recognizable by its odor. The IR spectrum (Fig. 6E) of a potassium bromide disk of sodium propionate is a satisfactory and characteristic test for this salt. It is suggested that identification test A for sodium remain in the monograph.

Tartaric Acid—In NF XIV identification test B for tartaric acid, the acid is ignited, emitting an odor resembling that of burnt sugar. The IR spectrum (Fig. 7) of a potassium bromide disk of tartaric acid is a satisfactory and characteristic test for this acid.

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NOTES

Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IX: Acetaminophen Prodrug

ANWAR HUSSAIN ˣ, PRAKASH KULKARNI, and DONALD PERRIER

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Abstract □ The synthesis, hydrolysis rate, and bioavailability of 1-(*p*-acetaminophenoxy)-1-ethoxyethane, an acetaminophen prodrug, are described. The prodrug is less soluble than acetaminophen and stable at neutral pH. However, in an acidic environment, the compound cleaves rapidly, generating acetaminophen. When both the prodrug and acetaminophen were administered to dogs in equivalent amounts, the blood acetaminophen levels were comparable.

Keyphrases □ Prodrugs—of acetaminophen, synthesis, hydrolysis rate, and bioavailability studied, dogs □ Acetaminophen prodrug—1-(*p*-acetaminophenoxy)-1-ethoxyethane synthesized, hydrolysis rate and bioavailability studied, dogs □ 1-(*p*-Acetaminophenoxy)-1-ethoxyethane—acetaminophen prodrug synthesized, hydrolysis rate and bioavailability studied, dogs □ Hydrolysis rate—acetaminophen prodrug studied, dogs □ Bioavailability—acetaminophen prodrug studied, dogs □ Analgesics—acetaminophen, prodrug synthesized, hydrolysis rate and bioavailability studied, dogs

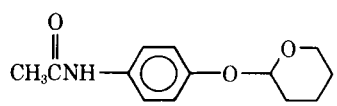
Acetaminophen, a well-known analgesic–antipyretic drug, is widely used in oral dosage forms. The drug, however, is unpleasantly bitter, and attempts made to formulate it in an acceptable chewable dosage form intended especially for pediatric use have apparently not been very successful.

Repta and Hack (1) were successful in masking the bitterness of acetaminophen *via* derivation of the hydroxy group to form 2-(*p*-acetaminophenoxy)tetrahydropyran (I). Prodrug I was stable at neutral pH (pH of the saliva) but hydrolyzed in the gastric juice. This paper reports the synthesis, hydrolysis rate, and absorption of another acetaminophen prodrug where the hydroxy group was transiently blocked using ethyl vinyl ether. This prodrug, 1-(*p*-acetaminophenoxy)-1-ethoxyethane (II), has an advantage over the corresponding tetrahydropyran derivative (I) in that it reverts to acetaminophen 10 times faster. Therefore, the possibility that the prodrug might be absorbed as such is greatly minimized.

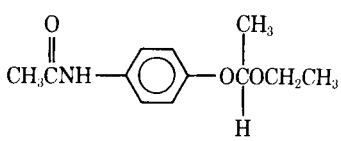
EXPERIMENTAL

Synthesis of II (2)—To a suspension containing 4 g of acetaminophen (0.26 mole) in freshly distilled ethyl acetate were added 30 ml (~0.4 mole) of freshly distilled ethyl vinyl ether and 0.2 ml of 0.4% *p*-toluenesulfonic acid in benzene. The suspension was stirred magnetically at room temperature until all suspended material was dissolved and a clear colorless solution was obtained, usually within 2–4 hr.

At the completion of the reaction, 0.2 ml of 0.4% pyridine in benzene was added. The solution obtained was transferred to a rotary evaporator,



I



II

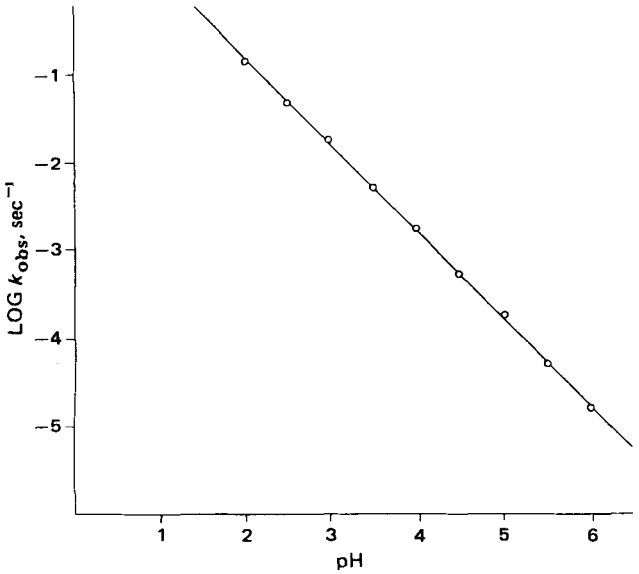


Figure 1—*The pH–rate profile for the hydrolysis of II at 25°.*

and some of the solvent and other volatile materials were removed at room temperature. Petroleum ether was added to the remaining viscous liquid, which was kept in the freezer for a few hours. The white precipitate which formed was filtered, washed with petroleum ether, and dried under vacuum at room temperature, yielding 5.6 g (88%), mp 60–61°. TLC of the solution of the prodrug in ethyl acetate showed only one spot.

