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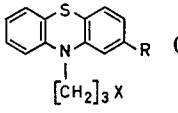
Activity correlations and the mode of action of aminoalkylphenothiazine tranquillizers

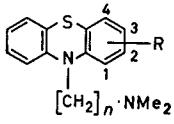
SIR,—Potent tranquillizing activity in the aminoalkylphenothiazine series is generally limited to those compounds (I) which have a substituent in the 2-position of the phenothiazine nucleus, and in which the phenothiazine nitrogen



(I) R = H, Cl, CF_3 etc.
X = Tertiary amino-group

atom and the terminal amino-group are separated by a trimethylene chain (Gordon, Craig & Zirkle, 1964). The amino-group and part of the side-chain may be incorporated into a ring system such as piperidine. Within this restricted range of structural variation, numerous correlations have been reported between

TABLE 1. CATALEPTIC ACTION, SURFACE ACTIVITY, IONIZATION CONSTANT, WATER SOLUBILITY AND EFFECT ON ATPase OF DIMETHYLAMINOALKYLPHENOTHIAZINES



R	*n*	ED50 (mg/kg) for catalepsy	Surface-active concn (μM)	I50 (μM) for ATPase inhibition	pK_a	Solubility (μM) of free base in water
H	3	25	800	250	9·4	50
1—Cl	3	none at 50	500	150	9·4	12
2—Cl	3	4	240	80	9·3	8
3—Cl	3	none at 20	180	120	9·2	10
4—Cl	3	none at 50	300	50	9·2	11
2—CF_3	3	2·5	70	100	9·2	5
4—CF_3	3	none at 50	50	80	9·3	7
2—Cl	2	none at 20	200	150	8·6	15
2—Cl	4	none at 25	140	200	9·7	5

ED50 is the dose of drug required to cause catalepsy in 3 out of 6 mice 1 hr after intravenous injection (Taeschler & Cerletti, 1958).
The surface-active concentration is that required to lower the surface tension of 10 mM sodium phosphate (pH 6·97) by 5 dynes/cm when measured with a Du Noüy tensiometer and platinum ring.
A rat brain microsomal suspension treated with sodium deoxycholate was used as a source of $(Na^+ + K^+)$-activated ATPase (Järnfelt, 1964). I50 is the concentration of compound required to inhibit the ouabain-sensitive fraction of the activity by 50% when measured at 37° in 30 mM tris buffer (pH 7·5) in the presence of 20 mM KCl, 100 mM NaCl, 5 mM $MgCl_2$ and 2·5 mM ATP.
The pK_a was derived from the pH dependence of the water solubility (Green, 1967).

the tranquillizing potency and the activity in isolated chemical or biochemical systems. Some, such as the correlations of tranquillizing potency and surface activity (Seeman & Bialy, 1963), or inhibition of ($Na^+ + K^+$)-activated ATPase (Davis & Brody, 1966), have been cited as evidence that tranquillization is causally connected with these simpler actions.

The results in Table 1 show that when the nuclear substituent is transferred to some other position in the ring, or when the polymethylene side-chain is altered in length, the marked fall in tranquillizing activity, assessed here from the ED50 for catalepsy, is not accompanied by any corresponding decrease in either surface activity or inhibitory potency against ($Na^+ + K^+$)-activated ATPase. Nor are there any marked changes in ionization constant or water solubility (cf. Green, 1967). The failure of any of the above systems to discriminate between the potent tranquillizers and the closely related but much less active compounds casts doubt on the significance of the activity correlations mentioned earlier.

The possibility that compounds with substituents in other than the 2-position fail to act as tranquillizers because they do not enter the brain in sufficient concentration has been largely excluded by the finding that all four chloro-10-dimethylaminopropylphenothiazines accumulate to roughly the same extent (13, 20, 34 and 26 μmole/kg for the 1-, 2-, 3- and 4-chloro isomers respectively) 1 hr after subcutaneous injection of equal doses (20 μmole/kg) into mice. The compounds were extracted with heptane from a basified brain homogenate (Wechsler & Forrest, 1959) and estimated spectrophotometrically (Salzman & Brodie, 1956). It is difficult to be certain that the compounds extracted are the unchanged drugs and not inactive metabolites, but the ultraviolet spectrum of each extract was the same as that of the pure drug. This eliminates the possibility of oxidation to sulphoxide or sulphone; but it remains to be established that there is no selective alteration of the side-chain, that might not change the spectra but could profoundly modify the biological activity.

Until a satisfactory explanation can be offered why a 2-substituent and a trimethylene side-chain are essential for potent tranquillizing activity in the aminoalkylphenothiazine series, activity correlations should be viewed with some scepticism as evidence for particular mechanisms of tranquillization.

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