solid was filtered, washed with water and dried to give 37.9 g., m.p. 200–211°. After digestion for one hour with 350 ml. of boiling acetone, there was obtained 24.9 g. (66%) of X, m.p. 217–222°.

The analytical sample was recrystallized from ethanol and had m.p. 225.5–228.5°, $[\alpha]_D$ +110° (1% in dioxane).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.20; H, 9.42.

21-Hydroxypregnane-3,11,20-trione (XI).—A solution of 6.4 g. of I in a mixture of 224 ml. of acetone and 96 ml. of water was treated with 6.4 g. of N-bromoacetamide and 12 drops of concentrated hydrochloric acid, and allowed to stand for five hours at 5°. A solution of 9.5 g. of sodium sulfite in 135 ml. of water was added to remove the yellow color and the solution was acidified with acetic acid. The resulting mixture was steam distilled thoroughly and then distilled under reduced pressure until precipitation took place. The solid was filtered, washed with water and dried to give 5.73 g. (91.5%) of XI, m.p. 138–142°. Concentration of the mother liquor gave another 0.44 g. (7.0%), m.p. 136–139°.

The analytical sample was recrystallized from ethyl acetate–hexane, and had m.p. 142.5–143.5°, $[\alpha]_D$ +112° (1% in dioxane).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.80: H, 8.73. Found: C, 72.88; H, 9.12.

21-Hydroxypregnane-3,11,20-trione 3,20-Bis-ethylene Ketal (XII).—A mixture of 7.0 g. of II, 165 ml. of benzene and 14 ml. of ethylene glycol was distilled to remove traces of water, and 0.70 g. of *p*-toluenesulfonic acid monohydrate was added. The mixture was refluxed with stirring for four hours and 65 ml. of distillate was removed through a Dean-Stark tube. After cooling, the mixture was neutralized with potassium hydroxide in methanol, washed with water, dried over magnesium sulfate, filtered, and evaporated to dryness under reduced pressure. Trituration of the residue with ether gave 3.75 g. (42.7%) of XII, m.p. 160–161.6°. From the mother liquor, another 1.29 g. (14.7%) was obtained, m.p. 160–161°.

The analytical sample was recrystallized from ethyl acetate–hexane and had m.p. 160–161°, $[\alpha]_D$ +59° (1% in dioxane).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.97; H, 9.23.

11β,21-Dihydroxypregnane-3,20-dione 21-Acetate (IX).—To a slurry of 6.0 g. of lithium aluminum hydride in 180 ml. of ether was added, with cooling, a solution of 6.0 g. of III in 180 ml. of dry tetrahydrofuran. The mixture was stirred for four hours at 25° and allowed to stand overnight. The excess hydride was destroyed by the addition of 45 ml. of ethyl acetate with ice-water cooling, and then 18 ml. of water was added. The insoluble inorganic material was removed by filtration and the filtrate was taken to a residue under reduced pressure, leaving a glass. This material, dissolved in a mixture of 60 ml. of chloroform and 210 ml. of methanol, was treated with a solution of 12.6 ml. of concentrated hydrochloric acid in 21 ml. of water. The mixture was allowed to stand 24 hours at 25°, then 600 ml. of water was added. Methylene chloride was added, the organic extract was washed with sodium bicarbonate solution and with water, then dried over magnesium sulfate, filtered and distilled to a residual oil. A solution of this product in 30 ml. of pyridine and 20 ml. of acetic anhydride was allowed to stand overnight at room temperature. After working up in the usual manner, the residue obtained was triturated with ether to give 1.78 g. (33% from XII) of IX, m.p. 151–153.5°. Recrystallization from ether gave m.p. 158–159°, $[\alpha]_D$ +128.5° (1% in acetone); lit.[9] m.p. 158°, $[\alpha]_D$ +128° (acetone). This material was identical in its infrared spectrum with an authentic sample.[8]

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH LABORATORY ATTACHED TO TAKEDA PHARMACEUTICAL INDUSTRIES, LTD.]

Santonin. II.[1] The Synthesis of New Stereoisomers of Santonin[2]

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

RECEIVED SEPTEMBER 23, 1954

The resolution of santonin A as well as the synthesis of new stereoisomers of santonin (designated as santonin C and santonin D) are described. The stereochemistry of the natural santonins and their synthetic isomers is discussed.

The synthesis of the racemic stereoisomers of santonin (santonin A and B) has been reported.[3] In recent years Barton[4] has shown conformational analysis to be an effective method for the elucidation of stereochemistry. We have used this method to obtain more detailed information on the structure of santonin and its related compounds. Since the dienone ring of santonin must be planar and a chair form is preferable for the B ring, the skeleton of santonin may be considered to correspond to the A and B rings of $\Delta^{1,4}$-3-ketosteroids, with the angular methyl group in the axial position.

