1)$^+$; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3, CH_3), 4.42 (m, 1, H-4′), 4.70 (br d, 2, 5′-CH_2, $J_{4',5'}$ = 4.7 Hz), 5.17 (dd, 1, H-2′, $J_{2',3'}$ = 0.3 Hz, $J_{2',F}$ = 49.8 Hz), 5.51 (dd, 1, H-3′, $J_{3',4'}$ = 2.6 Hz, $J_{3',F}$ = 16.2 Hz), 6.48 (dd, 1, H-1′, $J_{1',2'}$ = 2.6 Hz, $J_{1',F}$ = 22.3 Hz), 7.48 (m, 2, meta phenyl protons), 7.58 (m, 1, para phenyl proton), 8.07 (m, 2, ortho phenyl protons), 8.14 (d, 1, H-8, $J_{8,F}$ = 3.1 Hz); ^{19}F NMR ($CDCl_3$) δ −199.14.

9-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (4d). A solution of **4c** (1.22 g, 2.5 mmol) in EtOH (200 mL) was treated with Pd–C (5%, 165 mg) and hydrogenolyzed at atmospheric pressure for 5 h. The hydrogen atmosphere was changed after 2.5 h. The catalyst was removed by filtration and washed with $CHCl_3$ to dissolve any precipitated product. The combined filtrate and washings were evaporated to dryness, and the resulting residue was dissolved in boiling EtOH (80 mL). The crystals that formed on cooling were collected after chilling, washed with EtOH, and dried in vacuo at 56 °C for 6 h: yield, 865 mg (80%); mp 217–218 °C; TLC, 9:1 $CHCl_3$–MeOH, R_f = 0.50; exact mass, m/z (M + 1)$^+$ calcd 431.148, found 431.147; ^{1}H NMR (Me_2SO-d_6) δ 2.15 (s, 3, CH_3), 4.42 (m, 1, H-4′), 4.59, 4.70 (2 m, 2, 5′-CH_2), 5.47 (dm, 1, H-2′, $J_{2',3'}$ = 1.8 Hz, $J_{2',F}$ = 55.5 Hz), 5.57 (dm, 1, H-3′, $J_{3',4'}$ = 3.5 Hz, $J_{3',F}$ = 18.2 Hz), 5.92 (br s, 2, 2-NH_2), 6.25 (dd, 1, H-1′, $J_{1',2'}$ = 3.5 Hz, $J_{1',F}$ = 20.9 Hz), 6.81 (br s, 2, 6-NH_2), 7.55 (m, 2, meta phenyl protons, 7.68 (m, 1, para phenyl proton), 7.69 (d, 1, H-8, $J_{8,F}$ = 3.0 Hz), 8.01 (m, 2, ortho phenyl protons); ^{19}F NMR ($CDCl_3$) δ −197.97. Anal. ($C_{19}H_{19}FN_6O_5$) C, H, N.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (4e). A suspension of **4d** (200 mg, 0.46 mmol) in 1:1 MeOH–H_2O (13 mL) was treated in one portion with 1 N NaOH (0.6 mL). The mixture was stirred at room temperature for 19 h. A TLC aliquot of the resulting solution showed complete reaction. After adjusting the pH to 5 with dilute acetic acid, the reaction was evaporated to dryness and the residue crystallized from boiling H_2O (5 mL), triturated with ether, and dried to afford a first crop of 105 mg: softens at 150 °C; mp 225 °C (with some decomposition). A second crop (15 mg) with identical melting behavior and of identical purity was obtained by reducing the volume: total yield, 120 mg (91%); exact mass, m/z (M + 1)$^+$ calcd 285.111, found 285.112; UV λ_{max} ($\epsilon \times 10^{-3}$) [pH 1] 1) 252 (12.2), 290 (10.4), [pH 7] 255 (10.1), 278 (10.4), [pH 13] 255 (9.9), 278 (10.6); ^{1}H NMR (Me_2SO-d_6) δ 3.63 (m, 2, 5′-CH_2), 3.81 (m, 1, H-4′), 4.40 (dm, 1, H-3′, $J_{3',4'}$ = 4.6 Hz, $J_{3',F}$ = 18.9 Hz), 5.10 (br s, 1, 5′-OH), 5.09 (dm, 1, H-2′, $J_{2',3'}$ = 3.4 Hz, $J_{2',F}$ = 52.6 Hz), 5.88 (br s, 2, 2-NH_2), 5.91 (d, 1, 3′-OH, $J_{3',3'\text{-OH}}$ = 4.0 Hz), 6.18 (dd, 1, H-1′, $J_{1',2'}$ = 4.3 Hz, $J_{1',F}$ = 16.1 Hz), 6.75 (br s, 2, 6-NH_2), 7.80 (d, 1, H-8, $J_{8,F}$ = 2.3 Hz); ^{13}C NMR (Me_2SO-d_6) δ 60.27 (C-5′), 72.63 (C-3′, $J_{3',F}$ = 23.6 Hz), 81.06 (C-1′, $J_{1',F}$ = 17.0 Hz), 83.20 (C-4′, $J_{4',F}$ = 4.5 Hz), 95.11 (C-2′, $J_{2',F}$ = 191.2 Hz), 112.09 (C-5), 136.07 (C-8, $J_{8,F}$ = 3.7 Hz), 151.19 (C-4), 155.76 (C-6), 160.13 (C-2); ^{19}F NMR ($CDCl_3$) δ −197.40. Anal. ($C_{10}H_{13}FN_6O_3$·0.11HOAc·0.03Et_2O·0.4H_2O) C, H, N.

