The Stereochemistry of Santonin and the Desmotroposantonins

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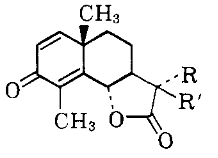
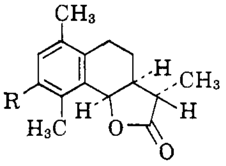
The recent revision of the configuration of santonin at C-11 from Ia to Ib,[1] supporting the conclusions reached by Abé, *et al.*,[2] presents serious difficulties in attempting to interpret the stereochemistry of the various desmotroposantonins (IIa, and stereoisomers thereof) derived from santonin on treatment with acid. The reactions of these compounds have been interpreted in an apparently logical manner to be indicative of structure Ia for santonin.[3] Two explanations are possible for this apparent anomaly; either the rather unlikely possibility that mild acid treatment of santonin to give *l*-α-desmotroposantonin gives rise to inversion at C-11, while more vigorous acid treatment to give *d*-β-desmotroposantonin does not; or alternatively, the configuration at C-11 is the same in santonin and *l*-α-desmotroposantonin, and the acid-catalyzed conversion of *l*-α-desmotroposantonin to *d*-β-desmotroposantonin is actually the conversion of a thermodynamically more stable isomer to one less stable.[4]



Ia. $R = H$; $R' = CH_3$
b. $R = CH_3$; $R' = H$



IIa. $R = OH$
b. $R = NH_2$
c. $R = H$

Reduction of the diazonium borofluoride derived from aminoisohyposantonin[5a] (IIb) with sodium borohydride[5b] gave isohyposantonin (IIc). Since the hyposantonins have been previously converted to *l*-α-desmotroposantonin,[5a] and have been shown to have the same configuration at C-11 as santonin,[1] *l*-α-desmotroposantonin must be IIa. Equilibration of either *l*-α- or *d*-β-desmotroposantonin with potassium *t*-butoxide in boiling *t*-butyl alcohol gave an α to β ratio of 8.7 ± 1 to 1 which corresponds to a free energy difference of 1.80 ± 0.1 kcal./mole at 83°.[6] It has been reported that treatment of *l*-α-desmotroposantonin with potassium carbonate in boiling xylene gives the β-isomer.[3d] Repetition of this experiment indicates that the α-isomer is soluble in hot xylene, while the β-isomer precipitates during the course of the reaction.[6] This will, of course, shift the equilibrium so that the principal product is the less soluble β-isomer. Thus it is apparent in contrast to the assumptions made by the earlier workers,[3] the α-desmotroposantonins are the more stable isomers and their conversion to the less stable β-isomers by acid was the cause of the incorrect assignment of configuration at C-11.[3] Since the acid-catalyzed rearrangements of either santonin or the α-desmotroposantonins to β-desmotroposantonins[7] are carried out under conditions such that the product precipitates during the course of the reaction it appears likely that the acid-catalyzed rearrangement is rendered effectively irreversible by the low solubility of the β-isomers in dilute sulfuric acid.[8]

In addition to clarifying the stereochemical relationships of the rearrangement products of santonin, the above experiments supply corroborative evidence for the configurational assignments at C-11 based on X-ray data[1b,c] and degradative evidence.[1a]

Experimental[9]

Hyposantonin.—Hyposantonin was prepared from santonin oxime using the method reported by Sumi and Dauben[10] for the preparation of hypoartemisin. From 22 g. of santonin oxime there was obtained 6.37 g. of hyposantonin m.p. 152–154° (lit.,[11] m.p. 152–153°).

Isohyposantonin.—(a) A solution of 0.2 g. of hyposantonin in 5 ml. of ethanol and 10 ml. of 10% aqueous potassium hydroxide was heated at reflux 2 hr. The solution was concentrated to about half its volume and acidified with concentrated hydrochloric acid to give an oil which slowly crystallized. Recrystallization from ethanol gave 0.19 g. (95%) of white crystals m.p. 164–167°, $[\alpha]^{27}\text{D}$ −72° (*c* 1.12 in benzene) (reported[12] m.p. 168°, $[\alpha]\text{D}$ −70.3).

