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Santonin. I.[1] The Synthesis of Two Optically Inactive Stereoisomerides of Santonin[2]

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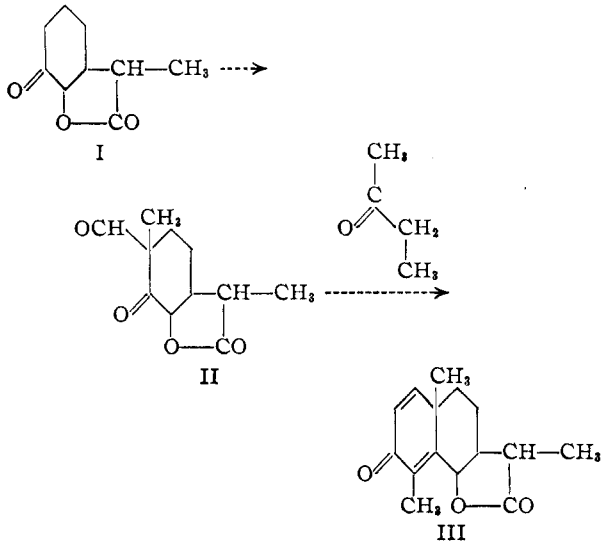
The synthesis of two optically inactive stereoisomerides of santonin starting from α-(3-ketocyclohexyl)-propionic acid has been described. These two isomers proved to differ at least in the configuration at C-11. The structure of santonin proposed by Clemo, *et al.*, has been confirmed synthetically.

More than twenty years ago Clemo, Haworth and Walton[3] showed that santonin was to be represented by the formula III, on the basis of the synthesis of racemic desmotroposantonin. The correctness of this formula was further confirmed by the experiments of Clemo and Haworth,[4] Ruzicka and Eichenberger[5] and Ruzicka and Steiner.[6]

Since then little has been reported on the synthesis of santonin, although many investigations have been developed in the fields of lactones. This may be ascribed to the difficulty in realizing both a lactone and a dienone structure with an angular methyl group in a molecule containing only two rings. In 1943 Paranjape, Phalnikar, Bhide and Nargund[7] claimed that they successfully effected the synthesis of an optically active santonin identical with natural santonin without using any optically active reagents. This synthesis has been severely criticized by several research groups.[8]



Earlier works[9,10] in this Laboratory also had confirmed the results obtained by Clemo, *et al.*, and Wilds and Djerassi, and consequently the synthesis cited appears to be very doubtful. Banerjea's attempt[11] to synthesize santonin seems not to have been completed.

The present paper records a useful method for the synthesis of stereoisomerides of santonin. In the hope that the lactone II of α-(2-hydroxy-3-keto-4-methyl-4-formylcyclohexyl)-propionic acid would condense, as described by Paranjape, *et al.*,[7] with methyl ethyl ketone to give a compound III with the santonin structure, we first prepared the lactone[10,12,13] I of α-(2-hydroxy-3-ketocyclohexyl)-propionic acid in ways fundamentally different from that of the Indian workers. But failure of all attempts to formulate this keto-lactone I suggested that it would be difficult to obtain santonin by the condensation of the two substances, *viz.*, II and methyl ethyl ketone. We, therefore, turned our attention to a more favorable process involving the construction of ring A which can easily be transformed into the dienone prior to the lactone formation at ring B. Robinson, *et al.*,[14] synthesized α-cyperone (VI) by the condensation of L-dihydrocarvone (V) with 1-diethylaminopentan-3-one methiodide (IV). We planned to prepare a similar cyclenone as the key intermediate by applying the said method to a methylcyclohexanone with a side-chain readily convertible to propionic acid, instead of an isopropenyl group as in Robinson's case.

The substituted methylcyclohexanone X was derived from α-(3-ketocyclohexyl)-propionic acid[15] (VII). By the action of methanol containing 7% of hydrogen chloride the acid VII led to its methyl ester VIII, which was condensed with ethyl formate in the presence of powdered sodium to yield the 4-hydroxymethylene derivative IX,[16] characterized

(1) This is Part X of "Studies on Anthelmintics."

(2) The preliminary announcement of this work was made at the General Meeting of the Japan Academy, October 13, 1952.

(3) G. R. Clemo, R. D. Haworth and E. Walton, *J. Chem. Soc.*, 1110 (1930).

(4) G. R. Clemo and R. D. Haworth, *ibid.*, 2579 (1930).

