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30. Masao Sumi: Studies on Anthelmintics. XXXII.* The Absolute Configuration of Santonin Isomers. (1). Naturally Occurring Santonins.

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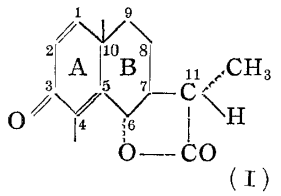
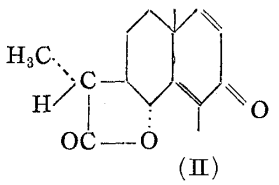
It is well known that of the twelve possible stereoisomers[1] of santonin, only two ((−)-α- and (−)-β-santonins) occur in nature, and their stereochemical structures have been considerably elucidated by a number of investigators[1~9] in recent times. With regard to their abosolute configuration the present author briefly reported in a previous communication.[10] Corey[2] independently reached a similar conclusion, except for the configuration at C_{11} (see below). This paper treats the problem in more detail.

As was already shown,[1] the A-ring in the santonin skeleton has a planar cross-conjugated dienone structure, the B-ring is a chair-formed cyclohexanone, and the angular methyl group adopts the axial position relative to the B-ring. The skeleton can, therefore, be considered to correspond to the A-B ring portion of $\Delta^{1,4}$-3-oxosteroids. Previously, Miki[6] discussed the configuration at C_{11} of santonins and deduced that the C_{11}-methyl group and the C_7-hydrogen are *cis* in α-santonin and *trans* in β-santonin. Woodward and Yates[8] and Corey[2] also discussed the same subject, but according to them, it is α-santonin that possesses the C_{11}-methyl *trans* to the C_7-hydrogen. Of these conflicting considerations, the one offered by Miki seems more reasonable, for it can well explain the stereospecific decarboxylation of 11-carboxysantonin as well as its analogs,[6] while the other can not. Since other con-



(I)



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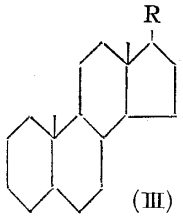
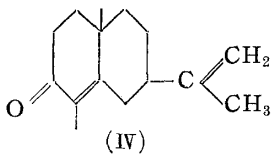
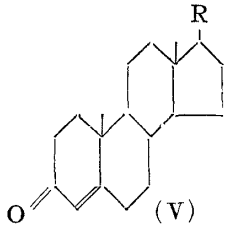


(III)



(IV)



(V)

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1) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga: J. Am. Chem. Soc., **78**, 1416(1956).
2) E. J. Corey: *Ibid.*, **77**, 1044(1955).
3) Huang-Milon, C. P. Lo, L. T. Y. Chu: *Ibid.*, **66**, 1954(1944).
4) D. H. R. Barton: J. Org. Chem., **15**, 467(1950).
5) H. Mitsuhashi: J. Pharm. Soc. Japan, **71**, 1115(1951).
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10) Y. Abe, M. Sumi: Chemistry & Industry, **1955**, 253.

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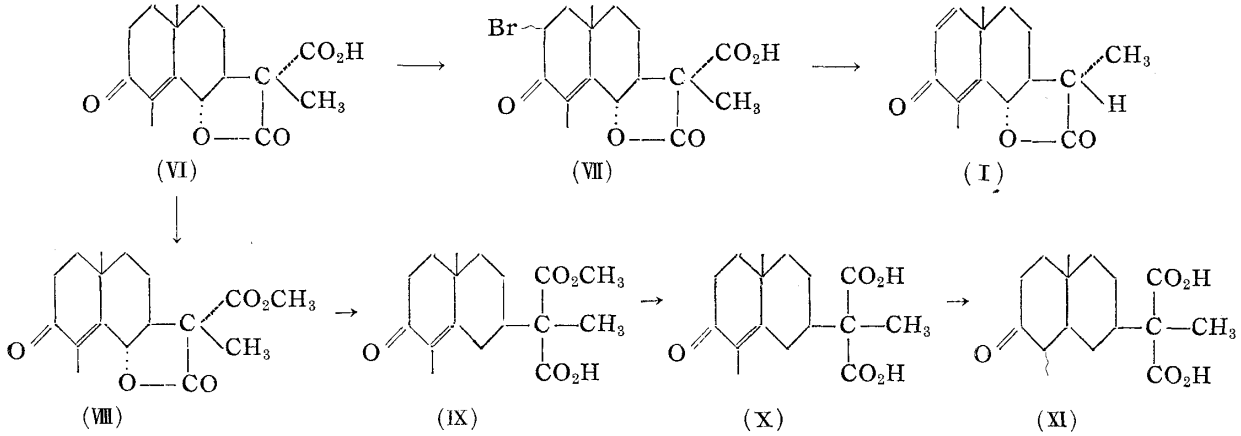
figurations have been established, (−)-α-santonin should be represented by either the formula (I) or its mirror image (II).

