A salt solution was added stepwise to a defined caffeine solution and after each addition the heat of reaction was determined. To eliminate the effect of the heats of dilution, the corrections were made as described above. In a second run the caffeine concentration was changed in order to produce a different ratio of caffeine–salt concentration.

The stability constants for the caffeine complexes (Table 1) are independent of the caffeine concentration, which is further evidence that the stoichiometric ratio 1 : 1 is correct.

The decrease in the number of free molecules detected by the isopiestic measurement for a given salt–caffeine mixture must be correlated with the stability of this complex. There is a linear relation between ΔR and the K_c-values (Fig. 1B), demonstrating the suitability of both methods for the determination of the stability of such systems.

Fig. 1B also shows that the amount of dissolved caffeine in a 0·5M salt solution is linearly dependent on the stability constants. Extrapolation to a stability constant of zero leads to the correct value of the solubility of caffeine in water. The results clearly show that the stability of the caffeine–salt complexes is the most important factor for the solubilization of caffeine by these substances.

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August 4, 1969

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Toxicity of ethanol-barbiturate mixtures

It is frequently stated that ethanol and barbiturates potentiate each other. Wiberg, Coldwell & Trenholm (1969) have published observations which they are inclined to interpret as support for this view. In our opinion, however, their data should be interpreted differently. This can be demonstrated by plotting isobols (Loewe, 1953, 1957). These are lines on a combined dose diagram connecting those dose pairs which are equi-effective in producing a defined pharmacological effect.

Fig. 1 shows Wiberg, Coldwell and Trenholm's data on acute toxicity of ethanol-barbiturate mixtures in male rats, calculated from the original mortality figures kindly provided by the authors. In each case the line indicates no more than a simple additive effect; there is no suggestion of potentiation.

Their findings on the prolongation of sleeping time might be explained by potentiation but might equally well be due to summation. The fact that two inactive doses produce a marked effect when given in combination does not necessarily indicate potentiation; summation could produce the same result, especially if the log dose-response curves were steep as they appear to be for ethanol and the barbiturates. Unfortunately, the data are insufficient to enable isobols to be constructed. The authors have used threshold or subthreshold doses of barbiturates in combination with ineffective doses of ethanol. If they had tested combinations of half these doses, or, alternatively, recorded the effects of double doses of either drug alone, summation and potentiation might have been distinguished.

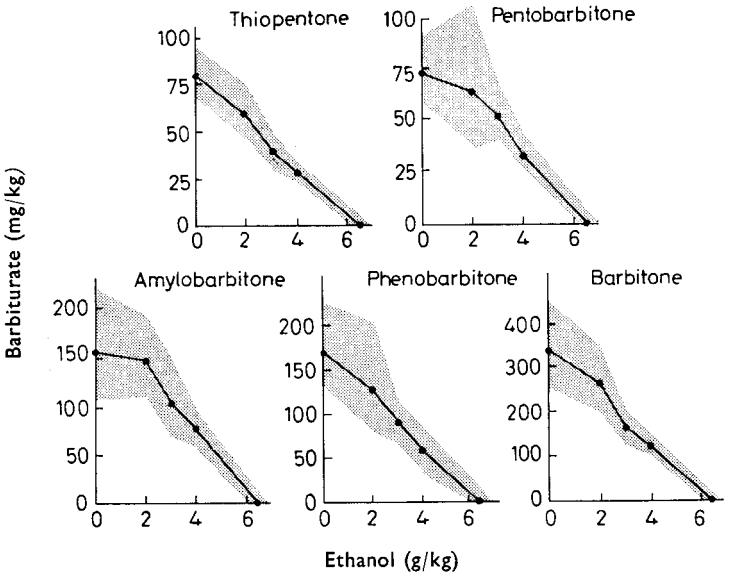

FIG. 1. Isobols showing combined lethal effects (LD50) of barbiturates and ethanol. Drug pairs were injected intraperitoneally at the same time. Horizontal axes: ethanol dose, g/kg. Vertical axes: barbiturate dose, mg/kg. Shaded areas represent 95% confidence limits.

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September 17, 1969

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