

92010-32-7; 45, 92010-33-8; 46, 92010-34-9; 47, 92010-35-0; HbS, 9035-22-7; 3,5-dinitrobenzoic acid, 99-34-3; *tert*-butyl bromoacetate, 5292-43-3; octanoyl chloride, 111-64-8; *p*-chlorobenzoyl chloride, 122-01-0; 3,4-dichlorobenzoyl chloride, 3024-72-4; *p*-bromobenzoyl chloride, 586-75-4; *L*-proline benzyl ester hydro-

chloride, 16652-71-4; hydrocinnamic acid, 501-52-0; benzyl salicylate, 118-58-1; 3,3-dimethylbutanoic acid, 1070-83-3; phenylacetic acid, 103-82-2; phenoxyacetic acid, 122-59-8; trimethylacetic acid, 75-98-9; 4-phenyl-4-butyrolactone, 1008-76-0; *tert*-butyldimethylsilyl chloride, 18162-48-6.

## Synthesis and Evaluation of Furan, Thiophene, and Azole Bis[(carbamoyloxy)methyl] Derivatives as Potential Antineoplastic Agents<sup>1</sup>

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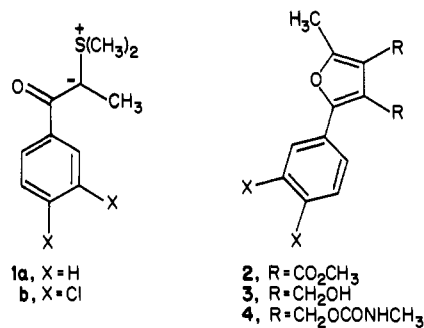
A series of bis(hydroxymethyl)-substituted heterocycles were synthesized and converted to the corresponding bis(methylcarbamate) derivatives. The heterocyclic systems studied were based on 2-phenyl-3-methylfuran (2-4), 1-phenylpyrazole (5-7), 1-phenyl-5-methylpyrazole (9-11), 1-phenyl-5-methylthiophene (13), 1-phenyl-1,2,3-triazole (14), 3-phenylisoxazole (15), 3-phenylisothiazole (16), 2-phenylthiazole (17), and 2-phenyloxazole (18). None of the bis(carbamates) prepared was active against murine P388 lymphocytic leukemia. Pyrrole bis(carbamates) 20 and 21, which exhibited antileukemic activity, also showed reactivity toward 4-(*p*-nitrobenzyl)pyridine while the inactive bis(carbamates) were unreactive in the 4-(*p*-nitrobenzyl)pyridine assay.

We have recently reported the synthesis and antineoplastic activity of a series of pyrroles and pyrrolizines.<sup>2</sup> The significant reproducible activity that selected agents in these classes have shown against several experimental murine leukemias and solid tumors as well as against human tumor xenografts in the nude mouse has provided a major impetus for continued studies with this group of compounds.<sup>3</sup>

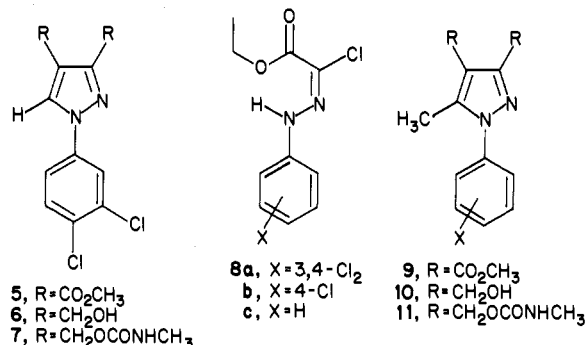
All of the compounds that we have described to date have been based on the pyrrole and pyrrole-fused nuclei where two adjoining pyrrole carbon atoms were substituted with potentially reactive (acyloxy)methyl groups while other positions in the pyrrole nucleus were substituted by groups that could either control the reactivity of the (acyloxy)methyl groups or retard the oxidative decomposition of the pyrrole. This report focuses upon the heteroaromatic nucleus and describes the preparation and antileukemic evaluation of "lead" structures based on furan, thiophene, and azole nuclei.

**Chemistry.** The furan diesters 2 were prepared from the ylides 1 by treatment with dimethyl acetylenedicarboxylate (DMAD).<sup>4</sup> Reduction of 2 with lithium aluminum hydride gave the diols 3, which were converted to the bis(methylcarbamates) 4a and 4b by treatment with methyl isocyanate.

The pyrazole diester 5 was prepared from 3-phenylsydnone by a 1,3-dipolar cycloaddition reaction with DMAD.<sup>5</sup> The diesters 9 were prepared from the appro-



appropriate anilines by conversion to the imino chlorides 8, using the Japp-Klingmann reaction, and subsequent treatment of 8 with the sodium salt of ethyl acetoacetate.<sup>6</sup> The bis(methylcarbamates) 7 and 11a-d were prepared from the corresponding diesters 5 and 9a-d, respectively, by reduction (lithium aluminum hydride) and acylation of the resulting diols (6 and 10a-d) with methyl isocyanate.



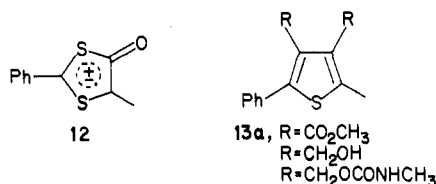
The pyrazole 7 was prepared in order to compare it with 11a and evaluate the steric effect of the 5-methyl group. The UV spectra of 7 and 11a showed absorption maxima at 268 ( $\epsilon$  25 300) and 255 nm ( $\epsilon$  18 000), respectively. The shift to lower wavelength and the reduction of the extinction coefficient of 11a, compared to 7, is consistent with

- (1) (a) Vinylogous Carbinolamine Tumor Inhibitors. 13. (b) For part 12 in this series, see: Anderson, W. K.; McPherson, H. L., Jr.; New, J. S.; Rick, A. C. *J. Med. Chem.* 1984, 27, 1321.
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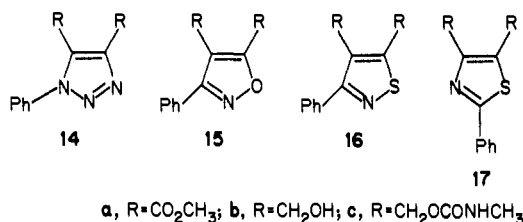
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a reduced coplanarity of the biaryl system in 11a; the steric barrier posed by the C-5 methyl group in 11a apparently retards coplanarity.

The thiophene 13a was prepared in a 1,3-dipolar cycloaddition reaction between DMAD and 12.<sup>7</sup> The deep-purple colored mesoionic 1,3-dithiol-4-one 12 was synthesized from sodium dithiobenzoate (prepared from benzyl chloride by treatment with sodium methoxide and sulfur) by treatment with  $\alpha$ -bromopropionic acid in sodium carbonate solution followed by treatment with acetic anhydride and triethylamine. The bis(carbamate) 13c was prepared in the usual manner through the intermediacy of 13b.



