T. & R. Söderbergs Stiftelser, M. Bergvalls Stiftelse, L. Hiertas Stiftelse, The Swedish Academy of Pharmaceutical Sciences, and the Medical Faculty, University of Göteborg, is gratefully acknowledged.

Registry No. (±)-**3**, 110270-99-0; (±)-**4**, 110271-02-8; (±)-**4**·HCl, 110271-00-6; (+)-**4**, 110271-03-9; (+)-**4**·HCl, 110271-05-1; (−)-**4**, 110271-04-0; (−)-**4**·HCl, 110271-06-2; (±)-**5**·HCl, 110271-01-7; (±)-**6**·HCl, 110271-07-3; (+)-**6**, 110271-08-4; (+)-**6**·HCl, 110271-10-8; (−)-**6**, 110271-09-5; (−)-**6**·HCl, 110271-11-9; (±)-**7**·HCl, 110271-12-0; (±)-**8**, 110312-33-9; (+)-**8**·HCl, 110351-03-6; (−)-**8**·HCl, 110312-35-1; (±)-**9**, 110312-34-0; 8-methoxy-2-tetralone, 5309-19-3.

Synthesis, Chemical Reactivity, and Antileukemic Activity of 5-Substituted 6,7-Bis(hydroxymethyl)pyrrolo[1,2-*c*]thiazole Biscarbamates and the Corresponding Sulfoxides and Sulfones[1]

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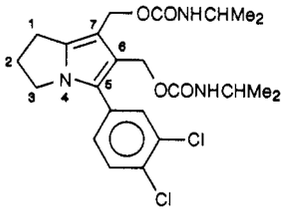
A series of bis(*N*-methylcarbamate) and bis[*N*-(2-propyl)carbamate] derivatives of 5-substituted 6,7-bis(hydroxymethyl)pyrrolo[1,2-*c*]thiazoles was prepared. The compounds were tested for activity in vivo against P388 lymphocytic leukemia, and the chemical reactivities of the compounds were compared by using the model nucleophile 4-(4-nitrobenzyl)pyridine (NBP). The 5-(3,4-dichlorophenyl)-substituted biscarbamates **6b**, **8b**, and **12b** were inactive and unreactive toward NBP. The 5-methyl-substituted biscarbamates **6a**, **7a**, **8a**, **9a**, **12a**, and **13a** were all active against murine P388 lymphocytic leukemia. The chemical reactivities of the active compounds depended on the oxidation state of the sulfur. The reactivity toward NBP followed the order S > SO >> SO_2. The sulfones **12a** and **13a** are the most active compounds in this series, and their lack of reactivity toward NBP led to the suggestion that **12a** and **13a** are activated in vivo.

The dihydropyrrolizine biscarbamate **1** has been shown to possess significant, reproducible activity against a wide range of experimental murine neoplasias and human tumor xenografts in nude (Nu/Nu) mice.[2] Thus, as part of our continuing interest in this and related systems, we undertook the synthesis and evaluation of a related pyrrolo[1,2-*c*]thiazole series, **2**. These compounds would be



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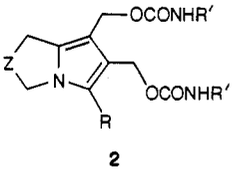


2

expected to have modified lipophilic and reactive characteristics compared to **1**. The replacement of the C-2 methylene in **1** by sulfur would be expected to reduce the lipophilicity of the compound and successive oxidation at sulfur would reduce the lipophilicity still further. This is apparent when the aromatic-based π values, or the aliphatic fragment values, Fr, are compared (Table I).

For example, the log P[3] (the logarithm of the partition coefficient, P) of **2** would be expected to be reduced by 2.68–3.55 (depending upon whether π or Fr was used) in the change from Z = CH_2 to Z = S(O).

Table I

substituent	π	Fr
CH_2	0.54	0.54
S	0.05[a]	−0.79[b]
S(O)	−2.14[a]	−3.01[b]
$S(O)_2$	−2.19[a]	

[a] Calculated from the π values[3] for XCH_3 by subtraction of 0.56 (π_{CH_3}). [b] Calculated from the Fr values[3] of XCH_3 by subtraction of 0.77 (Fr_{CH_3}).

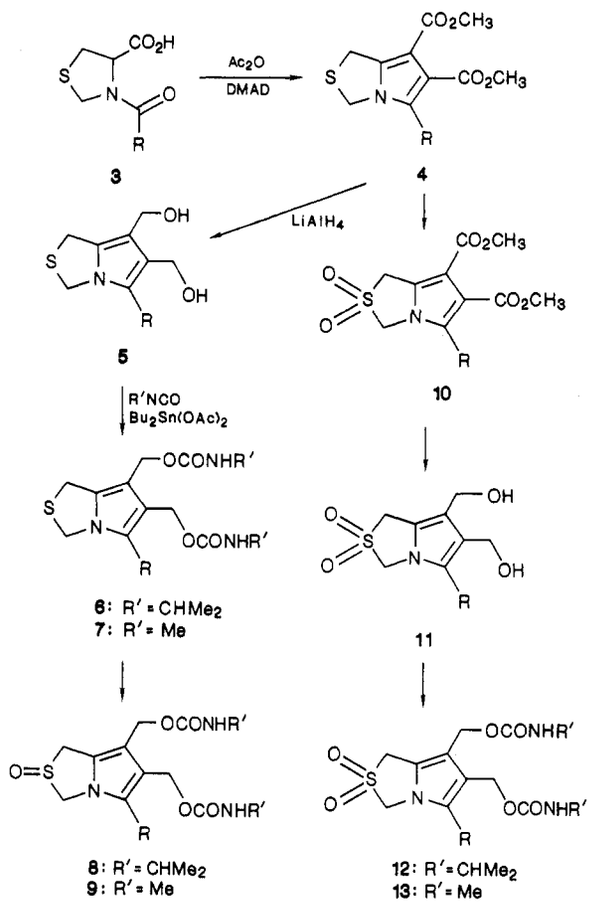
The pyrrolizine biscarbamate **1** was designed to act as a bifunctional electrophile where the carbamate moieties serve as leading groups in an *O*-alkyl ester cleavage reaction. Thus, electron-withdrawing substituents on the pyrrole ring would be expected to reduce the reactivity of the electrophile through destabilization of an electron-deficient transition state. The C-2 methylene group in **1** is a mild electron donating group (F = −0.04) while the sulfur (F = 0.25), sulfoxide (F = 0.50), and sulfone (F = 0.59) are all electron withdrawing. The sulfur/oxidized sulfur moieties would therefore be expected to reduce the reactivity of **2** (relative to Z = CH_2). Furthermore, the sulfide should be more reactive than either the corresponding sulfoxide or the sulfone. Consequently, the oxidized sulfur compounds could potentially serve as prodrugs for the sulfide, where the requisite reduction could occur in an hypoxic tumor cell.

