been accounted for as an impurity in the starting material. Syn-antiequilibrium mixtures also have been obtained by melting the syn-isomer or by photochemical irradiation in acetone at 5°.

Experiments on the stability and physical and chemical properties of I are underway. These will be reported in full publications at a later time.

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Theoretical Relationship Between Dose, Elimination Rate, and Duration of Pharmacologic Effect of Drugs

Sir:

Recent communications have dealt with the relationship between rate of decline of pharmacologic effects and drug elimination rate (1, 2), with the kinetics of multiple pharmacologic effects (3), as well as with the apparent potentiating effect of a second dose of drug administered immediately upon recovery from the effects of the initial dose (4). The purpose of this communication is to consider the quantitative relationship between dose, elimination rate, and duration of pharmacologic effect of a given drug.

Let it be assumed that (*a*) the intensity of a pharmacologic effect at any time is a function of body drug content at that time, (*b*) drug metabolites are essentially inactive (particularly with respect to the type of pharmacologic activity under consideration), (*c*) a minimum body drug content, d_m, is necessary to elicit a measurable pharmacologic effect, and (*d*) the drug is eliminated from the body by an exponential process or processes, the sum of whose rate constants is independent of dose.

The time necessary to decrease initial body drug content, d_0 (which would usually represent an amount of drug administered intravenously), to d_m can be calculated by rearranging the exponential expression for drug elimination

$$\log d_m = \log d_0 - \frac{K}{2.3}t \qquad \text{(Eq. 1)}$$

to

$$t = K_1(\log d_0 - \log d_m) \qquad \text{(Eq. 2)}$$

where K is the first-order drug elimination rate constant, $K_1 = 2.3/K$, and t is the duration of the pharmacologic effect. Rearranging Eq. 2 yields

$$t = K_1 \log d_0 - k \qquad \text{(Eq. 3)}$$

where $k = K_1 \log d_m$. Accordingly, a plot of duration of pharmacologic effect *versus* the logarithm of the dose (given intravenously or by other routes which afford rapid absorption relative to the rate of elimination) should be linear. While this linear relationship is well known (5, 6), it apparently has not been recognized that the first-order rate constant for drug elimination (K) can be calculated from the slope of the line since $K = 2.3/K_1$. The minimum effective dose (d_m) can be calculated from the intercept value since $\log d_m = k/K_1$. This method should be useful for determining the elimination rate constant (or half-life) of drugs in certain instances where measurement of drug concentration in blood, urine, or tissue is not possible but where a sufficiently accurate assessment of the duration of a given pharmacologic effect is feasible. A similar approach can be used (under certain special conditions) to determine absorption rate constants, as will be demonstrated by Lands *et al.* (7).

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