The NMR spectra were consistent with the structure of II; NMR ($CDCl_3$): δ 8.36–8.66 (s, 1H, CNA_R), 6.86–7.63 (m, 4H, ArH), 5.18–5.53 [q, 1H, $OCH(CH_3)$], 3.36–3.99 (m, 2H, OCH_2CH_3), 2.03–2.30 (s, 3H, $COCH_3$), 1.39–1.61 [d, 3H, $OCH(CH_3)$], and 1.00–1.39 (t, 3H, CH_2CH_3) ppm.

Anal.—Calc. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68. Found: C, 64.54; H, 7.73.

Kinetic Studies—A 0.03 *M* solution of the prodrug in spectral grade dioxane was freshly prepared. Approximately 150 μl was placed in a 2-cm UV cell, and approximately 6.5 ml of the buffer at the desired pH was added. The appearance of acetaminophen was followed spectrophotometrically at 290 nm. The aqueous solutions were prepared to contain 0.05 *M* total phosphate buffer, and the ionic strength was adjusted to 0.1 with potassium chloride. All solutions were equilibrated at 25 ± 0.1° before use.

Animal Studies—Two healthy male beagle dogs, 12 and 14 kg, were

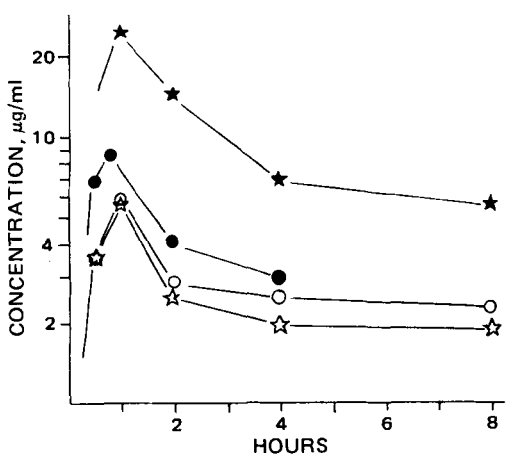


Figure 2—*Plasma acetaminophen concentration following the oral administration of acetaminophen and II. Dog 1 received 10-mg/kg doses of acetaminophen (○) and II (☆). Dog 2 received 25-mg/kg doses of acetaminophen (●) and II (★). The 0.5-hr prodrug and 8-hr acetaminophen samples for Dog 2 could not be obtained.*

Table I—Half-Lives and Observed First-Order Rate Constants of Hydrolysis of the Prodrug at Various pH Values at 25°

pH	Half-Life, sec	k_{obs}, sec^{-1}
2.0	4.24	1.62×10^{-1}
2.5	13	5.3×10^{-2}
3.0	42.7	1.62×10^{-2}
3.5	131	5.3×10^{-3}
4.0	421	1.62×10^{-3}
4.5	1,320	5.3×10^{-4}
5.0	4,218	1.62×10^{-4}
5.5	11,100	6.2×10^{-5}
6.0	43,780	1.59×10^{-5}

employed. Following a 24-hr fast, single doses of acetaminophen and the prodrug were administered with lactose in hard gelatin capsules 1 week apart. Water was available to the dogs during the experiment. Food was withheld for at least 6 hr postadministration. Dog 1 (12 kg) received 10 mg/kg, and Dog 2 (14 kg) received 25 mg/kg of acetaminophen and prodrug (as acetaminophen equivalents).

Blood samples, 5 ml, were withdrawn at 0.5, 1, 2, 4, and 8 hr postadministration. The blood was centrifuged, and the plasma was removed and stored at −20° until analyzed. The plasma acetaminophen levels were determined by GLC according to the procedure employed by Kostenbauder[1].

RESULTS AND DISCUSSION

To determine whether II does indeed cleave in an acidic environment, its hydrolysis rate was studied over the pH 2–6 range. As can be seen from the data in Table I and Fig. 1, the hydrolysis of the prodrug is acid catalyzed. The mechanism of hydrolysis of acetals was discussed thoroughly (3–5). In the pH 5–6 range, the prodrug remains intact for at least 1 hr. However, once in contact with an acidic environment such as that of the stomach, it cleaves rapidly, generating acetaminophen. The advantage of this prodrug over the corresponding tetrahydropyran prodrug (1) is that II cleaves 10 times faster. Therefore, the possibility that the prodrug is absorbed as such or passed to the more alkaline pH of the intestine is greatly minimized.

To compare the availability of II to that of acetaminophen, both compounds were given to dogs in capsule form. As can be seen from the data in Fig. 2, the plasma concentrations of the two compounds are comparable. Consequently, acetaminophen availability is not compromised *via* this approach.

It is not known at this time whether the prodrug is indeed less bitter than acetaminophen; human study is needed to obtain this information. However, based on the similarity of this prodrug to the corresponding tetrahydropyran derivative, the fact that II has equivalent aqueous solubility as the corresponding tetrahydropyran (solubility of II is 0.003 mole/liter; solubility of I is 0.003 mole/liter), and the fact that I is less bitter than acetaminophen, II also may possibly be less bitter than acetaminophen.

In view of the rapid hydrolysis rate of II to acetaminophen, the formulation parameters required to manufacture II in a conventional stable dosage form may be very stringent.

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