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THE STRUCTURE OF PETASITIN, A NEW SESQUITERPENE FROM PETASITES JAPONICUS MAXIM.

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This paper reports the proof of the structure and absolute configuration of petasitin (I), a new sesquiterpene, isolated from the methanolic extract of the flower stalks of wild butterburs, Petasites japonicus Maxim., Japanese name "Fuki".

Petasitin (I): $C_{20}H_{28}O_4$, exhibits the following spectroscopic properties: $[\alpha]_D^{22}$ -26°, negative RD Cotton effect; M^+ion m/e 332; λ_{max}^{EtOH} 235 mμ (ε, 14,200); ν^{film} 3460 (OH), 1710, 1632, 1235 (αβ-unsaturated ester), 1665, 1617 cm^{-1} (αβ-unsaturated ketone). The nmr spectrum of (I) indicates the presence of three olefinic protons (δ^{CDCl_3}, 6.93, s., 1H; 6.15, t., J=1 cps, 1H and 6.13 ppm, q., J=5 cps, 1H) and of a proton attached to a carbon bearing one alcoholic oxygen atom of ester (4.95 ppm, m.). In addition, it shows six methyl groups: two of them are fixed on a double bond (slightly split signals at 2.05 and 1.90 ppm), two others are fixed on a carbon which carries on an alcoholic function (sharp peak at 1.50 ppm, s., 6H), the fifth is fixed on an angular carbon (1.25 ppm, s.) and the last one agrees with a secondary methyl group (1.16 ppm, d., J=7 cps). The free hydroxyl group of petasitin was defined to be a tertiary hydroxyl group, for its resistance to Jones' oxidation reagent.

Petasitin (I) was hydrolyzed with methanolic potassium hydroxide to give diol (II): $C_{15}H_{22}O_3$, m.p. 110-113°C, M^+ion m/e 250, negative RD Cotton effect; λ_{max}^{EtOH} 244 mμ (ε, 11,600); ν^{KBr} 3340 (OH), 1655, 1610 cm^{-1} (αβ-unsaturated ketone); δ^{CDCl_3}, 6.92 (s., 1H, HC=C), 6.12 (t., J=1 cps, 1H, HC=C), 3.70 (m., 1H, HC-O-), 1.50 (s., 6H, $(CH_3)_2$-C-O-), 1.30 and 1.18 ppm (partly superimposed C_4 and C_5 methyl protons); and 2,4-DNPH, m.p. 230-232°C. From the acid fraction, angelic

acid and a small amount of tiglic acid which resulted form isomerization of angelic acid were identified by their authentic samples as p-phenylphenacyl esters, respectively. Therefore, petasitin (I) is an angelate of (II). The nmr spectrum of (II) shows a signal at 3.70 ppm attributable to HC-O- group, and indicates the absence of signals at 6.13, 2.05 and 1.90 ppm due to the angeloyl grouping.

Diol (II) was treated with acetic anhydride in pyridine to give monoacetate (III): $C_{17}H_{24}O_4$, m.p. 80-82°C, M^+ion m/e 292, λ_{max}^{EtOH} 242 mμ (ε, 14,700): ν^{KBr} 3420 (OH), 1735, 1240 (acetate), 1660, 1615 cm^{-1} (αβ-unsaturated ketone); δ^{CDCl_3}, 6.88 (HC=C), 6.10 (t., J=1 cps, 1H, HC=C), 4.90 (m., 1H, HC-O-), 2.06 (s., 3H, CH_3-CO-O-), 1.48 (s., 6H, $(CH_3)_2$-C-OH), 1.20 (s., 3H, CH_3-C), 1.10 ppm (d., J=7 cps, CH_3-CH). Diol (II) was refluxed with acetic anhydride and sodium acetate to afford a mixture of (III) and diacetate (IV): M^+ion m/e 334; ν^{film} 1735-1725, 1245-1240 (acetate), 1660, 1625 cm^{-1} (αβ-unsaturated ketone). On hydrogenation over Pd-C in ethanol, the allylic tertiary hydroxyl group of (II) was eliminated by hydrogenolysis, and the resulting mixture of conformational isomers at C-7 was treated with sodium methoxide in methanol to give a base-stable product (V)(1): $C_{15}H_{26}O_2$, m.p. 103-103.5°C, $[\alpha]_D^{22}$ +39.2°, negative RD Cotton effect; ν^{KBr} 3460 (OH), 1700 cm^{-1} (C=O); 2,4-DNPH, m.p. 168-168.5°C; Semicarbazone, m.p. 188-190 °C. The compound (V) was identical in all respects to tetrahydro isopetasol which was derived by a similar hydrogenation condition from isopetasol (VI)(1,2). The structure and the absolute configuration of (VI) has been established by C. Djerassi et al.. Isopetasol (VI) was obtained by alkaline hydrolysis of isopetasin (VII)(1,2) which also had been isolated from the same extract of this plant.

