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THE STRUCTURES OF EREMOFUKINONE, 9-ACETOXYFUKINANOLIDE AND S-JAPONIN FROM PETASITES JAPONICUS MAXIM

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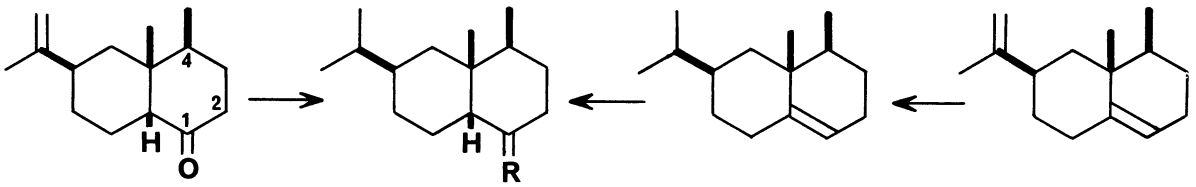
This paper deals with the structural determination of three new sesquiterpenes, eremofukinone (I), 9-acetoxyfukinanolide (II) and S-japonin (III), which were isolated from Petasites japonicus Maxim.

Recently we have investigated the constituents of wild[1] and cultivated[2] butterburs, Petasites japonicus Maxim. ("Fuki" in Japanese), and found many members of eremophilane and fukinane sesquiterpenes.

On the subsequent study of the minor constituents from the plant, three new sesquiterpenes, named eremofukinone (I), 9-acetoxyfukinanolide (II) and S-japonin (III), have been isolated; i.e., I from the rhizomes of the wild plant (P. japonicus Maxim. and its subspecies, subsp. gigantus Kitam.), II from the leaves of the wild subspecies and III from the leaves of a cultivated variety, "Aichiwasebuki".

Eremofukinone (I), $C_{15}H_{24}O$, a fragrant oil, bp 75-110° (bath temp)/0.15 mmHg, $[\alpha]_D^{24}$ +24.6° (c, 1.1, $CHCl_3$); m/e 220 M^+, m/e 151 base peak; is shown to possess an isopropenyl and a 6-membered ring ketone groups by IR: 3070, 1645, 890 (end-methylene), 1705 cm^{-1} (6-membered ring ketone) and δ^{CCl_4}: 0.77 (d, J=6.0 Hz, Me-CH), 1.03 (s, Me-C), 1.73 (d, J=1.0 Hz, Me-C=CH_2), 6.20 (br. s, H_2C=C). Hydrogenation of I with Pd-C yielded a dihydro derivative (IV), which showed no absorption due to an end-methylene group in the IR and NMR spectra, indicating that the isopropenyl group of I was saturated. The dihydro compound (IV) was converted into the thioketal and followed by desulfurization with Raney nickel to give the known eremophilane (V). A final problem was the position of the keto group on the eremophilane skeleton. The isopropenyl group of I showed no tendency to transform into an isopropylidene group in acidic and basic media. Considering the

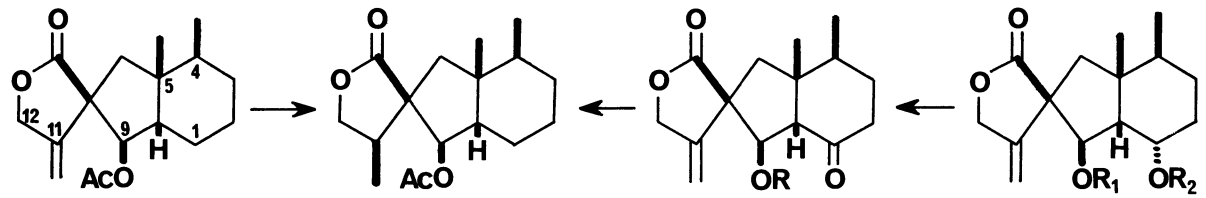
chemical shift of the C-4 methyl (0.77) and the ORD curve (— Cotton effect), the carbonyl group may be located at either C-1 or C-2. Since deuteration of I with Na_2CO_3-D_2O-MeOD gave rise to an incorporation of three D atoms (m/e 223 M^+, m/e 152 base peak), it was concluded that the position of the keto group was C-1. This conclusion was secured by the following conversion from the known eremophilene (VI)[3] into dihydroeremofukinone (IV). Eremophilene (VI) isolated from the rhizomes of P. japonicus Maxim. was hydrogenated with deactivated Raney nickel to afford mainly the dihydro compound (VII). The IR spectrum of VII shows bands at 1380, 1365, 845, 810 cm^{-1}, indicating that the end-methylene group in VI was hydrogenated. Hydroboration and subsequent oxidation of VII gave an alcohol, which without purification was followed by Jones' oxidation to furnish a ketone (IV). The ketone purified by preparative GLC is identical with dihydroeremofukinone (IV) obtained from I. Eremofukinone, therfore, can be represented by the formula I.



