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THE COMPARATIVE TOXICITIES AND ANALGESIC ACTIVITIES OF TWO FLUORINATED ANALOGUES OF PARACETAMOL

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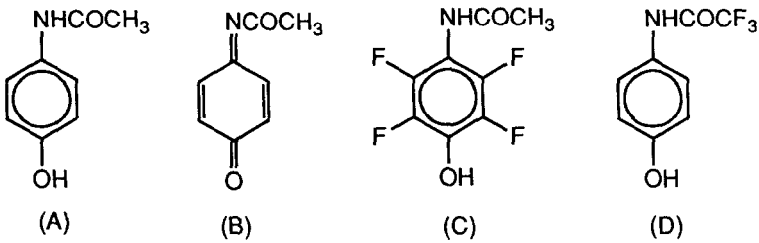

The widely used analgesic paracetamol (A) is known to cause serious hepatic necrosis at high doses in man and experimental animals [1]. An electrophilic metabolite (B) of Cytochrome P_{450} oxidation is implicated in this toxic reaction [2].

Two fluorinated analogues (C,D) were prepared in order to compare their hepatic toxicity and analgesic action with that of paracetamol. Compound (C) showed no analgesic activity in the mouse but (D) was 3.5 times more active than paracetamol. Neither showed the same severe hepatic necrosis as paracetamol. Significantly, both (C) and (D) have higher oxidation potentials than (A) and metabolic studies with (C) confirm that oxidation to an analogue of (B) does not occur. Comparison of other physiochemical properties of the two analogues with those of paracetamol throws considerable light on their toxicological, metabolic and pharmacological actions.

1 J. A. Hinson, in 'Reviews in Biochemical Toxicology', F. Hodgson, J. R. Bend, and R. M. Philpot (eds), Elsevier, New York, 1980, Vol. 2, p.103.

2 J. R. Mitchell, D. J. Jollow, W. Z. Potter, J. R. Gillette, and B.B. Brodie, J. Pharmacol. Exp. Ther., 187, 211 (1973).