LETTERS TO THE EDITOR

Correlation of analgesic potencies of *N*-substituted normeperidines and *in vitro* *N*-dealkylation

Structural variation of the substituent attached to the basic nitrogen in strong analgesics may cause substantial potency variations (Portoghese, 1965, 1966). It is not known whether the potency differences are a reflection of different drug concentrations in the biophase or to differing receptor affinities or a combination of these. Since it has been reported (Hardy, Lister & Stern, 1965; Christian, Gorodetzky & Lewis, 1971) that increasing the chain length of the *N*-substituent in normeperidine derivatives gives rise to large differences in ED50's, we have studied the *in vitro* *N*-dealkylation of homologues in this series (methyl to nonyl) in an effort to ascertain whether metabolism can be correlated with the structure-activity relations.

Enzymatic dealkylation of *N*-substituted normeperidines was examined in mouse liver homogenate. Equimolar concentrations of the compounds were individually incubated in air with the 9000 *g* supernatant of mouse liver homogenate for 60 min at 37°. The incubation mixture contained NADP and NADPH generating system in a pH 7·4 phosphate buffer.

The extent of *N*-dealkylation was determined by measuring the normeperidine produced using a g.l.c. assay. The normeperidine extracted from the basified incubation medium was mixed with 4-phenyl-4-piperidinol (internal standard) and acetic anhydride. A Perkin-Elmer 900 gas chromatograph equipped with 6 ft × 0·25 in o.d. glass column packed with 3% OV-17 on chromosorb W and a flame ionization detector was used at a column temperature of 205° and N_2 as carrier gas. The amount of normeperidine was determined from the peak-height ratio of *N*-acetylnormeperidine (Rt 9 min) to that of *N*-acetyl-4-phenyl-4-piperidinol (Rt 15 min).

Table 1 shows the percentage substrate dealkylated as determined by the amount of normeperidine produced after 60 min incubation. All the compounds were substrates for the microsomal enzymes. It is of interest that there is no linear dependence of dealkylation on liposolubility as has been reported for demethylation of tertiary amines (McMahon, 1961; McMahon & Easton, 1961; Hansch, Steward & Iwasa, 1965).

The ED50 values were determined by the Eddy hot-plate method (Eddy & Leimbach, 1953) after intravenous administration in mice (Christian, Gorodetzky, &

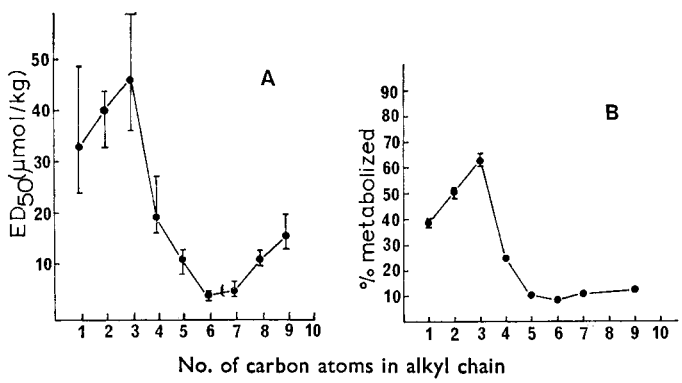
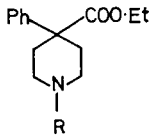


FIG. 1. Effect of chain length of the *N*-substituent on the analgesic activity and *in vitro* enzymatic *N*-dealkylation of meperidine congeners. One curve (A) represents ED50 as determined by the hot plate method in μmol/kg versus the number of carbons in the alkyl chain. The other curve (B) represents percent substrate *N*-dealkylated *in vitro* versus the number of carbons in the alkyl chain. Vertical lines represent 95% confidence limits in the hot plate graph and s.e. in the other graph.

Table 1. *Chain length of* N-*substituent and enzymatic* N-*dealkylation of meperidine congeners.*



Substrate[a] R=	Normeperidine produced[b] μmol (s.e.)	% Substrate *N*-dealkylated (s.e.)[b]
Methyl ..	0·192 (0·007)	38·4 (1·45)
Ethyl	0·255 (0·008)	51·0 (1·52)
n-Propyl ..	0·314 (0·012)	62·8 (2·43)
n-Butyl ..	0·124 (0·002)	24·8 (0·38)
n-Pentyl ..	0·053 (0·002)	10·6 (0·45)
n-Hexyl ..	0·043 (0·002)	8·6 (0·43)
n-Heptyl ..	0·055 (0·002)	11·0 (0·44)
n-Nonyl ..	0·061 (0·002)	12·4 (0·46)

a. Substrates used as hydrochloride salts in $1{\cdot}0 \times 10^{-4}$M concentration.
b. Each value is the mean of four experiments.

Lewis, 1971). Fig. 1 illustrates the remarkable similarities in the curves relating *N*-dealkylation and ED50 to chain length. Linear regression analysis of the data shows a high correlation ($r = 0{\cdot}978$) between *N*-dealkylation and ED50.

These results suggest that *N*-dealkylation is a major metabolic pathway for these compounds *in vivo*, and that the differences in analgesic potency between these congeners is due primarily to differences in their metabolism (and hence to differences of drug concentration in the biophase) rather than differences in their interaction with analgesic receptors.

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