

Acetaminophen Prodrug: 2-(*p*-Acetaminophenoxy)tetrahydropyran

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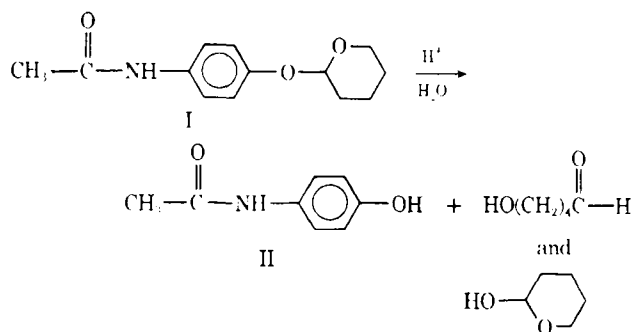
Abstract □ The synthesis and chemistry of 2-(*p*-acetaminophenoxy)tetrahydropyran, a prodrug of acetaminophen, are described. The utilization of a prodrug approach to the formulation of chewable acetaminophen tablets is discussed. Although the compound studied has many desired properties for use in chewable tablets, its aqueous solubility is very low so the dissolution rate may be rate determining in the release of acetaminophen.

Keyphrases □ Acetaminophen—synthesis of 2-(*p*-acetaminophenoxy)tetrahydropyran as a prodrug for chewable formulations, chemical properties □ 2-(*p*-Acetaminophenoxy)tetrahydropyran—synthesized as a prodrug of acetaminophen, hydrolysis, effects of temperature, ionic strength, pH, taste properties □ Acylals—synthesis of 2-(*p*-acetaminophenoxy)tetrahydropyran as a prodrug of acetaminophen for chewable formulations

The analgesic-antipyretic drug acetaminophen has been formulated in numerous dosage forms. However, there apparently has been no attempt to produce a chewable form, probably because of its unpleasant taste.

Since taste is known to be relatively specific and its intensity is concentration dependent, the taste problem should be overcome, at least in part, by preparing derivatives of acetaminophen that are much less soluble and thereby reduce the concentration of the drug at the taste buds. Alternatively, it should also be possible to alter the structure of the drug to produce a more acceptable taste.

For either approach to be successful, any chemical derivative employed should release the drug in the GI tract in the active form which would then be available for absorption. If the approach is to have merit, the rate of release of the drug under acid conditions must be much more rapid than the release rate at the relatively neutral pH of the mouth. If the prodrug form releases the drug rapidly in the mouth, the organoleptic sensations produced would be similar to those of the drug alone and no advantage would be realized. Therefore, the conversion of the prodrug to the active material must be greatly accelerated by the acid contents of the stomach.



The acylal class of organic compounds possesses chemical properties that appear to meet these criteria. For this study, 2-(*p*-acetaminophenoxy)tetrahydropyran (I) was selected to determine its feasibility as a prodrug of acetaminophen (II) suitable for a chewable dosage form (Scheme I).

The synthesis and chemistry of some 2-(aryloxy)tetrahydropyrans were reported previously (1, 2). Such substances are easily prepared by reaction of various phenols with dihydropyran in the presence of acid catalysts. The hydrolysis of the acylals was shown to be acid catalyzed at low pH but independent of pH at near neutral to alkaline conditions (1-3). The products of hydrolysis were reported to be the phenol, δ -hydroxyvaleraldehyde, and 2-(hydroxy)tetrahydropyran (1, 4)¹.

In previous studies, the rate of hydrolysis of compounds similar to I was dependent on the dielectric constant of the hydrolysis medium, and mechanisms were suggested (2, 3).

While much work has been done on the chemistry of such compounds, the acylal approach in the formulation of prodrugs apparently has not been used.

To determine whether the hydrolysis of 2-(*p*-acetaminophenoxy)tetrahydropyran would likely result in the rapid and complete release of acetaminophen under conditions similar to those encountered in the GI tract, the rate of hydrolysis was studied as a function of pH, temperature, and ionic strength. Some physical properties were also investigated.

EXPERIMENTAL²

Synthesis of I—A suspension containing II (4 g., 0.026 mole), dihydropyran (50 ml., 0.6 mole), and methylene chloride (40 ml.), saturated with hydrogen chloride gas, was prepared in a 250-ml., loosely stoppered flask. This suspension was stirred magnetically at room temperature until all suspended material was dissolved and a clear colorless solution was obtained. This normally occurred within 2-4 hr.

The solution obtained was transferred to a rotary evaporator, and some of the solvent and other volatiles were removed at room temperature and reduced pressure using an aspirator. Evaporation under these conditions was continued until most solvent was removed and a viscous suspension of a heavy white precipitate was obtained. About 10 ml. of anhydrous ether was added to the residue to facilitate its removal from the flask.

