The Conversion of (−)-α-Santonin into (−)-β-Santonin

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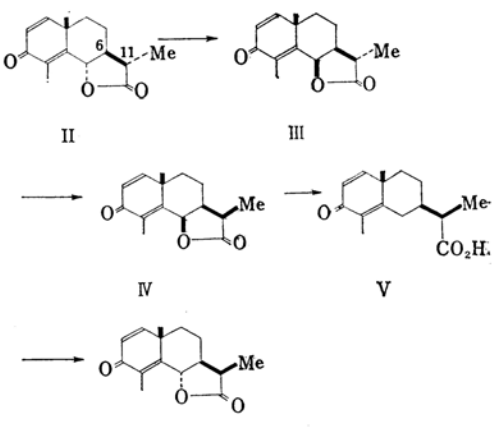
(−)-β-Santonin (I), together with (−)-α-santonin (II), was isolated by Clemo from samples of *Artemisia* obtained from the North-West Frontier of India[1] and was shown to be the C_{11} epimer of (−)-α-santonin by various chemical correlations.[2] Recently, Cocker and McMurry[3] converted (−)-β-santonin into (−)-α-santonin by boiling it with potassium carbonate in a xylene solution, but the reverse transformation has not yet been accomplished.

Since we happened to need a quantity of (−)-β-santonin for a stereochemical study of eudesmane-type sesquiterpene, we have tried to convert (−)-α-santonin into difficult-to-obtain (−)-β-santonin. In this communication we will report a successful attempt to effect this transformation.

Thermodynamical stability of the C_{11} methyl group is affected very subtly by the modes of the lactone-ring junctures of the santonin series of compounds. When both the C_{10} angular methyl group and the C_7 side chain have β-configurations,[4,5] the α-configuration is the choice for the stable configuration of the C_{11} methyl group in the *trans*-lactone, as can be seen from the above-mentioned work of Cocker and McMurry.[6] However, in the *cis*-lactone the situation is completely reversed; β-configuration is now favored by the C_{11} methyl group. These stereochemical relations were dramatically demonstrated by the stereospecific decarboxylations[7,8] of the epimeric pair of the lactone-acids, VIa and VIb, with *trans*-lactone junctures and the epimeric pair of the *cis*-lactone acids, VIIa and VIIb, with *cis*-lactone junctures; the former gave racemic α-santonin (II) exclusively, and the latter yielded racemic 6-epi-β-santonin (IV). Barton and his co-workers[9] made use of these experimental facts when they treated (−)-6-epi-α-santonin (III) derived from (−)-α-santonin following Ishikawa's procedure,[10] with potassium *t*-butoxide to obtain (−)-6-epi-β-santonin (IV), which is eventually our starting material.

The reductive cleavage of the *cis*-lactone



VIa X=CO_2H, Y=Me
b X=Me, Y=CO_2H

VIIa X=CO_2H, Y=Me
b X=Me, Y=CO_2H

1) G. R. Clemo, *J. Chem. Soc.*, **1934**, 1343. Kawatani also isolated (−)-β-santonin from various samples of *Artemisia* indigenous to Manchuria. T. Kawatani, *J. Pharm. Soc. Japan*, **73**, 783 (1953); T. Kawatani and T. Takeuchi, ibid., **74**, 793 (1954).

2) Summerized in J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge Univ. Press (1952), p. 320.

3) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, **1955**, 4430.

4) All configurations in this paper are depicted in absolute sense. Cf. M. Nakazaki and H. Arakawa, *Proc. Chem. Soc.*, **1962**, 151; This Bulletin, **37**, 464 (1964); M. Nakazaki and K. Ikematsu, ibid., **35**, 1904 (1962); **37**, 459 (1964).

5) According to the steroid convention, L. F. Fieser and M. Fieser, "Steroids," Reinhold Pub. Corp., New York (1959).

6) Unfortunately Cocker and co-workers interpreted this fact wrongly and assumed that (−)-α-santonin has β-configuration at the asymmetric center. (W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960)). Assuming that this *trans*-lactones of santonin series are isosteric with the C/D rings of steroids, Miki (T. Miki, *J. Pharm. Soc. Japan*, **75**, 416 (1955)) correctly deduced the α-configuration at this center, which was eventually proved by the Prelog's method. (Y. Abe, T. Miki, M. Sumi and T. Toga, *Chem. & Ind.*, **1956**, 953. Cf. Ref. 4.).

7) H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 500 (1956). He used the racemic compounds, but the ones with natural configurations are shown in VI and VII.

8) For these stereospecific reactions, the presence of the dienone structure is not necessarily requisite. M. Nishikawa, H. Hagiwara and K. Morita, ibid., **78**, 134 (1958).

9) D. H. R. Barton, J. E. D. Levisalles and J. T. Pinhey, *J. Chem. Soc.*, **1962**, 3472. To confirm the structure IV, IV was converted to (−)-β-desmotroposantonin. See Experimental section.

10) H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 504 (1956).

ring of IV with zinc powder afforded (−)-3-oxo-11-epi-eusantona-1,4-dienic acid (V),[11,12] b. p. 160～180°C/10^{-3} mmHg, $[\alpha]_D$ −107°.