(5) L. Ruzicka and E. Eichenberger, *Helv. Chim. Acta*, **13**, 1117 (1930).

(6) L. Ruzicka and A. Steiner, *ibid.*, **17**, 614 (1934).

(7) K. Paranjape, N. L. Phalnikar, B. V. Bhide and K. S. Nargund, *Rasayanam*, **1**, 233 (1943); *C. A.*, **38**, 4266 (1944); *Nature*, **153**, 141 (1944).

(8) J. W. Cornforth, R. H. Cornforth and M. J. S. Dewar, *ibid.*, **153**, 317 (1944); J. M. O'Gorman, THIS JOURNAL, **66**, 1041 (1944); G. R. Clemo, W. Cocker and S. Hornsby, *J. Chem. Soc.*, 616 (1946); A. L. Wilds and Carl Djerassi, THIS JOURNAL, **68**, 1715 (1946); R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950).

(9) Y. Abe, T. Harukawa and T. Toga, *J. Pharm. Soc. Japan*, **71**, 474 (1951).

(10) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *ibid.*, **72**, 418 (1952); also see, for example, Japanese Patent 192,589.

(11) P. Banerjea, *Science and Culture*, **13**, 347 (1948); *C. A.*, **42**, 5890 (1948).

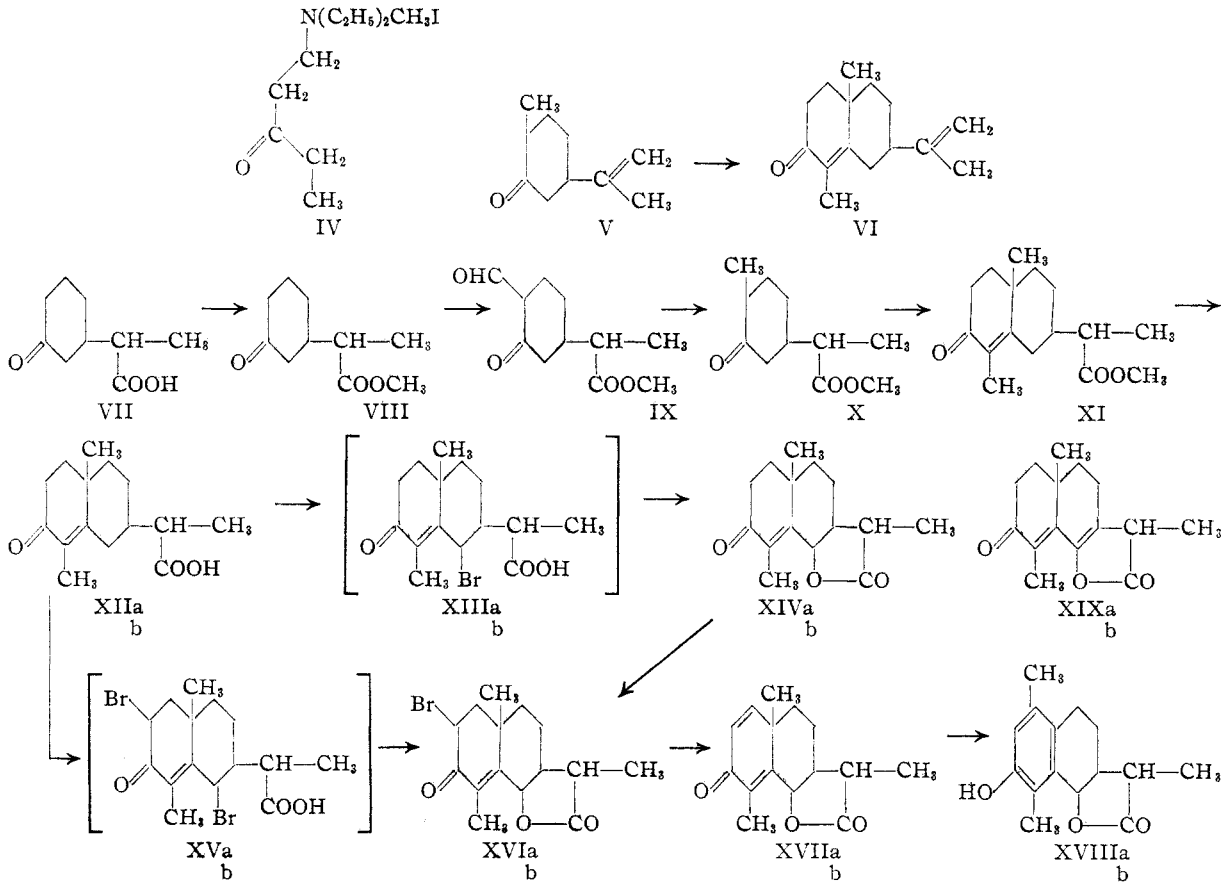
(12) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki and M. Sumi, *J. Pharm. Soc. Japan*, in press; also see, for example, Japanese Patent 192,592.

