tremely fast rate from the corresponding succinyl or phthalyl phosphate (Scheme I). Since ATP possesses phosphate groups in its molecule, it is conceivable that succinic anhydride is formed from succinyl ATP–magnesium-ion complex (Scheme II). A similar reaction pathway could be postulated for the formation of acetic anhydride.

2. *The rate of reaction between the sulfhydryl group of CoA and the anhydrides is much greater than the rate of hydrolysis of the anhydrides*—I have determined the rate of reaction between succinic anhydride and L-cysteine, a thiol-containing amino acid, and between propionic anhydride and 2-dimethylaminoethanethiol. The pH–rate profiles for these reactions are shown in Figs. 1 and 2.

The reaction rates were too rapid to be measured conveniently at pH's above 6. Thus, it would appear from these experiments that the reaction between a sulfhydryl group and anhydrides would proceed extremely fast under the conditions existing in the body, whereas the rates of hydrolysis of the anhydrides are relatively slow.

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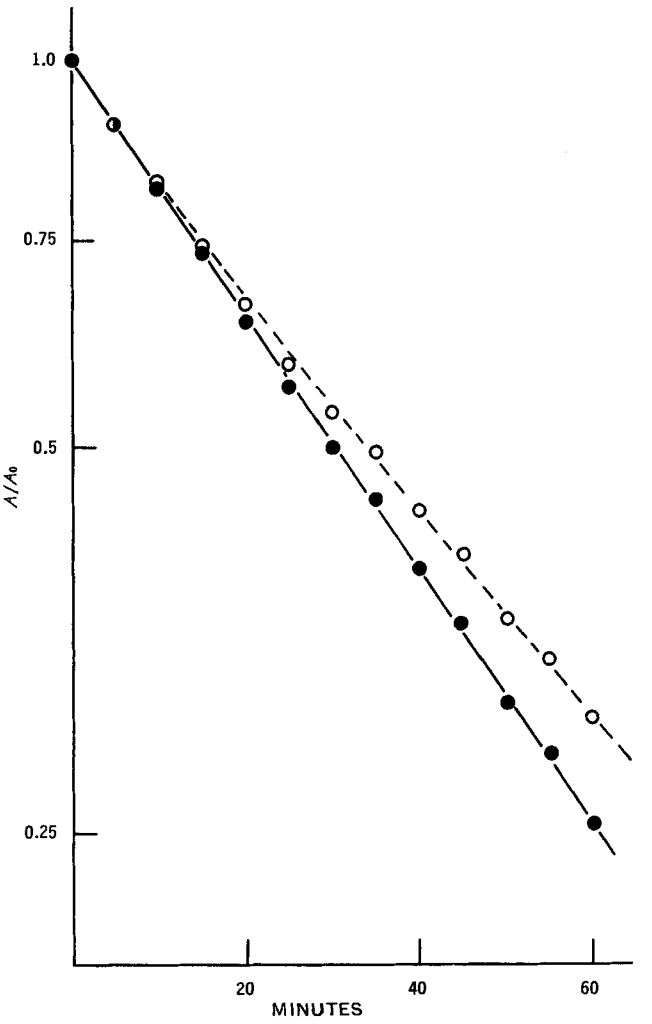

Figure 1—*Effect of dilution on diffusion of* p-*methoxyacetanilide from aqueous buffer to 1-octanol. Key:* ——, *in the absence of dilution;* - - -O- - -, *with dilution; and* —●—, *corrected for dilution.*

Correction for Effect of Dilution on Diffusion through a Membrane

Keyphrases ☐ Absorption kinetics, buccal—saliva dilution effect ☐ Dilution effect correction—first-order diffusion equation ☐ Diffusion equation, first order—dilution correction

Sir:

A number of steps in drug absorption and excretion involve simultaneous dilution of the fluid containing the drug. There does not, however, appear to be any published information concerning the effect of such dilution on diffusion rates. Beckett and Moffat (1) recognized that dilution by saliva affected buccal absorption, but they used an analog computer technique to allow for this condition. Our own work on buccal absorption, which showed that the rate of saliva production was constant during the period of a test (10 min.), led us to develop an equation to correct for the effect of such dilution on first-order diffusion.

