1 H, s, disappeared on deuteration, OH), 6.42 (1 H, unsym. t, *J*=9.5 Hz, C-6-H), 6.73 (1 H, d, *J*=10.0 Hz, C-5-H),[5d] 7.51 and 7.81 (each 3 H, s, two allylic methyls at C-3 and C-10) and 8.73 (3 H, d, *J*=6.0 Hz, methyl at C-11). The presence of an enolic hydroxyl group was indicated by a positive ferric chloride test (violet). Since White and Marx[1b] have synthesized from III desacetoxy matricarin, a C-11 epimer of achillin, VII seems to be a 3-hydroxy analogue of desacetoxy matricarin, although the isolation of this compound from natural sources has not been reported.

VII may be produced from the α-diketone VI after elimination of acetic acid, followed by enolization. This conversion to 2-keto-3-ol system is of interest, since the acetoxy compound V is known to be converted to a 3-keto-2-ol system VIII by alkaline hydrolysis.[1a] On the other hand, in steroid series, Fieser and Stevenson[6] have reported the isomerization of Δ^5-cholesten-4α-ol-3-one acetates (XII) to Δ^5-cholesten-3β-ol-4-one acetate (XIII).

Possibilities of the formation of VII from V by air oxidation upon alkaline hydrolysis were excluded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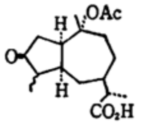
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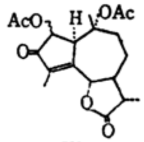
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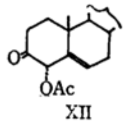
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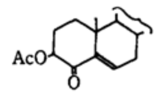
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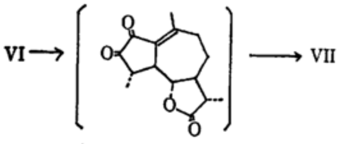

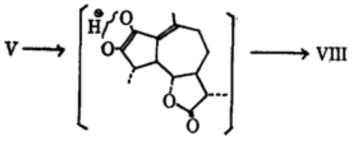

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4) a) E. H. White and R. K. Winter, *Tetrahedron Letters*, **1963**, 137; b) S. J. Smolensky, C. L. Bell and L. Bauer, *Lioydis*, **30**, 144 (1967).

5) a) M. Holob and V. Herout, *Coll. Czech. Chem. Commun.*, **27**, 2980 (1962); b) K. S. Rybako, *Zh. Obshch. Khim.*, **33**, 2734 (1963); c) T. A. Geissman, T. S. Stewart and M. A. Irwin, *Phytochemistry*, **6**, 901 (1967); d) H. H. A. Linde and M. S. Ragab, *Helv. Chim. Acta*, **50**, 1961 (1967).

6) L. F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **76**, 1728 (1954).

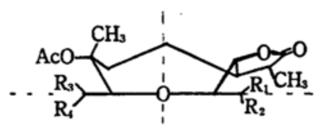
by the fact that V afforded exclusively compound VIII by alkaline treatment,[1] although it is known that 2-acetoxy tetrahydrosantonin gives its α-diketone derivative in a good yield upon alkaline hydrolysis.[7] The facile deacetoxylation and enolization of VI to VII was also shown by the isolation of VII from selenium dioxide oxidation of III, followed by chromatography on alumina.

Acetoxylation with lead tetraacetate is known to be catalyzed by a Lewis acid such as boron trifluoride-etherate[8] and in fact, Barton *et al.*[9] have reported the 2-acetoxylation of deoxygeigerin in an excellent yield using boron trifluoride - etherate as a catalyst. However, acetoxylation of III with lead tetraacetate by Barton's procedure using boron trifluoride-etherate as a catalyst did not proceed smoothly, and resulted in recovery of starting material, which was accompanied by a trace of a compound melting at 187—189°C. This compound had infrared absorption bands at 1770 (γ-lactone), 1750 (cyclopentanone), 1735 (acetate) and 1647 (double bond) cm^{-1}, and a weak ultraviolet absorption at 275 mμ (ε 205) and was tentatively assigned structure IX.

