# Design, Synthesis, Antineoplastic Activity, and Chemical Properties of Bis(carbamate) Derivatives of 4,5-Bis(hydroxymethyl)imidazole[1]

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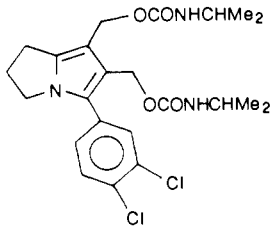
*Received March 30, 1988*

A series of bis(carbamate) derivatives of 1,2-substituted 4,5-bis(hydroxymethyl)imidazoles were prepared and evaluated against murine P388 lymphocytic leukemia. Electron-withdrawing substituents at either N-1 or C-2 gave rise to inactive compounds. However, electron-donating substituents gave active compounds and the 2-(methylthio)-1-methyl derivative **2i** (carmethizole), as the bis(*N*-methylcarbamate), was found to be very active. The derivative **2i**, referred to by the name carmethizole, was also shown to be active against the MX-1 mammary xenograft, the human amelanotic melanoma cell line (LOX) xenograft, the M5076 sarcoma, and L1210 lymphocytic leukemia. The solution stability, water solubility, $pK_a$, and log *P* of carmethizole are also reported.

We have found that bis(carbamate) derivatives of bis(hydroxymethyl) substituted pyrrolizines,[2] pyrroles,[3] and polycyclic benz-fused pyrroles[4] possess significant, reproducible antineoplastic activity.[5] The rationale used in the design of these agents led to the incorporation of two potentially reactive carbamate leaving groups (*O*-alkyl ester cleavage) on the heterocyclic system along with additional substituents on the heterocycle to modulate the reactivity of the electrophilic centers.[2a] This approach led to the discovery of a number of new agents with activity against a broad range of experimental murine neoplasias.[5] The pyrrolizine, **1**, is one such compound in this class. The

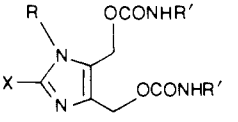



**1**

difficulty with **1** is that it is very lipophilic and is unstable in aqueous mixtures, problems that have made formulation of this agent very difficult.[6] One soluble analogue of **1** was prepared, but the compound was not stable in aqueous solution and was not active against murine P388 lymphocytic leukemias.[7]

The rationale used for the design of **1** can also be extended to imidazoles. Appropriate electron-donating or electron-withdrawing substituents can be added to the imidazole ring to modulate the reactivities of the two electrophilic centers. A potential advantage of the imidazole is that it is sufficiently basic to allow for the preparation of salts to enhance water solubility. Furthermore, in the protonated form, the imidazole ring would not be expected to stabilize developing positive charge in the reaction transition state involved in the displacement of the carbamate moieties. Thus, the salts of imidazole bis(carbamate) offer the potential of water solubility *and* stability.

This report describes the synthesis and antineoplastic evaluation of a series of imidazoles with the general structures **2** and **3**. In this series of compounds the groups




**2**: R′ = $CH_3$
**3**: R′ = $CH(CH_3)_2$

X, R, and R′ were varied to study the influence of these substituents upon antineoplastic activity and chemical reactivity. The C-2 substituent was varied to provide a range of electron-releasing character. The substituents selected were phenyl ($\sigma_p^+$ = −0.18[16a]), methyl ($\sigma_p^+$ = −0.31[16a]), methylthio ($\sigma_p^+$ = −0.60[16a]), benzyl ($\sigma_p^+$ = −0.23[16d]), and methoxy ($\sigma_p^+$ = −0.78[16b]). The carbamate substituent, R′, was only varied between methyl and isopropyl for this first series of compounds. Typically, in the pyrrole/pyrrolizine series of bis(carbamates), the *N*-methylcarbamates were slightly more reactive than the *N*-(2-propyl)carbamates.

## Chemistry

The bis(carbamates) **2** and **3** were synthesized from the corresponding diester **5** or **6** in a two-step sequence. The diester was converted to the diol **3** by hydride reduction and the bis(carbamates) were prepared from **7** by treatment with either methyl isocyanate or isopropyl isocyanate. The carbamoylation step was carried out in the presence of either triethylamine or dibutyltin diacetate as a catalyst. The tin catalyst proved to be far superior to the amine: the reaction times were shorter, the yields were higher, and

(1) (a) Vinylogous Carbinolamine Tumor Inhibitors. 22. For parts 14–21 in this series, see ref 1b–i. (b) Anderson, W. K.; DeRuiter, J.; Heider, A. R. *J. Org. Chem.* **1985**, *50*, 722. (c) Anderson, W. K.; Milowsky, A. S. *J. Org. Chem.* **1985**, *25*, 5423. (d) Anderson, W. K.; Heider, A. R. *Synth. Commun.* **1986**, *16*, 357. (e) Anderson, W. K.; Dabrah, T. T. *Synth. Commun.* **1986**, *16*, 559. (f) Anderson, W. K.; Mach, R. H. *Synth. Commun.* **1986**, *16*, 911. (g) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1986**, *29*, 2241. (h) Anderson, W. K.; Heider, A. R. *J. Med. Chem.* **1986**, *29*, 2392. (i) Anderson, W. K.; Mach, R. H. *J. Med. Chem.* **1987**, *30*, 2109.

(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*(I), 765. (c) Anderson, W. K.; McPherson, H. J., Jr. *J. Med. Chem.* **1982**, *25*, 84.

(3) (a) Anderson, W. K.; Corey, P. F. *J. Med. Chem.* **1977**, *20*, 1691. (b) Anderson, W. K.; Halat, M. J. *J. Med. Chem.* **1977**, *22*, 977. (c) Anderson, W. K.; Halat, M. J.; Rick, A. J. *J. Med. Chem.* **1980**, *23*, 87.

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(6) El-Sayed, A.-A. A.; Repta, A. J. *Int. J. Pharm.* **1983**, *13*, 303.

(7) Anderson, W. K.; Chang, C.-P.; McPherson, H. L., Jr. *J. Med. Chem.* **1983**, *26*, 1333.

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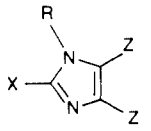
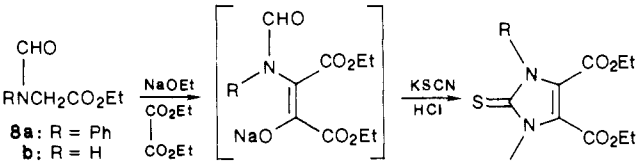


**4**: Z = $CO_2H$
**5**: Z = $CO_2CH_3$
**6**: Z = $CO_2C_2H_5$
**7**: Z = $CH_2OH$

**a**: R = H; X = Ph; **b**: R = H; X = $CH_3$; **c**: R = H; X = $SCH_3$; **d**: R = Ph; X = H; **e**: R = Ph; X = $SCH_3$; **f**: R = $CH_2Ph$; X = $SCH_3$; **g**: R = $CH_3$; X = Ph; **h**: R = X = $CH_3$; **i**: R = $CH_3$; X = $SCH_3$; **j**: R = $CH_3$; X = $OCH_3$

the products were purer when the tin catalyst was used instead of the amine.

Diethyl 1-phenylimidazole-4,5-dicarboxylate (**6d**) was synthesized from the ethyl ester of *N*-phenyl-*N*-formylglycine[8] (**8a**). Treatment of **8a** with diethyl oxalate–sodium ethoxide gave **9a**, which without isolation was treated with acid to cleave the formyl protecting group and condensed with thiocyanate to give **10a**.[9] Desulfurization[9] of **10a** with sodium nitrite–nitric acid gave **6d**.



**8a**: R = Ph
**b**: R = H

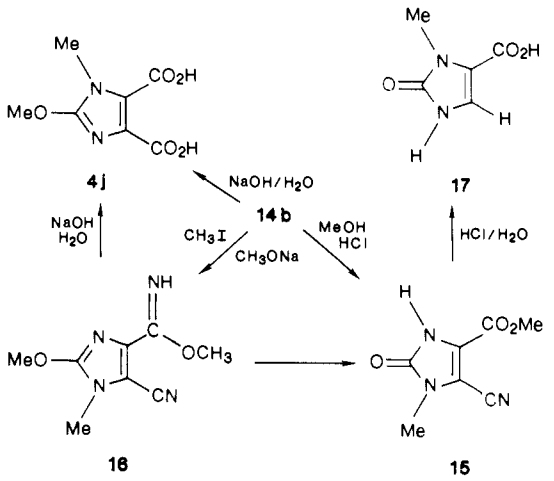
**9a**: R = Ph
**b**: R = H

**10a**: R = Ph
**b**: R = H

The thioureas **10a** and **10b** were also used to prepare the 2-(methylthio)imidazoles. Treatment of **10a** or **10b** (synthesized from *N*-formylglycine ethyl ester (**8b**) via the intermediate **9b**) with methyl trifluoromethanesulfonate or with iodomethane–sodium methoxide in methanol gave the 2-(methylthio)imidazoles **5e** and **6c**. In the sodium methoxide–methanol reaction the ethyl esters of the *N*-phenyl compound **10a** were converted to the methyl esters but the ethyl esters of **10b** were not. The 2-(methylthio)imidazole **6c** was N-methylated (diazomethane was used in small-scale reactions but sodium hydride–iodomethane was preferable in larger scale reactions) to give **6i**. Treatment of **6c** with sodium hydride gave an anion that was alkylated with benzyl bromide to give **6f**.

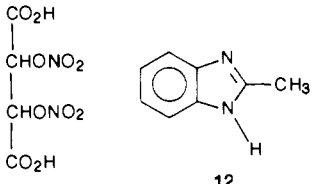
The 1-methyl-2-phenyl- and 1,2-dimethylimidazoles (**5g** and **5h**, respectively) were prepared from the corresponding 2-substituted imidazole-4,5-dicarboxylic acids (**4a** and **4b**). The methylations of **4a** and **4b** to give **5g** and **5h**, respectively, were carried out in one step by treatment with excess diazomethane. On a larger scale it was more expedient to prepare the diesters[11,12] **5a** and **5b** (anhydrous methanol–hydrogen chloride) and then N-methylate with diazomethane. The imidazole-3,4-dicarboxylic acids **4a** and **4b** were synthesized from tartaric acid dinitrate[10] (**11**) by treatment with ammonium hydroxide and either benzaldehyde or acetaldehyde. An easier synthesis of **4b** involves the oxidation of 2-methylbenzimidazole (**12**) with

**Scheme I**



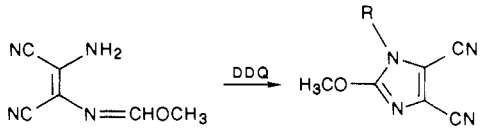
**4j** **14b** **17** **18** **15**

sodium dichromate–sulfuric acid. The workup of this one-step reaction is simple, and large quantities of **4b** can be prepared by this method.