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Registry No. **1b**, 103884-98-6; α-**2a**, 56632-79-2; β-**2a**, 56632-80-5; α-**2b**, 92283-83-5; β-**2b**, 93302-28-4; **3**, 5451-40-1; **4a**, 103884-99-7; **4b**, 103885-00-3; **4c**, 103885-01-4; **4d**, 103885-02-5; **4e**, 103884-97-5.

Comparison of the Chemical Reactivities and Antineoplastic Activities of α,β-, α,β′-, β,β′-, and α,α′-Bis[[[(2-propylamino)carbonyl]oxy]methyl]-Substituted Pyrroles[1]

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The bis[*N*-(2-propyl)carbamate] derivatives of 2,3-bis(hydroxymethyl)-4,5-diphenyl-1-methylpyrrole (**4a**), 3,4-bis(hydroxymethyl)-2,5-diphenyl-1-methylpyrrole (**4b**), 2,4-bis(hydroxymethyl)-3,5-diphenyl-1-methylpyrrole (**4c**), and 2,5-bis(hydroxymethyl)-3,4-diphenyl-1-methylpyrrole (**4d**) were synthesized and the reactivities of the four compounds were compared using the model nucleophile 4-(*p*-nitrobenzyl)pyridine (NBP). No significant correlation was seen between NBP reactivity and either toxicity or antineoplastic activity in this series. Three compounds **4a**, **4b**, and **4c** gave significant reproducible activity against P388 lymphocytic leukemia; the α,α′-bis(carbamate) **4d** was inactive. The α,β- and α,β′-bis(carbamates) **4a** and **4c** were evaluated against a panel of mouse tumor homografts and human tumor xenografts implanted under the kidney capsule of mice.

The class of antineoplastic agents broadly referred to as "acylated vinylogous carbinolamines" has been studied extensively over the past several years. Bis(carbamate) derivatives of bis-hydroxymethylated pyrroles,[2] pyrrolizines,[3] and other heterocycles[4] have been shown to possess significant antineoplastic activity in a number of different test systems.[5] The compounds that have been reported to date all have the hydroxymethyl moieties on adjacent carbon atoms; no study has been reported that evaluates the significance of different hydroxymethyl substitution patterns in the pyrrole skeleton.

This paper describes the synthesis and antitumor activity of four isomeric bis(hydroxymethyl)diphenyl-*N*-methylpyrrole bis(carbamates) that differ in the substi-

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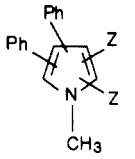
Table I. Structures of Key Compounds



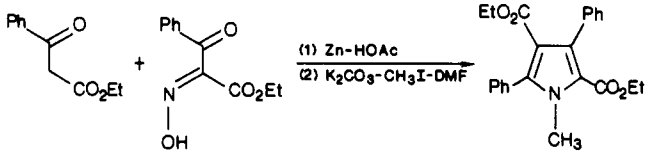
1, Z = CO_2Me
2, Z = CO_2Et
3, Z = CH_2OH
4, Z = $CH_2OCONHCHMe_2$

compd	substituent position Z	C_6H_5
a	C-2/C-3	C-4/C-5
b	C-3/C-4	C-2/C-5
c	C-2/C-4	C-3/C-5
d	C-2/C-5	C-3/C-4

tution pattern at C-2, C-3, C-4, and C-5.

