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.

(*Research Laboratory, Takeda Pharmaceutical Industries, Ltd.***)

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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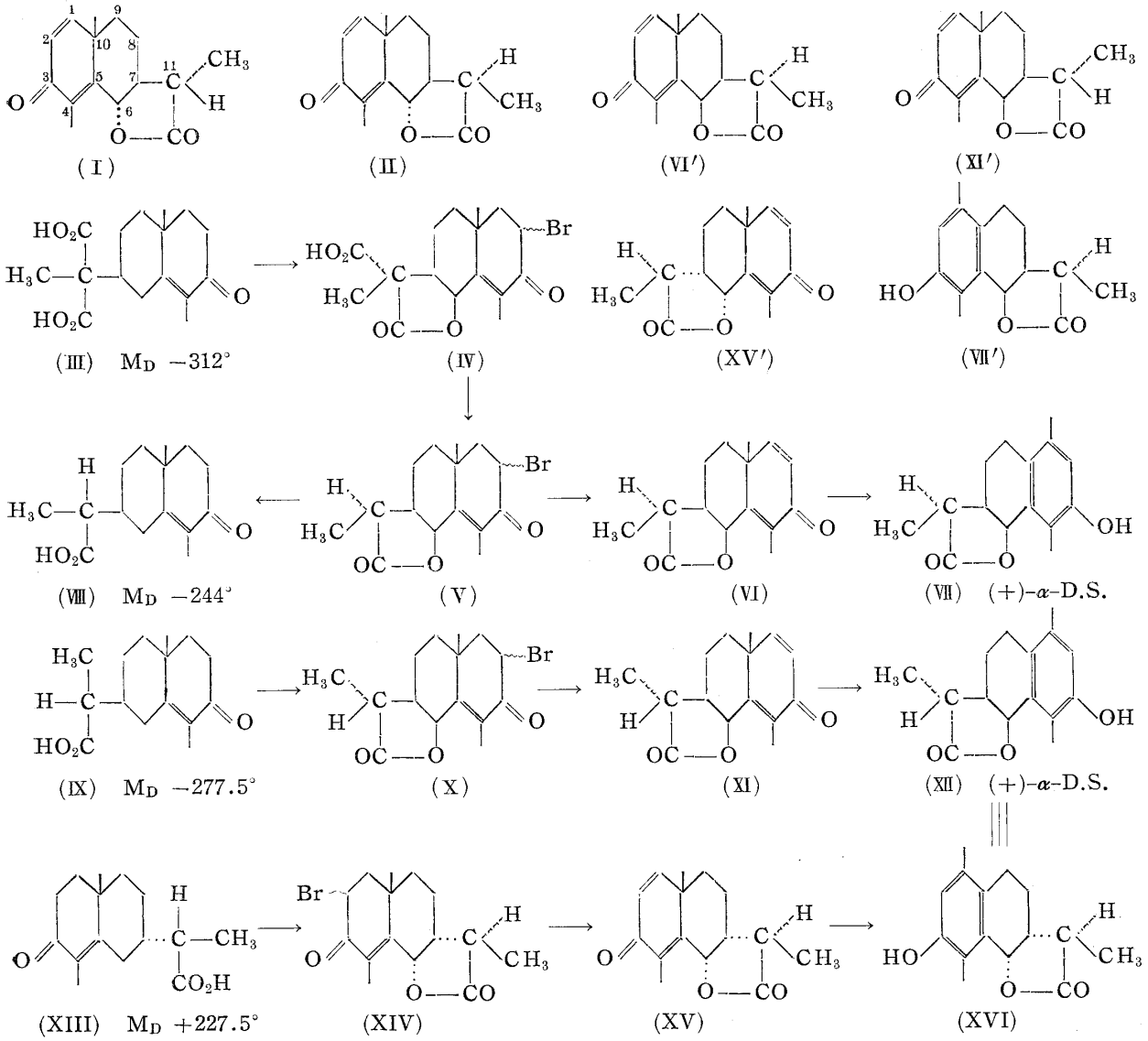
** Juso-nishino-cho, Higashiyodogawa-ku, Osaka (角 正夫)

