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The Structure of Petasitolone, a New Constituent of *Petasites japonicus* Maxim[1]

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Petasitolone(I), a new sesquiterpene isolated from *Petasites japonicus* Maxim. has been shown to be 8-oxo-11-hydroxy-$\Delta^{6(7)}$-eremophilene by a physico-chemical method, and synthesized from the known fukinone(VI).

The constituents of flower stalks of *Petasites japonicus* Maxim. have been studied.[2-4] We reported the isolation of fukinone (VI) from the methanolic extract of a cultivated variety "Aichiwasebuki" of this plant. We also isolated a new sesquiterpene named petasitolone from the extract.

Petasitolone (I), $C_{15}H_{24}O_2$, bp 92°C/0.15 mmHg, $[\alpha]_D^{24}+16.7°$, a colorless oil, was obtained by steam and vacuum distillation, and chromatography on silica gel. The two oxygen atoms and one double bond were readily characterized by spectroscopic data: IR bands (Fig. 1) at 3480, 1170 (OH), 1665 cm^{-1} and an UV maximum at 237.5 mμ (α,β-unsaturated C=O). Its NMR spectrum indicates one isolated olefinic proton at 6.6[5] due to a β-hydrogen of an α,β-unsaturated ketone, one hydroxyl proton at 3.52, two methyls attached to a carbon bearing a hydroxyl at 1.30, one tertiary methyl at 1.11 and one secondary methyl at 0.93 (d, J=7 Hz). Petasitolone I failed to yield a semicarbazone but afforded a mixture of two 2,4-dinitrophenylhydrazones, $C_{21}H_{28}O_5N_4$, mp 159—160°C and $C_{21}H_{26}O_4N_4$, mp 173—174°C, by Brady's method. The latter $C_{21}H_{26}O_4N_4$ shows no OH band in its IR spectrum and was found to be identical with anhydropetasitolone (II) by mixed melting point determination.

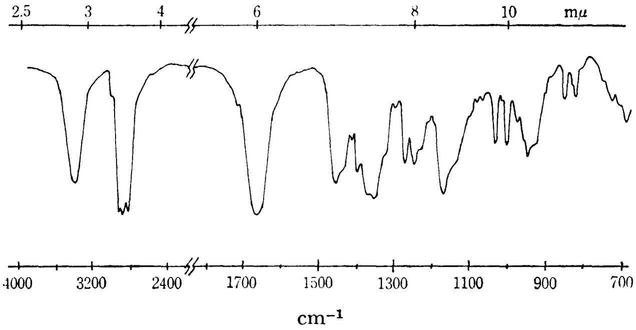

Fig. 1. IR spectrum of petasitolone.

From the above results, petasitolone is strongly presumed to be a bicyclic sesquiterpene containing an α, β-unsaturated carbonyl and a dimethylcarbinol group. The conclusion concerning the structure was confirmed by the following reactions.

Petasitolone was dehydrated with phosphorus oxychloride-pyridine in the cold to yield anhydropetasitolone (II), $C_{15}H_{22}O$, which exhibits an IR band at 1675 cm^{-1} and an UV maximum at 254 mμ (α,β-unsaturated C=O). Its NMR spectrum shows new signals: *i.e.*, a slightly split singlet at 1.86 for a vinyl methyl and two signals at 5.02 and 4.88, respectively for an end-methylene group.

Catalytic hydrogenation of petasitolone with platinum oxide-acetic acid yielded a mixture of dihydropetasitolone (III), $C_{15}H_{26}O_2$ and desoxydihydropetasitolone (IV), $C_{15}H_{26}O$ in the approximate ratio of 2: 3. Upon hydrogenation with palladium charcoal in ethanol, petasitolone furnished predominantly dihydropetasitolone III. Hydrogenolysis to the desoxydihydro compound IV implies that the hydroxyl group of petasitolone can be assumed to be located in the allylic position to the double bond. The desoxydihydro compound IV was found to be identical with the known dihydrofukinone (IV)[3] by comparison of IR spectra and ORD (-Cotton effect) curves, and mixed melting point determination of the two 2,4-dinitrophenylhydrazones.

Thus, from the above evidence the structure of petasitolone, dihydropetasitolone and desoxydihydro compound can be assigned as shown in stereoformulas I, III, and IV.

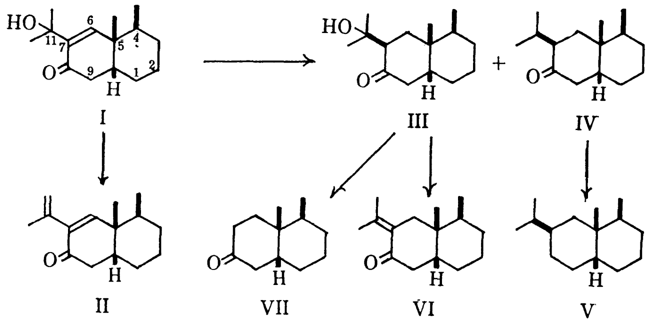

Fig. 2

Along with the above work, the following reactions were examined.

