Toxicity and Metabolism of the Chloral-Derived Mammalian Alkaloid 1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) in PC12 Cells[§]

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Chloral-derived β-carbolines, which are structurally similar to the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **5**), are discussed to contribute to neuronal cell death in idiopathic Parkinson's disease. The cytotoxicity of 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo, **4**) to neuronal-like clonal pheochromocytoma PC12 cells was examined by the determination of lactate dehydrogenase (LDH) release. After incubation for 48 h, **4** showed a strong dose-dependent cytotoxic activity towards PC12 cells with an ED_{50} value of 230 μM. In PC12 cells reductive dehalogenation of **4** was observed giving rise to the formation of 1-dichloromethyl-1,2,3,4-tetrahydro-β-carboline (**6**) as a main TaClo metabolite exhibiting a cytotoxic potential comparable to that of TaClo. An X-ray structure analysis, performed for the trifluoroacetyl derivative of **6**, revealed the *N*-substituent of such a highly chlorinated agent to be dramatically pushed out of the β-carboline ring 'plane' due to the high steric demand of the huge dichloromethyl group at C(1).

Key words: 1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo), Rat Phaeochromocytoma (PC12) Cells, Cytotoxicity, Parkinson's Disease