This prodrug approach offers two potential advantages. First, the prodrug may exhibit some selective toxicity against hypoxic (solid) tumor masses. Second, the prodrug with its potential enhanced stability may be easier to formulate than **1** in a clinical dosage form. The oxidized sulfur compounds may also be dual-function radiation sensitizers. This report describes the preparation and preliminary evaluation of **2** [Z = S, S(O), and $S(O)_2$; R = CH_3 and 3,4-Cl_2Ph; R′ = CH_3 and $CHMe_2$].[4]

(1) Vinylogous Carbinolamine Tumor Inhibitors, 21. For part 20 see: Anderson, W. K.; Heider, A. R. *J. Med. Chem.* **1986**, *29*, 2392.
(2) (a) Anderson, W. K.; Corey, P. F. *J. Med. Chem.* **1977**, *20*, 812. (b) Anderson, W. K.; New, J. S.; Corey, P. F. *Arzneim.-Forsch.* **1980**, *30*, 765. (c) Anderson, W. K.; Chang, C.-P.; Corey, P. F.; Halat, M. J.; Jones, A. N.; McPherson, H. L., Jr.; New, J. S.; Rick, A. C. *Cancer Treat. Rep.* **1982**, *66*, 91. (d) Anderson, W. K. *Cancer Res.* **1982**, *42*, 2168.
(3) Hansch, C.; Leo, A. J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

0022-2623/87/1830-2109$01.50/0

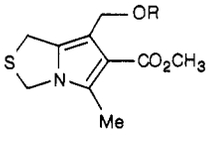
Scheme I



Chemistry. The 5-substituted dimethyl 1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylates, **4**, were prepared in 1,3-dipolar cycloaddition reactions with dimethyl acetylenedicarboxylate (DMAD) and mesoionic oxazolone intermediates generated in situ from the α-amido acids, **3**, as summarized in Scheme I. The biscarbamates **6a**, **6b**, and **7a** were prepared in a two-step sequence that involved liithium aluminum hydride reduction of **4a** and **4b** to the diols **5a** and **5b** followed by carbamoylation with methyl or 2-propyl isocyanate and di-*n*-butyltin diacetate. The biscarbamates **6a** and **6b** were treated with *m*-chloroperbenzoic acid in a biphasic mixture of dichloromethane and 0.5 M sodium bicarbonate solution to give the sulfoxide biscarbamates **8a** and **8b**. Oxidation of the bis(*N*-methylcarbamate) **7a** under the same conditions resulted in excessive decomposition of the starting material/product.

Several reaction conditions were explored, and it was found that **9a** could be prepared in fair yield by the addition of solid *m*-chloroperbenzoic to a solution of **7a** in dichloromethane at −12 °C. This method did not employ the biphasic reaction conditions as described for the preparation of **6a**; the *m*-chlorobenzoic formed during this reaction was removed by rapidly washing the reaction mixture with saturated aqueous sodium bicarbonate, and the product was purified as described for **6a**.

The sulfone bis[*N*-(2-propyl)carbamates] **12a** and **12b** were synthesized from the diesters **4a** and **4b** by oxidation of the sulfide to the sulfone **10** with *m*-chloroperbenzoic acid. Selective reduction of the diester **10b** with lithium borohydride gave the diol **11b**, which was directly converted to the biscarbamate **12b**. Lithium borohydride reduction of **10a** failed to give the desired diol **11a**. Instead, the monoester **14** was obtained. The monoester, **14**, was characterized as the monocarbamate **15**. The diol **11a**



14: R = H
15: R = CONH-*i*-Pr

was obtained from **10a** by reduction with aluminum hydride, but the reduction of the esters was also accompanied by some reduction at sulfur. Therefore, the crude aluminum hydride reduction product mixture was treated with 2-propyl isocyanate–dibutyltin diacetate, and this crude reaction mixture was carefully oxidized with *m*-chloroperbenzoic acid in dichloromethane–0.5 M sodium bicarbonate solutions to give **12a** in 43% overall yield from **10a**. The oxidation step simplified the purification of **12a**; the small amount of **6a** produced in the reduction step was converted to the polar sulfoxide **8a**, which was readily separated from the less polar sulfone, **12a**. Because of the decreased stability of the bis(*N*-methylcarbamates) toward oxidation with *m*-chlorobenzoic acid as described above, it became imperative to develop a method for the selective reduction of the ester groups in the presence of the sulfone, since this method of purification could not be used for the preparation of **13a**. Several variations of the reaction conditions were employed, and it was found that this selective reduction could be achieved by adding solid aluminum hydride–ether complex to a stirred solution of the diester **10a** in dry THF at 0 °C. No reduction of the sulfone was observed under these conditions, and **13a** was prepared in fair yield.[5]

The compounds prepared in this study were evaluated for chemical reactivity toward the model nucleophile 4-

Table II. Reactivities of Biscarbamates toward the Model Nucleophile 4-(4-Nitrobenzyl)pyridine[a]

compd	method	concn	k' (E^{570}/min)	r^2
1	B	8 μmol/10 mL	4.3×10^{-1}	0.998
6a	B	8 μmol/10 mL	8.85×10^{-1}	0.997
6b	B	8 μmol/10 mL	NR[b]	
7a	B	8 μmol/10 mL	1.00×10^{0}	0.999
8a	B	8 μmol/10 mL	1.57×10^{-1}	0.998
9a	B	8 μmol/10 mL	1.91×10^{-1}	0.993
12a	B	8 μmol/10 mL	NR[c]	
13a	B	8 μmol/10 mL	NR[c]	
16[d]	A	4 μmol/10 mL	3.60×10^{-1}	0.996
17[d]	A	4 μmol/10 mL	4.54×10^{0}	0.999
6a[d]	A	4 μmol/10 mL	6.0×10^{-2}	0.996

[a] The value k' represents a pseudo-first-order rate constant representing relative rates of alkylation (see the Experimental Section for a more detailed discussion). The value r^2 is the square of the correlation coefficient for the linear regression analysis. [b] Compound **6b** failed to react with NBP after 1 h under more vigorous conditions (60 °C, catalytic amount of glacial acetic acid) as well as the conditions described for **6a**. [c] No reaction was observed at 60 °C over a period of 30 min. [d] The concentrations of the more reactive biscarbamates **16** and **17** were reduced in order to produce rates that could be more easily monitored by the HPLC assay; the biscarbamate **6a** was also studied at this concentration to give a comparison.

(4) Compounds **7b**, **9b**, and **13b** were not prepared for evaluation because the preliminary antitumor test data for **6b**, **8b**, and **12b** showed that the compounds with a 3,4-dichlorophenyl substituent were inactive.

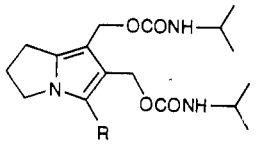
(5) Anderson, W. K.; Mach, R. H. *Synth. Commun.* **1986**, *16*, 911.

