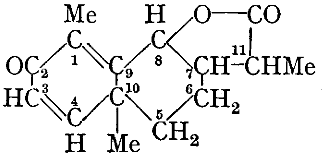
294. *β-Santonin.*

By George R. Clemo.

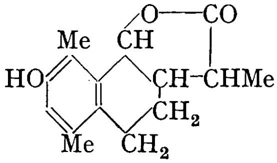
Although 16 stereoisomeric forms of santonin (I) are possible, only one, the naturally occurring *l*-santonin, appears to have been hitherto described. Some time ago, however, Messrs. T. & H. Smith kindly sent the author a quantity of a compound isolated from particular samples of *Artemisia* obtained from the N.W. Frontier of India. The compound was shown by analysis to be $C_{15}H_{18}O_3$, and whilst differing in m. p. and rotation from santonin, nevertheless resembled it very closely in its colour reactions. Further, *Artemisias* collected from other districts had been found to contain a small amount of this new compound in the mother-liquors after the separation of santonin.

It is now shown that the compound is a stereoisomeride of santonin, and it is therefore called β-*santonin*. It contains a carbonyl group, as indicated by the formation of an *oxime*, and two double bonds reducible by palladised charcoal and hydrogen. Of the four possible *tetrahydro*-compounds, two have been obtained pure by using acetic acid as solvent in the reduction, but only one of these results when ethyl alcohol is used. The carbonyl group of both tetrahydro-compounds is reduced by the Clemmensen method to give one and the same *deoxytetrahydro*-compound, which is dehydrogenated smoothly by selenium to 1-methyl-7-ethylnaphthalene.

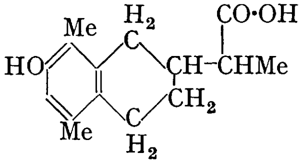
When β-santonin is treated with dilute sulphuric acid, it is transformed into the phenolic *l-desmotropo*-β-santonin (II) (cf. santonin, *Ber.*, 1898, **31**, 3131), m. p. 253°, *acetyl* derivative, m. p. 156—157°, depressed to 130—140° by admixture with acetyl-*l-desmotropo*santonin (m. p. 156—157°). It is somewhat remarkable that santonin and hydrochloric acid give a *d-desmotropo*santonin, but β-santonin gives again the above *l-desmotropo*-β-santonin. On reduction with zinc and dilute acetic acid this gives a d-β-*santonous acid* (III), m. p. 174°, depressed to 160—165° by admixture with *d*-santonous acid (m.p. 176—177°). When *d*-santonous acid is heated with barium hydroxide, a mixture of *r*-santonous acid and 1 : 4-dimethyl-β-naphthol is obtained, but the above isomeric β-acid when similarly treated gives a d-β-*santonous acid*, m. p. 153°, depressed to 140—145° by admixture with *r*-santonous acid (m. p. 153°), together with the above dimethylnaphthol.



(I.)



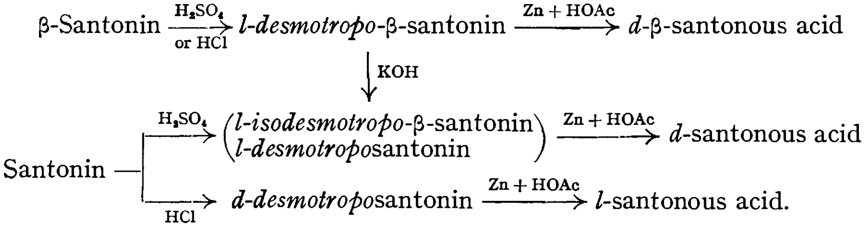
(II.)



(III.)

The results are bound up with the involved stereochemistry of the systems (I) and (II), and the production of the *d-desmotropo*santonin by hydrochloric acid must arise from an alteration at one or more of the three remaining asymmetric centres at $C_{8,\ 9,\ 11}$ as well as the destruction of the asymmetry at C_{10}. In view of the conversion of *desmotropo*-compounds by reduction into santonous acids of opposite sign, it may be that only C_8, and not C_9 and C_{11}, is involved in the above change. A model of (II) shows that the tetrahydro-ring is more rigid than the normal fully reduced one, and also that the lactone ring can only be fused on in the two *cis*-positions and not in the *trans*- to give a strainless system. Further, steric reasons indicate that one of the *cis*-forms might be expected to be more resistant to attack, and this might account for the failure to racemise the above *d*-β-santonous acid at C_7.

Eventually, however, contact was established between santonin and β-santonin as follows. When *l-desmotropo*-β-santonin is fused with potash, it is converted into *l-isodesmotropo*-β-santonin, identical with *l-desmotropo*santonin, and on reduction it gives a *d*-form of santonous acid identical in all respects with the *d*-santonous acid from santonin.



EXPERIMENTAL.

