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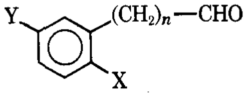
Substituted Aralkyl Aldehydes: Preparation and Antitumor Evaluation

JOHN H. BILLMAN and JOHN A. TONNIS*

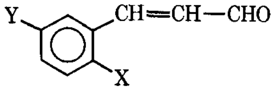
Abstract ☐ A series of substituted aralkyl aldehydes—substituted phenylacetaldehydes, hydrocinnamaldehydes, and cinnamaldehydes—was prepared and tested for antitumor activity. The substituted phenylacetaldehydes were prepared from the corresponding benzaldehydes *via* the Darzen glycidic ester synthesis, followed by hydrolysis and decarboxylation. The dihydrocinnamaldehydes were prepared by the lead tetraacetate oxidation of the corresponding alcohols. The cinnamaldehydes were prepared from the substituted benzaldehydes by reaction with ethyl vinyl ether. All intermediates in the preparation of the aralkyl aldehydes were also screened for antitumor activity.

Keyphrases ☐ Antitumor activity evaluation—substituted aralkyl aldehydes ☐ Phenylacetaldehydes, substituted—synthesis, antitumor activity evaluation ☐ Hydrocinnamaldehydes, substituted—synthesis, antitumor activity evaluation ☐ Cinnamaldehydes, substituted—synthesis, antitumor activity evaluation

A considerable number of aliphatic and aromatic aldehydes and their derivatives were shown to possess appreciable antitumor activity (1–6). Several of these aldehydes and their derivatives were also used in the clinic as antitumor agents (7–9). All of the aldehydes that have shown activity have been alkyl or aromatic aldehydes. No substituted aralkyl aldehydes of general types I and II have been tested as antitumor agents and, indeed, few have even been synthesized.



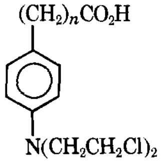
I



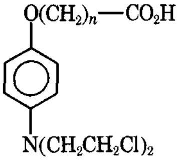
II

$n = 1$–2
X = OH, OCH_3, $-OCOCH_3$
Y = electron-donating or withdrawing groups

Various studies showed that the length of the alkyl chain in aralkyl compounds similar to I and II plays an important role in the antitumor activity. Some investigators (10–12) prepared a series of *N*,*N*-bis(2-chloroethyl)phenylalkanoic acids (III) and *N*,*N*-bis-(2-chloroethyl)phenoxyalkanoic acids (IV).



III



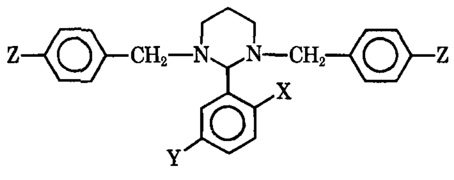
IV

$n = 0$–3

In type III compounds, they found that when *n* is 0, the compound was only slightly active; as *n* increased the activity likewise increased rapidly and reached a maximum at $n = 3$. The compound of Structure III, when *n* is 3, is called chlorambucil and has been used clinically for treatment of chronic lymphocytic leukemia (13, 14).

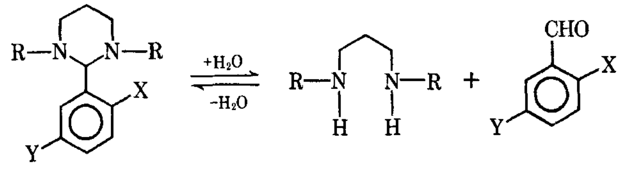
Type IV compounds also show the same increase of activity as the alkyl chain length increases and reaches a maximum when *n* is 2.

This relationship of antitumor activity to alkyl chain length has been demonstrated on other compounds similar to type I and II compounds.



V

X = OH, OCH_3
Y = electron-donating or withdrawing groups
Z = OCH_3, $-N(CH_3)_2$, $-N(CH_2CH_2Cl)_2$



Scheme I

This variance of the activity with the length of the alkyl side chain may also be operative in aralkyl aldehydes of general types I and II. If so, the antitumor activity of aldehydes of types I and II should be greater than that of the corresponding substituted benzaldehydes.

It was previously found that many hexahydropyrimidines (V) show extremely high antitumor activity (15). The hexahydropyrimidines can be looked upon as aldehyde derivatives which are extremely susceptible to hydrolysis, releasing the free aldehyde according to Scheme I.