Table III. Activity against Murine P388 Lymphocytic Leukemia[a]

compd (control group)[b]	dose,[c] mg/kg	TDS[d]	BWD,[e] T - C	% ILS[f]	KE[g]	compd (control group)[b]	dose,[c] mg/kg	TDS[d]	BWD,[e] T - C	% ILS[f]	KE[g]
1 (A)	100	6/6	-4.2	48	0.8	**8b** (A)	400	3/6	-3.4		
1 (B)	100	6/6	-4.6	(-14)			200	6/6	-3.1	(-11)	
1 (C)	100	6/6	-2.6	123	>6.68		100	6/6	-2.9		
1 (A)	50	6/6	-2.6	97	4.35		50	6/6	-1.9		
1 (B)	50	6/6	-3.1	95	5.71		25	6/6	-0.9		
1 (C)	50	6/6	-1.8	96	5.27	**9a** (C)	200	6/6	0.4	15	-0.08
1 (A)	25	6/6	-1.7	75	2.81		100	6/6	0.8	22	-0.05
1 (B)	25	6/6	-2.2	66	3.01		50	6/6	1.1	13	-0.09
1 (C)	25	6/6	-1.4	55	1.85		25	6/6	0.0	13	-0.09
1 (A)	12.5	6/6	-0.6	56	1.4	**12a** (B)	100	6/6	-4.0	118	>6.77
1 (B)	12.5	6/6	-1.9	45	1.08		50	6/6	-1.8	84	4.71
1 (C)	12.5	6/6	-1.1	32	-0.07		25	6/6	-1.8	59	2.39
1 (A)	6.25	6/6	0	51	1.07		12.5	6/6	-1.1	42	0.85
1 (B)	6.25	6/6	-0.5	41	0.69	**12b** (B)	100	6/6	-2.3		
1 (C)	6.25	6/6	-1.1	26	-0.55		50	6/6	-0.8	(-14)	
6a (A)	200	0/6					25	6/6	0.4		
	100	3/6	-4.9				12.5	6/6	1.3	(-13)	
	50	5/6	-3.5				6.5	6/6	-0.6	1	-1.47
	25	6/6	1.9	73	2.61	**13a** (C)	200	6/6	-2.1	(g)	
	12.5	6/6	-1.9	42	0.40		100	6/6	-2.5	104	0.33
	6.25	6/6	-1.3	54	1.27		50	6/6	0.6	40	0.03
6b (A)	400	6/6	-1.3	(-11)			25	6/6	0.3	22	-0.05
	200	6/6	-1.7	(-12)		**15** (B)	100	4/6	-5.7		
	100	6/6	-0.9	(-13)			50	5/6	-1.6	(-8)	
	50	6/6	-1.3	(-12)			25	6/6	-0.2	(-5)	
	25	6/6	-1.3	(-9)			12.5	6/6	-0.3	(-4)	
7a (C)	200	6/6	-1.9			**16** (B)	100	1/6	-3.6		
	100	6/6	-2.2				50	5/6	-4.4	26	-0.69
	50	6/6	-1.7	32	0.00		25	5/6	-4.5	28	-0.46
	25	6/6	-1.0	26	-0.03		12.5	5/6	-0.9	20	-1.23
8a (B)	400	3/6	-4.5								
	200	6/6	-2.6	76	3.94						
	100	6/6	-0.1	32	-0.08						
	50	6/6	-0.6	26	-0.69						

[a] Ascitic fluid containing ca. 1×10^6 cells was implanted intraperitoneally in CD_2F_1 mice. Antileukemic testing was conducted under the auspices of the National Cancer Institute. The protocol for the testing is described in NIH publication No. 84-2635, February 1984. See also: Geran, R. L.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*, 1. [b] The test compounds were evaluated in three groups: Compounds **6a**, **6b**, and **8b** in control group A; compounds **8a**, **12a**, **12b**, **15**, and **16** in control group B; and compounds **7a**, **9a**, and **13a** in control group C. The test data for a reference active drug, pyrrolizine **1**, are given for each control group. [c] Suspensions of the drug were prepared fresh daily in saline with Tween 80. The suspensions were injected intraperitoneally beginning 24 h after tumor inoculation and at 24-h intervals thereafter for a total of five doses. [d] Toxicity day survivors expressed as number of animals that survived to day five/number of test animals. [e] Body weight difference of test animals compared to control animal. [f] Percent increase in life span of test animals compared to untreated tumor-bearing control animals (average life span 10–12 days). A % ILS $\geq$ 27 is considered statistically significant but a % ILS $\geq$ 75 is necessary for additional studies in the NCI program. [g] KE = log cell population relative to cell population at the beginning of treatment. If KE > 0, the cell population at the end of treatment was less by this number of log 10 units relative to the beginning of treatment. If KE < 0, the cell population at the end of treatment was greater than that at the beginning of treatment, and the negative value is an estimate of the number of log 10 units of cell growth that occurred during the course of treatment. Log cell kill data are not given for tests where the % ILS is less than zero or when toxicity was excessive. [h] Two cures were recorded at this dose.

(4-nitrobenzyl)pyridine (NBP).[6] These data are reported in Table II. The carbon analogues **16** and **17** were synthesized for purposes of comparison in this study.



16: R = H
17: R = CH_3

Biological Results and Discussion

The antileukemic data for the compounds tested in this study are summarized in Table III. These data show that replacement of the C-2 methylene in **1** by S, S(O), or $S(O)_2$ results in inactive compounds. Compounds **1**, **6b**, **8b**, and **12b** are all bis[*N*-(2-propyl)carbamate] derivatives with a 5-(3,4-dichlorophenyl) substituent, yet **6b**, **8b**, and **12b** are inactive. The combined electron-withdrawing influence of the 3,4-dichlorophenyl substituent and the heterosulfur atom appear to reduce the chemical reactivity of the electrophilic centers below that which is required for antitumor activity [under the conditions used for the NBP assay, the pyrrolizine **1** had $k' = 4.30 \times 10^{-1}$ ($r^2 = 0.998$) while the sulfur analogue **6b** failed to react with NBP over a 1-h period].

When the 5-(3,4-dichlorophenyl) substituent was replaced by an electron-donating methyl substituent, the resulting bis[*N*-(2-propyl)carbamates] exhibited antileukemic activity. The S, S(O), and $S(O)_2$ compounds, **6a**, **8a**, and **12a**, respectively, were all active. The most active was sulfone **12a** (118% ILS at 100 mg/kg). The sulfoxide **8a** was less potent than the sulfone **12a**. The sulfide **6a** showed comparable activity to the sulfoxide **8a**, but the sulfoxide was less potent. The monocarbamate **15** was inactive, but it was toxic as judged by toxicity day survivors (TDS) and animal weight loss (BWD). These latter observations are consistent with previous observations made

(6) Bardos, T. J.; Datta-Gupta, N.; Hebborn, P.; Triggle, D. J. *Med. Chem.* **1965**, *8*, 167.

