MODIFICATION OF α-SANTONIN Ⅶ[1]

CHLORINATION OF α-SANTONIN DERIVATIVES

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Abstract —— Chlorination of α-santonin derivatives with iodobenzene dichloride or dichlorourethane under photo-irradiation has been investigated. The structures of the chlorides were elucidated by their ^{1}H-NMR data including decoupling experiments.

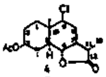
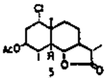
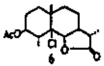
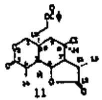
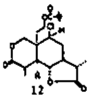
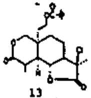
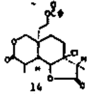
A number of antitumor sesquiterpenoids such as vernolepin, eupaserrin and euparotin have been isolated from the plants belonging to *Compositae*.[2] All these compounds contain oxygen functions at C-8 positions and α-methylene γ-lactone moieties in their molecules which have been presumed to be essential factors for the appearance of cytotoxicity against tumor cells. In continuation of our work on the synthesis of antitumor sesquiterpenoids, we have reported the synthesis of 8-deoxyvernolepin starting from α-santonin.[3]

In this paper, we describe some results on chlorination of α-santonin derivatives which may be a method to find a clue for introduction of the hydroxyl or acyloxy group to the C-8 position. We first examined chlorination of tetrahydrosantonin(1). Irradiation of a mixture of 1 and iodobenzene dichloride(3.0 eq.) in benzene with a 200 W tungsten lamp for 75 min in a stream of nitrogen gave a mixture of monochloride(2) and 1 which was separated by silica gel chromatography. The monochloride(2; 51.7% yield)[4] was confirmed as 2α-chlorotetrahydrosantonin(2)[5] by comparison of its IR and ^{1}H-NMR spectra with those of an authentic sample.

Next we examined chlorination of 3β-acetoxyeudesmanolide(3) which was prepared from 1 by two step procedures as follows. Reduction of 1 with $NaBH_4$ in methanol gave a mixture of alcohols(3β-OH : 3α-OH = 7 : 3) which was separated by column chromatography on silica gel and then the major alcohol was converted to the acetate [3 ; mp 140-142°C , ^{1}H-NMR[6] : 1.00(3H, s; H-15), 1.07(3H, d, J=6.4 Hz; H-14), 1.21(3H, d, J=6.8 Hz; H-13), 3.84(1H, t, J=10.5 Hz; H-6), 4.39(1H, sex; H-3)] by usual means. Chlorination of 3 under the same reaction conditions as mentioned above gave a mixture of 3 and chlorides which was subjected to silica gel column chromatography to remove 3, and then the chlorides were separated by high performance liquid chromatography (HPLC) to afford the chlorides (4)(33.3% yield, mp 172-174°C , ^{1}H-NMR; see Table 1), (5)(32.2% yield, mp 232-235°C ,

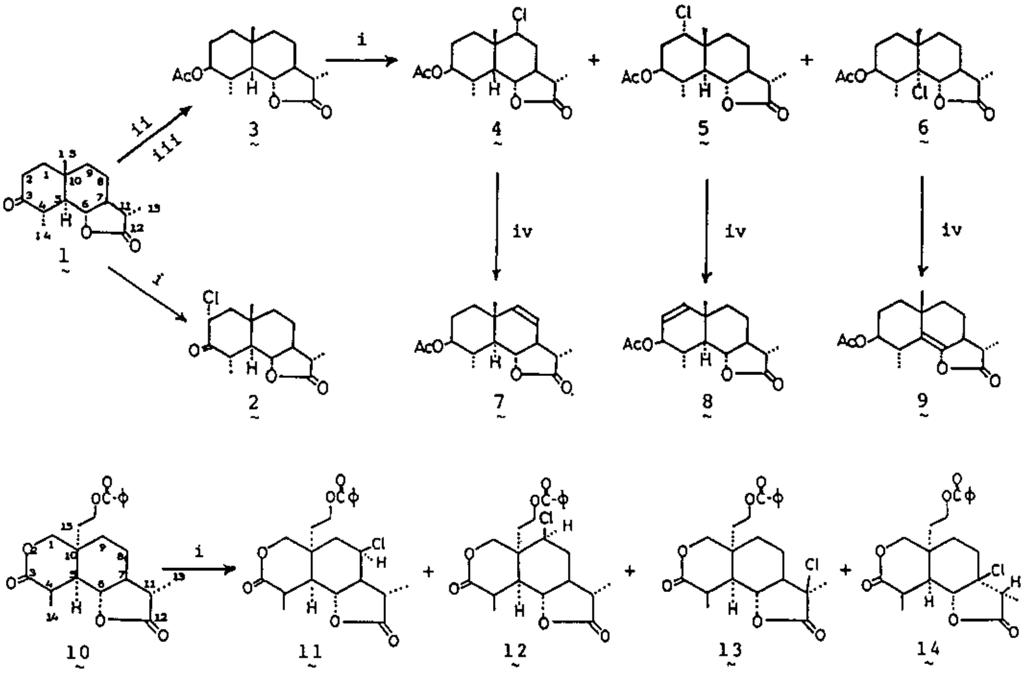
^{1}H-NMR; see Table 1) and (6)(27.9% yield, mp 178-180°C, ^{1}H-NMR; see Table 1).