The solid white precipitate was separated by vacuum filtration, washed twice with 20-ml. portions of anhydrous ether, and dried for 30 min. at room temperature in a vacuum oven at a pressure of 1-2 mm. Hg. The solid obtained (5.5 g., 88% yield) melted at 112-113°.

¹ No reports on toxicity of these agents were located. However, it seems likely that the valeraldehyde would probably be oxidized to glutaric acid which presents no problem of toxicity.

² The equipment used included the Cary models 14 and 15 spectrophotometers and a Corning model 12 pH meter. Temperatures were controlled by using a water bath thermostated at the desired temperature $\pm 0.1^\circ$. All reagents were of reagent grade, and the water was distilled from acid permanganate solution in an all-glass still.

Table I—Observed Rate Constants for Hydrolysis of I at 25° at Various pH and Ionic Strengths

Ionic Strength, μ	k_{obs} (sec. ⁻¹) at pH				
	1.11	2.0	3.0	4.135	5.0
0.1	6.73×10^{-2}	6.51×10^{-3}	6.6×10^{-4}	5.63×10^{-6}	7.9×10^{-6}
0.3	7.11×10^{-2}	9.63×10^{-3}	6.7×10^{-4}	—	—
0.5	7.53×10^{-2}	11.55×10^{-3}	8.8×10^{-4}	—	—
0.8	7.70×10^{-2}	13.8×10^{-3}	—	—	—
1.0	—	—	10.0×10^{-4}	—	—

The NMR³ spectrum of a solution of the solid in dimethyl sulfoxide was consistent with the formula of Compound I.

Anal.—Calc. for C₁₃H₁₇NO₃: C, 66.4; H, 7.3; N, 6.0. Found⁴: C, 66.6; H, 7.5; N, 6.2.

TLC of a solution of I in 2-butanone showed only one spot, at R_f 0.55, and differential scanning calorimetry⁵ indicated only one endotherm, at 112–113°. The melting point as conventionally determined⁶ was ~113° (uncorrected).

TLC—The TLC system employed to separate I and II utilized a polyamide layer⁷ with dry 2-butanone as the developing solvent. Detection was accomplished by UV light at 254 nm. The system was sensitive to 0.1 mcg. II. The R_f values were: I, 0.75; and II, 0.55. No spots indicating the presence or nature of the products of the tetrahydropyran product were detectable. The hydrolysis of a 0.1% solution of I was followed at pH 2.95, $\mu = 0.1$. At various times over several hours, a sample of the solution was withdrawn and added to pH 7 buffer to quench the hydrolytic reaction. The resulting solution was then spotted on the plate and developed.

Kinetic Studies—The kinetics of the hydrolysis of I were followed by UV at 290 nm. At this wavelength, the absorbance increased with time.

Since I did not dissolve rapidly in aqueous solutions, a 0.03 M stock solution of I in acetonitrile was prepared. Approximately 150 μ l. of the stock solution was placed in a 2-cm. cell. The desired buffer (6.5 ml.), equilibrated at the desired temperature, was then added. The cell was closed, inverted carefully and rapidly to assure mixing, and placed in the spectrophotometer, and the absorbance changes were then followed.

Normally the reactions were followed to completion. At a higher pH value and a slower reaction, the reaction was followed for only about 5–6 half-lives. In all cases, an apparent but minor problem of solubility was encountered. As the reaction proceeded, the dihydropyran and/or derivatives that resulted from hydrolysis appeared to separate from the solution, and this occurrence resulted in small changes in the apparent absorbance. To correct for the problem of changing absorbance, all kinetic data were plotted using the Guggenheim method.

All buffers used were prepared from reagent grade materials, and the ionic strength was adjusted by the addition of sodium or potassium chloride.

RESULTS AND DISCUSSION

The hydrolysis of I was followed over a pH range of 1–5 at $\mu = 0.1$ and 25° in aqueous solutions containing 2–3% acetonitrile. It can be seen from Fig. 1 that the hydrolysis of I is hydrogen-ion catalyzed. The solid line in Fig. 1 is drawn with a slope of unity. The good fit of the experimental points to the line shows that the catalysis is first order in [H⁺]. Although the reaction was not studied extensively or quantitatively at pH > 5, due to the very slow rate of hydrolysis, the rate began to reach a plateau in the region of pH > 6–7. This finding is in accord with previous studies on related systems (3, 4).

To be certain that the hydrolysis of I to yield II was neat and complete, the reaction at 25°, pH 3.0, and $\mu = 0.1$ was followed by TLC. The TLC method was able to separate I and II. The reaction was followed as a function of time, and it was found that the hydrolysis was complete and that there was no detectable degradation

of II under these conditions as indicated by the presence of a single TLC spot, which corresponded to II, at the end of the reaction.