Table IV. ^{1}H NMR Spectral Data of Pyrrolo[1,2-*c*]thiazoles **2–12**[a,b]

compd	C-1 (CH_2)	C-3 (CH_2)	C-5 substituent	C-6 and C-7
4a	4.20 (br)	4.90 (br)	2.40	3.80,[c] 3.90[c]
4b	4.40 (br)	4.95 (br)	7.50 (m)	3.80,[c] 3.85[c]
5a	4.00 (br)	4.80 (br)	2.20	3.10 (br),[d] 4.40,[e]
5b	4.20 (br)	5.10 (br)	7.50 (m)	3.10 (br),[d] 4.45,[e] 4.60[e]
6a[k]	4.15	4.95 (br)[e]	2.30	1.20 (d, 7),[f] 3.70 (m),[g] 6.10 (br)[h]
6b	4.20 (br)	5.10 (br)	7.40 (m)	1.20 (d, 7),[f] 3.80 (m),[g] 4.55 (br),[h] 4.95 (br)[e]
7a	4.00 (br)	4.80 (br)	2.20	3.70 (d, 6),[i] 4.60 (br),[h] 5.00[e]
8a	4.10,[j] 4.20[j]	4.70,[j] 4.90[j]	2.20	1.20 (d, 7),[f] 3.80 (m),[g] 4.90,[e] 5.05 (br)[h]
8b	4.25,[j] 4.35[j]	4.8–5.1 (m)[e]	7.30 (m)	1.10 (d, 6),[f] 3.80 (m),[g] 4.55 (br)[h]
9a	4.25[j]	4.90[j]	2.30	2.75 (d, 6),[i] 5.0,[e] 5.5 (br)[h]
10a	4.50 (br)	4.90 (br)	2.40	3.90,[c] 3.95[c]
10b[k]	4.70 (br)	5.30 (br)	7.55 (m)	3.75,[c] 3.80[c]
11b	4.30 (br)	4.80	7.20 (m)	4.40,[e] 3.60[d]
12a	4.50 (br)	4.90	2.35	1.20 (d, 6),[f] 3.80 (ht, 6),[g] 4.45,[h] 5.00,[e] 5.10[e]
12b	4.60 (br)	5.05	7.30 (m)	1.20 (d, 6),[f] 3.80 (m),[g] 4.50,[h] 4.80,[e] 5.00[e]
13a	4.55 (br)	4.95	2.30	2.80 (d, 6),[i] 4.9 (br),[h] 5.00[e]
14b	4.45 (br)[h]	4.85	2.50	1.20 (d, 7),[f] 3.80 (m),[g] 3.85,[c] 5.20[e]

[a] Signals are siglets unless otherwise specified as, br = broad; d = doublet; ht = heptet; m = multiplet. Coupling constant given in hertz in parentheses with multiplicity. [b] Spectra were determined for $CDCl_3$–TMS solutions unless otherwise specified. [c] CO_2CH_3. [d] *OH*. [e] CH_2-O. [f] $CH(CH_3)_2$. [g] $CH(CH_3)_2$. [h] NH. [i] $NHCH_3$. [j] Center peaks of partially obscured AB quartet. [k] $CDCl_3$–DMSO-d_6. TMS was used as solvent.

in our laboratory wherein bifunctional electrophiles were required for activity.

The substitution of sulfur for carbon (**6a** vs **17**) resulted in a marked decrease in chemical reactivity toward NBP. (It should be noted that the NBP assay is only a measure of relative reactivity; the assay gives no indication of whether an agent is reacting as a bifunctional or monofunctional electrophile.) The pyrrolothiazole **6a** is approximately 75-fold less reactive than the pyrrolizine **17**. The 5-methyl-substituted pyrrolizine **17** was not tested for antileukemic activity because it was highly unstable in aqueous media. Instead, the less reactive pyrrolizine **16**, unsubstituted at C-5, was tested. The biscarbamate **16** was 6-fold more reactive than **6a** toward NBP (Table II), and **16** was observed to be more toxic and less active than **6a**.

Oxidation of the sulfur in the pyrrolothiazoles led to a further reduction in the reactivity of the biscarbamates. The sulfoxides **8a** and **9a** are approximately 5-fold less reactive than the corresponding sulfides **6a** and **7a**. The *N*-isopropylcarbamates **6a**, **8a**, and **12a** are all slightly more active than the *N*-methylcarbamates **7a**, **9a**, and **13a**, respectively. The differences in activity are not explained by the NBP reactivity data since the methyl carbamates **7a** and **9a** are only slightly more reactive toward NBP than the corresponding isopropyl carbamates **6a** and **8a**. Further oxidation of sulfur to the sulfones, **12a** and **13a**, led to an additional decrease in reactivity; the sulfones **12a** and **13a** failed to react with NBP within a 30-min period at 60 °C.

The results of the NBP assay clearly indicates that substitution of sulfur for carbon at position 2 in the saturated ring of **1** substantially affect the reactivity of the system. The lack of chemical reactivity in the sulfones **12a** or **13a** in conjunction with high antileukemic activity is a strong prima facia argument that reduction of the sulfone is occurring in vivo. Such metabolic reductions of sulfones are rare and further experimentation will be required to investigate this proposal. The lower activities and potencies of the sulfoxides **8a** and **9a** is somewhat unexpected but may be associated with the observation that the sulfoxides, on silica gel TLC, are substantially more polar than the sulfones. It can be postulated that the low activities of the sulfoxides **8a** and **9a** are due either to rapid elimination of the drug or to poor uptake rather than inferior reduction.

In conclusion, it may be stated that the sulfones **12a** and **13a** represent excellent candidates for further development. The compounds show high reproducible in vivo activity against P388 lymphocytic leukemia and, unlike **1**, are stable in aqueous mixtures (i.e., show no evidence of decomposition over a period of 24 h).

Experimental Section

Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover Unimelt apparatus. IR spectra were determined with either a Perkin-Elmer 727B spectrophotometer or a Nicolet FT-IR interferometer for Nujol mulls unless otherwise specified. NMR spectra were determined with either a Varian T-60A or FT-80 spectrometer and are given in Table IV. Microanalyses were performed by Atlantic Microlab, Atlanta, GA, and were all with ±0.4% of the theoretical values.

