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The Structure of Futoamide: A Constituent of *Piper futokadzura* Sieb. et Zucc.

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Structure of futoamide, isolated from *Piper futokadzura* Sieb. et Zucc., was determined as N-isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2,6-dienoic amide, which was synthesized by an unambiguous route.

From the leaves and stem of *Piper futokadzura* Sieb. et Zucc., we isolated a crystalline constituent designated futoamide, $C_{18}H_{23}O_3N$, mp 128—130°, together with futoenone,[2] futoxide[3] and other components.[3]

The molecular formula of futoamide was calculated from the value (301.168) of molecular ion by high resolution mass spectrometry and elementary analysis. Catalytic hydrogenation furnished the tetrahydro derivative, $C_{18}H_{27}O_3N$, mp 59°, which exhibited a typical ultraviolet (UV) absorption of methylenedioxy benzene[4] and its infrared (IR) spectrum showed an amide band at 1665 cm^{-1}.[5] The nuclear magnetic resonance (NMR) spectrum of the tetrahydro derivative reveals signals due to geminal methyl group (6H, doublet) centered at 0.93 ppm, methylenedioxy group (2H, singlet) at 5.94 ppm and aromatic protons (3H, multiplet) centered at 6.70 ppm. Considering the above data, we could deduce the structure of the tetrahydro derivative from the mass spectrometry. The mass spectrum shows the molecular ion peak at *m/e* 305 and the peaks at *m/e* 262 ($C_{15}H_{20}O_3N$), 249 ($C_{14}H_{19}O_3N$), 232 ($C_{14}H_{16}O_3$), 204 ($C_{13}H_{16}O_2$), 148 ($C_9H_8O_2$) and 135 ($C_8H_7O_2$)[6] corresponding to a series of fragment ions by bond rupture of side chain.[7] Therefore, the structure of tetrahydrofutoamide should be N-isobutyl-7-(3,4-methylenedioxyphenyl)heptanoic amide.

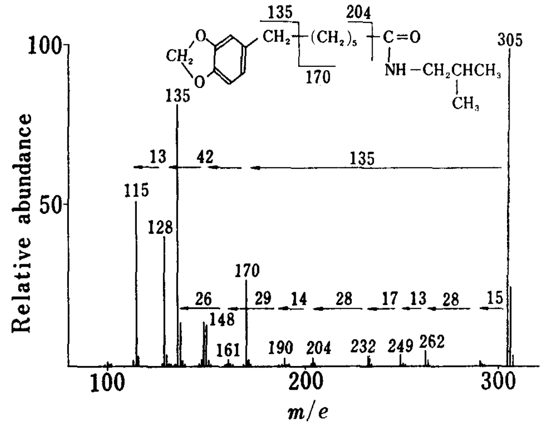

Fig. 1. Mass Spectrum of Tetrahydrofutoamide

Since the three absorption maxima in the UV spectrum of futoamide are characteristic of piperonylidene group, one of the two double bonds is conjugated to methylenedioxy benzene. The NMR spectrum of futoamide exhibits signals attributable to geminal methyl (6H, doublet) centered at 0.93 ppm, methine group (1H, multiplet) centered at 1.8 ppm coupled to the protons

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[1] Location: *Hiromachi, Shinagawa-ku, Tokyo.*

[2] A. Ogiso, M. Kurabayashi, H. Mishima, and M.C. Woods, *Tetrahedron Letters*, **1968**, 2003; M.C. Woods, I. Miura, A. Ogiso, M. Kurabayashi, and H. Mishima, *ibid.*, **1968**, 2009.

[3] S. Takahashi, *Phytochemistry*, **8**, 321 (1969).

[4] W.J. Gensler and C.M. Samour, *J. Org. Chem.*, **18**, 9 (1953).

[5] A. Chatterjee and C.P. Dutta, *Tetrahedron*, **23**, 1769 (1967).

[6] Molecular formulae in parentheses were calculated from *m/e* values by high resolution mass spectrometry.

[7] B. Willhalm, A.F. Thomas, and F. Gautschi, *Tetrahedron*, **20**, 1185 (1964).

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of geminal methyl and methylene group adjacent to nitrogen, allylic methylene group (4H, multiplet) centered at 2.33 ppm and aromatic and olefinic protons (7H, multiplet) at 5.8—7.1 ppm. The chemical shifts of olefinic protons in such low-field provides that one double bond is conjugated with other chromophore. On irradiation of the methylene protons at 2.33 ppm, assignment of the olefinic protons is clarified as shown in Fig. 3 and both double bonds are proved to be trans by their coupling constants (J=15.0 and 15.5 cps).

