acylammonium ion ($I^+$ in Scheme I), whereas the anhydride does not form the intermediate unless the catalyst is very powerful. When the solvent polarity is increased by adding water, intermediate formation is favored even in the anhydride systems. These conclusions are identical with those reached in the study of acylations with acetyl chloride and acetic anhydride (24). This insensitivity of mechanistic pathway to the nature of the acyl group suggests that the mechanism is determined primarily by three factors: the catalyst nucleophilicity, the leaving group ability, and the solvent polarity. Increases in any of these factors will promote the formation of intermediate and the possibility of product formation through the $k_I$ and $k_{IN}$ routes. That the acid anhydrides react mainly by the general base catalyzed ($k_{AN}$) route, even in the presence of strong nucleophilic catalysts, has been an unexpected finding of these studies.

Table II lists rate constants for the cinnamoylation reactions reported here and includes, for comparison, some data (24) on acetylation reactions. Several patterns can be seen. In comparable systems, the general base catalysis quantities $k_{AN}$ and $k_{IN}$ are larger for 4-dimethylaminopyridine than for *N*-methylimidazole, reflecting the greater base strength of the former catalyst. The acetyl substrates are two-fold more reactive than the corresponding cinnamoyl compounds. For a given acyl group and alcohol, the chloride–anhydride ($k_{IN}/k_{AN}$) ratio is >10 for *N*-methylimidazole and close to unity for 4-dimethylaminopyridine. Since $k_{IN}$ describes the reaction of the intermediate, this indicates that *N*-methylimidazole is a better leaving group than is a carboxylate, whereas 4-dimethylaminopyridine is about as good a leaving group as a carboxylate. These relationships are not expected on the basis of the leaving group basicities, but they may reflect a relatively greater resonance stabilization of the *N*-acyl-4-dimethylaminopyridinium intermediate.

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# Solvent Effects on the Cinnamoylation of *n*-Propyl Alcohol Catalyzed by *N*-Methylimidazole and 4-Dimethylaminopyridine


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**Abstract** □ The kinetics of reaction of *trans*-cinnamic anhydride or *trans*-cinnamoyl chloride with *n*-propyl alcohol, catalyzed by *N*-methylimidazole or 4-dimethylaminopyridine, were studied spectrophotometrically at 25° in methyl ethyl ketone, ethylene dichloride, methylene chloride, and toluene. The acid chloride reacted in all solvents *via* the intermediate formation of the *N*-acyl catalyst, which underwent reaction with the alcohol catalyzed by another molecule of the base. The anhydride did not form the intermediate in any of the solvents, but underwent direct general base catalysis. The rate of the anhydride reactions was not sensitive to solvent polarity, whereas the rate of the chloride reactions tended to increase as the solvent polarity decreased. A kinetic analysis is given of the effect of ion-pair formation on the kinetics of acyl transfer in systems where the charged *N*-acyl catalyst intermediate is formed.



**Keyphrases** □ Cinnamoylation—of *n*-propyl alcohol, catalysis by *N*-methylimidazole and 4-dimethylaminopyridine, solvent effects □ 4-Dimethylaminopyridine—catalyses, cinnamoylation of *n*-propyl alcohol □ *N*-methylimidazole—catalyses, cinnamoylation of *n*-propyl alcohol


Although the kinetics and mechanisms of acyl transfer reactions in water have been carefully studied (in large part because such reactions serve as models for enzyme-catalyzed reactions), acyl transfers in nonaqueous media are less well understood despite their great importance in synthesis and analysis. The relatively recent introduction of powerful acylation catalysts like 4-dimethylaminopyridine (1) and *N*-methylimidazole (2) has stimulated in-


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**Table I—Rate Constants for the Reaction of Cinnamoyl Chloride with *n*-Propyl Alcohol at 25°**

| Solvent | Catalyst[a] | $k_I \times 10^2$ $M^{-1}$ sec$^{-1}$ | $k_{IN}/M^{-2}$ sec$^{-1}$ |
|---|---|---|---|
| Methyl ethyl ketone | NMIM | 0.52(0.18)[b] | 0.192(0.009)[b] |
| Methyl ethyl ketone | DMAP | −0.006(0.39) | 3.06(0.30) |
| Ethylene dichloride | NMIM | 1.64(0.46) | 0.70(0.07) |
| Ethylene dichloride | DMAP | 0.18(0.67) | 65.1(1.42) |
| Methylene chloride | NMIM | 0.60(0.10) | 0.393(0.021) |
| Methylene chloride | DMAP | 2.5(2.0) | 47.0(4.1) |
| Toluene | NMIM | 1.7(2.5) | 6.70(0.30) |