***N*-(3,4-Dichlorobenzoyl)thiazolidine-4-carboxylic Acid (3b).** Thiazolidine-4-carboxylic acid (5 g, 37.6 mmol) was suspended in water (100 mL), and the mixture was made homogeneous by the dropwise addition of 15% sodium hydroxide solution to a pH of 8.0. 3,4-Dichlorobenzoyl chloride (8.65 g, 41.3 mmol) in diethyl ether (100 mL) was added dropwise over 30 min, and the pH of the reaction was maintained at 8.0 by periodic addition of 15% sodium hydroxide solution. The reaction mixture was allowed to stir at 25 °C for 16 h. The aqueous layer was acidified to a pH of 2.0 by dropwise addition of concentrated HCl and extracted twice with dichloromethane. The organic layer was collected, dried (sodium sulfate), and concentrated in vacuo to give **3b** as a light yellow foam (11.26 g, 98%): mp (softens at 55–58 °C); NMR ($CDCl_3$, TMS) δ 10.1 (s, 1 H), 7.55 (m, 3 H), 5.2 (m, 1 H), 4.6 (br s, 2 H), 3.4 (d, 2 H, J = 6 Hz); IR (KBr) 3449, 1734, 1635, 1409, 1297, 1198, 1127, 1035, 831, 753, 668 cm^{-1}.

Dimethyl 5-Methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (4a). Thiazolidine-4-carboxylic acid (5 g, 37.5 mmol) was dissolved in acetic anhydride (60 mL), and the reaction mixture was heated at 50 °C for 1 h. Dimethyl acetylenedicarboxylate (5.53 mL, 1.2 equiv) was added, and the reaction mixture was heated at 120 °C for 14 h. Volatile components were removed in vacuo, and the resultant brown oil was purified by silica gel column chromatography (dichloromethane–ethyl acetate, 1:1) to give the product **4a** as light tan prisms (5.97g, 63%); IR 3000, 2950, 1720 1540, 1440, 1390, 1310, 1220, 1175, 1100, 1050 cm^{-1}. Anal. ($C_{11}H_{13}NO_4S$) C, H, N.

Dimethyl 5-(3,4-Dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (4b). *N*-(3,4-Dichlorobenzoyl)-thiazolidine-4-carboxylic acid (**3b**; 10.0 g, 32.7 mmol) in acetic anhydride (75 mL) was treated with dimethyl acetylenedicarboxylate (5.78 g, 38.4 mmol) and heated at 120 °C for 6 h. The mixture was cooled and concentrated to dryness in vacuo, and the brown residue was crystallized from methanol–water to give dimethyl 5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**4b**) as a white prisms (9.18 g, 68%): mp 126–127 °C; IR ($CHCl_3$) 3000, 2950, 1720 (C=O), 1480, 1460, 1420, 1310, 1220, 1120, 1170, 1120 cm^{-1}. Anal. ($C_{16}H_{13}NO_4SCl_2$) C, H, N.

6,7-Bis(hydroxymethyl)-5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole (5b). A solution of dimethyl 5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**4b**; 10.0 g, 25.9 mmol) in anhydrous dichloromethane (50 mL) was added dropwise over a 10-min period to a stirred mixture of lithium aluminum hydride (2.31 g, 0.61 mmol) in anhydrous ether (75 mL) heated under reflux. The stirred mixture was heated at reflux for 1 h after the addition was completed, and then the mixture was cooled on an ice bath. The excess hydride was decomposed by careful addition of small amounts of wet ether followed by water until the salts were white. The mixture was filtered and washed with several portions of hot dichloromethane. The filtrate was concentrated in vacuo to a volume of ca. 50 mL, heated to boiling, and diluted with petroleum ether until the mixture became cloudy. The mixture was allowed to stand, and the diol **5b** was obtained as fluffy white crystals (6.15 g, 75%): mp 123–125 °C; IR ($CHCl_3$) 3150 (OH), 2900, 2850, 1460, 1370, 1130, 1000, 900, 830 cm^{-1}.

6,7-Bis(hydroxymethyl)-5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis[*N*-(2-propyl)carbamate] (6a). A solution of dimethyl 5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**4a**; 5 g, 19.63 mmol) in dry tetrahydrofuran (30 mL) was added dropwise, over a 15-min period, to a stirred suspension of lithium aluminum hydride (1.75 g, 2.3 equiv) in dry tetrahydrofuran (20 mL), and the reaction mixture was stirred at ambient temperature for 2 h. The excess lithium aluminum hydride was decomposed by dropwise addition of water (15 mL) and then 10% aqueous sodium hydroxide solution (10 mL); the mixture was filtered through a pad of basic alumina, and the collected solid was washed with several portions of cold tetrahydrofuran and ethyl acetate. The combined organic solution was dried (sodium sulfate) and concentrated in vacuo to give an ivory precipitate of **5a** (3.3 g, 85%). This precipitate was dissolved in anhydrous dichloromethane (30 mL) and treated with isopropyl isocyanate (5.79 mL, 3 equiv) and dibutyltin diacetate (0.1 mL). The reaction mixture was stirred at ambient temperature for 2 h. Volatile components were removed in vacuo, and the resultant white precipitate was purified by recrystallization from chloroform–hexane to give **6a** as fluffy tan flakes (4.64 g, 64%): mp 164–164.5 °C dec; IR 3310, 2910, 2850, 1680, 1530, 1460, 1380, 1330, 1250, 1090, 950 cm^{-1}. Anal. ($C_{17}H_{27}N_3O_4S$) C, H, N.

6,7-Bis(hydroxymethyl)-5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis[*N*-(2-propyl)carbamate] (6b). A solution of 6,7-bis(hydroxymethyl)-5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole (**5b**; 2 g, 6.06 mmol) in anhydrous dichloromethane (20 mL) was treated with isopropyl isocyanate (1.79 mL, 3 equiv) and dibutyltin diacetate (0.1 mL) and stirred at ambient temperature for 8 h. Volatile components were removed in vacuo, and the resultant white precipitates was crystallized from chloroform–hexane to give **6b** as fluffy white flakes (2.3837 g, 79%): mp 149.5–151 °C dec; IR 3330, 2900, 2840, 1700, 1520, 1450, 1380, 1240, 1100, 1080, 1060, 940 cm^{-1}. Anal. ($C_{22}H_{27}N_3O_4SCl_2$) C, H, N.

6,7-Bis(hydroxymethyl)-5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis(*N*-methylcarbamate) (7a). The diester **4a** (5 g, 19.63 mmol) was reduced to the diol **5a** as described in the preparation of **6a**. A solution of the crude diol (3.3 g) in dichloromethane (30 mL) was treated with methyl isocyanate (3.47 mL, 3 equiv) and dibutyltin diacetate (0.1 mL), and the mixture was stirred at room temperature for 12 h. The mixture was concentrated to dryness in vacuo, and the residue was crystallized from dichloromethane–hexane to give **7a** (3.965 g, 76%) as tan flakes: mp 162–163 °C dec; IR 3329, 2955, 2927, 2856, 2334, 1685, 1544, 1466, 1283, 1142, 972 cm^{-1}. Anal. ($C_{13}H_{19}N_3O_4S$) C, H, N.

