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Santonin. III.[1] The Total Synthesis of Santonin[2]

BY YASUO ABE, TADATSUGU HARUKAWA, HISASHI ISHIKAWA, TAKUICHI MIKI, MASAO SUMI AND TADASHI TOGA

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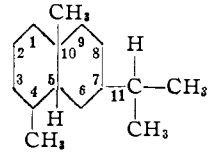
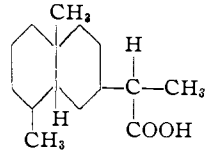
α- and β-santonins have been synthesized both in optically active and racemic forms from the Michael condensation product of diethyl methylmalonate and 3-keto-4,9-dimethyl-1,2,3,7,8,9-hexahydronaphthalene by two different methods.

All possible racemic stereoisomers of santonin having *cis*-fused lactone already have been synthesized.[3,4] In the present paper the synthesis of several isomers containing a *trans*-lactone are reported.

In the preceding paper the equatorial position was assigned as the most probable one for the side chain of the condensation product (II) of 3-keto-4,9-dimethyl-1,2,3,7,8,9-hexahydronaphthalene (I) with diethyl methylmalonate.[4] According to the new nomenclature[5] based on the fundamental

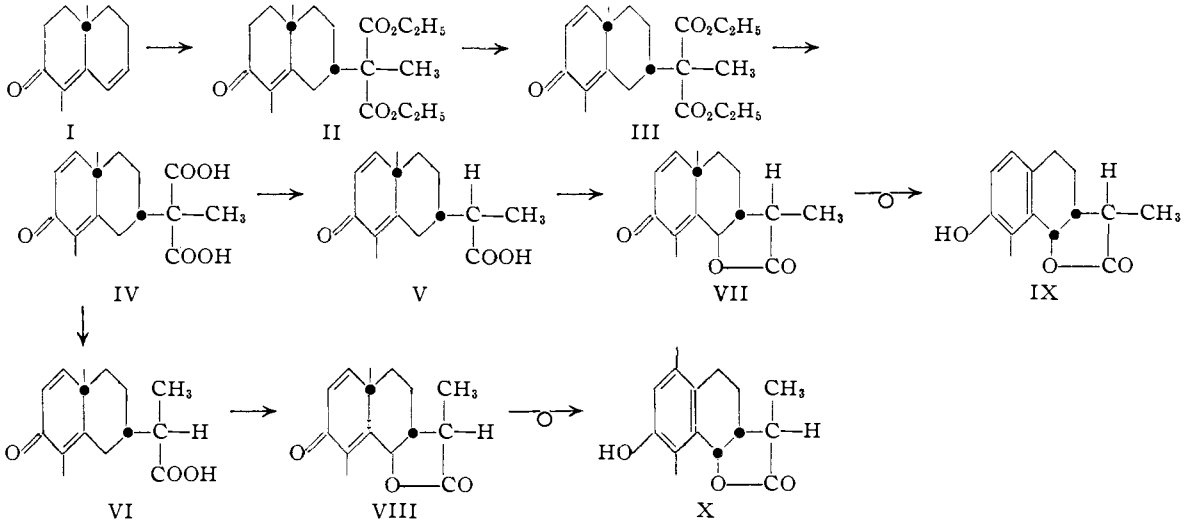


eusantonane



eusantonanic acid

hydrocarbon of santonin and its related compounds which has been termed "eusantonane," II is now called ethyl 11-carbethoxy-3-oxo-eusanton-4-enate.



The synthesis of natural santonin from this key intermediate might be accomplished by either of the following two routes: (i) introduction of an e-oriented hydroxyl group into C-6 after II is converted into an appropriate cross-conjugated dienone; (ii) construction of a *trans*-fused lactone in a monoenone easily derived from II, followed by transformation of its monoenone ring into the dienone structure. Since the possibility of undesired inversion of the lactone into the *cis* form cannot be excluded in the last step of the second route, the first plan seemed preferable, provided that the introduction of an equatorial hydroxyl into a dienone can be achieved.

Synthetic studies of the first route were commenced by dehydrogenation of II to ethyl 11-carbethoxy-3-oxo-eusantona-1,4-dienate (III) with selenium dioxide. The cross-conjugated dienone structure was assigned to the product on the basis of the ultraviolet absorption spectra of its 2,4-dinitrophenylhydrazone (λ_{max} 228, 256, 308, 396 mμ) and of the dicarboxylic acid IV (λ_{max} 241 mμ with inflection at 265 mμ) easily obtained through alkaline hydrolysis of III. Decarboxylation of IV in boiling collidine yielded a mixture of 3-oxo-eusantona-1,4-dienic acid (V) and its C-11 epimer VI. Separation was so difficult that only a poor yield of an isomer melting at 144° (VI) could be isolated. Therefore, hydroxylation at C-6 had to be effected on the mixture of the acids. Selenium dioxide in acetic acid proved to be useful again, for the introduction of an equatorial hydroxyl, accompanied by lactonization, and a mixture consisting of two racemic stereoisomers of santonin was obtained. These were separated by taking advantage of the difference between the lactonization velocity of the corresponding santoninic aicds. The more rapidly lactonized part furnished crystals melting at 181°; an isomer, which melts at 186°, was isolated from the slowly lactonized part.