[a] NMIM = N-methylimidazole; DMAP = 4-dimethylaminopyridine. [b] Standard deviations in parentheses.

vestigations of acylation reactions in nonaqueous solvents by several laboratories. There are features of these reactions, however, that remain obscure: one of these is the effect of the solvent on the mechanism and rate of the reaction. This is the subject of the present paper.

There are two general routes available in an acyl transfer reaction when a nucleophile (base) is present. One of these is a direct reaction of the acylating agent with the acyl acceptor, either general base-catalyzed or uncatalyzed; the other is transfer of the acyl group from the acylating agent to the nucleophile to give an ionic intermediate, which then reacts with the acyl acceptor (in catalyzed or uncatalyzed reactions). Since the latter nucleophilic route presumably involves extensive charge separation in the transition state, it would be expected that high solvent polarity should favor this route. Thus, solvent polarity must be considered in any treatment of solvent kinetic effects. Unfortunately there is no single measure of solvent polarity applicable in all circumstances, so quantitative description is difficult. Many measures of polarity have been devised (3). Besides this general effect of the solvent on the mechanistic route, several specific rate effects have been implicated in acylation reactions. In solvents of low dielectric constant, ionic dissociation is less extensive than in polar solvents and ionic aggregates (particularly ion-pairs) may be present, which may have kinetic consequences. Several workers have suggested that ion-pair formation between the cationic acylated nucleophile and the anionic leaving group may be responsible for some unusual kinetic behavior in these systems (4, 5). Molecular complex formation has been proposed as a factor of importance in nonpolar solvents (6). An interesting observation is that acylation may proceed faster in nonpolar aprotic solvents than in polar protic solvents; this has been attributed to the favored collapse of the charged intermediate to uncharged products (7). The rate equations observed for acylations in solvents of low polarity sometimes are very complex (8).

Earlier work in this laboratory made use of the acid chlorides and anhydrides of acetic and cinnamic acids as acylating agents, 4-dimethylaminopyridine and *N*-methylimidazole as catalysts, and acetonitrile or aqueous acetonitrile as solvents (9, 10). The cinnamoyl group is particularly useful because of its convenient spectral properties, which permit the sensitive observation of the intermediate, if present (10). In the present study the solvent effect on the mechanism and the rate of acylation of *n*-propyl alcohol by *trans*-cinnamoyl chloride or *trans*-cinnamic anhydride, catalyzed by 4-dimethylaminopyridine or *N*-methylimidazole, has been studied in several solvents that are less polar than acetonitrile.

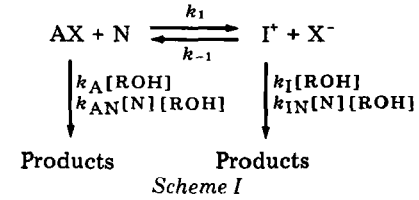
## EXPERIMENTAL

**Materials**—The *trans*-cinnamic anhydride, *trans*-cinnamoyl chloride, 4-dimethylaminopyridine, and *N*-methylimidazole used were as previously described (10, 11). The solvents were of spectrophotometric grade[1] and were used as obtained.

**Procedures**—Reactions were followed spectrophotometrically[2] as described previously (10). All kinetics reported here are at 25.0°.

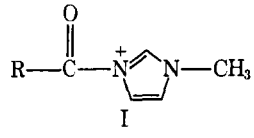
## RESULTS AND DISCUSSION

**Kinetic Scheme**—Earlier work (9, 10) in acetonitrile and acetonitrile–water mixtures showed that Scheme I describes most of the kinetic observations.