**11** **12**

The 2-methoxy-substituted imidazoles were synthesized from diaminomaleonitrile (DAMN). The treatment of DAMN with trimethyl orthoformate gave **13**, and cyclization of **13** to the imidazole **14a** was effected by the action of DDQ in acetonitrile.[13] N-Methylation of **14a** (iodomethane–sodium hydride in DMF) gave **14b**. The overall yield of **14b** from DAMN was poor (ca. 8%), but the reactions were easily carried out on a large scale to give sufficient quantities of **14b** for the subsequent work.



**13**

**14a**: R = H
**b**: R = $CH_3$

Hydrolysis of the dinitrile **14b** to the diacid **4j** was carried out under base-catalyzed conditions. Several attempts to convert the dinitrile **14b** directly to the diester **5j** were unsuccessful. The solvolysis of **14b** in methanolic hydrogen chloride led to cleavage of the ether and methanolysis of only one of the nitrile functions to give **15**. The remaining nitrile function of the insoluble urea **15** could be solvolyzed in methanolic or ethanolic HCl. Hydrolysis of **15** in aqueous acid gave the decarboxylated product **17**. Treatment of **14b** with excess sodium methoxide–iodomethane gave the mono(imino ether) **16** and the remaining nitrile function could not be converted to the imino ether. Mild acid hydrolysis of **16** gave **15**, while more vigorous acid hydrolysis of **16** gave **17**. Base hydrolysis of **16** gave **4j** (Scheme I).

The diacid **4j** was very insoluble, but treatment of a suspension of **4j** in ether with diazomethane gave the di-

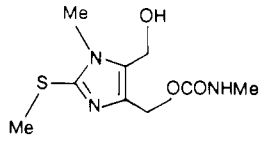
(8) (a) Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 644. (b) Godefroi, E. F.; Janssen, P. A. J.; van der Eycken, C. A. M.; van Heertum, A. H. M. T.; Viemergeers, C. J. E. *J. Med. Chem.* **1965**, *8*, 220. (c) Krimen, L. I. *Org. Synth.* **1975**, *50*, 1.
(9) Jones, R. G. *J. Am. Chem. Soc.* **1952**, *74*, 1085.
(10) Snyder, H. R.; Hendrick, R. G.; Broks, L. A. *Org. Synth.* **1947**, *22*, 65.
(11) Manecke, G.; Schlegel, R. *Chem. Ber.* **1974**, *107*, 892.
(12) Maquenne, A. *Beilstein 25*, 165. (b) Efros, L. S.; Khromov-Borisov, N. V.; Davidenkov, L. R.; Nedel, M. M. *Zh. Obshch. Khim.* **1956**, *26*, 455; *Chem. Abst.* **1956**, *50*, 13881g.
(13) Weigert, F. J. U.S. Patent 3,778,446, 1973; *Chem. Abstr.* **1974**, *80*, 59941n. (b) Begland, R. W.; Hartter, D. R.; Jones, F. N.; Sam, D. J.; Sheppard, W. A.; Webster, O. W.; Weigert, F. J. *J. Org. Chem.* **1974**, *39*, 2341.

ester **5j**. Attempts to use a variety of acid-catalyzed procedures to convert **4j** to **5i** either gave no reaction or led to ether cleavage and/or decarboxylation. An attempt to methylate the crude disodium salt of **4j** by treatment of the reaction mixture from the hydrolysis of **14b** (sodium hydroxide) with dimethyl sulfate also failed to give **5j**.

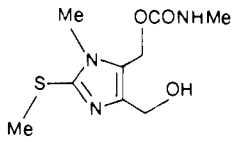
## Chemical Studies

The hydrolysis of carmethizole (**2i**) was studied by HPLC. A single monocarbamate was produced in the stepwise hydrolysis of carmethizole (**2i**) to diol **7i**. The isomeric monocarbamate (i.e. the one not produced by carmethizole hydrolysis) was prepared by partial carbamoylation of diol **7i**.

The structures of the two monocarbamates were tentatively assigned on the basis of $^{13}C$ NMR studies (Table II). Acylation of diol **7i**, to produce carmethizole (**2i**), causes an upfield shift of ca. 2.5–2.6 ppm for the imidazole C-4 and C-5 carbons and a comparable shift for the C-4′ and C-5′ carbons. The assignments for C-4 and C-5 in **2i** and **7i** were based on studies with a series of 1-methylimidazoles in which the C-5 carbons were upfield relative to the C-4 carbons.[14a] The same study showed that a C-5 methyl substituent appeared upfield relative to a C-4 methyl substituent (C-4′). On this basis, the monocarbamate obtained from the hydrolysis of carmethizole was assigned as **18** while the monocarbamate obtained from partial acylation of the diol was assigned as **19**.




**18**




**19**

2D-NMR NOESY experiments with the "hydrolysis product" monocarbamate did not support this initial assignment; the compound showed an NOE effect between the carbamate methylene and the imidazole *N*-methyl group; however, the isomeric synthetic monocarbamate failed to exhibit an unambiguous NOE effect between the hydroxymethyl methylene and the imidazole *N*-methyl. The NOESY data were in apparent conflict with the chemical shift data, so the compounds have been submitted for definative assignment by X-ray crystallography.

The hydrolysis of carmethizole (**2i**) in water at 25 °C proceeded with a half-life of 156 min (10% hydrolysis occurred in 24 min). The initial monocarbamate product of this hydrolysis, monocarbamate **18**, had a hydrolytic half-life (water at 24.3 °C) of 21.9 h ($t_{10\%}$ = 3.1 h). Hydrolysis of the isomeric, synthetic monocarbamate, **19** (water at 24.3 °C), was much faster ($t_{50\%}$ = 29 min, $t_{10\%}$ = 4 min) than the monocarbamate obtained from the hydrolysis of carmethizole. Clearly, the reactivities of the two carbamate moieties in carmethizole are significantly different.

(14) (a) Sattler, E. J.; Stoeck, V.; Schunak, W. *Arch. Pharm. (Weinheim, Ger.)* **1975**, *308*, 795. (b) Freeman, F.; Ziller, J. W.; Po, H. N.; Keindall, M. C. *J. Am. Chem. Soc.* **1988**, *110*, 2586. (c) Kister, J.; Hassanaly, P.; Faure, R.; Dou, H. *Spectrosc. Lett.* **1979**, *12*, 157. (d) Faure, R.; Vincent, E.-J.; Assef, G.; Kister, J.; Metzger, J. *Org. Magn. Reson.* **1977**, *9*, 688.

(15) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

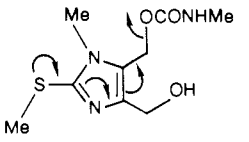
(16) (a) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979. (b) Hartman, G.; Traylor, T. *J. Am. Chem. Soc.* **1975**, *97*, 6147. (c) Hanstein, W.; Berwin, H. J.; Traylor, T. G. *J. Am. Chem. Soc.* **1970**, *92*, 829. (d) Baker, R.; Eaborn, C.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1972**, 97.

**Table I.** Temperature Dependence of the Hydrolysis of **2i**

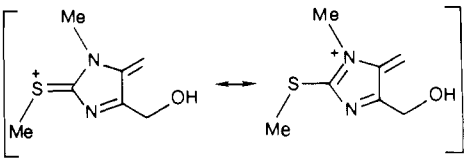
| temp, °C (K) | 1/temp (K) | $k$ | ln $k$ | $t_{1/2}$, min | $t_{1/10}$, min |
|---|---|---|---|---|---|
| 28.5 (301.5) | 0.003 317 | 0.006 81 | −4.98 | 99.6 | 14.2 |
| 25.0 (298.0) | 0.003 356 | 0.004 466 | −5.41 | 156 | 24.4 |
| 22.0 (295.0) | 0.003 390 | 0.003 879 | −5.55 | 179 | 27.2 |
| 20.0 (293.0) | 0.003 413 | 0.002 399 | −6.03 | 290 | 44.9 |
| 14.7[a] (287.7) | 0.003 476 | 0.001 052 | −6.86 | 671 | 112 |
| 8.8[a] (281.8) | 0.003 549 | 0.000 487 | −7.63 | 1341 | 134 |
| 3.2[a] (276.2) | 0.003 621 | 0.000 262 | −8.25 | 2627 | 382 |
| 2.0[a] (275.0) | 0.003 636 | 0.000 180 | −8.62 | 3900 | 634 |

[a] The reactions were all followed by HPLC. In these experiments, the eluting solvent was water–acetonitrile (85:15) rather than (80:20).

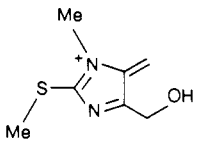
The reactivity of the C-5 carbamate moiety can be rationalized on the basis of sulfur participation in the expulsion of the carbamate moiety:



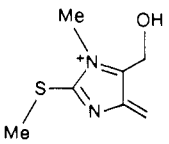

**19**




The heats of formation of **20** and **21** were calculated by using MINDO/3. The intermediate **20** was calculated to be 5.1 kcal/mol more stable than **21**. This calculation predicts that the C-5 carbamate will be more reactive than the C-4 carbamate moiety.




**20**




**21**

The hydrolysis of carmethizole was also studied as a function of temperature and solvent polarity as well as with added hydrochloric acid. The data and calculated pseudo-first-order-rate constants for the temperature dependence of the hydrolysis of carmethizole (**2i**) are given in Table I. A plot of $1/T$ (K) vs ln $K$ gave a straight line where the slope, calculated from the Arrhenius plot, gave an activation energy ($E_a$) of 22.6 kcal/mol ($r$ = 0.997).