I IV R = O V R = H_2 VII VI

9-Acetoxyfukinanolide (II), $C_{17}H_{24}O_4$, mp 96.0-97.0°, colorless needles, $[\alpha]_D^{25}$ -28.5° (c, 1.0, $CHCl_3$); showed IR: 1782 (γ-lactone), 1730, 1225 (AcO), 3100, 1670, 900 cm^{-1} (end-methylene) and δ^{CCl_4}: 0.98 (d, J=6.0 Hz, Me-CH), 1.05 (s, Me-C), 2.04 (s, AcO), 4.63 (t, J=4.0 Hz, OCH_2-C=CH_2), 5.15 (d, J=3.0 Hz, H_2C=C), 5.30 (d, J=9.9 Hz, HC-O). The NMR spectrum of II is closely similar to that of the fukinane[4] type sesquiterpene, fukinolide (VIII),[1a,5] except the signals due to the angelyl group and C-1 proton in VIII, suggesting the structure II for this compound. Therefore the conversion from the known fukinolidol (IX)[1a] into II was attempted as follows. Jones' oxidation of IX gave a monoketone (X),[1a] $C_{15}H_{20}O_4$, mp 144.5 -146.0°, which was treated with Ac_2O-pyridine to afford the acetate (XI), $C_{17}H_{22}O_5$, mp 132.5-133.0°, $[\alpha]_D^{24}$ -210.0° (c, 1.0, $CHCl_3$). The acetate (XI) was transformed into a thioketal followed by desulfurization with Raney nickel to give a product (XII); $C_{17}H_{26}O_4$, mp 132.0-132.5°. The compound (XII) shows IR: 1765 (γ-lactone),

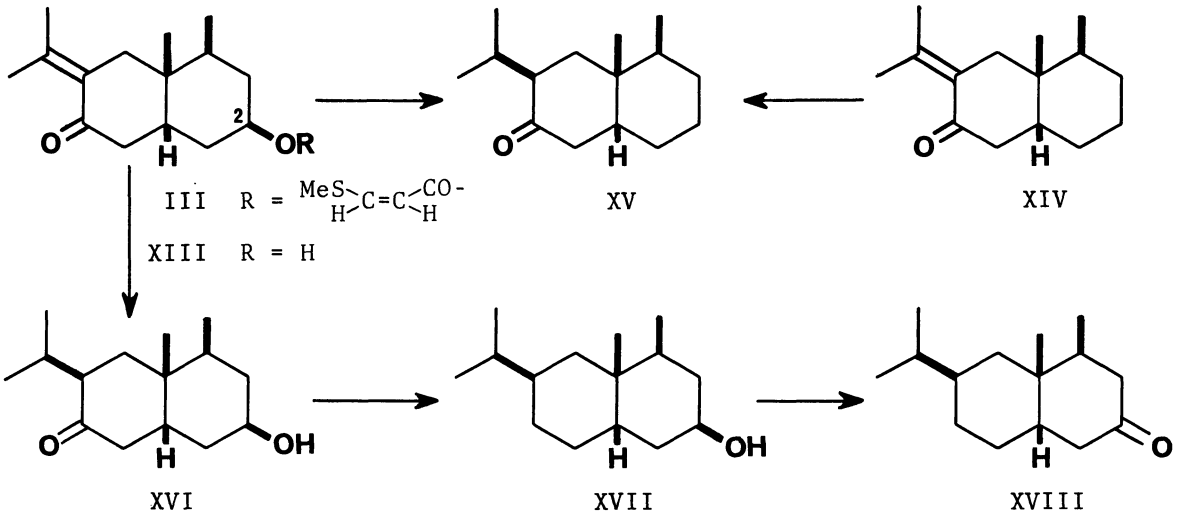
1735 cm^{-1} (AcO) and δ^{CCl_4}: 0.80 (d, J=5.0 Hz, 4-Me), 1.01 (s, 5-Me), 1.15 (d, J=6.7 Hz, 11-Me), 2.00 (s, AcO), 3.41 and 4.15 (each q, J=11.0, 9.0 and 9.0, 8.0 Hz, 12-CH_2), 5.55 (d, J=11.0 Hz, 9-CH), indicating that the end-methylene group of XI was also hydrogenated during desulfurization with Raney nickel. The compound (XII) is identical with the dihydro derivative of II obtained by treatment of II with Raney nickel under the similar condition as above. Consequently the structure of 9-acetoxyfukinanolide was established as shown in the stereoformula II.