The last of the synthetic sequence was achieved by selenium dioxide oxidation,[13] which has been shown to provide *trans*-lactone stereospecifically and which was successfully applied to the elegant total synthesis of (−)-α-santonin by the Takeda group.[14] This last operation afforded a 10% yield of (−)-β-santonin (I), m. p. 211～212°C, $[\alpha]_D$ −133° (in chloroform), the identity of which was established by mixed melting point determination and by a comparison of the infrared spectrum with an authentic sample of natural (−)-β-santonin,[15] as well as by the conversion into (−)-β-desmotroposantonin.

Experimental

(−)-6-Epi-α-santonin (III).—(−)-α-Santonin (II) was epimerized at C_6 according to the procedure of Ishikawa,[10] affording (−)-6-epi-α-santonin, m. p. 102～105°C, $[\alpha]_D^{19}$ −311° (*c* 1.5, ethanol); yield, 60%.

(−)-6-Epi-β-santonin (IV).—The epimerization of (−)-6-epi-α-santonin (III) at C_{11} was achieved following Barton's procedure.[9] Since the purification of III was accompanied by a considerable loss, the intermediate III was not purified but was directly converted into IV, m. p. 185～186°C, $[\alpha]_D^{19}$ −309° (*c* 0.56, ethanol), yield, 42% from (−)-α-santonin.

The Isomerization to (−)-β-Desmotroposantonin.—A solution of 0.1 g. of (−)-6-epi-β-santonin (IV) in 10 cc. of 55% sulfuric acid was kept at 55°C for 15 hr. Dilution with water precipitated crystals which were recrystallized from methanol to give needles, m. p. 250～252°C, $[\alpha]_D^{18}$ −115° (*c* 0.42, ethanol). A mixture of an equal amount of this (−)-β-desmotroposantonin with (+)-β-desmotroposantonin[2] was recrystallized from ethanol to yield racemic β-desmotroposantonin, m. p. 225～231°C.[2]

(−)-3-Oxo-11-epi-eusantona-1,4-dienic Acid (V).—To a solution of 3.6 g. of (−)-6-epi-β-santonin (IV) in 80 cc. of methanol, 8 g. of zinc powder was added. After 4 cc. of acetic acid had then been added, the reaction mixture was refluxed on a water bath for 8 min., cooled, and filtered. The solution was concentrated in vacuo to half volume and extracted with ether. After being washed with water, the ether solution was extracted with 10% aqueous sodium carbonate. The aqueous layer was made acidic with 2 N hydrochloric acid and extracted with benzene. The benzene extracts were combined, washed with water and a saturated sodium chlorine solution, and then dried over anhydrous magnesium sulfate. When the solvent was removed in vacuo, the residue ($[\alpha]_D^{13}$ −102° (*c* 3.0, ethanol)) was obtained; this was purified by chromatography on 80 g. of silica gel to yield 3.0 g. of a viscous oil. Distillation afforded a pale yellow liquid, b. p. 160～180°C (bath temperature)/10^{-3} mmHg, $[\alpha]_D^{24}$ −107° (*c* 3.8, ethanol). An ultraviolet spectrum in ethanol indicated a peak at 240 mμ (log ε 4.03).

Found: C, 71.25; H, 8.30. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

Cyclohexylamine Salt.—The salt was recrystallized from ethyl acetate to yield needles, m. p. 173～174°C, $[\alpha]_D^{24}$ −54.7° (*c* 0.7, ethanol).

Found: C, 72.30; H, 9.44; N, 4.01. Calcd. for $C_{21}H_{33}O_3N$: C, 72.58; H, 9.57; N, 4.03%.

2,4-Dinitrophenylhydrazone.—The 2,4-dinitrophenylhydrazone was prepared by the usual procedure and recrystallized from ethanol to give red needles, m. p. 216～218°C.

Found: N, 13.26. Calcd. for $C_{21}H_{24}O_6N_4$: N, 13.08%.

(−)-β-Santonin (I).—A mixture of 1.1 g. of the acid V, 1.1 g. of selenium dioxide, 22 cc. of acetic acid and 0.4 cc. of water was refluxed for 6 hr. The solution, freed from the selenium which precipitated, was then concentrated in vacuo, and the residue was extracted with benzene. The benzene extract was washed with water, 5% aqueous sodium carbonate, and water successively, and dried over anhydrous sodium sulfate. When the solution was concentrated, a crystalline solid separated. The product was filtered and recrystallized from methanol to give 0.1 g. of crystals, m. p. 211～212°C, $[\alpha]_D^{24}$ −133° (*c* 0.46, chloroform). A mixed melting point determination with an authentic (−)-β-santonin gave no depression. The identity was further confirmed by the infrared spectra of the synthetic and natural product, which were indistinguishable.

Found: C, 73.04; H, 7.44. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37%.

The Isomerization to (−)-β-Desmotroposantonin.—A solution of 50 mg. of the synthetic (−)-β-santonin (I) in 2 cc. of 55% sulfuric acid was kept at 55°C for 15 hr. The crystals, which were deposited upon the addition of water were recrystallized from methanol to give needles, m. p. 251～253°C. The mixed melting point with (−)-β-desmotroposantonin obtained from (−)-6-epi-β-santonin (vide supra) was 250～252°C.

Found: C, 72.66; H, 7.52. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37%.

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11) For the nomenclature, see Ref. 14.
12) The racemic compound, m. p. 147°C was prepared from racemic 6-epi-β-santonin "santonin D". T. Miki, *J. Pharm. Soc. Japan*, **75**, 412 (1955).
13) T. Miki, ibid., **75**, 407 (1955).
14) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956).
15) Generously supplied by Dr. Toyohiko Kawatani, National Hygienic Laboratory, Tokyo.