The hydrolysis of carmethizole (**2i**) was also shown to be solvent dependent. The $t_{50\%}$ ($t_{10\%}$) of carmethizole in water (25.0 °C) containing 0, 5, 10, and 15% acetonitrile was 156 (24), 233 (35), 345 (56), and 518 min (79 min), respectively. These data are consistent with the formation of an intermediate like **20** in the hydrolysis of carmethizole. The fact that carmethizole solutions can be rendered more stable by changing the polarity of the solvent may be important in the preparation of a clinical formulation of the drug.

The rate of carmethizole hydrolysis was reduced in the presence of acid. The $t_{50\%}$ ($t_{10\%}$) of carmethizole (**2i**) in water (25.0 °C) in the presence of 0, 0.8, 1.0, and 1.2 equiv of hydrochloric acid was 156 (24), 336 (59), 507 (77), and 1200 min (185 min), respectively. The increased stability of carmethizole in acidic solution is consistent with the initial design hypothesis: the protonated imidazole is less capable of stabilizing electron-deficient transition states than the unprotonated free base.

Table II. $^{13}C$ NMR Assignments for 2i, 7i, 18, and 19

| compd | chemical shift, ppm | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-2 | C-4[a] | C-5[a] | C-1′ | C-2′ | C-4′[a] | C-4″ | C-4‴ | C-5′[a] | C-5″ | C-5‴ |
| **2i** | 143.12 | 136.58 | 127.94 | 30.62 | 15.09 | 58.28 | 156.69 | 26.91 | 54.12 | 156.35 | 26.91 |
| **18** | 141.73 | 134.26 | 132.46 | 30.51 | 15.36 | 58.47 | 156.73 | 26.94 | 51.61 | | |
| **19** | 141.53 | 141.53 | 125.72 | 30.41 | 15.27 | 56.25 | | | 54.33 | 156.41 | 26.89 |
| **7i** | 140.62 | 139.16 | 130.47 | 30.40 | 15.49 | 56.01 | | | 51.58 | | |

[a] The assignment of the chemical shifts for C-4/C-5 and C-4′/C-5′ were based on literature assignments in imidazole $^{13}C$ NMR spectra.[14]

Carmethizole (**2i**) is a weak base, $pK_a \cong 5$ (the more stable diol **7i** had $pK_a = 4.97$) and will not be protonated to any significant extent at physiological pH. Carmethizole is soluble in water at 7 mg/mL and carmethizole hydrochloride is soluble at >580 mg/mL. The log *P* of carmethizole, as measured by HPLC, is 0.74.

## Biological Results and Discussion

The imidazole bis(carbamates) were evaluated for antineoplastic activity in the murine P388 lymphocytic leukemia assay. The antileukemic data are given in Table III. Three general structure–activity relationships emerge. These are (1) electron-withdrawing substituents at either N-1 or C-2 have a detrimental effect upon antitumor activity, (2) incorporation of electron-donating groups at C-2 give rise to active compounds, and (3) the bis(*N*-methylcarbamates) show superior activity compared to the bis[*N*-(2-propyl)carbamates].

The required substitution at N-1 and C-2 lead to the conclusion that electron-releasing substituents serve to stabilize reaction transition states in the displacement of the carbamate groups. The superior activity of the *N*-methylcarbamates compared to the *N*-(2-propyl)carbamates can be attributed to the more reactive nature of the *N*-methylcarbamate.

2-(Methylthio)imidazole **2i** (carmethizole) was selected for evaluation in the NCI tumor panel. The preliminary results with **2i** (Table IV) have shown the compound to possess significant reproducible activity against a number of different tumor models. The compound gave a 91% *reduction* in the size of the originally implanted tumor in the MX-1 breast xenograft assay in nude mice (T/C = −91% at a 50 mg/kg dose) with three of six animals "cured". The M5076 sarcoma model gave one of six "cures" at a 200 mg/kg dose with T/C = 184%. The compound gave five of six cures (T/C = 365% at 100 mg/kg) in a human amelanotic melanoma cell line (LOX) in athymic mice. These data clearly reveal that **2i** has a very high level of activity against murine leukemia and solid tumor models as well as human tumors in athymic (nude, NU/NU) mice. Carmethizole, like pyrrolizine **1**, did not show good activity against L1210 leukemia.

Imidazole **2i** and the hydrochloride salt of **2i** were compared directly in the MX-1 mammary xenograft and the LOX assays in the nude (NU/NU) mouse. The hydrochloride was equiactive, although somewhat more potent than the free base on a molar basis. The salt gave % T/C (complete remissions/total number of animals) = −63 (1/6), −85 (1/6), and −91 (3/6) at doses of 115, 57.5, and 28.75 mg/kg given ip on days 1, 5, and 9 following subrenal capsule implant of a human MX-1 mammary tumor (0.5 mg) on day 0. Carmethizole hydrochloride (**2i**·HCl) gave 198 (2/6), 156, and 145% T/C values (number of long-term survivors, 60 days/total number of test animals) in the ip ($10^6$ cells implanted on day 0) human LOX amelanotic melanoma at respective ip doses of 115, 57.5, and 28.75 mg/kg given on days 1, 5, and 9. Additional studies with advanced human tumor xenografts appear very promising, and details of these and other assays will be published when the studies have been completed.

In summary, it has been shown that the imidazole bis(carbamate) **2i** has very good broad-spectrum antineoplastic activity, that the compound can be formulated as a water-soluble salt, and that the salt is sufficiently stable to permit formulation as a drug. These attributes, in conjunction with the fact that carmethizole represents a new class of antineoplastic agents, make it an important candidate for further biological and chemical studies. Studies are currently in progress to bring carmethizole hydrochloride into clinical trials.

## 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 KBr wafers unless specified otherwise. NMR spectra were determined with either a Varian T-60A, a EM 390, or a FT-80 spectrometer for deuteriochloroform solutions containing tetramethylsilane as internal standard unless specified otherwise. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

**General Procedures for the Preparation of the Bis(carbamates) 2 and 3. Method A.** A mixture of the diol (10 mmol), freshly distilled isocyanate (30–40 mmol), and anhydrous triethylamine (0.5 mL) in dichloromethane (75 mL) was stirred at temperatures ranging from room temperature to reflux for 16 h to 6 days. The volatiles were removed in vacuo, and the product was crystallized from ethyl acetate and dried in vacuo to give **2d** (38%, mp 136–154 °C; pyridine was used as the catalyst; 24 h at room temperature), **2e** (82%, mp 137–138 °C; 6 days at reflux), and **2g** [84%; mp 129–132 °C (benzene); 16 h at reflux].

**Method B.** A mixture of the pure diol (10 mmol) and freshly distilled isocyanate (30–40 mmol) in anhydrous dichloromethane (100 mL) was treated with 2–3 drops of dibutyltin diacetate. The mixture was stirred at room temperature for 3 h (usually a clear solution developed within 15–30 min), then the volatiles were removed in vacuo at room temperature, and the product was crystallized from dichloromethane–hexanes and dried in vacuo to give **2f** (75%; mp 154–155 °C), **2i** (77%; mp 125–126 °C),[17] **3d** (86%; mp 180–182 °C), **3e** (92%; mp 140–141 °C), **3f** (84%; mp 146–147 °C), **3i** (94%; mp 105–107 °C), and **3j** (88%; mp 112–113 °C; 8 h reaction time).

The $^1H$ NMR spectral data for **2** and **3** are summarized in Table V. The IR spectrum of **2i** was typical of the bis(carbamates): 3323, 2956, 1713, 1692, 1558, 1529, 1466, 1255, 1120 $cm^{-1}$. All of the bis(carbamates) **2** and **3** gave satisfactory analyses for C, H, and N.

**2-Phenyl-4,5-imidazoledicarboxylic Acid (4a).** Tartaric acid (30 g, 0.20 mol) was suspended in a mechanically stirred mixture of concentrated (70%) nitric (35 mL) and fuming (90%) nitric (95 mL) acids. Concentrated sulfuric acid (130 mL) was added rapidly until the reaction temperature rose to 38 °C, ice bath cooling was applied, and the rapid addition of the sulfuric acid was continued so as to maintain a reaction temperature of 38–43 °C. After the addition was completed, the reaction mixture was chilled on ice 1 h. The resulting white cake was filtered on a large

(17) An improved yield (99%) of carmethizole (**2i**) was obtained when methyl isocyanate (0.136 mol), dibutyltin diacetate (20 drops), and pure diol **7i** (0.077 mol) in anhydrous dichloromethane (1.5 L) were stirred 15 h at ambient temperature under an anhydrous argon atmosphere. The volatiles were removed in vacuo at room temperature, and the residue was triturated with pentane to give pure carmethizole.

