Antitumor Agents VIII: Synthesis and Cytotoxic Activity of *O,O'*-Bis(acrylyl)-α,ω-alkanediols

KUO-HSIUNG LEE*[x], SUN-HYUK KIM*, CLAUDE PIANTADOSI*, ENG-SHANG HUANG‡, and T. A. GEISSMAN§

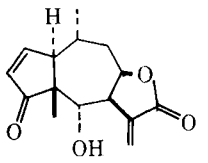
Abstract □ A short series of *O,O'*-bis(acrylyl)-α,ω-alkanediols was prepared to evaluate the potential significance of the O=C—C=CH_2 system for cytotoxic activity against the growth of tissue culture cells originating from human epidermoid carcinoma of larynx (HEp-2). These compounds showed significant cytotoxic activity; however, the chain length bridging the two O=C—C=CH_2 systems appeared to have no effect on cytotoxicity. Several *O,O'*-bis(β-bromopropionyl)-α,ω-alkanediols were prepared, tested, and found to have marginal cytotoxicity.

Keyphrases □ *O,O'*-Bis(acrylyl)-α,ω-alkanediols—synthesized as possible antitumor agents, cytotoxicity evaluated □ Helenalin analogs—synthesized as possible antitumor agents, cytotoxicity evaluated □ Antitumor agents, potential—synthesis and cytotoxic activity of *O,O'*-bis(acrylyl)-α,ω-alkanediols

In previous studies (1–3), the most immediate and direct factor responsible for cytotoxicity among the sesquiterpene lactones was the introduction of the O=C—C=CH_2 system, whether it be in the lactone or ketone. Additional alkylating groups appear to enhance cytotoxicity significantly (4, 5). In an effort to evaluate these hypotheses, several bisacrylyl esters (II*a*–II*e*) were prepared as bifunctional alkylating open-chain analogs related to helenalin (I).

DISCUSSION

The desired new bifunctional alkylating agents (II*a*–II*e*) (Table I) were best synthesized by dehydrobromination of *O,O'*-bis(β-bromopropionyl)-α,ω-alkanediols (III*a*–III*e*) (Table II), which were obtained by reaction of diols with β-bromopropionyl chloride (IV). Compound IV was prepared by refluxing β-bromopropionic acid (V) with thionyl chloride (Scheme I). Since all of these bisacrylyl derivatives (II*a*–II*e*) were unstable at room temperature, traces of *p*-hydroquinone were added to prevent polymerization.



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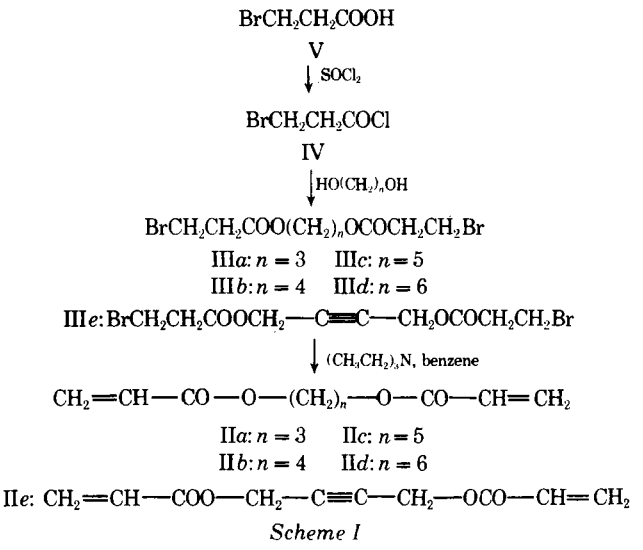

Scheme I

Compounds II*a*–II*e* and III*a*–III*e* were assayed for inhibitory activity *in vitro* against cells originating from human epidermoid carcinoma of larynx (HEp-2), according to a rapid microtiter method previously described (6). A comparison of the ED_{50} values for the cytotoxicity of the compounds listed in Table I indicated that the monofunctional alkylating acrolein and ethyl acrylate were inactive, whereas the bifunctional alkylating derivatives (II*a*–II*e*) were about equally active although they were about 7–10 times less active in comparison with helenalin (I). These findings are in agreement with the previous hypotheses indicating that the structural requirement for significant cytotoxicity is to

Table I—*O,O'*-Bis(acrylyl)-α,ω-alkanediols

Compound	Melting Point	Analysis[a], % Calc.	Found	IR[b]	NMR[c]	ED_{50}, μg/ml (HEp-2)
II*a*	—[d]	—[e]		—[f]	2.08 (2H, q, J = 6.0, OCH_2CH_2) 4.30 (4H, t, J = 6.0, OCH_2)[g]	0.84
II*b*	—[d]	C 60.59 H 7.12	60.54 7.21	—[f]	1.80 (4H, m, OCH_2CH_2) 4.22 (4H, m, OCH_2)[g]	0.89
II*c*	—[d]	C 62.25 H 7.60	61.77 7.70	—[f]	1.62 (6H, m, OCH_2CH_2) 4.28 (4H, m, OCH_2)[g]	0.77
II*d*[h]	—[d]	C 63.70 H 8.20	63.65 8.08	—[f]	1.55 (8H, m, OCH_2CH_2) 4.20 (4H, m, OCH_2)[g]	0.95
II*e*[i]	—[d]	C 61.85 H 5.19	61.77 5.20	1735, 1745, 1640 cm^{-1}	4.81 (4H, s, OCH_2) 5.75–6.72 (6H, m, olefinic protons)	0.76
Acrolein[j], CH_2=CH—CHO						>20
Ethyl acrylate[j], CH_2=CH—$COOCH_2CH_3$						>20
Mechlorethamine hydrochloride[k]						0.33
Helenalin 170–172° (Ref. 5)						0.10