Chemistry. The structures of the key compounds described are given in Table I. The bis(carbamates) **4** were prepared from the corresponding diol **3** by treatment with 2-propyl isocyanate. In turn, the diols **3** were prepared from the corresponding diester **1** or **2**. The diols **3a** and **3b** have already been reported.[2c]

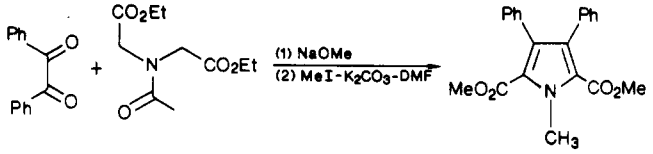
The diester **2c** was prepared by N-methylation of the pyrrole obtained in the Knorr reaction[6] with ethyl 3-oxo-3-phenylpropionate and ethyl 2-oximino-3-oxo-3-phenylpropionate:



2c

The oxime can be generated in situ and reduced in a one-pot procedure, but the overall yield and purity of the pyrrole are better if the oxime is isolated and purified. The pyrrole was N-methylated by treatment with iodomethane–potassium carbonate in anhydrous DMF. This methylation procedure was found to give superior results compared to the thallous ethoxide–iodomethane method.[7]

The diester **1d** was prepared in a sequence that involved reaction between benzil and *N,N*-bis(ethoxycarbonylmethyl)acetamide[8] followed by esterification and concomitant N-methylation of the resulting pyrrole diacid:



1d

The reactivities of several (hydroxymethyl)pyrroles (and the corresponding *N*-ethylcarbamates) have been compared using the model nucleophile 4-(*p*-nitrobenzyl)pyridine (NBP).[9] It was shown that the carbamates were more reactive than the corresponding alcohol and that the substituent on the pyrrole α-carbon was more reactive than the same substituent on the β-carbon.

The reactivities of **4a–d** with NBP were compared and the results are given in Table II. The data show that the α,α'-bis(carbamate) **4d** is more reactive than the β,β'-bis(carbamate) **4b**; however, the data do not correlate well with either toxicity or antineoplastic activity.

Table II. Pseudo-First-Order Rate Constants for the Reaction of **4a–4d** with 4-(*p*-Nitrobenzyl)pyridine

compd	k' (absorbance/time)
4a	3.21×10^{-3}
4b	4.98×10^{-3}
4c	1.12×10^{-3}
4d	6.69×10^{-3}

Table III. Activity of **4a–4d** against P388 Lymphocytic Leukemia in Vivo[a]

compd	dose, mg/kg	%T/C	KE	wt. diff (T – C) g	TDS
4a	240	181	3.74	−2.4	6/6
	120	160	2.06	1.5	6/6
	60	142	0.59	−1.1	6/6
4b	240		tox	−5.5	6/6
	120	94	tox	−4.4	6/6
	60	209	6.43	−2.2	6/6
	40	168	2.85	−1.6	6/6
	20	137	0.08	−0.1	6/6
4c	240		tox		0/6
	120		tox	−4.5	5/6
	60	180	3.89	−3.8	6/6
	30	150	0.88	−5.3	6/6
	15	134	−0.19	−3.7	6/6
4d	240	101	−1.51	−1.7	6/6
	120	98	−1.56	−0.2	6/6
	60	107	−1.44	0.0	6/6

[a] Determined under the auspices of the National Cancer Institute, DHEW. For general screening procedures and data interpretation, see: Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*(2), 1; also see NIH Publication 84-2635, *In Vivo Cancer Models, 1976–1982.* KE = log cell kill; the notation tox indicates a probable toxic dose of drug. TDS = toxicity day survivors and is the ratio of survivors to treated animals on day 5 of the test.

Results and Discussion

The P388 data summarized in Table III show **4a**, **4b**, and **4c** to have comparable activity, although **4b** and **4c** are more potent than **4a**. The C-2/C-5 bis(carbamate) **4d** is the least stable of the four isomers, so the inactivity of this compound may be due to rapid hydrolytic inactivation. The bis(carbamates) **4a** and **4b** have the two electrophilic sites on adjacent carbon atoms as part of a four carbon atom sequence, while the two electrophilic sites in **4c** form a five carbon atom sequence and are not on adjacent pyrrole carbon atoms.

