Prodrug Approach to Enhancement of Rate of Dissolution of Allopurinol

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Abstract □ The synthesis and physicochemical characteristics of 1-ethoxyethyl-4-allopurinyl ether and 2-tetrahydropyranyl-4-allopurinyl ether are described. These compounds have lower melting points, higher solubilities, and, consequently, considerably greater rates of dissolution than does allopurinol. The rate of hydrolysis of the ethyl vinyl ether derivative was examined at 37° in 1 and 0.1 *N* HCl, yielding half-lives of 13 sec and 7.7 min, respectively, for the pseudo-first-order hydrolysis to form allopurinol. The rate of hydrolysis of the tetrahydropyran derivative was somewhat slower; *i.e.*, the half-lives were 35 sec and 12 min, respectively, under the same conditions.

Keyphrases □ Allopurinol—prodrug approach used to enhance dissolution □ Dissolution—prodrug approach to increase rate of allopurinol dissolution □ Prodrugs—synthesis and physicochemical characteristics of 1-ethoxyethyl-4-allopurinyl ether and 2-tetrahydropyranyl-4-allopurinyl ether, enhanced rate of allopurinol dissolution □ Hydrolysis—allopurinol prodrugs, synthesis, dissolution rates determined

Allopurinol (4-hydroxypyrazolo[3,4-*d*]pyrimidine) (I) is widely used in the treatment of gout and hyperuricemia. However, the compound is relatively water insoluble (solubility = 0.78 mg/ml) and, consequently, it has been reported that about 20–25% of the usual dose is excreted in the stool unchanged (1). It was felt that the prodrug approach might be utilized to increase the solubility of allopurinol and, therefore, its rate of dissolution and bioavailability.

Generally, the term "prodrug" is used for compounds that undergo some chemical or biological transformation prior to exhibiting their pharmacological effect (2). In this paper, a prodrug is defined as a drug that is prepared by chemically modifying a pharmacologically active compound to form a new compound which reverts to the parent compound after administration. The modification alters the physicochemical properties and affects the absorption, distribution, or metabolism of the drug in some desirable manner. This concept also is known as "drug latentiation" (3–5). Several problems associated with formulation (*e.g.*, solubility and stability) have been solved by preparing prodrugs (6).

The absorption of a drug from a tablet depends on tablet disintegration, dissolution, diffusion, and absorption into the blood. Each step is essential to obtain blood levels adequate for therapeutic effectiveness, and the rate at which a drug appears in the bloodstream depends on the slowest step. For a slightly soluble drug, dissolution is often rate determining and may be conveniently considered in terms of a modified form of the Noyes–Whitney equation (7, 8):

$$\frac{dC}{dt} = \left(\frac{kDA}{Vh}\right)(C_s - C) \qquad \text{(Eq. 1)}$$

where C is the concentration of the drug in the bulk solution, k is a proportionality constant, D is the diffusion coefficient of the drug in the solvent, A is the surface area of the undissolved drug, V is the volume of the solution, h is the thickness of the diffusion layer around a particle, and C_s is the solubility of the drug in the solvent.

If one assumes that dissolution is rate limiting, this equation may be simplified to:

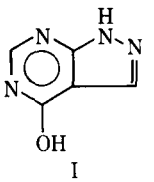
$$\frac{dC}{dt} = k'AC_s \qquad \text{(Eq. 2)}$$

The dissolution rate then becomes proportional to the surface area of the drug and its solubility.

Methods for increasing surface area and solubility are well known, but the preparation of a prodrug that has increased solubility and reverts to its original form after dissolution is a relatively new approach (6). The use of this approach for allopurinol is now reported. The high melting point of allopurinol (365°) suggested that transient blocking of some polar groups in the molecule might decrease intermolecular hydrogen bonding and enhance the solubility. This paper describes two prodrugs prepared on the basis of this concept.

EXPERIMENTAL

Preparation of 1-Ethoxyethyl-4-allopurinyl Ether (II) and 2-Tetrahydropyran-4-allopurinyl Ether (III)—One gram of allopurinol, contained in a stoppered, 150-ml, round-bottom flask, was dissolved in 50 ml of reagent grade dimethylformamide. Twenty milliliters of either ethyl vinyl ether or dihydropyran and 4 ml of 0.4% *p*-toluenesulfonic acid in dry benzene were added. After 4–5 hr at room temperature, 0.5 ml of 4% pyridine in benzene was added. The solution was filtered and solvent removed at 40° *in vacuo*. The resulting viscous liquid was dissolved in 100 ml of petroleum ether and 2–3 ml of benzene and allowed to recrystallize overnight in a refrigerator. The dihydropyran derivative mp 203°) and the ethyl vinyl ether (mp 185°) were obtained by



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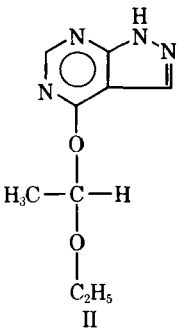

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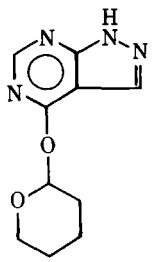

III

Table I—Rate of Hydrolysis of II and III

Hydrolytic Medium	Temperature	$t_{1/2}$, sec: Ethyl Vinyl Ether	$t_{1/2}$, sec: Tetrahydropyran
0.1 *N* HCl	37°	462	720
1 *N* HCl	37°	13	35
1 *N* HCl	25°	77	112

recrystallization from ethyl acetate–acetone and were further characterized by NMR, differential scanning calorimetry, TLC, and elemental analysis.

