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29. **Masao Sumi** : Studies on Anthelmintics.* XXXI. The Configuration of Stereoisomers of Ethyl 11-Ethoxycarbonyl-6α-hydroxy-3-oxoeusanton-4-enic Acid Lactone.

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It has been reported[1] that the peracid oxidation of the enol acetate (II) of ethyl 11-ethoxycarbonyl-3-oxoeusanton-4-enate (I) gave 11-ethoxycarbonyl-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid lactone (III,*** m.p. 127°), which became an important intermediate for the total synthesis of santonins. The present paper deals with the stereochemical correlation of (III) with its isomers obtained as minor products of the oxidation reaction. For conveinence, (III) is tentatively called "lactone ester-a."

After lactone ester-a was removed from the oxidation product, the remaining oily material was chromatographed on alumina to afford two crystalline products together with ethyl 11-ethoxycarbonyl-3-oxoeusantona-4,6-dienate, which was characterized as the 2,4-dinitrophenylhydrazone. Since both crystalline substances proved to be stereoisomers of lactone ester-a on the basis of their elementary analyses and ultraviolet and infrared spectra, the one with m.p. 132° is called "lactone ester-b" and the other with m.p. 117° "lactone ester-c." These three isomers were derived from (I) which bears an equatorial side chain at C_7,[2,3] so that the C_7-C_{11} bond in them must also be equatorial and their structures should be comprised among (III), (IV), (V), and (VII), of which the former two have a *trans*-fused lactone, while the other two possess a *cis*-fused one.

The mode of lactone-fusion in these stereoisomers was examined first. It has already been shown that the lactone ester-a possesses a *trans*-fused lactone. This was further verified by the fact that the acid (VIII) obtained by the hydrolysis of lactone ester-a was decarboxylated to give dihydro-α-santonin and the latter was converted into α-santonin (XI) via the 2-bromo compound (X). As for lactone ester-b, it was hydrolyzed to the same acid (VIII) as obtained from lactone ester-a. On the other hand, the 2-bromo compound derived from lactone ester-b was dehydrobrominated to a dienone (XIII) and this, on hydrolysis, furnished two lactonic acids, (XIV) and its C_{11}-epimer, both of which gave rise to α-santonin on decarboxylation as previously reported.[1] (XII) and (XIII) evidently differ from the corresponding compounds derived from lactone ester-a. It is thus concluded that in lactone ester-b the lactone is also *trans*-fused and, therefore, lactone ester-a (III) and lactone ester-b (IV) are epimeric at C_{11}. That the hydrolysis of both isomers produces the same lactonic acid (VIII) suggests the intermediate formation of a dicarboxylic acid by the fission of the lactone ring.

The above results indicate that lactone ester-c should have a *cis*-fused lactone. This was confirmed by the following observations. When lactone ester-c was hydrolyzed and subsequently decarboxylated, it yielded 6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid lactone (XVI), which was transformed into 6β-hydroxy-3-oxoeusantona-

