Phytochemistry, 1969, Vol. 8, pp. 321 to 322. Pergamon Press. Printed in England

SHORT COMMUNICATION

THE PRESENCE OF THE TUMOR INHIBITOR CROTEPOXIDE (FUTOXIDE) IN *PIPER FUTOKADZURA*

SHUJI TAKAHASHI

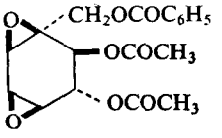
Central Research Laboratories, Sankyo Co., Ltd., Shinagawa-ku, Tokyo

(*Received* 15 *July* 1968)

Abstract—Extraction of *Piper futokadzura* Sieb. et Zucc. gave crotepoxide (I) as a major component.

Piper futokadzura Sieb. et Zucc. (Piperaceae, Japanese name-futokazura) is a common plant growing in the pacific coast of southern Japan, the leaves and stem of which are used as an indigenous medicine. As principles for the fragrant odor of this plant, α-pinene, camphene, β-pinene, sabinene, limonene and isoasarone were detected by means of fractional distillation and gas chromatography. Investigation of the ether extract of the leaves and stem led to the isolation of four new crystalline components designated as futoxide,[1,2] $C_{18}H_{18}O_8$, m.p. 153°, futoenone,[2,3] $C_{20}H_{20}O_5$, m.p. 197°, futoquinol,[4] $C_{21}H_{22}O_5$, m.p. 97–8° and futoamide,[4] $C_{18}H_{23}O_3N$, m.p. 128–130°, besides β-sitosterol and stigmasterol. Futoxide was obtained in the highest yield of these components.

Recently Kupchan *et al.*[5] isolated crotepoxide (I), having significant tumor inhibitory activity, from alcoholic extracts of the fruits of *Croton macrostachys* Hochst. ex A. Rich. (Euphorbiaceae). They elucidated the structure of crotepoxide by X-ray analysis. Comparison of futoxide with a sample of crotepoxide (by mixed m.p., mixed TLC, and i.r. spectral comparison) showed that the materials are identical.



(I) Crotepoxide

EXPERIMENTAL

Extraction of Piper futokadzura

Ten kg of the ground leaves and stem (collected at Miura Peninsula, Kanagawa), were extracted with ether 3 times at room temperature. The dark green residue was suspended in *n*-hexane and allowed to stand

[1] The structure of futoxide was reported at the 24th Annual Meeting of Pharmaceutical Society of Japan, Kyoto, April (1967).

[2] A. OGISO, M. KURABAYASHI, H. MISHIMA and M. C. WOODS, *Tetrahedron Letters* 2003 (1968).

[3] M. C. WOODS, I. MIURA, A. OGISO, M. KURABAYASHI and H. MISHIMA, *Tetrahedron Letters* 2009 (1968).

[4] Manuscript in preparation.

[5] S. M. KUPCHAN, R. J. HEMINGWAY, P. COGGON, A. T. MCPHAIL and G. A. SIM, *J. Am. Chem. Soc.* **90**, 2982 (1968).

overnight to complete the precipitation of crude crystals (75 g), which TLC showed mainly consisted of futoenone and futoxide. The crude material was dissolved in benzene and absorbed on silica gel (1·5 kg) deposited with benzene. Elution with benzene gave 20 g of an oily substance. The eluent was changed to benzene–ethyl acetate (1 : 1) which eluted 10 g of futoxide.

Recrystallization from ethyl acetate-*n*-hexane gave colorless prisms, m.p. 153°, (Found: C, 59·50; H, 5·02. Calc. for $C_{18}H_{18}O_8$: C, 59·66; H, 5·01), λ_{max} (ethanol) 230 (12860), 278(950), 280(790) nm, ν_{max} (nujol) 1765, 1755, 1730, 730 cm^{-1}, $\delta_{ppm}(CDCl_3)$ 2·02(3H, *s*), 2·12(3H, *s*), 3·10(1H, *q*), 3·44(1H, *q*), 3·67(1H, *d*), 4·23(1H, *d*), 4·61(1H, *d*), 5·00(1H, *q*), 5·73(1H, *d*), and 7·5–8·1(5H, *m*) *m/e* 362, 227, 207, 195, 163, 138, 122, 115, 105, 97.

Finally, elution with ethyl acetate gave 8·5 g of futoenone, m.p. 197°.

The mother liquor, after removal of the crystalline precipitate, was concentrated and allowed to stand several days to give a precipitation of crystals. Purification using a column chromatography and recrystallization from ethanol yielded colorless plates, m.p. 159–162°, (Found: C, 83·62; H, 11·66. Calc. for $C_{24}H_{40}O$: C, 83·65; H, 11·70 per cent). This was identified as β-sitosterol by means of gas chromatography (1·5 per cent SE30, 250°, He 60 ml/min). Gas chromatography of the mother liquor indicated to contain stigmasterol.

Further separation of the residue of extract was effected by a column chromatography on silica gel. Elution with benzene–ethyl acetate (1 : 1) gave 500 mg of futoamide, m.p. 128–130°. Combined benzene eluents was chromatographed on silica gel again to give 2·5 g of futoquinol, m.p. 97–98°.

Residual oil separated to give above components was submitted to a steam-distillation. The essential oil, 0·3 per cent of the dried plant, was shown to contain α-pinene, camphene, β-pinene, sabinene, limonene and isoasarone by means of fractional distillation and gas chromatography (PEG6000, 2·25 m, He 60 ml/min, 100° and PES, 2·25 m, He 40 ml/min, 100°).

Acknowledgement—The author thanks Professor S. M. Kupchan for the identification of the samples.