The *N*-methylcarbamate analogue of **4b** has already been evaluated in the NCI tumor panel and the results have been reported elsewhere.[5a] The compound was active against P388 lymphocytic leukemia (T/C = 205% at 20 mg/kg), L1210 lymphocytic leukemia (T/C = 147% at 25 mg/kg), and B16 melanocarcinoma (T/C = 206% at 25 mg/kg); it showed marginal activity against $CD8F_1$ mammary tumor and colon 38 and was inactive in the Lewis lung tumor assay.

The bis(carbamates) **4a** and **4c** were tested in three solid tumor models. These were M5076 ovarian carcinoma, MX-1 mammary xenograft, and LOX (a human amelanotic melanoma xenograft). Both compounds were active against all three of the solid tumor models; however, **4a** was more active and less potent than **4c**. The optimum activities are summarized in Table IV.

The differences in activities and potencies of the four compounds cannot be explained on the basis of log *P*, since all four compounds should have comparable lipophilic properties. The 2,3-bis(carbamate) **4a** is slightly more

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Table IV. Activity of 4a and 4c against Solid Tumor Models

compd	test tumor	dose, mg/kg	wt. diff (T - C), g	%T/C[a]
4a	LOX	400	-3.3	301
4c	LOX	100	-3.5	180
4a	MX-1	800	-5.3	0
4c	MX-1	200	-7.2	-3
4a	M5076	800	-2.8	178
4c	M5076	50	-2.5	139

[a] In the LOX and M5076 assays, %T/C data are for increased survival. In the MX-1 assay, %T/C data represent tumor weight reduction.

reactive than the 2,4-bis(carbamate) **4c**, but this difference does not satisfactorily account for the difference in potency, since the 3,4-bis(carbamate) **4b** is slightly more reactive than **4a** and is more potent than **4a** (in fact **4b** and **4c** appear to be nearly equipotent). It may not be concluded, on the basis of these data, that location of the putative reactive centers (the (carbamoyloxy)methyl groups) on adjacent carbons is necessary for activity. However, it does appear that toxicity (as expressed by test animal weight loss) is greater for the 2,4-isomer **4c** than the 2,3-isomer **4a** for comparable T/C values.

Further studies will be required to determine the nature of the interaction of these agents with DNA and specifically to determine whether these agents act as bifunctional electrophiles to cross-link DNA or as single monoalkylating agents. This kind of information cannot be obtained with the simple NBP studies. The ability or inability to cross-link DNA will obviously have a significant effect on the antineoplastic activity and toxicity of these agents. In our experience, monofunctional analogues of the bifunctional bis(carbamates) have shown less activity and greater toxicity than the comparable bifunctional agent.

Experimental Section

Melting points (uncorrected) were taken in open capillary tubes with a Thomas-Hoover Unimelt apparatus. Infrared spectra were determined as Nujol mulls unless otherwise specified, using a Nicolet FT-IR. NMR spectra were determined for deuteriochloroform solutions containing 1% tetramethylsilane, unless otherwise specified, using either a Varian T60A or FT-80 spectrometer. UV spectra were obtained with a Cary 118 UV-vis spectrophotometer. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA, and, unless otherwise specified, were within ±0.4% of the calculated values.

Dimethyl 1-Methyl-3,4-diphenylpyrrole-2,5-dicarboxylate (1d). A mixture of 3,4-diphenylpyrrole-2,5-dicarboxylic acid (3.07 g, 0.01 mol) and potassium carbonate (3.47 g, 0.025 mol) in dry DMF (50 mL) was treated with iodomethane (10 mL, 0.16 mol). The mixture was stirred at room temperature for 24 h; additional potassium carbonate (1.38 g; 0.01 mol) and iodomethane (10 mL; 0.16 mol) were added, and the mixture was heated at 80–90 °C for 40 h. The DMF was distilled in vacuo and the residue treated with ethyl acetate (75 mL) and water (50 mL). The layers were separated, and the organic layer was extracted with water (3 × 50 mL), dried (Na_2SO_4), and evaporated in vacuo to give an orange solid that was crystallized from ethanol to give **1d** as white needles (2.8 g, 80%): mp 148–149 °C; IR 2936, 1717, 1436, 1274, 1098, 844, 760 cm^{-1}; NMR δ 3.53 (s, 6 H), 4.17 (s, 3 H), 7.07 (m, 10 H). Anal. ($C_{21}H_{19}NO_4$) C, H, N.