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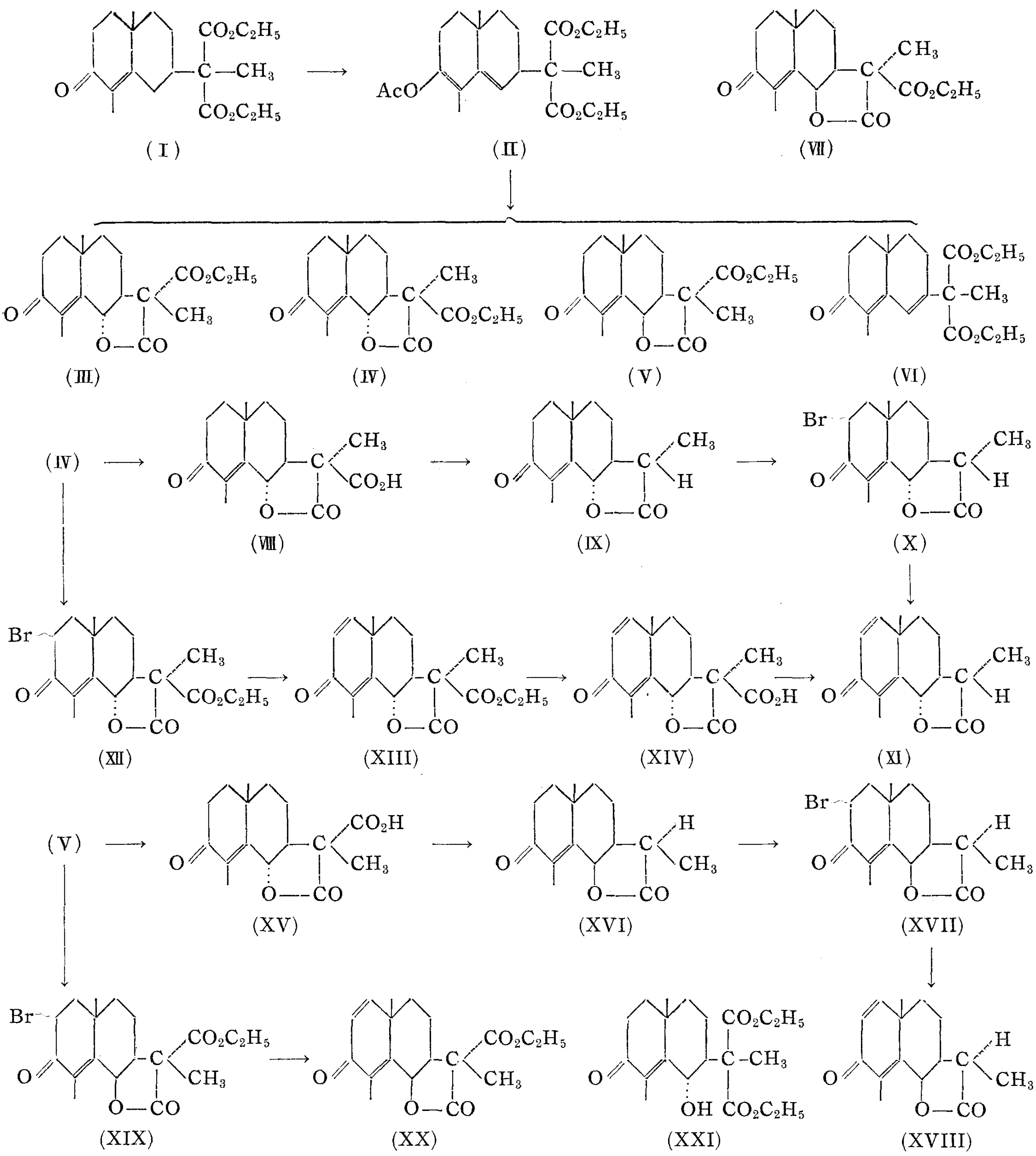
*** For simplification correct names and formulae are employed from the beginning.

[1] Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga : J. Am. Chem. Soc., **78**, 1422(1956).

[2] Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, T. Toga : *Ibid.*, **78**, 1416(1956).

[3] T. Miki : J. Pharm. Soc. Japan, **75**, 395(1955).



1,4-dienic acid lactone[2] (XVIII: lactone, *cis*) by the bromination-dehydrobromination method. Bromination of lactone ester-c resulted in the formation of its 2-bromo compound (XIX), which gave a dienone (XX) on dehydrobromination. Both substances (XIX and XX) have already been synthesized by Ishikawa,[4] who showed that they possess a *cis*-fused lactone.