An extensive study was made by Barton and others[11] on the relation between the molecular rotation of naturally occurring polycyclic compounds and their structures. Klyne[12] has further developed the work to find four principles, by the aid of which he deduced the stereochemical structure of many natural products. Assuming that the absolute configuration of the steroids is correctly represented by (III), he discussed the stereochemical relationship between triterpenes, diterpenes, and sesquiterpenes. Since correctness of Klyne's assumption was verified later,[13] all the configurations suggested by him became the absolute ones.

In santonins, the four asymmetric carbon atoms exist in close proximity, which is expected to cause the proximity effect,[14] and moreover, both the A-ring and the lactone ring have considerably great strain. Therefore, it may be dangerous to apply Klyne's generalization directly to santonins in order to deduce their absolute configuration from the molecular rotation (M_D*). Klyne[12] indicated that α-cyperone should be represented by (IV), since the molecular rotational difference (ΔM_D) between α-cyperone (IV) and tetrahydrocyperone is +267°, which is of the same sign and the same order of magnitude as that between Δ^4-3-oxosteroids (V) and 3-oxosteroids. According to his principles, the same conclusion should be drawn also from ΔM_D between the above compounds and their corresponding saturated hydrocarbons. The compounds with sufficiently large molecular rotation values such as α-cyperone, Δ^4-3-oxosteroids, etc. can be directly correlated with each other, because almost all of saturated polycyclic hydrocarbons have small M_D values, at most ca. 100°. It is possible, therefore, to say that "α-cyperone (M_D+300°) and Δ^4-3-oxosteroids (M_D +300~500°) belong to the same stereochemical type, since their molecular rotation values are of the same sign and the same order of magnitude." In the case of santonins, it is suitable to choose a compound with the monoenone structure, having the least asymmetric centers. The comparison of its molecular rotation with those of Δ^4-3-oxosteroids would validly correlate their absolute configuration.

11-Carboxy-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid lactone, which was previously prepared by the present author,[15] was found to be readily resolved



(VI) (VII) (I)

(VIII) (IX) (X) (XI)

* $M_D=[\alpha]_D\times$mol.wt./100

11) D. H. R. Barton : J. Chem. Soc., **1945**, 813, *et seq.*
12) W. Klyne : *Ibid.*, **1952**, 2916; **1953**, 3072.
13) J. W. Cornforth, I. Youhotsky, G. Dopjak : Nature, **173**, 536(1954); B. Riniker, D. Arigoni, O. Jeger : Helv. Chim. Acta, **37**, 546(1954).
14) Huang-Minlon : J. Am. Chem. Soc., **70**, 611(1948).
15) M. Sumi : This Bulletin, **4**, 152(1956).