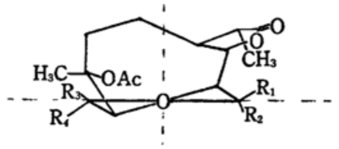
In the acetoxylation of I, the use of boron trifluoride-etherate was also ineffective and only the starting material was recovered, although its acetoxylation in refluxing benzene afforded 2-acetoxy derivative (XI)[1a] in a low yield.

Optical Rotatory Dispersion Studies. Successful applications of the Octant rule to the cyclopentanone series have been achieved by Klyne.[10] It is well known that ORD depends strongly on the conformation of a cyclopentanone ring itself.[11] Therefore, considerations on the conformation of the ring systems in question are required for ORD studies. The Dreiding stereomodel studies for our ring systems suggest three possible basic conformation, XIVa, b, and c.

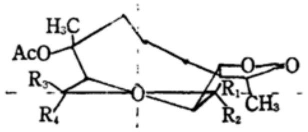
XIVa has a very flat half-chair or an almost planar cyclopentanone ring which could enter slightly in a positive or a negative octant, and a chair cycloheptane ring.[12] In this conformation, the effect of the cyclopentanone ring on the Cotton effect will be small since C-1 and -5 more or less lie in the plane, and substituents at C-2 and/or C-3 are expected to contribute strongly to the Cotton effect.[13] Thus in this conformation, we can anticipate a weak positive or a weak neagtive Cotton effect, depending on substituents. XIVb has a half-chair cyclopentanone ring and a twisted-chair cycloheptane ring.[12] In this conformation, C-1 and -5 are severely skewed in negative octants and we can, therefore, expect a strong negative Cotton effect. XIVc has a half-chair cyclopentanone ring, in which C-1 and -5 are strongly skewed in the positive octants, and a boat or a twisted boat cycloheptane ring.[12] In this conformation, a strong positive Cotton effect will be anticipated.



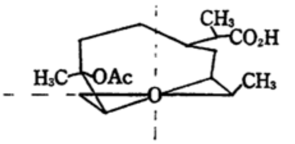
XIVa



XIVb



XIVc



Xa

The ORD curves of II and III are shown in Fig. 1 and those of IV, V, and X, in Fig. 2. As seen in Fig. 1, II showed a strong negative Cotton effect ($a=-112$) while III exhibited a weak positive Cotton effect ($a=+25$), but both exhibiting a fine structure of similar shape. The fact that II and III give such different values in amplitude indicates clearly that the whole molecular shape of II and III must be different, since the C-4-methyl

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[7] a) K. Yamakawa, *J. Org. Chem.*, **24**, 897 (1959); b) M. Yanagita and K. Yamakawa, *ibid.*, **24**, 903 (1959).

[8] a) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, N. Y. (1967), p. 541; b) H. B. Henbest, G. H. Phillips, G. P. Slater and D. A. Thomas, *J. Chem. Soc.*, **1965**, 6.

[9] D. H. R. Barton, J. T. Pinkey and R. J. Wells, *ibid.*, **1964**, 2518.

[10] W. Klyne, *Tetrahedron*, **13**, 29 (1961).

[11] For a recent review, see: P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco (1965), p. 90.

[12] For recent studies on the conformation of cycloheptane ring, see: J. B. Hendrickson, a) *J. Am. Chem. Soc.*, **89**, 7036 (1967); b) *ibid.*, **89**, 7043 (1967); c) *ibid.*, **89**, 7047 (1967).

[13] The effect of a cycloheptane ring on the Cotton effect will be small, since the replacement of a cyclohexane ring by a cycloheptane ring in the hexahydrindan-2-one system did not change the sign of the Cotton effect but only slightly decreased the amplitude; C. Djerrasi and J. E. Gurst, *J. Am. Chem. Soc.*, **86**, 1755 (1964).

