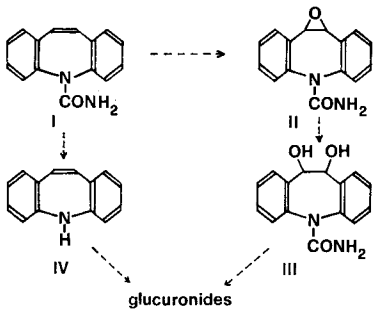
No hydrolysis of carbamazepine was found as a result of this treatment, therefore iminostilbene (IV) is a true metabolite of carbamazepine.

The presently known biodegradation pathway is thus:



Metabolic pathway of carbamazepine (I)

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REFERENCES

BAKER, K. M., CSETENYI, J., FRIGERIO, A., MORSELLI, P. L., PARRAVICINI, F. & PIFFERI, G. (1972). *J. medl Chem.*, in the press.

FRIGERIO, A., BIANDRATE, P., FANELLI, R., BAKER, K. M. & MORSELLI, P. L. (1972). *Proceedings International Symposium on Gas Chromatography-Mass Spectrometry*, Isle of Elba, Italy. Ed. A. Frigerio, p. 389. Milan: Tamburini.

FRIGERIO, A., FANELLI, R., BIANDRATE, P., PASSERINI, G., MORSELLI, P. L. & GARATTINI, S. (1972). *J. pharm. Sci.*, **61**, 1144–1147.

GOENECHEA, S. & HECKE-SEIBICKE, E. (1972). *Z. Klin. Chem.*, **10**, 112–113.

Interaction between DDT and lecithin in spread monolayers

Some time ago, evidence of an interaction occurring between pp'DDT and dipalmitoyl lecithin, in organic solvents (chloroform and carbon tetrachloride), was obtained by proton magnetic resonance measurements (Tinsley, Haque & Schmedding, 1971). This finding was an interesting contribution to the study of the mode of action of DDT at the molecular level. Its significance, however, was restricted by the fact that, in biological systems, phospholipids are dispersed in aqueous media where they are oriented with respect to water in well-defined structures (Dervichian, 1964; Phillips, 1972). In view of those considerations, it was thought desirable to reconsider the DDT-lecithin interaction but, this time, in spread monolayers. Indeed, monomolecular films of lecithins closely parallel the physical state of those phospholipids in biological systems (Phillips, 1972) and they have been extensively used to study

interactions of biological significance. Preliminary observations obtained with that technique could serve as a starting point for a more elaborate study involving both monolayers and bilayers.

pp'DDT(1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethane), 99% +, was purchased from Aldrich Chemical Company and L-α-lecithin (β-γ-dipalmitoyl), synthetic, A grade, from Calbiochem. Mother solutions of each component were made with the spreading solution (hexane, 95 parts; ethanol, 5 parts) and appropriate mixtures were prepared from those solutions. The measuring apparatus was a completely automatic recording Langmuir hydrophil balance built mainly according to the plans of Mann & Hansen (1960, 1964). Solutions of the film-forming substances were deposited on clean water surfaces (available area: 630 cm^2) with an Agla micrometer syringe and, after a waiting interval of 10 min, compression was started. The construction of a complete (compression) isotherm took about 15 min. In some cases, compression was followed by decompression and, then, by recompression but the rate of motion of the piston was always kept constant.

The isotherm of dipalmitoyl lecithin (Fig. 1) agrees with other published values (Vilalloga, 1968) [on 0·1 M sodium chloride solutions, the areas found at maximum compression are slightly higher (Phillips & Chapman, 1968; Paltauf, Hauser & Phillips, 1971)]. The relatively fast rate of compression used in the present set of experiments (0· 19 nm^2 $molecule^{-1}$ min^{-1}) did not seem to affect the shape of the isotherm which compares well with others obtained at 0·04, 0·08 and 0·12 nm^2 $molecule^{-1}$ min^{-1} (Vilalloga, 1968). As anticipated, lecithin had enough affinity for DDT to carry it along in the spreading process and retain it in the film [DDT is a highly hydrophobic substance which does not spread on water but spreadability can be brought about with certain surfactants (Burgess, 1949)]. This kind of behaviour has been recognized and studied in detail for polycyclic hydrocarbons and steroids (Clowes, Davis & Krahl, 1938; Davis, Krahl & Clowes, 1940; Crisp, 1949). Other studies have been reported more recently (Snart, 1967; Weiner, Chawdry & Felmeister, 1971; Felmeister, Tsai & Weiner, 1972). The nature of the interaction