(13) After this work had been completed, F. D. Gunstone and R. M. Heggie reported that they independently prepared the same keto-lactone in almost the same way as ours. See *J. Chem. Soc.*, 1354 (1952).

(14) P. S. Adamson, F. C. McQuillin, R. Robinson and J. L. Simonsen, *J. Chem. Soc.*, 1576 (1937).

(15) The preparation of this material is described in Part VIII. See ref. 12.

(16) The hydroxymethylene group was shown to be introduced into C-4 by a sequence of reactions described in Part IX. T. Harukawa, *J. Pharm. Soc. Japan*, in press.



as the anilide. Catalytic reduction of the hydroxymethylene compound IX over palladium-on-carbon afforded the desired methyl α-(3-keto-4-methylcyclohexyl)-propionate (X). This substance was also prepared from the original hydroxymethylene ketone IX by C-methylation and subsequent hydrolysis with loss of the formyl group as reported in Part IX[16] of this series. The products have been found to be identical by comparison of their oximes.

Methyl α-(3-keto-4-methylcyclohexyl)-propionate (X) thus obtained was condensed with 1-diethylaminopentan-3-one methiodide by the aid of sodamide in ether, and the oily intermediate was, without purification, further subjected to cyclization in the presence of sodium methylate in benzene to afford methyl α-(3-keto-4,9-dimethyl-1,2,3,5,6,-7,8,9-octahydronaphthyl-6)-propionate (XI). The yield was fairly improved by conducting the reaction in one step with the use of sodium methylate as a condensing agent. The ultraviolet spectrum of the resulting compound possessed an absorption maximum at 250 mμ in good agreement with the value for α-cyperone[17] (VI) and those expected for α,β,β-substituted α,β-unsaturated ketones.[18,19]

(17) A. E. Bradfield, B. J. Hedge, B. Sanjiva Rao, J. L. Simonsen and A. E. Gillam, *J. Chem. Soc.*, 667 (1936).

(18) R. B. Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 72 (1942); L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 815 (1941).

(19) Recently F. D. Gunstone and R. M. Heggie announced the preparation of 2-keto-1,10-dimethyl-2,5,6,7,8,10-hexahydronaphthalene, of which the absorption spectrum showed a maximum at 248 mμ in ethanol and its 2,4-dinitrophenylhydrazone showed absorption maxima at 260 and 394 mμ in chloroform. See *J. Chem. Soc.*, 1437 (1952). *Cf.* also ref. 13.

The ester XI was saponified by heating with methanolic potassium hydroxide to give a mixture of stereoisomeric acids XII, from which two of the four possible racemic modifications were isolated in crystalline forms. One, m.p. 181°, less soluble in ether, has been temporarily named A-acid[20] and the other, m.p. 125°, more soluble in ether, B-acid.[20] Both exhibited essentially the same ultraviolet absorption curve with a maximum at 250 mμ.

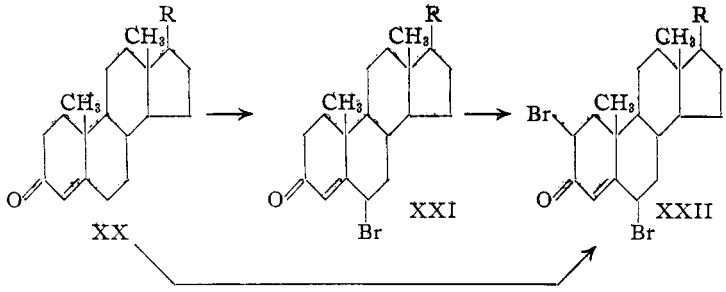
It is reported[21,22] that monobromination of Δ^4-3-ketosteroids XX according to the Wohl-Ziegler procedure leads to the 6-bromo derivatives XXI. When α-(3-keto-4,9-dimethyl-1,2,3,5,6,7,8,-9-octahydronaphthyl-6)-propionic acid A (XIIa) was heated with one mole of N-bromosuccinimide in carbon tetrachloride, a bromine-free, neutral compound was produced and this was assigned the structure XIVa, *viz.*, the lactone of α-(3-keto-4,9-dimethyl - 5 - hydroxyl - 1,2,3,5,6,7,8,9 - octahydronaphthyl-6)-propionic acid A, on the basis of analysis and behavior toward alkali. This transformation undoubtedly involved the intermediate formation of the 5-bromo derivative XIIIa and subsequent lactonization with loss of hydrogen bromide leading to XIVa.

