the isolation of the acetate. The residue from the chloroform–acetone filtrates was dissolved in 300 ml. of alcohol and to this was added 1–2 liters of water. An oil formed which settled out permitting the aqueous layer to be removed. After standing overnight the oil crystallized. The crystals were dissolved in 300 ml. of hot methyl alcohol from which the β-vicianose heptaacetate crystallized slowly in clusters of small needles. After two recrystallizations the product weighed 12.3 g., m. p. 158–159° (cor.), $[\alpha]^{24}\mathrm{D}$ 9.4° in chloroform (*c*, 2). Additional recrystallizations produced no change in either the melting point or the specific rotation. By working up filtrates an additional 2.2 g. was obtained; yield 34%. Six grams of a much lower melting product (144–149°) was isolated from residues.

Acknowledgment.—The authors wish to thank Dr. Giffin D. Jones and Mr. Harold Baker of this Laboratory for the preparation of the 1,2,3,4-tetraacetyl-β-D-glucose used in this investigation.

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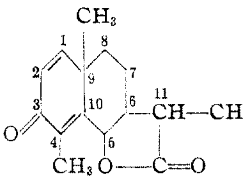
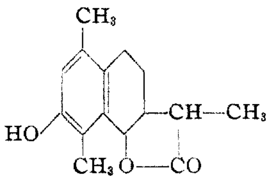
Studies in the Santonin Series. I. The Two New Desmotropo-santonins and the Two New Desmotropo-santonous Acids[1]

BY HUANG MINLON, CHIEN-PEN LO AND LUCY JU-YUNG CHU

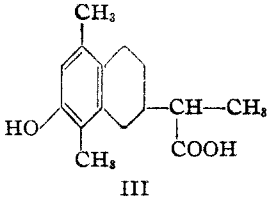
When santonin (I) is treated with mineral acids, a molecular rearrangement reaction takes place resulting in an aromatic compound, the desmotropo-santonin (II).[2,3,4] By an analogous reaction some transformation products of cholesterol with the dienone structure have been easily converted into the corresponding phenolic compounds by means of acetic anhydride and a drop of concentrated sulfuric acid.[5] The conversion is believed to be effected through an *enol*-acetylation reaction although the intermediate acetate has never been isolated. In the process of acetylation, the equilibrium between the enol- and the keto-forms is disturbed in favor of the former form. Now we have found that when santonin was subjected to the same treatment, in the cold or slightly warmed on a water-bath, it was almost quantitatively converted into an acetate of m. p. 156–157°[6a] which upon saponification yielded *l*-desmotropo-santonin (m. p. 194–195°).[6b]



I



II



III

It is also known that *l*-desmotropo-santonin (m. p. 194°) can be transformed into its stereoisomer, *d*-desmotropo-santonin (m. p. 260°) by prolonged heating with dilute sulfuric acid at 100°[4] and that the latter isomer in turn can be transformed into *d*-isodesmotropo-santonin (m. p. 194°), the enantiomorph of the former isomer by fusion with alkali.[7,8,9] Evidently, the dilute sulfuric acid is able to change the low-melting *l*-desmotropo-santonin into the high-melting *d*-desmotropo-santonin with an inversion of rotation, while the alkali is able to change the high-melting *d*-isodesmotropo-santonin with the direction of rotation unaltered. We therefore believe that the *d*-isodesmotropo-santonin, when treated with dilute sulfuric acid, will be transformed, not as was reported by Bargellini and Mannino[4] into the *d*-desmotropo-santonin, but into its high-melting levorotatory stereoisomer.

In fact, when *d*-iso-desmotropo-santonin was heated with dilute sulfuric acid on the water-bath, there were obtained colorless prisms melting at 260–261° and possessing the same physical and chemical properties but a specific rotation ($[\alpha]^{20}\mathrm{D}$ $-106.2°$) equal and opposite in sign to that of the *d*-desmotropo-santonin.[10] This new isomer formed with the latter compound a new racemic desmotropo-santonin (colorless plates, m. p. 231–232°) which yielded an inactive acetyl derivative (m. p. 182–183°) from which the original racemic mixture was recovered by saponification. Reduction

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[1] Original manuscript received July 17, 1942.

[2] Andreocci, *Gazz. chim. ital.*, **23**, II, 469 (1893).

[3] Andreocci and Bertolo, *Ber.*, **31**, 3131 (1898).

[4] Bargellini and Mannino, *Gazz. chim. ital.*, **39**, II, 103 (1909).

[5] Inhoffen and Huang Minlon, *Naturwissenschaften*, **26**, 756 (1938); *Ber.*, **73**, 451 (1940).

[6] (a) Gave no depression when mixed with *l*-desmotropo-santonin acetate prepared from *l*-desmotropo-santonin by acetylation. (b) Gave no depression by admixture with a specimen obtained directly from santonin.

[7] Cannizzaro, *Ber.*, **26**, 2311 (1893).

[8] Andreocci, *Gazz. chim. ital.*, **23**, II, 484 (1893); **25**, I, 476 (1895).

[9] Clemo, Haworth and Walton, *J. Chem. Soc.*, 1110 (1930).