**Table III.** Activity of Imidazole Bis(carbamates) against P388 Lymphocytic Leukemia in Mice[a,b]

| compd | dose/inj,[c] mg/kg | tox day surv[d] | BWD,[e] g | % T/C[f] | KE[g] |
|---|---|---|---|---|---|
| **2d** | 200 | 5/5 | −1.2 | 99 | −1.55 |
| | 100 | 5/5 | −0.4 | 101 | −1.52 |
| | 50 | 5/5 | −0.8 | 101 | −1.52 |
| | 25 | 5/5 | 0.2 | 95 | −1.61 |
| | 12.5 | 5/5 | −0.4 | 99 | −1.55 |
| **3d** | 400 | 6/6 | −2.3 | 90 | |
| | 200 | 6/6 | 0.2 | 90 | |
| | 100 | 6/6 | 0.6 | 91 | −1.69 |
| | 50 | 6/6 | 0.8 | 97 | −1.62 |
| | 25 | 6/6 | −0.1 | 103 | −1.53 |
| | 12.5 | 6/6 | −0.4 | 103 | −1.53 |
| **2e** | 400 | 4/5 | −5.2 | | |
| | 200 | 5/5 | −3.0 | 156 | 1.46 |
| | 100 | 5/5 | −1.6 | 133 | 0.17 |
| | 50 | 5/5 | −1.4 | 141 | 0.60 |
| **3e** | 400 | 6/6 | −4.8 | 100 | −1.52 |
| | 200 | 5/6 | −2.8 | 90 | −1.64 |
| | 100 | 6/6 | −2.0 | 97 | −1.62 |
| | 50 | 6/6 | 0.3 | 95 | −1.64 |
| | 25 | 6/6 | 0.6 | 101 | −1.55 |
| | 12.5 | 6/6 | −0.2 | 111 | −1.42 |
| **2f** | 400 | 6/6 | −1.2 | 127 | −0.71 |
| | 200 | 6/6 | −0.4 | 129 | −0.44 |
| | 100 | 6/6 | 0.4 | 116 | −1.19 |
| | 50 | 6/6 | 0.9 | 116 | −1.19 |
| **3f** | 400 | 3/6 | −3.2 | | |
| | 200 | 6/6 | −2.2 | 116 | −0.32 |
| | 100 | 6/6 | −0.3 | 111 | −0.39 |
| | 50 | 6/6 | −0.5 | 110 | −0.42 |
| | 25 | 6/6 | −1.5 | 101 | −1.59 |
| | 12.5 | 6/6 | −0.2 | 98 | −1.64 |
| **2g** | 200 | 5/5 | −2.2 | 119 | −1.28 |
| | 100 | 5/5 | −1.0 | 116 | −1.31 |
| | 50 | 5/5 | −0.8 | 112 | −1.38 |
| | 25 | 5/5 | 0.0 | 107 | −1.44 |
| | 12.5 | 5/5 | −0.2 | 98 | −1.56 |
| **2i** | 100 | 6/6 | −4.1 | 236 | 6.75 |
| | 50 | 6/6 | −2.6 | 184 | 4.21 |
| | 25 | 6/6 | −1.4 | 147 | 1.05 |
| | 12.5 | 6/6 | −1.2 | 147 | 1.05 |
| | 6.25 | 5/6 | −0.7 | 125 | −0.83 |
| **3i** | 400 | 6/6 | −3.4 | 70 | |
| | 200 | 6/6 | −1.8 | 184 | 4.21 |
| | 100 | 6/6 | −1.2 | 163 | 1.89 |
| | 50 | 6/6 | 0.0 | 130 | −0.56 |
| | 25 | 6/6 | 0.4 | 125 | −0.91 |
| | 12.5 | 6/6 | 2.6 | 113 | −1.40 |
| **3j** | 400 | 6/6 | −4.2 | 196 | 3.88 |
| | 200 | 6/6 | −2.6 | 189 | 3.41 |
| | 100 | 6/6 | −2.1 | 166 | 1.87 |
| | 50 | 6/6 | −1.0 | 147 | 0.54 |
| | 25 | 6/6 | −0.1 | 130 | −0.60 |

[a] Determined under the auspices of the National Cancer Institute. For general screening procedures and data interpretation, see: Geran, R. I.; Greenburg, N. H.; McDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*(2), I. [b] Ascitic fluid containing approximately $10^6$ cells was inoculated into CD2F1 mice. [c] The compounds were given by intraperitoneal injection as either solutions or suspensions in normal saline. Solutions of drug were prepared fresh daily. The drugs were given daily for 5 days beginning 24 h after tumor inoculation. [d] Toxicity day evaluations were carried out on day 5; number of survivors/number of animals in initial test groups are given. [e] BWD refers to the body weight difference (grams) of the test animals on day 5 for P388 and L1210, day 10 for LOX, and day 14 for M5076 minus day 1. [f] % T/C refers to the percent of the median survival time of test animals compared to control animals. [g] KE refers to tumor cell kill and is the log of the tumor cell population at the onset of treatment minus the log of the tumor cell population at the end of treatment.

**Table IV.** Antitumor Activity of Carmethizole (**2i**)[a]

| tumor[b] | dose,[c] mg/kg | toxicity survivors[d] | body weight[e] difference (T − C), g | % T/C[f] (cures)[h] | KE[g] |
|---|---|---|---|---|---|
| P388 | 100 | 6/6 | −4.1 | 236 | >6.75 |
| | 50 | 6/6 | −2.6 | 184 | 4.21 |
| | 25 | 6/6 | −1.4 | 147 | 1.05 |
| | 12.5 | 6/6 | −1.2 | 147 | 1.05 |
| | 6.5 | 6/6 | −0.7 | 125 | −0.83 |
| L1210 | 200 | 0/6 | −3.6 | | |
| | 100 | 6/6 | −1.9 | 145 | −0.29 |
| | 50 | 6/6 | −0.5 | 124 | −1.94 |
| | 25 | 6/6 | 0.0 | 111 | −2.23 |
| | 12.5 | 6/6 | −0.2 | 103 | −2.35 |
| M5076 | 400 | 1/10 | | | |
| | 200 | 10/10 | −1.9 | 184 (1/10) | 0.98 |
| | 100 | 10/10 | −1.2 | 151 | −0.34 |
| | 50 | 10/10 | −0.7 | 119 | −1.63 |
| | 25 | 10/10 | −2.0 | 122 | −1.51 |
| LOX | 200 | 3/6 | −11.5 | | |
| | 100 | 6/6 | −5.1 | 365 (5/6) | |
| | 50 | 6/6 | −3.3 | 231 | |
| | 25 | 6/6 | −3.0 | 219 | |
| MX-1[i] | 200 | 1/6 | | | |
| | 100 | 6/6 | −2.7 | −73 | |
| | 60 | 6/6 | −1.9 | −91 (3/6) | |

[a] See footnote *a* in Table III. [b] The tumors were implanted on day 0. The solid tumor (1 $mm^3$, 0.5 mg) in the MX-1 mammary xenograft assay was introduced as a subrenal capsule implant. All other tumors were inoculated ip, implant sizes equal $10^6$ cells for P388 lymphocytic leukemia, M5076 sarcoma, and human LOX amelanotic melanoma and $10^5$ cells for L1210 lymphocytic leukemia. [c] Carmethizole was given ip as a suspension (freshly prepared prior to the injection) in saline on the schedules: P388 and L1210, daily on days 1–5; M5076 B6C3$F_1$ mice) every fourth day on days 1, 5, 9, and 13; LOX (NCr-nu mice) and MX-1 (NCr-nu mice) every fourth day on days 1, 5, and 9. [d-g] See the corresponding footnotes in Table III. [h] The % T/C values include long-term survivors. The cures in M5076 and LOX were 60-day survivors. The MX-1 assays were evaluated on day 11 and "cures" refers to no remaining tumor. [i] The MX-1 % T/C refers to tumor size. A positive value is the change in treated tumor size relative to the change in control tumor size and a negative value is the percent reduction in the treated tumor relative to the size of the initial tumor implant.

glass wool lined Buchner funnel and air-dried as much as possible. The crude tartaric acid dinitrate 11 was added portionwise to crushed ice (400 g) with vigorous stirring. The mixture was cooled to −10 °C on a dry ice–acetone bath, and the dinitrate solution was neutralized (pH paper) with concentrated ammonium hydroxide (80–120 mL) at a rate such that the temperature remained between −5 and −10 °C. Additional concentrated ammonium hydroxide (60 mL) was added and then the mixture was treated with freshly distilled benzaldehyde (20.4 mL, 0.20 mol). The reaction was stirred for 20 h at 0 °C and then neutralized with concentrated hydrochloric acid; the product was filtered, washed first with water and then ether, and air-dried to give 20–30 g of diacid **4a** (43–54% yield): mp 270–273 °C dec (lit.[10] mp 265–270 °C dec); IR 3450, 3300, 3250, 3050, 1560, 1540, 1520, 1480, 1460, 1400, 1380, 1270, 1240, 710 $cm^{-1}$.

**2-Methyl-4,5-imidazoledicarboxylic Acid (4b). Method A.** Tartaric acid dinitrate (11; 0.67 mol) was prepared and neutralized to congo red test paper with concentrated ammonium hydroxide (ca. 500 mL) as in the synthesis of **4a**. Additional concentrated ammonium hydroxide (50 mL) was added followed by an acetaldehyde solution [previously prepared by the careful addition of acetaldehyde (195 mL, 3.5 mol) to concentrated ammonium hydroxide (250 mL) with ice bath cooling]. The dry ice–acetone bath was replaced with ice–water and the reaction mixture was allowed to warm to room temperature over 16 h. The precipitate was filtered, resuspended in water (400 mL) and stirred, and filtered, and the solid was washed with water (3 × 75 mL), methanol (2 × 40 mL), and ether (2 × 40 mL) and then dried under vacuum to give **4b** (70 g, 62%): mp 274–275 °C dec with effervescence (lit.[12a] dec pt 300 °C; lit.[12b] dec pt 273 °C); IR 3550, 3450, 3200, 2550, 1910, 1580, 1390, 1250, 1120, 950, 860, 770 $cm^{-1}$.

**Method B.** 2-Methylbenzimidazole (5 g) was added to a mixture of concentrated sulfuric acid (70 mL) and water (55 mL) at 90 °C. This was followed by the careful addition of powdered

Table V. $^1$H NMR Spectral Data of the Bis[(carbamoyloxy)methyl]imidazoles 2 and 3 and Bis(hydroxymethyl)imidazole 7[a]

| compd | C-2 substit | $NHCH_3$ or $NHCH(CH_3)_2$ | NH | $-CH_2-$ | N-1 substit |
|---|---|---|---|---|---|
| **2d** | 7.58 | 2.70 (d, 3), 2.78 (d, 3) | 5.2 (br) | 5.08, 5.20 | 7.20–7.53 (m) |
| **2e** | 2.55 | 2.51 (d, 3), 2.79 (d, 3) | 4.9 (br) | 4.97, 5.18 | 7.17–7.55 (m) |
| **2f** | 2.72 | 2.87, 2.97 | 4.73 (br) | 5.33, 5.42 | 5.30, 7.20–7.70 (m) |
| **2g** | 7.28–7.62 (m) | 2.74 (d, 3), 2.78 (d, 3) | 5.1 (br) | 5.15, 5.27 | 3.65 |
| **2i** | 2.60 | 2.73 (d, 3), 2.82 (d, 3) | 4.95 (br) | 5.10, 5.18 | 3.55 |
| **3d** | 7.58 | 1.12 (d, 6), 1.15 (d, 6), 3.78 (m) | 4.60 (br) | 5.07, 5.20 | 7.33–7.48 (m) |
| **3e** | 2.57 | 1.11 (d, 6), 1.15 (d, 6), 3.77 (m) | 4.52 (br) | 4.93, 5.15 | 7.20–7.55 (m) |
| **3f** | 2.62 | 1.08 (d, 6), 1.16 (d, 6), 3.73 (m) | 4.20 (br) | 5.15, 5.23 | 5.10, 6.93–7.4 (m) |
| **3i** | 2.62 | 1.15 (d, 6), 3.82 (m) | 4.63 (br) | 5.09, 5.18 | 3.55 |
| **3j** | 3.35 | 1.13 (d, 7), 3.83 (m) | 4.57 (br) | 5.00, 5.10 | 4.03 |
| **7d**[b] | 7.82 | 4.77–5.18 (m)[d] | | 4.42–4.55 (m) | 7.42–7.68 (m) |
| **7e**[b] | 2.48 | 4.73 (br),[d] 4.08 (br)[d] | | 4.28 (d, 5), 4.48 (d, 5) | 7.5 (br) |
| **7f**[b] | 2.51 | | | 4.13–4.46 (m)[e] | 5.06, 6.73–7.20 (m) |
| **7g**[b] | 7.40–7.40 (m) | 4.9 (br)[d] | | 4.43 (br), 4.62 (br) | 3.68 |
| **7h** | | | | | |
| **7i**[c] | 2.52 | | | 4.48, 4.53 | 3.58 |
| **7j**[b] | 3.29 | | | 4.13–4.85 (m)[e] | 3.87 |