Table 1. ^{1}H-NMR data for chlorides(δ, $CDCl_3$, 400 MHz)

Compound	H-1	H-3	H-4	H-5	H-6	H-7	H-8	H-9	H-11	H-13	H-14	H-15
 4		4.39m			3.90t J=10.3			4.01t J=2.7	2.34m	1.23d J=7.0	1.11d J=7.0	1.14s
 5	3.93t J=2.9	4.90m			3.84t J=10.3				2.23m	1.22d J=7.0	1.12d J=7.0	1.14s
 6		4.91m	2.31m		4.16d J=10.5	2.42m			2.26m	1.22d J=6.8	1.17d J=6.4	1.30s
 11	4.14dd J=1.5, 12.2 4.63d J=12.2		2.69m	1.67m	4.44t J=10.7	2.05m	4.52m	2.30m	2.75m	1.27d J=7.3	1.44d J=7.3	
 12	4.48dd J=1.5, 12.2 4.59d J=12.2		2.84m	2.04m	4.14t J=10.5	1.73m		4.33dd J=6.0, 11.0	2.43m	1.24d J=7.0	1.42d J=7.0	
 13	4.12br.d J=12.2 4.29d J=12.2		2.74m	1.67dd J=6.0, 10.5	4.35t J=10.5	2.00m				1.58s	1.44d J=7.0	
 14	4.10d J=12.2 4.30d J=12.2		2.87m	2.16dd J=2.0, 10.5	4.64d J=2.0				3.13q J=7.0	1.30d J=7.0	1.46d J=7.0	

The ^{1}H-NMR spectra of 4 and 5 showed the presence of the signals due to hydrogen atoms attached to the carbon bearing chlorine atoms at δ4.01(t, J=2.7 Hz) and 3.93(t, J=2.9 Hz) respectively (Table 1). The coupling patterns of these proton signals indicated that the chlorine atoms in 4 and 5 were introduced in axial configurations at the C-1 or C-9 position. In order to locate the chlorine atoms, 4 and 5 were converted to the corresponding olefins [7 : 46.9% yield, ^{1}H-NMR : 4.41(1H, m, H-3), 5.42(1H, dd, J=3.0, 9.0 Hz, H-9), 5.57(1H, dd, J=2.0, 9.0 Hz, H-8), 8 : 70.3% yield, ^{1}H-NMR : 5.00(1H, sex, J=2.0, 3.0, 9.0 Hz, H-3), 5.45(1H, dd, J=3.0, 10.0 Hz, H-1), 5.60(1H, dd, J=2.0, 10.0 Hz, H-2)] by the action of DBU in refluxing xylene, respectively. While the coupling pattern of H-3 in 7 did not show any change in comparison with that of 4, the couplings between H-3 and olefinic protons were observed in 8. From these chemical transformations and ^{1}H-NMR data, the structures of 4 and 5 should be represented as shown in Chart 1. In the ^{1}H-NMR spectrum of the chloride (6), the H-6 signal was appeared as a doublet and no signal due to the hydrogen on the chlorinated carbon atom was observed. On treatment with DBU-xylene, 6 gave an olefin[9 : 70.3% yield, ^{1}H-NMR : 1.17(3H, s, H-13), 1.27(3H, d, J=7.0 Hz, H-13), 4.46(1H, m, H-3)] which did not show any olefinic proton signals in its ^{1}H-NMR spectrum. Furthermore, the

H-3 signal resonated at 0.52 ppm down field as compared with that of 3, the fact suggesting the steric proximity (1,3-diaxial relation) between the H-3 and the chlorine atom. These spectral data indicated that the chlorine atom in 6 should be α-oriented at C-5



i) hν, iodobenzene dichloride or dichlorourethane, ii) $NaBH_4$, iii) Ac_2O-pyridine, iv) DBU-xylene

Chart 1

Finally, we investigated the chlorination of dilactone (10) which was an intermediate in our synthesis of deoxyvernolepin. Irradiation of a mixture of 10 and dichlorourethane (5.0 eq.) in benzene with two 200W tungsten lamps for 2 h afforded a mixture of chlorides (11, 12, 13, 14) and 10, which was submitted to silica gel column chromatography to separate the starting material and then the chlorides was separated by HPLC (Column : SENSHU Pack 8 × 300 mm, Nucleosil 50-5, Solvent : hexane :AcOEt = 4 : 1) to give 11[25.4% yield, oil, MS : m/z 420(M^+)] , 12[5.0% yield, oil, MS : m/z 420(M^+)] , 13[7.7% yield, oil, MS : m/z 420(M^+)] , and 14[12.0% yield, mp 62-65° , MS : m/z 420 (M^+)] .