(1) This is part XII of "Studies on Anthelmintics."

(2) A preliminary report of this work was made in *Proc. Japan Acad.*, **30**, 116, 119 (1954).

(3) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, THIS JOURNAL, **75**, 2567 (1953).

(4) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *ibid.*, **77**, 1416 (1955).

(5) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki and M. Sumi, *Chemistry and Industry*, 91 (1955).

Both compounds, which differ from all the known racemic isomers of santonin with a *cis*-fused lactone, must have a *trans*-lactone. This assumption was confirmed by the fact that their ultraviolet absorption spectra coincide completely with that of natural santonin. The former crystals, the infrared spectrum of which was identical with that of *l*-α-santonin, led to *rac*-α-desmotroposantonin (IX) by mild rearrangement conditions, whereas the latter, which showed an infrared spectrum identical with that of natural *l*-β-santonin,[6] rearranged to *rac*-β-desmotroposantonin (X). In addition, both displayed the pink color characteristic of natural santonin when treated with sodium methylate. All these findings indicate that the compound with m.p. 181° is *rac*-α-santonin (VII) and the one melting at 186° is *rac*-β-santonin (VIII).

In order to obtain the above santonins in their optically active forms, resolution was attempted at the stage of the dibasic acid IV using brucine. The less soluble brucine salt gave the dextro-acid and the more soluble one the levo-isomer, contaminated with some of its antipode. The resolution was successful also *via* the quinine salt. In the same manner as was described above for the racemate, the decarboxylation product of the dextro-acid led to a mixture of optically active isomers of santonin, from which two kinds of crystals were separated. One, m.p. 172°, exhibiting a specific rotation of +156.4° proved to be the antipode of natural *l*-α-santonin, and the other, m.p. 213°, $[\alpha]_D$ +137.9°, *d*-β-santonin. On the other hand, the levo-acid, on application of the same reaction sequence, also afforded two crystalline substances of m.p. 172 and 212°, respectively, after removal of some racemates. The former, though its melting point was undepressed on admixture with natural *l*-α-santonin, proved not to be completely pure, as it showed a specific rotation −153.0°, whereas the natural product shows −166.4° under the same conditions. The latter substance was found to be pure and identical with *l*-β-santonin both by mixed melting point test and by comparison of specific rotation.

An alternative synthesis according to the second route was concurrently studied with success. At first, the formation of a *trans*-lactone was attempted *via* the C-6 brominated compound. Since the steric hindrance of the diethyl methylmalonate group attached to C-7 was so great that treatment with molecular bromine caused a preferential attack of bromine at C-2 instead of C-6, a monoenone derivative carrying a less bulky side chain should be adopted for obtaining the C-6 bromo-compound. The mixture of 3-oxo-eusanton-4-enic acid (C-acid) and 3-oxo-11-epi-eusanton-4-enic acid[4] (D-acid) was methylated with diazomethane or with methanol–hydrochloric acid. After enol-acetylation of the mixed ester XI by heating with acetic anhydride and sulfuric acid, C-6 bromination was effected by N-bromoacetamide in the presence of water to give methyl 6-bromo-3-oxo-eusanton-4-enate and 6-bromo-3-oxo-11-epi-eusanton-4-enate (XIII). The bromine of XIII was assigned the equatorial configuration because the *trans*-orientation relative to the C-7 side chain might be more stable. Attempted replacement of the C-6 bromine with a hydroxyl group by the S_1-mechanism through treatment with silver oxide in ether was unsuccessful, whereas the corresponding isomer XIV having the axial C-7 side chain gave the C-6 hydroxy compound XV without difficulties.[7]

Our attention was then turned to the method of hydroxylation involving peracid oxidation of enol-acetate.[8] On heating with acetic anhydride in the presence of a catalytic amount of concd. sulfuric acid, II was easily converted into ethyl 3-acetoxy-11-carbethoxy-eusantona-3,5-dienate (XVI). Oxidation of XVI with performic acid or peracetic acid gave the lactone of 11-carbethoxy-6α-hydroxy-3-oxo-11-epi-eusanton-4-enic acid (XVII) in place of the C-6 hydroxy derivative of II. The junction between the lactone and the B ring was shown to be *trans* by the evidences given below.