The rate at which drug molecules enter the membrane is proportional to their concentration. Let A be the amount of drug in solution at time t, A_0 the initial amount of drug in solution, V_0 the initial volume of drug solution, and v the rate at which diluent is added.

For first-order diffusion in the absence of dilution, we thus have:

$$\frac{dA}{dt} = \frac{-kA}{V_0} \qquad \text{(Eq. 1)}$$

which on integration gives:

$$\ln \frac{A}{A_0} = \frac{-kt}{V_0} \qquad \text{(Eq. 2)}$$

When dilution occurs, we must write:

$$\frac{dA}{dt} = \frac{-kA}{V_0 + vt} \qquad \text{(Eq. 3)}$$

which on integration gives:

$$\ln \frac{A}{A_0} = \frac{-k}{v} \ln \left(1 + \frac{vt}{V_0}\right) \quad \text{(Eq. 4)}$$

Provided that vt/V_0 is <1, this expands to:

$$\ln \frac{A}{A_0} = \frac{-k}{v} \left(\frac{vt}{V_0} - \frac{v^2t^2}{2V_0^2} + \frac{v^3t^3}{3V_0^3} - \ldots\right) \quad \text{(Eq. 5a)}$$

$$= \frac{-kt}{V_0} + \frac{kvt^2}{2V_0^2} - \frac{kv^2t^3}{3V_0^3} + \ldots \quad \text{(Eq. 5b)}$$

Thus, to a good approximation, deviations from rectilinearity in the ln (A/A_0) *versus* t plot can be accounted for by the terms $[(kvt^2/2V_0^2) - (kv^2t^3/3V_0^3)]$.

We demonstrated the validity of the correction by examining the effect of dilution on the diffusion of *p*-methoxyacetanilide from 0.2 *M* phosphate buffer[1], pH 7.2, into 1-octanol. The compound is virtually completely unionized at this pH, since its pKb is about 13.

The octanol phase was stirred mechanically and the aqueous phase magnetically. The area of the interface was 81 cm.^{2}, and the temperature was 22°. Samples were taken from and returned to the aqueous phase with a syringe. Concentrations were determined on a Unicam SP.800 spectrophotometer. The initial volume of the aqueous phase was 350 ml., and the volume of octanol was 500 ml. The partition coefficient of *p*-methoxyacetanilide between these phases is 10.5, so that there was negligible back-diffusion, as shown by the straight-line logarithmic plot of diffusion in the absence of dilution (Fig. 1), up to test times of 1 hr.

When the aqueous phase was diluted with buffer at a rate of 3 ml. min.$^{-1}$, the rate of diffusion of drug decreased (Fig. 1). Applying the correction brought the loss curve back to the first-order line.

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BOOKS

REVIEWS

Animal Experiments in Pharmacological Analysis. By Floyd R. Domer, Charles C Thomas, Springfield, IL 62707, 1971. 669 pp. Price $26.50.

This treatise on the quantitative aspects of pharmacology stems from the teaching program of the author, who has taught this phase of pharmacology to graduate students for many years. It is therefore expressly intended to be of service to pharmacologic specialists who are constantly confronted with the problem of conducting quantitative evaluation of drug activity on specific organ systems.

The text is divided into chapters dealing with the evaluation of drugs on the various organ systems, such as the Neuromuscular Junction, the Autonomic Ganglic, Smooth Muscle, and others. These specific topic chapters are preceded by three general introductory chapters on the Five Areas of Pharmacology, Initial Screening Experiments, and Toxicity Determination.

The author develops the subject matter of each chapter with broad introductory comments regarding the purpose of the experiment. Detailed description is included of operational procedures, often well illustrated with pictures or diagrams. Constant-temperature baths, stimulating electrodes, and pieces of equipment used in many pharmacologic procedures are shown in the diagrams of experiments.

Chapter 11, Techniques for Evaluation of Anesthetics, is especially commendable and is abreast of progress in the field. This, like the other chapters of the book, is provided with an adequate bibliography indicating an extensive knowledge of the various areas of pharmacologic techniques with which the author is acquainted.

This text is clearly written and exemplifies an excellent command of expository writing by the author. It is destined to serve a very useful purpose as a guide to investigators in the complex field of specific organ quantitative pharmacology.

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