Now that the mode of lactone-fusion in three lactone esters has been made clear, their C_{11}-configurations must be considered. By the peracid oxidation of the enol acetate (II), lactone ester-a (III) and lactone ester-b (IV) were produced in the ratio of 12 : 1, and the yield of lactone ester-c was much less than that of (IV). Lactone ester-c, however, was obtained in 58% yield by the action of bromine on the enol

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[4] H. Ishikawa : J. Pharm. Soc. Japan, **76**, 500 (1956)

acetate (II), while its C_{11}–epimer was not isolated. Thus lactonization is stereospecific in both reactions and, furthermore, it has been shown[5] that in lactone ester–c only the configuration at C_6 is opposite to that of lactone ester–a, but their C_{11}–configurations are the same. These facts suggest* that a definite carboxyl group in the side chain of the enol acetate (II) would readily take part in the lactonization described above. Ethyl 11–ethoxycarbonyl–6α–hydroxy–3–oxoeusanton–4–enate (XXI) is most likely the intermediate product of the peracid–oxidation of (II), and the groups at C_{11} in (XXI) would validly occupy the positions as shown in Figs. 1 and 2, since it is of the greatest thermodynamic stability that bulky groups (in this case, COOEt–a and C_8 on the one hand, and COOEt–b and C_6 on the other) on two adjacent carbons are furthest removed. Then the preponderant formation of lactone ester–a can be reasonably explained by the preferential lactonization between the C_6–hydroxyl and ethoxycarbonyl–a nearer to the hydroxyl, and the formation of lactone ester–b in a smaller amount is also understood by the lactonization in which the more distant ethoxycarbonyl–b participates. On the action of bromine to (II) the carbonyl of ethoxycarbonyl–a nearer to C_6 would attack the carbon to form a lactone, which would be the more stable *cis*–fused one, the lactone ester–c being thus produced.

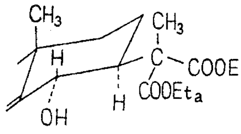


Fig. 1.

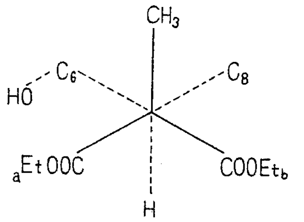


Fig. 2.

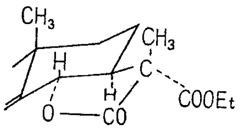


Fig. 3.

Accordingly, the structure of lactone ester–a should be partly represented by Fig. 3. Since the lactone of α–santonin has the configuration shown in Fig. 4,[7] lactone ester–a must be named 11–ethoxycarbonyl–6α–hydroxy–3–oxo–11–*epi*–eusanton–4–enic acid lactone,[8] which is correctly represented by (III). As a consequence, its C_{11}–epimer, lactone ester–b, is to be called 11–ethoxycarbonyl–6α–hydroxy–3–oxoeusanton–4–enic acid lactone (IV) and lactone ester–c, 11–ethoxycarbonyl–6α–hydroxy–3–oxo–11–*epi*–eusanton–4–enic acid lactone (V; Fig. 5).

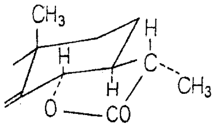


Fig. 4.

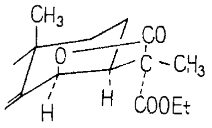
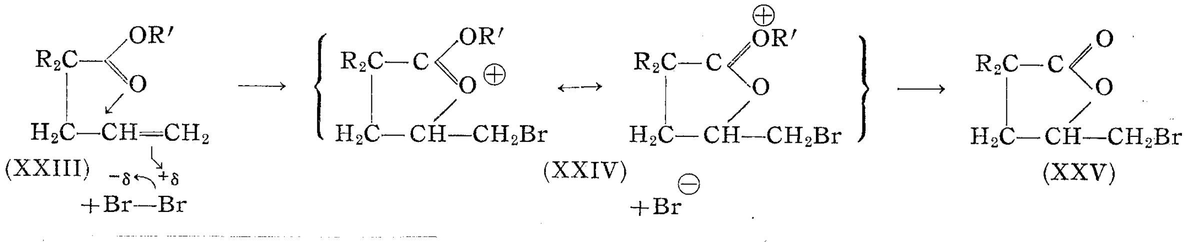


Fig. 5.



(XXIII) (XXIV) (XXV)

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* Cocker, *et al.*,[6] made a similar consideration, but he did not discuss in detail.