The stereochemical relationships of two natural santonins (*l*-α-santonin (I[5]) and *l*-β-santonin (II)) and four optically active desmotroposantonins (III, IV, V, VI) have been investigated by Clemo,[6] Huang-Minlon,[7] Barton[8] and Mitsuhashi.[9] It has been shown that *l*-α- and *l*-β-santonins are epimeric at C-11 and in both isomers the C-5 hydrogen is *cis* to the angular methyl group at C-9, and the lactone ring is *trans*-fused to the B ring; the relation between the angular methyl and the C-6 side chain must be *cis*. Therefore in *l*-α-santonin and also in *l*-β-santonin the C-5–O bond of the lactone, as well as the C-6 side chain should be equatorial to satisfy the relationships in configuration among C-5, C-6 and C-9. Furthermore, it is likely that all the six possible racemates of santonin (XII → XVII)[10] possess the same skeleton as natural santonin. Of the eight structures which may arise from the four asymmetric carbons, X and XI are impossible since a 6-5 ring fusion cannot exist in a diaxial configuration with chair-formed cyclohexanes.

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

(2) A preliminary report of this work was presented in *Proc. Japan Acad.*, **28**, 427 (1952); **29**, 113 (1953); **30**, 116 (1954).

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

(4) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(5) *l*-α-Santonin is arbitrarily represented by I not by II, or VII. All other formulas are based on this convention.

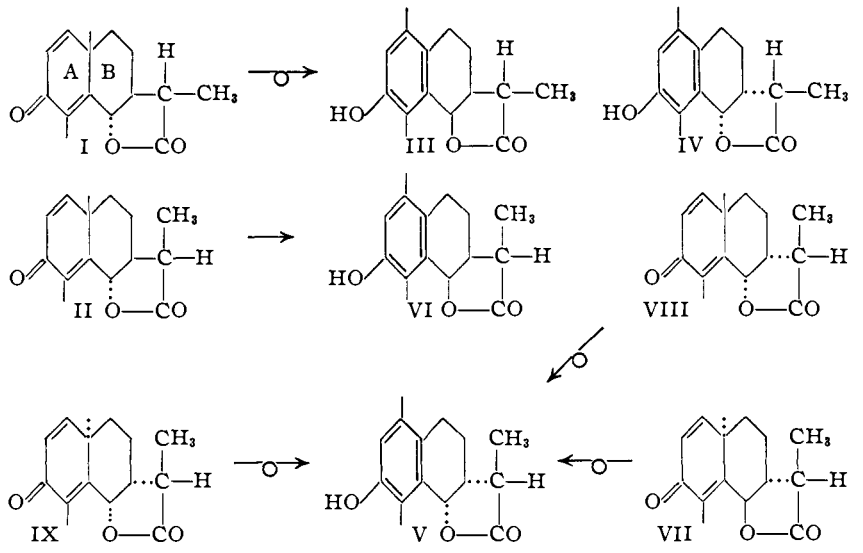
(6) G. R. Clemo, *J. Chem. Soc.*, 1343 (1934).

(7) Huang-Minlon, THIS JOURNAL, **70**, 611 (1948).

(8) D. H. R. Barton, *J. Org. Chem.*, **15**, 467 (1950).

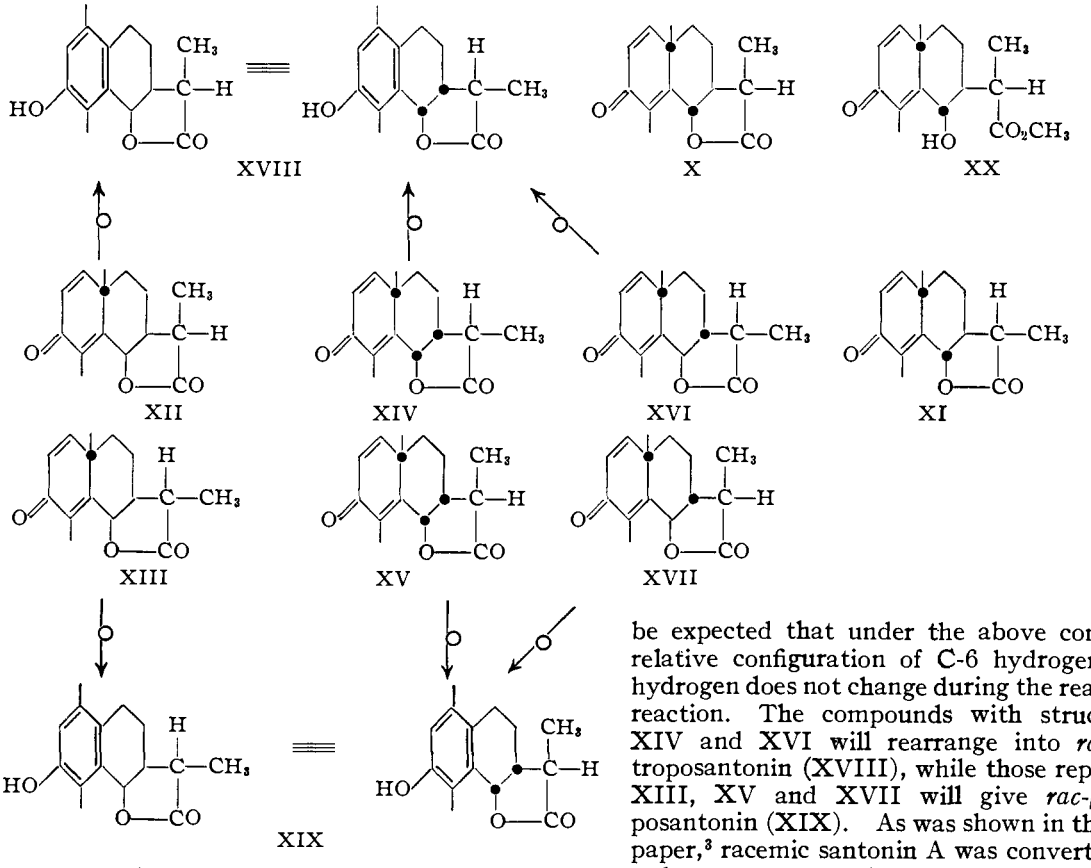
(9) H. Mitsuhashi, *J. Pharm. Soc. Japan*, **71**, 1115 (1951).