Diethyl 3,5-Diphenyl-1-methylpyrrole-2,4-dicarboxylate (2c). Method A. Thallous ethoxide (2.50 mL, 0.035 mol) was added to a stirred solution of diethyl 3,5-diphenylpyrrole-2,4-dicarboxylate[6] (12.4 g, 0.034 mol) in dichloromethane (80 mL) and anhydrous ether (500 mL). After 15 min, the precipitate formation was complete and the mixture was evaporated in vacuo. The yellow residue was stirred for 2.5 days with iodomethane (50 mL). During this period the flask was sealed and covered to exclude light. The yellow mixture was then diluted with benzene and filtered and the thallous iodide residue washed with benzene (3 × 200 mL). The combined filtrates were concentrated in vacuo, and the residue was dissolved in ethyl acetate and passed through a short column of silica gel. The ethyl acetate elutant was evaporated in vacuo, and the resulting solid was dissolved in benzene and diluted with ligroine (bp 90–105 °C) to give **2c** as light-pink crystals (9.8 g, 76%), mp 84–85 °C; IR 3080, 1695, 1605, 1580, 1545, 1410, 1290, 1255, 1180, 1105, 1070, 920, 880, 840, 790, 755, 695 cm^{-1}; NMR δ 0.70 (t, J = 7 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H), 3.70 (s, 3 H), 3.81 (q, J = 7 Hz, 2 H), 4.01 (q, J = 7 Hz, 2 H), 7.28 (s, 5 H), 7.38 (s, 5 H). Anal. ($C_{23}H_{23}NO_4$) C, H, N.

Method B. A mixture of diethyl 3,5-diphenylpyrrole-2,4-dicarboxylate[6] (2.48 g, 0.006 mol) and potassium carbonate (1.38 g, 0.01 mol) in *dry* DMF (50 mL) was treated with iodomethane (10 mL, 0.16 mol). The reaction mixture was allowed to stir at 75 °C for 48 h. The DMF was removed in vacuo and the residue treated with ethyl acetate (50 mL) and water (30 mL). The layers were separated, and the organic layer was extracted with water (3 × 30 mL), dried (Na_2SO_4), and evaporated in vacuo to give a solid that was crystallized from absolute ethanol to give a product (1.82 g, 78%) identical to that obtained from method A.

1-Methyl-3,5-diphenyl-2,4-bis(hydroxymethyl)pyrrole (3c). A solution of the diester **2c** (7.55 g, 0.020 mol) in dichloromethane (50 mL) was added dropwise to a stirring mixture of lithium aluminum hydride (1.7 g, 0.04 mol) in anhydrous ether (100 mL) at 0 °C. The reaction mixture was heated at reflux for 40 min and then cooled in an ice bath. The excess hydride was decomposed by sequential addition of water (2 mL), 15% aqueous sodium hydroxide solution (2 mL), and water (6 mL). The mixture was filtered and the inorganic residue washed with hot THF (400 mL); the filtrate was dried (Na_2SO_4) and concentrated in vacuo to give a syrup that was dissolved in hot THF and then diluted with ligroine (bp 90–105 °C) to yield **3c** as white crystals (4.9 g, 83%): mp 195–197 °C; IR 3200, 2930, 1580, 1540, 1535, 1490, 1325, 1260, 1225, 1180, 1145, 1080, 1045, 1015, 990, 980, 965, 925, 870, 780, 765, 740, 715, 700 cm^{-1}; NMR (Me_2SO-d_6/TMS) δ 3.60 (s, 3 H), 4.08 (d, J = 4 Hz, 2 H), 4.40–4.60 (m, 3 H, changes to s upon addition of D_2O, 2 H), 4.99 (t, J = 4 Hz, 1 H disappears on adding D_2O), 7.10–7.60 (m, 10 H). Anal. ($C_{19}H_{19}NO_2$) C, H, N.

