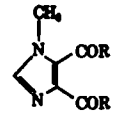

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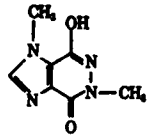

B

Table II—MAO Inhibitory Activity Evaluation of Hydrazides (Structures A and B)

Compound	R (Structure A)	Oral Dose, mmole/kg.	Activity Prior to Reserpine (2 mg./kg.)	Mean Ptotic Score	Body Temperature (± *SE*) after Reserpine (2 mg./kg.) 0 hr.	4 hr.	6 hr.	24 hr.	Hexobarbital-Induced Sleeping Time, min.[a]
Control[b]			Normal	3.75	35.8 ± 0.2°	29.9 ± 0.4°	26.3 ± 0.2°	26.6 ± 0.5°	8.3 ± 0.3
III*a*	$NHNH_2$	0.275	Increased	2.50	35.7 ± 0.3°	32.7 ± 0.3°	31.9 ± 0.4°	30.6 ± 0.5°	15.2 ± 0.2
III*b*	$NHNHCH_3$	0.275	Increased	2.90	36.1 ± 0.2°	31.5 ± 0.1°	31.0 ± 0.4°	33.6 ± 0.6°	12.7 ± 0.3
IV*b*	Structure B	0.275	Increased	2.66	35.9 ± 0.1°	32.2 ± 0.5°	30.9 ± 0.3°	28.9 ± 0.4°	13.4 ± 0.4
III*c*	$NHNHC_6H_5$	0.275	Increased	2.00	36.5 ± 0.3°	32.5 ± 0.2°	29.4 ± 0.5°	32.1 ± 0.3°	19.7 ± 0.1
V	$NHN{=}CHC_6H_5$	0.275	Increased	2.00	36.3 ± 0.3°	32.6 ± 0.4°	29.7 ± 0.6°	30.2 ± 0.5°	20.3 ± 0.3
VI	$NHN{=}CHCH_3$	0.275	Increased	2.50	35.7 ± 0.1°	32.6 ± 0.3°	31.6 ± 0.3°	32.7 ± 0.7°	14.9 ± 0.2
VII	$NHN{=}CHCH_3$	0.275	Increased	2.60	35.2 ± 0.4°	32.0 ± 0.5°	29.6 ± 0.5°	30.6 ± 0.3°	12.9 ± 0.1
VIII	$NHNHCH_2C_6H_5$	0.275	Increased	2.33	35.9 ± 0.1°	31.8 ± 0.3°	29.2 ± 0.6°	31.4 ± 0.5°	17.6 ± 0.3
IX	$NHNHCH(CH_3)_2$	0.275	Increased	1.83	35.6 ± 0.2°	32.6 ± 0.2°	30.8 ± 0.4°	32.4 ± 0.3°	22.0 ± 0.2
Isocarboxazid		0.1375	Increased	0.50	35.6 ± 0.5°	34.2 ± 0.1°	36.7 ± 0.4°	35.2 ± 0.4°	11.0 ± 0.1

[a] Hexobarbital was given intraperitoneally (5.5 mg./kg.) 2 hr. after intubation of the test compound. [b] Control implies reserpine in ptosis and hypothermia test and hexobarbital in sleeping time prolongation test.

REFERENCES

(1) J. Nematollahi and J. R. Nulu, *J. Med. Chem.*, **12**, 43(1969), and references therein.

(2) J. R. Nulu and J. Nematollahi, *ibid.*, **12**, 804(1969).

(3) R. G. Jones, *J. Amer. Chem. Soc.*, **78**, 159(1956).

(4) J. R. Nulu and J. Nematollahi, *Tetrahedron Lett.*, **1969**, 1321.

(5) R. M. Izatt, J. J. Christensen, and J. H. Tytting, *Chem. Rev.*, **71**, 439(1971), and references therein.