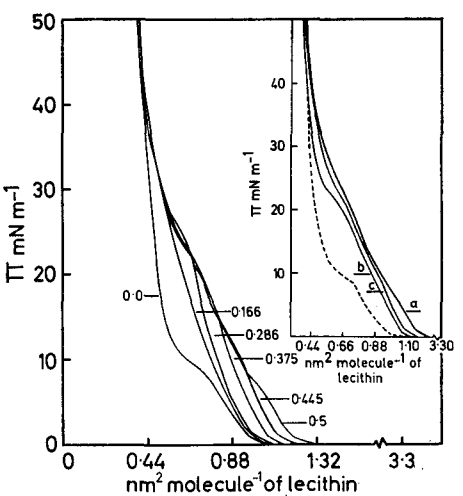

FIG. 1. Pressure-area curves for mixed films of dipalmitoyl lecithin and DDT, at room temperature. The decimals accompanying the individual curves give the mole fraction of DDT in the mixed film. In insert: (*a*) compression of the film containing 0·5 mole fraction DDT, followed by (*b*) complete decompression and (*c*) recompression. In dotted lines: compression isotherm of lecithin.

between DDT and lecithin in the mixed films is discussed with reference to those studies.

First, it can be seen in Fig. 1 that, as the proportion of DDT increases in the film, the area occupied per lecithin molecule also increases. At mole fractions of DDT greater than 0·5, it was verified that the isotherms obtained coincided with the one for 0·5. Secondly, a shoulder can be observed on every one of those curves at a surface pressure which decreases as the proportion of DDT increases in the film. A third point to be noted is that, past the shoulder (i.e., at higher pressures), those curves form a more or less common envelope (which, eventually, reaches the lecithin isotherm). It can easily be deduced from the first observation that an interaction occurs between lecithin and DDT and that the stoichiometry of that interaction is 1 to 1. However, the nature of the interaction, which should be inferred mainly from consideration of the second and third observations, is difficult to assess with certainty.

In fact, the characteristics of two kinds of interactions are simultaneously present: the one for a molecular association (below the shoulders) and the one for a surface solution (above the shoulders). Mixed films displaying molecular association manifest themselves by an increase in viscosity: surface rheology, which is a very sensitive method to study molecular interactions in monolayers (Joly, 1964) should give an unambiguous answer in the present case. It is interesting, also, to consider the behaviour of the mixed films upon decompression and recompression (illustrated in insert, Fig. 1, for the film containing 0·5 mole fraction DDT). It can be seen that, at the second compression, the shoulder previously observed has disappeared. (Upon further compressions and decompressions the curves for the first recompression and first decompression are reproduced). One is thus tempted to believe that an association could have existed in the organic solvent which was not destroyed in the spreading process: it was broken, however, by compression (at the shoulder, i.e., the collapse pressure) and could not reform on water. The surface solution type of interaction is less ambiguous (all the curves form a common envelope): the thermodynamic parameters have not been computed here because the systems were not at equilibrium (insert, Fig. 1).

Recently, the construction of bilayers capable of simulating axon membranes has been reported (Leuzinger & Schneider, 1972). [The action of DDT on lecithin bilayers has already received some consideration (Hilton & O'Brien, 1970)]. This suggests that the action of DDT should be verified first, on those simulated axon membranes. Then, its action on each component of those membranes (brain lipid extracts and acetylcholinesterase preparations), separately and mixed in various proportions, should be investigated in monolayers. Felmeister, Tsai & Weiner (1972) have attempted something of that sort in their study of the interaction of a carcinogenic hydrocarbon (3,4-benzpyrene) with monomolecular films.