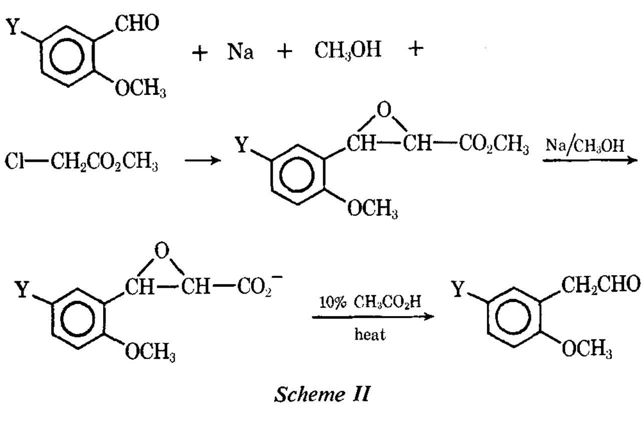
The hexahydropyrimidine may be serving as a carrier for the aldehyde which, upon hydrolysis, liberates the free aldehyde at the tumor site. Thus, part of the high activity may be due to the liberation of the free aldehyde at the slightly acidic tumor site.

The aralkyl aldehydes of type I, when *n* is 1 (substituted phenylacetaldehydes), were prepared from the corresponding substituted benzaldehydes using Darzen's glycidic ester synthesis, followed by hydrolysis of the ester and decarboxylation of the acid intermediate (Scheme II).

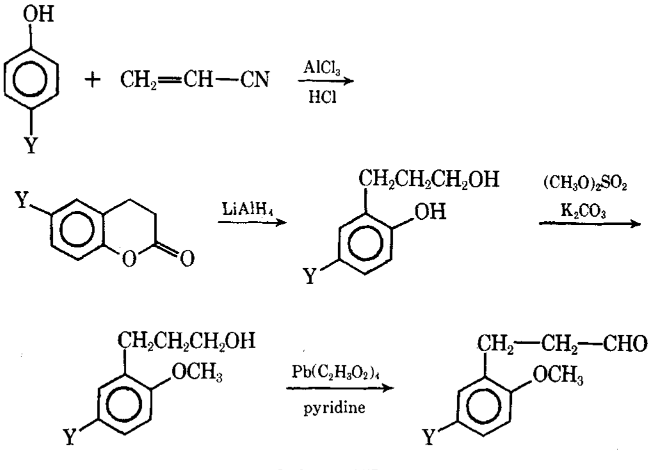
The decarboxylation of the intermediate glycidic acid gave a higher yield of the aldehyde when an equal molar quantity of 10% aqueous acetic acid was used than when using an equal molar quantity of glacial acetic acid.

The yield of the aldehyde was very dependent on the nature of the substituent Y. If Y was an electron-donating group, a good yield of the aldehyde was obtained. When Y was a strong electron-withdrawing group (—NO_2) or two chloro groups such as (3,5-dichloro-), the glycidic acid would not decarboxylate even at elevated temperatures.

Aldehydes of type I, where *n* is 2 (dihydrocinnamaldehydes), were prepared from the corresponding *p*-substituted phenols according to Scheme III. The 6-substituted dihydrocoumarins were prepared according to the procedure of Sato *et al.* (16). The alcohols were oxidized to the aldehydes in generally good yields, using a procedure similar to the one of Partch (17). The 5-acetyl-2-methoxyhydrocinnamyl alcohol could not be oxidized to the hydrocinnamaldehyde using this reagent.



Scheme II



Scheme III

The substituted cinnamaldehydes of type II were prepared from the corresponding substituted benzaldehydes according to Scheme IV (18).

The preparation of cinnamaldehydes of type II, which contain the *o*-phenolic group, is somewhat complicated by the presence of the phenol group. The phenol group must be protected as the acetate before reaction with the ethyl vinyl ether. The acetate-protecting group can then be removed by anhydrous Na/CH_3OH hydrolysis.

BIOLOGICAL DATA

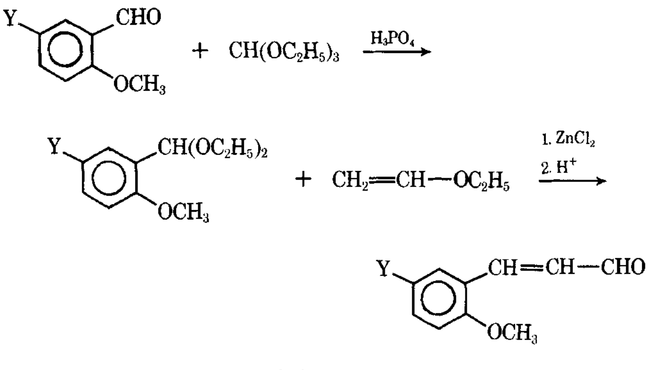
These compounds were screened primarily against the tumor system leukemia L-1210[1], for which they did not show significant antitumor activity.