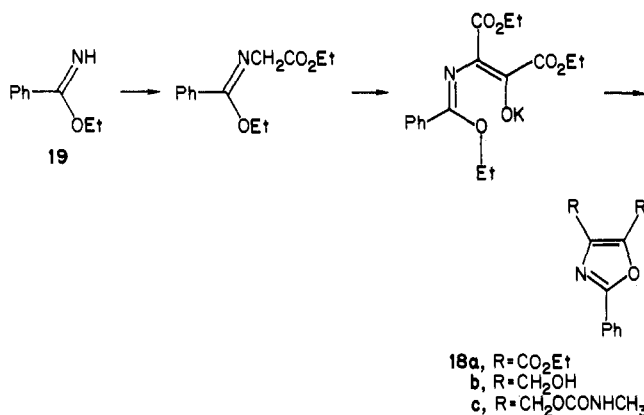
The triazole 14a,<sup>8</sup> isoxazole 15a,<sup>9</sup> and isothiazole 16c,<sup>9c,10</sup> were prepared in 1,3-dipolar cycloaddition reactions with dimethyl acetylenedicarboxylate using phenyl azide, benzonitrile oxide, and benzonitrile sulfide, respectively. Reduction to the respective diols (14b, 15b, and 16c) followed by carbamoylation led to the desired bis(carbamates) (14c, 15c, and 16c).



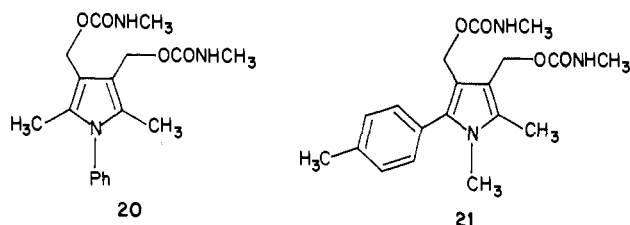
The thiazole 17a was synthesized from thiobenzamide by condensation with diethyl  $\alpha$ -chloro- $\beta$ -ketosuccinate.<sup>11</sup> Reduction of 17a gave 17b and carbamoylation gave 17c. The corresponding oxazole 18a could not be prepared in a similar manner from benzamide. The oxazole 18a was prepared from the imino ether 19, derived from benzonitrile (ethanolic hydrogen chloride) by successive treatment with ethyl glycinate, potassium ethoxide, diethyl oxalate, and acetic acid.<sup>12</sup>

## Results and Discussion

All of the bis(carbamates) prepared in this study were tested for antileukemic activity against murine P388 lymphocytic leukemia. None of the compounds was active. The chemical reactivity of the bis(carbamates) was studied



with use of 4-(*p*-nitrobenzyl)pyridine.<sup>35</sup> None of the compounds prepared in this study alkylated 4-(*p*-nitrobenzyl)pyridine. The two pyrrole bis(carbamates) 20<sup>1c</sup> and 21<sup>1d</sup> were used as positive controls in the alkylating test. Both 20 and 21 are active against murine P388 lymphocytic leukemia *in vivo* and both compounds reacted with 4-(*p*-nitrobenzyl)pyridine.



The rates of reaction of 20 and 21 with 4-(*p*-nitrobenzyl)pyridine depended on the conditions of the assay. The rates of alkylation increased as the solvent was changed from dimethoxyethane to water-dimethoxyethane (1:1) to water-dimethoxyethane-acetic acid (20:20:1).

The heterocycles examined in this study differ from one and other in several respects—aromaticity,  $pK_a$ , lipophilicity, dipole moments, charge-transfer donor/acceptor—but the most critical difference would appear to be the ability of the heterocycle to stabilize developing positive charge in a reaction transition state. The ability of the pyrrole system to stabilize these kinds of reaction transition states is reflected in reactivity toward electrophilic substitution; of the heterocycles prepared in this study, pyrrole is most reactive toward electrophilic substitution.<sup>36</sup> A conclusion that can be drawn from this study is that electrophilic reactivity is one requirement for antineoplastic activity in these bis(carbamates). It is also evident that the bis(carbamates) are not functioning as carbamoylating agents since so many of these nonpyrrole bis(carbamates) are inactive.

## Experimental Section

Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover Unimelt apparatus. UV spectra were determined for acetonitrile solution with a Cary 118 UV-vis spectrophotometer. IR spectra were determined for potassium bromide pellets (unless otherwise specified) with a Perkin-Elmer 727B or a Nicolet FT-IR spectrophotometer. NMR spectra were determined with a Varian T-60A or a Varian FT-80 spectrometer for deuteriochloroform solutions (unless otherwise specified) containing ~1% tetramethylsilane as the internal standard. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

**2-Methyl-3,4-bis(hydroxymethyl)-5-phenylfuran Bis(methylcarbamate) (4a).** Phenyl 1-bromoethyl ketone was prepared in 88% yield by a modification of an earlier procedure<sup>13</sup> as a pale yellow lacrimatory oil [bp 75.5 °C (0.16 torr) [lit.<sup>14</sup> bp 110–112

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°C (4 torr)]; NMR  $\delta$  1.90 (d,  $J$  = 6 Hz, 3 H), 5.30 (q,  $J$  = 6 Hz, 1 H), 7.4–7.7 (m, 3 H), 7.9–8.1 (m, 2 H); IR (neat) 1687  $\text{cm}^{-1}$  ( $\nu_{\text{C=O}}$ ).

In a modified literature procedure,<sup>15</sup> a solution of phenyl 1-bromoethyl ketone (33 mL, 0.222 mol) and dimethyl sulfide (16.3 mL, 0.22 mol) in reagent-grade acetone (50 mL) was allowed to stand for 1 week at 23 °C. The white crystalline sulfonium salt was collected, washed with acetone, and dried. The combined filtrate was concentrated in vacuo to a volume of 75 mL, dimethyl sulfide (8 mL) was added, and the above procedure was repeated to give a combined yield of 55.6 g (91%) of the sulfonium salt: mp 128–129 °C (from ethanol–acetone) (lit.<sup>4</sup> mp 138–139 °C); NMR (deuterium oxide) of the keto–enol mixture,  $\delta$  1.85 (d,  $J$  = 7 Hz, 3 H), 1.85 (s), 3.02 (s, 3 H), 3.07 (s, 3 H), 5.72 (q,  $J$  = 7 Hz, 0.5 H), 7.4–8.1 (m, 5 H); IR 1677  $\text{cm}^{-1}$  ( $\nu_{\text{C=O}}$ ).

The sulfonium salt was converted to the ylide according to the method of Payne.<sup>16</sup> Thus the salt (20.1 g, 0.0729 mol) was treated with potassium carbonate–sodium hydroxide to give the crude hygroscopic ylide. In a modified literature<sup>17</sup> procedure, freshly distilled dimethyl acetylenedicarboxylate (7 mL, 0.057 mol) in dimethyl sulfoxide (150 mL, freshly distilled from calcium hydride) was added dropwise to a vigorously stirred suspension of freshly prepared ylide in dry dimethyl sulfoxide (250 mL) cooled on an ice bath and maintained under a steady stream of nitrogen. Dimethyl sulfide was evolved and the reaction mixture darkened during the addition. The mixture was stirred for 4 h and poured into ice–water (800 mL), and the cloudy–brown mixture was extracted with diethyl ether (three 200-mL portions). The aqueous phase was heated at 49 °C for 3 h and was allowed to stand at room temperature for 72 h. A brown oil separated and slowly solidified. The solid was collected and crystallized (90% ethanol) to give **2a** (7.07 g, 32% based on the sulfonium salt): mp 62 °C dec (lit.<sup>4</sup> mp 62.7–63.7 °C); NMR  $\delta$  2.60 (s, 3 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 7.1–7.8 (m, 5 H); IR 1725  $\text{cm}^{-1}$  ( $\nu_{\text{C=O}}$ ).

