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Modification of α -Santonin. I. An Abnormal Chlorination of 3-Hydroxy-4,5-epoxy-6,11 β H-eudesm-1-en-6,12-olide with Methanesulfonyl Chloride

An abnormal, stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11 β H-eudesm-1-en-6,12-olide (**5**, **6**, **7** and **8**) with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)-pyridine is described.

The stereochemistry of the chlorides (**9**, **10**, **11** and **12**) were confirmed by their nuclear magnetic resonance spectra and chemical reactions.

It is well known that mesylation (or tosylation) of an allylic alcohol (**I**) with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)-pyridine produce a mixture of the corresponding mesylate (or tosylate (**II**)) and the rearranged isomer (**III**), but there are few reports on stereospecific chlorination under these conditions.

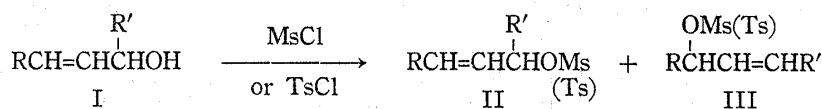


Chart 1

In this communication, we wish to report an abnormal stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11 β H-eudesm-1-en-6,12-olide (**5**, **6**, **7**, **8**) by the action of methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)-pyridine.

α -Santonin (**1**) was treated with *m*-chloroperbenzoic acid in the presence of 4,4'-thiobis-(6-*t*-butyl-3-methylphenol) as a radical inhibitor¹⁾ to give the α -epoxide (**2**)^{2a-c)} (yield 38.6%), β -epoxide (**3**)^{2a,c)} (yield 43.2%) and diepoxide (**4**)^{2c)} (yield 1.8%). Selective reduction of the carbonyl group of **2** with LiAlH₄ (tetrahydrofuran, -78°) afforded a mixture of the β -alcohol (**5**) (yield 16.7%, mp 200-202°, NMR (CDCl₃) δ : 4.27 (1H, d, *J*=5.0 Hz; C₃-H), 5.37 (1H, d, *J*=10.0 Hz; C₁-H), 5.65 (1H, dd, *J*=10.0, 5.0 Hz; C₂-H) and α -alcohol (**6**) (yield 65.6%, mp 196-197°, NMR (CDCl₃) δ : 4.18 (1H, dq, *J*=11.0, 2.0, 2.0 Hz; C₃-H), 5.26 (1H, dd, *J*=10.0, 2.0 Hz; C₁-H), 5.46 (1H, dd, *J*=10.0, 2.0 Hz; C₂-H), while reduction of **2** with NaBH₄ gave a mixture of **5**, **6** and corresponding dihydro derivatives (**13**, **14**).

Similar reduction of **3** with LiAlH₄ gave a mixture of the β -alcohol (**7**) (yield 65.9%, mp 106-107°, NMR (CDCl₃) δ : 4.12 (1H, m, C₃-H), 5.22 (1H, dd, *J*=10.5, 2.0 Hz; C₁-H), 5.43 (1H, dd, *J*=10.5, 2.0 Hz; C₂-H) and α -alcohol (**8**) (yield 15.6%, mp 158-160°, NMR (CDCl₃) δ : 4.20 (1H, d, *J*=5.0 Hz; C₃-H), 5.27 (1H, d, *J*=10.5 Hz; C₁-H), 5.57 (1H, dd, *J*=10.5, 5.0 Hz; C₂-H).

- 1) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *J. C. S. Chem. Comm.*, **1972**, 64.
- 2) a) E. Wedekind and K. Tettweiler, *Ber.*, **64**, 1796 (1931); b) J.B. Hendrickson and T.L. Bogard, *J. Chem. Soc.*, **1962**, 1678; c) M. Yanagita, T. Hirose, and T. Okura, The 91th Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, Apr. 1971.

The configurations of C_3 -H of the alcohols were assigned to those shown on the structures (5, 6, 7 and 8) respectively from the coupling patterns³⁾ of C_3 -H, C_2 -H and C_1 -H on their NMR spectra. Treatment of 5 with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)-pyridine (0°, 3 hr) did not afford the corresponding mesylate (or tosylate), but gave an unexpected chlorinated compound (9) (yield 92.3%, mp 189–191°, NMR (CDCl₃) δ : 4.51 (1H, m, C_3 -H), 5.32 (1H, dd, J =10.0, 2.0 Hz; C_1 -H), 5.49 (1H, dd, J =10.0, 2.0 Hz; C_2 -H). For the structure of the chlorinated compound, possibility of the rearranged isomer (17) was excluded by the following experiments.

