The metabolism of alicyclic amines to reactive iminium ion intermediates

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Keywords: Alicyclic amines, iminium ions, α-carbonyl compounds, covalent binding

SUMMARY

The evidence implicating the formation of iminium ions as reactive intermediates in the metabolism of alicyclic amines has been reviewed. The mechanism of formation of iminium ions and their conversion to α-carbonyl compounds or demethylated amines is discussed. The use of a simple cyanide trapping technique for iminium ions has been demonstrated to monitor a large number of alicyclic drugs for iminium ion formation. The possible role of iminium ions in the pharmacology and toxicology of alicyclic amines is considered.

INTRODUCTION

Tertiary and secondary alicyclic amines occur widely in drugs and environmental chemicals. This functional group may contain a further nitrogen or other heteroatom and be substituted in the ring system or at a constituent nitrogen. (Fig. 1). Alicyclic amines are susceptible to metabolic oxidation giving rise to end products of widely differing structures and physico-chemical properties. Metabolic reactions common to most alicyclic amines are: (a) α-carbonyl formation; (b) N-oxygenation; (c) N-dealkylation; (d) ring hydroxylation; and (e) ring opening (Fig. 2).

α-CARBONYL FORMATION

The formation of α-carbonyl compounds (cyclic amides or lactams) from alicyclic amines has long been known and occurs with a wide variety of hetero­alicyclic structures (1).

α-Carbonyl formation was originally thought to be formed via an initial α-hydroxylation to produce an α-carbinolamine which underwent further oxidation (dehydrogenation) to yield the carbonyl compound (2). Further, it was thought at that time that the initial reaction was a microsomal hydroxylation whilst the sec-

Fig. 1: Alicyclic amines used in medicinal compounds.
secondary oxidation was mediated via a soluble aldehyde or alcohol dehydrogenase (Fig. 3). Support for this mechanism came with the finding that the formation of cotinine, a cyclic amide from nicotine, a cyclic amine was inhibited by incorporation of cyanide into the incubation media. This was thought to be due to the well known inhibitory action of cyanide on alcohol dehydrogenase (2-4). This reaction sequence would require that the oxygen present in the carbonyl function originates from the atmosphere in common with other mixed function oxygenases (5).

Nicotine

During studies on nicotine metabolism (4), it was recognised that a new compound was formed when cyanide was present in the incubate. Murphy (6) showed that this new compound was 5'-cyanonicotine (Fig. 4), and that as the levels of the cyano compound increased, the level of cotinine formed decreased. Concomitant with this, Murphy found by isotopic studies that the oxygen of the carbonyl group of cotinine was not derived from air but from water. These seminal observations enabled Murphy to propose that nicotine-Δ15' iminium ion was formed as an early metabolite of nicotine. At this time, it still seemed possible that α-C-hydroxylation was the initial metabolic reaction followed by loss of a hydroxyl group (ion) to yield the iminium ion which then reacted with water to give cotinine. The synthesis of nicotine-Δ15' iminium ion (7) allowed the role of this compound as an intermediate in nicotine metabolism to be firmly established (7,8), as it was shown to be converted to cotinine in vitro and in vivo. Thus the sequence of reactions leading to carbonyl compounds was modified to include the metabolism of amine by a cytochrome P450 isozyme by hydrogen or electron abstraction to yield an iminium ion (9), which exists in equilibrium with the α-carbinolamine (10,11) and is...