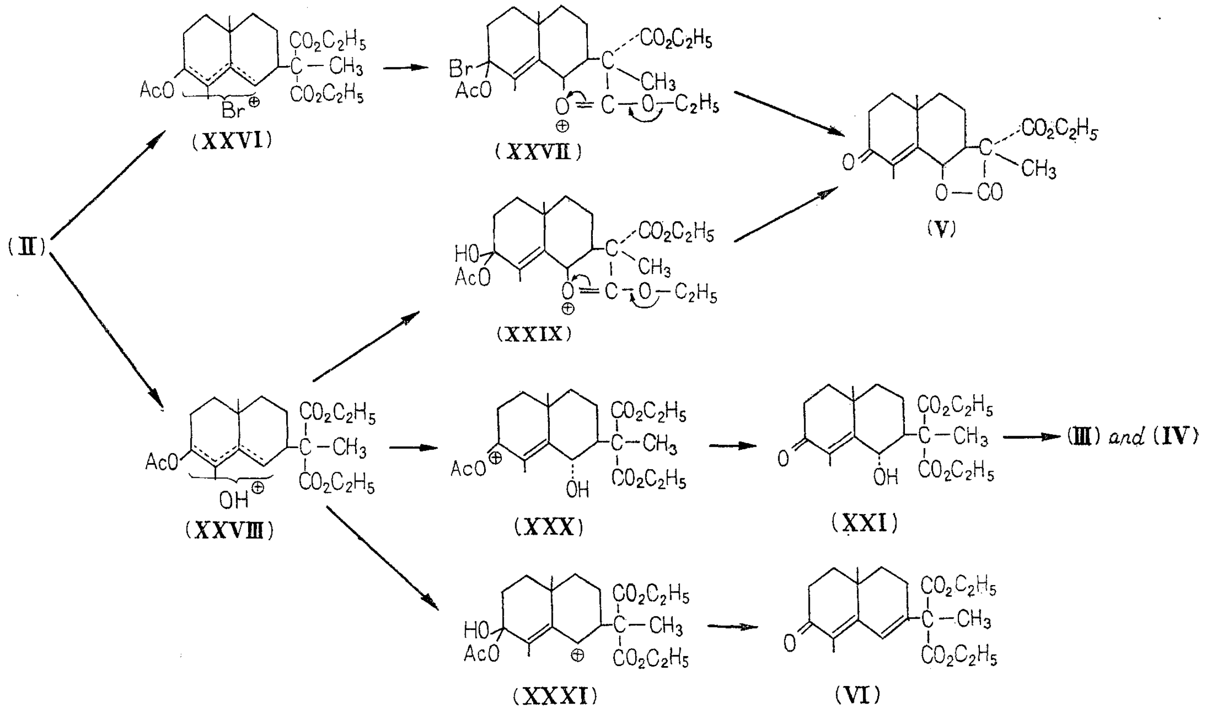
[5] H. Ishikawa: J. Pharm. Soc. Japan, **76**,

[6] N.M. Chopra, W. Cocker, J.T. Edward: Chemistry & Industry, **1955**, 41.

[7] T. Miki: J. Pharm. Soc. Japan, **75**, 416(1955).

[8] Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi.: Chemistry & Industry, **1955**, 91.

Arnold, *et al.*,[9] investigated the formation of a bromolactone (XXV) by the action of bromine on a γ,δ-unsaturated acid or ester (XXIII) and predicted that the carbonyl oxygen participated in the formation of a cyclic oxonium salt stabilized by resonance. Also in the reaction in which lactone ester-c was obtained from the enol acetate (II) and bromine the *cis*-lactone (V) was probably produced through a transition state like (XXVI) and an oxonium salt (XXVII). Since in the peracid-oxidation OH^+ or its equivalent[10] plays the role of Br^+ in bromination, it is considered that a transition state such as (XXVIII) is brought about and then three types of change occur. If an oxonium salt (XXIX) is produced by the attack of the carbonyl,* it affords a *cis*-lactone (V). This is similar to the case of (XXVII). When the hydroxyl group stays at the 6α-position in (XXVIII), two kinds of *trans*-lactone (III and IV) are formed via (XXX) and (XXI). When (XXVIII) leads to (XXXI), the latter gives the linear dienone (VI) with loss of a proton.