1-Methyl-3,4-diphenyl-2,5-bis(hydroxymethyl)pyrrole (3d). A solution of the diphenyl diester **1d** (3.17 g, 0.01 mol) in dry THF (30 mL) was added dropwise to a stirring suspension of lithium aluminum hydride (0.87 g, 0.023 mol) in dry THF (40 mL). The reaction mixture was allowed to stir at room temperature for 18 h (note: a complex mixture of products will form if the mixture is heated) and then cooled in an ice bath. The excess hydride was decomposed by sequential addition of water (0.9 mL), 15% aqueous NaOH solution (0.9 mL), and water (2.7 mL). The mixture was filtered and the inorganic residue washed with hot THF (100 mL). The filtrate was dried (Na_2SO_4) and concentrated in vacuo to give an oil that was crystallized from dichloromethane/petroleum ether to give 2.14 g (73%) of **3d**: mp 127–128 °C; IR 3288, 2922, 1605, 1464, 1386, 1471, 1006, 991, 984, 703 cm^{-1}; NMR δ 3.67 (s, 3 H), 4.43 (s, 4 H), 7.02 (s, 10 H).

1-Methyl-4,5-diphenyl-2,3-bis(hydroxymethyl)pyrrole Bis[*N*-(2-propyl)carbamate] (4a). A solution of the diol **3b** (3.17 g, 0.01 mol) and 2-propyl isocyanate (2.55 g, 0.03 mol) in dry dichloromethane (60 mL) was treated with 3–4 drops of dibutyltin diacetate, and the solution was then slowly heated to reflux. After 2 h, the volatiles were removed in vacuo and the residue was crystallized from ethyl acetate diluted with petroleum ether to give **4a** as a microcrystalline solid (4.08 g, 88%): mp 78–79 °C; IR 3345, 2936, 1682, 1534, 1471, 1457, 1245, 1069, 943, 696 cm^{-1}; NMR δ 1.07–1.22 (m, 12 H), 3.53 (s, 3 H), 3.53–4.20 (m, 2 H), 4.63 (br s, 2 H), 5.10 (s, 2 H), 5.35 (s, 2 H), 7.13–7.23 (m, 10 H). Anal. ($C_{27}H_{33}N_3O_4$) C, H, N.

1-Methyl-2,5-diphenyl-3,4-bis(hydroxymethyl)pyrrole Bis[*N*-(2-propyl)carbamate] (4b). A suspension of the diol **3b** (4.00 g, 0.0136 mol) in 2-propyl isocyanate (15 mL) was treated with 3–4 drops of dibutyltin diacetate. After the exothermic reaction had ceased (15 min), dry dichloromethane was added and the reaction was stirred and heated at 35 °C for 30 min. The volatiles were distilled in vacuo, and the white solid residue was dried under a steady stream of nitrogen. It was then crystallized from acetone to give 6.0 g (95%) of **4b** as fluffy white crystals: mp 171–172 °C; IR 3300, 2900, 1660, 1520, 1250, 1090, 950, 760, 720 cm^{-1}; NMR δ 1.14 (d, J = 5 Hz, 12 H), 3.31 (s, 3 H), 3.50–3.90 (septet J = 5 Hz, 2 H), 4.52 (br, s, 2 H), 4.99 (s, 4 H), 7.37 (s, 10

H). Anal. $C_{27}H_{37}N_3O_4$) C, H, N.

1-Methyl-3,5-diphenyl-2,4-bis(hydroxymethyl)pyrrole Bis[*N*-(2-propyl)carbamate] (4c). A suspension of the diol **3c** (1.85 g, 0.006 mol) and 2-propyl isocyanate (1.71 g, 0.03 mol) in dry dichloromethane (50 mL) was treated with 3–4 drops of dibutyltin diacetate. After several hours a clear solution was obtained. The mixture was stirred and heated at reflux for 18 h, and the volatiles were removed in vacuo. The resulting solid was kept under high vacuum for 4 h and then dissolved in dry dichloromethane. The resulting fluffy white crystals were collected and chromatographed (florisil eluted with ethyl acetate) to give 1.81 g (65%) of **4c**: mp 166–167 °C; IR 3323, 2922, 1682, 1541, 1534, 1456, 1450, 1253, 1076, 935, 760 cm^{-1}; NMR δ 1.16–1.22 (m, 12 H), 3.53 (s, 3 H), 3.60–4.03 (m, 2 H), 4.20–4.67 (br s, 2 H), 4.80 (s, 2 H), 5.11 (s, 2 H), 7.38 (m, 10 H). Anal. $C_{27}H_{33}N_3O_4$) C, H, N.

