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.

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

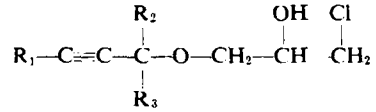
R. B. FUGITT, G. S. WU, and L. C. MARTINELLI▲

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

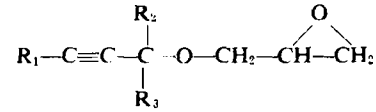
The possibility that the ethynyl group could act as a biological alkylating agent prompted the synthesis and screening of the title compounds as possible cytotoxic agents. It has been reported (1) that the presence of an acetylene group is essential for the oncolytic action of a series of ethynylmethyl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



halohydrins

I: $R_1 = CH_3$, $R_2 = R_3 = H$
II: $R_1 = CH_3(CH_2)_2$, $R_2 = R_3 = H$
III: $R_1 = H$, $R_2 = H$, $R_3 = CH_3$
IV: $R_1 = H$, $R_2 = R_3 = CH_3$
V: $R_1 = C_6H_5$, $R_2 = R_3 = H$
VI: $R_1 = H$, $R_2 + R_3 = CH_2(CH_2)_3CH_2$



oxiranes

VII: $R_1 = CH_3$, $R_2 = R_3 = H$
VIII: $R_1 = CH_3(CH_2)_2$, $R_2 = R_3 = H$
IX: $R_1 = H$, $R_2 = H$, $R_3 = CH_3$
X: $R_1 = H$, $R_2 = R_3 = CH_3$
XI: $R_1 = C_6H_5$, $R_2 = R_3 = H$
XII: $R_1 = H$, $R_2 + R_3 = CH_2(CH_2)_3CH_2$

Table I—Experimental Data

Compound	Boiling Point (mm. Hg)	Procedure	Yield, %	Formula	Analysis, % Calc.	Found
I	90–97° (0.30–0.50)	A	68	$C_7H_{11}ClO_2$	C 51.71 H 6.81 Cl 21.80	51.53 6.79 21.54
II	79–82° (0.04)	A	38	$C_9H_{15}ClO_2$	C 56.70 H 7.92 Cl 18.60	56.66 7.98 18.54
III	58–65° (0.04–0.06)	A	24	$C_7H_{11}ClO_2$	C 51.71 H 6.81 Cl 21.80	51.44 6.98 21.65
IV	49–52° (0.03)	B	23	$C_8H_{13}ClO_2$	C 54.40 H 7.41 Cl 20.07	54.21 7.51 20.18
V	125–135° (0.02–0.05)	B	45	$C_{12}H_{13}ClO_2$	C 64.14 H 5.83 Cl 15.77	63.98 5.89 15.91
VI	90–98° (0.10)	B	35	$C_{11}H_{17}ClO_2$	C 60.96 H 8.01 Cl 16.35	60.81 7.96 16.24
VII	89–92° (15.0)	–	82	$C_8H_{12}O_2$	C 66.64 H 7.99	66.73 8.10
VIII	62–66° (0.45)	—	77	$C_9H_{14}O_2$	C 70.10 H 9.15	70.11 9.22
IX	78–82° (25.0)	—	65	$C_7H_{10}O_2$	C 66.64 H 7.99	66.70 8.08
X	65–68° (20.0)	—	81	$C_8H_{12}O_2$	C 68.54 H 8.63	68.41 8.69
XI	87–91° (0.02)	—	85	$C_{12}H_{12}O_2$	C 76.56 H 6.43	76.32 6.57
XII	110–112° (9.0)	—	78	$C_{11}H_{16}O_2$	C 73.30 H 8.95	73.44 8.99