(10) Regarding optically active isomers, configurations in the formulae are indicated in the same way as in steroids, using full-lines and dotted lines, while for the racemates black dots are employed to show that the attached group lies above the plane of the molecule.

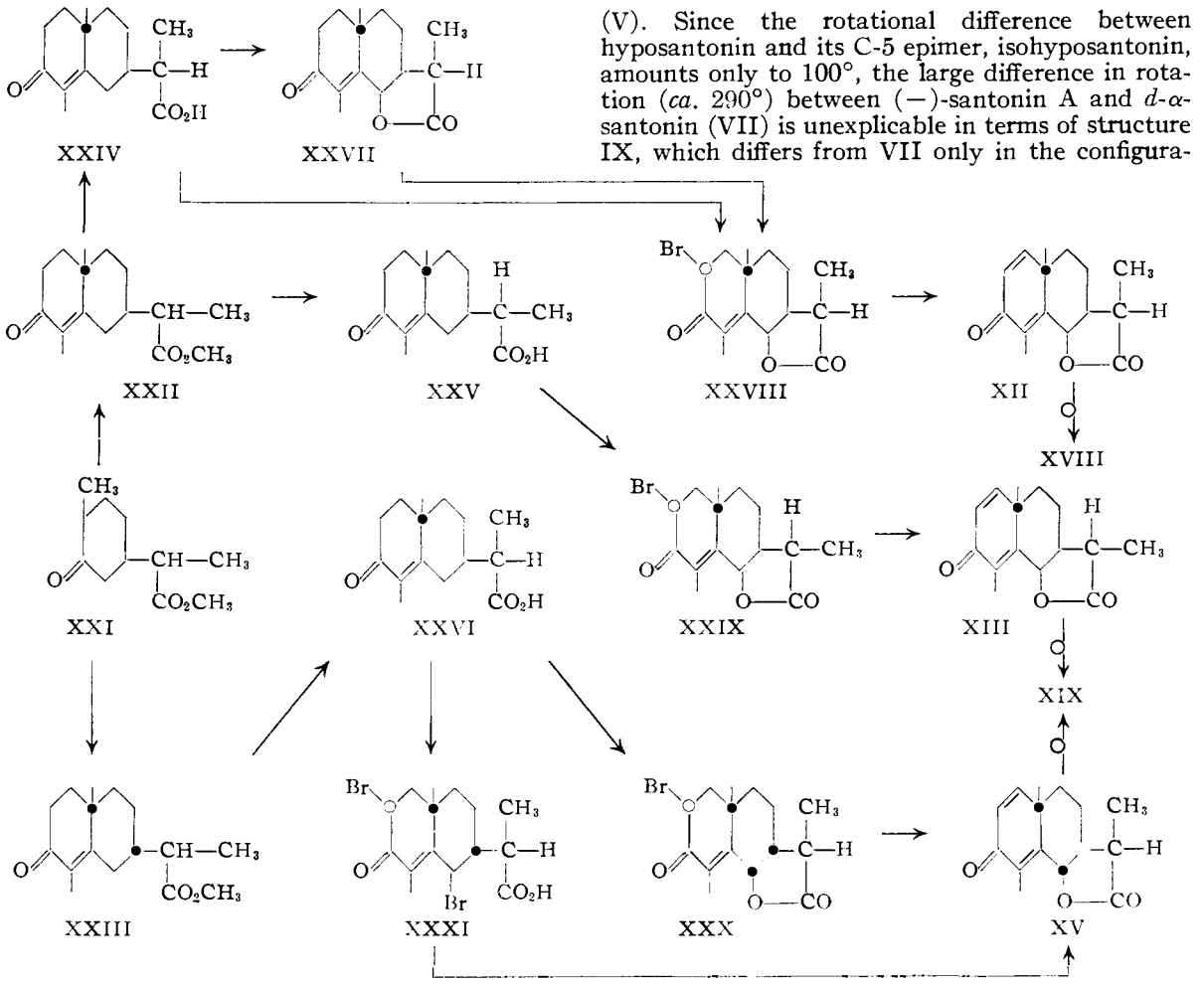


The structural differences of these six racemates are due to the bond nature of the C-6 side chain, the mode of the lactone fusion and the relationship between the configuration at C-11 and that at C-6; that is, the relative configuration of the C-6 and C-11 hydrogens. The C-6 side chain is axial in two racemates (XII, XIII) and equatorial in the remaining four (XIV, XV, XVI, XVII). As far as the lactone is concerned, there are two groups, those (XII, XIII, XIV, XV) containing the *cis*-fused lactone and those (XVI, XVII) the *trans*-fused one. In structures XII, XIV and XVI the relative configuration of the C-6 hydrogen and C-11 hydrogen is the same as in *l*-α-santonin, whereas XIII, XV and XVII are represented by the opposite configuration, that of *l*-β-santonin. Thus XVI represents the racemic form of natural α-santonin and XVII that of natural β-santonin.

When these santonins are subjected to the acid-catalyzed dienone–phenol rearrangement under mild conditions the conversion of the A ring into a phenolic structure takes place, accompanied by the migration of the angular methyl group, and the conversion of the *trans*-fused lactone into the *cis* form, to give desmotroposantonins. *l*-α-Santonin (I) and *l*-β-santonin (II) thus rearrange to *l*-α-desmotroposantonin (III) and *l*-β-desmotroposantonin (VI), respectively. In these instances the inversion occurs only at C-5 and the configurations at C-6 and C-11 remain intact. Accordingly, it may be expected that under the above conditions the relative configuration of C-6 hydrogen and C-11 hydrogen does not change during the rearrangement reaction. The compounds with structures XII, XIV and XVI will rearrange into *rac*-α-desmotroposantonin (XVIII), while those represented by XIII, XV and XVII will give *rac*-β-desmotroposantonin (XIX). As was shown in the preceding paper,[3] racemic santonin A was converted into *rac*-α-desmotroposantonin XVIII under the mild rearrangement conditions; this indicates that *rac*-santonin A possesses either structure XII, XIV or XVI.