*** 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).
2) M. Sumi : This Bulletin, **4**, 147(1956).
3) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga : J. Am. Chem. Soc., **75**, 2567(1953).
4) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga : *Ibid.*, **78**, 1422(1956).
5) M. Sumi : This Bulletin, **4**, 158(1956).
6) M. Nishikawa, K. Morita, H. Hagiwara : The work reported at the meeting of the Pharmaceutical Society of Japan, Osaka, March, 1955.



ol[6] resulted in the removal of the bromine atom as well as the reductive fission of the lactone to form (−)-3-oxo-11-*epi*-eusanton-4-enic acid (VIII), $[\alpha]_D^{30}$: −97.5°(M_D −244°).

(±)-3-Oxoeusanton-4-enic acid[7] derived from (±)-1,2-dihydro-α-santonin was resolved with quinine to furnish the levorotatory isomer (IX; $[\alpha]_D^{23}$: −111°; M_D −277.5°) and the dextrorotatory isomer in a less pure state ($[\alpha]_D^{22}$: +102.7°). The levo-isomer was brominated and derived to (+)-2-bromo-6β-hydroxy-3-oxoeusanton-4-enic acid lactone (X), which was further converted into (+)-6β-hydroxy-3-oxoeusantona-1,4-dienic acid lactone (XI; (+)-santonin C; $[\alpha]_D^{20}$: +302°) by dehydrobromination. This was changed to (+)-α-desmotroposantonin (XII) by the dienone-phenol rearrangement. In a similar way (−)-6β-hydroxy-3-oxoeusantona-1,4-dienic acid lactone (XI′; $[\alpha]_D^{32}$: −306.4°) was obtained from (+)-3-oxoeusanton-4-enic acid.

The Absolute Configuration of Synthetic Stereoisomers of Santonin

As was described above, (+)-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic acid lactone was derived from (−)-11-carboxy-3-oxoeusanton-4-enic acid (III). Since the latter belongs to the same stereochemical type as the antipodes of (−)-α- and (−)-β-santonins,[5,8] (+)-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic acid lactone is

7) M. Sumi : This Bulletin, **4**, 168(1956).
8) W. Klyne : J. Chem. Soc., **1952**, 2916; **1953**, 3072.

also of the type opposite to both natural santonins and should be represented by (VI). This was further verified by the observation that (+)-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic acid lactone was transformed into (+)-β-desmotroposatonin (VII) by the dienone-phenol rearrangement under the mild conditions, while (−)-β-santonin (II) was rearranged to (−)-β-desmotroposantonin (VII′). If (+)-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic acid lactone were to be represented by (VI′), the antipode of (VI), it would afford (−)-β-desmotroposantonin[9] like (−)-β-santonin (II), for (VI′) is the C_6-epimer of (II). Accordingly (VI′) should be forwarded for (−)-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic acid lactone.

Ishikawa[10] has recently found that (−)-α-santonin (I) is converted into (−)-6β-hydroxy-3-oxoeusantona-1,4-dienic acid lactone by a novel rearrangement which involves the inversion only at C_6. Moreover, both substances undergo the dienone-phenol rearrangement under the mild conditions to give (−)-α-desmotroposantonin. It is thus evident that they both belong to the same stereochemical type and (−)-6β-hydroxy-3-oxoeusantona-1,4-dienic acid lactone must be represented by (XI′), and its antipode by (XI).