1-Methyl-3,4-diphenyl-2,5-bis(hydroxymethyl)pyrrole Bis[*N*-(2-propyl)carbamate] (4d). A solution of diol **3d** (2.93 g, 0.01 mol) in dry dichloromethane (50 mL) was treated with freshly distilled 2-propyl isocyanate (3.71 g, 0.06 mol) followed by 3–4 drops of dibutyltin diacetate. The mixture was slowly heated to reflux for 1 h, and the volatiles were then removed. The solid residue was dried under high vacuum for 1 h and dissolved in dry dichloromethane, and the solution was diluted with petroleum ether. The resulting fluffy white crystals were collected and dried in vacuo to give 3.67 g (79%) of **4d**: mp 192–193 °C; IR 3295, 2929, 1682, 1541, 1464, 1245, 1076, 949, 703 cm^{-1}; NMR δ 1.21 (d, J = 5 Hz, 12 H), 3.67 (s, 3 H), 3.65–4.18 (m, 2 H), 4.45–4.68 (br m, 2 H), 5.07 (s, 4 H), 7.07 (s, 10 H). Anal. (C_{27}-$H_{33}N_3O_4$) C, H, N.

4-(*p*-Nitrobenzyl)pyridine (NBP) Assay.[10,11] The reaction of NBP with the alkylating agent has been shown to obey second-order kinetics, and the integrated rate equation is as follows:

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

where a and b are the initial concentrations of the alkylating agent and NBP, respectively, and x is the amount reacted in time t. This simplifies to

$$x \approx abkt$$

provided that $b \gg a$, $x \ll a$, and $bkt \ll 1$. The latter two conditions occur during the initial phase of the reaction, and the concentrations of a and b may be set experimentally. The amount of alkylating agent reacted with NBP (x') is equal to the amount of the alkylation product (P) that is formed, and this is proportional to the absorbance of 570 nm:

$$x' = [P] = \alpha E^{570} = abkt$$

therefore

$$k = (\alpha/ab)(E^{570}/t)$$

In comparing a series of compounds for alkylating ability, it is assumed that the proportionality factor α will show little variation since the chromophore system P is similar in each case. Any small differences will probably have little influence on the absorbance at 570 nm. By using the same initial concentration of the reactants (a = 0.2 μmol, b = 240 μmol), the comparative alkylating ability may be defined as

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

Thus, k' may be determined by plotting the absorbance readings vs. time and calculating the slopes of the plots. There is also a "competing" hydrolysis reaction for the alkylating agent, but this is assumed to be minor and similar for all the compounds in this series and may be neglected during the initial phase of the reaction whose duration is determined by k, the second-order rate constant, as well as k, the rate constant for the hydrolysis reaction. Thus, $x = x'$. For a more detailed discussion see ref 11. The compound to be tested was dissolved in absolute ethanol or 1,2-dimethoxyethane (2.0 μmol/10 mL), and 1.0-mL aliquots were placed in test tubes that already contained, 1.0 mL of NBP solution (10% w/v in dimethoxyethane) and 1.0 mL of water solution (1:1 v/v in water/dimethoxyethane). The tubes were stoppered tightly, mixed thoroughly, and inserted in a water bath maintained at 40 °C. A tube was removed, at different time intervals, and cooled in an ice-water bath, and 1.0 mL of base (1:1 triethylamine/acetone) was added. The contents were mixed for 3 s using a vortex-type mixer and chilled for another 30 s to allow for maximum color development. The mixture was diluted with acetone, mixed for 3 s, and transferred to a cuvette, and the absorbance of the reaction was read immediately at 570 nm using a Bausch and Lomb (Spectronic 20) spectrophotometer. The instrument had been previously adjusted to 0% absorbance against a solution containing NBP solution (1.0 mL), water solution (1.0 mL), absolute ethanol (1.0 mL), base solution (1.0 mL), and acetone (7.0 mL). The color of the reaction fades, and thus the readings must be taken quickly.

The rate constant k' was calculated from the slope of the line obtained from a plot of the absorbance readings vs. time. The slope was obtained by linear regression analysis, and the "r" values were >0.90.

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Registry No. **1d**, 103776-11-0; **2c**, 103776-12-1; **3a**, 72572-71-5; **3b**, 72572-67-9; **3c**, 103776-13-2; **3d**, 103776-14-3; **4a**, 95038-25-8; **4b**, 103776-15-4; **4c**, 95038-24-7; **4d**, 95038-26-9; 3,4-diphenylpyrrole-2,5-dicarboxylic acid, 1632-49-1; diethyl 3,5-diphenylpyrrole-2,4-dicarboxylate, 3651-14-7.

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