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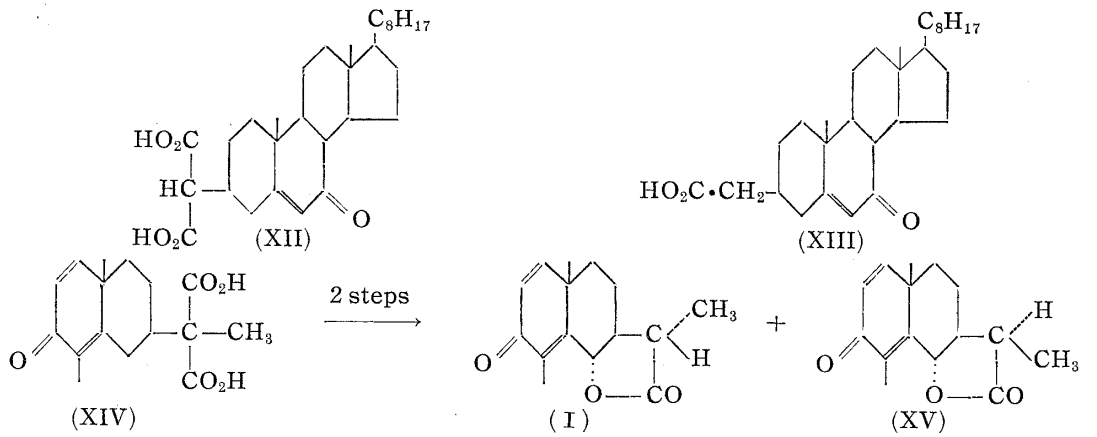
through its brucine salt. The dextrorotatory isomer (VI,* $[\alpha]_D$+108.7°) was brominated to the 2-bromo compound (VII), which by the collidine-dehydromination accompanied with decarboxylation led to pure (−)-α-santonin. On the other hand, treatment of the methyl ester of (VI) with zinc-acetic acid resulted in the reductive fission of the lactone ring to give (+)-11-methoxycarbonyl-3-oxo-11-*epi*-eusanton-4-enic acid (IX), and the latter was subsequently hydrolyzed to (+)-11-carboxy-3-oxoeusanton-4-enic acid (X). Accordingly, (−)-α-santonin has the same formal type as (X). Since (X) has the M_D value of +312°, which is of the same sign and order of magnitude as that of Δ^4-3-oxosteroids (M_D +300~500°), (X) and (−)-α-santonin must belong to the same stereochemical type as Δ^4-3-oxosteroids. It has thus become evident that the absolute configuration of (−)-α-santonin should be represented by the formula (I) and not by its mirror image (II). Although (X) differs from Δ^4-3-oxosteroids in having another asymmetric carbon atom at C_7, this does not prevent the present discussion, because the rotational contribution of this asymmetric carbon is small as shown in the case of α-cyperone.** 7-Oxo-3β-cholesterylmalonic acid[17] (XII) and 7-oxo-3β-cholesterylacetic acid (XIII), which involve a system enantiomeric with (X) as far as the rotation is concerned and which bear an equatorial side chain at C_3 (the position corresponding to C_7 of X), show molecular rotation values, −457° and −401°, respectively. This fact would confirm the correctness of the above deduction. Further, the molecular-rotational difference (+174°) between (X) and the saturated ketonic acid (XI) strongly supports the conclusion, since the ΔM_D value between Δ^4-cholestenone and cholestanone is +184°.



(−)-11-Carboxy-3-oxoeusantona-1,4-dienic acid (XIV) was decarboxylated and subsequently oxidized by selenium dioxide to result in the concurrent formation[9] of (−)-α- and (−)-β-santonins. Therefore, both are of the same stereochemical type, and (−)-β-santonin should be given the formula (XV), the C_{11}-epimer of (−)-α-santonin (I). This is in accordance with what was previously suggested by Barton.[4] It is noteworthy that the compound of biolgoical origin like steroids, cyperone, santonins, etc. belong to the same stereochemical type.

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* For simplification discussion is made in terms of formulae of correct absolute configuration.

** Natural α-cyperone (side chain : equatorial) possesses $[\alpha]_{5461}$: +119.2° and the synthetic sample (side chain : axial) $[\alpha]_{5461}$: +216.8°[16].

16) F. J. McQuillin : J. Chem. Soc., **1955**, 529.

17) J. W. Ralls : J. Am. Chem. Soc., **75**, 2123(1953).

