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In-vivo metabolism of 1,2-diethyl-3-hydroxypyridin-4-one (CP94) by rat

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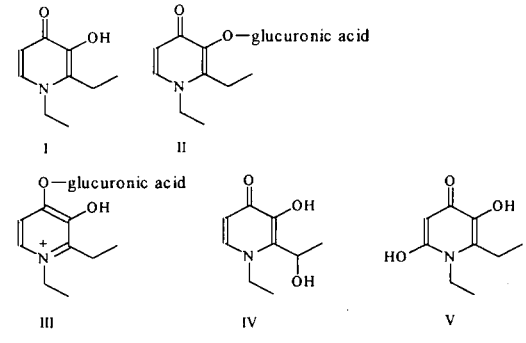
1,2-Diethyl-3-hydroxypyridin-4-one (CP94, **I**) is an extensively studied orally effective iron chelator. The metabolic profiles of this compound in the urine and blood of rats have been previously investigated (Epemolu *et al.* 1994; Singh *et al.* 1992; Epemolu *et al.* 1992). However, the biliary metabolic profile of CP94 and its relationship with iron excretion have not been investigated. As bile is the main pathway for iron secretion in rat, the establishment of the biliary metabolic profile of CP94 was considered to be critically important. The present study compares the biliary and urinary metabolic profiles of CP94 in the normal rat.

The rat bile duct cannulation model was used to collect bile samples up to a period of 10 hours after oral administration of a single dose of CP94 (450 μmole/kg). The urine samples were collected using separate animals without bile duct cannulation. The bile and urine samples were analysed using a HPLC method (Singh *et al.* 1992) and the amount of iron excreted in the bile and urine was determined using a colorimetric method (Gosriwatana and Hider, 1997). In order to determine the potential conjugated metabolites of CP94, the bile and urine samples were treated with either β-glucuronidase or sufatase before application for HPLC analysis.

The results confirmed the CP94 urinary metabolic profile reported by Singh (1992). Only low levels of unchanged CP94 were detected in the urine. However, two glucuronidated metabolites of CP94 were found to be major elimination forms in the urine. One is the 3-glucuronide (**II**), whilst the other is likely to be the 4-glucuronide (**III**). The precise assignment of these two peaks requires further investigation. In addition, the 2-(1-hydroxy) metabolite of CP94 (**IV**) was found to be the dominant metabolite in urine.

Unlike the urinary profile, the parent CP94 and its conjugated metabolites (**II** and **III**) were all found to be major excreted forms in the bile. Metabolite **IV** was also detected in the bile, but at low level. In addition, an unstable and potentially toxic metabolite, possibly the 6-hydroxy metabolite (**V**), was detected in the bile. When the bile was collected and processed under nitrogen, metabolite **V** was detected in much larger amounts, indeed it is clearly one of the major metabolites of CP94. This metabolite is destroyed when the bile is incubated in the presence of oxygen. It is likely that metabolite **V** is oxidised to a reactive semi-quinone or quinone and that this metabolite could therefore account for some of the toxicity associated with CP94.

The excretion of iron in bile showed a parallel pattern to the excretion of the parent CP94 but in the molar ratio range of 0.9-1.2. This range of values implies that the active metabolites of CP94, e.g. **IV** and **V**, may also play an important role in iron secretion as the iron will be excreted as a 3:1 ligand-metal complex.



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