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Synthesis and Anticancer Activity of 5-(Propargyloxymethyl)-2-oxazolidinones

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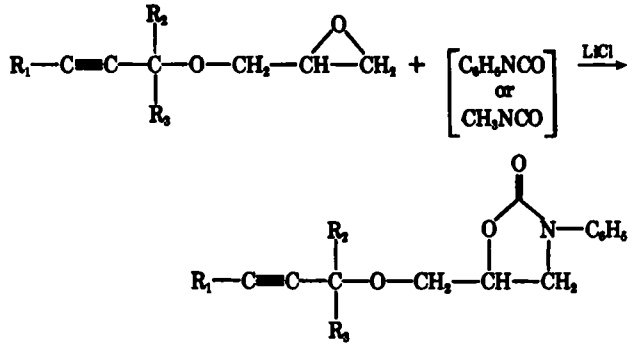
Abstract □ To determine the feasibility of producing a tissue-specific anticancer agent, a series of 2-oxazolidinones bearing an alkynoxymethyl side chain in the 5-position was prepared. These compounds were submitted to the National Cancer Institute for testing against L-1210 and/or P-388 tumor test systems. None of the compounds showed significant anticancer activity. The synthetic procedures and NMR spectral properties of the title compounds are described.

Keyphrases □ 5-(Propargyloxymethyl)-2-oxazolidinones—synthesis, screened for anticancer activity □ 2-Oxazolidinones, 5-(propargyloxymethyl)—synthesis, screened for anticancer activity □ Anticancer agents, potential—synthesis and screening of 5-(propargyloxymethyl)-2-oxazolidinones

Interest in carbamates bearing an acetylenic function developed from an interest in tissue- or organ-specific anticancer agents, particularly those specific for the CNS. The investigation of the title compounds stems, in part, from the work of Dillard *et al.* (1) who first demonstrated the oncolytic action of propargyl carbamates against plasma cell tumor X-5563 and the atypical myelogenous leukemia C-1498. Among the structure–activity relationships they observed was the necessity of the ethynyl moiety for significant oncolytic



Scheme I—See Table I for R-group identification

activity. In addition, carbamates, especially ethynylmethyl carbamates, are known to be potent CNS depressants (2), thus indicating that they are readily transported across the blood–brain barrier. With the intent of screening new chemical entities with potential anticancer activity, the title compounds (Table I), bearing both an ethynyl and a carbamate function, were synthesized and subjected to anticancer screening.

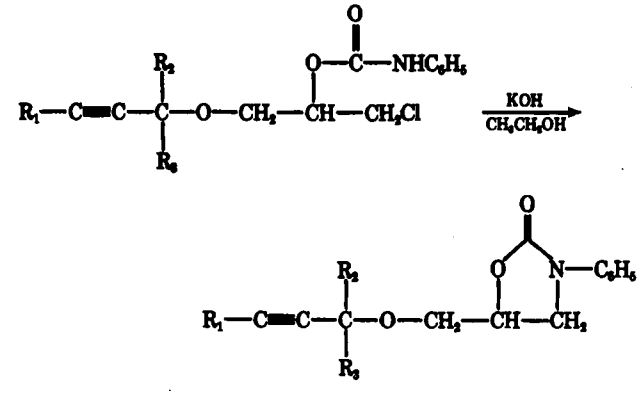
Additional impetus to study 2-oxazolidone ring compounds stems from observations that the potent anticancer agent 1,3-bis(2-chloroethyl)-1-nitrosourea decomposes in water to a Δ^2-oxazoline derivative (3). Similarly, the active *N*-acylethyleneimines readily rearrange to Δ^2-oxazolines (4).

The title compounds were synthesized by reported techniques, and their identification was achieved in part by comparison of NMR data with a compound with known ring stereochemistry. The six compounds were subjected to preliminary anticancer screening against L-1210 lymphoid leukemia and/or P-388 lymphocytic leukemia. Screening data are only available for I–IV; none showed significant activity in these systems.

