SHORT COMMUNICATIONS

LIPOID–WATER PARTITION COEFFICIENTS OF SOME PHENOTHIAZINES*

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The well-known anthelmintic phenothiazine possesses extremely low water-solubility, stated as 1 part in 800,000 by Davey and Innes (1942). It has been shown that phenothiazine enters nematode parasites largely through the cuticle (Lazarus and Rogers 1951). Since one of the factors influencing the permeability of a cell membrane to a drug molecule must be the lipoid-water partition coefficient of the drug, it was of interest to determine this constant for a number of substituted phenothiazines.

Method

Solubilities in water were too low to allow the method of Cymerman-Craig and Diamantis (1953) to be used. Accordingly, absolute solubilities were determined in water (S_W) and in *n*-heptane (S_L). Water was buffered to pH 6·5 with phosphate buffer (Clark 1928). *n*-Heptane (b.p. 98–99 °C) was obtained spectroscopically transparent by repeated treatment with chlorosulphonic acid.

S_L was determined by shaking an excess of the finely ground compounds with heptane at 20 ± 2 °C for 48 hr, filtering rapidly without suction, and diluting the filtrate to a concentration (usually 1 in 250) which gave a convenient value of the optical density d at the wavelength of maximum absorption. Comparison with the values of d in heptane for known concentrations gave the absolute solubility. The agreement with Beer's law was very close in all cases. S_W was determined by shaking the finely ground compound with M/120 phosphate buffer solution at 20 ± 2 °C for 48 hr, filtering without suction and extracting a known volume of the filtrate (usually 200 ml) with three portions of heptane, and making the heptane up to a known volume, usually 25 ml. Further extraction did not increase the optical density. Measurement of d and comparison with the standards enabled the concentration in water to be calculated. Duplicates for both S_L and S_W were within 10 per cent. Spectroscopic measurements were made with a Beckman model DU spectrophotometer in 1 cm quartz cells.

All samples were of analytical purity and had the highest m.p.'s recorded in the literature. The oxygen-sensitive 3-hydroxyphenothiazine was handled in an inert atmosphere.

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Results

Table 1 shows the partition coefficients obtained, together with the values of S_L and S_W, and the ultraviolet absorption maxima and intensities, for 18 phenothiazines.

Water-solubility is seen to decrease with increasing molecular complexity of the 3-substituent as expected, and the partition coefficients themselves show a 2 million-fold range, varying from 0·081 to 180,000. These results serve

TABLE 1

PARTITION COEFFICIENTS OF PHENOTHIAZINES

Phenothiazine	S_L (mg/100 ml)	S_W (mg/100 ml)	S_L/S_W	$\text{Log}_{10}\,\varepsilon$	$\lambda_{max.}$ (mμ)
3-Hydroxy-	4·62	57·3	0·081	4·61	253
2,7-Dichloro-	0·675	0·0106	6·4	4·67	261
3,7-Dichloro-	0·292	0·0043	6·8	4·90	260
2-Chloro-7-methoxy- ..	7·70	0·277	26·2	4·87	253
3-Methoxy-	43·7	0·161	270	4·42	253
3,7-Dimethoxy- ..	7·45	0·011	680	4·45	254
3-Methyl-	76·5	0·0445	1700	4·62	255
3,4-Benzo-	11·5	0·00667	1700	4·36	241
3,4-6,7-Dibenzo- ..	7·90	0·00396	2000	4·67	268
3-Chloro-	31·4	0·0153	2100	4·62	258·5
3-Bromo-	86·5	0·0215	4000	4·67	258
3-Fluoro-	116	0·0280	4100	4·37	259
1,2-Benzo-	220	0·0317	6900	4·44	254
Unsubstituted ..	387	0·0510	7600	4·52	253
3-Iodo-	33·8	0·00384	8800	4·46	255
3,7-Dimethyl-	112	0·0094	12000	4·55	255
10-Methyl-	2083	0·0544	38000	4·60	255
1,2-8,9-Dibenzo- ..	68·0	0·00037	180000	4·51	252

to indicate the tremendous influence of substitution on partition coefficients in this series, but do not in themselves suggest any direct correlation between this property and anthelmintic activity.

References

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