The results obtained for the series of carbamoylpiperidinodecanes thus seem to substantiate the observation of Thomas and Marlow (4) and also suggest that this property, in the case of variations around the carbonyl function (2, 3, 7), may be more critical in effecting inhibitory action than the surface activity of the compounds (2).

The fact that such relationships do not hold outside the scope of a particular series is shown by results obtained with the pyridinium analog (X). While this compound is an extremely potent inhibitor, it has a partition coefficient of zero.

REFERENCES

(1) Quintana, R. P., THIS JOURNAL, **53**, 1221(1964).
(2) *Ibid.*, to be published.
(3) Purcell, W. P., Beasley, J. G., and Quintana, R. P., *Biochim. Biophys. Acta*, **88**, 233(1964); *cf.* Purcell, W. P., *J. Phys. Chem.*, **68**, 2666(1964).
(4) Thomas, J., and Marlow, W., *J. Med. Chem.*, **6**, 107 (1963).
(5) Lasslo, A., and Waller, P. D., *J. Org. Chem.*, **22**, 837 (1957).
(6) Quintana, R. P., and Shrader, W. A., THIS JOURNAL, **52**, 1186(1963).
(7) Beasley, J. G., Quintana, R. P., and Nelms, G. G., *J. Med. Chem.*, **7**, 698(1964).
(8) Soloway, A. H., *Science*, **128**, 1572(1958).
(9) Lasslo, A., *et al.*, *J. Med. Chem.*, **6**, 811(1963).

Technique Utilizing Frog Immersed in Drug Solution to Study Drug Absorption Rates

By CLYDE W. WHITWORTH

The frog has been used to study the absorption of drugs from solution. The results so far indicate compliance with the pH-partition theory of passive absorption of weak electrolytes.

SIMPLE *in vivo* and *in vitro* processes are needed to study the effect of the many physicochemical factors involved in drug absorption. The objective of this study was to determine the usefulness of the frog in such studies.

EXPERIMENTAL

Ten frogs (*Rana pipiens*) were used in each determination. Each of the frogs was placed in 500 ml. of drug solution contained in glass animal jars of about 2500-ml. capacity. Separate tests indicated that the rate of evaporation of solvent was constant and thus had no appreciable effect on the relative results obtained. Samples of the drug solution were analyzed spectrophotometrically at 20-min. intervals over a 2-hr. period, and the amount of drug absorbed was determined from the amount remaining in solution.

Aqueous solutions of salicylic acid and sodium salicylate in the concentration of 2.5×10^{-4} moles/L. were utilized. Analyses were made in a Beckman DU spectrophotometer at a wavelength of 297 mμ. There is excellent compliance to the Beer-Lambert law with the concentration of drugs used.

The drug solutions were assayed directly without having to perform extracting procedures. The frogs were rinsed with distilled water prior to each experiment and were also forced to urinate by slight squeezing. Preliminary experimentation showed that the frogs excreted no interfering substances. The solution was returned to the container after analysis to try to maintain volume.

Received September 16, 1964, from the School of Pharmacy, Northeast Louisiana State College, Monroe.
Accepted for publication November 30, 1964.
The author thanks Mr. Charles E. Coger for technical assistance.

RESULTS AND DISCUSSION

Shore *et al.* (1) have supplied evidence that certain drugs cross the intestinal epithelium chiefly in their nonionized form and that their ions penetrate little. Various investigators (2–5) have found oil soluble drugs penetrate the skin more readily. Until now, results indicate conformity to the pH-partition theory of passive drug absorption, as seen in Fig. 1.

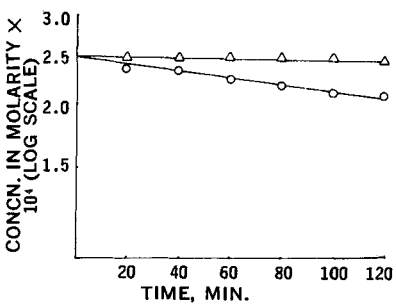

Fig. 1.—Plot of average salicylate concentrations in solution over 2-hr. period when 10 frogs each were placed in 500 ml. of aqueous drug solution. Key: △, sodium salicylate; ○, salicylic acid.

It is also apparent from Fig. 1 that the data exhibit characteristics of a first-order absorption rate.

Statistical analysis of the data by means of the Student-Fisher *t* test at 95% confidence level indicate the differences in absorption of the two forms of salicylic acid are significant. Standard deviations indicate highly reproducible results.

On the basis of the results so far, it appears that the frog may be useful for studying the passive absorption of certain drugs from solutions. The author is presently using the technique to study the effect of various additives on drug absorption.

REFERENCES

(1) Shore, P. A., Brodie, B. B., and Hogben, C. A. M., *J. Pharmacol. Exptl. Therap.*, **119**, 361(1957).
(2) Treherne, J. E., *J. Physiol. London*, **133**, 171(1956).
(3) Rothman, J., *J. Lab. Clin. Med.*, **28**, 1305(1943).
(4) Stolar, M. E., Rossi, G. V., and Barr, M., THIS JOURNAL, **49**, 148(1960).
(5) Nogami, H., Hasegawa, J., and Hanano, M., *Pharm. Bull. Tokyo*, **4**, 347(1956).