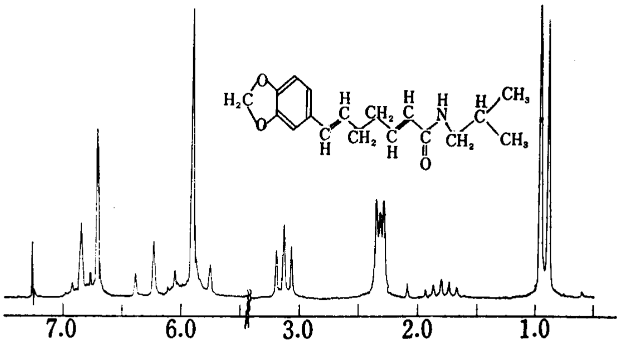

Fig. 2. NMR Spectrum of Futoamide in $CDCl_3$

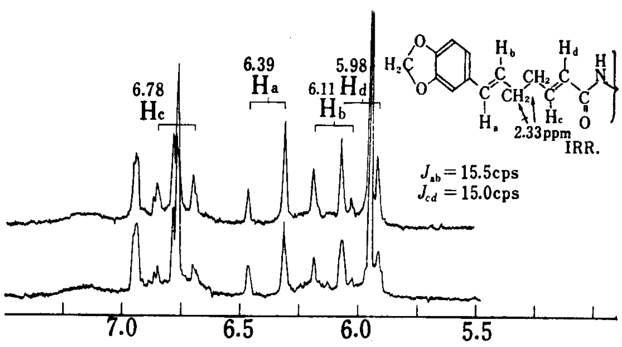

Fig. 3. NMR Spectrum of Futoamide in $(CD_3)_2CO$ Irradiation of Methylene Protons

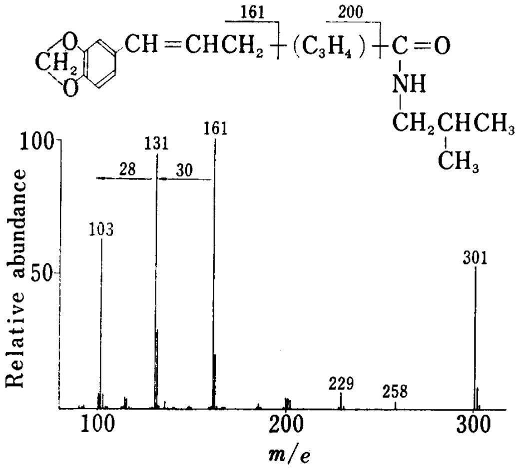

Fig. 4. Mass Spectrum of Futoamide

Confirmatory evidence for the proposed structure of futoamide was available from mass spectral analysis. The notable feature of the spectrum is the base peak at m/e 161, arising from β-fission of the piperonylidene group. Two strong peaks at m/e 131 and 103 are the fragment ions corresponding to C_9H_7O and C_8H_7 respectively by high resolution mass spectrometry. The former is most likely arisen from the cleavage of carbon–oxygen bond of methylenedioxy group with loss of formaldehyde. The latter is caused by the subsequent elimination of carbon monoxide from the ion of m/e 131 as shown in Chart 1.

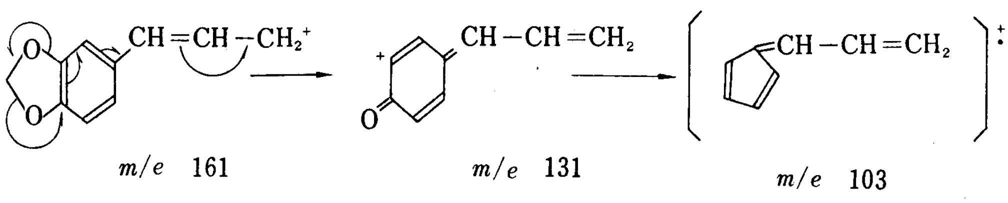

Chart 1

The structure advanced for futoamide was supported by an unambiguous synthesis. Condensation of piperonal with Wittig reagent,[8] prepared from triphenylphosphine and 4-acetoxybutyl bromide, gave an olefinic mixture, consisted of *cis* (60%) and *trans* (40%) isomer. Treatment of the mixture with iodine in boiling xylene afforded exclusively *trans* isomer (I). The alcohol (II), obtained by hydrolysis of I, was oxidized to an aldehyde (III) by Pfitzner–Moffatt reagent.[9] The aldehyde (III) was condensed with triethyl phosphono-

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[8] L.D. Bergel'son, V.A. Vaver, L.I. Bersubov, and M.M. Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1964**, 1453.