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Experimental*

Resolution of (±)-11-Carboxy-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone—To a solution of 20 g. of the (±)-lactonic acid in 95 cc. of MeOH was added 32 g. of brucine and the mixture was warmed for a while. After cooling, the separated solid was recrystallized from MeOH to colorless prisms, m.p. 100°(decomp.); yield, 15.3 g. $[\alpha]_D^{22}$: −30.0° (c=0.66 in $CHCl_3$). The brucine salt was dissolved in $CHCl_3$ and shaken with 10% NaOH. The alkaline layer was separated, acidified, and extracted with ether. Evaporation of the ether gave 6.1 g. of a crude acid, which was recrystallized from EtOAc to hygroscopic colorless needles, m.p. 172°. $[\alpha]_D^{24}$: −108.7° (c=0.66). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.64; H, 7.23.

After the less-soluble brucine salt was removed, the mother liquor was concentrated. The residual oil solidified on addition of ether. Recrystallization from MeOH afforded colorless plates, m.p. 141°. $[\alpha]_D^{25}$: 0° (c=0.66 in $CHCl_3$). By treating this salt in the same way as described for the less-soluble salt there was obtained 6 g. of the (+)-acid (VI), which recrystallized as hygroscopic colorless prisms, m.p. 172° $[\alpha]_D^{25}$: +108.7° (c=0.66). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.70; H, 7.08.

(+)-α-Santonin (II)—In 200 cc. of ether was dissolved 2 g. of the (−)-lactonic acid, which was obtained in the preceding experiment, and to the boiling solution was added 1.1 g. of Br_2 in 10 cc. of ether. Decolorization occurred in 30 mins. The solution was cooled, washed with water, dried, and concentrated to leave 2.2 g. of viscous oil. $[\alpha]_D^{25}$: −31.5° (c=0.66). The oil in 10 cc. of picoline was heated under reflux for 40 mins. After cooling, the reaction mixture was poured into 10% H_2SO_4 and extracted with ether. The extract was washed with Na_2CO_3 solution and water, and removal of the solvent gave 0.7 g. of a crystalline product. This was recrystallized from EtOH to colorless plates, m.p. 172°. $[\alpha]_D^{27}$: +170° (c=1.0). The melting point was not depressed on admixture with an authentic sample of (+)-α-santonin.

(−)-α-Santonin (I)—The same reactions as described in the preceding experiment were carried out with 1.2 g. of the (+)-lactonic acid (VI) to afford 0.3 g of (−)-α-santonin, m.p. 172°. $[\alpha]_D^{27}$: −170°(c=1.0). This showed no melting point depression on admixture with an authentic sample ($[\alpha]_D$: −170°, under the same conditions).

(+)-11-Methoxycarbonyl-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (VIII)—A mixture of 7.2 g. of the (+)-lactonic acid (VI), 75 cc. of MeOH, and 3.7 cc. of conc. H_2SO_4 was boiled for 4 hrs. MeOH was removed under reduced pressure and the residue was taken up in ether. The ether solution was washed with Na_2CO_3 and water, dried, and concentrated to give 7.0 g. of an oily material.

(+)-11-Methoxycarbonyl-3-oxo-11-*epi*-eusanton-4-enic Acid (IX)—To a solution of 7.0 g. of the oily ester (VIII) in 150 cc. of AcOH was added 15 g. of Zn dust and the mixture was refluxed under stirring for 12 hrs. After Zn was filtered off, the filtrate was concentrated under reduced pressure. The residue was dissolved in ether and extracted with Na_2CO_3 solution. Then the alkaline solution was acidified, extracted with ether, and the extract was concentrated to afford 2.1 g. of a crystalline material. Recrystallization from EtOAc gave colorless prisms, m.p. 148°. $[\alpha]_D^{28}$: +103.7°(c=0.40). *Anal.* Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.96; H, 7.99. In addition to the above crystalline product there was obtained 1.2 g. of an oily acidic material.

