THE METABOLISM OF N-HETEROCYCLES

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Most reports on the oxidative metabolism of drugs are confined to the membrane-bound microsomal cytochrome P-450 system. However, another enzyme, aldehyde oxidase, present in the cytosol of liver cells, is capable of catalysing the hydroxylation of certain aromatic N-heterocycles. Although it is present in man (Stanlovic & Chaykin, 1971), the level of this enzyme is species dependent, and is most abundant in rabbit liver, which was used in the present study. This paper reports the results of in vitro studies of the metabolism of some mono and diaza heterocycles by the above enzymes. Compounds were incubated with the aldehyde oxidase containing 100 000 g supernatant fraction and the products were identified by comparison of their chromatographic and spectroscopic properties with those of authentic compounds. High percentage conversion was observed in most cases. K_m values were determined directly or by the method of Krenitsky & others (1972) using partially purified enzyme. Oxidation by the cytochrome P-450 system was investigated using either the 10,000 g supernatant fraction or the 100 000 g microsomal pellet.

Table 1

	Aldehyde oxidase		P-450 system
Compound	Product	K_m (mol l^{-1})	Product
Quinoline	2-OH	2.86×10^{-3}	3-OH
7-Chloroquinoline	2-OH	5.12×10^{-3}	3-OH
2-Hydroxyquinoline	none	-	2,6-di OH
7-Chloro-2-hydroxyquinoline	none	-	2,6-di OH
Isoquinoline	1-OH	1.70×10^{-4}	trace
Phthalazine	1-OH	1.15×10^{-5}	*
Quinoxaline	2-OH	1.62×10^{-4}	trace,phenolic
2-Hydroxyquinoxaline	2,3-di OH	-	*
Quinazoline	4-OH	1.56×10^{-5}	*
2-Hydroxyquinazoline	none	-	*
4-Hydroxyquinazoline	2,4-di OH	-	*
Cinnoline	4-OH	2.32×10^{-4}	*

* none found

Except for cinnoline, hydroxylation occured at the carbon adjacent to the nitrogen atom when aldehyde oxidase was used. The best substrates for the cytochrome P-450 system were quinoline and 7-chloroquinoline (and their 2-hydroxy derivatives). This is reflected by the type of binding spectra observed. Only these compounds and quinoxaline yielded Type I, whereas the other compounds gave Type II binding spectra. As can be seen, the products of aldehyde oxidase hydroxylation in some cases act as substrates for the P-450 system as observed by Sax & Lynch (1964) in the case of quinoline.

The above results suggest that aldehyde oxidase may play a significant role in the metabolism of drugs containing an N-heterocyclic nucleus, e.g. 2-hydroxyquinine, a known metabolite of quinine (Knox, 1946) and 1-hydroxyphthalazine, a minor metabolite of Hydralazine (Zak & others, 1974), may arise in this way.

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