On treating with one mole of bromine in ether–

(20) To the names of compounds derived from A-acid and B-acid are suffixed the letters A and B, respectively; for example, santonin A and santonin B.

(21) H. H. Inhoffen, G. Stoeck and H. Martens, *Ann.*, **563**, 133 (1949).

(22) Carl Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4536 (1950).

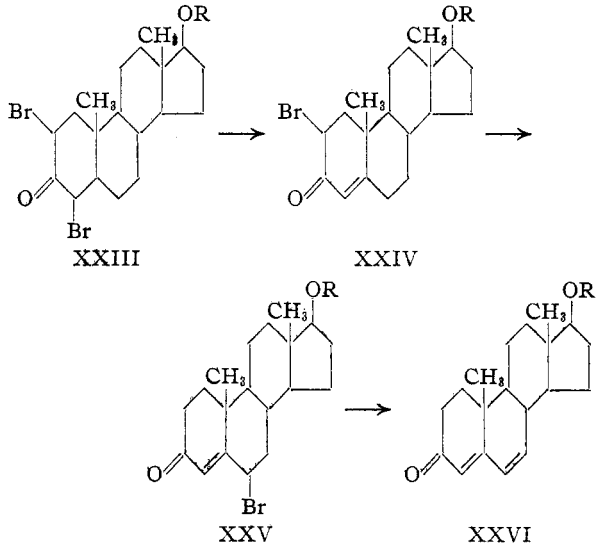


acetic acid, XIVa afforded the lactone of α-(3-keto-4,9-dimethyl-2-bromo-5-hydroxy-1,2,3,5,6,7,8-9-octahydronaphthyl-6)-propionic acid A (XVIa).

In the steroid series dibromination[22,23] of Δ^4-3-ketosteroids XX in ether–acetic acid leads to 2,6-dibromo-Δ^4-3-ketosteroids (XXII). Hence dibromination of A-acid XIIa was also anticipated to introduce bromine into C-2 and C-5, followed by lactonization with loss of hydrogen bromide analogous to the formation of XIVa from XIIa. This proved to be in fact the case, and when treated with two moles of bromine in ether–acetic acid, A-acid directly furnished the same bromolactone XVIa as obtained by monobromination of XIVa.

By heating with γ-collidine the bromolactone XVIa was smoothly dehydrobrominated to yield a racemic stereoisomeride XVIIa of santonin, which was named santonin A. This material showed an absorption curve having a maximum at 243 mμ with a characteristic shoulder around 270 mμ, in close resemblance with that of natural α-santonin. From the collidine dehydrobromination product of XVIa a small amount of another crystalline substance was isolated, to which was tentatively assigned the lactone of α-(3-keto-4,9-dimethyl - 1,2,3,7,8,9 - hexahydronaphthyl - 6) - propionic acid A structure XIX, although it exhibited the ultraviolet absorption maximum at 270 mμ, a little shorter than the values for the corresponding steroidal compounds.[24–26] It is not surprising that such an extended dienone could be produced, for Inhoffen and Zühlsdorff[25] had previously obtained the Δ^6-dehydrotestosterone ester (XXVI) as a by-product on collidine dehydrobromination of 2,4-dibromoandrostanolone ester (XXIII) and they considered that this conversion proceeded *via* the Δ^4-2-bromotestosterone ester (XXIV) and the 6-bromo isomer XXV resulting from bromine migration. Some other examples[26] are found in the literature. Also in our case an analogous migration of a bromine atom from C-2 to C-5 seems to have occurred in part and subsequent dehydrobromination resulted in the introduction of a double bond between C-5 and C-6. It was also shown that dimethylamine could be used for the dehydrobromination of the bromolactone XVIa in the place of γ-collidine, but the yield of *rac*-santonin A was remarkably low.