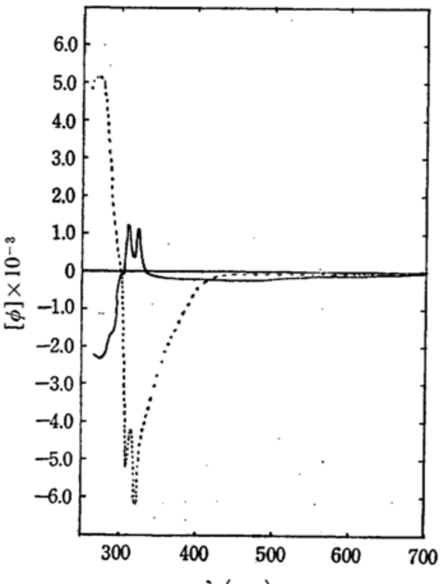

Fig. 1. ORD curves of II (……) and III (——).

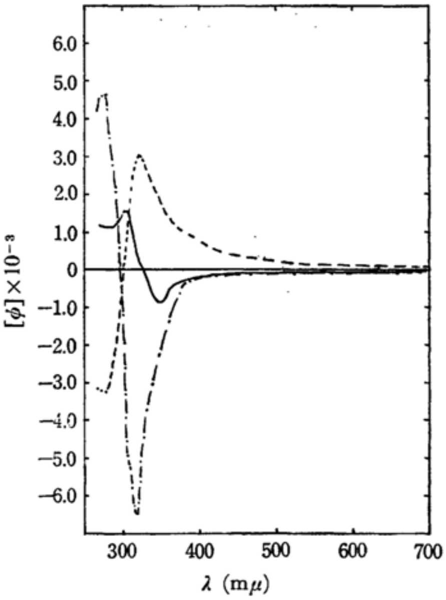

Fig. 2. ORD curves of IV (——), V (----) and X (·—·—).

alone should not cause such a large change. Only the conformation XIVb ($R_1=CH_3$; R_2, R_3, and $R_4=H$ for II) can explain the strong negative Cotton effect of II. The weak positive Cotton effect of III can not be explained by this conformation ($R_2=CH_3$; R_1, R_3, and $R_4=H$), since the negative contribution of the severely skewed cyclopentanone ring should be predominant, even if the C-4-methyl enters a positive octant. Thus, the weak positive Cotton effect of III can be explained most reasonably by conformation XIVb ($R_2=CH_3$; R_1, R_3, and $R_4=H$). The reason why II and III, respectively, adopt conformations of type XIVb and type XIVa are uncertain. The type XIVa conformation seems to be common to C-4α-methyl derivatives of this series, since IV is shown to have a very flat half-chair cyclopentanone ring and a chair cycloheptane ring by X-ray analysis.2) Therefore, assuming that IV has the conformation of type XIVa (R_1 and $R_3=H$; $R_2=CH_3$; $R_4=Br$), a weak negative Cotton effect might be predicted, since the contribution of 2α-bromine in a negative octant may surmount that of 4α-methyl in a positive octant.14) In fact, the observed value of IV was a weak negative Cotton effect ($a=-24$) as illustrated in Fig. 2.

The acetoxyl compound V showed a relatively weak positive Cotton effect, $a=+62$, indicating clearly that the 2-acetoxyl group is contributing more or less to the positive Cotton effect, since the amplitude is larger than that of III. Based on the conformation of type XIVa,15) the 2-acetoxyl group seems to enter in a front positive octant (for 2α-OAc, R_1 and $R_3=H$; $R_2=CH_3$; $R_4=OAc$) or in a front negative (for 2β-OAc, R_1 and $R_4=H$; $R_2=CH_3$; $R_3=OAc$).16) Thus, the 2α-acetoxyl structure (Va) is assigned to compound V.17) Ketol acetates often give abnormal ORD curves,18) even in the steroid series, and therefore, our assignment based on the ORD data might need further support, for which studies are in progress.19)

The stereochemistry at C-4 in compound X is unknown and its ORD showed a strong negative Cotton effect ($a=-112$) which is reminiscent of the ORD of II. Such a large negative amplitude can not be expected on the basis of conformations of type XIVa and XIVc. Therefore, the conformation Xa which belongs to the conformation of type

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14) For example, see C. Beard, C. Djerassi, J. Sicher, F. Sipos and M. Tichy, *Tetrahedron,* **19**, 919 (1963).

15) XIVb predicts a negative Cotton effect and XIVc, a strong positive, since the substituent effect will be small in these conformations. Such large effects of the substituents as seen in III, IV and V might also suggest the validity of the XIVa conformation.