[9] K.E. Pfitzner and J.G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).

acetate to give an unsaturated carboxylate (IV). Hydrolysis of IV with alkali followed by treatment with oxalyl chloride gave an acid chloride. Condensation of the acid chloride with isobutylamine afforded N-isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2,6-dienoic amide (VI), which was identified with futoamide by mixed melting point and by compariosn of IR and NMR spectra.

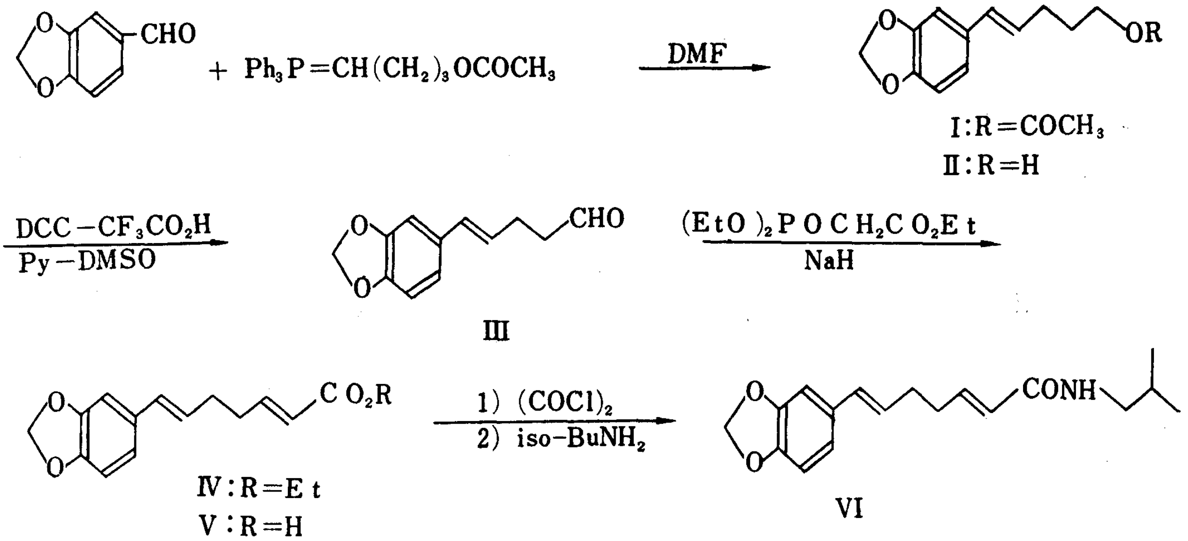

Chart 2

Experimental

The melting points were determined in capillary tubes and were uncorrected. The UV spectra were measured in 95% ethanol using a Beckman DK-2A spectrophotometer. IR spectra were determined on an Infracord spectrometer. NMR spectra were determined on a Varian HA-100 spectrometer using tetramethylsilane as an internal reference. Mass spectra were measured on a JMS-013G mass spectrometer by direct inlet method. Thin-layer chromatography was performed on silica-gel "G" of Merck and spots were detected by spraying with concentrated H_2SO_4 followed by heating.

Futoamide——Isolation of futoamide, mp 128—130° (recrystallized from acetone–*n*-hexane), has been described in the preceding paper.[3] *Anal.* Calcd for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.64; H, 7.76; N, 4.58. IR (Nujol) cm^{-1}: 3350, 1665, 1620, 1550, 1490, 975, 955. UV λ_{max} mμ (ε): 261 (15100), 269 (sh.), 304 (6700).

Tetrahydrofutoamide——A solution of futoamide (0.25 g) in ethanol (20 ml) was hydrogenated in a hydrogen atmosphere in the presence of PtO_2 (0.025 g). Hydrogen uptake corresponded to 2 mole equivalents (50 ml) per mole of futoamide. The alcoholic solution was filtered from the catalyst and the filtrate on evaporation of the solvent furnished a solid (0.20 g), which was recrystallized from acetone–*n*-hexane in needles, mp 56—59°. *Anal.* Calcd. for $C_{18}H_{27}O_3N$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.80; H, 8.98; N, 4.73. IR (Nujol) cm^{-1}: 3350, 1645, 1560, 1510, 1490. UV λ_{max} mμ (ε): 234 (3900), 288 (3800).