Bromination of XVII with molecular bromine in ether afforded the lactone of 2-bromo-11-carbethoxy-6α-hydroxy-3-oxo-11-epi-eusanton-4-enic acid (XVIII), which differs from both the lactone of 2-bromo-11-carbethoxy-6β-hydroxy-3-oxo-eusanton-4-enic acid (XXIV) and its C-11 epimer XXV,[9] derived from II through partial saponification and subsequent treatment with two moles of bromine.

Collidine dehydrobromination of XVIII caused neither inversion of the lactone ring nor elimination of the C-11 carbethoxy group, but gave the lactone of 11-carbethoxy-6α-hydroxy-3-oxo-11-epi-eusantona-1,4-dienic acid (XIX), whose ultraviolet absorption spectrum with a maximum at 241 mμ strikingly resembles that of natural santonin. Saponification of XIX with potassium hydroxide or methanolic potash yielded the dipotassium salt of the dibasic acid, which on acidification was converted into two epimers at C-11 of the lactone of 11-carboxy-6α-hydroxy-3-oxo-eusantona-1,4-dienic acid (XX and XXI), one melting at 210° with decomposition and the other at 186° (monohydrate), both of which exhibit very similar ultraviolet absorption curves. Decarboxylation of both XX and XXI by heating in collidine yielded a single product melting at 181°, which proved to be identical with *rac*-α-santonin synthesized by the other method described above. In this case *rac*-β-santonin was not produced, indicating the marked stereospecificity of the decarboxylation reaction.

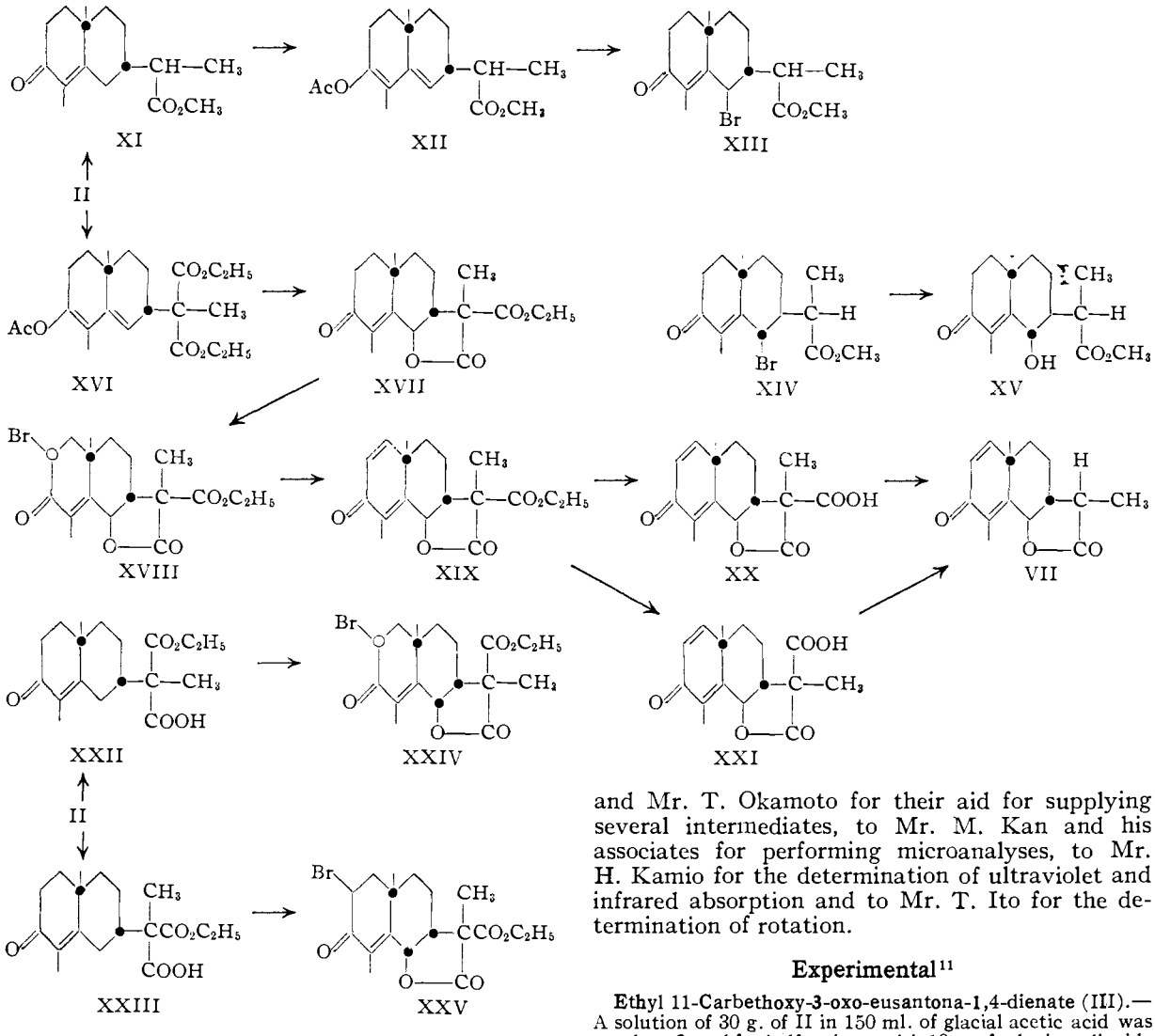
XX (m.p. 210°) was resolved through its brucine salt, and decarboxylation of an optically active acid obtained from the less soluble salt, yielded pure *l*-α-santonin melting at 172°. The identity of the product with naturally occurring santonin was established by comparison of the infrared spectra, mixed melting point determination and by complete agreement in rotatory power (−165.9°). Quinine was also employed for resolution, and the less soluble salt of XXI afforded a *d*-acid with