An optically active isomer of santonin A is required for comparison with the natural one.



Paranjape, *et al.*,[11] reported that they resolved their synthetic santonin through its strychnine salt, but our attempt to prepare the brucine salt of natural santoninic acid from brucine hydrochloride and sodium santoninate failed and santonin was recovered. Resolution at an earlier stage seemed more promising, and it was found that α-(3-keto - 4,9 - dimethyl - 1,2,3,5,6,7,8,9 - octahydro - 6-naphthyl)-propionic acid A (XXIV) (A-acid[3]) could be resolved with brucine and with ephedrine. From the less methanol-soluble brucine salt of the A-acid the *dextro*-isomer was isolated; the more soluble salt gave the *levo*-acid but in a less pure form. The reactions used for the racemic acid were then applied to the (+)-A-acid to afford the first synthetic, optically active isomer of santonin. Although (−)-santonin A thus obtained proved to be levorotatory like natural santonin, in contrast to the latter it rearranged into *d*-α-desmotroposantonin (V) under mild conditions.

The non-identity of (−)-santonin A with natural santonin reduces the three possible structures for santonin A to two, XII and XIV. (−)-Santonin A should, therefore, be represented either by VIII or IX, both of which, as well as *d*-α-santonin[12] (VII), would rearrange to *d*-α-desmotroposantonin (V). Since the rotational difference between hyposantonin and its C-5 epimer, isohyposantonin, amounts only to 100°, the large difference in rotation (*ca.* 290°) between (−)-santonin A and *d*-α-santonin (VII) is unexplicable in terms of structure IX, which differs from VII only in the configuration at C-5. Thus formula IX is excluded and structures VIII and XII are assigned to (−)-santonin A and *rac*-santonin A, respectively. The configuration of the C-6 side chain of santonin A is now assigned the axial position; this holds true also for A-acid, which is represented by formula XXIV. Strong support for this assumption is furnished by the observation[13] that alkali treatment of *rac*-methyl santoninate A (XX), which is derived from A-acid (IV) and has the C-5 hydroxyl *trans* to the side chain, yields santonin A (XII) instead of the expected racemic santonin isomer (X) with a *trans*-lactone, whereas under the same conditions natural methyl santoninate gave santonin without an inversion of the lactone ring.