The structures of chlorides were determined by their ^{1}H-NMR data and decoupling experiments as follows. In the ^{1}H-NMR spectrum of 11, the multiplicity of signals due to hydrogen on the chlorinated carbon indicated that a chlorine atom must be introduced at C-8 position, and this was further confirmed by the fact that the H-8 proton signal was clearly decoupled and appeared as a sharp doublet ($J_{7,8}$=3.4 Hz) on irradiation of H-9 methylene protons. Thus, the structure of the chloride (11) was proved to be 11 in Chart 1. In the ^{1}H-NMR spectrum of the chloride (12), the proton signal attributable to the hydrogen on the chlorinated carbon was observed as a double doublet at δ4.33(J=6.0, 11.0 Hz). This signal collapsed to a doublet by irradiation of H-8α or H-8β proton. From these results, the configuration of the chlorine atom in 12 was assigned to β-equatorial orientation at C-9 as shown in Chart 1. In the ^{1}H-NMR spectrum of 13, the H-13 signal was observed at 1.58 ppm as a singlet and the H-6 signal (δ 4 35) resonated at 0.38 ppm downfield as compared with that of 10[δ3.97(t, J=10.5 Hz), H-6] . Thus, the structure of 13 can be represented as depicted in Chart 1

The ^{1}H-NMR spectrum of 14 showed no signal attributable to hydrogen on the chlorinated carbon. In addition, the H-11 and the H-6 signals were appeared as a quartet [δ3.13(q, J=7.0 Hz. H-11)] and a doublet [δ4.64(d, J=2.0 Hz, H-6)] , respectively, this fact suggesting that the chlorine atom was introduced at C-7. Whereas the *trans*-γ-lactone compounds (4-13) showed large coupling constants ($J_{5,6}$=10.3-10.7 Hz) between H-5 and H-6 in their ^{1}H-NMR spectra ($\angle H_5$-H_6=180°), a small coupling constant ($J_{5,6}$=2.0) was observed in 14. From the consideration based on Dreiding models, the small coupling constant between H-6 and H-5 may be expected in a *cis*-lactone ($\angle H_5$-H_6= ~ 80°). Furthermore, the H-6 and H-11 signals were appeared at 0.5 ppm and 0.70 ppm down field respectively as compared with those of 12, these downfield shifts suggesting the β-oriented configuration of the H-6, chlorine and the H-11. Thus, the structure of the chloride (14) was confirmed as depicted in Chart 1.

It is surmizable that the compound (14) was formed by the formation of an α,β-unsat. lactone by hydrogen abstraction at C-7 by chlorine radical followed by the Michael addition of hydrogen chloride to the resulting double bond Studies on transformation of the chlorides to the corresponding acetoxy or hydroxy compound are now in progress.

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REFERENCES AND NOTES

1) Part Ⅶ. T.Shimizu, M.Saito, Y.Ohgoshi, Y.Fujimoto and T.Tatsuno, *Heterocycles*, 17 53 (1982).

2) a) S.M.Kupchan; M.Maruyama, R.J.Hemingway, S.Shibuya, P.D.U.Hardy and G.A.Sim, *J. Am. Chem. Soc.*, 93, 4914 (1971).

   b) R.W.Doskotch, C.D.Hufford and F.S.El-Fetaly, *J. Org. Chem.*, 37, 2740 (1972).

   c) W.Herz and I.Wahlberg, *J. Org. Chem.*, 38 2485 (1973).

   d) A.T.McPhail, K.D.Onan, K.H.Lee, T.Ibuka and H.C.Huang, *Tetrahedron Lettters*, *3203* (*1974*).

e) A.T.McPhail and K.D.Onan, *J. Chem. Soc., Perkin* II, 578 (1976).

f) W.Herz, R de Groote and R.Murari, *J. Org. Chem.*, 43, 3559 (1978).

g) K.Ito, Y.Sakakibara, M Haruna and K.H.Lee, *Chem. Letters*, 1469 (1979).

3) Y.Fujimoto, H.Miura, T.Shimizu and T.Tatsuno, *Tetrahedron Letters*, 21, 3409 (1980). An alternative synthesis of (+)-8-deixyvernolepin from α-santonin was reported by M. Watanabe and A. Yoshikoshi, *Chem. Letters*, 1315 (1980).

4) The all chlorination reactions in the text were carried out on 0.3-0.5 mmol scale. The yields on chlorination were based on consumed starting material and 50~ 70% of starting material was recovered in all cases.

5) W.Cocker and T.B.H.McMurry, *J. Chem. Soc.*, 4549 (1956).

6) The ^{1}H-NMR(δ, 400MHz) data in the text were taken in $CDCl_3$ containing TMS as an internal standard unless otherwise stated.

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