β-*Santonin*.—The *compound* is sparingly soluble in and crystallises from ethyl alcohol in stout colourless prisms, m. p. 216—218°; $[\alpha]_D^{19°}$ – 137·2° (c = 5 in chloroform) (Found: C, 73·1; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). It turns yellow slowly in the light, gives no colour with concentrated sulphuric acid, but a light carmine with alcoholic potassium hydroxide. The *oxime* was obtained as stout colourless prisms, m. p. 224°, from alcohol (Found : C, 69·1; H, 7·7. $C_{15}H_{19}O_3N$ requires C, 69·0; H, 7·3%).

Tetrahydro-β-*santonins*-a *and* -b.—β-Santonin (6 g.) was dissolved in acetic acid (80 c.c.), palladised charcoal (0·2 g.) added, and the mixture well stirred for 8 hours in an atmosphere of hydrogen. Further catalyst (0·2 g.) was added, the stirring continued for 4 hours, and the filtrate evaporated to 10 c.c.; on standing over-night in the refrigerator, 1·55 g. of stout prisms separated, m. p. 195—200°. Recrystallisation from ethyl acetate, in which the compound is almost insoluble in the cold, gave colourless prisms of *tetrahydro*-β-*santonin*-a, m. p. 207—208° (Found : C, 72·4; H, 9·2. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%). The compound is very slightly soluble in boiling water and sparingly so in most organic solvents. When the filtrate from the 1·55 g. was evaporated, and the residue dissolved in alcohol (2 c.c.) and left over-night, 1·85 g. of prisms separated, m. p. 80—110°. These were powdered, extracted thrice with boiling light petroleum (b. p. 60—80°), and the residue crystallised first from light petroleum (b. p. 80—100°) and then from alcohol, whereupon stout prisms of the *tetrahydro*-β-*santonin*-b separated, m. p. 125—126° (Found : C, 72·1; H, 8·6%). When β-santonin (5 g.) was dissolved in boiling alcohol (100 c.c.) containing palladised charcoal (0·4 g.) and treated with a current of hydrogen for 8 hours, followed by a further 4 hours after addition of more catalyst, 3·4 g. of crystalline solid separated from the filtrate after it had been evaporated to 2 c.c. and left in the refrigerator. The addition of water to the residual filtrate gave only an oil. The 3·4 g. of solid, which was easily soluble in cold ethyl acetate and so probably free from the *a* form, were powdered and extracted twice with boiling light petroleum (50 c.c., b. p. 60—80°), leaving 2 g. undissolved, m. p. 118—122°. This was crystallised from light petroleum (b. p. 80—100°), giving 1·9 g. of prisms, m. p. 120—123°, raised to 125—126° by two further crystallisations from alcohol. The extract deposited 0·72 g. of crystalline solid, m. p. 90—105°, but only the above *a*- and *b*-forms have yet been obtained pure.

Deoxytetrahydro-β-*santonin*.—The *a* compound above (0·75 g.), amalgamated zinc (7·5 g.), and concentrated hydrochloric acid (12 c.c.) were left for 2 hours and heated under reflux for 18 hours. A further 3 c.c. of hydrochloric acid were added, and the heating continued for 6 hours. The oily liquid suspension was decanted from the zinc residues, and the solid obtained on cooling was collected, pressed on porous plate, and crystallised from light petroleum (2 c.c., b. p. 40—50°) in a refrigerator; stout colourless prisms were obtained, m. p. 70—71°, raised to 75—76° by recrystallisation from the same solvent (Found : C, 75·5; H, 10·1. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). Tetrahydro-β-santonin-*b* on similar reduction gave a good yield of the same *deoxy*-compound, but when the unseparated mixture of tetrahydro-compounds, m. p. 90—105°, was used, only a poor yield of the deoxy-compound, m. p. 75°, resulted, together with much oil.

Dehydrogenation of Deoxytetrahydro-β-*santonin*.—The compound (1·05 g.) and selenium (1·5 g.) were heated at 280—340° for 48 hours in a glass bulb fused to a 6-ft. air condenser. On extraction with light petroleum (b. p. 60—80°) and distillation over sodium, 0·45 g. of oil was obtained, b. p. 95—105°/1 mm. A redistillation over sodium gave 0·34 g., b. p. 95°/1 mm., whose picrate formed orange needles, m. p. 92°, from alcohol, raised to 96° by one recrystallisation and not depressed by admixture with an authentic specimen of 1-methyl-7-ethylnaphthalene picrate (m. p. 96°).

l-desmotropo-β-*Santonin from* β-*Santonin*.—(1) Powdered β-santonin (1·5 g.) was added to a cold mixture of concentrated sulphuric acid (15 c.c.) and water (22·5 c.c.) and heated in a water-bath at 50° for 20 hours. The mixture was diluted and filtered, the resulting solid extracted with dilute aqueous sodium hydroxide, and the akaline solution acidified. The solid was crystallised from alcohol, in which it is much less soluble than the corresponding santonin derivative, and gave long colourless prisms, 1·25 g., m. p. 253°; $[\alpha]_D^{20°}$ – 101·7° (c = 0·30 in ethyl acetate) (Found : C, 73·2; H, 7·45. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). The *acetyl* derivative formed long lustrous prisms from alcohol, m. p. 156—157° (Found : C, 70·5; H, 7·0. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%).