A solution of **2a** (5.96 g, 0.0217 mol) in anhydrous ether (35 mL) was added dropwise to a vigorously stirred suspension of lithium aluminum hydride (1.94 g, 2.3 equiv) in anhydrous diethyl ether (55 mL) heated under reflux. The mixture was heated under reflux for 1.5 h after addition was completed; it was cooled, and with continuous stirring, water (2 mL), 15% aqueous sodium hydroxide (2 mL), and water (6 mL) were added dropwise with a 5-min pause between each reagent. The mixture was filtered, the residue was washed with diethyl ether, the combined filtrate was concentrated in vacuo, and the dark–yellow syrupy residue was dissolved in dichloromethane and dried over anhydrous sodium sulfate for 20 h. The mixture was filtered, the residue was washed with dichloromethane, the combined dichloromethane solution was concentrated to dryness in vacuo, and the residue was dried under high vacuum for 18 h to yield **3a** (4 g, 85%): mp 71.5 °C (from chloroform–hexane); NMR  $\delta$  2.23 (s, 3 H), 4.36 (s, 2 H, exchanged by deuterium oxide), 4.44 (s, 2 H), 4.62 (s, 2 H), 7.2–7.7 (m, 5 H).

A solution of **3a** (3.48 g, 0.0159 mol) in dichloromethane (45 mL) containing dry triethylamine (0.9 mL) as a catalyst was treated with methyl isocyanate (5.2 mL, 0.0886 mol). The stirred mixture was heated under reflux for 17.5 h (anhydrous conditions), the solvent was removed in vacuo, and the slightly reddish residue was crystallized from ethyl acetate to give 4.79 g (85%) of **4a** as a white powdery solid: mp 148–149 °C; NMR  $\delta$  2.37 (s, 3 H), 2.78 (d,  $J$  = 4 Hz, 6 H), 4.7–5.3 (br s, 2 H), 5.03 (s, 2 NH), 5.17 (s, 2 H), 7.20–7.72 (m, 5 H); IR 1685  $\text{cm}^{-1}$  ( $\nu_{\text{C=O}}$ ). Anal. ( $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5$ ) C, H, N.

**2-Methyl-3,4-bis(hydroxymethyl)-5-(3,4-dichlorophenyl)-furan Bis(methylcarbamate) (4b).** 3,4-Dichlorophenyl 1-bromoethyl ketone [mp 50–51 °C (absolute ethanol); NMR  $\delta$  1.92 (d,  $J$  = 7 Hz, 3 H), 5.20 (q,  $J$  = 7 Hz, 1 H), 7.47–8.08 (m, 3 H); IR 1685  $\text{cm}^{-1}$  ( $\nu_{\text{C=O}}$ )] was prepared in 80% yield by treatment of a mixture of 2-bromopropionyl chloride and aluminum chloride

in 1,1-dichloroethane with *o*-dichlorobenzene at 20 °C (followed by heating at 50 °C for 3 h).

The ketone was converted to [1-(dimethylsulfonio)ethyl 3,4-dichlorophenyl ketone] bromide [mp 124 °C; NMR ( $\text{D}_2\text{O}$ )  $\delta$  1.97 (s, 3 H), 3.17 (s, 3 H), 3.30 (s, 4 H), 7.52–8.05 (m, 3 H); IR 1680  $\text{cm}^{-1}$  ( $\nu_{\text{C=O}}$ )] in 89% yield. The salt was converted to the hygroscopic ylide which, after drying, was used to prepare **2b** (72% yield from the sulfonium salt): mp 72.5–73.5 °C (95% ethanol); NMR  $\delta$  2.62 (s, 3 H), 3.87 (s, 3 H), 3.92 (s, 3 H), 7.37–7.38 (m, 3 H); IR 1710 and 1730  $\text{cm}^{-1}$  ( $\nu_{\text{C=O}}$ ).

Reduction of **2b**, as described for **2a**, gave **3b** in 95% yield as a white crystalline solid: mp 124.5–125.5 °C (chloroform–hexane); NMR  $\delta$  2.33 (s, 3 H), 2.78 (br s, 2 H, exchanged by  $\text{D}_2\text{O}$ ), 4.52 (s, 2 H), 4.65 (s, 2 H), 7.18–7.73 (m, 3 H); IR 3320  $\text{cm}^{-1}$  (broad hydroxyl absorption). Treatment of **3b** as described for **3a** (except chloroform was used as the solvent) gave **4b** in 74% yield: mp 151–153 °C dec; NMR  $\delta$  2.37 (s, 3 H), 2.79 (d,  $J$  = 5 Hz, 6 H), 4.67–5.20 (br s, 2 NH), 5.03 (s, 2 H), 5.15 (s, 2 H), 7.45 (br s, 2 H), 7.70 (br s, 1 H); IR 3320, 1705, 1695  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5\text{Cl}_2$ ) C, H, N.

**Dimethyl 1-(3,4-Dichlorophenyl)pyrazole-3,4-dicarboxylate (5).** A mixture of 3,4-dichloroaniline (19.6 g, 0.117 mol) was heated on a steam bath for 2 h and allowed to stand at room temperature for 14 h. The mixture was reheated, water (200 mL) and then potassium hydroxide (24 g) were added, and the heating was continued for 45 min. The hot solution was extracted with toluene (3  $\times$  75 mL) and the aqueous phase was acidified with concentrated HCl to pH  $\leq$  2 to give a thick white precipitate of *N*-(3,4-dichlorophenyl)glycine. The mixture was diluted to a volume of 600 mL with water, cooled to 0–2 °C, and slowly treated, with constant stirring, with a solution of sodium nitrite (6.4 g, 0.093 mol) in water (30 mL) such that the temperature never rose above 5 °C. The stirred mixture was allowed to warm to room temperature over 14 h, and the solution was acidified with concentrated HCl to pH  $\leq$  2 and was tested for excess nitrite with potassium iodide–starch paper. The brown precipitate that formed was collected, washed with cold water, and dried (60 °C, vacuum) to give 16.7 g (76%) of *N*-nitroso-*N*-(3,4-dichlorophenyl)glycine as a light brown solid, mp 109–110 °C.

The nitrosoglycine prepared above (16.7 g, 0.067 mol) was heated in acetic anhydride (75 mL) for 4 h at 55 °C with stirring. The mixture was then stirred at room temperature for 19 h, warmed to 55 °C, and treated with a solution of dimethyl acetylenedicarboxylate (8.6 mL, 0.07 mol) in xylene (25 mL). The mixture was heated at 120 °C for 4 h and concentrated to dryness in vacuo, and the residue was crystallized from methanol–benzene. The pyrazole **5**, obtained as colorless needles in 36% yield from the aniline, had the following: mp 156 °C; IR 1740, 1700, 1540, 1470, 1440, 1290, 1270, 1240, 1230, 1200, 1170, 1090  $\text{cm}^{-1}$ ; NMR  $\delta$  3.88 and 4.00 (2 s, 6 H), 7.40 (d, 2 H), 7.89 (t, 1 H), 8.35 (s, 1 H). Anal. ( $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_4\text{Cl}_2$ ) C, H, N.

**1-(3,4-Dichlorophenyl)-3,4-bis(hydroxymethyl)pyrazole (6).** A solution of **5** (10 g, 0.03 mol) in anhydrous ether (25 mL) and anhydrous dichloromethane (150 mL) was added slowly to a stirred mixture of lithium aluminum hydride (2.7 g, 0.07 mol) in anhydrous ether (160 mL) heated under reflux. The stirred mixture was heated under reflux for 2.5 h after the addition was completed and the reaction was worked up as described for **10** to give, after crystallization from ethyl acetate–petroleum ether, 6.4 g (77%) of **6**: mp 121–123 °C; IR 3275, 2850, 2800, 1600, 1570, 1490, 1430, 1390, 1350, 1240, 1130, 1020, 1010, 870, 810, 780  $\text{cm}^{-1}$ ; NMR ( $\text{Me}_2\text{SO}-d_6/\text{acetone}-d_6$ ,  $\text{Me}_4\text{Si}$ )  $\delta$  4.69 (d,  $J$  = 3 Hz) and 4.5–5.0 (br, 6 H), 7.53–8.03 (m, 3 H), 8.27 (s, 1 H). Anal. ( $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_4\text{Cl}_2$ ) C, H, N.