As indicated above, the compound (V) exhibits a negative Cotton effect, characteristic of A/B cis-fused 3-keto steroids. Thus, this interconversion confirmed the structure and absolute configuration of (V), and subsequently those of petasitin (I).

The other interconversions were performed as follows.

Monoacetate (III) was dehydrated by treatment with phosphorus oxychloride in pyridine to yield a product (VIII): M^+ion m/e 274, λ_{max}^{EtOH} 240 mμ (ε, 12,500); ν^{film} 1737, 1242 (acetate), 1664, 1637 cm^{-1} (αβ-unsaturated ketone); δ^{CDCl_3},

6.82 (s., 1H, HC=C), 6.04 (t., J=1 cps, 1H, HC=C), 5.11 (d., J=7 cps, 2H), 4.87 (m., 1H, HC-O-), 2.06 (s., 3H, CH_3-CO-), 1.97 (d., J=1 cps, 3H, CH_3-C=C), 1.22 (s., 3H, CH_3-C), 1.10 ppm (d., J=7 cps, 3H, CH_3-CH). The nmr spectrum of (VIII) shows signals due to an exo-methylene group (5.11 ppm) and a vinyl methyl group (1.97 ppm) at the expense of the two methyl signals at 1.48 ppm due to $(CH_3)_2$-C-OH of (III). Thus we located the tertiary hydroxyl group unambiguously on the isopropyl group, as in formula (III).

On hydrogenation over Pd-C in ethanol, the compound (VIII) absorbed three moles of hydrogen to yield a hexahydro derivative (IX): M^+ ion m/e 280, ν^{film} 1730, 1245 (acetate), 1710 cm^{-1} (C=O). The compound (IX) was hydrolyzed and isomerized in methanolic sodium methoxide to give tetrahydro-isopetasol (V).

Upon hydrogenation with platinum oxide in ether, monoacetate (III) yielded a tetrahydro compound (X): $C_{17}H_{28}O_4$, m.p. 92-95°C; ν^{CCl_4} 3500 (OH), 1735, 1240 (acetate), 1700 cm^{-1} (C=O); δ^{CDCl_3}, 4.81 (m., 1H, HC-O-), 4.28 (broad, 1H, OH), 2.05 (s., 3H, CH_3-CO-), 1.23 (s., 6H, $(CH_3)_2$-C-O-), 1.18 (s., 3H, CH_3-C), 0.95 ppm (d., 3H, CH_3-CH); 2,4-DNPH, m.p. 142.5-144.5°C.

Dehydration of the compound (X) with phosphorus oxychloride in pyridine provided a mixture of unsaturated isomers, which was treated with alumina column chromatography to give the isopropylidene compound (XI): $C_{17}H_{26}O_3$, λ_{max}^{EtOH} 251 mμ (ε, 5,160); ν^{film} 1735, 1240 (acetate), 1682, 1630 cm^{-1} (αβ-unsaturated ketone with exo-cyclic double bond); δ^{CDCl_3}, 4.80 (m., 1H, HC-O-), 2.05 (s., 3H, CH_3-CO), 1.98 (s., 3H, CH_3-C=C), 1.81 (s., 3H, CH_3-C=C), 1.04 (s., 3H, CH_3-C), 0.90 ppm (d., J=7 cps, 3H, CH_3-CH).