When heated at 50° with 55% sulfuric acid, santonin A (XVIIa), in analogy with natural santonin, readily underwent the dienone–phenol rearrangement to racemic α-desmotroposantonin (XVIIIa)[3,27] which was confirmed by direct comparison with an authentic sample derived from natural santonin. This furnished an irrefutable evidence to the structure of santonin A.



B-Acid XIIb was subjected to the same reaction sequence as that for A-acid and led to another racemic stereoisomeride (santonin B) of santonin *via* the steps XIIb → XVIb → XVIIb, although in low yield. The absorption spectrum of santonin B bears a striking resemblance to that of santonin A, but the dienone–phenol rearrangement product of the former was found to be racemic β-desmotroposantonin (XVIIIb).[28] Since it has been shown[29] that racemic α- and β-desmotroposantonin are epimeric at C-11, also santonin A and B undoubtedly differ, at least, in configuration at C-11. From the dehydrobromination product of XVIb, a second crystalline material was obtained, and to this was assigned, just as in the case of the A-series, the extended dienone structure (XIXb) on the basis of analysis and the ultraviolet absorption spectrum.

Thus the structure III of santonin proposed by Clemo, *et al.*, was synthetically verified through this work. As for the preparation of optically active stereoisomerides we shall report in the near future.

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 Mr. J. Ishikawa, Mr. T. Okamoto and Mr. K. Yamamoto and his collaborators for their aid in

(23) G. Rosenkranz, Carl Djerassi, St. Kaufmann, J. Pataki and J. Romo, *Nature*, **165**, 814 (1950); R. Yashin, G. Rosenkranz and Carl Djerassi, THIS JOURNAL, **73**, 4654 (1951); H. H. Inhoffen, *Angew. Chem.*, **63**, 300 (1951).

(24) L. Ruzicka and W. Bosshard, *Helv. Chim. Acta*, **20**, 328 (1937); A. Wettstein, *ibid.*, **23**, 388 (1940). Gunstone and Heggie also obtained a compound with a similar structure, *viz.*, 2-keto-1,10-dimethyl-2,3,4,5,6,10-hexahydronaphthalene, λ_{max} 286 mμ; *cf.* ref. 19.

(25) H. H. Inhoffen and G. Zühlsdorff, *Ber.*, **72**, 233 (1943).

(26) A. L. Wilds and Carl Djerassi, THIS JOURNAL, **68**, 1712, 2125 (1946).

(27) A. Andreocci and P. Bertolo, *Ber.*, **31**, 3131 (1893).

(28) Huang-Minlon, Lo and Chu, THIS JOURNAL, **65**, 1780 (1943).

(29) Huang-Minlon, *ibid.*, **70**, 611 (1948); D. H. R. Barton, *J. Org. Chem.*, **15**, 466 (1950); H. Mitsuhashi, *J. Pharm. Soc. Japan*, **71**, 1115 (1951).

preparing intermediates, to Mr. M. Kan, Miss F. Suzuki and Miss Y. Kobayashi for performing the microanalyses, to Mr. H. Kamio for the determination of ultraviolet absorption and to Mr. T. Ito for the determination of X-ray diffractions.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

Substance	λ_{max}^{MeOH}	log E	λ_{min}^{MeOH}	log E
Condensation product (XI) of the Robinson reaction	250	4.05		
A-Acid (XIIa)	250	4.11		
B-Acid (XIIb)	250	4.16		
Natural santonin	241	4.10		
rac-Santonin A (XVIIa)	243	4.27		
rac-Santonin B (XVIIb)	245	4.01		
Extended dienone A (XIXa)	270	4.31		
Extended dienone B (XIXb)	268	4.24		
L-α-Desmotroposantonin	290	3.45	252	2.17
rac-α-Desmotroposantonin (synthetic)	290	3.46	253	2.39
rac-β-Desmotroposantonin (synthetic)	290	3.33	251	1.84

Experimental[30]

Methyl α-(3-Ketocyclohexyl)-propionate (VIII).—A solution of 125 g. of α-(3-ketocyclohexyl)-propionic acid (VII), b.p. 170° (12 mm.), in 700 ml. of 7% methanolic hydrogen chloride was allowed to stand at room temperature overnight. After the methanol was removed under diminished pressure, ether was added to the residue, and the resulting solution was washed with water and dilute sodium carbonate, dried over anhydrous sodium sulfate. Distillation gave 105 g. of pale yellow oil, b.p. 119–124° (3 mm.).