CHEMISTRY

Compounds I–IV were synthesized (Scheme I) by lithium chloride-catalyzed condensation of the known epoxides (5) with phenylisocyanate or methylisocyanate in dry dimethylformamide at 100–150° (6). This method allows a high yield synthesis of *N*-alkyl- and *N*-aryl-2-oxazolidinones in one step from the epoxide. Compound II was also synthesized (Scheme II) by potassium hydroxide–ethanol cyclization (7) of the appropriate β-chloroethyl *N*-phenylcarbamate to provide a compound with known C-5 ring substitution.

Cyclization of the *N*-phenyl-β-chlorocarbamate ester resulted in the isolation of a small amount of a six-membered ring carbamate as a by-product, which arose from the isomeric γ-chlorohydrin formed in the synthesis of the starting β-chlorohydrins. Careful fractional



Scheme II—See Table I for R-group identification

distillation of the β-chlorohydrin prior to use eliminates this problem. The chlorohydrins were prepared from the reaction of the appropriate alcohol with epichlorohydrin (5).

The isocyanate–epoxide reaction is known to produce both C-4 and C-5 substitution products through breaking either the C_1—O or C_2—O epoxide bonds (8), although the C-5 isomer is generally the only product observed. From the limited study of Herweth *et al.* (6), only aryl-substituted epoxides led to the C-4 isomer regardless of the type of isocyanate (alkyl or aryl). The possibility existed, therefore, that the π-electron-rich ethynyl group may help direct C-4 isomer formation through π-interactions with the incoming isocyanate. That this did not occur is evident by comparison of the NMR data of II with the only products isolated from the isocyanate–epoxide reactions (I–IV).

The NMR spectral shift data (Table I) for H_A, H_B, and $H_{C,D}$ of I–IV are essentially identical with equivalent protons for II synthesized unambiguously. Further, these data are consistent with C-5 isomers reported in the literature (6). Compounds V and VI, the N—CH_3 analogs, are assigned as C-5 substitution since they exhibit proton NMR absorption consistent with the loss of anisotropic deshielding by a phenyl ring. The observation that the $\Delta\delta$ of H_A is larger than the $\Delta\delta$ of H_B when *N*-phenyl is replaced by *N*-methyl is not readily explainable, but it is consistent with similar findings by Herweth *et al.* (6).

BIOLOGICAL ASSAY[1]

Compounds I–IV were assayed against P-388 lymphocytic leukemia in BFD_1 mice, while only I was screened against L-1210 lymphoid leukemia (Table II). The compounds were administered at three dosages, 400, 200, and 100 mg./kg. i.p., every 4th day for three injections, and the percent increase in median survival time (percent test/control) was calculated at Day 30. Compound I was administered in hydroxypropylcellulose, while II–IV were administered in saline. The term "survivors" in Table II is a measure of toxicity and was determined at Day 5 after the first injection.

EXPERIMENTAL[2]

Melting points were obtained in open capillaries and are uncorrected. IR spectra[3] were obtained as neat oils between sodium chloride plates or in potassium bromide wafers for solids. All compounds, except III, exhibited acetylenic and carbonyl stretching frequencies at 2105–2290 and 1733–1740 $cm.^{-1}$, respectively. Compound III had no discernible acetylenic absorption but exhibited an acetylene C—H stretch at 3300 $cm.^{-1}$ as well as a carbonyl absorption at 1737 $cm.^{-1}$. All NMR spectra were obtained at 60 MHz. in deuteriochloroform containing 1% tetramethylsilane as internal standard.

1-(2-Butynyloxy)-3-chloro-2-propyl *N*-Phenylcarbamate—To a 250-ml. flask was added 25 g. (0.150 mole) of 1-(2-butynyloxy)-3-chloro-2-propanol prepared from the condensation of 2-butyn-1-ol and epichlorohydrin (5). Dried benzene (100 ml.) and 21.5 g. (0.180 mole) of freshly distilled phenylisocyanate were added and the reaction was stirred. Following a procedure similar to that of Loev and Kormendy (9), 1.5 ml. of trifluoroacetic acid was added; the reaction was topped with a calcium chloride tube and stirred for 4 hr. at room temperature. The reaction was cooled and filtered to remove diphenylurea and reduced to an oil by water aspiration. The oil was chromatographed on a 20 × 2-mm. alumina column using 1,2-dichloroethane, and the resulting oil was distilled *in vacuo* to give 22.4 g. (52%) of the desired product, b.p. 165–180° (0.1–0.2 mm.).

