# CXL.—*The Constitution of Santonin. Part II. The Synthesis of Racemic* desmotropo*Santonin.*

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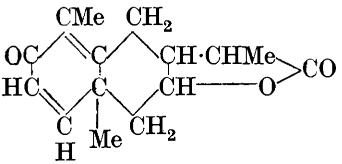
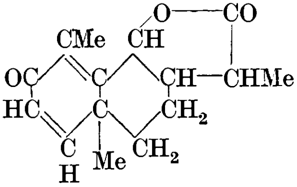
In Part I (J., 1929, 2368) a constitution (I) was suggested for santonin and the β-position of the propionic acid side-chain was established by a synthesis of *dl*-santonous acid, and as a result, two formulæ (III and IV) can be suggested for the lactone desmotropo-*santonin*, which is prepared by the action of mineral acids on santonin (Andreocci, *Gazzetta*, 1893, **23**, ii, 469; *Ber.*, 1898, **31**, 3131). Structure (III) appears to have been generally accepted, although hitherto there has been no evidence to enable a decision to be made between the two formulæ and older publications (compare Gucci and Grassi-Cristaldi, *Gazzetta*, 1892, **22**, i, 1) employ structure (IV).


(I.)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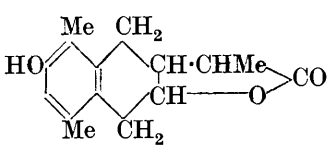
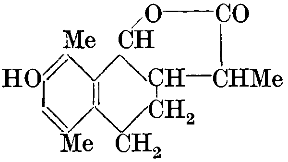
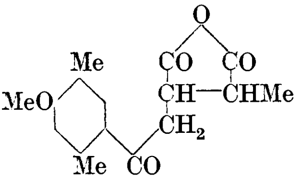



(IV.)

The present communication describes the synthesis of a lactone possessing the structure (IV), which is identical in all respects with racemic *desmotropo*santonin (Andreocci, *loc. cit.*). This synthesis establishes the α-position of the lactonic oxygen atom and provides a further illustration of the preference shown in biosynthesis for the angular fusion of ring systems. At the same time, this necessitates a corresponding modification of the structure (I) which has been suggested for santonin and the structure (II), now adopted, is in agreement with the chemical behaviour of this substance.

The starting point in these synthetical experiments was ethyl δ-4-methoxy-2 : 5-dimethylbenzoylbutane-ββγ-tricarboxylate (XVI; R = Me in Part I), and an improved method is described for its conversion into α-(β-4-methoxy-2 : 5-dimethylphenylethyl)-α′-

methylsuccinic acid (VI). The tricarboxylate was hydrolysed with aqueous-alcoholic sodium hydroxide and the mixed racemates



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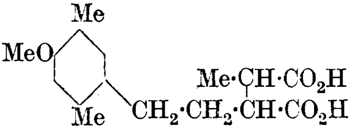
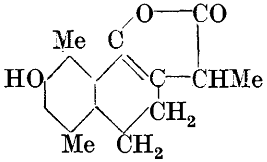
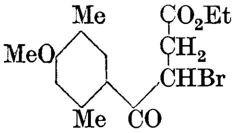


(VI.)

of δ-4-methoxy-2 : 5-dimethylbenzoylbutane-βγ-dicarboxylic acid (XVII ; R = Me in Part I, compare p. 2385) were converted into the *anhydride* (V) by heating at 180°. One form only of this anhydride has been isolated, and when this was reduced by Clemmensen's method, the succinic acid derivative (VI) was obtained. Two racemic modifications of this acid were described in Part I (p. 2386), but the lower-melting isomeride only is obtained by reducing the anhydride (V).

(VII.)





(VIII.)

The succinic acid derivative (VI) was refluxed with hydriodic acid and converted into α-(β-4-hydroxy-2 : 5-dimethylphenylethyl)-α′-methylsuccinic acid, which was not isolated in the crystalline state, but converted into the *lactone* (VII) of the enolic form of α-7-*hydroxy*-1-*keto*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*propionic acid* by the action of warm concentrated sulphuric acid.