**1-(3,4-Dichlorophenyl)-3,4-bis(hydroxymethyl)pyrazole Bis(methylcarbamate) (7).** The diol **6** was converted to **7** in 84% yield as described for **11**. The diol **6** had the following: mp 180–181 °C (ethyl acetate–petroleum ether); IR 3425, 3375, 1710, 1600, 1550, 1490, 1289, 1270, 1140  $\text{cm}^{-1}$ ; NMR ( $\text{Me}_2\text{SO}-d_6/\text{CDCl}_3/\text{Me}_4\text{Si}$ )  $\delta$  2.70 (d,  $J$  = 1 Hz) and 2.79 [(d,  $J$  = 1 Hz) 6 H total for two signals], 5.10 (s), 5.22 (s), and 5.1–5.5 (br, 6 H), 7.48 (d,  $J$  = 2 Hz), 7.47–7.83 (m, 1 H), 7.95 (s, 1 H); UV 218 nm ( $\epsilon$  19500). Anal. ( $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_4\text{Cl}_2$ ) C, H, N.

**A General Procedure for the Synthesis of the (Phenylhydrazino)chloromethylenecarboxylates 8.** A stirred solution

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of the appropriate aniline (0.11 mol) in concentrated HCl (28 mL) and water or ethanol (28 mL) was cooled below 5 °C (additional 90% ethanol was required in some instances to keep the salt in solution) and treated with a chilled solution of sodium nitrite (8.2 g, 0.12 mol) in water (38 mL) by slow addition, 2–3-mL aliquots, such that the reaction temperature never rose above 10 °C (note: the outlet of the addition funnel was kept below the surface of the reaction mixture). The addition of sodium nitrite solution was discontinued when the reaction mixture gave a sustained positive test for nitrite with potassium iodide–starch paper. The stirred, cooled reaction mixture was then treated with a chilled solution of ethyl chloroacetate (15.2 mL, 0.11 mol) and sodium acetate (1.5 equiv) in ethanol–water (9:1, 300 mL) by addition of 10-mL aliquots. The reaction mixture was cooled in an ice bath and stirred for 4 h after the addition was completed. It was then poured into water (4 L) and allowed to stand for 18 h. The mixture was filtered, and the precipitate was washed with water and crystallized from ethanol–water. The imino chlorides thus prepared were **8a** (mp 154–155 °C, 86%), **8b** (mp 144–145 °C, 92%), **8c** (mp 78–79 °C, 87%) and **8d** [mp 104–105 °C (methanol), 68%]; the initial diazotization of distilled anisidine was conducted at –4 °C under a nitrogen atmosphere).

The spectral characteristics of ethyl [(3,4-dichlorophenyl)hydrazino]chloromethylenecarboxylate (**8a**) were typical: IR 3275, 1720, 1570, 1480, 1250, 1230 cm<sup>-1</sup>; NMR  $\delta$  1.38 (t,  $J = 7$  Hz, 3 H), 4.38 (q,  $J = 7$  Hz, 2 H), 6.9–7.5 (m, 3 H), 8.28 (br s, 1 H).

**A General Procedure for the Synthesis of the Pyrazoles 9 from the Imino Chlorides 8.** A solution of ethyl acetoacetate (2.8 mL, 0.021 mol) in anhydrous benzene or anhydrous ethanol (20 mL) was added to a solution of sodium metal (0.48 g, 0.021 mol) in absolute ethanol (8 mL) and the mixture was stirred for 1.5 h. The powdered imino chloride **8** (0.021 mol) was added (if benzene cosolvent is not used, then additional ethanol may be required to keep **8** in solution) and the mixture was stirred for 22 h at room temperature and then it was heated under reflux for 10 min. The mixture was concentrated to dryness in vacuo, water (10 mL) was added, and the mixture was heated for 30 min on a steam bath. The mixture was cooled and the oil was extracted with dichloromethane, and the organic solution was treated with activated carbon, dried over magnesium sulfate, and concentrated in vacuo. Subsequent purification was effected by chromatography and/or crystallization. The pyrazoles thus prepared were **9a** [mp 68.5–69.5 °C; purified by silica gel chromatography with elution by hexane–ethyl acetate (10:1 to 4:1), crystallization from ethanol–water (9:1), silica gel chromatography (chloroform), and crystallization from ethyl acetate–petroleum ether; 79% yield; anal. (C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>) C, H, N], **9b** [mp 106–107 °C (from aqueous methanol, twice, then ethyl acetate); 47% yield; anal. (C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>Cl) C, H, N], **9c** [mp 47–49 °C (lit.<sup>18</sup> mp 51.5 °C); bp 194 °C (0.8 torr); purified by silica gel chromatography (chloroform) and then crystallized from ethyl acetate–petroleum ether; 91% yield; anal. (C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N], and **9d** [bp 184–186 °C (0.21 torr); neutral alumina chromatography (chloroform) and then distillation; 81% yield; anal. (C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> + 0.05% CHCl<sub>3</sub>) C, H, N].

The spectral characteristics of diethyl 1-(3,4-dichlorophenyl)-5-methylpyrazole-3,4-dicarboxylate (**9a**) were typical: IR 1710, 1480, 1440, 1400, 1360, 1310, 1270, 1200, 1120, 1110, 1090, 1010 cm<sup>-1</sup>; NMR  $\delta$  1.35 (t,  $J = 7$  Hz) overlapped 1.39 (t,  $J = 7$  Hz) for a total of 6 H, 2.52 (s, 3 H), 4.38 and 7.1–7.7 (m, 3 H).

**A General Procedure for the Reduction of 9 to 10.** A solution of the pyrazole diester **9** (0.012 mol) in anhydrous ether (30 mL) was added slowly to a mechanically stirred mixture of lithium aluminum hydride (1.13 g, 0.03 mol) in anhydrous ether (50 mL) which was heated under reflux. The mixture was refluxed 1 h after the addition was completed, cooled, and worked up by slow addition of water (1.1 mL), 10% aqueous hydroxide (1.1 mL), and then water (3.3 mL). The mixture was filtered, the salts were washed with ether (75 mL) and then boiling tetrahydrofuran [75 mL (except that **10a** and **10b** were poorly soluble and required repeated extraction with boiling tetrahydrofuran and then with boiling ethyl acetate)]. The organic solution was concentrated

to dryness in vacuo and the residue was purified by crystallization. The diols thus prepared were **10a** [mp 155–156 °C (ethanol–ether), 85%; anal. (C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>) C, H, N], **10b** [167–169 °C (ethyl acetate), 80%; anal. (C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>OCl<sub>2</sub>) C, H, N], **10c** [mp 95 °C (ethyl acetate–petroleum ether), 81%; anal. (C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N], and **10d** [mp 105–106 °C (ethyl acetate), 74%; anal. (C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>) C, H, N].

The spectral characteristics of 1-(3,4-dichlorophenyl)-5-methyl-3,4-bis(hydroxymethyl)pyrazole (**10a**) were typical: IR 3400, 3200, 1610, 1590, 1500, 1459, 1440, 1380, 1320, 1150, 1100, 1020, 890, 850 cm<sup>-1</sup>; NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>/Me<sub>4</sub>Si)  $\delta$  2.35 (s, 3 H), 3.60 (OH), 4.50 (t,  $J = 5$  Hz, 4 H), 4.98 (m, 2 H), 7.37–7.87 (m, 3 H).