Table II—Spectral Data for Propynyloxy Propanols

Compound	NMR, p.p.m. R_1		R_2		R_3		OCH_2	$-\underset{\vert}{C}H-$	CH_2Cl	IR, $cm.^{-1}$ OH	HC≡	C≡C	COC
I	CH_3	1.85	H	=	H	4.15	3.60	3.90	3.60	3400	—	2280 2210	1100
II	CH_3 $\vert$ CH_2 $\vert$ CH_2	1.00 1.55 2.25	H	=	H	4.20	3.65	4.00	3.60	3400	—	2275 2225	1100
III	H	2.55	H	4.25	CH_3	1.45	3.70	3.95	3.50	3400	3280	2105	1114
IV	H	2.55	CH_3	=	CH_3	1.45	3.65	3.85	3.60	3400	3270	2100	1095
V	C_6H_5	7.30	H	=	H	4.35	3.65	4.00	3.60	3412	—	2235	1110
VI	H	2.60	$CH_2(CH_2)_3CH_2$			1.60	3.65	3.85	3.62	3400	3280	2105	1100

epoxides compared to bisepoxides (2), prompted the investigation of the anticancer activity of ethynyl-substituted oxiranes. It seemed reasonable that the ethynyl group might also be acting as a biological alkylating site and that ethynyl derivatives of oxiranes might, therefore, possess significant anticancer activity. The halohydrins were prepared as intermediates to the oxiranes and were also screened since they may be converted *in vivo* to their corresponding oxiranes.

EXPERIMENTAL

Chemistry[1]—Table I gives the experimental data for the individual compounds, and Tables II and III give their NMR and IR spectral characteristics. NMR spectra[2] were taken in deuteriochloroform containing 1% tetramethylsilane as a standard. The IR spectra[3] were taken as thin films between sodium chloride plates.

The 1-chloro-3-(2-propynyloxy)-2-propanols were synthesized by acid-catalyzed condensation, similar to a published procedure (4), of the appropriate alcohol with epichlorohydrin. In the cases of the two tertiary alkynols and phenylpropargyl alcohol, phosphoric acid was employed (Procedure B) to eliminate the excessive tarring and lowered yields experienced when sulfuric acid was used (Procedure A). The 2-[(2-propynyloxy)methyl]oxiranes were prepared from the acetylenic halohydrins in good yield using a published method (4).

Synthesis of 1-Chloro-3-(2-propynyloxy)-2-propanols—*Procedure A, Compounds I–III*—Concentrated sulfuric acid (2 ml./mole epichlorohydrin) was added dropwise at room temperature to a flask containing a stirred mixture of 1 equivalent of epichlorohydrin and 2 equivalents of the acetylenic alcohol. The reaction vessel was equipped with a reflux condenser protected by a drying tube. The reaction solution was warmed to 100–110° for 24–48 hr. when it began to darken appreciably. After cooling, 1.5 equivalents of powdered barium carbonate was added; after stirring for 1–2 hr., the salts were removed by filtration. Unchanged epichlorohydrin was removed by a water aspirator, and the residual oil was carefully fractionated *in vacuo* to give the product. When the alcoholic starting material is sufficiently water insoluble to resist emulsification, the acid catalyst may also be removed by diluting the reaction mixture with methylene chloride and washing it with water.

Procedure B, Compounds IV–VI—These compounds were prepared as in Procedure A with the following modifications. Concentrated phosphoric acid (10 ml.) is substituted for every 2 ml. of con-

[1] All microanalyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga.
[2] Hitachi Perkin-Elmer R20A.
[3] Perkin-Elmer 237B spectrometer.

Table III—Spectral Data for Propynyloxymethyl Oxiranes

Compound	NMR, p.p.m.									IR, cm.$^{-1}$			
	R_1		R_2		R_3		OCH_2	—CH—	$—CH_2$	HC≡	H_2C—	C≡C	Δ
VII	CH_3	2.10	H	=	H	4.37	3.85	3.33	2.88	—	3040	2280 2205	1260
VIII	CH_3	1.20	H	=	H	4.36	3.84	3.28	2.85	–	3040	2280 2220	1260
	CH_2	1.75											
	CH_2	2.42											
IX	H	2.77	H	4.45	CH_3		1.62	3.85	3.30	2.95	3260	3045	2100	1255
X	H	2.54	CH_3	=	CH_3		1.49	3.64	3.12	2.66	3270	3055	2105	1255
XI	C_6H_5	7.35	H	=	H		4.36	3.60	3.12	2.65	—	3050	2230	1260
XII	H	2.60	$CH_2(CH_2)_3CH_2$				1.60	3.64	3.08	2.67	3250	3035	2100	1260