[a] Unless otherwise noted, samples were dissolved in $CDCl_3$–TMS. The peaks are singlets unless designated as m = multiplet, d = doublet, or br = broad in parentheses; coupling constants, in hertz, are also given in parentheses. [b] DMSO-$d_6$–TMS was the solvent. [c] DMSO-$d_6$–$CDCl_3$–TMS was the solvent. [d] The O*H* signal. [e] Overlapping signal (6 H) for O*H* and $CH_2$.

potassium dichromate (37 g). After 15–20 min the mixture was quenched with ice-cold water and cooled to 0 °C. Crystallization was induced by scratching the sides of the vessel. The precipitated acid was filtered and washed with water, alcohol, and finally with ether. Acid **4b** (4.19 g; 50% mp 273–275 °C) was sufficiently pure for the next step.

**1-Methyl-2-methoxyimidazole-4,5-dicarboxylic Acid (4j) and 1-Methyl-2-methoxyimidazole-4,5-dicarboxylic Acid Hydrochloride.** A mixture of 1-methyl-2-methoxyimidazole-4,5-dicarbonitrile (**14b**) (1 g, 0.0062 mol) and 10% sodium hydroxide solution (30 mL) was heated at reflux for 4 h (ammonia was evolved). The mixture was cooled, water (130 mL) was added, and the mixture was neutralized with concentrated hydrochloric acid. The precipitate was collected, dried (0.81 g, 65%), and crystallized from 90% ethanol to give **4j** as colorless crystals: mp 192–4 °C (dec with evolution of carbon dioxide); $^1$H NMR (DMSO-$d_6$–TMS) $\delta$ 8.0 (br s), 4.02 (s, 3 H), 3.63 (s, 3 H). Anal. ($C_7H_8N_2O_5$) C, H, N.

The hydrochloride salt of **4j** was obtained if the reaction mixture was neutralized with concentrated hydrochloric acid before dilution with water. The salt of **4j** had mp 300 °C dec. Anal. ($C_7H_8N_2O_5$·HCl) C, H, N.

**Dimethyl 2-Phenyl-4,5-imidazoledicarboxylate (5a).** 2-Phenyl-4,5-imidazoledicarboxylic acid (**4a**; 18 g, 77.5 mmol) was suspended in absolute methanol (1.2 L, dried over magnesium turnings with a catalytic amount of carbon tetrachloride) and treated with hydrogen chloride gas (dried by bubbling through concentrated sulfuric acid) until the solution became saturated and all the diacid had dissolved. The mixture was stirred 3 weeks at room temperature. The solvent was removed, water (500 mL) was added, and the resultant suspension was stirred until all the residue had dissolved. This acidic solution was carefully treated with concentrated sodium hydroxide until a pH of 9 was obtained (multirange pH test paper). The resultant precipitate was extracted with dichloromethane (3 × 150 mL). The extracts were combined, dried (magnesium sulfate), and concentrated in vacuo, and the residue (mp 155–6 °C) was crystallized from hot ethyl acetate to give diester **5a** as colorless needles: mp 156–8 °C (lit.[11] mp 157 °C). A second crop was obtained from the mother liquor to give a total of 14.4 g (72% yield): $^1$H NMR $\delta$ 3.90 (s, 6 H), 7.33–8.13 (m, 5 H), 11.78 (br, 1 H); IR 3450, 2975, 1730, 1540, 1490, 1470, 1440, 1400, 1300, 1260, 1210, 1170, 1070, 960 cm$^{-1}$.

**Dimethyl 2-Methyl-4,5-imidazoledicarboxylate (5b).** Diester **5b** was prepared from diacid **4b** in 26% yield with the same method used for the synthesis of **5a**. Diester **5b** had the following: mp 138–140 °C (lit.[10-12] 139–140 °C); $^1$H NMR $\delta$ 2.52 (s, 3 H), 3.87 (s, 6 H), 12.23 (br s, 1 H).

**Dimethyl 2-(Methylthio)-1-phenylimidazole-4,5-dicarboxylate (5e).** Sodium methoxide (1.8 g, 0.033 mol) was slowly added to a suspension of diethyl 2-mercapto-1-phenylimidazole-4,5-dicarboxylate (**10a**) (10 g, 0.031 mol) in absolute methanol (100 mL) and the iodomethane (5 g, 0.035 mol) was added. The mixture was allowed to stir overnight, additional iodomethane (5 g, 0.035 mol) was added, and the mixture was stirred for 1 h. The methanol was removed in vacuo and ice-cold water was added to the residue. The mixture was filtered, and the collected solid was washed with water and dried to give 7.6 g (80%) of pure dimethyl 2-(methylthio)-1-phenylimidazole-4,5-dicarboxylate (**5e**): mp 121–122 °C (white needles from methanol–water); IR 3450, 3075, 2975, 1730, 1550, 1500, 1460, 1430, 1380, 1340, 1270, 1210, 1200, 1170, 1070, 1000, 980, 770, 700 cm$^{-1}$; $^1$H NMR $\delta$ 7.57–7.13 (m, 5 H), 3.93 (s, 3 H), 3.68 (s, 3 H), 2.63 (s, 3 H). Anal. ($C_{14}H_{14}N_2O_4S$) C, H, N.

**Dimethyl 1-Methyl-2-phenyl-4,5-imidazoledicarboxylate (5g). Method A.** From imidazole diacid **4a**: 2-Phenyl-4,5-imidazoledicarboxylic acid (**4a**; 3.45 g, 14.8 mmol) was suspended in absolute methanol (10 mL) and anhydrous ether (100 mL) at room temperature. An ethereal solution of diazomethane was added until no further reaction occurred and the yellow diazomethane color persisted. The reaction mixture was then stored at 0 °C and additional ethereal diazomethane was added as necessary to maintain the yellow color. After 15 h acetic acid was added dropwise to the mixture until all the excess diazomethane had reacted, as determined by the loss of its characteristic color and the cessation of gas evolution. The slightly cloudy solution was concentrated in vacuo, the residue was dissolved in absolute ethanol, filtered, and concentrated in vacuo to give a yellowish oil (which crystallized on seeding with material obtained from method B). The diester was crystallized from 2-propanol to give 3.64 g (89% yield) of **5g**.

**Method B.** From dimethyl 2-phenyl-4,5-imidazoledicarboxylate, **5a**: Diester **5a** (12.0 g, 46 mmol) was suspended in anhydrous ether (200 mL) and a large excess of ethereal diazomethane was added. The reaction, capped with a calcium sulfate drying tube, was then stored at 0 °C for 68 h. Acetic acid was added to the vigorously stirred, ice-cooled solution until the yellow diazomethane color disappeared. The solution was concentrated in vacuo and the residual oil was crystallized from 2-propanol to give **5g** (9.5 g), mp 77–79 °C; an additional 1.4 g was obtained from the mother liquor for a total 10.9 g (86%): $^1$H NMR $\delta$ 3.86 (s), 3.95 (s), 3.97 [s (9 H total for the three singlets)], 7.42–7.70 (m, 5 H); IR 2950, 1710, 1550, 1430, 1390, 1330, 1280, 1170, 1110, 1030, 960 cm$^{-1}$. Anal. ($C_{14}H_{14}N_2O_4$) C, H, N.

**Dimethyl 1,2-Dimethylimidazole-4,5-dicarboxylate (5h).** A solution of diazomethane (1.5 g, 35.7 mmol) in ether (100 mL) was slowly added at 0 °C with stirring to a suspension of ester **5b** (4.2 g, 18.59 mmol) in ether (100 mL). After the addition was completed, the solution was stirred at room temperature overnight. Excess diazomethane was decomposed by the slow and careful addition of dilute acetic acid and the mixture was concentrated in vacuo. Water (50 mL) was added and the mixture was thoroughly extracted with dichloromethane. The organic phase was washed with water, saturated sodium bicarbonate, and again with water. The solution was dried and the solvent was removed in vacuo to give **5h** (4.46 g, 100%) as a pale yellow oil which was homogeneous on TLC: $^1$H NMR ($CDCl_3$–TMS) $\delta$ 4.4 (q, 4 H),

3.7 (s, 3 H), 2.4 (s, 3 H), 1.4 (t, 6 H).

**Dimethyl 1-Methyl-2-methoxyimidazole-4,5-dicarboxylate (5j).** 1-Methyl-2-methoxyimidazole-4,5-dicarboxylic acid (**5j**) (8.0 g, 0.04 mol) was slowly added in small portions to a solution of diazomethane (ca. 3 g) in ether (nitrogen was evolved). The mixture was allowed to stand overnight at room temperature, the excess diazomethane was decomposed by the addition of dilute acetic acid, and the mixture was concentrated to dryness in vacuo. Water (100 mL) was added to the residue and the suspension was neutralized by the addition of sodium bicarbonate. The mixture was extracted with dichloromethane, and the organic phase was dried (sodium sulfate) and concentrated to dryness in vacuo. The oily residue slowly crystallized and the solid was recrystallized from dichloromethane–hexanes to give 7.60 g (83%) of **5j** as colorless needles: mp 62–63 °C; IR 2955, 1741, 1713, 1558, 1508, 1438, 1374, 1275, 1176, 1113, 1014 $cm^{-1}$; $^1H$ NMR $\delta$ 4.12 (s, 3 H), 3.88 (s, 6 H), 3.58 (s, 3 H). Anal. ($C_9H_{12}N_2O_5$) C, H, N.