16) The degree of the contribution of 2-OAc to the positive or the negative front octant depends on the conformation of the actoxyl group but molecular model studies indicate clearly the contribution to the front octant assuming some stable conformations of the 2-OAc.

17) It may be noted that 2α-OAc will be more stable than the 2β-isomer, since in the latter, oxygen atoms of the two acetoxyl groups at C-2 and C-10 are very close to each other and therefore, an electrostatic or a dipole-dipole repulsion might be expected.

18) For example, see; a) C. Djerassi, J. Fishman and T. Nambara, *Experientia,* **17**, 565 (1961); b) C. Djerassi, D. Halpern, V, Halpern and C. Tamm, *Helv. Chim. Acta,* **41**, 250 (1958).

19) The NMR data might be useful in some cases but in the cyclopentanone series, their application to the stereochemistry require model compounds, since for example, *cis* and *trans* lactones in our systems have almost the same coupling constants for C-6 and C-7 protons; see Refs. 1b and 5d.

XIVb, was suggested and thus, the C-4β-methyl structure was assigned to X.

Experimental[20]

***O*-Acetylisophotosantonic Lactone (I).** This was prepared by irradiation of α-santonin by the known method[3] and it melted at 182—134°C (recrystallized from methanol).

Dihydro-*O*-acetylisophotosantonic Lactone (II). Catalytic hydrogenation of I (10% Pd-C in ethyl acetate) afforded II, mp 171—173°C (from ethyl acetate).[1]

Hydrogenolysis Product of I (X). After more than 1 mol of hydrogen was uptaken in the above reduction, acidic portion was purified by crystallization from an acetone - *n*-hexane mixture to give an acid X with a melting point of 154—156°C (lit.[1a] 156—157°C).

Isodihydro-*O*-acetylisophotosantonic Lactone (III). This was obtained from II as needles with a melting point of 165.5—167°C (benzene - *n*-hexane) by epimerization on alumina.[1]

Oxidation of III with Lead Tetraacetate in Benzene. The same procedure as that of White *et al.*[1] was applied except the use of a small amount of acetic anhydride. A mixture of 1.54 g of III, 0.5 m*l* of acetic anhydride and 3.10 g of lead tetraacetate (a commerical sample was dried *in vacuo* on KOH pellets just before use) in 50 m*l* of benzene (dry benzene was distilled from $Pb(OAc)_4$) was refluxed for 12 hr until KI-strach paper became negative and the cooled reaction mixture was washed with water several times and dried over anhydrous sodium sulfate. The removal of the solvent afforded a sticky residue, from which needles with a melting point of 166—168°C was isolated in a 38% yield after crystallization from methanol. The spectral data (infrared, ultraviolet and NMR) of this compound were the same with those of the reported[1a] and thus this was identified as V.

The mother liquor was dried up to a sticky residue which was dissolved in 10 m*l* of methanol and stirred for 2 hr at room temperature in nitrogen stream after addition of 5 m*l* of 1 N aqueous potassium hydroxide. Neutralization with acetic acid and concentration afforded precipitates which were recrystallized from methanol to give needles of VII (130 mg, 9.9%), mp 207—210°C. TLC examination of the residue showed the presence of III and some unidentified materials. Mass spectrum of VII had peaks at 262.121 (M^+), 247.097 ($M-CH_3$) and 244.108 ($M-H_2O$).

Found: C, 68.21; H, 6.96%. Calcd for $C_{15}H_{18}O_4$: C, 68.16; H, 7.63%.

Oxidation of III with Selenium Dioxide. A mixture of 0.308 g of III and 0.133 g of selenium dioxide (sublimed before use) in 5 m*l* of dioxane was heated at 60°C for 5 hr. Dioxane was removed *in vacuo* and the residue was purified on alumina (neutral, activity grade III) to give crude VII from ether eluent after elution with benzene. Recrystallization from methanol gave VII with a melting point of 206—209°C in a 14% yield.