(6) The authors are indebted to Dr. T. Kawatani of the National Hygienic Laboratory, Tokyo, for *l*-β-santonin.

(7) H. Ishikawa, to be published.

(8) Recently, two papers on this method of hydroxylation at C-6 of Δ^4-3-ketosteroids have appeared; *cf.* R. B. Moffett and G. Slomp, Jr., THIS JOURNAL, **76**, 3678 (1954); J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(9) H. Ishikawa, to be published.



m.p. 213° and another *d*-acid (m.p. 200°) was obtained from the less soluble salt of XX. Decarboxylation of both acids furnished *d*-α-santonin exhibiting $[\alpha]_D$ +165° and m.p. 172°. Accordingly the two lactonic acids XX and XXI are epimeric at C-11.

The successful achievement of the total synthesis of santonin has established not only the hitherto suggested relationships in the configurations of natural santonins and desmotroposantonins,[10] but also the validity of our conformational analysis[4] extended over several stereoisomers and their intermediates.

Acknowledgments.—The authors wish to acknowledge the continued advice and encouragement of Professor Y. Asahina and Dr. S. Kuwada in this work. The authors are also indebted to Dr. T. Matsukawa for his kind arrangement in prosecuting studies and to Mr. Kurabayashi and Mr. Kawamura and his staffs for their great help in preparing materials throughout this work. Also we are grateful to Mr. J. Ishikawa and his collaborators and Mr. T. Okamoto for their aid for supplying several intermediates, to Mr. M. Kan and his associates for performing microanalyses, to Mr. H. Kamio for the determination of ultraviolet and infrared absorption and to Mr. T. Ito for the determination of rotation.

(10) Huang-Minlon, THIS JOURNAL, **70**, 611 (1948); D. H. R. Barton, *J. Org. Chem.*, **15**, 467 (1950); H. Mitsuhashi, *J. Pharm. Soc. Japan*, **71**, 1115 (1951).

Experimental[11]

Ethyl 11-Carbethoxy-3-oxo-eusantona-1,4-dienate (III).—A solution of 30 g. of II in 150 ml. of glacial acetic acid was gently refluxed for half an hour with 10 g. of selenium dioxide dissolved in 10 g. of water. After the selenium which separated was removed and the solvent was distilled under reduced pressure, the residue was diluted with ether. The ethereal solution was washed with sodium carbonate solution and water, dried over anhydrous sodium sulfate and evaporated. On distillation of the residual oil, there was obtained 18 g. of yellow oil contaminated with a small quantity of selenium, b.p. 198–240° (2 mm.). This was redissolved in ether, and the ether solution washed well with 10% potassium hydroxide, dried and evaporated. Distillation gave 10 g. of pale yellow oil (IV), b.p. 203–220° (3 mm.).

The 2,4-dinitrophenylhydrazone was recrystallized from a mixture of benzene and alcohol as red needles, m.p. 190°, λ_{max}^{EtOH} 228 mμ (log *E* 4.20), 256 mμ (log *E* 4.19), 308 mμ (log *E* 3.80), 396 mμ (log *E* 4.48).

Anal. Calcd. for $C_{26}H_{32}O_8N_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.31; H, 6.05; N, 10.38.