EXPERIMENTAL[2]

Methyl-3-(3,5-disubstituted-2-methoxyphenyl)glycidates—These were prepared according to the procedure of Henecka (19) (Table I).

5-Substituted-2-methoxyphenylacetaldehydes—These were prepared according to the procedure of Ban and Oishi (20) (Table II).

6-Nitrodihydrocoumarin—This was prepared according to the procedure of Ingle and Bhide (21).



Scheme IV

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[1] By the Cancer Chemotherapy National Service Center, National Institutes of Health.

[2] The starting 5-substituted salicylaldehydes were purchased from either Aldrich Chemical Co. or Eastman Organic Chemicals. Melting points, obtained on a Thomas-Hoover apparatus, are uncorrected. Microanalyses were carried out by Midwest Microlab, Indianapolis, Ind., and Alfred Bernhardt, Muhlheim, Germany.

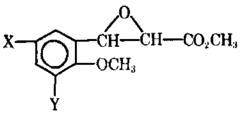


Table I—Methyl-3-(3,5-disubstituted-2-methoxyphenyl)glycidates

X	Y	Yield, %	Melting or Boiling Point	Formula	Analysis, % Calc.	Analysis, % Found	IR, μ(C=O)
H	H	79	49–50.5°	$C_{11}H_{12}O_4$	C, 63.45 H, 5.77	C, 63.94 H, 5.92	5.74
Cl	H	70	58–59.5°	$C_{11}H_{11}ClO_4$	C, 54.44 H, 4.57	C, 54.69 H, 4.71	5.73
Br	H	66	68–69.5°	$C_{11}H_{11}BrO_4$	C, 46.01 H, 3.86	C, 46.28 H, 4.12	5.74
—OCH$_3$	H	70	161–163°/0.3 mm.	$C_{12}H_{14}O_5$	C, 60.50 H, 5.92	C, 60.11 H, 6.27	5.78
NO$_2$	H	37	144–145°	$C_{11}H_{11}NO_6$	C, 52.17 H, 4.38	C, 52.23 H, 4.37	5.82
Cl	Cl	69	84–85°	$C_{11}H_{10}Cl_2O_4$	C, 47.68 H, 3.64	C, 47.96 H, 3.93	5.77

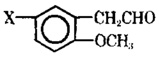


Table II—5-Substituted-2-methoxyphenylacetaldehydes

X	Yield, %	Boiling Point	Formula	Analysis, % Calc.	Analysis, % Found	IR, μ(C=O)
H	66	65–67°/0.3 mm.	$C_9H_{10}O_2$	C, 71.98 H, 6.71	C, 71.98 H, 6.72	5.82
Cl	45	115–117°/0.6 mm.	$C_9H_9ClO_2$	C, 58.55 H, 4.91	C, 58.63 H, 5.04	5.80
Br	47	124–126°/0.5 mm.	$C_9H_9BrO_2$	C, 47.18 H, 3.96	C, 47.12 H, 3.95	5.81
—OCH$_3$	22	112–113°/0.7 mm.	$C_{10}H_{12}O_3$	C, 66.65 H, 6.72	C, 66.62 H, 6.71	5.82

6-Bromodihydrocoumarin—This was prepared according to the procedure of Barnes *et al.* (22).

6-Substituted Dihydrocoumarins—The other 6-substituted dihydrocoumarins were prepared according to the procedure of Sato *et al.* (16).

5-Substituted-2-hydroxyhydrocinnamyl Alcohols—By use of a continuous extraction apparatus, 36.3 g. (0.18 mole) of 6-bromodihydrocoumarin was added to a refluxing suspension of 6.70 g. (0.18 mole) of lithium aluminum hydride in 400 ml. of diethyl ether. After complete addition (6 hr.), the mixture was refluxed an additional 1 hr. and the excess reducing agent was destroyed by the addition of water. The resulting mixture was poured into 300 ml. of cold 4 *N* sulfuric acid. The ether layer was separated, and the aqueous layer was extracted with ether. The ether extracts were combined and dried over anhydrous sodium sulfate, and the ether was removed *in vacuo*. The resulting white solid was recrystallized from benzene, yielding a white solid (Table III).

