ABSTRACT

SYNTHETIC APPROACHES TO AZAROTENOIDS

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Isosteric replacement of atoms or groups of atoms is of central importance for the further development of lead drugs. Natural products, on their own, possess a wide range of biological activity and it is the job of the synthetic chemist to, not only attempt to mimic these compounds through laboratory preparations, but to improve on them. This may be accomplished through replacement of a single atom in the core structure of these compounds. The synthesis of novel nitrogen analogues of the naturally-occurring rotenoids is the focus of this thesis.

In Chapter One, the effect of isosterism is outlined. In this chapter also is featured a review of specific syntheses of rotenoids as well as some of their thio- and aza-analogues.

The synthesis of 5,7-diaza-derivatives of the rotenoids is the focus of Chapter Two, whereby both oxygen atoms of the core ring structure are replaced. Readily available 2'-nitrobenzaldehyde is utilized as starting material to explore these synthetic routes.

In Chapter Three the systematic replacement of only a single oxygen atom of the rotenoid core ring structure to prepare 5-aza- or 7-azarotenoids is explored. The synthesis of a novel dehydro-7-azarotenoid is also discussed.

The palladium-mediated intramolecular aryl-aryl coupling reaction is an important consideration of any modern synthetic pathway, and a review of this reaction is the focus of Chapter Four. Mechanistic considerations of this approach to carbon-carbon bond formation are compared with that of the standard Heck mechanism.

The preparation of the novel tetracycle 12-chloro-10-methoxy-6*H*-chromeno[3,4-*b*]quinoline under 'Heck' conditions, is discussed in Chapter Five.