(+)-シス-フェノトリンのラットにおける新代謝産物

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Short Communication

New Metabolites of (+)-*cis* Fenothrin, 3-Phenoxybenzyl (+)-*cis* Chrysanthemumate, in Rats

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Although metabolic studies have been extensively carried out on (+)-*trans* isomer of synthetic pyrethroids,[1-4] the corresponding (+)-*cis* isomer has hardly been studied hitherto except that unlike *trans* isomers *cis* counterparts prove to be apparently resistant against hydrolytic attack at ester linkage *in vivo*.[3-6] During the course of mammalian metabolism study of (+)-*cis* fenothrin, 3-phenoxybenzyl (+)-*cis* chrysanthemumate, we isolated and identified 3 ester metabolites in rat feces, as Fig. 1 indicates.

On oral administration of 200 mg/kg (^{14}C-benzyl)-(+)-*cis* fenothrin to male Sprague Dawley rats, 65% of the radiocarbon was recovered in feces for 3 days post-treatment. The labelled products were extracted with methanol, separated by silica gel column chromatography by successively using benzene/diethyl ether (9/1), benzene/diethyl ether (1/1) and methanol. The separated metabolites were then methylated with diazomethane and purified on silica gel thin layer chromatography (tlc) using following solvents. (A) *n*-hexane/chloroform/acetic acid (4/1/1), (B) chloroform, (C) ethyl acetate/methanol (7/3), (D) benzene/ethyl acetate/acetic acid (8/2/1), (E) benzene/diethyl ether/methanol/acetic acid (8/2/1/1), (F) benzene/diethyl ether/methanol (8/2/1).

Metabolite I, eluted with 9 to 1 mixture of benzene and diethyl ether, was extensively methylated with diazomethane and purified by tlc with solvent (A), (B) and (C). The methylated I, *m/e* 380 (M^+), was shown to have one methoxy group by nmr (δ=3.72 (s) in CCl_4), intact ester linkage by ir (1730 cm^{-1}) and 3-(4′-methoxy)phenoxybenzyl ion by mass spectra at *m/e* 213. The methylated I was identified as 3-(4′-methoxy)phenoxybenzyl (+)-*cis* chrysanthemumate based on the above as well as by comparison of nmr, ir and mass spectra of the authentic compound synthesized by reaction of 3-(4′-methoxy)phenoxybenzyl alcohol with (+)-*cis* chrysanthemumoyl chloride in benzene in the presence of triethylamine.

Metabolite II, also eluted with 9 to 1 mixture of benzene and diethyl ether, was methylated and purified by tlc with solvent (A) and (C). The nmr, ir and mass spectra of methylated II indicated the presence of ester linkage by nmr (-COOC$\underline{H}_3$, δ=3.66 (s) in CCl_4) and by ir (1720 and 1735 cm^{-1}, 2 ester linkage), with mass spectra at *m/e* 394 (M^+) and 183 (3-phenoxybenzyl$^+$). The nmr, ir and mass spectra of methylated II agreed well with those of the authentic 3-phenoxybenzyl (+)-*cis* pyrethrate obtained by reaction of 3-phenoxybenzyl chloride with (+)-*cis* pyrethric acid.

Metabolite III, separated by silica gel column chromatography with methanol, was methylated and purified by tlc with solvent (D), (E) and (F). The structure of methylated III was identified as 3-(4′-hydroxy) phenoxybenzyl (+)-*cis* 2-hydroxymethyl-3-(2′-E-methoxycarbonyl-1′-propenyl)-2-methyl-1-cyclopropane carboxylate on the following evidence; nmr in $CDCl_3$ δ=1.30 ppm (s) (C$\underline{H}_3$ attached to cyclopropane ring), 1.88 ppm (d) (C$\underline{H}_3$ attached to double bond), 2.00 -2.50 ppm (m) (2H attached to cyclopropane ring), 3.51 ppm (s) (C$\underline{H}_2$OH attached to cyclo-

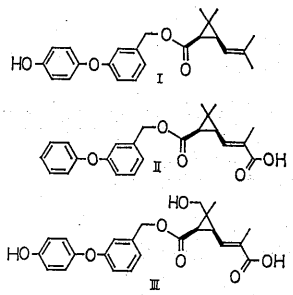

Fig. 1 Ester metabolites of (+)-*cis* fenothrin.

propane ring), 3.71 ppm (s) (−COOC$\underline{H}_3$), 5.05 ppm (benzyl 2H) and 6.50–7.50 ppm (m) (8H attached to both benzene ring and 1H in propenyl group). The position of methoxycarbonyl group was determined by chemical shift of proton at 1′ of the propenyl group and 2 protons attached to cyclopropane ring appearing respectively in relatively low and high field.[7] Whether the position of hydroxymethyl group attached to cyclopropane ring is *cis* or *trans* in regard to –COOR group has not yet been clarified (Different from metabolite I, 4′–OH of the metabolite was not methylated by diazomethane, apparently due to the presence of more amount of contaminants).

The amount of these metabolites relative to the administered radioactivity was 1.4%, 10.4% and 2.1% for I, II and III. Among other fecal metabolites, a trace amount of 3-phenoxybenzoic acid (1.4%) and (+)-*cis* fenothrin amounting to 18.1% of the applied radiocarbon were also identified.

Thus, we identified 3 ester metabolites of (+)-*cis* fenothrin.

The detailed studies establishing metabolic differences between *cis* and *trans* isomers of the pyrethroid are now in progress and the results will be published in the following paper.

要　　約

ベンジル基を ^{14}C で標識した(+)-シスフェノトリン(3-フェノキシベンジル(+)-シスクリサンセムメート)をラットに 200 mg/kg の割合で経口的に与えたところ，投与後，3日間で 65% の放射能が糞中に回収された．糞中代謝産物を，メタノール抽出，シリカゲル・カラムクロマトグラフィー，シリカゲル・薄層クロマトグラフィーで分離，精製し，NMR, IR およびマス・スペクトルを得，合成標品との比較などによって，エステル結合を保持した新しい3個の代謝産物を同定した．( )の中の数字は投予量に対する % である．(1) ベンゼン環の4′位が水酸化されたもの (1.4%)．(2) キク酸部分のプロペニル基の 2′ 位のメチル基 (二重結合に対しトランス位)が，カルボン酸に変化したもの (10.4%)．(3) ベンゼン環の 4′ 位，gem ジメチル基の一つが水酸化され，かつ (2) と同じく，キク酸部分のメチル基がカルボン酸になったもの (2.1%)．これらのエステル結合を保持した，シス型ピレスロイドの代謝産物の *in vivo* における分離，同定は，これまで報告されていない．

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