**Diethyl 2-(Methylthio)imidazole-4,5-dicarboxylate (6c). Method A.** A stirred suspension of the sparingly soluble thiourea (**10b**, vacuum *dried* and powdered, 54.4 g, 0.243 mol) in anhydrous dichloromethane (2.2 L) was heated at reflux and part of the solvent was removed (ca. 1 L) by distillation (to help remove the trace amount of water that is frequently complexed with the thiourea and also to make the suspension more "colloid-like"). The material on the side of the flask was washed down into the colloid-like solution with anhydrous dichloromethane (500 mL) under an argon atmosphere. The mixture was allowed to cool to room temperature under an argon purge and methyl trifluoromethanesulfonate [50 g, 0.305 mol (1.25 equiv)] was added as a single injection, with a dry syringe, to the stirred (argon) mixture. The reaction mixture was stirred at ambient temperature for 5 h, cooled to 0 °C, and quenched with water (32 mL). The mixture was stirred at 0 °C for 1 h, and the pale yellow solid precipitate was collected, washed with hexane (3 × 100 mL), and dried in vacuo (0.1 Torr) at *room temperature* to give **6c** (61.8 g, 99%). The crude product, which was homogeneous on silica gel TLC [$R_f$ 0.68, dichloromethane–ethyl acetate (4:1)] and sufficiently pure for the next step, had the following: mp 125–127 °C; $^1H$ NMR (DMSO-$d_6$–TMS) $\delta$ 1.3 (t, $J$ = 7 Hz, 6 H), 2.68 (s, 3 H), 4.3 (q, $J$ = 7 Hz, 4 H), 8.9 (br s, 1 H); IR (KBr) 3136 (br s), 3030 (s), 2992 (m), 1758 (s), 1731 (m), 1516 (s), 1454 (w), 1290 $cm^{-1}$ (s). An analytical sample (white needles), prepared by crystallization from ethyl acetate–hexane (or from hot water), had mp 164–166 °C.

**Method B.** Iodomethane (15.62 g, 0.11 mol) was added to a solution of 24.4 g (0.10 mol) of diethyl 2-mercaptoimidazole-4,5-dicarboxylate (**10b**; 24.4 g, 0.10 mol) and sodium methoxide (6.0, 0.11 mol) in absolute methanol (500 mL) at room temperature. Additional iodomethane (**5g**) was added after 1 h and the yellow solution was allowed to stir at room temperature for 3 h. The methanol was then removed in vacuo, the residue was treated with cold water, and the light yellow solid was filtered and dried to give diethyl 2-(methylthio)imidazole-4,5-dicarboxylate (**6c**; 22.3 g, 86%). An analytically pure sample was obtained as white needles (recrystallization from ethyl acetate–hexane): mp 164–166 °C; IR 3492, 2900, 2851, 2689, 2647, 1746, 1732, 1499, 1407, 1294, 1259, 1062 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$–TMS) $\delta$ 8.9 (br s, 1 H), 4.39 (q, $J$ = 7.2 Hz, 4 H), 2.67 (s, 3 H), 1.37 (t, $J$ = 7.2 Hz, 6 H). Anal. ($C_{10}H_{14}N_2O_4S$) C, H, N.

**Diethyl 1-Phenylimidazole-4,5-dicarboxylate (6d).** Diethyl 2-mercapto-1-phenylimidazole-4,5-dicarboxylate (**10a**) was added portionwise to a stirred mixture of concentrated nitric acid (32 mL) in water (80 mL) containing sodium nitrite (0.2 g). The temperature was maintained between 33 and 38 °C by means of an oil bath. The mixture was stirred for 1 h and excess sodium carbonate (30–40 g) was added to give a pH of 9 (indicator paper). The aqueous solution was extracted with chloroform (4 × 100 mL). The combined chloroform extract was dried (sodium sulfate) and concentrated in vacuo to give a brown oil (26.67 g, 93%) that slowly crystallized under high vacuum; the solid had mp 75–80 °C. The solid was recrystallized from ethanol–water to give **6d**: mp 81–83 °C (lit.[9] mp 84–85 °C); $^1H$ NMR $\delta$ 1.17 (t, $J$ = 7 Hz), 1.42 [t, $J$ = 7 Hz, 6 H (total for both triplets)], 4.26 (q, $J$ = 7 Hz), 4.44 [q, $J$ = 7 Hz, 4 H (total for both quartets], 7.42–7.58 (m), 7.65 [s (6 H total for both signals)]; IR 3450, 3125, 3000, 1750, 1720, 1600, 1570, 1510, 1490, 1380, 1350, 1260, 1240, 1190, 1140, 1060, 780, 770 $cm^{-1}$. Anal. ($C_{15}H_{16}N_2O_4$) C, H, N.

**Diethyl 1-Benzyl-2-(methylthio)imidazole-4,5-dicarboxylate (6f).** Sodium hydride in an oil dispersion (2.16 g, 0.45 mol) was added to a stirred solution of **6c** (7.74 g, 0.04 mol) and benzyl bromide (5.13 g, 0.03 mol) in anhydrous dimethylformamide at room temperature. The reaction mixture was stirred at room temperature for 3 h and then poured into ice–water (500 mL). The aqueous mixture was extracted with chloroform, and the combined chloroform extract was washed with water, dried (sodium sulfate), and concentrated to dryness in vacuo. The residual dimethylformamide was removed by distillation to give **6f** as an oil that was used as such in the synthesis of **7f**.

**Diethyl 1-Methyl-2-(methylthio)imidazole-4,5-dicarboxylate (6i). Method A.** A stirred solution of the dried diethyl 2-(methylthio)imidazole-4,5-dicarboxylate (**6c**; 38.7 g, 0.15 mol) in *anhydrous* DMF (600 mL) under an argon atmosphere was cooled to 0–10 °C and treated with 60% sodium hydride in mineral oil (18 g, 0.45 mol). The mixture was stirred at 0–10 °C for 0.5 h under an argon atmosphere, iodomethane [63.88 g (28 mL), 0.45 mol] was added, the mixture was stirred at 0–10 °C for 0.5 h, and then the mixture was stirred at 30–35 °C for 5 h and, finally, stirred overnight at room temperature. A brownish-white cake formed. The reaction mixture was quenched with water (50 mL) and then concentrated to dryness in vacuo at 30 °C. The residue was treated with water (200 mL) and extracted with dichloromethane (3 × 600 mL). The organic phase was filtered and concentrated to dryness in vacuo. The oily residue was distilled azeotropically with benzene at 40 °C and dried in vacuo at room temperature (0.1 Torr) to give diethyl 1-methyl-2-(methylthio)imidazole-4,5-dicarboxylate (**6i**; 38.0 g, but contains mineral oil). The product was homogeneous on silica gel TLC [$R_f$ 0.46, dichloromethane–ethyl acetate (85:15), blue fluorescence under UV light] and sufficiently pure for use in the next step.

**Method B.** Diethyl 2-(methylthio)imidazole-4,5-dicarboxylate (**6c**; 10 g, 0.039 mol) was slowly added in small portions to a solution of diazomethane in ether (containing approximately 3 g of diazomethane). Nitrogen was evolved immediately and the solution was allowed to stand at room temperature overnight. Excess diazomethane was then decomposed by the addition of dilute acetic acid and the reaction mixture was worked up in the usual way. Diethyl 1-methyl-2-(methylthio)imidazole-4,5-dicarboxylate (**6i**, 10.2 g, 97%) was obtained as a thick yellow oil: IR 2985, 2935, 1728, 1714, 1544, 1467, 1368, 1326, 1276, 1191, 1107, 1022 $cm^{-1}$; $^1H$ NMR $\delta$ 4.38 (q, $J$ = 7.2 Hz, 2 H), 4.35 (q, $J$ = 7.2 Hz, 2 H), 3.73 (s, 3 H), 2.70 (s, 3 H), 1.38 (overlapping triplets, $J$ = 7.2 Hz, 6 H). The crude oil was reasonably pure by TLC and was used as such in the preparation of **7i**.

**General Procedure for the Reduction (Lithium Aluminum Hydride) of Diesters 5 and 6 to Diols 7.** A solution of the diester (23 mmol) in freshly distilled anhydrous dichloromethane (50 mL) was added slowly to a stirred suspension of lithium aluminum hydride (69 mmol) in anhydrous ether (140 mL) at 0–5 °C. The mixture was stirred at 0–5 °C for 3 h after the addition was completed and then for 1 h at room temperature. The excess hydride was carefully decomposed by the slow, sequential addition of water (2.6 mL), 15% sodium hydroxide solution (2.6 mL), and water (7.8 mL). The precipitate of inorganic salts was filtered and extracted continuously for 24 h with tetrahydrofuran heated under reflux in a Soxhlet apparatus. The tetrahydrofuran solution was combined with the filtrate from the reaction mixture and concentrated to dryness in vacuo. The product was dried in vacuo and crystallized from tetrahydrofuran to give **7d** (65%; mp 111–112 °C), **7e** (81%; mp 167–168 °C), **7f** (46% overall from **6c**; mp 129–130 °C), **7g** (70%; mp 159–163 °C), **7i** [79%; mp 121–122 °C from acetone–ethyl acetate (2:1) containing 1% methanol], and **7j** (90%; mp 118–119 °C). The $^1H$ NMR spectra data for **7** are summarized in Table V. The IR spectrum of **7i** was typical for the diols: 3302, 3069, 2936, 2865, 2767, 1463, 1414, 1006 $cm^{-1}$. All of diols **7** gave satisfactory analysis for C, H, and N.