**A General Procedure for the Carbamoylation of 10.** A solution of the diol **10** (0.0045 mol), methyl isocyanate (0.53 mL, freshly distilled, 0.009 mol), and anhydrous triethylamine (5 drops) in anhydrous dichloromethane (20 mL) was heated under reflux for 24 h. The reaction mixture was concentrated to dryness in vacuo and the residue was crystallized to yield **11**. In the cases of **10a** and **10b**, the diols were not completely dissolved; even in a larger volume of dichloromethane also, the reaction was carried out as a stirred suspension. The bis(carbamates) thus prepared were **11a** [mp 168.5–169.5 °C (ethyl acetate–petroleum ether); 67% anal. (C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>Cl<sub>2</sub>) C, H, N], **11b** [mp 180–181 °C (dichloromethane–hexanes); 93%; anal. (C<sub>16</sub>H<sub>19</sub>N<sub>4</sub>O<sub>4</sub>Cl) C, H, N], **11c** [mp 136–138 °C (ethyl acetate–petroleum ether); 84%; anal. (C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>) C, H, N], and **11d** [mp 151–152 °C (ethyl acetate–petroleum ether); 85%; anal. (C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>O<sub>5</sub>) C, H, N].

The spectral characteristics of 1-(3,4-dichlorophenyl)-5-methyl-3,4-bis(hydroxymethyl)pyrazole bis(methylcarbamate) (**11a**) were typical: UV 251 nm ( $\epsilon$  18 600); IR 3350, 1700, 1560, 1510, 1380 cm<sup>-1</sup>; NMR  $\delta$  2.33 (s, 3 H), 2.78 (d,  $J = 5$  Hz, 6 H), 4.6–5.1 (br), 5.07 (s), 5.20 [(s) 6 H total for 4.6–5.2], 7.1–7.6 (m, 3 H).

**Dimethyl 2-Methyl-5-phenylthiophene-3,4-dicarboxylate (13a).** Freshly distilled benzyl chloride (43 mL, 0.37 mol) was converted to sodium dithiobenzoate by treatment sodium methoxide and sulfur.<sup>7b,19</sup> The red oily product was partially purified by acidification of the reaction mixture, extraction with ether, and extraction of the ether with 8% aqueous sodium carbonate (500 mL). The aqueous sodium carbonate extract was cooled (ice bath) and treated portionwise with  $\alpha$ -bromopropionic acid (20 mL) in ice water (75 mL). When the pH rose above 6 during the addition of the acid, the pH was adjusted to 6 by addition of sodium carbonate. The mixture was stirred for 14 h at 5 °C, acidified to pH 2 (50% aqueous HCl) with cooling, and extracted with ether. The ether extract was dried and concentrated in vacuo to give 64 g of the air-sensitive dithioester as a red liquid, which was used directly in the cyclization.

Dry, cold (0 °C) triethylamine (120 mL) was added portionwise to an ice-cooled solution of the crude dithioester in acetic anhydride (120 mL) which was maintained under a nitrogen atmosphere. The mixture was stored at 5 °C for 1 h and at –20 °C for an additional hour. The fine violet needles that arose were collected and washed well with ice-cold cyclohexane–ether (1:1) to give 26.7 g (27% yield, based on benzylchloride) of crude 5-methyl-2-phenyl-1,3-dithiolium 4-oxide (**12**): mp 134–135 °C [(dec) 172–175 °C] (lit.<sup>7b</sup> mp 149–150 °C dec); NMR  $\delta$  2.35 (s, 3 H), 7.35–7.67 (m, 5 H) [1.48 (t,  $J = 7$  Hz, 9 H), 3.21 (q,  $J = 7$  Hz, 6 H), Et<sub>3</sub>N]; IR (KBr) 1578, 760, 684 cm<sup>-1</sup>. From NMR data, the crude product was a 4:1 mixture of **12** and triethylamine salts. Attempts to remove the contaminant resulted in decomposition of the unstable heterocycle so the impure material was used directly in the cycloaddition reaction.

Crude **12** (19.6 g) from the previous step (containing 15.8 g, 76 mmol of **12**) and dimethyl acetylenedicarboxylate (20 mL, 163 mmol) in xylene (80 mL) were heated under a nitrogen atmosphere. Gas evolution became extremely vigorous at 85 °C, necessitating temporary removal of the heat source. After 10 min at 105 °C, the solvents were removed under vacuum, the black residue was cooled, methanol was added to give a volume of 125 mL, and the solution was filtered to give colorless or light tan crystals (13.06 g), mp 74–75 °C (lit.<sup>7a</sup> mp 78–79.5 °C). An additional 2.78 g was obtained from the concentrated mother liquor

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for a total yield of 72%. Compound **13a** had the following: NMR  $\delta$  2.65 (s, 3 H), 3.77 (s), 3.83 [s, 6 H (total for two singlets)], 7.27–7.53 (m, 5 H); IR (KBr) 2959, 1719, 1707, 1475, 1435, 1382, 1376, 1309, 1225, 1201, 1195, 1159, 983, 977, 787, 764, 759, 738, 696  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{15}\text{H}_{14}\text{O}_4\text{S}$ ) C, H, N.

**2-Methyl-5-phenyl-3,4-bis(hydroxymethyl)thiophene (13b).**

The thiophene diester **13a** (13 g, 45 mmol) in anhydrous ether (175 mL) was added dropwise to a refluxing, vigorously stirred solution of lithium aluminum hydride (4.9 g, 110 mmol) in anhydrous ether (100 mL). The reaction mixture was heated at reflux for 4 h after the addition and then cooled. It was worked up by the sequential addition of water (4.9 mL), 10% aqueous sodium hydroxide (4.9 mL), and water (14.7 mL). The resulting white sludge was extracted in a Soxhlet apparatus with ether for 14 h; concentration of the extract gave the diol (10.03 g), mp 99–107 °C. This was crystallized from ethyl acetate/ligroin to give diol **13b** (7.0 g), mp 100–102 °C; concentration of the mother liquor gave a second crop of 2.5 g (91% yield). Compound **13b** had the following: NMR  $\delta$  2.45 (s, 3 H), 3.57 (t,  $J = 5$  Hz, 2 H), 4.60 (d,  $J = 4$  Hz, 4 H), 7.42 (s, 5 H); IR (KBr) 3279, 2954, 1477, 1443, 1423, 1261, 994, 984, 972, 756, 745, 707, 701, 696, 662  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{13}\text{H}_{14}\text{O}_2\text{S}$ ) C, H, N.

**2-Methyl-5-phenyl-3,4-bis(hydroxymethyl)thiophene Bis(methylcarbamate) (13c).** The diol **13b** (7 g, 30 mmol), methyl isocyanate (5.4 mL, 90 mmol), and dry triethylamine (0.5 mL) were heated at reflux in dry dichloromethane (250 mL) for 24 h. The white solid, resulting from vacuum removal of the volatiles, was crystallized from ethyl acetate and vacuum dried to give 6.88 g of carbamate, mp 169–170 °C. An additional 1.88 g was obtained from the concentrated mother liquor (84% yield). Compound **13c** had the following: NMR  $\delta$  (s, 3 H), 2.78 (d,  $J = 5$  Hz, 6 H), 4.8 (br), 5.08 (s), 5.12 [s, 6 H (total for the three absorptions)], 7.40 (s, 5 H); IR (KBr) 3333, 1686, 1551, 1421, 1281, 1151, 1142, 1136, 976, 966, 757, 700  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ ) C, H, N.