The rate of hydrolysis of I was followed as a function of acetate concentration (0.1–1.0 M) in buffers at 25°, pH 3.0, $\mu = 0.1$; no buffer catalysis was observed.

Ionic strength, on the other hand, affected the rate greatly. The observed rate constants as a function of ionic strength at pH 1.1–5 are shown in Table I. The rate was increased by increasing ionic strength, and the magnitude of the effect increased with increasing pH. These observations seem to be in agreement with the suggested mechanism of hydrolysis for related compounds (3, 4).

The effect of temperature on k_{obs} was studied at pH 3.0 and $\mu = 0.1$; k_{obs} (sec.⁻¹) ($\times 10^4$) was found to be 2.3 (288°K.), 6.6 (298°K.), and 21.8 (310°K.). The energy of activation of the reaction was about 19.5 kcal./mole degree, which is again in agreement with values determined for related systems (2, 3).

While the half-life of hydrolysis at 25°, pH 3.0, and $\mu = 0.1$ was a rather slow 17.5 min., the rate at 37° resulted in a half-life of only 5 min. Since the environment of the stomach would be similar to the conditions of the *in vitro* study at 37°, it would be expected that the

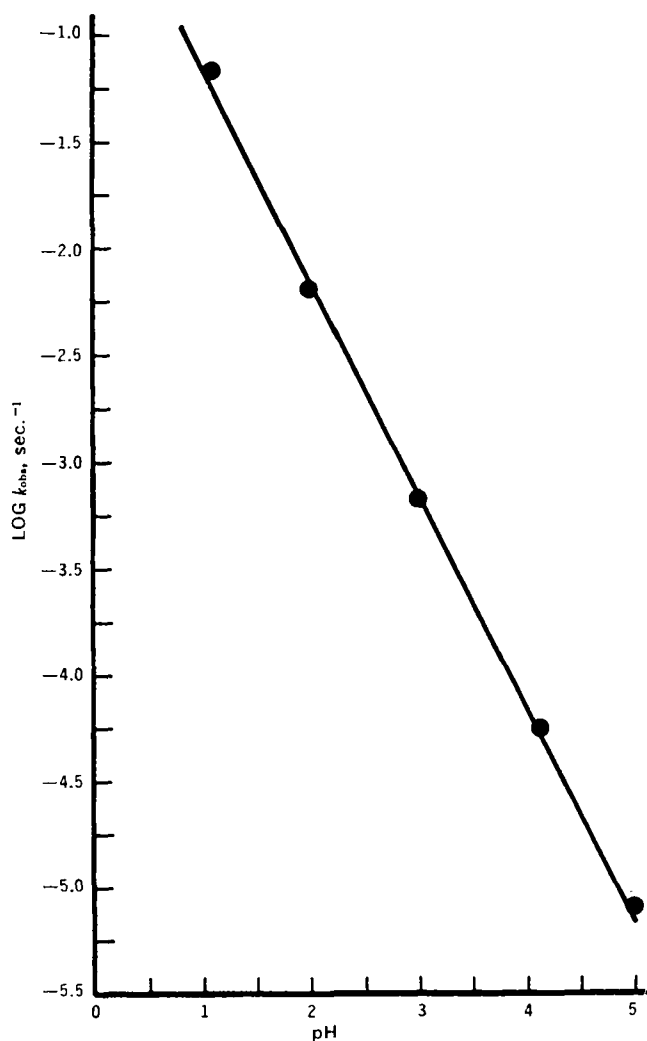


Figure 1—The pH-rate profile for hydrolysis of I at 25° and $\mu = 0.1$.

³ Varian model T-60 NMR spectrometer.
⁴ Elemental analysis was performed at the Medicinal Chemistry Department, University of Kansas, Lawrence, Kans.
⁵ Perkin-Elmer model DSC-1B differential scanning calorimeter.
⁶ Thomas-Hoover capillary melting-point apparatus.
⁷ Polygram Sil N-HR precoated on plastic sheets, available from Brinkmann Instruments, Inc.

release of II from I in the stomach would be about 95% complete in 25 min. In the mouth, however, the half-life would be expected to be 1 hr. or more since a pH > 5 would be normal. Thus, there should not be a sufficient amount of II released in the mouth to cause the taste problem associated with II, yet it should be rapidly released in the stomach. When small amounts of II were placed on the tongues of volunteers, they reported the lack of any significant taste associated with the material.