2-Oxo-5-methyl-6,7-bis(hydroxymethyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis[*N*-(2-propyl)carbamate] (8a). Solid *m*-chloroperbenzoic acid (1.285 g, 5.95 mmol) was added slowly to a stirred mixture of **6a** (2 g, 5.42 mmol) in dichloromethane (30 mL) and 0.5 M aqueous sodium bicarbonate (20 mL). The reaction mixture was stirred at 25 °C for 15 min, the organic layer was collected and dried (sodium sulfate). The solvent was removed in vacuo to give a white precipitate that was purified by Florisil column chromatography (acetone–ethyl acetate, 1:1) to give **8a** as hard white prisms (1.76 g, 84%): mp 132–134 °C dec; IR 3310, 2900, 2850, 1690, 1530, 1460, 1380, 1370, 1270, 1090, 1050, 950, 920, 840, 770 cm^{-1}. Anal. ($C_{17}H_{27}N_3O_5S$) C, H, N.

2-Oxo-6,7-bis(hydroxymethyl)-5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis[*N*-(2-propyl)carbamate] (8b). 6,7-Bis(hydroxymethyl)-5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole bis[*N*-(2-propyl)carbamate] (**6b**) was oxidized by the method used to prepare **8a**. The solvent was removed in vacuo to give a white precipitate that was recrystallized from hot chloroform–hexane to give **8b** as hard white prisms (2.194 g, 53.2%): mp 202–203 °C; IR 3275, 2920, 2850, 1680, 1550, 1460, 1380, 1270, 1100, 1040 cm^{-1}. Anal. ($C_{22}H_{27}N_3O_5SCl_2$) C, H, N.

2-Oxo-6,7-bis(hydroxymethyl)-5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis(*N*-methylcarbamate) (9a). Solid *m*-chloroperbenzoic acid (1.52 g, 1.05 equiv) was added to a magnetically stirred solution of 6,7-bis(hydroxymethyl)-5-methyl-1,3-dihydropyrrolo[1,2-*c*]-thiazole bis(*N*-methylcarbamate) (**7a**; 2.1 g, 6.71 mmol) in dry dichloromethane (50 mL) at −12 °C (salt–ice bath) and the reaction mixture was stirred at that temperature for 5 min. The reaction mixture was rapidly extracted with saturated sodium bicarbonate (30 mL), the organic layer was dried (sodium sulfate), and the volatiles were removed in vacuo to give a white solid that was purified by crystallization from dichloromethane–hexane to give **9a** as a fluffy white solid (1.18 g, 54%): mp 171–172.5 °C dec; IR 3316, 3288, 2957, 2859, 1710, 1682, 1570, 1464, 1379, 1288, 1154, 1041, 964 cm^{-1}. Anal. ($C_{13}H_{19}N_3O_5S$) C, H, N.

Dimethyl 2,2-Dioxo-5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (10a). Solid *m*-chloroperbenzoic acid (16.28 g, 86.5 mmol) was added slowly, in small portions, to a magnetically stirred solution of dimethyl 5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**4a**; 10 g, 39.3 mmol) in dichloromethane (75 mL) at 0 °C (ice bath). The reaction mixture was stirred at 0 °C for 30 min, the ice bath was removed, and the reaction mixture was heated at reflux for 90 min. The reaction mixture was washed once with 10% aqueous sodium bisulfite and once with 10% aqueous sodium carbonate. The organic layer was dried (sodium sulfate) and evaporated in vacuo to give a white precipitate that was crysallized from hot ethyl acetate–isopropyl ether to give **10a** as hard white prisms (6.51 g, 58%): mp 164–166 °C; IR 2950, 2850, 1700, 1590, 1520, 1450, 1370, 1310, 1250, 1200, 1170, 1130, 995, 860, 820, 780 cm^{-1}. Anal. ($C_{11}H_{13}NO_6S$) C, H, N.

Dimethyl 2,2-Dioxo-5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (10b). Solid *m*-chloroperbenzoic acid (2.97 g, 17.2 mmol) was added slowly to a magnetically stirred solution of dimethyl 5-(3,4-dichlorophenyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**4b**; 2 g, 5.18 mmol) in dichloromethane (40 mL) maintained at 0 °C. The ice bath was removed, and the reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was filtered, and the dichloromethane solution was extracted with 10% aqueous sodium bisulfite and twice with 15% aqueous sodium bicarbonate. The organic layer was dried (sodium sulfate) and concentrated in vacuo to give a white precipitate that was crystallized from ethyl acetate–hexane to give **10b** as stout white prisms (1.635 g, 76%): mp 202–204 °C; IR 2900, 2840, 1710, 1460, 1380, 1340, 1220, 1180, 1060, 1040, 900 cm^{-1}. Anal. ($C_{16}H_{13}NO_6SCl_2$) C, H, N.

2,2-Dioxo-5-methyl-6,7-bis(hydroxymethyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis[*N*-(2-propyl)carbamate] (12a). Solid aluminum hydride–ether complex (1.582 g, 0.279 mmol) was added slowly to a stirred solution of dimethyl 2,2-dioxo-5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (2.0 g, 6.98 mmol) in anhydrous tetrahydrofuran (100 mL). The reaction mixture was stirred at room temperature for 5 h and then cooled to 0 °C (ice bath). The unreacted hydride was decomposed by the dropwise addition of water (5 mL) followed by 10% sodium hydroxide solution (5 mL). The mixture was filtered through a pad of basic alumina, and the inorganic material was washed with several portions of cold ethyl acetate. The combined filtrate was dried (sodium sulfate) and concentrated to dryness in vacuo. The white residue was suspended in anhydrous chloroform (40 mL) and treated with isopropyl isocyanate (2 mL, 3 equiv, 0.203 mmol) and dibutylin diacetate (0.1 mL). The mixture was stirred at room temperature for 14 h and then concentrated to dryness in vacuo. The orange residue was dissolved in dichloromethane (40 mL), 0.5 M sodium bicarbonate (30 mL) and *m*-chloroperbenzoic acid (2 g, 0.927 mmol) were added, and the mixture was stirred at room

temperature for 15 min. The organic layer was separated, washed with 0.5 sodium bicarbonate solution, dried (sodium sulfate), and concentrated to dryness in vacuo. The organge residue was purified by Florisil column chromatography (dichloromethan–ethyl acetate, 1:1) to give **12a** as fluffy white crystals (43% yield): mp 141–142 °C; IR 3330, 2900, 2850, 1680, 1530, 1490, 1370, 1325, 1260, 1130, 1095, 1085 cm^{-1}. Anal. ($C_{17}H_{27}N_3O_6S$) C, H, N.