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Experimental**

Separation of the Lactone Ester Isomers.—Thirty grams of the enol acetate (II) was oxidized by performic acid[1] to give 11.5 g. of lactone ester-a. The mother liquor (12 g.) was adsorbed

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* An alternative route cannot de excluded, in which the hydroxyl is introduced into the 6β-position and subsequently lactonized.

** All ultraviolet absorption spectra were measured in EtOH.

[9] R. T. Arnold, M. de Moura Campos, L. K. Lindsay: J. Am. Chem. Soc., **75**, 1044(1953); M. de Moura Campos: *Ibid.*, **75**, 4480(1954).

[10] H. Gilman: "Organic Chemistry," John Wiley & Sons, Inc., New York, **IV**, 1165(1953); Carl Djerassi, O. Mancera, M. Velasco, G. Stork, G. Rosenkranz: J. Am. Chem. Soc., **74**, 3321 (1952); L. F. Fieser, Wei-Yuang Huang: *Ibid.*, **75**, 5356(1953).

from 190 cc. of petr. ether-benzene (3:1) on 180 g. of alumina and washed with petr. ether-benzene (3:1, 2:2 and 1:3), benzene, benzene-ether (3:1, 2:2, and 1:3), and ether, in turn. The fractions eluted with petr. ether-benzene (3:1 and 2:2) showed absorption maxima at 241 mμ (log ε 3.65) and 294 (3.36), and its 2,4-dinitrophenylhydrazone was repeatedly recrystallized from EtOH to dark red prisms (the derivative of VI), m.p. 172°. λ_{max} 260 mμ (log ε 4.19), 308 (4.15), 398 (4.50). From the petr. ether-benzene (1:3) and the benzene eluates there was obtained 0.85 g. of lactone ester-b, m.p. ca. 127°, in total and this was recrystallized from EtOH as colorless prisms, m.p. 132°. The melting point was depressed to ca. 100° on admixture with lactone ester-a. λ_{max} 243 mμ (log ε 4.19), ν_{max}^{Nujol} 5.61 (lactonic CO), 5.87 (ester CO), 6.04 (conjugated CO), and 6.21 μ (double bond). *Anal.* Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found : C, 67.51; H, 7.54.

The fractions eluted with benzene-ether and ether afforded 0.2 g. of lactone ester-a. In another experiment a very small amount of lactone ester-c was obtained, which, on recrystallization from EtOH, gave colorless prisms, m.p. 117°. λ_{max} 244 mμ (log ε 4.08), ν_{max}^{Nujol} 5.64 (lactonic CO), 5.81 (ester CO), 6.00 (conjugated CO), and 6.20 μ (double bond). *Anal.* Calcd. for $C_{18}H_{24}O_5$; C,67.48; H, 7.55. Found C, 67.64; H, 7.35.

11-Carboxy-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (VIII). —(**a**) From 11-Ethoxycarbonyl-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (III; Lactone Ester-a) : A mixture of 20 g. of lactone ester-a, 40 g. of KOH, and 400 cc. of water was stirred for 16 hrs. at room temperature. After unchanged ester was removed, the alkaline solution was acidified to afford 15 g. of the lactonic acid (VIII), which was recrystallized from AcOEt to colorless prisms, m.p. 213°(decomp.). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found : C, 65.86; H, 7.15.

(**b**) From 11-Ethoxycarbonyl-6α-hydroxy-3-oxoeusanton-4-enic Acid Lactone (IV; Lactone Ester-b) : A mixture of 0.5 g. of lactone ester-b, 5 cc. of MeOH, 1 g. of KOH, and 10 cc. of water was stirred for 4 hrs. at room temperature. MeOH was removed by suction and the alkaline solution was acidified, extracted with ether, and the solvent evaporated to give 0.3 g. of a crystalline product, m.p. 213°(decomp.), undepressed on admixture with (VIII) obtained in the preceding experiment.