***N*-Phenyl-*N*-formylglycine Ethyl Ester (8a).** A mechanically stirred mixture of aniline (71 g, 0.76 mol), ethyl bromoacetate (127.5 g, 0.76 mol), and anhydrous sodium acetate (62.6 g, 0.76 mol) in absolute ethanol (10 mL) was heated at reflux for 6 h. The mixture was cooled, water was added to precipitate the product, and the solid was filtered and dried. The crude product was crystallized from ethanol–water to give *N*-phenylglycine ethyl

ester (107 g, 79%): mp 48–49 °C; $^1$H NMR δ 7.33–6.98 (m, 2 H), 6.87–6.47 (m, 3 H), 4.20 (q, $J$ = 7 Hz, 2 H), 3.83 (s, 2 H), 1.25 (t, $J$ = 7 Hz, 3 H).

*N*-Phenylglycine ethyl ester (100 g, 0.56 mol) was added in small portions to acetic formic anhydride (100 g, 1.14 mol) with vigorous stirring. The temperature rose to 50–60 °C. The mixture was allowed to stir overnight, and then it was poured into water and extracted with ether. The ether solution was washed with sodium bicarbonate solution and then with water. The ether was evaporated in vacuo to give an oil which was distilled to give *N*-phenyl-*N*-formylglycine ethyl ester (**8a**; 81 g, 70%): bp 115–117 °C (ca. 1 mm) (lit.[8] bp 157–159 °C/7 mm); IR (neat) 3325, 3000, 1750, 1690, 1600, 1500, 1440, 1350, 1300, 1270, 1200, 1020, 980, 760, 700 cm$^{-1}$; $^1$H NMR δ 8.47 (s, 1 H), 7.67–7.07 (m, 5 H), 4.52 (s, 2 H), 4.22 (q, $J$ = 7 Hz, 2 H), 1.27 (t, $J$ = 7 Hz, 3 H).

**Ethyl 2-(*N*-Formylamino)ethanoate (8b).** A hot solution (90–100 °C) of sodium formate (150 g) in formic acid (200 mL) was added to a hot solution of glycine ethyl ester hydrochloride (228.7 g, 1.64 mol) in hot formic acid (250 mL). This was allowed to stir at room temperature for 3 h (sodium chloride separated). Small aliquots of acetic anhydride (450 g) were added over a 6-h period to the well-stirred suspension as an exothermic reaction ensued. The suspension was stirred overnight, the solid was filtered, and the filtrate was distilled in vacuo to remove excess reagents. The residue was filtered and then distilled to give ethyl 2-(*N*-formylamino)ethanoate (**8b**; 182 g, 85%) as a colorless liquid: bp 105–110 °C under vacuum; $^1$H NMR δ 8.24 (s, 1 H), 6.57 (br, 1 H), 4.25 (q, $J$ = 7.2 Hz, 2 H), 4.08 (d, $J$ = 5.5 Hz, 2 H), 1.30 (t, $J$ = 7.2 Hz, 3 H); IR (neat) 3315, 2985, 1746, 1676, 1528, 1379 cm$^{-1}$.

**Diethyl 2-Mercapto-1-phenylimidazole-4,5-dicarboxylate (10a).** Absolute ethanol (50 mL) was slowly added to a mechanically stirred suspension of finely cut sodium metal (19.3 g, 0.84 mol) in anhydrous ether (500 mL). When most of the metal had dissolved, diethyl oxalate (114 mL, 0.84 mol) was slowly added followed by the slow addition of *N*-phenyl-*N*-formylglycine ethyl ester (**8a**) (130 g, 0.67 mol). The mixture was stirred at room temperature overnight and then ice–water (700 mL) was added. The resulting emulsion was broken by sequential addition of a saturated sodium chloride solution (150 mL) and water (200 mL). The aqueous layer was removed, potassium thiocyanate (114 g, 1.18 mol) was added, then concentrated hydrochloric acid (160 mL), followed by absolute ethanol (900 mL). The resultant mixture was warmed at 60–65 °C for 1 h and then at 50 °C for 6 h and finally allowed to stir at room temperature overnight. The light yellow precipitate was filtered, washed with ethanol, and dried to give 103 g (48%) of diethyl 2-mercapto-1-phenylimidazole-4,5-dicarboxylate (**10a**): mp 145–146 °C (lit.[9] mp 146–147 °C). This material was pure enough to be used in the next step, but a recrystallized sample (ethanol–water) had the following: mp 146–147 °C; IR 3050, 2925, 1730, 1630, 1600, 1480, 1400, 1370, 1340, 1240, 1200, 1060, 1000, 860, 750, 690 cm$^{-1}$; $^1$H NMR δ 1.05 (t, $J$ = 7 Hz), 1.33 [t, $J$ = 7 Hz (6 H for the two triplets)], 4.15 (q, $J$ = 7 Hz), 4.38 [q, $J$ = 7 Hz (4 H for two quartets)], 7.48 (s, 5 H), 12.00 (br s, 1 H). Anal. ($C_{15}H_{16}N_2O_4S$) C, H, N.

**Diethyl 2-Mercapto-4,5-imidazoledicarboxylate (10b).** Absolute ethanol (58 g, 1.25 mol) was added to a suspension of clean sodium (29 g, 1.25 g-atom cut into small pieces) in anhydrous ether (700 mL). Diethyl oxalate (182 g, 1.25 mol) was added slowly to this mixture so that the exothermic reaction did not become too vigorous. Ethyl 2-(*N*-formylamino)ethanoate (**8b**; 131 g, 1.0 mol) was added dropwise with stirring to the resulting solution and a red-brown precipitate formed. The mixture was allowed to stand overnight and then water (1 L) was added to dissolve the precipitate and the ether layer was separated. Potassium thiocyanate (170 g, 1.75 mol) and concentrated hydrochloric acid (240 mL) were added to the aqueous solution. The yellow aqueous solution was slowly heated to 40–60 °C for 6 h and cooled. The yellow granular precipitate of **10b** was filtered. The filtrate was concentrated to give an additional amount of the same product. The total yield of diethyl 2-mercapto-4,5-imidazodicarboxylate (**10b**) was 109.0 g (45%). The material was of suitable purity to use in the subsequent step, but a small amount was recrystallized from hot water to give light yellow crystals: mp 202–204 °C (lit.[9] mp 204–205 °C); $^1$H NMR (DMSO-$d_6$–TMS) δ 1.3 (t, $J$ = 7 Hz, 6 H), 4.3 (q, $J$ = 7 Hz, 4 H), 8.6 (s, 2 H); IR 3263, 2992, 1743, 1689, 1495, 1441, 1373 cm$^{-1}$.

**2-Amino-3-[(methoxymethylene)amino]maleonitrile (13).** Trimethyl orthoformate (31.8 g, 0.3 mol) was added dropwise to a slowly distilling solution of diaminomaleonitrile (32.4 g, 0.3 mol) in 1,4-dioxane (250 mL). The methanol that formed during the reaction was removed by distillation. The reaction mixture was concentrated in vacuo and cooled to room temperature. The precipitate was collected and crystallized from THF–pentane to yield 33.6 g (62%) of **13** as colorless needles: mp 138–139 °C (lit.[13a] mp 134 °C); $^1$H NMR δ 7.92 (s, 1 H), 6.62 (br s, 2 H), 3.85 (s, 3 H).

**2-Methoxyimidazole-4,5-dicarbonitrile (14a).** A solution of 2-amino-3-[(methoxymethylene)amino]maleonitrile (**13**; 20 g, 0.11 mol) and 2,3-dichloro-5,6-dicyanobenzoquinone (25.5 g, 0.11 mol) in acetonitrile (750 mL) was heated at reflux for 4 days. Silica gel (100 g) was added and the acetonitrile was removed in vacuo. The silica gel was extracted with dichloromethane. The dichloromethane solution was concentrated to dryness in vacuo, the yellow residue was suspended in dichloromethane (150 mL), and the mixture was stirred. The mixture was filtered and the filtrate was concentrated in vacuo to yield a light yellow solid that was crystallized from water to give **14a**: mp 137–138 °C (lit.[13a] mp 134–136.5 °C); $^1$H NMR (DMSO-$d_6$–$CDCl_3$–TMS) δ 4.10 (s, 3 H).

**1-Methyl-2-methoxyimidazole-4,5-dicarbonitrile (14b).** Sodium hydride (1.1 g, 60% in an oil dispersion) was added in small portions to a stirred solution of 2-methoxyimidazole-4,5-dicarbonitrile (**11a**) (3.25 g, 0.022 mol) in dimethylformamide (25 mL). Hydrogen gas was evolved. The mixture was cooled, iodomethane (3.2 g) was slowly added, and the mixture was stirred overnight. The mixture was poured into ice–water and extracted with chloroform. The combined chloroform extract was washed with water, dried (magnesium sulfate), and concentrated to dryness in vacuo. The residue was chromatographed (silica gel eluted with dichloromethane–hexanes) and the product was crystallized from dichloromethane–hexanes to give 1.6 g (45%) of **14b**: mp 65–66 °C; $^1$H NMR δ 4.15 (s, 3 H), 3.53 (s, 3 H).

**Methyl 1-Methyl-2-oxo-5-cyano-2,3-dihydroimidazole-4-carboxylate (15). Method A.** From **14b**: A mixture of **14b** (1 g, 6.2 mmol) in hydrogen chloride–saturated anhydrous methanol (20 mL) was stirred for 12 h at room temperature, additional hydrogen chloride was added, and the mixture was heated at reflux for 1 h. The cooled reaction mixture was filtered and the collected solid was crystallized from methanol to give **15** (0.92 g, 82%): mp 257–259 °C; $^1$H NMR (DMSO-$d_6$–TMS) δ 3.22 (s, 3 H), 3.83 (s, 3 H). Anal. ($C_7H_7N_3O_3$) C, H, N.

**Method B.** From **16**: A mixture of **16** (0.5 g, 2.6 mmol) and concentrated HCl (15 mL) was warmed at 50–60 °C for 10 min. A precipitate formed in the initially clear solution. The solid was collected to give **15** (0.43 g, 91%): mp 257–59 °C (undepressed in a mixture melting point with the material obtained above).