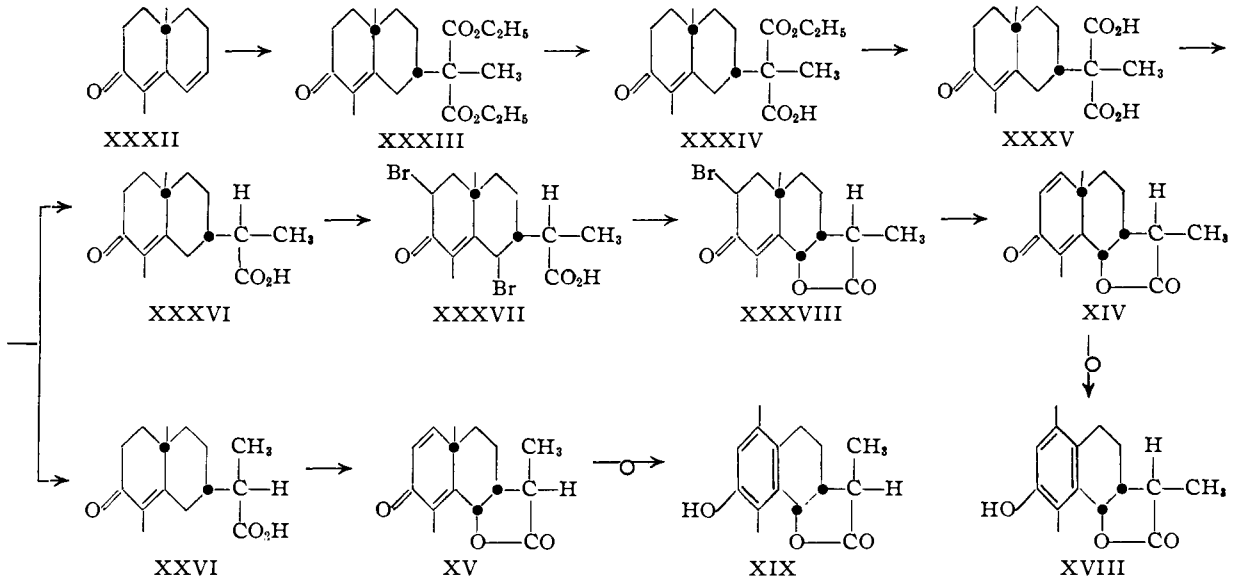
The formation of the *cis*-lactone in the synthesis of santonin A can be explained by the following mechanisms, which seem to be the most probable. As was described in part I of this series,[3] A-acid XXIV was treated with NBS or molecular bromine to afford, respectively, *rac*-dihydrosantonin A (XXVII) and its 2-bromo-derivative XXVIII, with the same junction of the lactone. In molecular bromination, the incoming bromine would initially take up the axial position[14] at C-5 of A-acid. Prior to the stabilization to equatorial,

(11) K. D. Paranjape, N. L. Phalnikar, B. V. Bhide and K. S. Nargund, *Nature*, **153**, 141 (1944).

(12) The hitherto unknown antipode of natural α-santonin.

(13) Unpublished work of this laboratory.

(14) E. J. Corey, *Experientia*, **9**, 329 (1953); THIS JOURNAL, **76**, 175 (1954).



rearward attack by the carboxyl group in the C-5 side chain would occur, giving rise to a *cis*-lactone, whose junction is more favorable when a six-membered ring is fused with a five-membered one.[15] The expected ease of the equatorial attack is in accordance with the observation that a C-5 brominated compound could not be isolated in contrast to the case of isomeric acids having the side chain equatorial as described later. Since the Wohl–Ziegler bromination is considered to proceed *via* a free radical form,[16] the carbon (C-5) with an unpaired electron might be attacked by the carboxyl in the molecule before reacting with a bromine atom; here again a *cis*-lactone would be formed.

Coincidence of the ultraviolet spectra of santonin B and its precursors with those of corresponding A-isomers, together with the production of B-acid in a yield almost equal to that of A-acid, indicates that compounds of B-series are the C-11 epimers of A-series and formulation XXV is assigned to B-acid and XIII to santonin B.

Although the product of the Robinson condensation consisted mainly of methyl esters of the two acids, carrying the axial side chain, the remainder of an acidic oil after exhaustive crystallization of A- and B-acids suggested the possibility of the existence of another isomer. This has proved to be the case; bromination of the oil provided a new isomer of the lactone XXX of α-(3-keto-4,9-dimethyl-2-bromo-5-hydroxy-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionic acid. Dehydrobromination of this bromolactone XXX with boiling collidine led to a third racemic stereoisomer of santonin, which melts at 190° (designated as *rac*-santonin D). Besides the bromolactone XXX, a dibromoacid XXXI was obtained and it also gave rise to santonin D by collidine dehydrobromination.

The ultraviolet absorption spectrum of the new santonin exhibits a maximum at 245 mμ, but differs from those of natural santonins, santonin A and B, in lacking the characteristic shoulder around 270 mμ. Further, the infrared spectrum of santonin D measured in chloroform is not identical with those of two natural santonins. Production of *rac*-β-desmotroposantonin (XIX) from santonin D under mild rearrangement conditions led to the conclusion that this racemate should be assigned the structure XV, for XIII already proved to represent *rac*-santonin B and XVII *rac*-β-santonin. Attempts to isolate the C-11 epimer of santonin D from the mother liquor of bromolactone D were unsuccessful. Hence, the cyclenone synthesis using *o*-methylated cyclohexanone with a side chain has been shown unfavorable for preparing intermediates of natural configuration.