**Dimethyl 1-Phenyl-1,2,3-triazole-4,5-dicarboxylate (14a).**

Dimethyl acetylenedicarboxylate (27 mL, 0.22 mol) was added to an ethereal solution of phenyl azide [prepared by treatment of diazotized aniline (0.22 mol) with sodium azide, extraction with ether (4  $\times$  75 mL) and drying ( $\text{CaCl}_2$ )]<sup>20,21</sup> and the volume of the solution was reduced to ca. 175 mL in vacuo. The concentrated reaction mixture was then heated under reflux for 66 h. The precipitated white crystalline triazole was filtered, giving 41.8 g (73% yield) of crude product. This was crystallized from ethyl acetate to give **14a**: mp 123–127 °C (lit.<sup>22,23</sup> mp 126–127 °C; 127 °C); NMR  $\delta$  3.92 (s), 4.02 (s) [6 H (total for both singlets)], 7.57 (s, 5 H); IR (KBr) 1720, 1560, 1500, 1470, 1450, 1440, 1380, 1310, 1290, 1240, 1200, 1180, 1090, 1070, 770  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_4$ ) C, H, N.

**1-Phenyl-4,5-bis(hydroxymethyl)-1,2,3-triazole (14b).**

Triazole diester **14a** (10 g, 38 mmol) was placed in the extraction thimble of a Soxhlet apparatus over a 500-mL flask containing 3.8 g (96 mmol) lithium aluminum hydride in 300 mL of refluxing anhydrous ether. After 9 h the mixture was cooled and stirred at room temperature an additional 15 h, at which point TLC [silica gel, methanol–chloroform (1:9)] showed only diol and decomposition products. The reaction was worked up by the sequential addition of water (3.8 mL), 10% sodium hydroxide solution (3.8 mL), and water (11.4 mL). The resulting salts were extracted in a Soxhlet apparatus using ether (24 h) and then tetrahydrofuran (24 h) to give 7.2 g of crude product. Crystallization from methanol–ether–petroleum ether afforded **14b** (3.75 g): mp 153–135 °C (lit.<sup>22</sup> mp 161–162 °C). A second crop of 0.51 g was obtained from the mother liquor (54% yield). The diol **14b** had the following: NMR ( $\text{Me}_2\text{SO}-d_6/\text{Me}_4\text{Si}$ )  $\delta$  4.64 (d,  $J = 5$  Hz), 4.72 (d,  $J = 5$  Hz, 4 H total for both doublets), 5.53 (t,  $J = 5$  Hz, 2 H total for both triplets), 7.53–7.82 (m, 5 H); IR (KBr) 3429, 3260, 1590, 1499, 1463, 1407, 1365, 1245, 1153, 1132, 1027, 801, 780, 696

$\text{cm}^{-1}$ . Anal. ( $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_2$ ) C, H, N.

**1-Phenyl-4,5-bis(hydroxymethyl)-1,2,3-triazole Bis(methylcarbamate) (14c).** A mixture of triazole diol **14b** (5.8 g, 28 mmol), methyl isocyanate (6.7 mL, 114 mmol), and triethylamine as catalyst was heated at reflux for 15 h in dry dichloromethane (250 mL). The suspension clarified as the reaction proceeded. The volatiles were removed in vacuo, and the residue crystallized from dichloromethane–hexanes to give 7.2 g (79% yield) of **14c**: mp 134–135 °C; NMR  $\delta$  2.72 (d,  $J = 5$  Hz), 2.76 (d,  $J = 5$  Hz, 6 H (total for both doublets)), 5.2 (br), 5.22 (s), 5.35 (s, 6 H total for the three absorptions), 7.52 (s, 5 H); IR (KBr) 3228, 3089, 2952, 2765, 1695, 1596, 1563, 1461, 1419, 1248, 1158, 1152, 989, 767, 692, 656  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{14}\text{H}_{17}\text{N}_5\text{O}_4$ ) C, H, N.

**Dimethyl 3-Phenylisoxazole-4,5-dicarboxylate (15a).**<sup>24–26</sup> Benzaldoxime<sup>24</sup> [21.7 g, 0.18 mol (prepared from benzaldehyde by treatment with hydroxylamine hydrochloride and sodium hydroxide followed by carbon dioxide: bp 123 °C (28 torr); mp 28–231 °C)] was dissolved in 8.3 M ethanolic HCl, cooled to 0 °C, and treated with chlorine until the blue solution turned yellow. The excess chlorine was removed (nitrogen gas and slight water aspirator vacuum), the mixture was concentrated in vacuo, and the residue was extracted with dichloromethane. The organic solution was dried ( $\text{CaCl}_2$ ) and concentrated in vacuo and the light brown syrup was solidified by treatment with ether. The ether was removed to give 20 g (74%) of chlorobenzaldoxime,<sup>25,26</sup> which was used immediately in the next step (the solid, dried under high vacuum had mp 43–49 °C).

Anhydrous triethylamine (44.7 mL, 0.321 mol) was added to a stirred, cooled (–78 °C in a dry ice–acetone bath) solution of freshly prepared chlorobenzaldoxime (20 g, 0.128 mol) and dimethyl acetylenedicarboxylate (15.8 mL, 0.128 mol) in anhydrous ether (200 mL). The mixture was stirred for 30 min at –78 °C, allowed to warm to room temperature over 4 h, and stirred at room temperature for 12 h. The precipitated triethylamine hydrochloride was removed by filtration and the collected solid was thoroughly washed with anhydrous ether. The filtrates were combined and concentrated in vacuo; 2-propanol (200 mL) was added to the maroon residue and 23.1 g of the crystalline diester was obtained. The mother liquor was concentrated and an additional 3.4 g of diester was obtained for a total yield of 79%. The product was recrystallized from 2-propanol to give **15a** as a white crystalline solid: mp 63–64 °C; NMR  $\delta$  3.90 and 4.00 (two singlets, 6 H), 7.40–7.80 (m, 5 H); IR (KBr) 2960, 1730, 1620, 1460, 1440, 1420, 1320, 1300, 1280, 1230, 1180, 1130, 1060, 980, 930, 820, 810, 790, 710, 690. Anal. ( $\text{C}_{13}\text{H}_{11}\text{NO}_5$ ) C, H, N.

**3-Phenyl-4,5-bis(hydroxymethyl)isoxazole (15b).** A mixture of sodium borohydride (20.8 g, 0.55 mol) and lithium bromide (47.9 g, 0.55 mol) in anhydrous tetrahydrofuran (1200 mL) was heated under reflux for 1 h. Dimethyl 3-phenyl-4,5-isoxazole-dicarboxylate (**15a**; 48.0 g, 0.184 mol) was added and the mixture was heated under reflux for 20 h [progress of the reaction was monitored by TLC, silica gel with methanol–chloroform (1:9), after 20 h the starting material had been completely consumed and three major products, along with several other minor products were seen on the TLC]. The reaction mixture was concentrated in vacuo and the tarry yellow residue was suspended in a mixture of water (800 mL) and ether (350 mL); the suspension was thoroughly mixed and the organic layer was removed; the process was repeated two more times. The ether extracts were combined, dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo to yield 16.4 g of a viscous orange oil.