The solubility of I in distilled water at 25° was only 0.002 mole/l., while the solubility of II under the same conditions was about 0.1 mole/l. (5). By applying the approach of Hussain (6) in the calculation of time required for 50% dissolution, it can be calculated that, for a material with an average particle size of 100 μ, about 19 min. would be required for 50% dissolution at 25°. Thus, the rate-determining step in the release of II would be the rate of dissolution at pH 3. Therefore, the solubility of I may limit its usefulness as a chewable tasteless prodrug form of II.

To establish whether the lack of taste associated with I is due solely to its limited solubility, saturated solutions of I in both 40 and 30% alcohol in water were prepared. These solutions were tasted by volunteers who again reported no objectionable taste, which suggested that I was relatively free of taste problems.

CONCLUSIONS

The prodrug of acetaminophen investigated appears to be suitable, from the taste standpoint, for use in a chewable tablet.

In vitro studies of the hydrolysis of I in aqueous solution showed

that the rates of hydrolysis of I were sufficiently rapid to ensure release of acetaminophen in the stomach. However, the low solubility of I suggests that the rate-determining step in the release of acetaminophen would be the dissolution rate of the prodrug rather than its hydrolytic rate. Therefore, on the basis of these data, it appears that 2-(*p*-acetaminophenoxy)tetrahydropyran may not be especially suited for use in chewable tablets, although other uses may exist.

REFERENCES

- (1) R. V. Peterson, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 750(1960).
- (2) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081(1968).
- (3) T. H. Fife and L. H. Brod, *ibid.*, **92**, 1681(1970).
- (4) R. Paul, *Bull. Soc. Chim. Fr.*, **1**, 973(1934).
- (5) Y. P. Chow and A. J. Repta, *J. Pharm. Sci.*, **61**, 1454(1972).
- (6) A. Hussain, *ibid.*, **61**, 811(1972).

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Synthesis and Pharmacological Screening of 1-Chloro-3-(2-propynyloxy)-2-propanols and 2-[(2-Propynyloxy)methyl]oxiranes

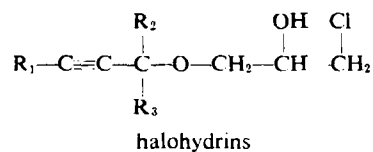
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Abstract □ Some researchers have found that an ethynyl group is essential for optimal anticancer activity of carbamate esters. In addition, it has been observed that bisepoxides are generally more potent anticancer agents than monoepoxides. These observations led to the syntheses and screening of the title compounds, ethynyl derivatives of oxiranes and their synthetic precursors, since the presence of both an ethynyl group and an oxirane group in a molecule may lead to significant anticancer activity. One compound, 2-[(2-butynyloxy)methyl]oxirane, showed confirmed, but weak, activity in the P-388 test system employed.

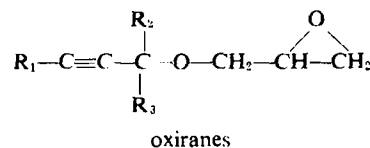
Keyphrases □ 1-Chloro-3-(2-propynyloxy)-2-propanols—synthesis and pharmacological screening as possible anticancer agents □ 2-[(2-Propynyloxy)methyl]oxiranes synthesis and pharmacological screening as possible anticancer agents □ Oxiranes, ethynyl derivatives and synthetic precursors—synthesis and screening as possible anticancer agents □ Anticancer agents, potential—synthesis and screening of 1-chloro-3-(2-propynyloxy)-2-propanols and 2-[(2-propynyloxy)methyl]oxiranes

The possibility that the ethynyl group could act as a biological alkylating agent prompted the synthesis and screening of the title compounds as possible cytotoxic agents. It has been reported (1) that the presence of an acetylene group is essential for the oncolytic action of a series of ethynylmethyl carbamate esters.

The requirements of an ethynyl group for oncolytic activity in ethynylmethyl carbamates, as well as a generally observed lower anticancer activity for mono-



- I: R₁ = CH₃, R₂ = R₃ = H
 II: R₁ = CH₃(CH₂)₂, R₂ = R₃ = H
 III: R₁ = H, R₂ = H, R₃ = CH₃
 IV: R₁ = H, R₂ = R₃ = CH₃
 V: R₁ = C₆H₅, R₂ = R₃ = H
 VI: R₁ = H, R₂ + R₃ = CH₂(CH₂)₃CH₂



- VII: R₁ = CH₃, R₂ = R₃ = H
 VIII: R₁ = CH₃(CH₂)₂, R₂ = R₃ = H
 IX: R₁ = H, R₂ = H, R₃ = CH₃
 X: R₁ = H, R₂ = R₃ = CH₃
 XI: R₁ = C₆H₅, R₂ = R₃ = H
 XII: R₁ = H, R₂ + R₃ = CH₂(CH₂)₃CH₂