Chemical Modification of the Mitochondrial Complex I Inhibitor 1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline: Synthesis and Evaluation of *N*-Alkanoyl Derivatives[§]

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Chloral-Derived Tetrahydro-β-carbolines, 1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline, Mitochondrial Respiration

Several *N*-alkanoyl derivatives (**4**-**9** and **13**-**16**) of the potent mitochondrial complex I inhibitor TaClo (1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline, **2**) have been synthesized in order to elucidate the role of hydrophobic portion in the inhibitory action. Using rat brain homogenates or submitochondrial particles, the inhibitory effects of these compounds towards NADH-ubiquinone reductase (complex I) activity indeed appeared to correlate quite strongly with their lipophilic character. An X-ray structure analysis, exemplarily performed for *N*-acetyl-TaClo (**4**), revealed the *N*-substituent of such chlorinated agents to be dramatically pushed out of the β-carboline ring 'plane' due to the high steric demand of the huge trichloromethyl group at C-1.