This lactone (VII) was not reduced by palladium and hydrogen in acetic acid solution, but with sodium amalgam in alcoholic solution, the lactone (IV) of α-1 : 7-*dihydroxy*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*propionic acid* was obtained. This was identical with a specimen of racemic *desmotropo*santonin, prepared from santonin by the method outlined by Andreocci (*loc. cit.*), supplementary details of which will be found in the experimental section of this communication, and further the identity of the natural and the synthetic product has been confirmed by a comparison of their *acetyl* derivatives.

In Part I (p. 2374), the structure of ethyl δ-4-methoxy-2 : 5-dimethylbenzoylbutane-ββγ-tricarboxylate was discussed and an interesting result has now been obtained in an attempt to confirm the suggested structure. *Ethyl* β-*bromo*-β-4-*methoxy*-2 : 5-*dimethyl*-

*benzoylpropionate* (VIII), prepared by bromination of *ethyl* β-4-*methoxy*-2 : 5-*dimethylbenzoylpropionate* (compare Part I, p. 2382), was condensed with ethyl sodiomethylmalonate. A tricarboxylate was obtained which, after hydrolysis and heating, gave the anhydride (V). This indicates that hydrogen bromide is eliminated in one or both of the methods for preparing the anhydride (V), and that the ethyl sodiomethylmalonate condenses with the acrylic ester derivative by a Michael reaction. These observations, however, do not demand any alteration in our views with regard to the structure of ethyl δ-4-methoxy-2 : 5-dimethylbenzoylbutane-ββγ-tricarboxylate.

## EXPERIMENTAL.

*Methyl and Ethyl* β-4-*Methoxy*-2 : 5-*dimethylbenzoylpropionates*.—β-4-Methoxy-2 : 5-dimethylbenzoylpropionic acid (5 g.) in methyl alcohol (30 c.c.) was saturated with dry hydrogen chloride with cooling in an ice-bath. After some hours, the mixture was refluxed for 2 hours on the water-bath, the bulk of the alcohol then removed, water added, followed by a slight excess of sodium hydroxide, the solid collected and dried (4·8 g.). Crystallisation from light petroleum (b. p. 80—100°) gave large colourless prisms (4·4 g.), m. p. 94—95° (Found : C, 67·1 ; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2 ; H, 7·2%). The *ethyl* ester, prepared similarly, formed stout colourless prisms, m. p. 49—50° (Found : C, 68·3 ; H, 7·3. $C_{15}H_{20}O_4$ requires C, 68·2 ; H, 7·5%).

*Methyl and Ethyl* β-*Bromo*-β-4-*methoxy*-2 : 5-*dimethylbenzoylpropionates* (VIII).—A solution of bromine (3·5 g.) in light petroleum (b. p. 60—80° ; 33 c.c.) was added to a solution of methyl β-4-methoxy-2 : 5-dimethylbenzoylpropionate (5 g.) in light petroleum (b. p. 60—80° ; 40 c.c.); the bromine was rapidly decolorised and hydrogen bromide was evolved. The solvent was removed under reduced pressure; the residual oil crystallised from light petroleum (b. p. 40—60°) in large colourless prisms, m. p. 96° (Found : C, 51·3 ; H, 5·3 ; Br, 24·4. $C_{14}H_{17}O_4Br$ requires C, 51·1 ; H, 5·1 ; Br, 24·3%). The *ethyl* ester, prepared similarly, separated from light petroleum (b. p. 40—60°) in large colourless prisms, m. p. 98—100°, which gave a considerable depression in m. p. when mixed with ethyl α-bromo-β-4-methoxy-2 : 5-dimethylbenzoylpropionate (compare Part I, p. 2382) (Found: C, 52·6; H, 5·6 ; Br, 23·1. $C_{15}H_{19}O_4Br$ requires C, 52·5 ; H, 5·5 ; Br, 23·3%).