An aliquot of the mixture (10.4 g) was purified by rapid linear gradient chromatography on silica gel (500 g; E. Merck, 63–200 mesh) using dichloromethane as the nonpolar solvent and 6% methanol in dichloromethane as the polar solvent. The crude diol (6.86 g; 66% of the applied mixture which corresponds to a 25% yield in the reaction) was obtained as an oil which was crystallized from ethyl acetate–ligroin to give white needles: mp 58–61 °C; NMR ( $\text{Me}_2\text{SO}-d_6/\text{Me}_4\text{Si}$ )  $\delta$  4.48 (d,  $J = 5$  Hz), 4.70 [d,

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$J = 6$  Hz, 4 H (total for both doublets)], 5.22 (t,  $J = 5$  Hz, 1 H), 5.58 (t,  $J = 6$  Hz, 1 H), 7.48–7.98 (m, 5 H); NMR  $\delta$  4.20 (br s, 1 H), 4.52–4.70 (m, 5 H), 7.20–7.75 (m, 5 H); IR (KBr) 3475, 3250, 2975, 2925, 1640, 1590, 1480, 1460, 1430, 1370, 1290, 1240, 1190, 1010, 930, 770, 730, 700  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{11}\text{H}_{11}\text{NO}_3$ ) C, H, N.

**3-Phenyl-4,5-bis(hydroxymethyl)isoxazole Bis(methylcarbamate) (15c).** A mixture of **15b** (6.0 g, 29 mmol), dry triethylamine (0.5 mL), and methyl isocyanate (5.3 mL, 88 mmol) in dry dichloromethane was heated under reflux. The reaction was monitored by TLC [silica gel, methanol–chloroform (1:9)]; after 6 h the diol had been consumed and two, higher  $R_f$  products were observed on the TLC; after 24 h of reflux, one of these two new spots had disappeared and only a single spot remained on the TLC. The volatiles were removed from the reaction mixture in vacuo and the oily residue, which slowly solidified on standing, was crystallized from benzene–hexanes to give, after high vacuum drying, 8.23 g (88%) of **15c**: mp 100–106 °C; NMR  $\delta$  2.76 (d,  $J = 5$  Hz), 2.78 [d,  $J = 5$  Hz, 6 H (total for both doublets)], 5.12 (s), 5.37 (s), 5.2 [br, 6 H (total for the three signals)], 7.35–7.85 (m, 5 H); IR (KBr) 3350, 1730, 1710, 1670, 1630, 1580, 1560, 1530, 1450, 1420, 1360, 1280, 1150, 1120, 970, 910, 770, 660  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_5$ ) C, H, N.

**3-Phenyl-4,5-bis(hydroxymethyl)isothiazole (16b).** 5-Phenyl-1,3,4-oxathiazol-2-one<sup>27</sup> [28 g, 156 mmol (prepared from benzamide by treatment with perchloromethyl mercaptan: mp 65–67 °C)] and dimethyl acetylenedicarboxylate (26 mL, 223 mmol) heated at 130 °C in chlorobenzene (100 mL) for 22 h. The mixture was concentrated to dryness in vacuo and the black residue was crystallized from methanol to yield 29 g (67%) of **16a**, which was recrystallized from methanol–water: mp 70–72 °C (lit.<sup>28</sup> mp 72–73 °C). Anal. ( $\text{C}_{13}\text{H}_{11}\text{NO}_4\text{S}$ ) C, H, N.

The diester **16a** (31.7 g, 0.11 mol) in anhydrous ether (400 mL) was added dropwise to a refluxing, mechanically stirred suspension of lithium aluminum hydride (10.8 g, 0.29 mol) in anhydrous ether (200 mL). The mixture was stirred under reflux for an additional 45 min after the end of the addition. The cooled reaction mixture was carefully treated with water (10.8 mL), 10% aqueous sodium hydroxide (10.8 mL), and finally water (32.4 mL). The resulting salts were extracted 16 h in a Soxhlet apparatus with ether, the ether removed in vacuo, and the residue crystallized from ethyl acetate/ligroin to give 11.3 g of **16b** (45%). Recrystallization gave 9.1 g of **16b**: mp 111–113 °C; NMR ( $\text{Me}_2\text{SO}/\text{Me}_4\text{Si}$ )  $\delta$  4.50 (br s, 2 H), 5.00 (br s, 2 H), 5.25 (br, 1 H), 5.95 (br, 1 H), 7.35–7.88 (m, 5 H); IR (KBr) 3375, 3175, 1540, 1460, 1430, 1410, 1390, 1350, 1230, 1150, 1070, 1050, 1020, 990, 980, 860  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$ ) C, H, N.

**3-Phenyl-4,5-bis(hydroxymethyl)isothiazole Bis(methylcarbamate) (16c).** The isothiazole diol **16b** (9 g, 41 mmol), methyl isocyanate (12 mL, 0.2 mol), and triethylamine (0.5 mL) were refluxed 26 h, in dry dichloromethane (250 mL). The mixture was concentrated to dryness in vacuo and the residue was crystallized twice from ethyl acetate/ligroin to give, after drying under high vacuum, 10 g (75%) of the carbamate: mp 115–124 °C; NMR  $\delta$  2.72 (d,  $J = 2$  Hz), 2.80 [d,  $J = 2$  Hz, 5 H (total for both doublets)], 5.1 (br), 5.13 (s), 5.47 [s, 6 H (total for the three signals)], 7.27–7.72 (m, 5 H); IR (KBr) 3350, 3000, 2875, 1700, 1550, 1430, 1280, 1140, 990, 940, 820, 780, 750  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ ) C, H, N.

**2-Phenyl-4,5-bis(hydroxymethyl)thiazole (17b).** A solution of diethyl  $\alpha$ -chloro- $\beta$ -ketosuccinate [44.5 g, 200 mmol; bp 127–130 °C (9 torr) (lit.<sup>29</sup> bp 150–152 °C (56 torr))], prepared from diethyl oxalate and ethyl chloroacetate and thiobenzamide (21.5 g, 157 mmol) in anhydrous toluene (25 mL) was heated briefly to initiate the slight exothermic reaction. The mixture was stirred at room temperature (2 h), heated to 75–80 °C (1.5 h), and then allowed to stand at room temperature (15 h). The solid mass was melted on a steam bath and poured into ice water. The mixture was extracted with dichloromethane and the organic phase was washed with 5% aqueous sodium carbonate (3  $\times$  100 mL) and saturated sodium chloride solution (100 mL). The organic solution was dried (sodium sulfate) and concentrated to dryness in vacuo, and the

residue was crystallized from dichloromethane–hexanes and then from ethyl acetate–ligroin to give 18.9 g (40%) of **17a**: mp 92–95 °C (lit.<sup>31</sup> mp 104 °C). Anal. ( $\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S}$ ) C, H, N.

A stirred suspension of lithium aluminum hydride (3.75 g, 98 mmol) in anhydrous ether (200 mL) was heated to reflux and a solution of thiazole diester **17b** (12.0 g, 39 mmol) in anhydrous ether (500 mL) was added rapidly. The stirred mixture was heated under reflux for 3.5 h after the addition. The cooled reaction mixture was worked up by the sequential addition of water (3.7 mL), 10% aqueous sodium hydroxide (3.7 mL), and then water (11.1 mL). The resultant salts were extracted with ether in a Soxhlet apparatus for 24 h and then extracted again with tetrahydrofuran to give, after crystallization from ethyl acetate–hexanes, 7.61 g (81% yield) of **17b**: mp 121–123 °C; NMR ( $\text{Me}_2\text{SO}-d_6/\text{Me}_4\text{Si}$ )  $\delta$  4.73 (d,  $J = 6$  Hz, 1 H), 4.93 [d,  $J = 6$  Hz, 4 H (total for both doublets)], 5.30 (t,  $J = 6$  Hz, 1 H), 5.75 (t,  $J = 6$  Hz, 1 H), 7.47–8.12 (m, 5 H); IR (KBr) 3326, 2878, 1464, 1438, 1311, 1045, 1029, 1015, 1001, 989, 767, 756, 686, 621  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$ ) C, H, N.