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REFERENCES

BURGESS, B. F., Jr. (1949). *Soap Chem. Specialities*, **25**, 127–131.

CLOWES, G. H. A., DAVIS, W. W. & KRAHL, M. E. (1938). *Am. J. Cancer*, **36**, 98–109.

CRISP, D. J. (1949). In: *Surface Chem. Research*, pp. 23–35, London: Butterworths.

DAVIS, W. W., KRAHL, M. E. & CLOWES, G. H. A. (1940). *J. Am. chem. Soc.*, **62**, 3080–3098.

DERVICHIAN, D. G. (1964). In: *Progress in Biophysics and Molecular Biology*, Vol. 14, pp. 263–342. Editors: Butler, J. A. V. and Huxley, H. E., London: Pergamon.

FELMEISTER, A., TSAI, D. & WEINER, N. D. (1972). *J. pharm. Sci.*, **61**, 1065–1068.
HILTON, B. D. & O'BRIEN, R. D. (1970). *Science*, **168**, 841–843.
JOLY, M. (1964). In: *Recent Progress in Surface Science*. Vol. 1, pp. 35–44. Editors: Danielli, J. F., Pankhurst, K. G. A. and Riddiford, A. C., London: Academic Press.
LEUZINGER, W. & SCHNEIDER, M. (1972). *Experientia*, **28**, 256–257.
MANN, J. A., Jr. & HANSEN, R. S. (1960). *Rev. Scient. Instrum.*, **31**, 961–963.
MANN, J. A., Jr. & HANSEN, R. S. (1964). *Ibid.*, **35**, 702–703.
PALTAUF, F., HAUSER, H. & PHILLIPS, M. C. (1971). *Biochem. biophys. Acta*, **249**, 539–547.
PHILLIPS, M. C. & CHAPMAN, D. (1968). *Ibid.*, **163**, 301–313.
PHILLIPS, M. C. (1972). In: *Progress in Surface and Membrane Science*. Vol. 5, pp. 139–221. Editors: Danielli, J. F., Pankhurst, K. G. A. and Riddiford, A. C., London: Academic Press.
SNART, R. S. (1967). *Biochem. biophys. Acta*, **144**, 10–17.
TINSLEY, I. J., HAQUE, R. & SCHMEDDING, D. (1971). *Science*, **174**, 145–147.
VILALLOGA, F. (1968). *Biochem. biophys. Acta*, **163**, 290–300.
WEINER, N. D., CHAWDRY, I. & FELMEISTER, A. (1971). *J. pharm. Sci.*, **60**, 425–428.

Preparation of Δ^9-tetrahydrocannabinol for intravenous injection

Fenimore & Loy (1971) and Moreton & Davis (1972) have described the preparation of Δ^9-tetrahydrocannabinol (Δ^9-THC) suspensions. Perez-Reyes, Timmons & others (1972) have described an infusion based on human serum albumin. We now wish to report a formula for a clear, intravenous saline solution of Δ^9-THC and related cannabinoids, which can be injected in a relatively small volume.

The formulation consists of Δ^9-THC, 0·1% w/v; alcohol USP, 5% v/v; Emulphor EL-620 0·6 v/v (or Tween 80, 1·5% v/v); saline q.s. The Δ^9-THC is prepared as a 2% w/v solution in ethanol to facilitate handling and measurement. The surfactant is added next with mixing and finally the saline solution is added slowly with gentle mixing to final volume.

The above preparation can easily be sterilized by use of a 0·22 μm filter. The preparation is infinitely dilutable in water without visual precipitation and gives the appearance of a clear solution. Negligible haemolysis was observed in saline solution. The concentration of 1 mg Δ^9-THC ml^{-1} of saline solution is practical for use in man (injection range 1–5 ml of saline).

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REFERENCES

FENIMORE, D. C. & LOY, P. R. (1971). *J. Pharm. Pharmac.*, **23**, 310.
MORETON, J. E. & DAVIS, W. M. (1972). *Ibid.*, **24**, 176.
PEREZ-REYES, M., TIMMONS, M. C., LIPTON, M. A., DAVIS, K. H. & WALL, M. E. (1972). *Science*, **177**, 633–635.