The ethyl ester was condensed with ethyl sodiomethylmalonate in benzene solution and the product after hydrolysis and heating yielded the anhydride, m. p. 171°, described below.

δ-4-*Methoxy*-2 : 5-*dimethylbenzoylbutane*-βγ-*dicarboxylic Anhydride* (V).—Ethyl δ-4-methoxy-2 : 5-dimethylbenzoylbutane-ββγ-tricarboxylate (12 g.) was dissolved in ethyl alcohol (24 c.c.), sodium hydroxide (24 c.c. of 2*N*) added, and the mixture refluxed for 2 hours on the water-bath and then evaporated to a small bulk under reduced pressure. Water (30 c.c.) was added, and after standing, the precipitated 4-methoxy-2 : 5-dimethylacetophenone (0·5 g.) was filtered off. The filtrate was acidified with a mixture of concentrated hydrochloric acid (30 c.c.) and water (30 c.c.), the resulting milky emulsion rapidly extracted with ether, and the extract allowed partly to evaporate spontaneously over-night. The colourless δ-4-methoxy-2 : 5-dimethylbenzoylbutane-βγ-dicarboxylic acid (5·3 g.) was collected and washed with a little ether and the ethereal filtrates were combined (A). The residue was heated in two portions for 1 hour in a metal-bath at 180°. After a brisk effervescence, a viscid, pale yellow gum resulted, which was stirred with ether while still warm and the colourless solid collected (2·85 g.). The ethereal filtrate on evaporation and reheating in the metal-bath gave 0·1 g. more of ether-insoluble solid. This solid was moderately easily soluble in boiling benzene, and separated in stout rhombic prisms, m. p. 171° (Found : C, 66·4; H, 6·2. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%). The *anhydride* is insoluble in cold sodium hydroxide solution, and sparingly soluble in ethyl alcohol, from which it separates in jagged prisms. On evaporation of filtrate (A), a yellow viscid oily acid resulted, from which no solid could be obtained by solution in sodium hydroxide and reprecipitation with acid; but on being heated in a metal-bath as above, it gave 1·65 g. of the crude anhydride, together with a further 0·1 g. when the ethereal extract was again heated.

*Methyl* δ-4-*methoxy*-2 : 5-*dimethylbenzoylbutane*-βγ-*dicarboxylate* was obtained on esterifying the anhydride with methyl alcohol and hydrogen chloride, and after distillation crystallised from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 73—74° (Found : C, 64·3; H, 7·1. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·1%).

α-(β-4-*Methoxy*-2 : 5-*dimethylphenylethyl*)-α′-*methylsuccinic Acid* (m. p. 131—132°; compare Part I, p. 2386).—The anhydride (V) (1 g.), amalgamated zinc (5 g.), and concentrated hydrochloric acid (7 c.c.) were refluxed for 24 hours. The oil produced was decanted from the zinc residues, which were extracted with a small amount of ethyl alcohol, diluted with water and left over-night, and the colourless solid was collected and dried on porous plate (0·95 g.). The compound dissolved completely in hot benzene (4—5 c.c.) and on dilution with light petroleum (12 c.c.) gave colourless prisms, m. p. 131—132° (Found : C, 65·2; H, 7·8. Calc. : C, 65·3; H, 7·5%).