5-(3,4-Methylenedioxyphenyl)pent-4-enol (II)——Triphenylphosphonium salt, prepared from triphenylphosphine (75 g) and 4-acetoxybutyl bromide (66 g), was dissolved in dimethylformamide (150 ml). This solution was added dropwise to a suspension of freshly prepared sodium methoxide (13 g) in dimethylformamide (60 ml) under stirring. Stirring was continued for 2 hr at room temperature. To the ylide solution was added a solution of piperonal (30 g) in dimethylformamide (50 ml) with stirring under ice-cooling. After being kept overnight, the reaction mixture was diluted with water and extracted with benzene. The benzene extract was washed with water and evaporated under reduced pressure. To the ether solution of the oily residue, lithium bromide was added and stirred for 1 hr to remove resulting triphenylphosphine oxide. The ether solution was filtered from the adduct, washed with water, saturated aqueous $NaHSO_3$ and water successively, dried over Na_2SO_4 and evaporated. The residue consisted of the alcohol (II) and the acetate (I).

Acetylation of the mixture (13 g) with acetic anhydride (20 ml) and pyridine (20 ml) gave the acetate (I). IR (Liquid) cm^{-1}: 1735, 1245. UV λ_{max} mμ: 262, 268 (sh.), 305. NMR ppm: 2.02. This product was proved to be a mixture of *cis* and *trans* isomers showing the ratio of 6 to 4 by GLC (SE30-1%, column temperature 150°).

A solution of the acetate mixture (15 g) in xylene (30 ml) containing iodine (0.3 g) was refluxed for 3 hr. After dilution with benzene, the reaction mixture was washed with aqueous $Na_2S_2O_3$ and water, dried over Na_2SO_4 and evaporated to give the *trans* isomer (13 g). The acetate dissolved in ethanol (50 ml) was refluxed with NaOH (5 g) in aqueous ethanol (60%, 50 ml) for 1 hr. The reaction mixture was concentrated and poured into water. Ether extract was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residual oil was distilled under reduced pressure to give the alcohol (II), bp 140—150° (0.005 mmHg), mp 66—67°. Yield was 10 g. *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.16; H, 7.01.

5-(3,4-Methylenedioxyphenyl)pent-4-enal (III)——The alcohol (II) (8.2 g) was dissolved in dimethylsulfoxide (60 ml) and benzene (60 ml) containing pyridine (3.2 ml) and trifluoroacetic acid (1.6 ml). After addition of dicyclohexylcarbodiimide (25 g), the reaction mixture was kept at room temperature for 3 hr. The mixture was diluted with ether (1 liter) and treated with a solution of oxalic acid (12 g) in methanol (100 ml). After gas evolution ceased, water (1 liter) was added and the insoluble material was removed by filtration. The organic layer was washed with 5% aqueous $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated to dryness leaving an oily material, which was distilled at 140—150° under 0.005 mmHg. The distillate, containing still some impurities, weighed 6.0 g. IR (liquid) cm^{-1}: 2780, 1725, (transparent in the hydroxyl region).

Ethyl 7-(3,4-Methylenedioxyphenyl)hept-2,6-dienoate (IV)——A solution of triethyl phosphonoacetate (7.7 g) in dimethoxyethane (20 ml) was added dropwise to a suspension of sodium hydride (1.7 g as 50% mineral oil) in dimethoxyethane (30 ml) with stirring at room temperature, until gas evolution ceased, for 1 hr. To the ylide solution was added a solution of the crude aldehyde (7.5 g) in dimethoxyethane (30 ml) at room temperature. After being kept overnight, the mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried over Na_2SO_4 and evaporated to dryness leaving an pale yellow oil. The oil was chromatographed on alumina (100 g, Woelm, Grade–I) by using *n*-hexane–benzene as an eluent. The resulting ester showed single spot on thin–layer chromatography. Yield was 7.5 g. *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 72.09; H, 6.97. IR (liquid) cm^{-1}: 1720, 1655, 1250, 965. UV λ_{max} mμ: 263, 268 (sh.), 305.

N-Isobutyl-7-(3,4-methylenedioxyphenyl)hepta-2,6-dienoic Amide (VI)——The above ester (5.0 g) dissolved in ethanol (50 ml) was refluxed with NaOH (0.8 g) in water (20 ml) for 1 hr. The mixture was concentrated, diluted with water, acidified with 5% HCl and extracted with ether. The ether extract was washed with water, dried over Na_2SO_4 and evaporated to give a semi-solid (3.5 g).

To the crude acid was added oxalyl chloride (4.0 g) at room temperature and kept overnight. After removal of volatile materials under reduced pressure, the residue was dissolved in benzene (10 ml). A solution of isobutylamine (1.6 g) in benzene (10 ml) was added to the above solution with stirring at room temperature. After 2 hr, the organic layer was washed with water, 5% HCl, water, 5% $NaHCO_3$ and water successively. Drying over Na_2SO_4 and removal of the solvent gave an oil, which was crystallized by trituration with ether. Recrystallization from acetone–*n*-hexane gave colorless needles, mp 128—130°, which was identified with futoamide by mixed melting point and comparison of IR and NMR spectra.

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