The compound (XI) was dehydrogenated with 2,3-dichloro-5,6-dicyano-benzoquinone (3) and a catalytic amount of hydrogen chloride in dioxane to yield a small amount of (XII): ν^{nujol} 1735, 1245 (acetate), 1662, 1630 cm^{-1} (αβ-unsaturated ketone); λ_{max}^{EtOH} 242 mμ (ε, 7,550), 278 mμ (sh.) (ε, 2,900). This substance (XII) was identical with isopetasol acetate, m.p. 87°C, which was derived from isopetasol (VI).

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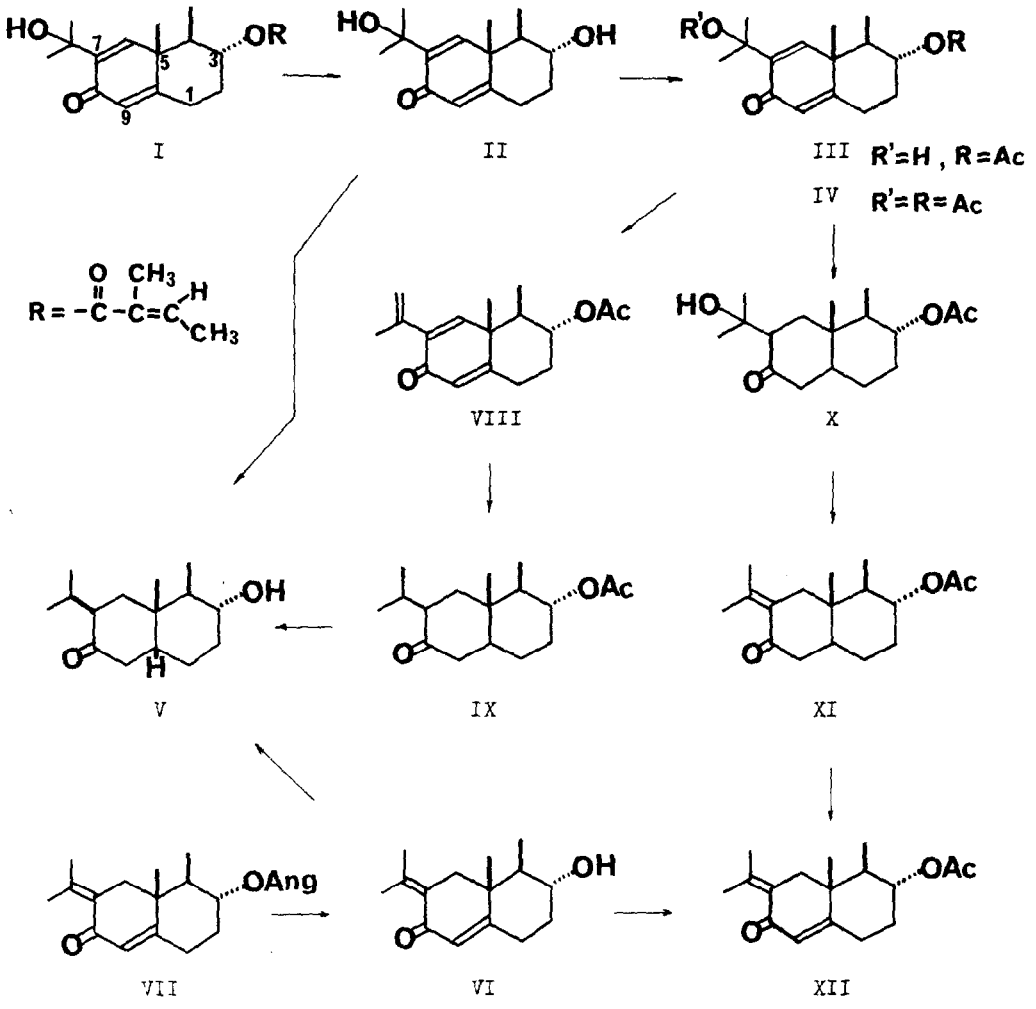

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