Anal.—Calc. for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; Cl, 12.58; N, 4.97. Found: C, 59.74; H, 5.80; Cl, 12.74; N, 5.02.

The IR and NMR data were consistent with this structure. IR (neat): 3305 (N—H), 2220 and 2300 (C≡C), and 1625 (C=O) $cm.^{-1}$. NMR: 1.75 (t, 3), 3.72 (d, 4), 4.10 (d, 2), 4.30 (m, 1), 5.15 (m, 1), and 7.30 (m, 5) p.p.m.

[1] The screening was performed by Drug Research and Development, Chemotherapy, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014

[2] Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga.

[3] Recorded on a Perkin-Elmer 237B spectrometer.

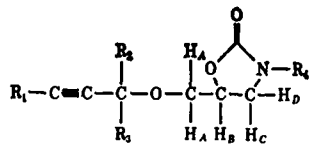


Table I—Structures and NMR Data of 2-Oxazolidinones

Compound	R_1	R_2	R_3	R_4	NMR Data (δ) H_A	H_B	$H_{C,D}$	R_2R_3	R_1	R_4
I	H	H	H	C_6H_5	3.78 (d, J_{AB} = 4.5 Hz.)	4.75(m)	3.98(m)	4.23 (d, J = 2.3 Hz.)	2.50 (t, J = 2.3 Hz.)	7.40(m)
II	CH_3	H	H	C_6H_5	3.74 (d, J_{AB} = 5.0 Hz.)	4.72(m)	3.95(m)	4.20 (q, J = 2.5 Hz.)	2.20 (t, J = 2.5 Hz.)	7.37(m)
III	H	—$CH_2(CH_2)_3CH_2$—		C_6H_5	3.85 (d, J_{AB} = 4.5 Hz.)	4.70(m)	3.96(m)	—	2.51 (s)	7.38(m)
IV	C_6H_5	H	H	C_6H_5	3.85 (d, J_{AB} = 5.0 Hz.)	4.75(m)	4.00(m)	4.45 (s)	7.35(m)	7.35(m)
V	H	H	H	CH_3	3.60 (d, J_{AB} = 4.4 Hz.)	4.65(m)	3.50(m)	4.25 (d, J = 2.3 Hz.)	2.74 (t, J = 2.3 Hz.)	2.87(s)
VI	CH_3	H	H	CH_3	3.62 (d, J_{AB} = 4.4 Hz.)	4.62(m)	3.54(m)	4.13 (q, J = 2.5 Hz.)	1.84 (t, J = 2.5 Hz.)	2.86(s)

3-Phenyl-5-[(2-propynyloxy)methyl]-2-oxazolidinone (I)—From the procedure of Herweth *et al.* (6), a 100-ml. flask equipped with a calcium chloride tube, condenser, and dropping funnel was charged with 7 g. (0.063 mole) of 1,2-epoxy-3-propargyloxypropane, 25 ml. of dry dimethylformamide, and 0.5 g. of lithium chloride and the contents were warmed at 100°. A solution of 7.5 g. of freshly distilled phenylisocyanate in 7.5 ml. of dry dimethylformamide was added dropwise (less than 1 drop/sec.), and the reaction was warmed at 150° for 4 hr. The solvent was removed *in vacuo* (pot 120–130°), and the residue was diluted with 50 ml. of carbon tetrachloride and enough methylene chloride to ensure that the liquids were miscible; the lithium chloride was removed by filtration. Upon evaporation of solvent, 11.2 g. (83%) of I was isolated and recrystallized from ethanol, m.p. 83–86° [lit. (10) m.p. 80°].

Anal.—Calc. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.42; H, 5.71; N, 6.06.

