could be expected due to the steric effect of bulky substituents attached at different sites on the aromatic nucleus or on the exocyclic nitrogen. The concentration of positive charge in 9-aminoacridinium cations at the exocyclic nitrogen atom also appears to be in agreement with the observation that 2,7-di-*tert*-butyl-9-aminoacridinium monocation intercalates with DNA (5), while 2,7-di-*tert*-butylproflavin monocation does not (19). In the former compound the bulky *tert*-butyl groups are directed toward the exterior of the helix where steric hindrance is minimal. In the proflavin derivative, however, the *tert*-butyl groups would be directed toward the interior of the helix if intercalation occurred, resulting in a strongly destabilizing steric interaction.

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Correlation and Prediction of Mass Transport across Membranes II: Influence of Vehicle Polarity on Flux from Solutions and Suspensions

SAMUEL H. YALKOWSKY [x] and GORDON L. FLYNN*

Abstract □ The effects of systematic alteration of vehicle composition on the release rate of drugs from their vehicle were studied. Equations were developed which quantitatively predict the rate of transport of a drug across a membrane separating two identical binary aqueous solvents. Separate equations were derived for solutions and for suspensions, which account for both the resistance of the membrane and the resistance of the solvent to drug diffusion.

Keyphrases □ Membrane diffusion—effect of vehicle polarity on flux from solutions and suspensions, systematic alteration of vehicle composition, equations □ Vehicle polarity—effect of systematic alteration of vehicle composition on release rates of drugs, equations □ Drug release rates—effects of systematic alteration of vehicle composition, solutions and suspensions, equations

One significant factor governing drug activity is the release rate of the drug from its vehicle. For nonsolid dosage forms (fluids, ointments, *etc.*), the ability of the vehicle to retain the drug can be conveniently altered by the addition of a second fluid, which may be a solvent or a nonsolvent for the drug. Of the many recent papers dealing with drug release from fluid vehicles, few have attempted to study, generalize, and quantitate the effects of incremental changes in vehicle composition systematically. The work of Poulsen (1) is a notable exception. In this regard, the authors have attempted to show the effects of vehicle composition upon solubility, the membrane vehicle partition coefficient, and, ultimately, the drug release rate.

THEORETICAL

Dependence of Flux upon Solubility and Partition Coefficient—The resistance, R_m, of a membrane to transport of a substance is proportional to the membrane's thickness, h_m, and inversely proportional to the diffusivity, D_m, of the substance in the membrane:

$$R_m = \frac{h_m}{D_m} \qquad \text{(Eq. 1)}$$

If the membrane separates two similar solvent phases, the regions of unstirred solvent (diffusion layers) adjacent to the membrane also offer resistance to the transport of a solute from the donor to the receptor phase. This solvent resistance is given by:

$$R_s = \frac{h_s}{D_s} \qquad \text{(Eq. 2)}$$

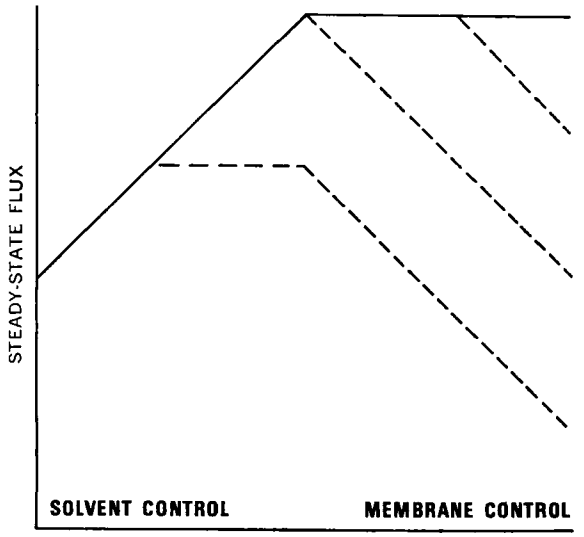

Figure 1—*Idealized relationships between solvent composition and membrane transport. Saturated solutions are indicated by a solid line; equimolar solutions of arbitrary concentrations are represented by the dashed lines. These curves are based on the assumption of a linear dependency of log (solubility) on the volume fraction of cosolvent.*

where h_s is the sum of the donor and receptor diffusion layer thicknesses, and D_s is the solute diffusivity in the solvent.

If C is the concentration gradient across the diffusion layer membrane system and PC is the membrane–solvent partition coefficient, the rate of solute transport or flux, F, across the membrane is (2–5):

$$F = \frac{C}{R_s + \frac{R_m}{PC}} \qquad \text{(Eq. 3)}$$

or, in logarithmic form:

$$\log F = \log C + \log PC - \log [R_s(PC) + R_m] \qquad \text{(Eq. 4)}$$

Generally, for a given membrane system, R_m and R_s are constants. Changes in R_s values resulting from alteration of solvent viscosity or solvation and changes in R_m resulting from alteration of the membrane by the solvent are ignored in this report. The flux is determined only by the values of C and PC. If the maximum possible flux of a particular compound across a given membrane is desired, Eqs. 3 and 4 can be modified by replacing C by S, the solubility of the compound. (This is physically accomplished by saturating the donor phase and maintaining the receptor phase at zero concentration, the perfect sink condition.) Under this condition, Eq. 3 becomes:

$$F^s = \frac{S}{R_s + (R_m/PC)} \qquad \text{(Eq. 5)}$$

and Eq. 4 becomes:

$$\log F^s = \log S + \log PC - \log [R_s(PC) + R_m] \qquad \text{(Eq. 6)}$$

Some ramifications of the chain-length dependencies of Eqs. 4 and 6, in terms of solute structure, were extensively discussed previously (5–7) and will not be repeated here. However, it can be seen that any alteration in either solubility or the partition coefficient will have a parallel effect on flux.

Effect of Binary Solvent Composition on Solubility—The solubility of a substance that is insoluble in a particular solvent can usually be increased significantly by the addition of a cosolvent in which the solute is more soluble. It has been shown (8) that for a large number of binary aqueous solvent systems, the logarithm of the solubility of various semipolar compounds is directly proportional to the volume fraction of cosolvent, f_c. That is:

$$\log S_f = \log S_w + \gamma f_c \qquad \text{(Eq. 7)}$$

where S_f and S_w are the solubilities of the solute in a system of a given cosolvent volume fraction and in water, and γ is a constant that is dependent on the polarity of the drug and the cosolvent. A review of the literature revealed that this relationship is sufficiently general so as to be useful in estimating or predicting solubilities in binary systems, provided that the polarity of the drug is significantly less than that of either solvent.

Table I—Solubility and Partition Coefficient Data for *p*-Aminoacetophenone

Percent Propylene Glycol in Water	Solubility in Binary Aqueous Solvent, mg/ml	Membrane–Solvent Partition Coefficient (P/D), mg/ml	Calculated Membrane Solubility, mg/ml
0	10.0	16.5	165
10	15.6	11.1	173
20	23.5	6.94	163
30	35.6	5.03	180
40	56.1	3.16	177
50	85.6	1.90	163
60	94.0	1.55	145
70	105	1.41	148
80	125	1.25	156
90	147	0.98	145
100	181	0.75	136
		Average	159

Effect of Binary Solvent Composition on Partitioning—The partition coefficient of a compound between a series of binary aqueous solvents and another totally immiscible nonpolar phase, such as a membrane, can be estimated by the ratio of the solubilities of the drug in the two phases. If the drug's solubility in the membrane is assumed to be independent of the composition of the binary solvent, the partition coefficient for a drug is equal to its solubility in the membrane, S_m, divided by its solubility in the binary solvent, which is described by Eq. 7; that is:

$$PC = \frac{S_m}{S_w 10^{\gamma f_c}} \qquad \text{(Eq. 8)}$$

or:

$$\log PC_f = \log PC_w - \gamma f_c \qquad \text{(Eq. 9)}$$

where PC_w is the ratio of the solubilities in the membrane and in water, S_m/S_w, or the membrane–water partition coefficient. The situation in which the solvent has an effect on membrane solubility was discussed by Poulsen (1).

Dependence of Flux on Binary Solvent Composition—From the previous sections, it can be seen that both log S and log PC are linearly dependent on f_c by Eqs. 7 and 9, respectively. If these equations are substituted into Eqs. 4 and 6, the following equations are obtained:

$$\log F^c = \log C + \log PC_w - \gamma f_c - \log [R_s PC_w 10^{-\gamma f_c} + R_m] \qquad \text{(Eq. 10)}$$

$$\log F^s = \log S_w + \log PC_w - \log [R_s PC_w 10^{-\gamma f_c} + R_m] \qquad \text{(Eq. 11)}$$

where the superscripts c and s represent equimolar concentration and saturation, respectively. Equations 10 and 11 each can be simplified under certain conditions, depending on whether the flux-determining step of the diffusion process is passage through the diffusion layers adjacent to the membrane.

Membrane Control of Flux—If the passage of the solute through the actual membrane is the rate-determining step in the diffusion process, the system is said to be under membrane control of flux (2–6). This condition is characterized mathematically by $R_m/PC \gg R_s$. The significance of this inequality can be seen when it is used to modify Eqs. 10 and 11. Under this condition, the last term of these equations becomes simply $-\log R_m$, so Eqs. 10 and 11 reduce to:

$$\log F^c = \log C + \log PC_w - \gamma f_c - \log R_m \qquad \text{(Eq. 12)}$$

and:

$$\log F^s = \log S_w + \log PC_w - \log R_m \qquad \text{(Eq. 13)}$$

respectively. Equation 12 predicts that at constant concentration

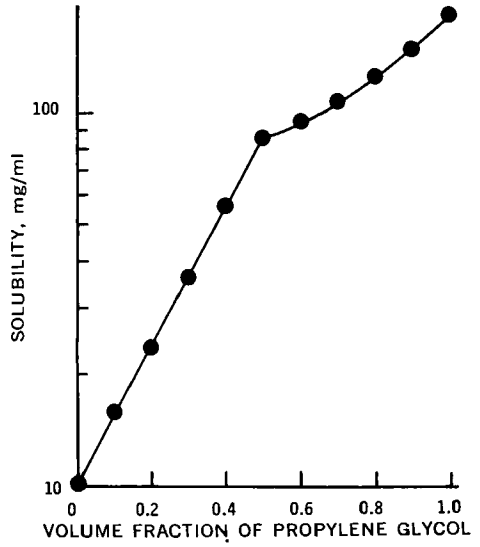

Figure 2—*Solubility of* p-*aminoacetophenone in propylene glycol–water mixtures.*

of diffusant, the flux is inversely proportional to the fraction of nonaqueous cosolvent present. On the other hand, according to Eq. 13, the flux from saturated solutions under membrane control is independent of solvent composition; that is, the effect of decreasing partition coefficient with increasing f_c is exactly offset by the resulting increase in drug solubility. These two relationships are graphically illustrated in the left-hand portion of Fig. 1.

Diffusion Layer Control of Flux—If, instead of lying within the membrane, the major barrier to transport is the stagnant solvent adjacent to the membranes, the system is said to be under diffusion layer control of flux. For this condition to exist, R_s must exceed R_m/PC and the last term of Eqs. 10 and 11 becomes $-\log[R_s PC_w\, 10^{-\gamma f_c}]$ or $-\log R_s - \log PC_w + \gamma f_c$. Using this approximation, Eq. 10 reduces to:

$$\log F^{\infty} = \log C - \log R_s \qquad \text{(Eq. 14)}$$

and Eq. 11 becomes:

$$\log F^{\infty} = \log S - \log R_s + \gamma f_c \qquad \text{(Eq. 15)}$$

Unlike the situation under membrane control, in diffusion layer control the flux at normalized concentration is independent of f_c while the flux from saturated solutions increases with increasing concentration of nonaqueous cosolvent. These relationships are illustrated in the right-hand portion of Fig. 1.

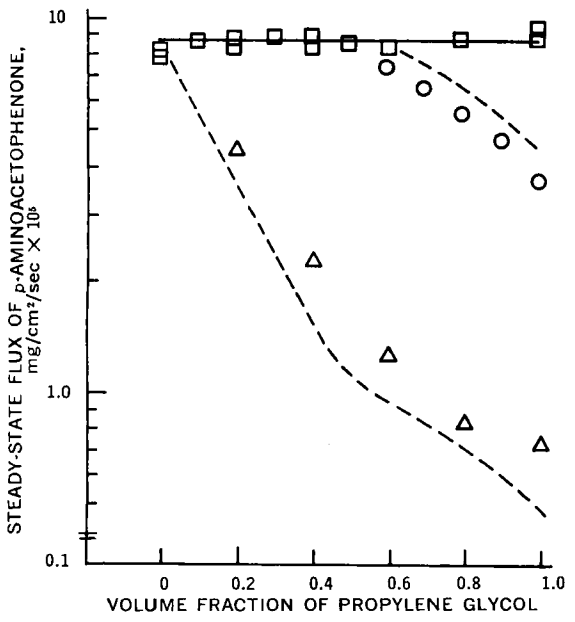

Figure 3—*Steady-state flux data for* p-*aminoacetophenone. Key:* □, *saturated solution;* ○, *equimolar solutions, 85 mg/ml;* △, *equimolar solutions, 10 mg/ml;* ——, *predicted by Eq. 6; and* - - -, *predicted by Eq. 4.*

In Fig. 1, it is possible to go from membrane to diffusion layer control or from constant concentration to saturation by simply increasing the volume fraction of water. This figure is only an attempt to illustrate the conditions described in this report. In general, a set of data ranging from 0 to 100% cosolvent will resemble either the right or left half of the figure. Whether or not the central portion, including the transition region, is observed depends upon the drug, the solvent system, and the experimental conditions.

EXPERIMENTAL

Materials—*p*-Aminoacetophenone[1] was used as received, and hexyl *p*-aminobenzoate was synthesized as described previously (4, 5). Deionized water, propylene glycol USP, and alcohol USP were used to prepare all solutions. Silicone rubber membranes were prepared as described previously (4, 5).

Procedure—All flux data were obtained on the same apparatus and by the same method described previously (4, 5). Solubilities in the pure and mixed solvents at 37° were determined as described previously (6).

RESULTS AND DISCUSSION

Solubility of *p*-Aminoacetophenone in Binary Aqueous Solvents—The solubility of *p*-aminoacetophenone in the binary solvent system of propylene glycol and water is shown in Fig. 2 as a function of the volume fraction of propylene glycol, f_{PG}. For f_{PG} up to 0.5, the solubility of *p*-aminoacetophenone (I) can be described by a specific form of Eq. 7:

$$\log S_f^{\,I} = \log (10.0) + 0.185\, f_{PG} \qquad \text{(Eq. 16)}$$

where $S_f^{\,I}$ is the solubility of the phenone in the binary solvent of volume fraction f_{PG} of propylene glycol, and 10.0 mg/ml is the drug's aqueous solubility. The complete range of solubilities described in Fig. 2 cannot be represented by such a simple equation but can be described by:

$$\log S_f^{\,I} = 1.0065 + 1.3386 \times 10^{-2} f_{PG} + 4.2419 \times 10^{-4} f_{PG}^{\,2} - 9.5312 \times 10^{-6} f_{PG}^{\,3} + 5.7986 \times 10^{-8} f_{PG}^{\,4} = 5.9172 \times 10^{-9} f_{PG}^{\,5} \qquad \text{(Eq. 17)}$$

with good correlation. The solubility data of a number of workers for many drugs in various binary aqueous solvents can be shown to fit equations such as Eq. 16 or 17. The qualification for a linear dependence of log (solubility) on the volume fraction of nonaqueous solvent component appears to be that the solubility parameters of the solvents are much higher than the solubility parameter of the drug. This point will be covered in a forthcoming publication.

Partition Coefficients and Membrane Solubility of *p*-Aminoacetophenone—If it is assumed that the membrane and solvent do not alter each other's properties, the partition coefficient of a drug between a membrane and a completely immiscible solvent can be approximated by the ratio of membrane to solvent solubilities of the drug. Conversely, if the partition coefficient is known along with the solvent solubility, it is possible to estimate the drug's solubility in the membrane. Table I shows the solubilities and membrane partition coefficients of *p*-aminoacetophenone for various propylene glycol–water mixtures. The partition coefficients were determined by dividing the previously determined permeabilities by the diffusivity of the phenone in the membrane (4). The membrane solubilities were determined by simply multiplying the partition coefficients by the binary solvent solubility for each mixture listed.

The consistency of the membrane solubility with solvent composition is noteworthy. The slight decrease in the calculated value with increasing propylene glycol composition results because the effects of viscosity on diffusivity and thus on solvent resistance are ignored. Some of these factors were discussed by Poulsen (1) for membrane control. This value is in good agreement with the experimentally determined solubility of *p*-aminoacetophenone in sili-

[1] Eastman.

cone fluid of 15 mg/ml. The utility of silicone fluid in studying silicone rubber permeability was discussed previously (5).

Calculation of Steady-State Flux under Membrane Control—At any volume fraction of propylene glycol, the steady-state flux of *p*-aminoacetophenone can be calculated from the solubility data by Eq. 10 provided that R_m and R_s are known and are nearly constant. Since these experiments were conducted with 47.6-nm membranes, in which Flynn and Smith (4) determined the diffusivity of *p*-aminoacetophenone to be 4.10×10^{-7} cm²/sec, the membrane resistance is 1.16×10^4 sec/cm.

The fluxes calculated, using these values for the resistances, the experimental donor phase concentration of drug, the silicone oil solubility, and the binary solvent solubilities given by Eq. 17 for various volume fractions of propylene glycol in water are shown in Fig. 3 along with the experimentally measured values. It can be seen that the agreement between the theoretical and experimental data is excellent. The decreasing permeability that accompanies an increase in the proportion of nonaqueous solvent parallels the reciprocal of the change in drug solubility with vehicle composition (Fig. 2).

This type of dependence of flux on solvent composition has been observed for other drugs and membranes (9–13) but has not been quantitatively correlated with physical-chemical parameters. Poulsen *et al.*'s (13) observation that the maximum release rate from propylene glycol–water mixtures containing a fixed concentration of drug occurs when a minimum amount of the glycol is used is also in agreement with this discussion.

The steady-state fluxes from saturated solutions of *p*-aminoacetophenone are indicated in Fig. 3. These values are again in excellent agreement with the theory. The compensating effects of increased solubility and decreased partition coefficient are obvious from the data and from the theory. (Note that the nonlinearity of the solubility data in Fig. 2 does not restrict the use of the model.) From a practical pharmaceutical point of view, the rate of release of a drug from a topical preparation can be expected to be proportional to the polarity of the vehicle for solutions of a given concentration. However, for suspensions of drug in the vehicle, the polarity has no effect on the release rate under membrane control.

Calculation of Steady-State Flux under Diffusion Layer Control—While the condition of diffusion layer control of flux is relatively uncommon in laboratory diffusion cells, it is frequently encountered in biological systems (3–7). To illustrate the effects of altering solvent composition when the system is under solvent control of transport, the value of R_m was minimized by reducing the membrane thickness from 0.047 mm (as was used in the previous experiments) to 0.005 mm. Further reduction in membrane thickness would produce a very fragile membrane. The value of PC was increased by choosing a solute having a low polarity. Previous studies (5) indicated that the diffusion of hexyl *p*-aminobenzoate from water across a 0.047-mm dimethylpolysiloxane membrane is under aqueous diffusion layer control. This ester was chosen because of this fact and the linear dependence of the logarithm of its solubility on propylene glycol or alcohol concentration, which was already determined as part of another study (8). Thus, it would be possible to illustrate the shift from membrane control to diffusion layer control simply by altering solvent composition.

The molar solubility expression for hexyl *p*-aminobenzoate (II) in alcohol–water solutions is[2]:

$$\log S^{II} = -4 + 4.3 f_{\text{ethanol}} \qquad \text{(Eq. 18)}$$

The theoretical fluxes were calculated by using this equation and assuming R_m and R_{aq} to be the same as the *p*-aminoacetophenone values. The relative experimental and theoretical fluxes for saturated solutions of hexyl *p*-aminobenzoate are shown in Fig. 4, with the flux from saturated purely aqueous solution being taken as unity. Here, as predicted by Eqs. 11 and 15, the flux from saturated solutions increases exponentially with increasing percentages of cosolvent present, with the slight deviation from theory being due to changes in viscosity and hydration with increasing alcohol composition. These solvent diffusion layer control data can be contrasted with the membrane control data from saturated solutions (Fig. 3). If the hexyl *p*-aminobenzoate data are normalized, the resulting data will of necessity show independence of equimolar flux on solvent composition as predicted by Eq. 14.

[2] The 37° molar solubilities of hexyl *p*-aminobenzoate in water and 10, 20, 30, and 40% alcohol are 1.07×10^{-4}, 2.7×10^{-4}, 7.3×10^{-4}, 1.9×10^{-3}, and 5.1×10^{-3}, respectively.

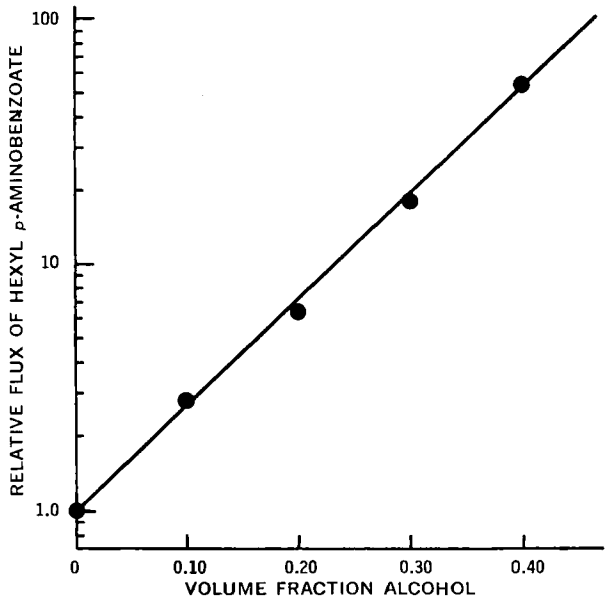

Figure 4—*Effect of cosolvent on steady-state flux from saturated solutions of hexyl* p-*aminobenzoate under solvent control. Key:* ——, *theoretical; and* ●, *experimental.*

CONCLUSIONS

The equations developed on the basis of diffusion theory and the relationship between solubility partitioning and solvent composition can describe and predict the rate of transport of a drug across a membrane separating two identical solvents as a function of solvent composition. Two distinct types of transport are described, one in which the membrane is the major transport barrier and the other in which diffusion through the unstirred solvent is rate limiting. In the former case, all saturated solutions produce equal fluxes and the flux from equimolar solutions is proportional to the polarity of the phase. Under the latter condition, the flux from equimolar solutions is independent of solvent polarity and the flux from saturated solutions is proportional to solvent polarity. These relationships have direct applicability to drug absorption from topical dosage forms where there is a great deal of flexibility in vehicle composition. The commonly observed relationships between solvent composition and permeability are those described by membrane control. These relationships, however, are not generally applicable to very nonpolar solutes whose transport can be limited by the solvent diffusion layers as described here.

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Partial Synthesis of Harringtonine Analogs

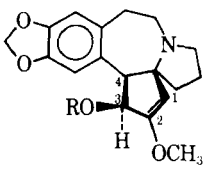
K. L. MIKOLAJCZAK[x], C. R. SMITH, Jr., and R. G. POWELL

Abstract □ Three analogs of harringtonine (II), an ester alkaloid which is active in the P-388 experimental leukemia system, were prepared by acylating cephalotaxine (I). They were the 2-hydroxy-2-methylbutyryl (III), 2-carbomethoxymethyl-5-methylhexanoyl (IX*c*), and 2-carbomethoxymethylene-5-methylhexanoyl (VII*d*) esters of I. A special sequence was developed for the synthesis of III. All of these harringtonine analogs, with the possible exception of III, are inactive in the P-388 system. In addition, data are presented which show that a rearranged harringtonine isomer (X) also is inactive. These results emphasize some highly specific structural requirements for antitumor activity of *Cephalotaxus* alkaloids.

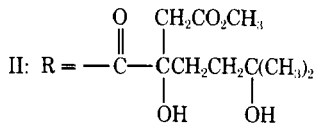
Keyphrases □ Harringtonine alkaloid analogs—partial synthesis, screened for antitumor activity □ *Cephalotaxus harringtonia* alkaloid analogs—partial synthesis, screened for antitumor activity □ Cephalotaxine esters—partial synthesis □ Antitumor agents, potential—partial synthesis of harringtonine analogs

Cephalotaxus harringtonia plant materials contain cephalotaxine (I) as well as esters of this alkaloid incorporating various dicarboxylic acids. Harringtonine (II) and certain other naturally occurring esters of cephalotaxine exhibit significant antitumor activity (1, 2). Because of its novel chemical structure and the pharmacological activity of its esters, the total synthesis of I was undertaken by at least three groups (3–5), two of which reported successful syntheses in preliminary form (3, 4). Cephalotaxine, although inactive, is by far the most abundant of the *Cephalotaxus* alkaloids; the active ester alkaloids needed for clinical testing remain in short supply.

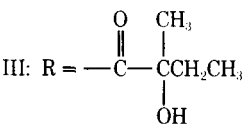
The active alkaloids are not readily prepared by direct esterification of cephalotaxine because of marked steric hindrance at the reaction site in both the acid and alkaloid moieties. An α-hydroxy group in the acid moiety further complicates synthetic efforts. A sequence was developed for the preparation of a harringtonine analog (III) whose acid moiety (2-hydroxy-2-methylbutyric acid, V*a*) incorporates some structural features found in the active compounds. The purpose of the present study was to develop synthetic procedures by which active *Cephalotaxus* alkaloids could be prepared from cephalotaxine as well as to ascertain which structural features are essential for the antitumor activity of this group of alkaloids.



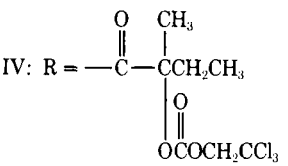
I: R = H



II: R = —C(=O)—CH(CH$_2$CO$_2$CH$_3$)—CH$_2$CH$_2$C(CH$_3$)$_2$(OH)—OH



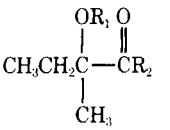
III: R = —C(=O)—CH(CH$_3$)—CH$_2$CH$_3$ (OH)



IV: R = —C(=O)—CH(CH$_3$)—CH$_2$CH$_3$ (O—C(=O)—CH$_2$CCl$_3$)

DISCUSSION

The first attempt to prepare 2-hydroxy-2-methylbutyrylcephalotaxine (III) was made with the α-hydroxy group blocked by a benzyl ether linkage. Treatment of cephalotaxine with the blocked acid chloride provided the desired ester, but the benzyl group could not be removed by hydrogenolysis. Therefore, the sequence described here was employed to solve the problem of protecting the hydroxy group. It is anticipated that this route will be useful in the preparation of other α-hydroxy esters of cephalotaxine.



V*a*: R_1 = H, R_2 = OH

V*b*: R_1 = H, R_2 = —OCH$_2$C$_6$H$_5$

V*c*: R_1 = —C(=O)—CH$_2$CCl$_3$, R_2 = —OCH$_2$C$_6$H$_5$

V*d*: R_1 = —C(=O)—CH$_2$CCl$_3$, R_2 = OH

V*e*: R_1 = —C(=O)—CH$_2$CCl$_3$, R_2 = Cl