Dihydro-α-santonin (IX)—Fifteen grams of the lactonic acid (VIII) in 20 cc. of collidine was heated under reflux for 5 mins., cooled, and diluted with AcOEt. The solution was washed with dil. H_2SO_4, Na_2CO_3 solution, and water, dried, and concentrated to furnish 9 g. of a crystalline material. This was recrystallized from MeOH to colorless prisms, m.p. 132°. λ_{max} 245 mμ (log ε 4.19). *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found : C, 72.83; H, 8.37.

2-Bromodihydro-α-santonin (X)—To a solution of 0.4 g. of dihydro-α-santonin (IX) in 50 cc. of ether was added dropwise 0.26 g. of Br_2 in 2 cc of AcOH. After being washed with $NaHCO_3$ solution and water, the solvent was removed under reduced pressure. Recrystallization of the crude crystalline product (0.4 g.) from MeOH afforded colorless prisms, m.p. 138°(decomp.). *Anal.* Calcd. for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.87. Found : C, 55.20; H, 6.05.

2-Bromo-11-ethoxycarbonyl-6α-hydroxy-3-oxoeusanton-4-enic Acid Lactone (XII)—A solution of 0.7 g. of lactone ester-b (IV) in 100 cc. of ether was refluxed with 0.35 g. of Br_2 in 10 cc. of ether for 20 mins. After decolorization, the ether solution was cooled, washed with water, and evaporated. The resulting crystalline material (0.8 g.) was recrystallized from MeOH to colorless plates, m.p. 167°(decomp.). *Anal.* Calcd. for $C_{18}H_{23}O_5Br$: C, 54.14; H, 5.81. Found : C, 54.14; H, 6.19.

11-Ethoxycarbonyl-6α-hydroxy-3-oxoeusantona-1,4-dienic Acid Lactone (XIII)—The 2-bromo compound (XII) (0.7 g.) in 10 cc. of picoline was heated under reflux for 1 hr. The reaction mixture was cooled, poured into cold dil. H_2SO_4, and extracted with ether. Purification of the ether solution gave 0.4 g. of the dienone ester (XIII), which was recrystallized form EtOH as colorless plates, m.p. 148°. When mixed with the C_6-epimer[1](m.p. 129°), the melting point was depressed to 95°. λ_{max} 241 mμ (log ε 4.20). *Anal.* Calcd. for $C_{18}H_{22}O_5$: C, 67.91, H, 6.97. Found : C, 68.04 ; H, 7.15.

α-Santonin (XI)—(a) From 2-Bromodihydro-α-santonin (X) : A mixture of 0.3 g. of (X) and 1.5 cc. of collidine was refluxed for 20 mins, cooled, and diluted with ether. The ether solution was washed with dil. H_2SO_4 and water, dried, and evaporated to afford 0.1 g. of a crystalline product. Recrystallization from MeOH gave colorless prisms, m.p. 181°, undepressed on admixture with an authentic sample of α-santonin.

(b) From 11-Ethoxycarbonyl-6α-hydroxy-3-oxoeusantona-1,4-dienic Acid Lactone (XIII) : The dienone lactone ester (XIII) (0.3 g.) was hydrolyzed by stirring with 1 g. of KOH in 10 cc. of water at 90° for 1 hr. The alkaline solution was washed with ether and acidified. The separated crystalline material was recrystallized from AcOEt to give two compounds, m.p. 186° and m.p. 210°(decomp.), undepressed when respectively admixed with authentic samples of the dienone lactonic acids.[1] Eighty milligrams of the mixture of both isomers was refluxed with 0.2 cc. of collidine for 2 mins. To this was added ether and the ether solution was treated in the usual way to afford 40 mg. of crystals, m.p. 181°. It showed no melting point depression when mixed with an authentic sample of α-santonin.