The alcohol 5 and 6 was hydrogenated with H₂/PtO₂ to give 13 and 14. Chlorination of 13 and 14 with SOCl₂-pyridine gave the corresponding chloride 15 and 16 respectively which was obtained by reduction of 9 and 10.

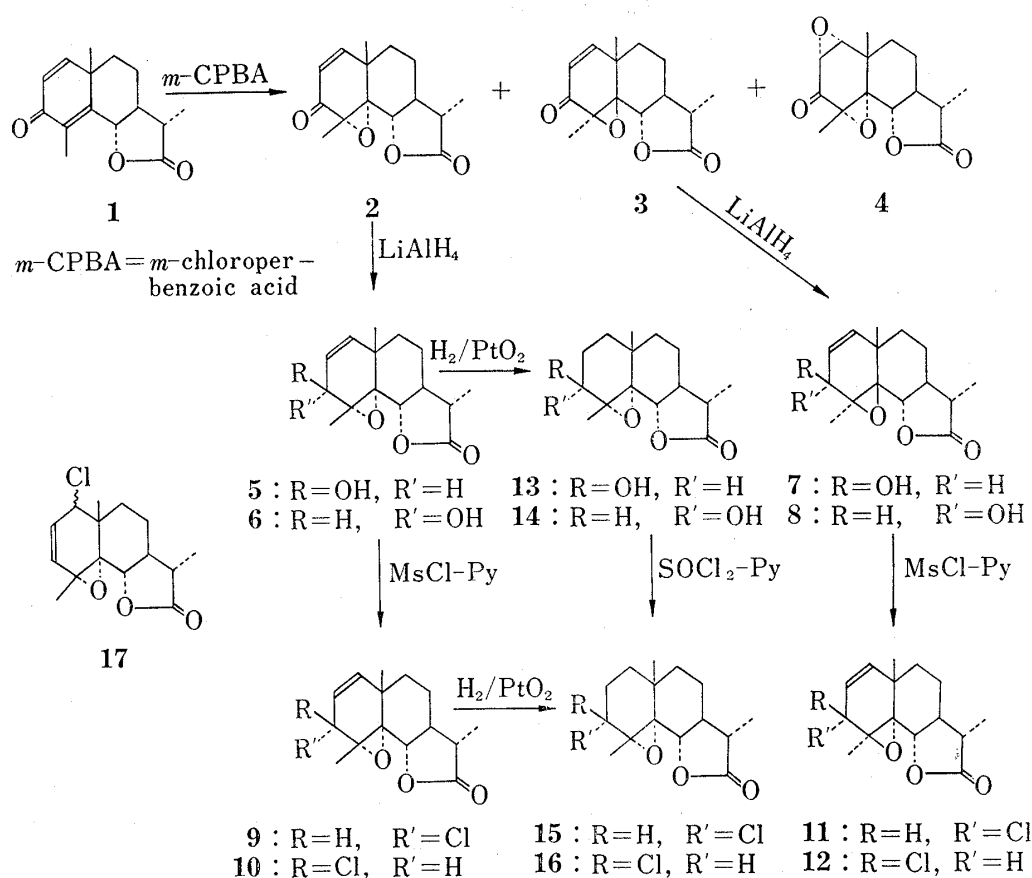


Chart 2

Inversion of the configuration of C_3 -H during the chlorination was verified by the comparison of the coupling constants of C_3 -H of the original alcohol (5) and the chloride (9).

By the same treatment, the other three alcohols (6, 7 and 8) were also converted stereospecifically into the corresponding chlorides (10, 11 and 12) having the inverted configuration of C_3 -H (10; yield 85.6%, mp 189°, NMR (CDCl₃) δ : 4.55 (1H, d, J =5.0 Hz; C_3 -H), 5.34 (1H, d, J =10.0 Hz; C_1 -H), 5.64 (1H, dd, J =10.0, 5.0 Hz; C_2 -H), 11; yield 90.8%, mp 223–224°, NMR (CDCl₃) δ : 4.70 (1H, m, C_3 -H), 5.29 (1H, dd, J =10.0, 2.0 Hz; C_1 -H), 5.47 (1H, dd, J =10.0, 2.0 Hz; C_2 -H), 12; yield 98.0%, mp 176–178°, NMR (CDCl₃) δ : 4.56 (1H, d, J =5.0 Hz; C_3 -H), 5.24 (1H, d, J =10.5 Hz; C_1 -H), 5.64 (1H, dd, J =10.5, 5.0 Hz; C_2 -H). Further

3) S. Sternhell, *Quart. Rev.*, 1969, 236.

studies on this abnormal, stereospecific chlorination and reactivities of the chlorides are now in progress.

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