(−)-3-Oxo-11-*epi*-eusanton-4-enic acid was derived from (−)-11-carboxy-3-oxoeusanton-4-enic acid (III) and, on the other hand, (−)-3-oxoeusanton-4-enic acid is of the same type as (+)-6β-hydroxy-3-oxoeusantona-1,4-dienic acid (XI). Therefore, they all belong to the type opposite to that of the natural santonins. This indicates that (−)-3-oxo-11-*epi*-eusanton-4-enic acid should be given the formula (VIII) and (−)-3-oxoeusanton-4-enic acid the formula (IX). The molecular rotations of (III), (VIII), and (IX) (−312°, −244°, and −277°, respectively) are opposite in sign to those of Δ^4-3-oxosteroids, but their magnitudes are roughly the same, showing that Klyne's principles[5,8] are also applicable in this case. Since (VIII) and (IX) bear one more asymmetric carbon than (III), and (VIII) and (IX) are epimeric at C_{11}, it was also proved that the molecular rotational contribution of the asymmetry at C_{11} is not too large.

In all the santonin isomers discussed so far, the propionic acid side chain at C_7 adopts the equatorial position,[1] but (−)-6α-hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone ((−)-santonin A), which was synthesized by Abe, *et al.*,[1] possesses the axial side chain and it is to be represented by either (XV) or its mirror image (XV′). (−)-6α-Hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone was derived from (+)-3-oxo-11-*epi*-isoeusanton-4-enic acid (A-acid[1]; M_D : +227.5°). The molecular rotation of the latter is of the sign opposite to those of (III), (VIII), and (IX), but their magnitudes are of the same order. Furthermore, it has already been shown that the rotational contribution of the asymmetry at C_{11} as well as at C_7[5] is not too large. (+)-3-Oxo-11-*epi*-isoeusanton-4-enic acid should, therefore, be assigned the structure(XIII) of the same type as the natural santonins, and (−)-6α-hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone must have the formula(XV). It is consistent with the observation that (XV) was converted to (+)-α-desmotroposantonin (XVI≡XII) by the dienone-phenol rearrangement under mild conditions.

According to Barton,[9] the configurations at C_6, C_7, and C_{11} in (−)-α-desmotroposantonin are tentatively represented by (X), (Y), and (Z), respectively, and that of C_{10} in (−)-α-santonin by (W). Then the configuration of santonin isomers except optically active 6α-hydroxy-3-oxoisoeusantona-1,4-dienic acid lactone are as shown in Table I which summarizes the results in the present and the preceding papers.

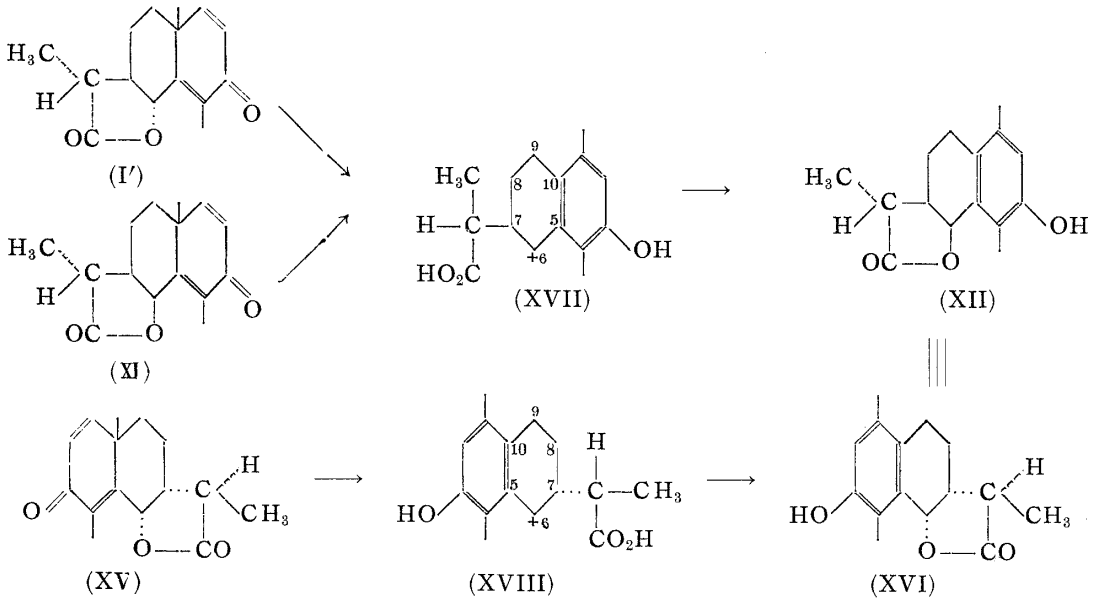
Cocker, *et al.*,[11] predicted that in desmotroposantnins the alicyclic cyclohexene