11-Ethoxycarbonyl-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (V; Lactone Ester-c)—To a solution of 23.4 g. of the enol acetate (II) in 700 cc. of ether was added 14.7 g. of AcOK in 300 cc. of 85% AcOH and then 9.6 g. of Br_2 in 100 cc. of AcOH was added dropwise. After being kept standing for 1 hr., water was added and the ether layer was purified to afford a crystalline material. Recrystallization from EtOH gave 10.5 g. of colorless prisms, m.p. 115°, undepressed on admixture with lactone ester-c which was obtained by the performic acid oxidation of the enol acetate. Chromatographic purification of the mother liquor of lactone ester-c gave 0.3 g. of a crystalline material, m.p. 128°, λ_{max} 279 mμ, which was not the C_{11}-epimer of (V).

11-Carboxy-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (**XV**)—A mixture of 10 g. of lactone ester-c, 20 g. of KOH, and 200 cc. of water was stirred for 15 hrs. at room temperature. Unchanged ester was removed by filtration and the filtrate was acidified. The separated acid (4.2 g.) was recrystallized from AcOEt to colorless prisms, m.p. 220°(decomp.). λ_{max} 246 mμ (log ε 4.08). *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found : C, 65.85; H, 6.70.

6β-Hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (**XVI**)—To 1.3 g. of the lactonic acid (XV) obtained above was added 2 cc. of collidine. The mixture was refluxed for 5 mins., cooled, and diluted with petr. ether. By filtration there was obtained 1 g. of the lactone (m.p. 137°), which was recrystallized from MeOH as colorless prisms, m.p. 140°. λ_{max} 245 mμ (log ε 4.16). *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found : C, 72.34; H, 7.83.

2-Bromo-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (**XVII**)—A solution of 0.4 g. of (XVI) in 75 cc. of ether was treated under reflux with 0.26 g. of Br_2 in 10 cc. of ether. On boiling for 20 mins. decolorization took place and crystals separated. There was obtained 0.4 g. of the bromolactone, m.p. 179°(decomp.).

6β-Hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic Acid Lactone (**XVIII**; **Santonin D**)—A mixture of 0.4 g. of the bromolactone (XVII) and 3 cc. of collidine was refluxed for 15 mins. After cooling. ether was added to the reaction mixture and the ether solution was washed with dil. H_2SO_4 and water, dried, and evaporated to afford 0.1 g. of a crystalline product. This was recrystallized from MeOH as colorless plates, m.p. 189°, giving no depression on admixture with an authentic sample of (XVIII).[2)]

2-Bromo-11-ethoxycarbonyl-6β-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid Lactone (**XIX**)—To a boiling solution of 1.3 g. of lactone ester-c in 120 cc. of ether was added in one portion 0.65 g. of Br_2 in 10 cc. of ether. After boiling for 40 mins., decolorization occurred. The solution was purified to give 1.0 g. of a bromo compound, which, on recrystallization from MeOH, afforded colorless plates, m.p. 162°, undepressed on admixture with an authentic sample of (XIX).[4)] *Anal.* Calcd. for $C_{18}H_{23}O_5Br$: C, 54.14; H, 5.81. Found : C, 54.09; H, 5.58.

11-Ethoxycarbonyl-6β-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic Acid Lactone (**XX**)—A solution of 0.9 g. of the 2-bromo compound in 5 cc. of picoline was heated under reflux for 1 hr. and cooled. The reaction mixture was diluted with ether, washed with dil. H_2SO_4 and water, and dried. Removal of the solvent afforded 0.4 g. of a crystalline product, which was recrystallized from EtOH to colorless needles, m.p. 142°. The melting point was not depressed when mixed with the dienone lactone ester (XX) prepared by Ishikawa.[4)]

Summary

Configurational assignment has been made for three isomeric compounds obtained by the performic acid-oxidation of the enol acetate (II). The major product, which became an important intermediate for the total synthesis of santonin, has been given the structure of ethyl 11-ethoxycarbonyl-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic acid lactone (III), and the other two were proved to be the C_{11}- and the C_6-epimer of (III). The mechanism of the oxidation reaction is also discussed briefly.

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