In order to realize natural configuration an alternative route, which involves a later introduction of the side chain into a properly constructed bicyclic compound, appeared more promising, since the entering bulky group should occupy the equatorial position. As is to be reported in another place,[17] the Michael type condensation of 3-keto-4,9-dimethyl-1,2,3,7,8,9-hexahydronaphthalene[18] (XXXII) with diethyl methylmalonate afforded diethyl 3-keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthylmethylmalonate[19] (XXXIII) as a sole product, showing the complete stereospecificity of the reaction in contrast to the condensation utilizing Robinson's procedure. The configuration of the C-6 side chain is considered to be equatorial, by analogy with the β-configuration of the malonate moiety introduced at C-3 of $\Delta^{3,5}$-7-ketosteroid.[20]

Hydrolysis of XXXIII with alcoholic potassium hydroxide gave 3-keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthylmethylmalonic acid (XXXV)

(15) R. P. Linstead, *Ann. Repts. on Prog. Chem. (Chem. Soc. London)*, **32**, 306 (1935); W. Klyne, *J. Chem. Soc.*, 3078 (1953); E. E. van Tamelen, G. Van Zyl and G. D. Zuidema, THIS JOURNAL, **72**, 488 (1950).

(16) M. J. Dewar, "The Electronic Theory of Organic Chemistry." Oxford University Press, 1949, p. 273.

(17) T. Miki, *J. Pharm. Soc. Japan*, **75**, 395 (1955); Japanese Patent (applied on April 28th, 1953).

(18) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952).

(19) After this work had been completed M. Matsui, *et al.*, and F. J. McQuillin reported their independent synthesis of the compound in the same way; see *Bull. Chem. Soc. Japan*, **27**, 5 (1954), and *Chemistry and Industry*, 311 (1954).

(20) J. W. Ralls, THIS JOURNAL, **75**, 2123 (1953).

via its half ester XXXIV. On decarboxylation XXXV yielded a mixture of isomeric acids, which, however, included neither A-acid XXIV nor B-acid XXV. This serves as evidence for the configuration at C-6 of the products, because only four racemates are possible for α-(3-keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionic acid, of which two must have an e-oriented side chain and the other two have already been obtained as A- and B-acids. It is clear that this mixture was composed of two acids epimeric at C-11 and resulting from the single dibasic acid XXXV, but separation of the individual isomers was extraordinarily difficult compared with the case of A- and B-acids.[3] Two crystalline products, m.p. 145° and 135° (designated as C- and D-acid, respectively) were isolated, but in a poor yield, by laborious fractional recrystallizations. The fourth racemic isomer of santonin, which melts at 180° (designated as *rac*-santonin C), was synthesized starting from C-acid (XXXVI) through the same procedure as described for the preparation of santonin A and B, except that treatment with sodium bicarbonate of dibrominated acid was needed for complete lactonization to the bromolactone XXXVIII. The new *rac*-santonin, whose ultraviolet absorption spectrum is almost identical with that of santonin D (XV) but differs from those of natural santonins, rearranged into *rac*-α-desmotroposantonin (XVIII) under mild conditions. Comparison of the infrared spectrum also showed that santonin C differs from natural α-santonin. Consequently the structure represented by XIV should be assigned to this fourth racemate. The product derived from D-acid through the same series of reactions proved to be identical with santonin D (XV) obtained from the minor product of the Robinson condensation described above.

The mechanism for the *cis*-lactone formation in santonin C and D may be similar to that for santonin A and B. But in this case the bromine atom would be stabilized to equatorial after its initial attachment in the axial position and the subsequent reaction with the carboxyl by a SN2 mechanism causes the *cis* junction. Isolation of the 2,6-dibromocompounds is compatible with some difficulties expected in the axial approach of the carboxyl group.

Thus all possible racemates of santonin with a *cis*-lactone have been synthesized.

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. M. Yago and his collaborators for their aid in preparing intermediates, to Mr. M. Kan and his associates for performing the microanalyses, to Mr. H. Kamio for the determination of ultraviolet absorption and to Mr. T. Ito for the determination of rotation.

Experimental[21]

Resolution of α-(3-Keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionic Acid A (XXIV). (a) (+)-**A-Acid.**—A solution of 12 g. of A-acid XXIV[3] and 2.2 g. of brucine in 30 ml. of methanol was heated, and allowed to stand at room temperature. After several hours the separating crystals were collected by suction and washed with methanol. There was obtained 15 g. of the brucine salt of (+)-A-acid. Recrystallization from methanol gave colorless needles, m.p. 123–125°, $[\alpha]^{15}D$ 0° (*c* 1.0).

Anal. Calcd. for $C_{39}H_{47}O_7N_2 \cdot 2H_2O$: C, 67.13; H, 7.56; N, 4.12. Found: C, 66.99; H, 7.84; N, 4.06.

Three grams of the salt was shaken with 5% sodium hydroxide and chloroform to complete its decomposition. The alkaline solution was then acidified with hydrochloric acid, and 1.1 g. of (+)-A-acid was obtained. This was recrystallized from dilute methanol or petroleum ether as colorless prisms, m.p. 122°, $[\alpha]^{16}D$ +91° (*c* 1.0).

(b) (−)-**A-Acid.**—After removal of the less soluble brucine salt described in the preceding experiment, the mother liquor was concentrated and treated with aqueous alkali to give crude (−)-A-acid. A solution of 5.1 g. of the crude acid and 3.3 g. of *d*-ephedrine in 25 ml. of ethyl acetate was warmed and then allowed to stand at room temperature. The separated crystalline salt was filtered (8.2 g.). Several recrystallizations from ethyl acetate afforded colorless needles, m.p. 123°, $[\alpha]^{15}D$ −37.0° (*c* 0.5).