3-Phenyl-5-[(2-butynyloxy)methyl]-2-oxazolidinone (II)—*Procedure A: Potassium Hydroxide Method*—To a 50-ml. flask containing 12 g. (0.043 mole) of 1-(2-butynyloxy)-3-chloro-2-propyl *N*-phenylcarbamate and 35 ml. of 70% ethanol was added 29 g. (0.043 mole) of potassium hydroxide. The reaction was immediately warmed at 100° for 9 min. and then poured into 50 ml. of cold water, extracted with ether, and dried over magnesium sulfate. The ether was concentrated and the solution was cooled (5°), which afforded 5.8 g. (38%) of II. Recrystallization was from ethanol–water, m.p. 83–86°. Concentration of the mother liquor yielded 1.0 g. (7%) of a second compound, m.p. 62–65°, tentatively identified as 3-phenyl-5-(2-butynyloxy)-oxazin-2-one.

Procedure B: Epoxide–Isocyanate Method—The same procedure was followed as for I except that the oil bath was maintained at 145–150° throughout. The pot residue, after removal of dimethylformamide, was diluted with 40 ml. carbon tetrachloride; lithium chloride was removed by filtration. After concentrating to 25 ml. and cooling at 5°, 12.8 g. (85%) of II was isolated. The product was recrystallized from ethanol–water, m.p. 83–85°.

Anal.—Calc. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.46; H, 6.23; N, 5.67.

3-Phenyl-5-{[(1-ethynylcyclohexyl)oxy]methyl}-2-oxazolidinone (III)—Following Procedure B for II, 6.1 g. (0.034 mole) of 2-{[(1-ethynylcyclohexyl)oxy]methyl}oxirane, 4.1 g. (0.034 mole) of freshly distilled phenylisocyanate, and 0.5 g. lithium chloride were reacted. Following workup in carbon tetrachloride and recrystallization from methanol, 7.3 g. of III was obtained (72%), m.p. 70–72°.

Anal.—Calc. for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.07; H, 7.12; N, 4.61.

3-Phenyl-5-{[(3-phenyl-2-propynyl)oxy]methyl}-2-oxazolidinone (IV)—Following Procedure B for II, 10 g. (0.053 mole) of 2-{[(3-phenyl-2-propynyl)oxy]methyl}oxirane, 6.55 g. (0.055 mole) of freshly distilled phenylisocyanate, and 0.4 g. of lithium chloride were reacted. Following workup and crystallization from ethanol, 12.5 g. of IV was isolated (77%), m.p. 70–73°.

Anal.—Calc. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.37; H, 5.70; N, 4.52.

3-Methyl-5-[(2-propynyloxy)methyl]-2-oxazolidinone (V)—To a 250-ml. flask containing 20 g. (0.180 mole) of 1,2-epoxy-3-propargyloxypropane and 75 ml. dry dimethylformamide at 130° was added 1.0 g. lithium chloride, followed immediately by the slow addition (1 drop every 6–7 sec.) of a solution of 10.5 g. (0.184 mole) freshly distilled methylisocyanate in 18 ml. dry dimethylformamide. After 6 hr., dimethylformamide was removed (vacuum aspirator at 130°), the resulting oil was diluted with ethylene chlo-

Table II—Anticancer Activity

Compound	NSC Number	Tumor	Dosages[a]	Vehicle[b]	Percent T/C	Survivors
I	154295	L-1210	400	M	91	4/6
			200	M	100	6/6
			100	M	100	6/6
		P-388	400	M	100	6/6
			200	M	100	6/6
			100	M	95	6/6
II	159150	P-388	400	S	100	7/7
			200	S	92	7/7
			100	S	92	7/7
III	159151	P-388	400	S	100	7/7
			200	S	100	7/7
			100	S	100	7/7
IV	159149	P-388	400	S	92	7/7
			200	S	107	7/7
			100	S	92	7/7

[a] mg./kg. i.p. (per injection). [b] M is hydroxypropylcellulose; S is saline.

ride, and the lithium chloride was removed. After removal of the solvent, the oil was fractionally distilled to yield 22 g. (73%) of V, b.p. 122° (0.02 mm.).