*Lactone of* α-7-*Hydroxy*-1-*keto*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*propionic Acid* (VII).—α-(β-4-Methoxy-2 : 5-dimethylphenylethyl)-α′-methylsuccinic acid (2·5 g.) was refluxed for 1 hour with hydriodic acid (7·5 c.c.; *d* 1·7), water (7·5 c.c.) added, the mixture extracted with ether, the extract freed from iodine by shaking three times with saturated sodium bisulphite solution and dried over sodium sulphate, and the ether removed. α-(β-4-Hydroxy-2 : 5-dimethylphenylethyl)-α′-methylsuccinic acid remained as a gum, which was stirred for 2 minutes in the water-bath with concentrated sulphuric acid (7·5 c.c.), the resulting dark brown solution cooled, and ice added; a straw-coloured gum was then obtained. After 1 hour, the dilute acid solution was decanted, the residue stirred with a cold saturated solution of sodium bicarbonate, and the colourless solid collected, washed with water, and dried on the water-bath. The material from three such experiments was dissolved in boiling acetic acid (80 c.c.) and water (10 c.c.), charcoal added to remove a faint purple coloration, and the filtrate diluted with boiling water (35 c.c.). On cooling, colourless, stout, rhombic prisms (3·1 g.), m. p. 250—253° (decomp.), separated (Found: C, 73·8; H, 6·8. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·5%). The *lactone* is hydrolysed by warming for 15 minutes with methyl-alcoholic potassium hydroxide to give α-7-*hydroxy*-1-*keto*-5 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthyl*-2-*propionic acid*, which dissolves in two-thirds strength acetic acid to give a persistent intense green solution, but crystallises from methyl alcohol in colourless prisms, m. p. 191° (Found: C, 68·4; H, 6·8. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

*Synthetic Racemic* desmotropo*Santonin* (IV).—The above lactone (1 g.) was dissolved in ethyl alcohol (50 c.c.), washed sodium amalgam (80 g. of 4%) added, and the mixture refluxed for 15 hours on the water-bath. The solution was decanted from the mercury and filtered from a trace of sediment and the alcohol was removed under reduced pressure. The residue was dissolved in a small volume of water, acidified with hydrochloric acid, and extracted three times with ether and the extract was dried with sodium sulphate and evaporated to about 2 c.c. After 12 hours, 0·2 g. of a crystalline solid separated, m. p. 178—184°, raised to 194—196° after four recrystallisations from alcohol. When the above dried ethereal extract was evaporated, however, and the residue again refluxed over-night with alcohol (10 c.c.) and washed amalgam (40 g. of 4%), then, after removal of the alcohol and solution in water, acidification yielded a solid which was collected and crystallised once from alcohol, giving colourless prisms (0·3 g.), m. p. 199°, raised to 200—201° by one recrystallisation (Found: C, 73·4; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). The compound is sparingly soluble in ethyl alcohol, readily in ethyl acetate, and almost insoluble in ether, and its m. p. is not depressed by admixture with racemic *desmotropo*santonin prepared from santonin as described below. Synthetic *acetyl* desmotropo*santonin*, obtained by treatment with acetic anhydride and sodium acetate, separated in colourless prisms, m. p. 146°, again not depressed by mixture with acetyl*desmotropo*santonin prepared from santonin (Found: C, 71·1; H, 7·2. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%).

*Racemic* desmotropo*Santonin from Santonin.*—*d-desmotropo*Santonin was prepared as follows: Santonin (10 g.) and fuming hydrochloric acid (60 c.c.) were heated in a sealed tube at 35° for 36 hours. The product was diluted with water, and the solid collected, dissolved in dilute sodium hydroxide solution, and filtered. The filtrate was acidified and warmed and the *d-desmotropo*santonin (8·5 g.) was collected; it crystallised from ethyl alcohol in fine prisms, m. p. 260° (compare Andreocci, *Gazzetta*, 1893, **23**, ii, 469). *isodesmotropo*Santonin was prepared from the *d*-form according to the method of Andreocci (*loc. cit.*), the reaction being complete in about 1½ hours. *isodesmotropo*Santonin melts at 194° [Andreocci gives 187—188° (decomp.)] and its acetyl derivative melts at 154°. *l-desmotropo*Santonin (the enantiomorph of *isodesmotropo*santonin) and racemic *desmotropo*santonin were prepared as described by Andreocci (*Ber.*, 1898, **31**, 3131).

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