II XII X R = H XI R = Ac VIII R_1 = Ac, R_2 = Angelyl IX R_1 = R_2 = H

S-japonin (III), $C_{19}H_{28}O_3S$, mp 116.5-117.0°, colorless needles, $[\alpha]_D^{24}$ +7.0° (c, 1.01, $CHCl_3$), indicates the presence of an unsaturated ester, cis-MeSCH=CHCOO-, [IR: 1690, 1560 cm^{-1}; UV: λ_{max} 288 mμ (ε 17000); δ^{CDCl_3}: 2.38 (s, MeS), 5.77 and 7.02 (each d, J=10.0 Hz, CH=CHCOO)] and of an α,β-unsaturated ketone [IR: 1680, 1625 cm^{-1}; UV: λ_{infl} 255 mμ (ε 11000); δ^{CDCl_3}: 1.81 and 1.94 (each s, Me_2C=CCO)]. Alkaline hydrolysis of III gave a ketol (XIII), $C_{15}H_{24}O_2$, and cis-β-methylthio-acrylic acid,[1a] mp 118.0-119.5°. The compound (XIII) shows IR: 3425, 1680, 1625 cm^{-1} and UV: λ_{max} 250 mμ (ε 9500). The spectra of XIII were closely similar to those of known fukinone (XIV),[2b] suggesting that XIII is a hydroxy derivative of XIV. This was confirmed by the following chemical method. Treatment of XIII with $POCl_3$-pyridine followed by catalytic hydrogenation gave a saturated ketone (XV) which was identical, in all respects, with the known dihydrofukinone.[2b] The remaining problem was the location and the configuration of the ester function in S-japonin (III). In the NMR spectrum of III the proton at the carbon bearing the ester group exhibited a signal (δ^{CDCl_3}: 5.04, heptad, J=5 Hz) characteristic of an axial methine proton coupled with adjacent methylenes on both sides. Consequently the 2β-orientation of the ester group was established. Further support for the structure III was obtained by the following reactions. Hydrogenation of XIII gave a dihydroketol (XVI) which

was converted into an alcohol (XVII) via a thioketal. Oxidation of XVII with CrO_3-pyridine gave a ketone (XVIII), (IR: 1710 cm^{-1}; MS: m/e 222 M^+, m/e 136 base peak). On deuteration of XVIII with NaOD-MeOD incorporation of four D atoms was observed in the MS spectra. Thus S-japonin can be represented by the stereo-formula III.



It is of interest that eremofukinone (I) and S-japonin (III) are the first examples of the eremophilane derivatives oxygenated at C-1 and C-2, respectively, isolated from P. japonicus Maxim.

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