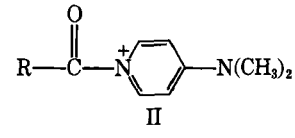



*Scheme I*

In this kinetic scheme, AX represents the acylating agent (cinnamic anhydride or cinnamoyl chloride), N is the catalyst (4-dimethylaminopyridine or *N*-methylimidazole), $X^-$ is the leaving group (cinnamate or chloride ion), ROH is *n*-propyl alcohol, and $I^+$ is the *N*-cinnamoylated catalyst I or II, where R is $C_6H_5CH{=}CH$.




I




II

Although Scheme I does not include possible ion-pair formation (this phenomenon is treated in the later discussion), it was found to account for most of the observed behavior. Reaction of AX with ROH (the "A" route) may occur *via* uncatalyzed ($k_A$) or general base-catalyzed ($k_{AN}$) reactions; nucleophilic reaction of AX with N to form the intermediate $I^+$ may lead to reaction of $I^+$ with ROH (the "I" route) *via* uncatalyzed ($k_I$) and general base-catalyzed ($k_{IN}$) reactions[3].

The system was examined spectrophotometrically for evidence of the intermediate and the kinetics were measured by following the loss of AX or $I^+$ as appropriate. The initial concentrations of alcohol and catalyst were much larger than the acylating agent concentration and pseudo first-order rate constants were obtained from plots of log $(A_t - A_\infty)$ against time, where *A* represents absorbance. For most systems these plots were linear for >3 half-lives; exceptions are noted. Rate constants $k_A$, $k_{AN}$, $k_I$, and $k_{IN}$ were determined as described in detail elsewhere (9).

**Kinetics in Nonpolar Solvents**—The results of these studies consist, in general terms, of two components: (*a*) demonstration of the presence or absence of the intermediate $I^+$ and (*b*) evaluation of the pertinent rate constants in Scheme I, *i.e.*, $k_A$ and $k_{AN}$ if the intermediate is absent or $k_I$ and $k_{IN}$ if $I^+$ is present. It is conceivable that these assignments of rate constants are in error because an intermediate, though present, may not be on the reaction path. On the other hand, the intermediate may be present at undetectably low concentrations even though all of the reaction occurs by this route. However, the interpretation given here is the simplest one and is consistent with the observations.

The acid chloride was studied with both catalysts; the anhydride was studied only with 4-dimethylaminopyridine. The anhydride–*N*-methylimidazole system was not studied because earlier work (9, 10) made it clear that no intermediate would be detected in this system. The solvents used were methyl ethyl ketone, ethylene dichloride, methylene chloride, and toluene.

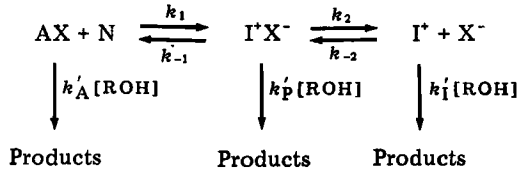
In all solvents, the acid chloride showed evidence of intermediate formation, with both catalysts, with intense absorption in the 340–350 nm region (10). The acid chloride–*N*-methylimidazole system gave strict

[1] Burdick and Jackson.
[2] Cary 14 spectrophotometer.
[3] The $k_I$ route in Scheme I is widely described as nucleophilic catalysis, but it should be observed that if $k_I < k_A$, diversion through this route will actually inhibit the reaction. The $k_{IN}$ reaction can be described as general base-catalyzed nucleophilic reaction.

first-order kinetics in all solvents; however, in toluene the intermediate salt precipitated and it was necessary to increase the concentration of *n*-propyl alcohol (to at least 0.04 *M*) to solubilize the intermediate. The acid chloride–dimethylaminopyridine system gave first-order kinetics in ethylene dichloride and toluene (in toluene at least 0.2 *M* propyl alcohol was added to solubilize the intermediate). In methyl ethyl ketone this system showed first-order behavior for ~3 half-lives and then showed a slight upward curvature. In methylene this system gave more complicated kinetics: the reaction became faster with time and finally, after up to 1 half-life, became satisfactorily first order. The values of $k_I$ and $k_{IN}$ were obtained, for all the acid chloride systems, from the dependence of the observed first-order rate constants on the catalyst and alcohol concentrations by methods described earlier (9, 10). The first-order rate constants were linearly dependent on catalyst and alcohol concentrations[4]. Table I lists the $k_I$ and $k_{IN}$ values found for the acid chloride systems. Most of the $k_I$ values are not significantly different from zero. A qualitative summary of the eight acid chloride systems shows: (*a*) first-order kinetics were observed in six systems, with minor deviations in two; (*b*) in one system the rate seemed to be independent of alcohol concentration (this system is therefore omitted from Table I); and (*c*) in two systems anomalous dependence on catalyst concentration was seen[4]. In general the kinetics appear to be fairly uncomplicated.