5-Substituted-2-methoxyhydrocinnamyl Alcohols—To a warm (80°) solution of 5-bromo-2-hydroxyhydrocinnamyl alcohol (23.1 g., 0.1 mole), dissolved in 80 ml. of 10% NaOH solution, was added dropwise 25.2 g. (0.2 mole) of dimethyl sulfate. After complete addition, the reaction mixture was heated at 90° for 3 hr., then rendered basic by the addition of 50 ml. of 10% NaOH solution, and then heated at 90° for an additional 30 min. The mixture was extracted with diethyl ether, and the ether extracts were dried over sodium sulfate. Removal of the ether *in vacuo* gave a light-yellow oil, which was distilled under reduced pressure. The pure product was obtained as a clear oil (Table IV).

5-Substituted-2-methoxyphenylhydrocinnamaldehydes—To a cooled (5°) solution of 12.3 g. (0.05 mole) of 5-bromo-2-methoxyhydrocinnamyl alcohol dissolved in 150 ml. of anhydrous pyridine was added 22.2 g. (0.05 mole) of lead tetraacetate. The resulting dark-red mixture was stirred at 5° for 4 hr. and then at 25° for 20 hr. The pyridine was removed *in vacuo*. The resulting brown residue was extracted with three 150-ml. portions of diethyl ether. The ether extracts were dried over anhydrous Na_2SO_4, and the ether was removed *in vacuo*. The resulting brown liquid was fractionally distilled under reduced pressure, and the fraction boiling at 124°/0.5 mm. was collected. The aldehyde was obtained as a clear liquid (Table V).

5-Acetyl-2-methoxyhydrocinnamyl Alcohol—A mixture of 2-methoxyhydrocinnamyl alcohol (16.6 g., 0.1 mole), acetic anhydride (20.4 g., 0.20 mole), and $ZnCl_2$ (0.1 g.) was heated at gentle reflux for 6 hr. After cooling, the reaction mixture was poured into 400 ml. of cold water. The oil, which separated, was extracted with four 150-ml. portions of diethyl ether. The ether extracts were washed with saturated $NaHCO_3$ solution and then with water. The ether extracts were dried over anhydrous sodium sulfate, and the ether was re-

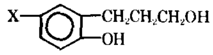
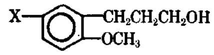


Table III—5-Substituted-2-hydroxyhydrocinnamyl Alcohols

X	Yield, %	Melting or Boiling Point	Formula	Analysis, % Calc.	Analysis, % Found
H	95	177–179°/12 mm.	$C_9H_{12}O_2$[a]		
Cl	94	79–80°	$C_9H_{11}ClO_2$	C, 57.91 H, 5.95	C, 58.09 H, 5.94
Br	88	86–87°	$C_9H_{11}BrO_2$	C, 46.77 H, 4.76	C, 46.96 H, 5.05
CH$_3$	92	145–147°/1 mm.	$C_{10}H_{14}O_2$[b]		
OCH$_3$	94	63–65°	$C_{10}H_{14}O_3$	C, 65.91 H, 7.74	C, 65.96 H, 7.67

[a] *J. Chem. Soc.*, **1939**, 787. [b] *J. Amer. Chem. Soc.*, **62**, 3067(1940).

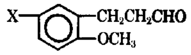
Table IV—5-Substituted-2-methoxyhydrocinnamyl Alcohols



X	Yield, %	Melting or Boiling Point	Formula	Analysis, %	
				Calc.	Found
H	86	84–87°/0.2 mm.	$C_{10}H_{14}O_2$[a]		
Cl	91	108–111°/0.2 mm.	$C_{10}H_{13}ClO_2$	C, 59.85 H, 6.53	C, 59.49 H, 6.62
Br	85	124–127°/0.4 mm.	$C_{10}H_{13}BrO_2$	C, 49.00 H, 5.34	C, 49.39 H, 5.40
—CH_3	84	96–99°/0.4 mm.	$C_{11}H_{16}O_2$	C, 73.28 H, 8.98	C, 73.58 H, 8.86
—OCH_3	82	105–108/0.1 mm.	$C_{11}H_{16}O_3$	C, 67.32 H, 8.22	C, 67.54 H, 8.02
—$COCH_3$	88	46.5–48°	$C_{12}H_{16}O_3$	C, 69.27 H, 7.75	C, 69.40 H, 7.57

[a] *J. Chem. Soc.*, **1939**, 787.