(b) To a chilled solution of 0.3 g. of aminoisohyposantonin[5a] in 1.5 ml. of 50% fluoboric acid and 1.5 ml. of water was added 0.15 g. of sodium nitrite. A pale brown solid precipitated, which was collected and washed with chilled 5% fluoboric acid and ether. This solid was suspended in 5 ml. of methanol, 0.3 g. of sodium borohydride was added and the reaction mixture allowed to stand at room temperature 30 min. The pale yellow solution was poured into water, acidified with dilute hydrochloric acid; the precipitated solid collected and recrystallized from ethanol to give 0.08 g. (28%) of isohyposantonin, m.p. 165–168° undepressed on mixture with material from part a above. The infrared spectra of both compounds were superimposable, and both compounds had the same sign of rotation.

Equilibrations.—To a solution of 0.3 g. of potassium in dry *t*-butyl alcohol was added 0.25 g. of either *l*-α- or *d*-β-desmotroposantonin. The reaction mixture was heated at reflux 2 hr., cooled, poured into water, boiled to drive off the *t*-butyl alcohol, and acidified with concentrated hydrochloric acid to give 0.21 g. of cream-colored crystals. A portion of this sample was dissolved in ethyl acetate and its rotation determined. The values obtained indicated an α/β ratio of 8.7 ± 1, which was confirmed semiquantitatively by the infrared spectrum of the sample.

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[1] (a) M. Nakazaki and H. Arakawa, *Proc. Chem. Soc.*, 151 (1962); (b) J. D. M. Asher and G. A. Sim, *ibid.*, 111 (1962); (c) D. H. R. Barton, T. Miki, J. T. Pinhey, and R. J. Wells, *ibid.*, 112 (1962).

[2] Y. Abé, T. Miki, M. Sumi, and T. Toga, *Chem. Ind.* (London), 953 (1956).

[3] (a) R. B. Woodward and P. Yates, *ibid.*, 1391 (1954); (b) E. J. Corey, *J. Am. Chem. Soc.*, **77**, 1044 (1955); (c) N. M. Chopra, W. Cocker, and T. B. H. MacMurray, *Chem. Ind.* (London), 41 (1955); (d) W. Cocker and T. B. H. MacMurray, *Tetrahedron*, **8**, 181 (1960), give a concise summary of these arguments.

[4] It should be noted that in the revised stereoformula, Ib, the methyl at C-11 is *cis* to the hydrogen at C-6, while in Ia the methyl is *cis* to the C-7 carbon atom.

[5] (a) Y. Asahina and T. Momose, *Ber.*, **71**, 1421 (1938); (b) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 1251 (1961).

[6] In our hands the solubility of *d*-β-desmotroposantonin in boiling xylene is of the order of 3 mg./ml. while that of *l*-α-desmotroposantonin is greater than 40 mg./ml. In the repetition of Cocker's work there was only a trace of material left in the xylene used as solvent for the isomerization.

[7] (a) Huang-Minlon and C. P. Lo, *J. Chinese Chem. Soc.*, **10**, 126 (1943); (b) G. R. Clemo, *J. Chem. Soc.*, 1343 (1934).

[8] We have attempted to carry out homogeneous acid-catalyzed rearrangements; however the products have proven to be intractable tars.

[9] Infrared spectra were carried out as potassium bromide pellets using a Perkin-Elmer Model 137 spectrophotometer. Melting points were determined on a Hershberg melting point apparatus and are uncorrected. Rotational values were obtained using a Rudolph Model 70 polarimeter.

[10] M. Sumi and W. G. Dauben, *J. Am. Chem. Soc.*, **80**, 5704 (1958).

[11] J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, University Press, Cambridge, 1951, p. 252.