STUDIES ON THE SYNTHESIS AND REARRANGEMENT OF INDAZOLYLPYRIDINIUM DERIVATIVES, PRECURSORS TO POTENTIAL NEUROPROTECTIVE PRODRUGS BEARING A 1,2,3,6-TETRAHYDROPYRIDINYL CARRIER

By

Emre M. Işın

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Professor Neal Castagnoli, Jr., Chairman
Professor David R. Bevan
Professor Paul R. Carlier
Professor David G.I. Kingston
Professor James M. Tanko

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ABSTRACT

The neuronal nitric oxide synthase (nNOS) inhibitor 7-nitroindazole (7-NI) protects against the neurotoxicity of MPTP in a mouse model of neurodegeneration. Since 7-NI also inhibits the monoamine oxidase-B (MAO-B) catalyzed bioactivation of MPTP, the role of nNOS inhibition as a mediator of 7-NI's neuroprotective properties have been challenged. In order to examine in greater detail the neuroprotective effects of indazolyl derivatives, the synthesis of water soluble indazolyltetrahydropyridinyl derivatives as potential "prodrugs" that may undergo MAO bioactivation in the brain was undertaken. During the course of the studies on the synthesis of indazolylpyridinium derivatives, precursors to these "prodrugs", an interesting reaction involving the rearrangement of 4-(2*H*-indazolyl)-1-methylpyridinium iodide to the corresponding 1*H*-isomer was encountered. A detailed investigation of this rearrangement reaction is reported in this thesis.

The syntheses and interaction of nitroindazolyltetrahydropyridinyl "prodrugs" with MAO-B have been investigated previously. Molecular docking studies that attempt to explain the MAO-B substrate and inhibitor properties of members of this series of compounds are described. Finally, the MAO-A substrate properties of nitroindazolyltetrahydropyridinyl derivatives are reported.

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dedicated to my parents,
biologic:

İnci Işın and Dűndar A.F. Işın

and academic:

Professor Neal Castagnoli, Jr. and Mrs. Kay Castagnoli

TABLE OF CONTENTS:

LIST OF FIGURES:

LIST OF SCHEMES:

LIST OF TABLES: