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KINETICS OF ALKYLATION REACTIONS OF PYRROLIZIDINE ALKALOID DERIVATIVES

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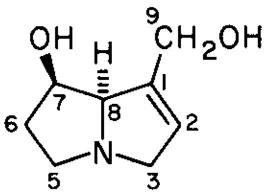
Abstract - Comparison is made of the alkylating activities of a series of semi-synthetic pyrrole esters and pyrrole derivatives of pyrrolizidine alkaloids under pseudo-first-order reaction conditions. Examination of the rate data indicates two reaction patterns; those compounds whose rate data fit a simple first-order rate expression and a second group of compounds whose rate data fit a biexponential expression.

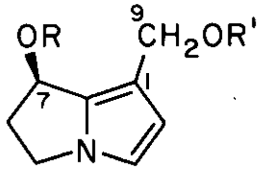
Pyrrolizidine alkaloids are widely distributed throughout the world in a variety of plant species. Concern has arisen over involvement of the alkaloids in livestock poisoning and possible contamination of human food sources.[1,2] Retronecine (I) forms the pyrrolizidine nucleus for many of these alkaloids when esterified with various necic acids. Toxicity of the pyrrolizidine alkaloids may be exerted through the action of pyrrole derivatives which should be highly active alkylation agents. Mattocks has proposed a scheme for enzymatic conversion of the alkaloids to pyrrole analogs in the liver and their subsequent distribution and fate.[3] Robertson, et al., have presented evidence that nucleophilic substitution by cysteine and glutathione occurs preferentially at C-7 of dehydroretronecine (II).[4]

In this study, the alkylating activities of a series of semi-synthetic pyrrole esters (III-XII) and pyrrole derivatives of pyrrolizidine alkaloids (II,XIII-XV) are compared using 4-p-nitrobenzylpyridine as a nucleophile in aqueous acetone at 30° under acid catalyzed pseudo-first-order reaction conditions.[5,6] Product formation was followed colorimetrically in the prescribed manner.[7] Data for alkylation by the diester pyrroles VII, VIII, X and jacobine pyrrole XV fit (r^2 = 0.9991-0.9999) a simple first-order rate expression for product formation[8,9] (Equation 1, Figure 1). The observed product absorbance at time t is C and the final product absorbance at reaction completion is C_∞. Rate constants (K_1) varied from 2.6 to 8.9 min^{-1} (Table 1). As expected, the alkylating activity decreased with increasing ester size. However, the large increase in reaction rate for jacobine pyrrole is suggestive of an electronic effect due to the epoxide ring in proximity to the C-7 ester moiety.

$$C = C_\infty - C_\infty e^{-K_1 t} \qquad (1)$$



(I)

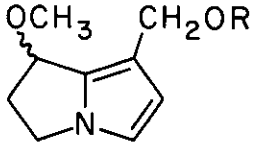


II R = R' = H

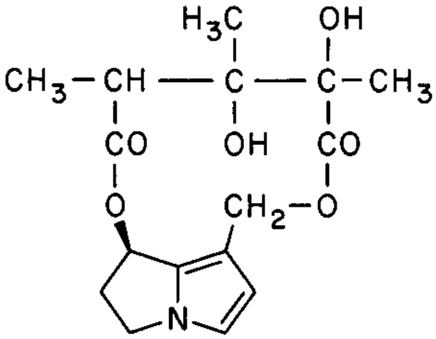
III R = H, R' = CH_3CO
IV R = H, R' = CH_3CH_2CO
V R = H, R' = $(CH_3)_2CHCO$

VI R = H, R' = $(CH_3)_3CCO$

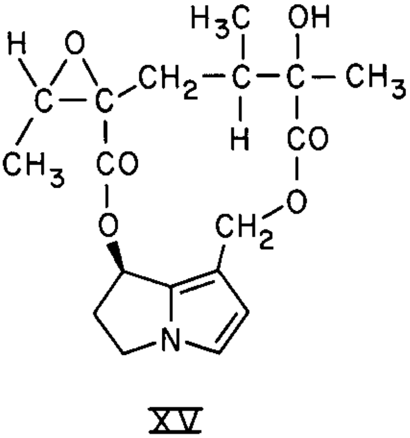
VII R = R' = CH_3CO
VIII R = R' = CH_3CH_2CO
IX R = R' = $(CH_3)_2CHCO$
X R = R' = $(CH_3)_2C(OH)CO$



XI R = CH_3CH_2CO
XII R = $(CH_3)_2CHCO$
XIII R = CH_3



XIV



XV

TABLE 1

Pseudo-first-order rate constants (K_1) for alkylation of 4-p-nitrobenzylpyridine by pyrrole derivatives at 30°C

Compound	K_1 (min^{-1})
VII	3.7
VIII	2.6
X	4.7
XV	8.9

Rate data for the remaining compounds studied (II-VI, IX, and XI-XIV) only fit a simple first-order rate expression for the initial reaction period (e.g., 3-5 min.) Initial rates (K_1) for these compounds thus obtained from Equation 1 varied from 0.016 to 0.45 min^{-1} (Table 2). When examined for longer reaction periods, data for these compounds were found to fit (r^2 = .9971-.9999) the general form of a biexponential (Equation 2, Figure 2).[9] In Equation 2, C is the absorbance at time t and C_∞ the final absorbance corresponding to product formation. Values of the exponential terms γ_1 and γ_2 are shown in Table 2. In Figure 2 only the first 60 minutes of the reaction are shown in order to give expanded detail.