The semicarbazone was recrystallized from methanol as colorless prisms, m.p. 172°.

Anal. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.77; H, 7.87; N, 17.40. Found: C, 54.90; H, 8.18; N, 17.20.

Methyl α-(3-Keto-4-hydroxymethylenecyclohexyl)-propionate (IX).—To a cooled (ice-bath) and stirred suspension of 11.5 g. of powdered sodium in 300 ml. of benzene were added 185 g. of ethyl formate over a period of 2 hours and 92 g. of VIII after a 30-minute interval. The mixture was kept at room temperature overnight, and poured into ice-water. The aqueous layer was separated, and the benzene solution washed thoroughly with dilute sodium hydroxide. All of the aqueous solutions were combined, washed once with ether, and acidified with dilute hydrochloric acid. The resulting oily suspension was extracted with ether, and the extract dried over anhydrous sodium sulfate. On distillation was obtained 60 g. of yellow oil, b.p. 148–151° (3 mm.).

The anilide was recrystallized from methanol as pale yellow needles, m.p. 141°.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.12; H, 7.89; N, 4.89.

Methyl α-(3-Keto-4-methylcyclohexyl)-propionate (X).—A solution of 4.2 g. of IX in 40 ml. of methanol was shaken with 1 g. of 10% palladium-on-carbon in a hydrogen stream, and 1000 ml. of hydrogen (20°, 1 atm.) was absorbed immediately. After the solvent and catalyst were removed, the residue was distilled at a reduced pressure, and 3 g. of colorless oil was obtained, b.p. 150–155° (16 mm.).

The oxime was recrystallized from methanol as colorless prisms, m.p. 126°.

Anal. Calcd. for $C_{11}H_{19}O_3N$: C, 61.94; H, 8.98; N, 6.57. Found: C, 62.01; H, 9.09; N, 6.47.

Methyl α-(3-Keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydronaphthyl-6)-propionate (XI). Method a.—A mixture of 79.2 g. of methyl α-(3-keto-4-methylcyclohexyl)-propionate (X), 18 g. of powdered sodamide and 600 ml. of ether was refluxed for 4 hours in a nitrogen stream. Then a solution of 119.6 g. of 1-diethylaminopentan-3-one methiodide in 100 ml. of dry pyridine was added dropwise with stirring. After 3 hours, 9.2 g. of sodium dissolved in 300 ml. of anhydrous methanol was added dropwise over a period of 3 hours below 0°, the mixture was kept at room temperature overnight and the reaction was completed by refluxing for 3 hours. Water was then added and the oil taken up in ether. The extract was dried over anhydrous sodium sulfate and evaporated. On distillation of the residue, X was first recovered and 10 g. of yellow oil (XI) was obtained, b.p. 170–185° (3 mm.). The pure oil showed an absorption maximum at 250 mμ (log E 4.05).

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.54; H, 9.16.

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate as red needles, m.p. 185°, λ_{max} 258 mμ (log E 4.25) and 388 mμ (log E 4.45).

Anal. Calcd. for $C_{22}H_{28}O_6N_4$: C, 59.46; H, 6.34. Found: C, 59.63; H, 6.57.

Method b.—To a methiodide prepared from 160 g. of 1-diethylaminopentan-3-one and 150 g. of methyl iodide a solution of 205 g. of methyl α-(3-keto-4-methylcyclohexyl)-propionate (X) in 500 ml. of dry benzene and then 24 g. of sodium dissolved in 500 ml. of anhydrous methanol were added dropwise with stirring and cooling at 0°. After standing overnight at room temperature, the mixture was refluxed for 1.5 hours with stirring. The cooled solution was diluted with ether, 60 g. of glacial acetic acid added and the organic solvent was removed under reduced pressure. The resulting oily product was extracted with ether, and the extract was washed with water, sodium carbonate solution, again with water, and dried over anhydrous sodium sulfate. The ether was evaporated, and distillation of the residue gave 105 g. of yellow oil (XI), b.p. 176–190° (5 mm.), together with 50 g. of recovered X.