2,2-Dioxo-5-(3,4-dichlorophenyl)-6,7-bis(hydroxymethyl)-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis[*N*-(2-propyl)carbamate] (12b). A stirred mixture of the diester **10b** (2.0 g, 4.78 mmol) and lithium borohydride (0.26 g, 11.9 mmol, 2.5 equiv) in anhydrous tetrahydrofuran (25 mL) was heated at 35 °C for 5 h. The reaction mixture was allowed to cool to room temperature, and the excess reducing agent was decomposed by dropwise addition of water (5 mL) and 10% aqueous sodium hydroxide (5 mL). The solvent was removed in vacuo to give a cloudy oil that was extracted with ethyl acetate. The ethyl acetate extract was washed with 10% aqueous sodium carbonate solution and dried (sodium sulfate), and the solvent was removed in vacuo. The resultant white precipitate was suspended in anhydrous chloroform (25 mL) and treated with isopropyl isocyanate (1.4 mL) and dibutyltin diacetate (0.1 mL). The reaction mixture was stirred at 25 °C for 12 h, the volatiles were removed in vacuo, and the resultant white precipitate was purified by Florisil column chromatography (dichloromethane–ethyl acetate, 1:1) to give **12b** as a fluffy white powder (1.872 g, 62%): mp 176–178 °C dec; IR 3340, 2925, 2860, 1690, 1550, 1460, 1380, 1330, 1265, 1140, 1090 cm^{-1}. Anal. ($C_{22}H_{27}N_3O_6SCl_2$) C, H, N.

2,2-Dioxo-6,7-bis(hydroxymethyl)-5-methyl-1,3-dihydropyrrolo[1,2-*c*]thiazole Bis(*N*-methylcarbamate) (13a). Solid aluminum hydride–ether complex (1.53 g, 27.92 mmol) was added slowly to a stirred solution of dimethyl 2,2-dioxo-5-methyl-1,3-dihydropyrrolo[2,3-*c*]thiazole-6,7-dicarboxylate (**10a**; 2 g, 6.98 mmol) in dry tetrahydrofuran (40 mL) at 0 °C (ice bath), and the reaction mixture was stirred at that temperature for 1 h. The excess hydride reducing agent was decomposed by dropwise addition of water (3 mL) followed by aqueous 15% sodium hydroxide (3 mL), the mixture was filtered, and the collected solid was washed with several portions of acetonitrile and ethyl acetate. The solvent was removed in vacuo to give the diol as a white solid (1.18 g, 73%). The diol was dissolved in dry dichloromethane (40 mL) and treated with methyl isocyanate (0.75 mL, 2.5 eq) and dibutyltin diacetate (0.1 mL). The reaction was stirred at ambient temperature for 20 h, the solvent was removed in vacuo, and the resultant white precipitate was purified by recrystallization from dichloromethane–hexane to give **13a** as a fluffy off-white solid (1.174 g, 66%): mp 164.5–166 °C dec; IR 3309, 3274, 3091, 2915, 2866, 1710, 1682, 1577, 1457, 1415, 1400, 1323, 1288, 1203, 1161, 1133, 1105, 992, 970, 781 cm^{-1}. Anal. ($C_{13}H_{19}N_3O_6S$) C, H, N.

Methyl 2,2-Dioxo-5-methyl-7-[[[*N*-(2-propyl)carbamoyl]oxy]methyl]-1,3-dihydropyrrolo[1,2-*c*]thiazole-6-carboxylate (15). A stirred mixture of the diester **10a** (5 g, 17.44 mmol) and lithium borohydride (0.836 g, 38.4 mmol, 2.2 equiv) in anhydrous tetrahydrofuran (30 mL) was heated at 35 °C for 5 h. The reaction mixture was cooled to 0 °C (ice bath), and the excess reducing agent was decomposed by dropwise addition of distilled water (5 mL) and then 10% aqueous sodium hydroxide (5 mL). The mixture was filtered through a pad of basic alumina, and the inorganic material was washed with several portions of cold ethyl acetate and chloroform. The combined filtrate was dried (sodium sulfate) and concentrated in vacuo to give **15** as a white precipitate. The crude solid was suspended in dry chloroform (25 mL) and treated with isopropyl isocyanate (5.14 mL, 3 equiv) and dibutyltin diacetate (0.1 mL). The reaction mixture was stirred at 25 °C for 10 h. The solvent was removed in vacuo to give a white precipitate that was purified by Florisil column chromatography (ethyl acetate–dichloromethane, 1:1) to give **15** as a fluffy white powder (1.53 g, 22%): mp 147–148 °C; IR 3350, 2920, 2850, 1690, 1685, 1530, 1460, 1380, 1330, 1320, 1290, 1150, 1080 cm^{-1}. Anal. ($C_{14}H_{20}N_2O_6S$) C, H, N.

6,7-Bis(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizine Bis[*N*-(2-propyl)carbamate] (16). *N*-Formylproline[7] was treated with excess acetic anhydride and dimethyl acetylenedicarboxylate at 50–60 °C for 12 h (higher temperatures, e.g. 120–130 °C for 1–2 h, gave lower yields and more impure product) to give dimethyl 2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate (70%, crystallized from methanol–water) as fine white needles, mp 85–86.5 °C (lit. mp 86–88 °C). Dimethyl 2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate was reduced to the diol as described for **6a** except the reaction time was 1 h. The crude diol (a colorless oil) was carbamoylated as described for **6b** to give **16** (53%, crystallized from dichloromethane–ether) as a fluffy white solid: mp 141–143 °C; ^1H NMR ($CDCl_3$, TMS) δ 1.20 (d, J = 7 Hz, 12 H), 2.4–3.0 (m, 4 H), 3.6–4.1 (m, 4 H), 4.3–4.6 (br s, 2 H), 5.0 (s, 4 H), 6.70 (s, 1 H); IR 3329, 2891, 1678, 1530, 1466, 1374, 1254, 1078 cm^{-1}. Anal. ($C_{17}H_{27}N_3O_4$) C, H, N.

6,7-Bis(hydroxymethyl)-5-methyl-2,3-dihydro-1*H*-pyrrolizine Bis[*N*-(2-propyl)carbamate] (17). A solution of 6,7-bis(hydroxymethyl)-5-methyl-2,3-dihydro-1*H*-pyrrolizine[2a] in anhydrous tetrahydrofuran was carbamoylated as described for **6b** to give **17** (50%, crystallized from dichloromethane): mp 142.5–144 °C dec; ^1H NMR ($CDCl_3$, TMS) δ 1.20 (d, J = 7 Hz, 12 H), 2.20 (s, 3 H), 2.40–3.0 (m, 4 H), 3.60–4.10 (m, 4 H), 4.30–4.6 (br s, 2 H), 5.0 (s, 4 H); IR 3329, 2920, 2857, 1678, 1530, 1459, 1374, 1269, 1078, 844 cm^{-1}. Anal. ($C_{18}H_{29}N_3O_4$) C, H, N.