Oxidation of III with Lead Tetraacetate in the Presence of Boron Trifluoride - etherate. A mixture of 0.308 g of III, 1.0 of lead tetraacetate, 1.0 m*l* of acetic anhydride and 2.0 m*l* of BF_3 - etherate in 20 m*l* of glacial acetic acid was stirred for 24 hr at room temperature. After the TLC examination indicated that no more starting material was remained, the reaction mixture was diluted with water and extracted with chloroform (20 m*l*×5). The combined extracts were washed with water, dried over sodium sulfate and dried up to a brownish residue which was chromatographed on a silica gel column. The first fraction eluted with chloroform gave crystals of IX with a melting point of 187—189°C (from methanol) in a 3.5% yield.

Found: C, 66.53; H, 7.31%. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.31%.

The second fraction gave 100 mg of the starting material (32% recovery).

Oxidation of I with Lead Tetraacetate. Oxidation was carried out in benzene by the method of White *et al.*[1a] and the acetoxyl compound XI with a melting point of 174—176°C (lit.[1a] 175—176°C) was obtained in an 11% yield. The oxidation in the presence of BF_3 - etherate was carried out as follows: A mixture of I (0.306 g), lead tetraacetate (1.0 g), acetic anhydride (0.5 m*l*) and BF_3 - etherate (1.0 m*l*) in 15 m*l* of glacial acetic acid was stirred for 20 hr at room temperature and the worked-up product was needles with a melting point of 176—181°C, infrared spectrum of which was identical with that of the starting materials (77% recovery).

2-Bromo-isodihydro - *O* - acetylisophotosantonic Lactone (IV). This was prepared by the Barton's procedure and had a melting point of 115—117°C dec. (lit.[21] 117—118°C dec.).

Optical Rotatory Dispersion Measurements. All ORD measurements were carried out in dioxane solution at room temperature (at *ca.* 20°C).

II (*c* 0.522): $[\phi]_{700}$ -29.2, $[\phi]_{350}$ -2028.7, $[\phi]_{320}$ -6086.2, $[\phi]_{313}$ -4210.4, $[\phi]_{310}$ -5186.6, $[\phi]_{290-291}$ $+3725.2$, $[\phi]_{278}$ $+5132.5$, $[\phi]_{250}$ $+3725.2$.

III (*c* 0.521): $[\phi]_{700}$ -94.8, $[\phi]_{390}$ -213.7, $[\phi]_{322}$ $+1101.8$, $[\phi]_{315}$ $+391.2$, $[\phi]_{311}$ $+1172.8$, $[\phi]_{303}$ -236.9, $[\phi]_{299}$ -79.0, $[\phi]_{290-291}$ -1409.8, $[\phi]_{274}$ -2203.6.

IV (*c* 0.336): $[\phi]_{700}$ -86.4, $[\phi]_{400}$ -331.3, $[\phi]_{346}$ -878.7, $[\phi]_{307}$ $+1527.3$, $[\phi]_{300-298}$ $+1472.2$, $[\phi]_{280}$ $+1166.8$.

X (*c* 0.350): $[\phi]_{700}$ -187.8, $[\phi]_{350}$ -2000.0, $[\phi]_{318}$ -6429.4, $[\phi]_{311-309}$ -5186.1, $[\phi]_{273}$ $+4789.2$.

The authors are much indebted to Professor E. H. White (Johns Hopkins Univ., U. S. A.) for his deep interests and kind suggestions for this studies and to the Nippon Shinyaku Co., Ltd., for his kind supply of Santonin. Thanks are also due to Mr. Akiho Ishihara for elemental analyses and ORD measurements.

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20) All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were carried out on a Yanagimoto C. H. N. Coder, Model MT-1. Infrared spectra were recorded on a JASCO Model IR-S infrared spectrophotometer and NMR spectra were obtained with a Varian A-60 spectrometer, using TMS as an internal standard. Ultraviolet spectra and ORD curves were measured on a JASCO Model ORD/UV-5 spectrophotometer. Mass spectrum of VII was obtained by a Mattauch-Herzog type high resolution mass spectrometer, JMS-O1S, using PFK as an internal standard.

21) D. H. R. Barton, J. E. B. Levisalleo and J. T. Pinkey, *J. Chem. Soc.*, **1962**, 3472.