This was treated in the same way as for (+)-A-acid to yield 2.8 g. of (−)-A-acid, recrystallized from dilute methanol as colorless prisms, m.p. 122°, $[\alpha]^{15}D$ −91.0° (*c* 0.5).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.76; H, 8.80.

(+)-**1,2-Dihydro-2-bromosantonin A.**—To a solution of 2.0 g. of (+)-A-acid in 60 ml. of dry ether was added a few drops of a solution consisting of 2.5 g. of bromine and 15 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 1.8 g. of the crude product, which was recrystallized from methanol as colorless prisms, m.p. 97° dec., $[\alpha]^{15}D$ +86° (*c* 0.5).

Anal. Calcd. for $C_{15}H_{19}O_3Br$: C, 55.05; H, 5.86; Br, 24.42. Found: C, 55.13; H, 6.00; Br, 24.03.

(−)-**Santonin A (VIII).**—A mixture of 2.6 g. of (+)-bromodihydrosantonin A and 13 ml. of γ-collidine was heated for 40 minutes at 170–180° under reflux in a current of nitrogen. After dilution with ether and subsequent filtration of collidine hydrobromide, the ethereal solution was washed with dilute sulfuric acid and water, dried over anhydrous sodium sulfate and evaporated. After removing some red crystals, m.p. 210–215° dec., not further investigated, 0.9 g. of (−)-santonin A (VIII) was obtained, and was recrystallized from methanol as colorless prisms, m.p. 144°, λ_{max}^{MeOH} 244 mμ (log *E* 3.95), $[\alpha]^{15}D$ −115° (*c* 0.5).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.03; H, 7.50.

The Dienone–Phenol Rearrangement of (−)-Santonin A (VIII).—One hundred and fifty milligrams of powdered (−)-santonin A (VIII) was added to 6 g. of cold 55% sulfuric acid and stirred at 50° 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 120 mg. and recrystallization from methanol gave colorless prisms, m.p. 196–197°, $[\alpha]^{14}D$ +135° (*c* 0.5).

This showed no m.p. depression on admixture with an authentic sample of *d*-α-desmotroposantonin (V).[3]

Lactone of α-(3-Keto-4,9-dimethyl-2-bromo-5-hydroxy-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionic Acid D (XXX). From the Mother Liquors of A- and B-Acids.—To a solution of 33 g. of oily acid free from A- and B-acid XXIV and XXV[3] in 500 ml. of ether was added a solution of 42 g. of bromine in 200 ml. of glacial acetic acid. After decolorization, the reaction mixture was washed with water several times and with sodium thiosulfate and water successively, and dried over anhydrous sodium sulfate. On evaporation, followed by filtration, 5.5 g. of crystalline product was obtained, from which 0.7 g. of the bromolactone XXX and 2 g. of a dibromocompound XXXI were obtained through recrystallization from methanol. The former crystallizes in colorless prisms, m.p. 181° dec., λ_{max}^{EtOH} 249 mμ (log *E* 4.14).

(21) All melting points and boiling points are uncorrected. The ultraviolet absorption spectra were measured with a Beckman quartz spectrophotometer, and all rotations were determined in ethyl alcohol.

Anal. Calcd. for $C_{15}H_{19}O_3Br$: C, 55.05; H, 5.86; Br, 24.42. Found: C, 55.31; H, 5.87; Br, 24.62.

The latter crystallizes in colorless prisms, m.p. 145–147° dec., λ_{max}^{EtOH} 263 mμ (log *E* 4.00).

Anal. Calcd. for $C_{15}H_{18}O_3Br_2$: C, 44.36; H, 4.47; Br, 39.26. Found: C 44.92; H, 4.84; Br, 39.26.

***rac*-Santonin D (XV).**—(a) From 0.7 g. of *rac*-monobromodihydrosantonin D (XXX) and 5 ml. of γ-collidine there was obtained *rac*-santonin D (XV) by the same procedure as described for (+)-2-bromodihydrosantonin A. This was recrystallized from petroleum ether–benzene as colorless prisms, m.p. 186–189°, λ_{max}^{MeOH} 245 mμ (log *E* 4.19).

(b) From 1.0 g. of the dibromocompound (XXXI) and 10 ml. of γ-collidine there was obtained *rac*-santonin D (XV) as described above; colorless prisms, m.p. 183°, λ_{max}^{MeOH} 245 mμ (log *E* 4.14).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.11; H, 7.48.