Table V—5-Substituted-2-methoxyphenylhydrocinnamaldehydes



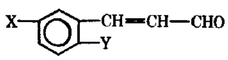
X	Yield, %	Boiling Point	Formula	Analysis, %		IR, μ(C=O)
				Calc.	Found	
H	57	77–80°/0.4 mm.	$C_{10}H_{12}O_2$	C, 67.32 H, 8.22	C, 67.54 H, 8.02	5.83
Cl	42	115–116°/0.5 mm.	$C_{10}H_{11}ClO_2$	C, 60.46 H, 5.58	C, 60.65 H, 5.72	5.81
Br	54	120–124°/0.5 mm.	$C_{10}H_{11}BrO_2$	C, 49.40 H, 4.56	C, 49.71 H, 4.89	5.80
$COCH_3$	31		$C_{12}H_{14}O_3$	C, 69.88 H, 6.84	C, 69.72 H, 7.01	5.82 (aldehyde) 5.98 (ketone)
—CH_3	52	108–111°/0.2 mm.	$C_{11}H_{15}O_2$	C, 74.13 H, 7.92	C, 73.98 H, 8.00	5.82
—OCH_3	28	114–115°/0.2 mm.	$C_{11}H_{15}O_3$	C, 68.02 H, 7.26	C, 68.28 H, 7.25	5.82

moved *in vacuo*. The resulting brown oil was distilled *in vacuo*, giving the 5-acetyl-2-methoxyhydrocinnamyl acetate as a clear oil. The acetate ester and 100 ml. of 10% NaOH were heated at gentle reflux for 5 hr. The mixture was extracted with diethyl ether, and the ether extracts were dried over anhydrous sodium sulfate. Removal of the ether gave an oil which was distilled under reduced pressure. The product was obtained as a clear oil which crystallized to a white solid.

5-Substituted-2-methoxycinnamaldehydes—A mixture of 5-bromo-2-methoxybenzaldehyde (18.0 g., 0.084 mole), triethyl orthoformate (13.6 g., 0.092 mole), and 0.2 ml. of 85% phosphoric acid was stirred at 25° under a nitrogen atmosphere for 24 hr. The resulting diethyl acetal was cooled to 0°, and 2.2 ml. of 10% $ZnCl_2$–ethyl acetate solution was added. Freshly distilled ethyl vinyl ether (12.2 g., 0.17 mole) was then added dropwise at a rate to maintain the temperature below 0°. After complete addition, the solution was stirred at room temperature for 12 hr. A solution of 83 ml. of glacial acetic acid, 8.7 g. of sodium acetate, and 7.7 ml. of water was added, and the solution was heated at 95° for 2 hr. The solution was then poured into 700 ml. of cold water where a brown solid formed. Recrystallization of the solid from a 1:1 benzene–petroleum ether mixture gave the product as a light-yellow solid (Table VI).

5-Substituted-2-acetoxycinnamaldehydes—To a cooled solution (0°) of 5-methoxysalicylaldehyde (38.0 g., 0.25 mole) in 100 ml. of

Table VI—2,5-Disubstituted Cinnamaldehydes



Y	X	Yield, %	Melting Point	Formula	Analysis, %		IR, μ(C=O)
					Calc.	Found	
OCH_3	H	75	46–47°	$C_{10}H_{10}O_2$[a]			5.99
OCH_3	Cl	65	78–79.5°	$C_{10}H_9ClO_2$	C, 61.08 H, 4.61	C, 60.93 H, 4.62	6.02
OCH_3	Br	54	89–90.5°	$C_{10}H_9BrO_2$	C, 49.81 H, 3.73	C, 50.07 H, 3.87	5.97
OCH_3	NO_2	40	143–144°	$C_{10}H_9NO_4$	C, 57.97 H, 4.38	C, 58.17 H, 4.61	5.98
OCH_3	OCH_3	59	86–87°	$C_{11}H_{12}O_3$	C, 68.45 H, 6.69	C, 68.38 H, 6.40	6.00
$OCOCH_3$	H	63	81–82°	$C_{11}H_{10}O_3$	C, 69.41 H, 5.30	C, 69.60 H, 5.07	5.76 (ester) 6.01 (aldehyde)
$OCOCH_3$	Cl	47	112–113.5°	$C_{11}H_9ClO_3$	C, 58.81 H, 4.04	C, 58.65 H, 4.14	5.71 (ester) 5.98 (aldehyde)
$OCOCH_3$	OCH_3	63	70.5–71.5°	$C_{12}H_{12}O_4$	C, 65.44 H, 5.45	C, 65.34 H, 5.46	5.71 (ester) 5.96 (aldehyde)
OH	H	88	132–133°	$C_9H_8O_2$[a]			6.02
OH	Cl	87	155–156°	$C_9H_7ClO_2$	C, 59.20 H, 3.87	C, 59.48 H, 3.88	6.05
OH	OCH_3	85	124–125°	$C_{10}H_{10}O_3$	C, 67.96 H, 5.66	C, 68.13 H, 5.89	6.03