9) D. H. R. Barton : J. Org. Chem., **15**, 467(1950).
10) H. Ishikawa : J. Pharm. Soc. Japan, **76**, 504(1956).
11) N. M. Chopra, W. Cocker, J. T. Edward : Chemistry & Industry, **1955**, 41.

Table I. Absolute Configuration of Stereoisomers of Santonin

	C_6	C_7	C_{11}	C_{10}
(−)-α-Santonin (I)	X′	Y	Z	W
(−)-β-Santonin (II)	X′	Y	Z′	W
(−)-6β-Hydroxy-3-oxoeusantona-1,4-dienic Acid Lactone (XI′)	X	Y	Z	W
(−)-6β-Hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic Acid Lactone (VI′)	X	Y	Z′	W
(−)-6α-Hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic Acid Lactone (XV)	X′	Y′	Z′	W

ring is in a half-chair form and the propionic acid side chain at C_7 takes the equatorial position. It has been shown,[1,3,4] that the isomers with an equatorial side chain and those with an axial one equally undergo rearrangement to desmotroposantonins with an equatorial side chain. This would be explicable by the following considerations. As was suggested by Barton,[9] (+)-α-santonin (I′) and (+)-6β-hydroxy-3-oxoeusantona-1,4-dienic acid lactone (XI) are considered to change to (+)-α-desmotroposantonin (XII≡XVI) via (XVII) by the dienone-phenol rearrangement under mild conditions. In the case of (−)-6α-hydroxy-3-oxo-11-*epi*-isoeusantona-1,4-dienic acid lactone (XV) it would also undergo rearrangement to (+)-α-desmotroposantonin via (XVIII). Since in those intermediate states (XVII, XVIII) the inversion of their alicyclic ring is no longer prevented by the fusion of the lactone, it can take the more stable conformation.[12] Further, (XVII) and (XVIII) have a carbonium cation at C_6, so that C_5, C_6, C_7, C_9, and C_{10} atoms in them come to lie in a plane, which would make the inversion extremely easy. Accordingly, the configuration of the side chain in (XVII), which is produced from (I′) and (XI) (side chain : equatorial), remains intact, while in (XVIII) derived from (XV) (side chain : axial) the inversion of the cyclohexene



ring occurs to place the side chain in the more stable equatorial position. Subsequent lactonization gives rise to (+)-α-desmotroposantonin. By such considerations, it is well explained that the same desmotroposantonin (e.g. XII≡XVI) is produced from santonin isomers of the opposite stereochemical type (in this case, (I′) and (XV) or (XI) and (XV)).

As for 6α-hydroxy-3-oxoisoeusantona-1,4-dienic acid lactone (santonin B), its optically active isomers have not been prepared as yet. However, the results so

12) D. H. R. Barton, R. C. Cookson. W Klyne, C. W. Shoppee : *Ibid.* **1954**, 21.

far obtained with other stereoisomers predict that the levorotatory isomer would probably belong to the same type as the natural santonins.

The absolute configuration of not only the natural santonins but also their synthetic stereoisomers except one have thus been made clear as discussed in the two papers. It may be said that the stereochemistry of santonins have been established almost completely.