11-Carboxy-3-oxo-eusantona-1,4-dienic Acid (IV).—To a solution of 30 g. of III in 250 ml. of methanol was added 50 g. of 50% methanolic potassium hydroxide, and the mixture was boiled under reflux for 5 hours. After cooling, the reaction mixture was diluted with water, washed with ether, and acidified with dilute hydrochloric acid. The oil which separated was extracted with ethyl acetate, and the extract washed with water and concentrated. On cooling the res-

(11) All melting points and boiling points are uncorrected. The ultraviolet absorption spectra were measured with a Beckman model DU spectrophotometer, and the infrared absorption spectra with a Perkin-Elmer model 21 spectrophotometer.

idue there was obtained 21 g. of crystalline material (IV). Recrystallization from dilute methanol gave colorless needles, m.p. 192° dec., λ_{max}^{EtOH} 242 mμ (log E 4.04).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.88; H, 6.95.

3-Oxo-eusantona-1,4-dienic Acid (V, *rac*-Desoxy-α-santoninic Acid) and 3-Oxo-11-*epi*-eusantona-1,4-dienic Acid (VI, *rac*-Desoxy-β-santoninic Acid).—A solution of 15 g. of IV in 50 ml. of γ-collidine was refluxed for 15 minutes. After cooling, the reaction mixture was diluted with ether, and the ethereal solution was washed with hydrochloric acid, then shaken with 10% sodium carbonate solution to extract the product. The aqueous extract was acidified with dilute hydrochloric acid and the separated oil taken into ethyl acetate. The organic layer was washed with water, dried and evaporated. Ice cooling and scratching gave a crystalline product, which was recrystallized from ethyl acetate as colorless prisms (VI), m.p. 147°, λ_{max}^{EtOH} 242 mμ (log E 4.10).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.30; H, 8.21.

The solvent of the mother liquor was removed under reduced pressure, and the resulting oily product amounted to 7 g., λ_{max}^{EtOH} 242 mμ (log E 4.03).

***rac*-α-Santonin (VII) and *rac*-β-Santonin (VIII).**—A solution of 10 g. of decarboxylation product of IV in 160 ml. of acetic acid was boiled under reflux with 5 g. of selenium dioxide in 2 ml. of water. After the selenium was removed, the solvent was distilled under reduced pressure, and the residue was diluted with ether. The ethereal solution was washed with sodium carbonate solution, dried and freed of the solvent. The resulting oil (2 g.) was dissolved in 5 ml. of methanol, and boiled with 5 ml. of 20% potassium hydroxide for 2 minutes. The alkaline solution was diluted with 10 ml. of water, washed with ether and acidified with 3 ml. of 30% hydrochloric acid. The separated oil was extracted with ethyl acetate, and the extract shaken with 10% sodium carbonate solution to divide it into the lactonic and non-lactonic part. The ethyl acetate solution—the lactonic part—was freed of solvent, and the resulting solid material was recrystallized from methanol as colorless rectangular plates (VII), m.p. 181°, λ_{max}^{EtOH} 242 mμ (log E 4.01), yield 0.4 g.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.94; H, 7.26.

The sodium carbonate solution—the non-lactonic part—was acidified with dilute hydrochloric acid, and warmed on a water-bath for a few minutes. The resulting oil was extracted with ethyl acetate, and the extract washed with sodium carbonate solution, dried and concentrated. The residue soon crystallized, and recrystallization from methanol gave colorless prisms (VIII), m.p. 186°, λ_{max}^{EtOH} 242 mμ (log E 4.19), yield 0.6 g.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.84; H, 7.44.

The Dienone-Phenol Rearrangement. (a) Of *rac*-α-Santonin (VII).—To 60 mg. of VII was added 5 ml. of 55% sulfuric acid and the mixture stirred at 50° for 15 hours. The mixture was then diluted with water, and the solid which separated dissolved in 10% sodium hydroxide. The alkaline solution was acidified with hydrochloric acid. The resulting crystalline product IX was recrystallized from methanol as colorless prisms, m.p. 201°, yield 50 mg. This showed no m.p. depression on admixture with an authentic sample of *rac*-α-desmotroposantonin.

(b) Of *rac*-β-Santonin (VIII).—A similar experiment was carried out with 15 mg. of VIII and 3 ml. of 55% sulfuric acid. The product X was recrystallized from methanol as colorless prisms, m.p. 231°, yield 11 mg. The melting point was not depressed by mixing with an authentic sample of *rac*-β-desmotroposantonin.

Resolution of 11-Carboxy-3-oxo-eusantona-1,4-dienic Acid (IV).—A mixture of 37 g. of V and 55 g. of brucine was dissolved in 180 ml. of hot methanol, and the solution was allowed to stand at room temperature for several hours. The resulting solid was recrystallized from methanol as colorless prisms, m.p. 159° dec., $[\alpha]^{18}D$ +15.0° (*c* 0.40 in $CHCl_3$).