centrated sulfuric acid used in Procedure A, and the reaction solution is heated an additional 4–24 hr.

Synthesis of 2-[(2-Propynyloxy)methyl]oxiranes, Compounds VII–XII– Freshly powdered sodium hydroxide (1.5 equivalents) was added to an ice-cold solution of the 1-chloro-3-(2-propynyloxy)-2-propanol dissolved in a volume of absolute ether equal to 10 times the weight of sodium hydroxide used. The reaction vessel was stoppered and allowed to stir magnetically overnight. The suspended inorganic salts were removed by filtration, the ether solution was concentrated on a rotary evaporator, and the residual oil was distilled *in vacuo*.

Biological[1]–The experimental animals were BDF_1 mice inoculated intraperitoneally (i.p.) or intracerebrally (i.c.) with L-1210 or P-388 tumor systems. The test compounds (all were racemic mixtures) were administered at 400, 200, 100, and 50 mg./kg. body weight i.p. in sonified saline or saline with polysorbate 80. Doses were administered, beginning on Day 1, either daily for nine doses or every 4th day for three doses, and test results were evaluated at Day 30. Evaluations were made as mean survival time and are expressed as % T/C (test/control), with a value of 125 or greater representing activity in these systems.

RESULTS AND DISCUSSION

Chemistry–The possibility exists that condensation of the acetylenic alcohol with epichlorohydrin may occur at both the primary and secondary carbons of the epichlorohydrin to give a γ-halohydrin in addition to the desired β-halohydrin. This inconvenient side reaction was observed in only one instance, in the case of 2 butyn-1-ol. Apparently, the reaction conditions used for the conversion of the β-halohydrin to the oxirane are insufficient to convert also the γ-halohydrin to the corresponding oxetane, since oxetane has not been observed in the IR or NMR of any 2-[(2-propynyloxy)-methyl]oxirane. Isolation of the lower boiling β-halohydrin in pure form is achieved by careful fractional distillation of the reaction mixture *in vacuo*.

Biological–The compounds were tested against L-1210 and P-388 leukemia according to the standard protocol of The Division of Cancer Treatment, National Cancer Institute, National Institutes of Health. The 1-chloro-3-(2-propynyloxy)-2-propanols (I–VI) showed no significant activity as indicated by changes in the mean survival time of the test animals over that of the control animals (% T/C < 125). The activity of oxirane VII, 2-[(2-butynyloxy)methyl]oxirane (NSC 153427), was confirmed by duplicate screening in the intraperitoneal P-388 test system (% T/C 129 and 134) when administered daily, at doses as low as 44 mg./kg. body weight, for nine doses. Oxirane XI, 2-{[(3-phenyl-2-propynyl)oxy]methyl}oxirane (NSC 156628), showed unconfirmed preliminary activity in intraperitoneal P-388 (% T/C 133) and intracerebral P-388 (% T/C 154) when administered daily for nine doses (400 and 100 mg./kg., respectively). The other oxiranes were devoid of activity but did exhibit slightly larger % T/C values than their corresponding β-halohydrins.

The marginal activity exhibited by only one oxirane, VII, and perhaps oxirane XI does not appear to support the hypothesis that the ethynyl group can act as a biological alkylating agent in these compounds. Further work will be conducted in this area, however, before final conclusions are made.

[1] The biological data were made available through the courtesy of Dr. Harry B. Wood, Jr., and Dr. John S. Driscoll, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

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