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Experimental*

(−)-11-Carboxy-3-oxoeusanton-4-enic Acid (III)—To a warm solution of 12 g. of (±)-11-carboxy-3-oxoeusanton-4-enic acid[1] in 60 cc. of MeOH was added 15 g. of brucine. After cooling, the crystalline solid was filtered and recrystallized from MeOH as colorless prisms (7.6 g.), m.p. 160°(decomp.), $[\alpha]_D^{28}$: −42.5°(c=0.40 in $CHCl_3$). This was treated with 5% NaOH and resultant acid was recrystallized from hydr. MeOH to give colorless prisms, m.p. 203°(decomp.), $[\alpha]_D^{28}$: −104.5° (c=0.40). Yield; 2.6 g.

(+)-2-Bromo-11-carboxy-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone(IV)—To a boiling solution of 2 g. of the (−)-acid (III) in 490 cc. of ether was added 2.2 g. of Br_2 in 20 cc. of AcOH and 20 cc. of ether. The solution was decolorized in 20 mins. This was cooled, extracted with Na_2CO_3 solution, and the extract was acidified, giving 0.8 g. of a crystalline material. Recrystallization from 50% MeOH afforded colorless prisms, m.p. 183°(decomp.), $[\alpha]_D^{30}$: +44.0°(c = 0.40). *Anal.* Calcd. for $C_{16}H_{19}O_5Br$: C, 51.76; H, 5.16. Found: C, 51.85; H, 5.42.

(+)-2-Bromo-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (V)—A mixture of 0.45 g. of (IV) and 5 cc. of pyridine was refluxed gently for 30 mins., poured into cold 10% H_2SO_4, and shaken with ether. The ether layer was washed with Na_2CO_3 solution and water, dried, and evaporated. The crystalline solid (0.25 g.) was recrystallized from MeOH to colorless prisms, m.p. 188°, $[\alpha]_D^{30}$: +80.0°(c=0.50). *Anal.* Calcd. for $C_{15}H_{19}O_3Br$: C, 55.05; H, 5.86. Found: C, 55.21; H, 5.91.

(+)-6β-Hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic Acid Lactone (VI)—To 0.45 g of the (+)-bromolactone (V) was added 10 cc. of picoline and the mixture was refluxed for 1.5 hrs., poured into cold 10% H_2SO_4, and extracted with ether. The extract was washed with Na_2CO_3 solution and water, dried, and evaporated to give 0.17 g. of a crystalline product. This on recrystallization from 50% EtOH afforded colorless needles, m.p. 182°, $[\alpha]_D^{18}$: +265.0°(c=0.40), λ_{max}^{EtOH} 245 mμ (log ε 4.15). *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.27; H, 7.55.

The Dienone-Phenol Rearrangement of (+)-6β-Hydroxy-3-oxo-11-*epi*-eusatona-1,4-dienic Acid Lactone (VI)—Fifty milligrams of (VI) in 2 cc. of 55% H_2SO_4 was stirred at 50° for 15 hrs. and diluted with water. The separated solid was dissolved in 10% NaOH and the alkaline solution was acidified with HCl. The resultant crystalline material was recrystallized from EtOH as colorless needles, m.p. 260°, $[\alpha]_D^{23}$: +103°(c=0.40). This showed no melting point depression on admixture with an authentic sample of (+)-β-desmotroposantonin.

(−)-3-Oxo-11-*epi*-eusanton-4-enic Acid (VIII)—A mixture of 0.4 g. of the (+)-bromo-lactone (V), 20 cc. of MeOH, 0.4 g. of Zn dust, and 2 cc. of AcOH was refluxd for 30 mins. Zn was filtered off and the filtrate was concentrated under reduced pressure. The residue dissolved in ether was washed with water and extracted with $NaHCO_3$ solution. Acidification of the extract afforded 0.2 g. of a crystalline solid, which was recrystallized from aq. MeOH to colorless plates, m.p. 122°, $[\alpha]_D^{30}$: −97.5°(c=0.40). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.62.