Twenty grams of the salt was shaken with 5% sodium hydroxide solution and chloroform, and the alkaline solution was acidified with hydrochloric acid to give 7.3 g. of an acid. This was recrystallized from dilute methanol as colorless prisms, m.p. 196° dec., $[\alpha]^{16}D$ +72.5° (*c* 0.40 in EtOH).[12]

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.57; H, 7.05.

After removal of the less soluble brucine salt, the mother liquor was concentrated, and treated with 5% sodium hydroxide and chloroform. On acidification of the alkaline solution with hydrochloric acid there was obtained 6.8 g. of the *l*-acid.

***d*-α-Santonin and *d*-β-Santonin.**—Fourteen grams of the *d*-acid obtained in the preceding experiment was dissolved in 30 ml. of γ-collidine and decarboxylated in the same way as for the racemic isomer to yield 9 g. of the decarboxylation product. This was dissolved in 80 ml. of acetic acid and treated with 7 g. of selenium dioxide and 3.5 ml. of water in the same manner as for the racemate to yield from easily lactonizing part 0.3 g. of colorless plates, m.p. 172°, $[\alpha]^{17}D$ +156.4° (*c* 1.0 in $CHCl_3$). The melting point raised to 181° when mixed with an authentic sample of natural *l*-α-santonin, and the mixture showed no m.p. depression on admixture with an authentic sample of *rac*-α-santonin.

From the less easily lactonizing part was obtained 0.3 g. of colorless rhombic plates, m.p. 213°, $[\alpha]^{17}D$ +137.9° (*c* 1.1 in $CHCl_3$). The melting point was depressed to 190° by mixing with an authentic sample of natural *l*-β-santonin, and the mixture showed no m.p. depression on admixture with an authentic sample of *rac*-β-santonin.

***l*-α-Santonin and *l*-β-Santonin.**—Seventeen grams of *l*-acid obtained by the resolution of IV was decarboxylated in 50 ml. of γ-collidine to yield 8 g. of an oily product. This was dissolved in 100 ml. of acetic acid, and treated with 7 g. of selenium dioxide and 3.5 ml. of water in the same way as for the racemic isomer. After the easily lactonizing part was freed of solvent, the resulting solid product was recrystallized from methanol to yield 0.1 g. of colorless rectangular plates, m.p. 181°, which showed no m.p. depression on admixture with an authentic sample of *l*-α-santonin. The filtrate was diluted with water to yield another crystalline product. Recrystallization from methanol gave 0.1 g. of colorless plates, m.p. 172°, $[\alpha]^{19}D$ −153.0° (*c* 1.8 in EtOH). The melting point was not depressed by mixing with an authentic sample of natural *l*-α-santonin.

From the less easily lactonizing part was obtained 0.1 g. of colorless plates, m.p. 212°, $[\alpha]^{19}D$ −136.7° (*c* 1.0 in $CHCl_3$). The melting point was not depressed by mixing with an authentic sample of natural *l*-β-santonin.

Ethyl 3-Acetoxy-11-carbethoxy-eusantona-3,5-dienate (XVI).—To a solution of 200 g. of acetic anhydride and 1 g. of concd. sulfuric acid was added 100 g. of ethyl 11-carbethoxy-3-oxo-eusanton-4-enate (II), and the mixture was heated at 55° for 3 hours. The reaction mixture was concentrated *in vacuo*, taken up into ether, and washed with water, 10% sodium bicarbonate solution and water, successively. The solvent was evaporated and the residue, when cooled and digested with ether–petroleum ether, gave 75 g. of a crystalline product. This was recrystallized from methanol as colorless prisms, m.p. 68°, λ_{max}^{EtOH} 238–239 mμ (log E 4.37).

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 67.32; H, 8.22. Found: C, 66.98; H, 8.01.

Lactone of 11-Carbethoxy-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid (XVII).—To a solution of 10 g. of the enolacetate XVI in 100 ml. of 80% formic acid was added 3.15 ml. of 30% hydrogen peroxide, and the mixture was allowed to stand at 20° for 3 hours. The reaction mixture was diluted with water, the separated oil taken up in ether and the ether layer washed successively with water, 10% sodium bicarbonate solution and water. The solvent was evaporated and the residue, cooled and digested with ether–petroleum ether, gave 3.7 g. of a crystalline product. This was recrystallized from methanol as colorless prisms, m.p. 124°, λ_{max}^{EtOH} 243 mμ (log E 4.14).