Anal.—Calc. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.27. Found: C, 56.61; H, 6.64; N, 8.21.

3-Methyl-5-[(2-butynyloxy)methyl]-2-oxazolidinone (VI)—A 50-ml. flask was equipped with a pressure-equalizing dropping funnel and a reflux condenser topped with a clamped rubber tube slit longitudinally for release of pressure. To this was added 4.2 g. (0.033 mole) of 2-[(2-butynyloxy)methyl]oxirane and 13 ml. of dry dimethylformamide. The solution was heated to 130° and 0.2 g. of lithium chloride was added, followed immediately by the slow addition (less than 1 drop every 6 sec.) of 2.0 g. (0.035 mole) of freshly distilled methylisocyanate in 3.5 ml. dry dimethylformamide. After 6 hr. at 130°, solvent was removed and the oil was diluted with methylene chloride; the lithium chloride was removed. The oil was distilled to give 4.3 g. of VI (70%), b.p. 110–125° (0.08 mm.).

Anal.—Calc. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64. Found: C, 58.81; H, 7.28; N, 7.57.

RESULTS AND DISCUSSION

The isocyanate–epoxide reaction provides high yield quantities of the title compounds and represents a method by which a variety of *N*-alkyl-2-oxazolidinones can be readily synthesized. Attempts to cyclize β-chloroethyl *N*-unsubstituted carbamates with several bases (potassium hydroxide–ethanol and sodium hydride–dimethylformamide) failed. Stronger bases are precluded because of the known ease of rearrangement of propargyl groups to allenes (11).

With the isocyanate–epoxide reaction, only C-5 substitution products were obtained; no C-4 products were isolated. Thus, the stereospecific nature of this reaction in the synthesis of the title compounds is apparently independent of π-electron interactions between isocyanate and acetylene π-electrons. From the work of Herweth *et al.* (6), such π-interactions might have been hypothesized for their isolation of C-4 as well as C-5 substitution products. That C-5 substitution appears exclusive in the present study is probably a result only of steric factors.

Compounds I–IV, the *N*-phenyl analogs, exhibited no anticancer activity against the L-1210 or P-388 tumor test systems employed. Based on reports preliminary to receiving testing data, the *N*-methyl Compounds V and VI are inactive as well. Activity is defined as percent T/C (test/control) of 125 or greater.

The lack of activity of the title compounds in the less sensitive L-1210 and P-388 tumor systems cannot be adequately explained at this time. The possibility exists that cyclic carbamates possess *in vivo* reactivities to nucleophiles significantly different from acyclic carbamates. Whether this or other physical–chemical and biological factors are important remains unanswered.

REFERENCES

(1) R. B. Dillard, G. Poore, D. R. Cassady, and N. R. Easton, *J. Med. Chem.*, **10**, 40(1967).

(2) "The Pharmacological Basis of Therapeutics," 3rd ed., L. S. Goodman and A. Gilman, Eds., Macmillan, New York, N. Y., 1965, chap. 10, p. 136.

(3) J. A. Montgomery, R. James, G. S. McCaleb, and T. P. Johnston, *J. Med. Chem.*, **10**, 668(1967).

(4) W. H. Heine, *Angew. Chem. Int. Ed. Engl.*, **1**, 528(1962).

(5) H. Flores-Gullardo and C. B. Pollard, *J. Org. Chem.*, **12**, 831(1947).

(6) J. E. Herweth, T. A. Foglia, and D. Swern, *ibid.*, **33**, 4029 (1968).

(7) R. Adams and J. B. Segur, *J. Amer. Chem. Soc.*, **45**, 785 (1923).

(8) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197(1967).

(9) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).

(10) C. Douzon, C. Fouran, G. Raynaud, G. Huguet, and C. Couret, German pat. 1,803,186 (1969); through *Chem. Abstr.*, **71**, P91460e(1969).

(11) T. F. Rutledge, "Acetylenes and Allenes," Part Two, Reinhold, New York, N. Y., 1969, p. 35.

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