In all of the anhydride systems, there was no spectral evidence of intermediate formation, strict first-order kinetics were observed, and the first-order rate constant was linearly dependent on the initial concentrations of catalyst and alcohol[5]. The treatment of the kinetic data (9, 10) yields estimates of $k_1$, $k_A$, and $k_{AN}$ (Table II). There appears to be neither high sensitivity nor direct dependence of $k_1$ on the solvent polarity [in acetonitrile (10) $k_1$ is 0.096 $M^{-1}$ sec$^{-1}$], which is surprising if this assignment of $k_1$ is correct.

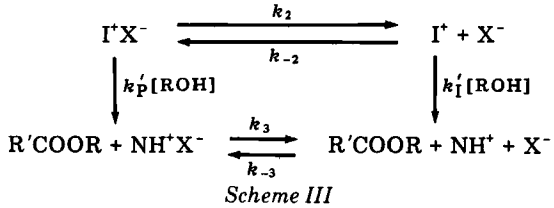
**Kinetic Effects of Ion-Pairs**—It was pointed out that in solvents of low dielectric constant, ion-pair formation is possible, and since in general ion-pairs and dissociated ions may have different properties, kinetic consequences of ion-pairing may be anticipated. To analyze this quantitatively, Scheme I was modified by incorporating the ion-pair $I^+X^-$ as shown:




*Scheme II*

In Scheme II it is expected that the primed quantities have the form $k_A' = k_A + k_{AN}[N]$, *etc.*

In systems such as acid chlorides in the presence of strongly nucleophilic catalysts, intermediate formation is essentially quantitative and Scheme II can be drawn as:




*Scheme III*

An expression was sought for the rate of loss of reactant. The basic rate equation is:

$$-\frac{d([I^+X^-] + [I^+])}{dt} = k_I'[ROH][I^+] + k_P'[ROH][I^+X^-] \quad \text{(Eq. 1)}$$

The ion-pair equilibrium is assumed to be much faster than the reactions with ROH, so the ion-pair dissociation constant expression ($K_d^{IX}$) is always satisfied. This may be expressed as:

$$K_d^{IX} = \frac{[I^+][X^-]}{[I^+X^-]} \quad \text{(Eq. 2)}$$

Setting $[X^-]/K_d^{IX} = P$ gives $[I^+X^-] = P[I^+]$, so $-d[I^+X^-]/dt = -P(d[I^+]/dt)$, and Eq. 2 may be expressed as:

$$-\frac{d([I^+X^-] + [I^+])}{dt} = -(1 + P)\frac{d[I^+]}{dt} \quad \text{(Eq. 3)}$$

Equating Eqs. 1 and 3 gives:

$$-\frac{d[I^+]}{dt} = \left(\frac{k_I' + Pk_P'}{1 + P}\right)[I^+][ROH] \quad \text{(Eq. 4)}$$

and similarly:

$$-\frac{d[I^+X^-]}{dt} = \left(\frac{k_I' + Pk_P'}{1 + P}\right)[I^+X^-][ROH] \quad \text{(Eq. 5)}$$

It follows from the above relationships:

$$-\frac{d([I^+X^-] + [I^+])}{dt} = \left(\frac{k_I' + Pk_P'}{1 + P}\right)[ROH]([I^+X^-] + [I^+]) \quad \text{(Eq. 6)}$$

Equation 6 has a first-order form, with apparent first-order rate constant $k_{obs}$ given by:

$$k_{obs} = \left(\frac{k_I' + Pk_P'}{1 + P}\right)[ROH] \quad \text{(Eq. 7)}$$

$P$ is inversely proportional to $K_d^{IX}$; in solvents of high dielectric constant, $P$ will approach zero, whereas in low dielectric constant solvents, $P$ will become very large. Under pseudo first-order conditions of large catalyst and alcohol concentrations, the quantity $k_{obs}$ will be equal to $k_I'[ROH]$ in polar dissociating solvents, but $k_{obs}$ will approach $k_P'[ROH]$ in nonpolar nondissociating solvents. In solvents whose *polarity permits* the significant coexistence of both the ion-pair and the dissociated ions, $k_{obs}$ is given by Eq. 7.