$$C = C_\infty - \beta_1 e^{-\gamma_1 t} - \beta_2 e^{-\gamma_2 t} \qquad (2)$$

TABLE 2

Kinetic parameters for the alkylation of 4-p-nitrobenzylpyridine by pyrrole derivatives under pseudo-first-order reaction conditions at 30°C

Compound	K_1 (min^{-1})	γ_1	γ_2
II	.037	.34	.006
III	.049	.20	.003
IV	.042	.17	.003
V	.039	.10	.003
VI	.020	.08	.004
IX	.45	1.14	.003
XI	.019	.16	.009
XII	.017	.04	.003
XIII	.016	.27	.009
XIV	.13	.56	.004

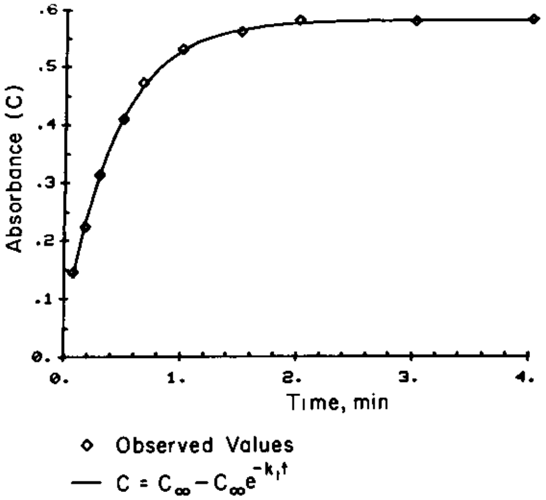


FIGURE 1. Product build-up from the reaction of compound VIII with excess nucleophile.

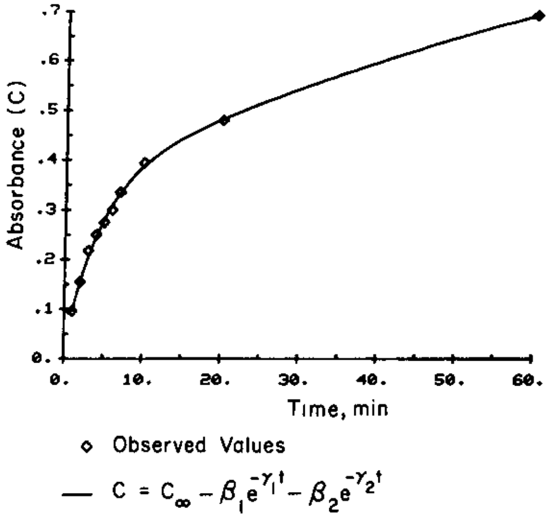


FIGURE 2. Product build-up from the reaction of compound IV with excess nucleophile.

Comparing the data in Tables 1 and 2, it appears that the correlation of rate data with either a simple first-order rate expression (Equation 1) or a biexponential fit (Equation 2) depends directly on the rate of alkylation of 4-p-nitrobenzylpyridine. When K_1 is $\geq 2.6 \text{ min}^{-1}$, the experimental data fits Equation 1. When $K_1 \leq .45 \text{ min}^{-1}$ the experimental data fits Equation 2. This suggests that when alkylating activity becomes low enough, a second as yet undefined reaction sequence is occurring, which is also color forming with 4-p-nitrobenzylpyridine. We are presently investigating the mechanistic implications of these observations.

Mattocks originally used 4-p-nitrobenzylpyridine in aqueous acetone at 75°C under pseudo-first-order reaction conditions to study the alkylation by six pyrrole derivatives of pyrrolizidine alkaloids.[5] Rate curves suggested that hydrolysis (solvolysis) of pyrrole esters (A) competes with the alkylation reaction and it was proposed that there were two parallel reactions occurring with the nucleophile, a fast reaction with the esters (A) and a slower reaction with the hydrolysis products (B) (Equation 3).

$$\begin{tikzcd}
A \arrow[r, "K_1"] \arrow[d, "\text{Hydrolysis}"'] & C \\
B \arrow[r, "K_2"] & C
\end{tikzcd} \qquad (3)$$

Equation 3 can be expressed mathematically in a form of Equation 2.[10] That is the kinetics of two parallel first-order reactions with a common product can be described with a biexponential expression. Thus at first one might be tempted to explain our results in terms of Mattock's proposal of a competing hydrolysis and parallel alkylation reactions. However, it appears that this is not the case since dehydroretronecine (II) which would be the hydrolysis product of these esters also falls into a category of data fitting a biexponential function.

Elucidation of this second reaction sequence is important to the understanding of the chemistry and toxicology of the pyrrole analogs of the naturally occurring pyrrolizidine alkaloids since they might be expected to undergo similar reactions *in vivo*. We are continuing investigations into the nature of these complex reaction kinetics.

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