**2-Phenyl-4,5-bis(hydroxymethyl)thiazole Bis(methylcarbamate) (17c).** Thiazole diol **17b** (5.07 g, 22.6 mmol), methyl isocyanate (5.3 mL, 90 mmol), and dry triethylamine (1 mL) as catalyst were heated at reflux in dry dichloromethane (250 mL) for 28 h. The mixture was concentrated to dryness in vacuo and the residue was crystallized from ethyl acetate/ligroin and dried under high vacuum to give 7.0 g (92% yield) of **17c**: mp 139–141 °C; NMR  $\delta$  2.78 (d,  $J = 5$  Hz, 6 H), 4.90 (br), 5.28 (s), 5.40 [s, 6 H (total for the three absorptions)], 7.27–7.98 (m, 5 H); IR (KBr) 3328, 2946, 1710, 1699, 1566, 1550, 1542, 1464, 1269, 1148, 1134, 985, 766, 687  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_5\text{S}$ ) C, H, N.

**2-Phenyl-4,5-bis(hydroxymethyl)oxazole (18b).** Benziminoethyl ether hydrochloride<sup>33,34</sup> [100 g, 0.54 mol (prepared from benzonitrile by treatment with hydrogen chloride: mp 131–132 °C dec; lit.<sup>34</sup> frothing at 118–120 °C and then melting at 125 °C)] was suspended in ether (540 mL) at 5 °C with vigorous mechanical stirring and treated with potassium carbonate (86 g, 0.622 mol) in water (76 mL) for 10 min. The organic phase was separated and added to a vigorously stirred solution of ethyl glycinate hydrochloride (75.7 g, 0.542 mol) in water (45 mL). The mixture was stirred at 35 °C for 1.5 h, and the organic phase was separated and dried (sodium sulfate) and concentrated in vacuo. The residue was distilled to give 54.4 g of benziminoethyl ether, bp 45–50 °C (0.055 torr) and ethyl [(ethoxyphenylmethylidene)amino]acetate (38.46 g, 30%), bp 103–105 °C (0.11 torr) [lit.<sup>32</sup> bp 115–123 °C (0.06 torr)].

Potassium metal (5.82 g, 0.149 mol) was dissolved in absolute ethanol (25 mL) and anhydrous ether (100 mL) and then cooled to –7 to –10 °C. Additional ether (500 mL) was added, followed by a solution of ethyl [(ethoxyphenylmethylidene)amino]acetate (35 g, 0.149 mol) and diethyl oxalate (21.74 g, 0.149 mol) in ether (160 mL). After 13 h at 0 °C, the ether was removed under vacuum, and boiling acetic acid (125 mL) was added. The mixture was cooled, water (760 mL) was added, and the mixture was neutralized with saturated aqueous sodium carbonate (900 mL). Chloroform (100 mL) was added; the organic layer was removed, dried (sodium sulfate) and then magnesium sulfate), and con-

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centrated. The residual red oil slowly crystallized and was recrystallized from methanol to give 17.7 g (41%) of the diester. A second crystallization from methanol gave pure 18a: mp 54-58 °C (lit.<sup>32</sup> mp 59 °C). Anal. (C<sub>15</sub>H<sub>15</sub>NO<sub>5</sub>) C, H, N.

The oxazole diester 18a (11.7 g, 40 mmol) in anhydrous ether (150 mL) was added dropwise to lithium aluminum hydride (3.84 g, 101 mmol) in refluxing anhydrous ether. The reaction was refluxed 1 h and cooled and then water (3.8 mL), 10% sodium hydroxide (3.8 mL), and water (11.4 mL) were added. The resulting salts were extracted with ether for 26 h in a Soxhlet apparatus, the ether was removed, and the residue was crystallized from ethyl acetate to give 3.3 g (40%) of 18b: mp 127-129 °C; NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>/Me<sub>4</sub>Si) δ 4.52-4.70 (m, 4 H), 5.27 (br s, 3 H), 7.50-8.07 (m, 6 H); IR (KBr) 3575, 3425, 1650, 1630, 1580, 1500, 1460, 1030, 720 cm<sup>-1</sup>. Anal. (C<sub>11</sub>H<sub>11</sub>NO<sub>3</sub>) C, H, N.

**2-Phenyl-4,5-bis(hydroxymethyl)oxazole Bis(methylcarbamate) (18c).** The oxazole diol 18b (3.18 g, 15.5 mmol), methyl isocyanate (5.6 mL, 94.9 mmol), and triethylamine (1 mL) were heated at reflux for 3 h in dichloromethane (125 mL). The suspension cleared after 10 min, and within 40 min, a precipitate occurred. The reaction was stirred an additional 9 h at room temperature. The precipitate was filtered and dried under a stream of nitrogen and then under high vacuum to give 3.93 g, mp 190-192 °C. The filtrate was concentrated and crystallization of the residue from ethyl acetate gave an additional 0.63 g for a total yield of 18c of 92%: NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>/Me<sub>4</sub>Si) δ 2.57 (s), 2.65 [s, 6 H (total for both singlets)], 5.03 (s, 2 H), 5.22 (s, 2 H), 7.1 (br, 2 H), 7.47-8.03 (m, 5 H); NMR (CDCl<sub>3</sub>/Me<sub>4</sub>Si) δ 2.77 (d, *J* = 1 Hz), 2.84 [d, *J* = 1 Hz, 6 H (total for both doublets)], 4.9 (br, 2 H), 5.16 (s), 5.29 [s, 4 H (total for both singlets)], 7.40-8.10 (m, 5 H); IR (KBr) 3350, 2975, 1700, 1550, 1490, 1470, 1450, 1430, 1350, 1290, 1270, 1260, 1140, 1070, 990, 960, 780, 720 cm<sup>-1</sup>. Anal. (C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>5</sub>) C, H, N.

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## Synthesis of 5-Aryl-2H-tetrazoles, 5-Aryl-2H-tetrazole-2-acetic Acids, and [(4-Phenyl-5-aryl-4H-1,2,4-triazol-3-yl)thio]acetic Acids as Possible Superoxide Scavengers and Antiinflammatory Agents<sup>1</sup>

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A series of 5-aryl-2H-tetrazoles, 5-aryl-2H-tetrazole-2-acetic acids, and [(4-phenyl-5-aryl-4H-1,2,4-triazol-3-yl)thio]acetic acids were synthesized and tested in vitro for superoxide scavenging activity, in vivo in the carrageenan-induced rat paw edema assay, and in the reverse passive Arthus reaction. The hydroxy-substituted compounds were effective as in vitro scavengers of superoxide but were not effective as in vivo antiinflammatory agents.

A possible role of the superoxide anion radical (O<sub>2</sub><sup>-</sup>) in the pathology of rheumatoid arthritis has been proposed.<sup>2</sup> Experimental evidence indicates that excess superoxide generates a chemotactic factor that perpetuates the inflammatory process.<sup>3-6</sup> Treatment of affected joints with polymer-stabilized bovine superoxide dismutase greatly lowers the activity of the inflammatory process and allows

healing of the damaged tissue to ensue.<sup>7</sup> Stabilized superoxide dismutase was also found effective in both the reverse passive Arthus reaction and carrageenan-induced foot edema.<sup>2</sup> In lieu of isolating and modifying an enzyme from living tissue, a low molecular weight chemical agent was sought as a scavenger of superoxide and hence an antiinflammatory agent. Molecules containing gallic acid and catechol moieties are known to scavenge superoxide<sup>8</sup> and exhibit some antiinflammatory activity.<sup>9</sup> The selection of a proper carrier molecule into which these polyphenolic moieties could be incorporated is the subject of this paper.

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