There is a possible kinetic consequence of Eq. 7 that can be observed if $P$ makes a finite contribution to $k_{obs}$. During the time course of a reaction, if $P$ is a function of time, $k_{obs}$ may vary detectably and deviations from first-order kinetics may be seen. (This is a possible cause of the deviations that were observed in some of the cinnamoyl chloride systems.) This variaton can be analyzed as follows. The ion $Cl^-$ is a much weaker base than is N in these systems, where N represents 4-dimethylaminopyridine or *N*-methylimidazole. Therefore, the protons produced in the acylation of the alcohol will be accepted predominantly by the catalyst. As a consequence there are two ion-pair equilibria in the solution, as shown in Scheme III. The dissociation constant $K_d^{NHX}$ is defined by:

$$K_d^{NHX} = \frac{[NH^+][X^-]}{[NH^+X^-]} \quad \text{(Eq. 8)}$$

It is instructive to write this in the logarithmic form:

$$pX = pK_d^{NHX} + \log\frac{[NH^+]}{[NH^+X^-]} \quad \text{(Eq. 9)}$$

which is analogous to the Henderson–Hasselbalch equation for aqueous buffer action. That is, the concentration $[X^-]$ is established by a buffer consisting of the protonated catalyst. Since $P$ in Eq. 7 *is equal to* $[X^-]/K_d^{IX}$, evidently the buffer capacity with respect to $[X^-]$ is important in determining the constancy of $k_{obs}$. This buffer capacity should be maximal when $pX = pK_d^{NHX}$, and it should increase with time since the total buffer concentration ($[NH^+] + [NH^+X^-]$) increases with time. (This may explain why, in the cinnamoyl chloride–dimethylaminopyridine–methylene chloride system, the first-order plot became linear after an initial nonlinear portion.) Whether $P$ increases or decreases with time

**Table II—Rate Constants for the 4-Dimethylaminopyridine-Catalyzed Reaction of Cinnamic Anhydride with *n*-Propyl Alcohol at 25°**

| Solvent | $k_1/M^{-1}$ sec$^{-1}$ | $k_A, \times 10^4 M^{-1}/$ sec$^{-1}$ | $k_{AN}/M^{-2}$ sec$^{-1}$ |
|---|---|---|---|
| Methyl ethyl ketone | 0.063(0.019)[a] | 19.0(13.3)[a] | 1.50(0.11)[a] |
| Ethylene dichloride | 0.274(0.049) | 19.0(2.0) | 2.93(0.13) |
| Methylene chloride | 0.179(0.063) | 10(40) | 2.45(0.27) |
| Toluene | 0.198(0.028) | 4(10) | 3.62(0.10) |

[a] Standard deviations in parentheses.

[4] For the dimethylaminopyridine system in toluene the rate constants were linearly dependent on catalyst but independent of alcohol concentration. In methyl ethyl ketone the chloride–dimethylaminopyridine system, and in toluene the chloride–*N*-methylimidazole system, gave different intercepts at different catalyst concentrations when $k_{obs}$ was plotted against alcohol concentration. This may have been caused by reaction with a second trace constituent, possibly water (12).

[5] At high alcohol concentrations the linear dependence is lost for the ethylene dichloride system.

**Table III—Third-Order Rate Constants for the Cinnamoylation of *n*-Propyl Alcohol at 25°**

| Solvent | $\epsilon$[a] | $k_{AN}$ (anhydride, DMAP)[b] | $k_{IN}$ (chloride, DMAP)[b] | $k_{IN}$ (chloride, NMIM)[b] |
|---|---|---|---|---|
| Acetonitrile[c] | 35.9 | 2.18 | 2.18 | 0.23 |
| Methyl ethyl ketone | 18.5 | 1.50 | 3.06 | 0.19 |
| Ethylene dichloride | 10.4 | 2.93 | 65.1 | 0.70 |
| Methylene chloride | 8.9 | 2.45 | 47.0 | 0.39 |
| Toluene | 2.4 | 3.62 | — | 6.70 |