The desoxydihydro compound IV was converted into the known 7β-eremophilane (V)[3,6] *via* ethylene thioketal followed by desulfurization with Raney nickel. On the other hand, when dihydropetasitolone III was subjected to preparative glc for purification, it gave a de-

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[1] K. Naya, H. Yoshimura and M. Kobayashi, 22nd Annual Meeting of Chemical Society of Japan (1969), Collective Papers Vol. 3, p. 1885.

[2] K. Naya and I. Takagi, *Tetrahedron Lett.*, **1968**, 629.

[3] K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, **24**, 5871 (1968).

[4] K. Naya, I. Takagi, M. Hayashi, S. Nakamura, M. Kobayashi, and S. Katsumura, *Chem. Ind.* (London), **1968**, 318.

[5] All chemical shifts are reported in ppm as δ-values.

[6] L. Novotny, J. Jizba, V. Herout, F. Sorm, L. H. Zalkow, S. Hu, and C. Djerassi, *Tetrahedron*, **19**, 1101 (1963).

composition product $C_{12}H_{20}O$ with loss of the dimethylcarbinol unit. The product was identical with desisopropylidenefukinone (VII) obtained previously by base catalyzed retro-aldol reaction from fukinone VI. Dehydration of dihydropetasitolone III with phosphorus oxychloride-pyridine yielded the known fukinone VI as expected.

Synthesis of Petasitolone (I). We postulated that naturally occurring intermediate for petasitolone I is fukinone VI which is converted in the plant to petasitolone I by photochemical oxidation. Little is known about the photosensitized addition of oxygen to an α,β-unsaturated carbonyl system. In fact, the mode of addition to the double bond conjugated with the carbonyl group was found to be similar to that found by Schenck in simple olefinic systems.[7]

When fukinone was irradiated in the presence of rose bengal in atmospheric oxygen followed by reduction with sodium sulfite, petasitolone I was obtained as the main product (45%). The details of the oxidation products will be reported later.

Experimental

All the melting and boiling points are uncorrected. Mass spectra were measured with a Hitachi RMU-6 mass spectrometer; ion source temperature 250°C; evaporation temperature 150°C. IR spectra were recorded with a JASCO DS-402G spectrophotometer and UV spectra were obtained with a Cary Model 14 spectrophotometer. ORD curves were measured with a JASCO spectropolarimeter Model ORD-5. NMR spectra were determined with a Japan Electron Optics JNM-C-60 spectrometer, using TMS as an internal standard ($\delta=0$) and $CDCl_3$ as solvent. Analytical and preparative glc were performed with a Shimadzu GC-1C apparatus on a stainless steel column ($\phi=3$ mm). Tlc were run on silica gel (Merck Kieselgel G). Microanalyses were carried out in the microanalytical section of Shionogi Research Laboratory, Shionogi and Co., Ltd.

Isolation of Petasitolone (I). The dried flower stalks of *P. japonicus* Maxim. (4.5 kg) cultivated in Osaka Prefecture were extracted with methanol at room temperature for 2 weeks. The extract was evaporated *in vacuo* and the residue was extracted with ether to give a dark brown oil (100 g). The oil was chromatographed on silica gel (1 kg). Elution with benzene gave crude fukinone (VI) (40 g) and further elution with methanol afforded an oil (50 g) which was subjected to steam distillation. The distillate was extracted with ether to give an oil (10 g) which contained petasitolone (I) as a major component. The crude petasitolone was purified by silica gel column chromatography using light petroleum-acetone (50: 1) as eluent and by vacuum distillation to give an almost pure sample (1 g) as a colorless oil, bp 92°C/0.15 mmHg; MS: M^+ion *m/e* 236, base peak *m/e* 43; IR (film): 3480, 1665, 1170 cm^{-1}; UV: $\lambda_{\max}^{\mathrm{MeOH}}$ 237.5 mμ (ε, 8279); $[\alpha]_D^{24}$ +16.7° (*c*, 0.99, MeOH); NMR: 0.93 (d, $J=7$ Hz, 3H), 1.11 (s, 3H), 1.30 (s, 6H), 3.52 (br s, 1H), 6.6 (s, 1H).

Petasitolone (I) was recovered unchanged on both attemted acetylation and Jones' oxidation. The crude product obtained from petasitolone and 2,4-dinitrophenylhydrazine by Brady's method was chromatographed on silica gel and eluted with light petroleum-ether (50: 1) to afford II- and then I-2,4-dinitrophenylhydrazones.

Anhydropetasitolone (II) 2,4-dinitrophenylhydrazone, red needles, mp 173—174°C.

Found: C, 63.30; H, 6.52; N, 13.85%. Calcd for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.58; N, 14.06%.