The Dienone–Phenol Rearrangement of *rac*-Santonin D (XV).—*rac*-Santonin D (XV) was rearranged with 55% sulfuric acid as described above for (−)-santonin A. There was obtained *rac*-β-desmotroposantonin, m.p. 228°, which showed no m.p. depression on admixture with authentic sample of *rac*-β-desmotroposantonin (XIX).[3]

Diethyl 3-Keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthylmethylmalonate (XXXIII).—To a solution of sodium ethoxide in ethanol prepared from 23.5 g. of sodium and 470 ml. of anhydrous ethanol was added 520 g. of diethyl methylmalonate and 150 g. of 3-keto-4,9-dimethyl-1,2,3,7,8,9-hexahydronaphthalene (XXXII).[18] After standing overnight at room temperature, the mixture was poured into a large amount of water, and the oily material taken up in benzene. The benzene extract was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Distillation of the residue gave 214 g. of pale yellow oil, b.p. 203° (1.5 mm.), which, cooled and digested with petroleum ether, gave 197 g. of crystalline product. This was recrystallized from petroleum ether as colorless prisms, m.p. 63°, λ_{max}^{EtOH} 247 mμ (log *E* 4.18).

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol as red plates, m.p. 123°.

Anal. Calcd. for $C_{26}H_{34}O_8N_4$: C, 58.85, H, 6.46; N, 10.56. Found: C, 59.14; H, 6.44; N, 10.65.

3-Keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthylmethylmalonic Acid (XXXV).—Into 390 ml. of methanol was dissolved 45 g. of XXXIII, and 60 g. of 50% potassium hydroxide solution was added with stirring and cooling at 10°. After keeping at room temperature overnight,[22] an equal amount of caustic potash was added. The mixture was boiled under reflux for 8 hours and, after cooling, acidified with 10% hydrochloric acid. The resulting oil soon solidified, and recrystallization from dilute methanol gave colorless prisms, m.p. 204°, λ_{max}^{EtOH} 248 mμ (log *E* 4.14).

(22) When the reaction was stopped at this stage, a half-ester XXXIV was obtained in crystalline form. But in order to obtain the dibasic acid XXXV in high yield, it is advantageous to effect the hydrolysis without isolation of the half-ester.

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.43; H, 7.25.

α-(3-Keto-4,9-dimethyl-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionic Acid C (XXXVI) and D (XXVI).—On heating at 200° under reduced pressure, 7 g. of XXXV was decarboxylated to give a mixture of XXXVI and XXVI m.p. 108–112°. This was dissolved in hot ethyl acetate–petroleum ether, and on cooling the solution there was obtained crystalline material, which, after three recrystallizations from dilute methanol, gave 0.7 g. of XXVI as colorless prisms, m.p. 135°, λ_{max}^{EtOH} 250 mμ (log *E* 4.15).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.18; H, 8.96.

From the ethyl acetate–petroleum ether filtrate was obtained another crystalline product, which after recrystallization from dilute methanol, gave 0.1 g. of XXXVI as colorless prisms, m.p. 146°. This on admixture with XXVI showed m.p. depression to 108°.

Lactone of α-(3-Keto-4,9-dimethyl-2-bromo-5-hydroxy-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionic Acid C (XXXVIII).—To a solution of 1.6 g. of XXXVI in 150 ml. of ether was added a few drops of a solution consisting of 2.1 g. of bromine and 20 ml. of glacial acetic acid. After decolorization by gentle heating, the remainder of the bromine solution was added dropwise, washed with water, and the solvent was removed under reduced pressure. To the resulting crystalline product of dibromide was added 10 ml. of 10% sodium carbonate solution, and the mixture stirred at room temperature for 15 hours. After filtration, the reaction product was washed with water and methanol to yield 1.5 g. of XXXVIII, m.p. 143° dec.

Lactone of α-(3-Keto-4,9-dimethyl-2-bromo-5-hydroxy-1,2,3,5,6,7,8,9-octahydro-6-naphthyl)-propionic Acid D (XXX).—This was prepared as described in the preceding experiment for the C-isomer XXXVIII. From 1.3 g. of XXVI in 120 ml. of ether and 1.7 g. of bromine in 15 ml. of acetic acid was obtained dibromide, m.p. 145° dec., and treatment with 10 ml. of 10% sodium carbonate gave 0.9 g. of XXX, m.p. 177–179° dec.

Anal. Calcd. for $C_{15}H_{19}O_3Br$: C, 55.05; H, 5.86. Found: C, 54.84; H, 5.98.

***rac*-Santonin C (XIV).**—A solution of 1.5 g. of XXXVIII in 5 ml. of γ-collidine was boiled for 18 minutes. After cooling, the solution was diluted with ether, washed with 10% sulfuric acid, dilute sodium hydroxide and water, dried over anhydrous sodium sulfate, and evaporated. On cooling the residue, 0.1 g. of crystalline material separated. Recrystallization from methanol gave colorless prisms, m.p. 179°, λ_{max}^{EtOH} 246 mμ (log *E* 4.18).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.95; H, 7.22.

The Dienone–Phenol Rearrangement of *rac*-Santonin C (XIV).—An experiment similar to that described for *rac*-santonin D was carried out with 20 mg. of *rac*-santonin C (XIV) and 2 ml. of 55% sulfuric acid. The product was recrystallized from methanol as colorless prisms, m.p. 197°. This showed no m.p. depression by mixing with an authentic sample of *rac*-α-desmotroposantonin (XVIII).[3]

OSAKA, JAPAN