EFFECT OF STRUCTURAL MODIFICATIONS ON DRUG-HEPATIC MICROSOMAL INTERACTIONS

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Many drugs which are metabolised by the hepatic oxidative route produce characteristic spectral absorbance changes when they are added to liver microsomal suspensions (Remmer & others, 1966, Imai & Sato, 1966). The difference spectrum recorded on addition of drug to microsomes is thought to represent the binding of substrate to cytochrome P-450 and the relative binding affinity is defined by a spectral dissociation constant 'K_s' which is the concentration of substrate giving rise to half maximal spectral change.

The difference spectra of 32 non-ionised drug analogues were determined by the method of Schenkman & others (1967) using hepatic microsomes from normal and phenobarbitone treated rats. All compounds studied showed Type 1 binding, characterised by an absorption peak at 385 nm and a trough at 420 nm. The degree of binding was substrate concentration dependent and analysed in terms of Michaelis-Menton kinetics by means of Lineweaver-Burk plots.

The compounds studied were classified into 4 series, I - alkylbenzenes and alkyl cyclohexanes, II - naphthyl analogues, III - biphenyl analogues and IV - aliphatic carbamates. An increase in the number of methylene groups in the alkyl straight chain in series I and IV resulted in a decrease in K_s (increase in affinity). However, introduction of branched chain alkyl groups resulted in smaller decreases in K_s than those observed with straight chain analogues. Comparison of members of series I, II and III demonstrated that cyclic compounds containing saturated carbons showed higher affinity than those where the carbon ring was aromatic. The rank order of K_s which resulted from these structural effects corresponded to the rank order of the partition coefficients 'P'(octanol/water) for these compounds (Figure 1).

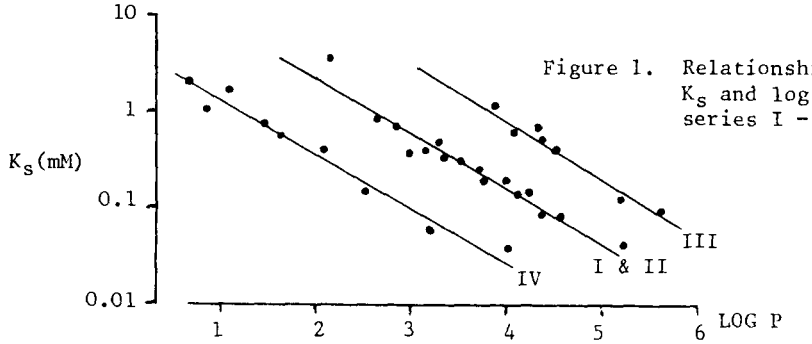

Figure 1. Relationship between K_s and log P for series I - IV.

Three distinct regression lines are apparent. The intercepts but not slopes of the lines are statistically significantly different ($p < .01$).

In contrast to the K_s, the maximum spectral change 'A_{max}' measured for each compound did not show any obvious trends within each series. Values ranged from 0.033 to 0.061 O.D. units/2 mg protein. Comparison of microsomes from normal rats with those obtained from phenobarbitone pretreated rats showed no significant change in K_s but a statistical significant increase ($p < .05$) in A_{max} was observed.

Remmer, H. & others (1966). Mol. Pharmac., 2,187.
Imai, Y. & Sato, R. (1966). Biochem. Biophys. Res. Commun., 22,620.
Schenkman, J.B. & others (1967). Mol. Pharmac., 3,113.