α-(3-Keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydronaphthyl-6)-propionic Acid (XII).—One hundred and sixty-five grams of the ester XI was boiled under reflux for 3 hours with 180 g. of potassium hydroxide and 1500 ml. of methanol. After cooling, the mixture was acidified with glacial acetic acid and the solvent was removed under reduced pressure. The residue was diluted with water, the separating oil taken up in ether and the ether layer extracted with sodium carbonate solution. The alkaline solution was then acidified with hydrochloric acid, extracted with ether, and the extract was washed with water, dried over anhydrous sodium sulfate and evaporated. On cooling the residue, 33 g. of crystalline material (XIIa) separated. Recrystallization from ethyl acetate gave colorless prisms, m.p. 181°, λ_{max} 250 mμ (log E 4.11).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.68; H, 8.98.

From the mother liquors of XIIa, 24.6 g. of a second crystalline product XIIb was obtained and this was recrystallized from petroleum ether as colorless prisms, m.p. 125°, λ_{max} 250 mμ (log E 4.16).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.72; H, 9.08.

Lactones of α-(3-Keto-4,9-dimethyl-5-hydroxy-1,2,3,5,-6,7,8,9-octahydronaphthyl-6)-propionic Acid A and B (XIV). (a) A-Isomer.—A mixture of 2.1 g. of A-acid (XIIa), 1.7 g. of N-bromosuccinimide and 300 ml. of dry carbon tetrachloride was refluxed under illumination for 2 hours. After cooling, the succinimide was filtered off, and the filtrate washed with sodium bicarbonate and water. The solvent was removed quickly under reduced pressure and the residue, cooled and digested with ether–petroleum ether, gave 1.0 g. of crystalline product. This was recrystallized from dilute methanol as colorless prisms, m.p. 87°, λ_{max} 248 mμ (log E 4.02).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.78; H, 8.14.

This material is insoluble in cold alkali, but soluble in hot, and the alkaline solution reproduces the initial compound on acidification.

(b) B-Isomer (XIVb).—This isomer was prepared as described above for the A-isomer. From 4.0 g. of B-acid (XIIb) and 3.0 g. of N-bromosuccinimide in 400 ml. of carbon tetrachloride there was obtained 0.5 g. of the crude

(30) All melting points and boiling points are uncorrected. All absorption spectra were measured in methanol, using a Beckman quartz spectrophotometer.

B-isomer. Recrystallization from methanol afforded colorless plates, m.p. 115°, λ_{max} 245 mμ (log E 4.03).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.49; H, 7.90.

Lactone of α-(3-Keto-4,9-dimethyl-2-bromo-5-hydroxy-1,2,3,5,6,7,8,9-octahydronaphthyl-6)-propionic Acid A (XVIa). (a) **By Monobromination of XIVa.**—To a solution of 1.2 g. of XIVa in 100 ml. of dry ether containing 3 drops of hydrogen bromide–acetic acid was added a few drops of a solution consisting of 0.8 g. of bromine and 10 ml. of glacial acetic acid. After decolorization by gentle heating, the remainder of the bromine was added dropwise. The solvent was then removed under reduced pressure and the residue poured into water. Filtration gave 0.4 g. of the crude product. This was recrystallized from methanol as colorless plates, m.p. 107° dec., λ_{max} 251 mμ (log E 4.00).

Anal. Calcd. for $C_{15}H_{19}O_3Br$: C, 55.05; H, 5.86. Found: C, 55.05; H, 6.14.

An additional 0.1 g. of the same product was obtained from the ether extract of the above filtrate.

(b) **By Dibromination of A-Acid (XIIa).**—A solution of 1.0 g. of XIIa in 80 ml. of dry ether was treated with 1.2 g. of bromine in 12 ml. of glacial acetic acid as described above and the crude product amounted to 1.0 g. Recrystallization from methanol gave colorless plates, m.p. 107° dec., undepressed on admixture with the product obtained in part (a).

Lactone of α-(3-Keto-4,9-dimethyl-2-bromo-5-hydroxy-1,2,3,5,6,7,8,9-octahydronaphthyl-6)-propionic Acid B (XVIb).—This was prepared as described in the preceding experiment for the A-isomer (XVIa). From 3.7 g. of B-acid (XIIb) in 130 ml. of dry ether and 4.7 g. of bromine in 56 ml. of glacial acetic acid there was obtained 2.3 g. of XVIb. This was recrystallized from methanol to colorless prisms, m.p. 117° dec., λ_{max} 248 mμ (log E 3.89).

Anal. Calcd. for $C_{15}H_{19}O_3Br$: C, 55.05; H, 5.86. Found: C, 55.30; H, 6.12.