Resolution of (±)-3-Oxoeusanton-4-enic Acid—A mixture of 20 g. of (±)-3-oxoeusanton-4-enic acid in 200 cc. of EtOAc and 26 g. of quinine in 400 cc. of EtOAc was warmed on a water bath and cooled. On recrystallization of the separated solid from EtOH there was obtained 14.5 g. of a quinine salt as colorless prisms, m.p. 214°, $[\alpha]_D^{23}$: −156°(c=0.66 in $CHCl_3$). The salt was treated with 10% NaOH and the acidic fraction was recrystallized from EtOAc to colorless prisms, m.p. 130°; yield, 4.5 g. $[\alpha]_D^{23}$: −111.0°(c=0.66). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.85. Found: C, 72.05; H, 8.97.

After removal of the less soluble salt described above, the mother liquor was concentrated and allowed to stand. Another crystalline solid separated, which was recrystallized from hydr. EtOH as colorless prisms, m.p. 112°. $[\alpha]_D^{24}$: −42.7°(c=0.66 in $CHCl_3$). This was treated with 10%

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

NaOH and the resultant acid was recrystallized to colorless prisms, m.p. 129°; yield, 3 g. $[\alpha]_D^{24}$: +102.7°(c=0.66).

(+)-**2-Bromo-6β-hydroxy-3-oxoeusanton-4-enic Acid Lactone** (**X**)—To a stirred solution of 3.9 g of the (−)-acid (IX) in 320 cc. of ether was added dropwise 5.15 g. of Br_2 in 5 cc. of AcOH at 20°. The reaction mixture was washed with Na_2CO_3 solution and water, dried, and concentrated to give 1.0 g. of a crystalline product. This was recrystallized from MeOH to colorless prisms, m.p. 141°(decomp.), $[\alpha]_D^{20}$: +48.7°(c=0.66). *Anal.* Calcd. for $C_{15}H_{19}O_3Br$: C, 55.05; H, 5.86. Found: C, 54.97; H, 5.82.

(+)-**6β-Hydroxy-3-oxoeusantona-1,4-dienic Acid Lactone** (**XI**)—In 7 cc. of collidine, 0.9 g. of the bromolactone (X) was dissolved, the mixture was refluxed for 15 mins., cooled, and the product was isolated with ether in the same way as for (VI). The crystalline material (0.2 g.) thus obtained was recrystallized from EtOAc-petr. ether to colorless needles, m.p. 106°. λ_{max}^{EtOH} 247 mμ(log ε 4.15). $[\alpha]_D^{20}$: +302°(c=0.40). *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.40; H, 7.26.

The Dienone-Phenol Rearrangement of (+)-6β-Hydroxy-3-oxoeusantona-1,4-dienic Acid Lactone (**XI**)—Forty milligrams of (XI) was stirred with 2 cc. of 55% H_2SO_4 at 50°. There was obtained 30 mg. of a crystalline product, m.p. 197°, $[\alpha]_D^{22}$: +127.5°(c=0.33). The melting point was undepressed when mixed with an authentic sample of (+)-β-desmotroposantonin ($[\alpha]_D^{23}$: +127.7°).

(−)-**6β-Hydroxy-3-oxoeusantona-1,4-dienic Acid Lactone** (**XI′**)—The same series of reactions as for (XI) was carried out with 2.9 g. of (+)-3-oxoeusanton-4-enic acid ($[\alpha]_D^{23}$: +102.7°) to give 0.15 g. of (XI′), m.p. 106°, $[\alpha]_D^{21}$: −306.4°(c=0.40). *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.14; H, 7.38. No melting point depression was observed by mixing with an authentic sample.[10]

Summary

New optically active stereoisomers of santonin were synthesized and their absolute configurations investigated. It has been shown that (−)-6α-hydroxy-3-oxo-11-*epi*-isoeusatona-1,4-dienic acid lactone, (−)-6β-hydroxy-3-oxoeusantona-1,4-dienic acid lactone, and (−)-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic acid lactone are of the same stereochemical type as that of the naturally occurring santonins. An aspect of the mechanism of the dienone-phenol rearrangement in santonin series was also considered.

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