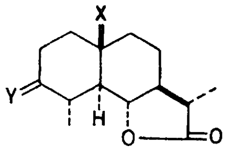
Synthesis of Tetrahydrosantonin Derivatives Functionalised at their Angular Methyl Groups

By MASATAKA WATANABE and AKIRA YOSHIKOSHI*
(*Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai* 980, *Japan*)

Summary Functionalisation of the angular methyl group of the tetrahydrosantonin (**1**) was achieved by a method involving, as the key step, the photochemical oxidation of the bromohydrin (**7**) derived therefrom, subsequently leading to compounds (**3**) and (**10**).

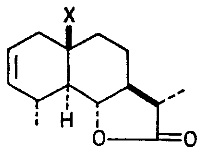
Tetrahydrosantonins as well as α-santonin have frequently been used as starting materials for sesquiterpene synthesis.[1] Similarly, tetrahydrosantonin derivatives such as (**3**) functionalised at their angular methyl groups would be useful for the synthesis of sesquiterpenoids which have oxygenated angular methyl groups. We now describe the functionalisation of the angular methyl group of the tetrahydrosantonin (**1**).[2,3]



(1); X = Me, Y = O

(2); X = Me, Y = p-$MeC_6H_4SO_2NHN$

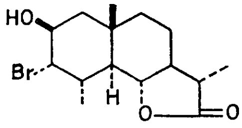
(3); X = CO_2Me, Y = O



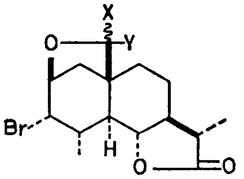
(4); X = Me

(5); X = CO_2H

(6); X = CHO

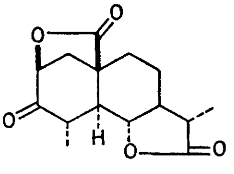


(7)



(8) X,Y = O

(9) X = OAc, Y = H



(10)

The tosylhydrazone (**2**) derived from (**1**) (97%) was treated with lithium di-isopropylamide giving the olefin (**4**) (76%),[4] which was then converted into the bromohydrin (**7**) (N-bromosuccinimide–H_2O–Me_2SO; 15 °C; 90%), m.p. 118—120 °C. Irradiation of a refluxing cyclohexane solution of (**7**) with a tungsten lamp in the presence of lead tetra-acetate and iodine afforded a mixture of the bromolactone (**8**) (*ca.* 60%), m.p. 193—194 °C, and the hemiacetal acetate (**9**) ($<$ 10%), m.p. 159—162 °C.† In practice, the bromohydrin (**7**) was, without purification, photochemically oxidised as above, and then the crude product was treated with Jones reagent yielding the bromolactone (**8**)‡ (67% overall yield).

Treatment of (**8**) with zinc and acetic acid at 60—70 °C gave the carboxylic acid (**5**) (82%) (methyl ester, m.p. 123·5—126 °C). Similarly, (**9**) gave the aldehyde (**6**) (68%), m.p. 128—130 °C, with zinc–acetic acid. *m*-Chloroperbenzoic acid oxidation followed by Jones oxidation of (**5**) produced the ketolactone (**10**) (61%), m.p. 238—241 °C; reductive cleavage of the lactone ring of (**10**) with zinc–acetic acid and subsequent esterification with diazomethane gave the keto-ester (**3**) (85%). The overall yield of (**3**) from (**1**) was *ca.* 18%.

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† When calcium carbonate was added the yield of (**8**) decreased, while the formation of (**9**) increased.

‡ On Jones oxidation, (**8**) was obtained from (**9**) in 61% yield.

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[1] For a recent review, see C. H. Heathcock, 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, 1973, pp. 197—558.

[2] E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, 1965, **87**, 5736.

[3] Another functionalisation of an angular methyl group in the santonin system was recently reported using the C(6)-β-axial hydroxy-group; A. Murai, K. Nishizakura, N. Katsui, and T. Masamune, *Tetrahedron Letters*, 1975, 4399; *Bull. Chem. Soc. Japan*, 1977, **50**, 1206.

[4] Recently the preparation of this olefin by the same procedure was reported; P. A. Grieco and M. Nishizawa, *J. Org. Chem.*, 1977, **42**, 1717.