[10] Three measurements by us gave the same value +106.2°. However, a value of +112.7° was reported by Andreocci.[2]

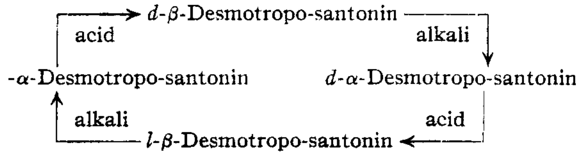
with zinc and dilute acetic acid changed this new active isomer into a new *d*-desmotropo-santonous acid (III) (colorless prisms, m. p. 175–176°[11]; $[\alpha]^{21}\text{D}$ +54.0°) which formed with the known levorotatory desmotropo-santonous acid (from *d*-desmotropo-santonin) a new racemic acid (colorless plates, m. p. 180–181°). This same acid can also be obtained by reducing the above racemic desmotropo-santonin. The conclusion of Bargellini and Mannino[4] that all the known stereoisomers of desmotropo-santonin were changed into the same *d*-desmotropo-santonin by treatment with sulfuric acid is thus found to be wrong.

As was expected, alkali fusion converted this new levorotatory desmotropo-santonin into the low-melting *l*-desmotropo-santonin, the direction of rotation remaining unaltered.

Now six desmotropo-santonins are known, thus completing the two of the four theoretically possible diastereoisomeric series. We propose to change the old confusing system[12] (in parentheses) of naming these compounds and the corresponding acids as following, where prefixes α and β denote low- and high-melting compounds, respectively

d-α-Desmotropo-santonin (iso-desmotropo-santonin) ⟶ *l*-α-desmotropo-santonous acid (*l*-santonous acid)
l-α-Desmotropo-santonin (*l*-desmotropo-santonin) ⟶ *d*-α-desmotropo-santonous acid (*d*-santonous acid)
dl-α-Desmotropo-santonin (*dl*-desmotropo-santonin) ⟶ *dl*-α-desmotropo-santonous acid (*dl*-santonous acid)
d-β-Desmotropo-santonin (desmotropo-santonin) ⟶ *l*-β-desmotropo-santonous acid (desmotropo-santonous acid)
l-β-Desmotropo-santonin (new) ⟶ *d*-β-desmotropo-santonous acid (new)
dl-β-Desmotropo-santonin (new) ⟶ *dl*-β-desmotropo-santonous acid (new)

The discovery of the *l*-β-desmotropo-santonin makes it possible to transform any known active isomer of this substance into any other form by treatment with acid or alkali, as is indicated in the cycle below. The racemic α- (m. p. 200–201°) and the racemic β- (m. p. 231–232°) desmotropo-santonins were also found to be interconvertible by treatment with acid or alkali.



dl-α-Desmotropo-santonin ⇄ *dl*-β-desmotropo-santonin

Furthermore, we believe that our *l*-β-desmotropo-santonin should be identical with the *l*-desmotropo-β-santonin (m. p. 253°[13]) obtained by Clemo[14] from the β-santonin isolated from Indian *Artemisia.* According to this author, the *l*-desmo-β-santonin yielded *l*-α-desmotropo-santonin (*l*-desmotropo-santonin) when fused with alkali and *d*-β-desmotropo-santonous acid (*d*-β-santonous acid) when reduced with zinc and acetic acid. This is just what we should expect of our new *l*-β-desmotropo-santonin. Theoretically, since three of the four possible active desmotropo-santonous acids have been known, one and only one dextrorotatory isomer is missing. Hence our new acid cannot be different from Clemo's acid obtained by reducing the *l*-desmotropo-β-santonin.

It appears that santonin and *l*-α-desmotropo-santonin possibly have the same configuration with respect to the three asymmetric centers at C_5, C_6, and C_{11}, whereas the configuration of β-santonin is similar to that of *l*-β-santonin. This would account for the facts that santonin changes into *l*-α-desmotropo-santonin when treated with dilute sulfuric acid at lower temperature but into *d*-β-desmotropo-santonin at a higher temperature or when treated with concentrated hydrochloric acid. There is perhaps in the first case only an aromatization of the dienone ring, while in the latter case a further configurational change of the lactone ring into a structure stable toward acids. Like the *l*-β-desmotropo-santonin, the β-santonin is already in possession of the acid-stable lactone ring. When it is treated with either sulfuric or hydrochloric acid, only the aromatization reaction is involved, and the same product, *l*-β-desmotropo-santonin, is obtained in both cases. This is what Clemo[14] actually found to be the case. The above supposition is further supported by the fact that the decrease in specific rotation accompanying the conversion of santonin into *l*-α-desmotropo-santonin is substantially the same as that accompanying the conversion of β-santonin into *l*-β-desmotropo-santonin.

Work on the stereoisomerism of desmotropo-santonin is in progress in this Laboratory and results will be published later.

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[11] Gave depression by admixture with *d*-santonous acid, m. p. 178–179° (Cannizzaro and Carnelutti, *Ber.*, **12**, 1574 (1879)).

[12] See, for example, Beilstein's "Handbuch," 4th Ed. Vol. X, pp. 317–323; Vol. XVIII, pp. 38–43.

[13] Perhaps still impure.

[14] Clemo, *J. Chem. Soc.*, 1343 (1934).