**1-Methyl-2-methoxy-4-(methoxyiminomethyl)-5-imidazolecarbonitrile (16).** Methyl iodide (10 g) was added to a suspension of **14b** (10 g, 0.0676 mol) and sodium methoxide (3.65 g, 0.0676 mol) in anhydrous methanol. The mixture was stirred at room temperature for 24 h. Additional quantities of sodium methoxide (3.65 g, 0.0676 mol) and methyl iodide (10 g) were added, and the mixture was stirred for an additional 24 h at room temperature. The mixture was poured into cold water, and the precipitate was collected and crystallized from dichloromethane–hexanes to give **16** (8.3 g, 63%) as colorless needles: mp 113–114 °C; $^1$H NMR δ 3.50 (s, 3 H), 4.03 (s, 3 H), 4.20 (s, 3 H), 8.30 (s, 1 H); IR 3250, 2220, 1625 cm$^{-1}$. Anal. ($C_8H_{10}N_4O_2$) C, H, N.

**1-Methyl-2-oxo-2,3-dihydroimidazole-4-carboxylic Acid (17).** A mixture of **15** (0.5 g, 2.76 mmol) and 6 N hydrochloric acid (10 mL) was heated under reflux for 1 h. The mixture was cooled and the precipitate that formed was collected and crystallized from water to give **17** (0.35 g, 90%) as colorless prisms: mp 270–272 °C (dec with gas evolution); $^1$H NMR (DMSO-$d_6$–TMS) δ 3.13 (s, 3 H), 7.25 (s, 1 H). Anal. ($C_5H_6N_2O_3$) C, H, N.

**Stability and Hydrolysis Studies.** The stability studies were conducted with a Spectra-Physics 8000 HPLC equipped with a 25 cm × 4.6 mm 600-RP8 (10 μm) reverse-phase column (Alltech). The mobile phase was 80% (v/v) water in acetonitrile at a con-

Table VI

| compd | $T_R$,[a] min | $T_S$, min | $K'$ | $T_M$, min |
|---|---|---|---|---|
| **7i** | 5.5 | 2.5 | 0.83 | 3.0 |
| **18** | 12 | 9.3 | 3.1 | 3.0 |
| **19** | 16 | 13 | 4.3 | 3.0 |
| **2i** | 39 | 36 | 12.0 | 3.0 |

[a] Mobile phase was water–acetonitrile (9:1). $T_R$ was the retention time ($T_S + T_M$): $T_S$ was the time between solvent front elution and compound elution; $K'$ was $T_S/T_M$, and $T_m$ was the time between injection and solvent front elution.

stant flow rate of 1.5 mL/min. Detection (Varian Varichrome variable-wavelength UV–visible detector) was at 221 nm, sensitivity of 1.0 AUFS, and a bandwidth setting of 4 nm. Injection volumes of 10 μL (ca. 1 mg/mL) were used. Quantitation was done by electronic integration (HP-3392A integrator) of peak areas. The experiments were carried out with an autoinjector programmed to analyze samples every 15–20 min. The reservoir of the autoinjector containing the sample to be analyzed was maintained at 25.0 ± 0.1 °C (unless otherwise specified). Initial experiments were run with and without an internal standard (benzyl alcohol) and the results were identical.

The rate constants for the pseudo-first-order hydrolysis reactions were determined from the slope of the line obtained in a plot of time (min) vs [ln (initial peak area/peak area)]. The hydrolysis of **2i** was studied as a function of temperature, acetonitrile concentration, and hydrochloric acid concentration. The chromatographic characteristics of the four compounds are shown in Table VI.

**Determination of the p$K_a$ of Diol 7i.** Diol **7i** (0.1224 g, 0.7846 mmol) was dissolved in 0.1 N HCl (9.0 mL) and the solution was titrated with 0.20 N NaOH. The pH of the solution was monitored with a Radiometer/Copenhagen PHM82 standard pH meter. Approximately 0.7 mL of sodium hydroxide solution was added initially, then 0.1-mL aliquots were added, and the pH of the solution was measured after each addition. The p$K_a$ of **7i** was determined from a plot of the pH vs volume of 0.20 N NaOH. The p$K_a$ of **7i** was 4.97. The p$K_a$ of imidazole was measured as a control constant by using the above procedure; imidazole had p$K_a$ = 7.08 (lit.[19] p$K_a$ = 6.95).

**Solubility Studies.** The solubility of **2i** was determined by UV spectroscopy (Cary 118 UV–visible spectrophotometer). A standard Beer's law plot of concentration vs absorbance at 220 nm was prepared for **2i**. The solubility study was conducted as follows: excess **2i** was added to water (2 mL), and the mixture was triturated and swirled for 10 min and then shaken for 5 min. The mixture was filtered to remove excess compound and diluted with water (1.0 mL diluted to 2.0 L), and the UV absorbance of the resulting solution was measured. The solubility of **2i** was determined to be 7.2 mg/mL.

**Determination of log *P* values by HPLC.**[18] A solution of benzyl alcohol, acetophenone, toluene, and naphthalene (ca. 1 mg/mL of each in the mobile phase) was injected (10-μL injection volume) into a C-18 reverse-phase column (10 μm, 250 × 4.6 mm) and eluted with a mobile phase consisting of 55% methanol and 45% aqueous ammonium phosphate buffer (0.05 M, adjusted to pH 7) at a flow rate of 2 mL/min (constant-flow mode). The column eluant was monitored by UV at 221 nm (4-nm bandwidth). Sodium nitrite (ca. 0.5 mg/mL) was used as a solvent front indicator. The chromatographic capacity factor ($k'$) for each compound was calculated by the formula $k' = (t - t_0)/t_0$ where $t$ is the compound retention time and $t_0$ is the retention time of the solvent front indicator, sodium nitrite. The standard plot was prepared by plotting log $k'$ vs log $P$ for the four standard compounds. The values for [log $k'$ (log $P$)] for benzyl alcohol [0.136 (1.16)], acetophenone [0.411 (1.66)], toluene [1.02 (2.74)], and naphthalene [1.27 (3.37)] gave a straight line plot, $r$ = 0.998.

The carmethizole test solution was prepared immediately before injection and contained the imidazole (ca. 1 mg/mL) along with the four standard compounds (each ca. 1 mg/mL) and sodium nitrite (ca. 0.5 mg/mL) dissolved in the mobile phase. The capacity factors, $k'$, of carmethizole was calculated and the log $P$ value was determined from the standard plot.

**1-Methyl-2-(methylthio)-4,5-bis(hydroxymethyl)imidazole Bis(*N*-methylcarbamate) Hydrochloride (Carmethizole Hydrochloride). Method A.** A stirred solution of bis(carbamate) **2i** (23.0 g, 0.0761 mol) in a mixture of anhydrous dichloromethane (350 mL) and anhydrous methanol (20 mL) was slowly treated with anhydrous 32–35% ethanolic hydrogen chloride (10 mL) until the pH remained constant at pH 2–3. The volatiles were removed in vacuo at 30–35 °C to yield a white solid [TLC, silica gel, $R_f$ 0.65, dichloromethane–methanol (7:1) and was similar to bis(carbamate) **2i**; it appeared that the hydrochloride was changing quantitatively to **2i** on silica] that was crystallized from anhydrous methanol–ether (2:1). The crystalline solid was dried in vacuo (0.1 Torr) at room temperature to give carmethizole hydrochloride (**8**; 22.0 g, 94%).

**Method B.** The hydrochloride salt of **2i** was prepared by treatment of a solution of **2i** (0.386 g) in anhydrous dichloromethane (20 mL) with a constant flow of anhydrous hydrogen chloride gas through a gas dispersion tube for 10 min. The mixture was concentrated to dryness in vacuo, and the residue was triturated with anhydrous dichloromethane (20 mL) and filtered to give the salt (0.427 g, 99%) as a white crystalline solid: mp 117–118 °C (effervescent), 133–135 °C dec; IR 3300, 2650 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$–TMS) δ 7.22 (2 H), 5.28 (2 H), 5.20 (2 H), 3.80 (3 H), 2.90 (3 H), δ 2.69 (6 H); $^{13}$C NMR (DMSO-$d_6$–TMS) δ 156.05, 154.94, 143.78, 131.02, 129.27, 54.96, 53.33, 32.25, 26.91, 16.23. Anal. ($C_{11}H_{18}N_4O_4S$·1.3HCl) C, H, N, S. Cl.

**Acknowledgment.** This investigation was supported by Public Health Service Grant CA 22935 and Contracts CM-27570 and CM-67678 awarded by the National Cancer Institute, DHHS.

**Registry No.** **2d**, 117120-84-0; **2e**, 117120-85-1; **2f**, 117120-86-2; **2g**, 117120-87-3; **2i**, 117120-88-4; **3d**, 117120-89-5; **3e**, 117120-90-8; **3f**, 117120-91-9; **3i**, 117120-92-0; **3j**, 117120-93-1; **4a**, 888-60-8; **4b**, 5313-35-9; **4j**, 117120-94-2; **4j**·HCl, 117120-95-3; **5a**, 52122-98-2; **5b**, 34913-20-7; **5e**, 117120-96-4; **5g**, 117120-97-5; **5h**, 117120-98-6; **5j**, 117120-99-7; **6c**, 117121-00-3; **6d**, 117121-01-4; **6f**, 1098-38-0; **6i**, 1086-05-1; **7d**, 33457-06-6; **7e**, 117121-02-5; **7f**, 117121-03-6; **7g**, 117121-04-7; **7i**, 117121-05-8; **7j**, 117121-06-9; **8a**, 54915-69-4; **8b**, 3154-51-6; **10a**, 117121-07-0; **10b**, 69039-88-9; **11**, 13171-63-6; **11a**, 51850-82-9; **12**, 615-15-6; **13**, 51850-81-8; **14a**, 51850-82-9; **14b**, 117121-08-1; **15**, 117121-09-2; **16**, 117121-10-5; **17**, 17245-61-3; **18**, 117121-11-6; **19**, 117121-12-7; **20**, 117121-13-8; **21**, 117121-14-9; $EtOCOCO_2Et$, 95-92-1; methyl isocyanate, 624-83-9; isopropyl isocyanate, 1795-48-8; tartaric acid, 87-69-4; acetaldehyde, 75-07-0; ethyl bromoacetate, 105-36-2; *N*-phenylglycine ethyl ester, 2216-92-4; glycine ethyl ester hydrochloride, 623-33-6; diaminomaleonitrile, 1187-42-4.

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