Determination of the Relative Rates of Alkylation. Method A. The compounds tested were dissolved in 1,2-dimethoxyethane (4.0 μmol/10 mL) and 0.5-mL aliquots placed in five or six test tubes that already contained NBP solution [10% w/v 1,2-dimethoxyethane, 1.0 mL] and water solution [1:1 v/v water–dimethoxyethane, 1.0 mL]. The tubes were stoppered tightly, the contents were mixed thoroughly, and the tubes were placed in a water bath maintained at 40 °C. At different time intervals, a tube was cooled in an ice bath and base [1:1 v/v triethylamine–acetone, 1.0 mL], was added. The contents were mixed for 3 s with a vortex-type mixer and diluted with acetone (7.0 mL). The solution was transferred to a curvette, and the absorbance of the reaction was read at 570 nm with a Bausch and Lomb (Spectronic 20) spectrometer. The instrument had been previously adjusted to 0% absorbance against a mixture contained NBP solution (1.0 mL), water solution (1.0 mL), dimethoxyethane (0.5 mL), base solution (1.0 mL), and acetone (7.0 mL). The color of the reaction fades with time, and the absorbance readings should be taken as quickly as possible. The slope of the line obtained by the technique of least squares when absorbances was plotted against time gave the comparative alkylating activity k', which was calculated by an unweighted linear regression analysis. The reaction obeys integrated second-order rate equation:

$$kt = [1/(a - b)] \ln [b(a - x)/a(b - x)]$$

where a is the initial concentration of the alkylating agent, b is the initial concentration of NBP, and x is the amount reacted in time t. If pseudo-first-order conditions are employed ($b >> a$), and the rate is measured only at the initial phase of the reaction ($x << a$ and $bkt << 1$), then the above equation simplifies to the following expression:

$$k = \alpha E^{570}/abt$$

where α is a proportionality constant that is a function of the chromophore system, k is the pseudo-first-order rate constant, and E^{570} is the absorbance reading at 570 nm. If the structures of the alkylating agents under comparison are similar, then α will show little variation and the above equation simplifies to the following:

$$k' = \beta k = E^{570}/t$$

where β includes the standard initial concentration of the reactants and k' is the comparative alkylating activity. Therefore, the relative rates of alkylation may be determined by plotting the absorbance readings vs time and determining the slopes of the linear plots.[6] Duplicate determinations were made for each compound studied.

Method B. The test compounds were dissolved in 1,2-methoxyethane (8 μmol/10 mL) and added (0.5-mL aliquots) to NBP solution (1 mL, prepared as in method A) and aqueous acid (20:20:1, water–dimethoxyethane–acetic acid). The tubes were stoppered, the contents were mixed, and the tubes were placed

(7) Pizzorno, M. T.; Albonico,S. M. *J. Org. Chem.* **1974**, *39*, 731.

in a water bath at 60 °C and the contents analyzed as in method A.

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Registry No. **3b**, 110271-24-4; **4a**, 75475-91-1; **4b**, 110271-25-5; **5a**, 110271-26-6; **5b**, 110271-27-7; **6a**, 110271-28-8; **6b**, 110271-29-9; **7a**, 110271-30-2; **8a**, 110271-31-3; **8b**, 110271-32-4; **9a**, 110271-33-5; **10a**, 107124-28-7; **10b**, 107124-27-6; **11**, 110271-34-6; **12a**, 107124-34-5; **12b**, 107124-32-3; **13a**, 110271-35-7; **15**, 110271-36-8; **16**, 110271-37-9; **17**, 110271-38-0; thiazolidine-4-carboxylic acid, 444-27-9; 3,4-dichlorobenzoyl chloride, 3024-72-4; dimethyl acetylenedicarboxylate, 762-42-5; *N*-formylproline, 13200-83-4; dimethyl 2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylate, 62563-06-8; 6,7-bis(hydroxymethyl)-5-methyl-2,3-dihydro-1*H*-pyrrolizine, 62523-01-7; 4-(4-nitrobenzyl)pyridine, 1083-48-3.

Congener Derivatives and Conjugates of Histamine: Synthesis and Tissue and Receptor Selectivity of the Derivatives†

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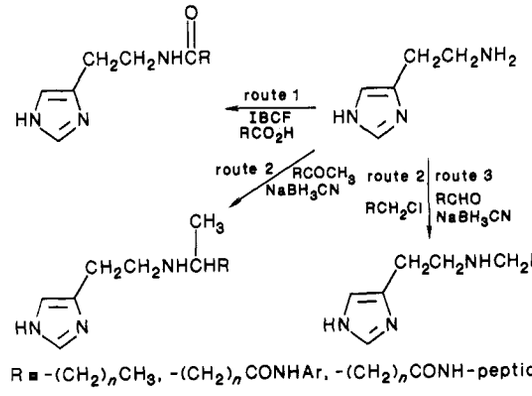
A series of 19 congener derivatives and conjugates of histamine was synthesized and tested to determine whether the ligands would alter the conventional histamine activity in various tissues. The derivatives, which contained either branched or unbranched aliphatic groups, aromatic amide groups, or dipeptides, exhibited affinities for histamine type 1 and/or type 2 receptors that were widely different from the progenitor. The *p*-trifluoromethyl derivative of histamine with an intermediate chain length of four methylenes (compound **13**) was the most potent lymphocytes H_2 receptor agonist but was inactive on guinea pig myocardium H_2 receptors. The deletion of a single methylene chain (compound **12**) from this compound resulted in total loss of its H_2 activity on lymphocytes and its H_1 activity on aorta. Compound **12** became an exclusive H_1 agonist on lymphocytes H_1 receptors. The dipeptide conjugate (compound **17**) and the aliphatic congener derivative (compound **18**), both with four methylenes, retained some of the activity on guinea pig myocardium H_2 receptors, but lost their activity on lymphocytes H_2 receptors. Therefore, histamine can be modified at sites that are at a distance from the imidazole moiety, resulting in tissue selective histamine receptor agonists.

If histamine could be derivatized so that its effects became tissue and effect specific, the derivatives would be useful in probing the structure of the receptor microenvironment and of the receptor itself. If the selective effects were maintained in vivo, the derivatives could be used to explore their immune cardiovascular modulatory roles with a view toward developing them as therapeutic agents.

We have previously reported the effects of two parallel series of derivatives of a β-adrenergic agonist and two β-antagonists.[1-8] In each series, the synthesis utilized the amine end of the molecule even though this moiety was not considered responsible for recognition of the receptor. The effects of these derivatives included alterations of potency and effect and tissue specificity in each series.[1-8] What was most striking was that generally the analogous derivatives of the agonist and antagonists had an analogous skew of their pharmacologic effects. That is, the most potent or selective drugs were the closely related derivatives of each series.[1-8] Since the derivatization process did not manipulate the receptor recognition moiety (imidazole group) of the progenitor drugs, we reasoned that the ligands attached to some microenvironment of the β receptor. If such were the case, histamine might be made effect specific by similar derivatization. We took advantage of the side-chain terminal amino group on histamine to make a third series of derivatives.

This paper describes the synthesis and summarizes the comparative pharmacology of our new histamine derivatives with an emphasis on their effects on peripheral vasculature—the effects for which this amine is predominantly known. A limited report of the effects of 13 con-

Scheme I. General Methods of Histamine Modifications



R = -$(CH_2)_nCH_3$, -$(CH_2)_n$CONHAr, -$(CH_2)_n$CONH-peptide

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