(+)-11-Carboxy-3-oxoeusanton-4-enic Acid (X)—A mixture of 1.8 g. of the half-ester (IX), 14 cc. of MeOH, 3.5 g. of KOH, and 3.5 cc. of water was refluxed for 3 hrs. After dilution with water, MeOH was removed under reduced pressure. The alkaline solution was washed with ether, acidified, and the resultant solid (1.4 g) was recrystallized from 50% MeOH to colorless prisms, m.p. 203°(decomp.). Hydrolysis of the oily material obtained in the preceding experiment also gave 0.6 g. of the same product. λ_{max}^{EtOH} 250 mμ (log ε 4.15). $[\alpha]_D^{28}$: +106.2°(c=0.40). *Anal.* Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.59. Found: C, 65.33; H, 7.33. This acid was esterified with a large excess of CH_2N_2 to afford an oily dimethyl ester, $[\alpha]_D^{20}$: +74.2°(c=0.40 in $CHCl_3$).

Catalytic Reduction of (+)-11-Carboxy-3-oxoeusanton-4-enic Acid (X)—A solution of 1.1 g. of the (+)-acid (X) in 40 cc. of EtOH was shaken in H_2 in the presence of 0.5 g. of 4% Pd-$CaCO_3$ catalyst. Uptake of H_2 was 115 cc.(25°, 765 mm.). The catalyst was filtered off and the solvent was removed *in vacuo* from the filtrate. After the residue wes dissolved in ether, the solution was extracted with Na_2CO_3 solution. On acidification of the alkaline extract 0.5 g. of a crystalline product separated. This was recrystallized from EtOAc-petr. ether to colorless prisms, m.p. 195°(decomp.). $[\alpha]_D^{25}$: +47.5°(c=0.40). *Anal.* Calcd. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.98, H, 8.51.

* Unless otherwise noted, rotations were determined in EtOH solution.

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Summary

(−)-α-Santonin has been correlated stereochemically with (+)-11-carboxy-3-oxoeusanton-4-enic acid (X) and by the investigation of molecular rotation of the latter the absolute configuration of the former has been deduced. It has been shown that (−)-α-santonin belongs to the same stereochemical type as steroids. (−)-β-Santonin proved to be the C_{11}-epimer of (−)-α-santonin.

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31. Masao Sumi : Studies on Anthemintics. XXXIII.* The Absolute Configuration of Santonin Isomers. (2). Synthetic Santonins.

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Eight racemic stereoisomers of santonin are assumed to arise from the four asymmetric carbons contained in its structure, but two of them must be eliminated[1,2] since a 6-5 ring fusion cannot exist in a diaxial configuration with chair-formed cyclohexanes. All the other six racemates were synthesized by Abe, *et al.*[1,3,4] and three of them were also obtained as their optically active isomers, two of which, (−)-α- and (−)-β-santonins, were found to be identical with the two naturally occurring santonins. The absolute configuration of both was discussed in the preceding paper[5], and it was shown that (−)-α-santonin should be represented by (I), and (−)-β- santonin by (II). This paper deals with other stereoisomers.

Synthesis of New Optically Active Stereoisomers of Santonin***

(−)-11-Carboxy-3-oxoeusanton-4-enic acid (III) can be derived from (−)-11-carboxy-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid lactone.[5] It was also obtained by the resolution of (±)-11-carboxy-3-oxoeusanton-4-enic acid[3] through its brucine salt. The acid (III) was brominated with two moles of bromine to (+)-2-bromo-11-carboxy-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid lactone (IV), which, on gentle heating with pyridine, was stereospecifically decarboxylated[6] to give (+)-2-bromo-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid lactone (V). When heated with picoline, (+)-bromolactone (V) led to (+)-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic acid lactone (VI, (+)-santonin D), $[\alpha]_D^{18}$: +265.0°, and the latter underwent the dienone-phenol rearrangement under the mild conditions (at 50° in 55% sulfuric acid) to afford (+)-β-desmotroposantonin (VII). On the other hand, treatment of (+)-2-bromo-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid(V)with zinc-acetic acid-methan-

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*** For convenience formulae of correct absolute configuration are used from the beginning,

1) Y. Abe, T. Harukawa, H. Ishikawa,, T. Miki, M. Sumi, T. Toga : J. Am. Chem. Soc., **78**, 1416(1956).
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