The Absolute Configuration of the Asymmetric Center at Position of 7 of α- and β-Desmotroposantonin

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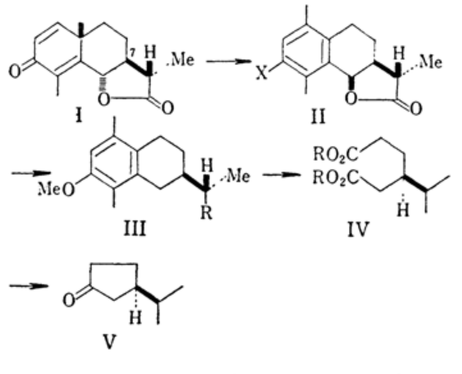
Although the bulk of the evidence[1] mainly deduced from the stereochemistry of α-(II: X, OH) and β-desmotroposantonin strongly favors R-configuration at position 11 of (−)-α-santonin (I), recent publications[2,3] confirmed Abe's assignment[4] of the S-configuration at this center. To settle this discrepancy, the determination of the absolute configuration of α- and β-desmotroposantonin seemed necessary.

The methyl ester of (+)-α-desmotroposantonous acid methyl ether (III: R, CO_2Me) was reduced with lithium aluminum hydride to the alcohol (III: R, CH_2OH), b.p. 160~180°C/10^{-2} mmHg, $[\alpha]_D^{27}$ +60.8° (*c* 2.90 in ethanol), (phenylurethane: m. p. 125~126°C, $[\alpha]_D^{27}$ +47.3° (*c* 0.65 in ethanol)), which was converted with phosphorus tribromide/pyridine to the bromide (III: R, CH_2Br), b. p. 150~160°C/10^{-2}mmHg, $[\alpha]_D^{28}$ +66.4° (*c* 2.24 in ethanol). The bromide was refluxed with lithium aluminum hydride in tetrahydrofuran to afford the methyl ether (III: R, Me), b. p. 145~155°C/3 mmHg, n_D^{29} 1.5328, $[\alpha]_D^{25}$ +60.0° (*c* 2.52 in ethanol), (Found: C, 83.0; H, 10.4. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41%). Exhaustive ozonolysis (30 hr.) of III (R, Me) followed by peracetic acid oxidation gave crude β-isopropyladipic acid (IV: R, H) which was purified via the dimethyl ester (IV: R, Me), b. p. 100~150°C (bath temp.)/5 mmHg. Heating IV (R, H) with barium hydroxide at 280~300°C gave 3-isopropylcyclopentan-1-one (V) which was directly converted into the semicarbazone, m.p. 181~183°C, $[\alpha]_D^{31}$ +43.8° (*c* 0.48 in ethanol), (Found: C, 59.2; H, 8.9: N, 22.7. Calcd. for $C_9H_{17}ON_3$: C, 58.98; H, 9.35; N, 22.93%). Its identity with R-(+)-3-isopropylcyclopentan-1-one semicarbazone[5,6], m. p. 186~187°C, $[\alpha]_D^{26}$ +65.2° (*c* 0.62 in ethanol) prepared from R-(+)-dihydrolimonene[7] was established by mixed melting point (181~183°C) and comparison of infrared absorption (in chloroform).



This correlation established the R-configuration of (−)-α-desmotroposantonin (II: X, OH) at position 7. Since (−)-α-desmotroposantonin may be derived from (−)-α-santonin via isohyposantonin (II: X, H) without affecting the configuration at C_7[8], the R-configuration of (−)-α-santonin at this center is also confirmed.

The fact that (+)-β-desmotroposantonin has the opposite configuration from (−)-α-desmotroposantonin at C_7 was established by the conversion of the former into the enantiomer of III (R, Me), b. p. 110~120°C/0.1 mmHg, n_D^{29} 1.5322, $[\alpha]_D^{28}$ −65.1° (*c* 1.51 in ethanol), (Found: C, 82.6; H, 10.3. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41%), whose infrared absorption spectrum was found superimposable on that of III (R, Me).

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[4] Y. Abe, T. Miki, M. Sumi and T. Toga, *Chem. & Ind.*, **1956**, 953.

[5] J. v. Braun and G. Werner, *Ber.*, **62**, 1050 (1929).

[6] G. Burger and K. Macbeth, *J. Chem. Soc.*, **1946**, 145.

[7] A. J. Birch, *Ann. Reports*, **47**, 191 (1950).

[8] Y. Asahina and T. Momose, *Ber.*, **71**, 1421 (1938), and our unpublished observation on the conversion of (−)-3-amino-isohyposantonin (II: X, NH_2) back to isohyposantonin (II: X, H).