FUSARIC ACID DERIVATIVES: THE EFFECT ON DOPAMINE β-HYDROXYLASE

Sir:

It is known that fusaric acid, 5-*n*-butylpicolinic acid, inhibits dopamine β-hydroxylase *in vitro*, and lowers the blood pressure of spontaneously hypertensive rats.[1] But it was reported by N. TAKEMOTO, *et al.*[2] that when fusaric acid was administrated orally to rats, rabbits, dogs, or monkeys, a small amount of the acid was recovered from the urine of the animals, and metabolites oxidized in the butyl group, such as 5-(4′-hydroxybutyl)picolinic acid, 5-(3′-hydroxybutyl)picolinic acid, 5-(3′-carboxypropyl)picolinic acid, and β-[5-(3′-carboxypropyl)pyridyl-2]acrylic acid, were excreted. The enzyme-inhibiting activity of these metabolites was less than one-twentieth that of the original acid. To obtain analogues resistant to metabolism, we synthesized some 5-alkyl homologues of fusaric acid. In the new compounds the terminal methyl group of the side chain is substituted by a halogen atom or phenyl group, or is branched terminal. The synthetic methods will be reported elsewhere.

The spectrophotometric assay using tyramine as the substrate was used to determine the enzyme-inhibiting activity as described in a previous paper[1]. The concentrations of these acids giving 50% inhibition of enzyme are summarized in Table 1. These novel acids inhibit the enzyme markedly except 5-(5′-phenylpentyl)picolinic acid (No. 12). The activity depends on the length of the chain and the halogen atom. Particularly, the ID_{50} of 5-(4′-chlorobutyl)picolinic acid was 4.3×10^{-9} M, while that of fusaric acid was 10^{-8} M. These novel acids also showed a marked hypotensive effect in spontaneously hypertensive rats, as will be shown in forthcoming publication.

Table 1. Concentrations of 5-substituted alkyl picolinic acids for 50% inhibition of dopamine β-hydroxylase

No.	Alkyl chain	ID_{50} (M)
1	$-CH_2CH_2CH_2CH_3$	10^{-8}
2	$-CH_2CH_2CH_2CH_2CH_3$	6.6×10^{-9}
3	$-CH_2CH_2CH_2CH_2F$	2.4×10^{-8}
4	$-CH_2CH_2CH_2CH_2CH_2F$	1.5×10^{-8}
5	$-CH_2CH_2CH_2Cl$	4.0×10^{-8}
6	$-CH_2CH_2CH_2CH_2Cl$	4.3×10^{-9}
7	$-CH_2CH_2CH_2CH_2CH_2Cl$	4.6×10^{-9}
8	$-CH_2CH_2CH_2CH_2CH_2CH_2Cl$	1.35×10^{-8}
9	$-CH_2CH_2CHCH_3$ Cl	6.9×10^{-9}
10	$-CH_2CH_2CH_2Br$	3.1×10^{-8}
11	$-CH_2CH_2CH_2CH_2Br$	5.7×10^{-9}
12	$-CH_2CH_2CH_2CH_2CH_2C_6H_5$	4.0×10^{-7}
13	$-CH_2CHCH_3$ CH_3	1.29×10^{-8}
14	$-CH_2CH_2CHCH_3$ CH_3	6.1×10^{-9}

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