[a] Performed by Atlantic Microlab, Inc. [b] Determined in liquid film with a Perkin-Elmer 257 grating IR spectrophotometer. [c] Measured in $CDCl_3$ with a Jeolco C 60 HL NMR spectrometer, using tetramethylsilane as an internal standard. Chemical shifts are reported in δ units (parts per million); s refers to singlet, t to triplet, q to quintet, and m to multiplet, and the J values are in hertz. [d] Oil. [e] The attempted analysis of this compound was unsuccessful because of rapid polymerization at room temperature. [f] Showed IR absorption maxima at 1725 (C=O) and 1635 and 1618 (C=C) cm^{-1}. [g] 5.72–6.78 (6H, m, olefinic protons). [h] Reference 7 reported the synthesis of this compound in 27% yield. [i] Reference 8 reported the synthesis of this compound in 18% yield. [j] Aldrich Chemical Co., Milwaukee, Wis. [k] Sigma Chemical Co., St. Louis, Mo.

Table II—*O,O'*-Bis(β-bromopropionyl)-α,ω-alkanediols

Compound	Melting Point	Yield, %	Analysis[a], % Calc.	Found	IR[b]	NMR[c]	ED_{50}, μg/ml (HEp-2)
III*a*	—[d]	75	C 31.23 H 4.07	31.48 4.19	—[e]	2.02 (2H, q, J = 6.0, OCH_2CH_2) 4.25 (4H, t, J = 6.0, OCH_2)[f,g]	7.17
III*b*	—[d]	80	C 33.35 H 4.47	33.56 4.57	—[e]	1.75 (4H, m, OCH_2CH_2)[f,g,h]	5.20
III*c*	—[d]	90	C 35.31 H 4.85	35.49 4.93	—[e]	1.58 (6H, m, OCH_2CH_2)[f,g,h]	4.76
III*d*	—[d]	90	C 37.13 H 5.19	37.21 5.28	—[e]	1.50 (8H, m, OCH_2CH_2)[f,g,h]	5.80
III*e*	—[d]	90	C 33.73 H 3.39	33.61 3.37	—[e]	3.55 (4H, t, J = 6.0, $BrCH_2$) 4.75 (4H, s, OCH_2)[f]	2.36
III*g*[i], $BrCH_2CH_2COOCH_2CH_3$							>20

[a] Performed by Atlantic Microlab, Inc. [b] Determined in liquid film with a Perkin-Elmer 257 grating IR spectrophotometer. [c] Measured in $CDCl_3$ with a Jeolco C 60 HL NMR spectrometer, using tetramethylsilane as an internal standard. Chemical shifts are reported in δ units (parts per million); s refers to singlet, t to triplet, q to quintet, and m to multiplet, and the J values are in hertz. [d] Oil. [e] Showed IR absorption maximum at 1740 cm^{-1} (C=O). [f] 2.95 (4H, t, J = 6.0, CH_2CO). [g] 3.60 (4H, t, J = 6.0, $BrCH_2$). [h] 4.18 (4H, m, OCH_2). [i] Aldrich Chemical Co., Milwaukee, Wis.

have an O=C—C=CH_2 system as the active alkylating center, especially when two of these systems are linked together. The chain length bridging these two systems does not appear to affect cytotoxicity among the compounds studied (II*a*–II*e*). The marginal cytotoxicity exhibited by III*a*–III*e* (Table II) suggests that there might be a dehydrogenation or dehydrobromination reaction for these compounds to take place in tissue culture cells. The dehydrogenated or dehydrobrominated products might act in a manner analogous to II*a*–II*e*. The monofunctional bromoester (III*g*) was completely inactive. Pipobroman [1,4-bis(3-bromopropionyl)-piperazine, NSC-25154], which has two N—$COCH_2CH_2Br$ moieties, is listed in the National Cancer Institute compilation[1] of "Drugs Active in Clinical Cancer."

EXPERIMENTAL

General Synthetic Method for *O,O'*-Bis(β-bromopropionyl)-α,ω-alkanediols (III*a*–III*e*)—Diols (1 mmole) were added dropwise to β-bromopropionyl chloride (2 mmoles) with stirring in an ice bath, and the resulting mixture was heated to 70° for 5 hr. Ether was then added, and the mixture was washed with 1% sodium bicarbonate and water, dried over anhydrous sodium sulfate, and distilled *in vacuo*, leaving a viscous oily product which was purified by column chromatography on silica gel[2] by elution with benzene.

General Synthetic Method for *O,O'*-Bis(acrylyl)-α,ω-alkanediols (II*a*–II*e*)—To III*a*–III*e* (1 mmole) in dry benzene (5 ml) was added triethylamine (3 mmoles) and a small amount of *p*-hydroquinone (~1% of the reactants). The mixture was refluxed for 18–20 hr. The solid triethylamine salt, which separated upon cooling, was filtered and the filtrate was evaporated *in vacuo*. The product was purified in benzene by passing through a column (1.3 × 3 cm) of silica gel[2] to furnish the quantitative yield of II*a*–II*e*, which was rapidly stabilized by addition of traces of *p*-hydroquinone. TLC [silica gel[3] G developed with chloroform–acetone (3:1)], IR, and NMR data indicated that these esters (II*a*–II*e*) were homogeneous.

[1] *Chemotherapy*, Sept. 1971.
[2] Baker A.R. No. 3405.
[3] Merck.

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[x] To whom inquiries should be directed.