[a] *Ber.*, **56**, 606(1923).

pyridine was added slowly 25.5 g. (0.25 mole) of acetic anhydride. The solution was stirred at 0° for 5 hr. and diluted with 1.0 l. of cold water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The organic layer and ether extracts were combined and dried over anhydrous Na_2SO_4, and the ether was removed *in vacuo*. The resulting yellow oil was distilled *in vacuo*, and the collected fraction distilled at 113–116°/0.2 mm. The 2-acetoxy-5-methoxybenzaldehyde was collected as a white solid (TableVI).

2-Acetoxy-5-substituted Cinnamaldehydes—The procedure described for 5-substituted-2-methoxycinnamaldehydes was followed.

5-Substituted-2-hydroxycinnamaldehydes—To a cooled (10°) solution of 2-acetoxy-5-methoxycinnamaldehyde (6.6 g., 0.03 mole) in 60 ml. of $CHCl_3$ was added a solution of Na (0.69 g., 0.03 mole) in 25 ml. of CH_3OH. After complete addition (30 min.), the solution was stirred at 10° for 15 min. and then at room temperature for 1 hr. The reaction mixture was diluted with 100 ml. of water, and the $CHCl_3$ layer was separated. The aqueous layer was rendered acidic by the addition of dilute H_2SO_4. The solid that formed was collected and washed thoroughly with water. Recrystallization from benzene gave the product as a bright-yellow solid (Table VI).

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Triazenes of Phenylbutyric, Hydrocinnamic, Phenoxyacetic, and Benzoylglutamic Acid Derivatives

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Abstract □ *p*-Dialkyltriazeno derivatives of the ethyl esters and acid hydrazides of phenylbutyric, hydrocinnamic, phenoxyacetic, and benzoylglutamic acids were synthesized. The triazenophenylbutyric acid derivatives are structurally related to chlorambucil, and the hydrocinnamic and phenoxyacetic acid derivatives are related to other antineoplastic aromatic nitrogen mustards. All of the triazeno groups contained unsubstituted alkyl groups (except for a hydroxyethyl group in a derivative of benzoylglutamic acid). In initial tests of these compounds *versus* mouse lymphatic leukemia L-1210, ethyl *p*-(3-butyl-3-methyl-1-triazeno)hydrocinnamate (VI*b*) was the most effective compound in increasing the survival time of treated animals. Certain other hydrocinnamic and phenylbutyric acid derivatives caused small increases in survival time.

Keyphrases □ Triazenes of phenylbutyric, hydrocinnamic, phenoxyacetic, and benzoylglutamic acid esters and hydrazides—synthesis, antileukemic activity □ Antileukemic activity—*p*-dialkyltriazene derivatives

After antineoplastic activity was found among triazenoimidazoles (*e.g.*, 1, 2), it seemed reasonable to suppose that combining substituted triazeno groups with structural moieties that can presumably serve as carrier groups might also produce derivatives having antineoplastic activity. Studies of aromatic nitrogen mustards included a series of phenylalkanoic acid derivatives. Of the initial series, chlorambucil, 4-{*p*-[bis(2-chloroethyl)-amino]phenyl}butyric acid, was the most effective derivative in inhibiting the transplanted Walker rat carcinoma (3, 4) and proved to be a clinically useful agent (*e.g.*, 5, 6). The enhanced activity of chlorambucil was attributed (3, 4) to the constitution of its phenylbutyric acid moiety rather than to its chemical reactivity or physical properties, and the phenylbutyric acid portion was used as a carrier for other cytotoxic groups (7).

Nitrogen mustard derivatives of hydrocinnamic acid (3) and of phenoxyalkanoic acids (8, 9)—notably the phenoxypropionic acid derivative—were also active antineoplastic agents, and activity was retained in certain ester derivatives (3, 9). The ethyl esters of phenylbutyric acid, hydrocinnamic acid, and phenoxyacetic acid were chosen, therefore, for attachment of triazeno