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THE SYNTHESIS OF A DECARBOXYLATED DERIVATIVE OF THE NEUROTOXIN KAINIC ACID

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Kainic acid (1), an anthelmintic isolated from the seaweed *Digenea simplex*[1] is a very potent neuronal excitant[2,3]. Besides this action, presumably as a conformationally restricted analogue of the amino acid excitant glutamic acid (2), kainic acid has also come into prominance recently as a pharmacological "tool" for selective degeneration studies because of its neurotoxic properties[4,5]. On decarboxylation in the mammalian central nervous system, glutamic acid (2) is converted into the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (3). Decarboxylation of kainic acid (1) to (4) would therefore furnish an important conformationally restricted analogue of GABA which would provide information on how far a structure-activity analogy between glutamate and GABA "receptors" may be taken.

This paper reports a convenient two step procedure for decarboxylating kainic acid (1) via oxidative decarboxylation to an unsaturated intermediate which was subsequently reduced to the secondary amine.

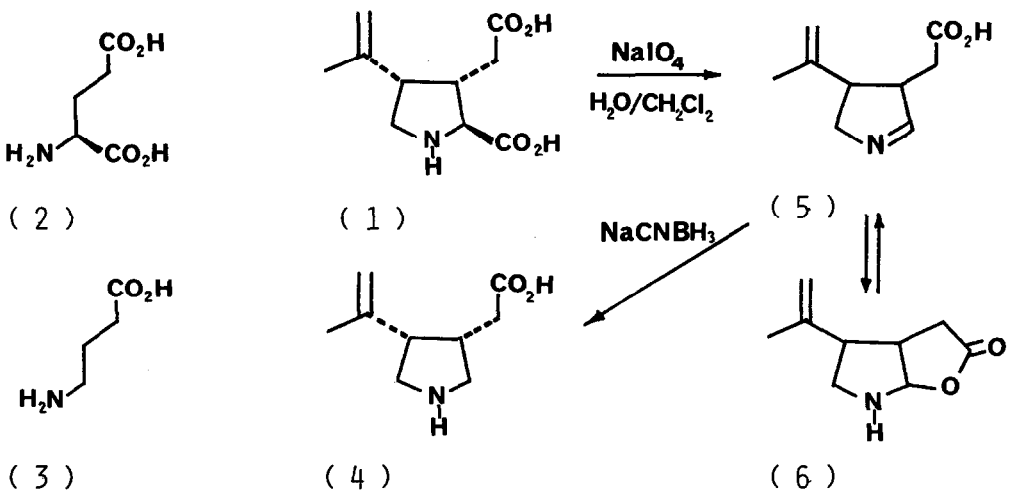
Sodium periodate was chosen for the oxidative decarboxylation because of three factors; the unsaturated side chain should not be affected, both the reagents are water soluble, and a previous study indicated a reasonable reaction rate with secondary amino acids[6]. A three-fold excess of sodium periodate in water (13 ml) effected decarboxylation of kainic acid (2 mmole) within 30 minutes in 90% crude yield provided the product was repeatedly extracted with methylene chloride (70 ml portions). Without the use of the two phase system the intermediate was contaminated with over-oxidation products and unconsumed (1) whether one or four equivalents of periodate were used.

Reduction of the crude intermediate with sodium cyanoborohydride in methanol at pH 4 proceeded rapidly. Workup on Dowex 50W (H^+) ion exchange resin, elution with 1 M NH_4OH and crystallisation from absolute ethanol gave the crystalline decarboxylated derivative 4-(1-methylethenyl)-3-pyrrolidineacetic acid, (4), $C_9H_{15}NO_2$, mp 227-234° (dec), $[\alpha]_D^{19}$ + 39°

(c=1 in H_2O), M^+ m/e 169, in 49% yield from kainic acid.

The organic soluble intermediate could only be obtained as an amorphous powder. T.l.c. behaviour and the infra-red spectrum of this product in nujol suggested the presence of two interconvertible structures; an imino acid form (5) ν_{max} 1650, 1700 cm^{-1} and a cyclic form (6) ν_{max} 1760 cm^{-1}. In $CHCl_3$ the cyclic form was by far the major component. In 1M NaOD the p.m.r spectrum displayed the complexity and decoupling behaviour consistent with the salt of (5) rather than the corresponding enamine form and no deuterium exchange was detected over three days. The p.m.r. spectrum of (4) at 100 or 270 MHz, while consistent with the assigned structure, was too complex to permit assignment of relative configuration from coupling constants. The decarboxylated amino acid has been tentatively assigned the *cis* configuration as shown in (4) until more definitive proof of structure, e.g. X-ray crystal data, can be obtained.

On biological testing[7], (4) was only a weak inhibitor (23 ± 2% at 10^{-4}M) of sodium-independent binding of GABA to rat brain membranes[8], suggesting that decarboxylated glutamate agonists do not necessarily interact with GABA receptors. Indeed, when tested microelectrophoretically *in vivo* on feline spinal neurones (4) was a weak excitant rather than a depressant, consistent with inhibition (84 ± 4% at 10^{-4}M, IC_{50} 17 ± 2 x 10^{-6}M) of kainic acid binding to rat brain membranes[5].



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