Dihydropyran—

Anal.—Calc. for $C_{10}H_{12}N_4O_2$: C, 54.5; H, 5.5; N, 25.4. Found: C, 53.8; H, 5.0; N, 25.0.

Ethyl Vinyl Ether—

Anal.—Calc. for $C_9H_{12}N_4O_2$: C, 51.9; H, 5.8; N, 26.9. Found: C, 51.6; H, 5.8; N, 27.2.

Solubility—The solubilities of allopurinol (0.78 mg/ml), the tetrahydropyran derivative (3.64 mg/ml), and the ethyl vinyl ether derivative (1.91 mg/ml) were measured at 247 nm, using an equilibrium spectrophotometric technique (9).

Dissolution Rates—The dissolution rates of the three test compounds were determined by the method of Poole (10), using approximately 100-mg tablets compressed[1] at 18,000 psi. Dissolution was measured in 300 ml of 0.1 *N* HCl at a stirring rate of 55 rpm. At 30-min intervals, the dissolution medium was replaced with 300 ml of fresh solvent to maintain sink conditions and the solution was assayed. In the assay procedure, 10% HCl was added and allowed to react for at least 10 min with an aliquot of each sample to hydrolyze the derivatives to allopurinol; the concentration of allopurinol was then determined spectrophotometrically at 247 nm.

Rate of Hydrolysis—An effective prodrug must revert to the active drug of interest within a reasonable time. Therefore, the hydrolysis of the two derivatives was examined.

The rates of formation of allopurinol from II and III in acid solution were monitored[2] at 25 and 37° at 277 nm.

In the case of allopurinol ethyl vinyl ether (II) in 0.1 *N* HCl, the two species had approximately the same absorbance and, thus, the absorbance changes with time were very small. Consequently, a liquid chromatograph[3] (0.5-m column) was used. The chromatograph was operated at 600 lb pressure, and the mobile phase consisted of an aqueous solution of 0.04 *M* NaH_2PO_4 and 0.05 *M* KNO_3 having a pH of 4.5. Using these conditions, the disappearance of the peak for Compound II was followed.

RESULTS AND DISCUSSION

The increase in solubility observed for the ethyl vinyl ether and tetrahydropyran derivatives compared with the parent compound is probably due to the decrease in the solute–solute intermolecular forces in the crystal form caused by blocking the hydroxyl group in allopurinol, as reflected in the decrease in melting points (from 365 to ~200°).

The results of the dissolution study are shown in Fig. 1. The tetrahydropyran derivative showed the greatest rate of dissolution, followed by the ethyl vinyl ether derivative and finally by the parent compound allopurinol. The rates appear to be roughly in proportion to the solubilities of the compounds studied, although allopurinol dissolves somewhat more slowly than expected.

The half-lives for the pseudo-first-order hydrolysis are reported in Table I.

The tetrahydropyran dissolves more rapidly than the ethyl vinyl ether, but it hydrolyzes more slowly. The acid-catalyzed hydrolyses are similar to those previously reported for acylals (11, 12) and indicate adequate allopurinol release, despite the less acidic conditions encountered in the stomach. The increased solubility, more rapid dissolution, and adequate reconversion to allopurinol imply a potential usefulness of the tetrahydropyran and ethyl vinyl ether derivatives as prodrugs.

[1] Carver press.
[2] Thermostated Cary 16 recording spectrophotometer.
[3] Dupont 840 with Dupont SCX support.

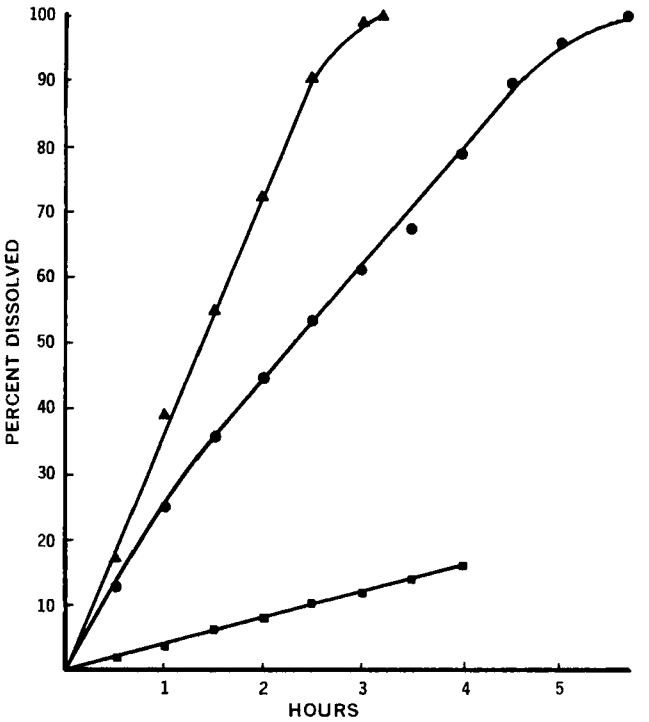

Figure 1—*Rate of dissolution of tablets containing allopurinol* (■), *1-ethoxyethyl-4-allopurinyl ether* (●), *and 2-tetrahydropyranyl-4-allopurinyl ether* (▲) *at 25°.*

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