Petasitolone (I) 2,4-dinitrophenylhydrazone, red needles, mp 159—160°C.

Found: C, 60.40; H, 6.85; N, 13.47%. Calcd for $C_{21}H_{28}O_5N_4$: C, 60.56; H, 6.78; N, 13.45%.

Preparation of Anhydropetasitolone (II). Phosphorus oxychloride (3 m*l*) was added slowly to a solution of petasitolone (470 mg) in pyridine (4 m*l*). After being kept standing for 2 days the reaction mixture was added dropwise into ice water, extracted with ether, washed with water and dried over anhydrous sodium sulfate. The solvent was then evaporated. The residue was chromatographed on silica gel (10 g) with light petroleum-ether (50: 1) as eluent to give pure anhydropetasitolone (II) (140 mg) ; MS: M^+ion *m/e* 218, base peak *m/e* 147; UV: $\lambda_{\max}^{\mathrm{hexane}}$ 254 mμ (ε, 4110); IR (film): 1675, 895 cm^{-1}; NMR: 1.86 (s, 3H), 5.02 and 4.88 (2H). Anhydropetasitolone 2,4-dinitrophenylhydrazone, $C_{21}H_{26}O_4N_4$, mp 173—174°C.

Found: C, 63.62; H, 6.71; N, 13.99%. Calcd for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.58; N, 14.06%.

Catalytic Hydrogenation of Petasitolone. a) Platinum Oxide as Catalyst: Petasitolone I (1 g) in acetic acid (10 m*l*) was hydrogenated over Adams' catalyst (80 mg) at room temperature and atmospheric pressure to yield dihydropetasitolone (III) (300 mg) and a desoxydihydro compound (IV) (450 mg). Dihydropetasitolone III : a colorless oil, IR (film): 3340, 1690 cm^{-1}. IR spectrum and glc retention time of compound IV were identical with those of dihydrofukinone obtained from fukinone.[3] ORD in MeOH (*c*, 0.125): $[\phi]_{311}$ -904, $[\phi]_{272}+1848$, $a=-27.5$; 2,4-Dinitrophenylhydrazone, mp 170.5—171°C (authentic sample, [3] mp 171—171.5°C, mixed mp 170.5—171°C).

b) Palladium Charcoal as Catalyst: Petasitolone (600 mg) in ethanol (10 m*l*) was hydrogenated over 10% palladium charcoal (150 mg) at room temperature and atmospheric pressure for 16 hr. About 70 m*l* of hydrogen was absorbed and crude dihydropetasitolone III (560 mg) was obtained as the main product.

Conversion of Desoxydihydro Compound (IV) into 7β-Eremophilane(V). A mixture of IV (25 mg), ethanedithiol (2 m*l*), and BF_3-etherate (4 drops) was allowed to stand for 1 hr, and extracted with ether affording crude thioketal (40 mg). The crude thioketal in ethanol (2m*l*) was refluxed with Raney nickel (1 g) to give 7β-eremophilane (24 mg), which is identical with the authentic sample[3] by glc (PEG-20M, 2.6 m; 30 m*l*/min H_2, column temperature 180°C; retention time 6 min 20 sec).

Conversion of Dihydropetasitolone (III) into Desisopropylidenefukinone (VII) in Glc Column. Dihydropetasitolone III was passed through a glc column (PEG-20M; column temperature 180°C) to give desisopropylidenefukinone (VII), identical with the authentic sample[3] by comparison of IR spectra and glc.

Conversion of Dihydropetasitolone (III) into Fukinone (VI). Dihydropetasitolone III (250 mg) and phosphorus oxychloride (1 m*l*) was dissolved in pyridine (2 m*l*). After being kept standing for a week, the reaction mixutre was poured into ice-water and extracted with ether affording crude fukinone VI (200mg), which was purified by preparative glc (SPE, 2.6 m; 86 m*l*/min H_2; column temperature 190°C; retention time 8 min 20 sec).

Preparation of Petasitolone from Fukinone by Photosensitized Oxidation. A mixture of fukinone (2 g) and rose bengal (50 mg) dissolved in absolute methanol (250 m*l*) was irradiated with a fluorescent lamp (30 watt) under bubbling

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[7] G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann. Chem.*, **674**, 93 (1964).

of air for 4 days, when all fukinone was consumed (on tlc analysis). A solution of sodium sulfite (4 g) and water (60 m*l*) was added to the reaction mixture and stirred for 10 hr. The solvent was evaporated *in vacuo*, and the residue was extracted with ether to give a crude oil (1.75 g). The crude oil was chromatographed repeatedly over silica gel eluted with benzene or light petroleum-ether (10 : 1) to afford pure petasitolone (0.9 g) which was identical with the natural specimen by comparison of IR and glc (SE-30, 2.6 m; 60-m*l*/min H_2; column temperature 130°C; retention time 8 min).

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