***rac*-Santonin A (XVIIa).** (a) **By Collidine Dehydrobromination.**—A mixture of 4.0 g. of the bromolactone XVIa and 25 ml. of γ-collidine was refluxed gently for 15 minutes in a current of nitrogen. Dilution with ether and filtration afforded 95% of the theoretical amount of collidine hydrobromide. The ether filtrate was washed free of collidine with dilute sulfuric acid and water, dried over anhydrous sodium sulfate and evaporated. After removing some red crystals, not further characterized in this investigation, 1.7 g. of santonin A (XVIIa) was obtained, and this was recrystallized from methanol as colorless prisms, m.p. 145–146°, λ_{max} 243 mμ (log E 4.27).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.98; H, 7.41.

After santonin A was separated, 0.4 g. of another crystalline material (XIXa) was obtained from the mother liquors. Repeated recrystallization from methanol gave pale yellow leaflets, m.p. 189°, λ_{max} 270 mμ (log E 4.31).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.46; H, 7.23.

(b) **By Dimethylamine Dehydrobromination.**—A solution of 1.0 g. of the bromolactone XVIa in 10 ml. of benzene was added to a solution of 2.0 g. of dimethylamine in 30 ml. of dry benzene. The mixture was stoppered and allowed to stand for a fortnight at 37–38°. After filtering to remove dimethylamine hydrobromide, the solvent was removed under reduced pressure. The residue was taken up in ether and the ether solution was washed with water, dried over anhydrous sodium sulfate, and evaporated. On cooling the residue, *ca.* 0.2 g. of crystalline material separated. Recrystallization from methanol gave colorless prisms, m.p. 145–146°, undepressed on admixture with the product obtained in part (a).

***rac*-Santonin B (XVIIb).**—A mixture of 4.0 g. of the bromolactone XVIb and 20 ml. of collidine was refluxed and worked up as described above for the A-isomer. After removing a red crystalline material, not further examined, there was obtained 0.2 g. of santonin B (XVIIb), which was recrystallized from methanol as colorless prisms, m.p. 139°, λ_{max} 245 mμ (log E 4.01).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.26; H, 7.29.

From the mother liquors of santonin B, 0.1 g. of another product (XIXb) was isolated. Recrystallization from methanol gave pale yellow needles, m.p. 192°, λ_{max} 268 mμ (log E 4.24).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.56; H, 7.34.

The Dienone–Phenol Rearrangement. (a) **Of *rac*-Santonin A (XVIIa).**—According to Andreocci and Bertolo,[27] 300 mg. of powdered *rac*-santonin A was added to 10 g. of cold 55% sulfuric acid and stirred at 50–53° for 20 hours. The mixture was diluted with water and filtered, the resulting solid substance was dissolved in 5% aqueous sodium hydroxide, washed with ether and the alkaline solution acidified. The product amounted to 285 mg. and recrystallization from methanol gave long colorless prisms, m.p. 201°, λ_{min} 253 mμ (log E 2.39) and λ_{max} 290 mμ (log E 3.46).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.08; H, 7.65.

This showed no m.p. depression on admixture with an authentic sample of *rac*-α-desmotroposantonin derived from natural santonin, and both exhibited the same X-ray powder diffraction diagram, as follows: *rac*-α-desmotroposantonin (synthetic), 10.67 (3),[31] 9.40 (2), 7.57 (3), 6.41, 5.56 (5), 4.60 (4), 4.20 (3), 3.97 (4), 3.75 (4), 3.52 (2), 3.26, 3.06 (1): *rac*-α-desmotroposantonin (natural), 10.65 (3), 9.42 (2), 7.57 (3), 6.41, 5.57 (5), 4.60 (4), 4.22 (3), 4.00 (4), 3.76 (4), 3.52 (2), 3.27, 3.08 (1).

(b) **Of *rac*-Santonin B (XVIIb).**—A similar experiment was carried out with 100 mg. of *rac*-santonin B and 3 g. of 55% sulfuric acid. The product was recrystallized from methanol as long colorless prisms; yield 80 mg., m.p. 231°, λ_{min} 251 mμ (log E 1.84) and λ_{max} 290 mμ (log E 3.33).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.26; H, 7.53.

The melting point was not depressed by mixing with an authentic sample of *rac*-β-desmotroposantonin derived from natural santonin.

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(31) The figures in the parentheses show approximately relative intensity, 5 being the strongest.