[a] Dielectric constant. [b] (Acylating agent, catalyst); units of rate constants are as given in Tables I and II. [c] Data from Ref. 10.

depends on the ratio $K_d^{NHX}/K_d^{IX}$, because as reaction occurs the species $I^+X^-/I^+$ are replaced by $NH^+X^-/NH^+$:

$$P = \frac{[X^-]}{K_d^{IX}} = \frac{[I^+X^-]}{[I^+]} = \frac{K_d^{NHX}[NH^+X^-]}{K_d^{IX}[NH^+]} \qquad \text{(Eq. 10)}$$

Values of ion-pair dissociation constants are extremely sensitive to the solvent dielectric constant, with typical values (13) of $10^{-16}$–$10^{-12}$ at dielectric constants of 2–3 and as high as $10^{-5}$ at dielectric constants near 6. In solvents more polar than acetonitrile, ion-pair formation is probably kinetically negligible. In a given solvent the ratio of ion-pair dissociation constants for two ion-pairs is controlled largely by the effective ionic sizes.

**Solvent Effect on Rates and Mechanism**—Table III collects $k_{AN}$ and $k_{IN}$ values for the cinnamoylation of *n*-propyl alcohol in five solvents. The $k_{AN}$ values, describing the general base catalysis, are not very sensitive to the nature of the solvent; this is consistent with earlier data on alcohol acetylation by acetic anhydride catalyzed by *N*-methylimidazole (14)[6]. The $k_{IN}$ values for the acid chloride systems reveal considerable variation with solvent polarity, the less polar solvents tending to give higher rates. In solvents that are very nonpolar $k_{IN}$ may be influenced by ion-pair formation, as discussed in connection with Scheme III; therefore, the $k_{IN}$ in Table III may be a composite reflecting both the ion-pair and the dissociated ion routes.

[6] The titrimetrically determined third-order rate constants in these acetic anhydride systems (14) can be interpreted as $k_{AN}$ in Scheme I.

Since the acid chloride and the anhydride react by different mechanisms, it is dangerous to compare them. Several workers have noted that an anhydride appears to be more reactive than the acid chloride in nonpolar solvents, yet (according to Table III) $k_{IN} > k_{AN}$ for a common catalyst. An explanation of these apparently contradictory observations (9) is that formation of the intermediate from the acid chloride consumes an equimolar amount of catalyst, whereas in the anhydride system this depletion of catalyst concentration does not occur, causing $k_{AN}[N]$ in the anhydride system to be greater than $k_{IN}[N]$ is in the acid chloride system.

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# Prodrugs of 6-Thiopurines: Enhanced Delivery Through the Skin


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**Abstract** □ Soft-alkylated derivatives of 6-mercaptopurine, its riboside, and 2-amino-6-mercaptopurine riboside have been prepared and evaluated to improve the delivery of the thiopurines through the skin. The soft-alkylated derivatives were prepared by the alkylation of the thiopurines with acylheteroalkyl halides under neutral or basic conditions. The penetration of the derivatives through hairless mouse skin was measured using diffusion cells. All of the derivatives underwent extensive degradation during their diffusion through skin so that the parent thiopurine, even in the case of the ribosides, was the major product observed in the receptor phase. The pivaloyloxymethyl derivatives showed the greatest potential for enhancing the penetration of the thiopurines through the skin. Among the 6-mercaptopurine derivatives, VII and XI were the most effective; they delivered 5 and 13 times, respectively, more 6-mercaptopurine than 6-mercaptopurine itself.



**Keyphrases** □ Prodrugs of 6-thiopurines—soft-alkylated derivatives of 6-mercaptopurine, enhanced delivery through the skin, pivaloyloxymethyl derivatives □ Hairless mouse skin—penetration of prodrugs of 6-thiopurines, pivaloyloxymethyl derivatives. □ Pivaloyloxymethyl derivatives—prodrugs of 6-thiopurines, penetration through hairless mouse skin


Many high-melting drugs are insoluble in water and organic solvents; consequently, they have poor biphasic solubilities and are also poorly absorbed through biological membranes. The thiopurines represent one class of such drugs that exhibit these properties. One approach to increasing the solubilities of the thiopurines, while at the




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