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 66.94; H, 7.48.

(12) The acid was reported to have m.p. 183° dec., $[\alpha]^{16}D$ −10° in the preliminary paper, but it later proved to be contaminated with the monoenonedicarboxylic acid ($[\alpha]^{28}D$ −106.2°). A pure sample possesses the constants described here.

Lactone of 2-Bromo-11-carbethoxy-6α-hydroxy-3-oxo-11-*epi*-eusanton-4-enic Acid (XVIII).—To a solution of 5.0 g. of the lactone-ester XVII in 200 ml. of ether was added 2.5 g. of bromine and 25 ml. of ether. After decolorization by gentle heating and stirring, the reaction mixture was washed with water, 10% sodium bicarbonate solution and again water, and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and on cooling the residue, 2.3 g. of crystalline material separated. Recrystallization from methanol gave colorless plates, m.p. 126°, λ_{max}^{EtOH} 248 mμ (log *E* 4.07).

Anal. Calcd. for $C_{15}H_{23}O_5Br$: C, 54.14; H, 5.81. Found: C, 54.01; H, 5.78.

From the mother liquors of the bromolactone-ester, 3.0 g. of yellow oil was obtained, λ_{max}^{EtOH} 248 mμ (log *E* 3.96).

Lactone of 11-Carbethoxy-6α-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic Acid (XIX).—A mixture of 2.2 g. of the crystalline bromolactone-ester (XVIII) and 20 ml. of γ-collidine was refluxed gently for 25 minutes. After dilution with ether, the mixture was washed with water, freed of collidine with dilute sulfuric acid and water, dried over anhydrous sodium sulfate and evaporated. On cooling the residue, 0.8 g. of a crystalline product separated. Recrystallization from methanol gave colorless prisms, m.p. 129°, λ_{max}^{EtOH} 241 mμ (log *E* 4.10).

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.61; H, 7.16.

The oily bromolactone-ester was treated with collidine to give the same crystalline product melting at 129°. This showed no m.p. depression on admixture with an authentic sample of the dienonelactone-ester XIX.

Lactone of 11-Carboxy-6α-hydroxy-3-oxo-eusantona-1,4-dienic Acid (XXI, *rac*-11-Carboxy-α-santonin) and Lactone of 11-Carboxy-6α-hydroxy-3-oxo-11-*epi*-eusantona-1,4-dienic Acid (XX, *rac*-11-Carboxy-β-santonin).—Twenty grams of 11-carbethoxy-santonin (XIX) was refluxed on a water-bath for 2 hours with 20 g. of potassium hydroxide and 180 g. of methanol. On cooling the mixture, 21 g. of a crystalline product separated. Recrystallization from methanol gave colorless prisms.

Anal. Calcd. for $C_{16}H_{18}O_6K_2 \cdot 1.5\,H_2O$: C, 46.70; H, 5.15; K, 18.98. Found: C, 46.64; H, 5.01; K, 18.75.

Twenty grams of the potassium salt of 11-carboxysantoninic acid described above was dissolved in 100 ml. of water and then acidified with hydrochloric acid. The product melting at 135–140° dec. amounted to 13.0 g. and fractional recrystallization from dilute methanol gave two kinds of colorless needles, m.p. 210° dec., λ_{max}^{EtOH} 241 mμ (log *E* 4.17), and m.p. 185° dec., λ_{max}^{EtOH} 241 mμ (log *E* 4.19).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.48; H, 6.55. Calcd. for $C_{15}H_{18}O_5 \cdot H_2O$: C, 62.32; H, 6.54. Found: C, 62.05; H, 6.47.

***rac*-α-Santonin.** (a) **From *rac*-11-Carboxy-santonin with M.p. 185° dec.**—A mixture of 3.9 g. of *rac*-11-carboxy-santonin and 3 ml. of γ-collidine was refluxed gently for 5 minutes. On cooling the solution, and diluting with ether-petroleum ether, 2.8 g. of a crystalline product separated. Recrystallization from methanol gave colorless plates, m.p. 181°, λ_{max}^{EtOH} 241 mμ (log *E* 4.10).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 73.14; H, 7.37. Found: C, 72.94; H, 7.26.

(b) **From *rac*-11-Carboxy-santonin with M.p. 210° dec.**—A mixture of 5.2 g. of dienone-lactonic acid and 2.5 ml. of γ-collidine was worked up as described above. The product thus obtained amounted to 3.9 g., and the m.p. was undepressed on admixture with the product obtained in (a).