(2) Powdered β-santonin (1·5 g.) and fuming hydrochloric acid (9 c.c.) were sealed in a glass tube and quickly gave a solution on shaking. This was heated for 45 hours at 30°, and the

resulting crystalline solid collected, washed with hydrochloric acid and then with water. On extraction with dilute sodium hydroxide solution, all but 0·15 g. dissolved, and the same *l-desmotropo*-β-santonin as above was obtained, 0·65 g. (Found: C, 73·1; H, 7·4%). This compound also results when the reactants are left at room temperature or for 2 weeks in a refrigerator.

l-isodesmotropo-β-*Santonin.*—*l-desmotropo*-β-Santonin (1 g.), potassium hydroxide, and water (1 g.) were heated in a test-tube with an air condenser in a metal-bath at 210° for an hour, so that at the end all the water had distilled off. The solid was dissolved in water, the boiling solution acidified, and the collected precipitate crystallised from alcohol, giving 0·7 g. of colourless prisms, m. p. 194°, not depressed by admixture with *l-desmotropo*santonin (m. p. 194°); $[\alpha]_D^{20^\circ}$ − 136·8° (*c* = 0·9 in ethyl acetate) (Found : C, 73·4; H, 7·5%).

d-β-*Santonous Acid.*—*l-desmotropo*-β-Santonin (4·5 g.) was refluxed for 6 hours with zinc dust (20 g.) and glacial acetic acid (112 c.c.) diluted with water (48 c.c.). The filtrate was evaporated to dryness, the solid crystallised from dilute alcohol (1 : 2) and a few drops of hydrochloric acid, and 4·1 g. of colourless prisms obtained, m. p. 174°, depressed to 160° by admixture with *d*-santonous acid; $[\alpha]_D^{20^\circ}$ + 54·9° (*c* = 1·0 in alcohol) (Found : C, 72·5; H, 8·3. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·0%). This *acid* is unchanged by fusion with potassium hydroxide as above for 10 minutes.

Heating with barium hydroxide. *d*-β-Santonous acid (0·5 g.) was well mixed with barium hydroxide (1·5 g.) and heated during ¾ hour in a test-tube in a metal-bath at 360° with frequent stirring. A stiff paste resulted, although much less readily than with *d*-santonous acid, which forms a melt at 330°. It was extracted with boiling water, carbon dioxide passed into the filtrate, and the resulting precipitate (A) collected. The filtrate was acidified with hydrochloric acid, and the solvent removed from the dried ethereal extract, leaving 0·2 g. of acid. This solidified on extraction with a small volume of light petroleum, and when crystallised from dilute alcohol (1 : 2) gave colourless prisms, m. p. 152°, depressed to 140—145° by admixture with *r*-santonous acid (m. p. 152°); $[\alpha]_D^{20^\circ}$ + 60·9° (*c* = 0·6 in alcohol) (Found : C, 72·8; H, 8·3%). Fusion with potassium hydroxide for 10 minutes raised the rotation to + 64·2°. The precipitate (A) was extracted with dilute sodium hydroxide solution, and the filtrate acidified, extracted with ether, and distilled under 1 mm., giving 0·2 g. of solid, which crystallised from dilute alcohol in long colourless prisms, m. p. 134°, not depressed by admixture with 1 : 4-dimethyl-β-naphthol (m. p. 134—135°) as made similarly from santonin (Found : C, 83·3; H, 7·1. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 6·9%).

The Santonous Acid from l-isodesmotropo-β-*Santonin.*—*l-isodesmotropo*-β-Santonin (0·75 g.) was reduced with zinc dust as above and gave 0·5 g. of colourless prisms after two crystallisations from dilute alcohol (1:2), m.p. 177—178°, depressed to 160° by *d*-β-santonous acid, but unchanged by admixture with *d*-santonous acid (m. p. 179°); $[\alpha]_D^{20^\circ}$ + 75° (*c* = 2·47 in alcohol) (Found : C, 72·95; H, 8·0%). The ethyl ester formed long colourless prisms from light petroleum, m. p. 117°, not depressed by admixture with ethyl *d*-santonite from santonin, and had $[\alpha]_D^{20^\circ}$ + 75° (*c* = 1·0 in ethyl alcohol).

Thanks are due to Dr. R. Raper for rotation measurements and to Mr. O. Telfer for micro-analyses.

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[*Received, July* 30*th*, 1934.]