Resolution of 11-Carboxy-santonin (XX and XXI). (−)-11-Carboxy-santonin.—A mixture of 12.3 g. of dienone-lactonic acid (m.p. 210° dec.) and 20.5 g. of brucine was dissolved in 30 ml. of methanol. On cooling the solution, crystals were collected and fractional recrystallization from methanol gave 10.5 g. of tetragonal plates, m.p. 134–138° dec., $[\alpha]_D^{20}$ −9.8° (*c* 0.91 in EtOH).

The salt was shaken with 10% potassium hydroxide and ether to complete decomposition, and then 10% hydrochloric acid added and shaken again. The ether layer was washed with water and extracted with sodium carbonate solution. The alkaline solution was acidified with hydrochloric acid to afford 4.0 g. of (−)-11-carboxy-santonin, m.p. 213° dec., λ_{max}^{EtOH} 241 mμ (log *E* 4.10), $[\alpha]_D^{18}$ −75.1° (*c* 1.01 in EtOH).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.25; H, 6.15.

(+)-11-Carboxy-santonin. (a) **From 11-Carboxy-santonin with M.p. 185° dec.**—A mixture of 8.5 g. of the dienone-lactonic acid XXI and 9.2 g. of quinine was dissolved in 10 ml. of methanol. Dilution with ether and filtration afforded 4.5 g. of a crystalline product, and this was recrystallized from methanol as colorless needles, m.p. 182° dec., $[\alpha]_D^{18}$ −57.7° (*c* 0.61 in EtOH).

Anal. Calcd. for $C_{36}H_{42}O_7N_2$: C, 70.34; H, 6.89; N, 4.56. Found: C, 69.76; H, 6.75; N, 4.42.

Three grams of the salt was shaken with 10% potassium hydroxide and ether. The alkaline solution was then acidified with hydrochloric acid and 1.1 g. of (+)-11-carboxy-santonin was obtained. This was recrystallized from methanol as colorless needles, m.p. 213° dec., λ_{max}^{EtOH} 241 mμ (log *E* 4.10), $[\alpha]_D^{18}$ +75.4° (*c* 1.03 in EtOH).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 65.82; H, 6.23.

(b) **From 11-Carboxy-santonin with M.p. 210° dec.**—A mixture of 6.0 g. of the dienone-lactonic acid XX and 6.5 g. of quinine was dissolved in 50 ml. of methanol. Four grams of a crystalline product separated and recrystallization from methanol gave colorless needles, m.p. 170° dec., $[\alpha]_D^{18}$ −41.6° (*c* 0.32 in EtOH).

Anal. Calcd. for $C_{36}H_{42}O_7N_2 \cdot H_2O$: C, 68.33; H, 7.01; N, 4.43. Found: C, 68.33; H, 7.16; N, 4.29.

Two grams of the salt was shaken with 10% potassium hydroxide solution and the alkaline solution was treated as described in part a. The product was recrystallized from methanol as colorless needles, m.p. 200° dec., λ_{max}^{EtOH} 241 mμ (log *E* 4.01), $[\alpha]_D^{20}$ +140.7° (*c* 1.03 in EtOH).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 65.90; H, 6.01.

***l*-α-Santonin.**—A mixture of 4.0 g. of (−)-11-carboxy-santonin and 2.0 ml. of γ-collidine was refluxed gently for 5 minutes. Dilution with ether and filtration afforded 2.8 g. of a crystalline product. Recrystallization from methanol gave colorless plates, m.p. 172°, λ_{max}^{EtOH} 241 mμ (log *E* 4.14), $[\alpha]_D^{20}$ −165.9° (*c* 1.92 in EtOH).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.44; H, 7.12.

This showed no m.p. depression on admixture with an authentic sample of natural *l*-α-santonin, and both exhibited the same infrared spectrum.

***d*-α-Santonin.** (a) **From (+)-11-Carboxy-santonin with M.p. 213° dec.**—A mixture of 1.1 g. of (+)-11-carboxy-santonin and 0.5 ml. of γ-collidine was refluxed gently for 5 minutes. After the mixture was diluted with ether and cooled, 0.6 g. of a crystalline product separated. Recrystallization from methanol gave colorless plates, m.p. 172°, λ_{max}^{EtOH} 241 mμ (log *E* 4.14), $[\alpha]_D^{20}$ +165.0° (*c* 1.03 in EtOH).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.29; H, 7.44.

(b) **From (+)-11-Carboxy-santonin with M.p. 200° dec.**—A mixture of 1.0 g. of (+)-11-carboxy-santonin and 1.0 g. of γ-collidine was refluxed and worked up as described in part a. There was obtained 0.8 g. of *d*-α-santonin, which was recrystallized from methanol as colorless plates, m.p. 172°. The melting point was not depressed by mixing with an authentic sample obtained in part a.

OSAKA, JAPAN