applied in doses of 500, 250, 100, 50, 25, and 10 mg/kg until the blood glucose level was significantly higher than that caused by 25 mg/kg tolbutamide (more than 20% decrease in blood glucose level). After 1 h blood samples were taken from the carotid. The blood glucose content was determined enzymatically by the glucose–oxidase–peroxidase method.[17] The statistical evaluation of the results utilized the Student's t test ($p < 0.05$).

Registry No. 1, 2901-76-0; 2, 37002-52-1; 4, 103733-65-9; 5, 74163-81-8; 6, 115732-14-4; 7, 115732-15-5; 8, 495-69-2; 9, 17606-70-1; 10, 15732-43-1; 11, 26348-47-0; 12, 57427-85-7; 13, 85114-36-9; 14, 85856-40-2; 15, 105746-35-8; 16, 105746-32-5; 17, 75691-91-7; 18, 115732-16-6; 19, 74204-45-8; 20, 115732-17-7; 21, 115732-18-8; 22, 115732-19-9; 23, 115794-99-5; 24, 115732-20-2; 25, 115795-00-1; 26, 115795-01-2; 27, 105746-33-6; 28, 105746-25-6; 29, 115732-21-3; 30, 115732-22-4; 31, 86808-12-0; 32, 105746-34-7; 33, 115732-23-5; 34, 105746-24-5; 35, 115732-24-6; 36, 105746-38-1; 37, 105746-43-8; 38, 115732-25-7; 39, 105746-42-7; 40, 115732-26-8; 41, 105746-31-4; 42, 115732-27-9; 43, 115732-28-0; H-D-Phe-OH, 673-06-3; H-Phe-OH, 63-91-2; PhCHO, 100-52-7; PhCOCl, 98-88-4; 4-MeC_6H_4COCl, 874-60-2; 3-MeC_6H_4COCl, 1711-06-4; 2-MeC_6H_4COCl, 933-88-0; 4-EtC_6H_4COCl, 16331-45-6; 4-(*i*-Pr)C_6H_4COCl, 21900-62-9; 4-PrC_6H_4COCl, 52710-27-7; 4-(*t*-Bu)C_6H_4COCl, 1710-98-1; 4-BuC_6H_4COCl, 28788-62-7; 4-$MeOC_6H_4COOH$, 100-09-4; 4-$EtOC_6H_4COOH$, 619-86-3; H-D-Phe-OMe, 21685-51-8; cyclohexanoyl chloride, 2719-27-9; cyclohex-3-enoyl chloride, 932-67-2; cyclopentanoyl chloride, 4524-93-0; cycloheptanoyl chloride, 6557-86-4; nicotinic acid, 59-67-6; pyridine-4-carboxylic acid, 55-22-1; quinoline-6-carboxylic acid, 10349-57-2; quinoline-2-carboxylic acid, 93-10-7; quinoline-3-carboxylic acid, 6480-68-8; (*S*)-*N*-acetyl-2-pyrrolidinecarboxylic acid, 68-95-1; (*S*)-*N*-benzoyl-2-pyrrolidinecarboxylic acid, 5874-58-8; (*R*)-*N*-benzoyl-2-pyrrolidinecarboxylic acid, 115795-02-3; benzofuran-2-carbonyl chloride, 41717-28-6; 2-naphthoyl chloride, 2243-83-6; 2,3-dihydroindene-5-carbonyl chloride, 15497-40-2; 1-naphthoyl chloride, 879-18-5; benzodioxole-5-carboxylic acid, 94-53-1.

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Synthesis and Antileukemic Activity of Bis[[(carbamoyl)oxy]methyl]-Substituted Pyrrolo[2,1-*a*]isoquinolines, Pyrrolo[1,2-*a*]quinolines, Pyrrolo[2,1-*a*]isobenzazepines, and Pyrrolo[1,2-*a*]benzazepines[1]

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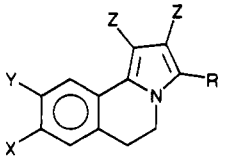
A series of bis[[(carbamoyl)oxy]methyl]-substituted pyrrole-fused tricyclic heterocycles were synthesized by using 1,3-dipolar cycloaddition reactions with a trifluoromethanesulfonate salt of an appropriate Resissert compound or with a mesoionic oxazolone intermediate. All of the bis(carbamates) were active in vivo against P388 lymphocytic leukemia with 5,6-dihydro-8-methoxy-1,2-bis(hydroxymethyl)pyrrolo[2,1-*a*]isoquinoline bis[*N*-(2-propyl)carbamate] (**3c**) showing the highest level of activity.

The design of antineoplastic agents in the "acylated vinylogous carbinolamine" class is based on the concept that these agents can act as bifunctional electrophiles in which [(carbamoyl)oxy]methyl groups serve as reactive electrophilic centers. These agents are not carbamoylating agents; instead the carbamate moieties are leaving groups in an alkyl–oxygen cleavage mechanism.[2] The reactions take place on methylenic carbons bonded directly to a heteroaromatic nucleus. The role of the heteroaromatic system is to stabilize reaction transition states, and this provides a means to control the reactivity of the two electrophilic centers. Control may be achieved through alteration of the heteroaromatic system.[3] Furthermore, if the heterocycle is not symmetrically substituted, it is possible to have different reactivities for each of the two putative electrophilic centers. The ability to control the reactivities of these bifunctional electrophiles along with the ability to exercise independent control at each center has led to the development of a number of very active compounds in this class.[3]

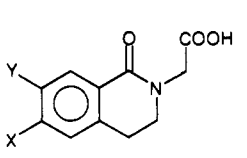
The antineoplastic activities of some pyrrolo[2,1-*a*]isoquinoline derivatives were reported in an earlier publication.[4] This paper compares a number of different tricyclic bis[[(carbamoyl)oxy]methyl] derivatives.

Chemistry

The bis(carbamates) were all prepared from the corresponding diol by treatment with 2-propyl isocyanate. The diols were synthesized from the appropriate dicarboxylic acid dister by hydride reduction. The synthesis of the diol **2b** and the bis(carbamate) **3e** have been reported.[4] The diesters **1a**, **1c**, and **1d** were prepared from the appropriately substituted 2-(1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)acetic acid **4**. The isoquinolone precursor



1: Z = CO_2CH_3
2: Z = CH_2OH
3: Z = $CH_2OCONHCH(CH_3)_2$
a: R = X = Y = H
b: R = CH_3; X = Y = H
c: R = Y = H; X = OCH_3
d: R = H; X = Y = Cl
e: R = CH_3; X = OCH_3; Y = H



4a: X = Y = H
b: X = OCH_3; Y = H
c: X = Y = Cl

to **4a** was synthesized in a polyphosphoric acid induced

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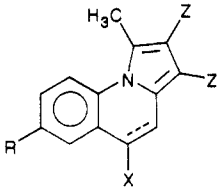
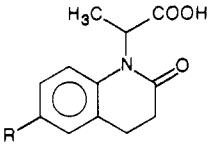
cyclization of *N*-(ethoxycarbonyl)phenethylamine.[5,6] The isoquinolone precursors to **4b** and **4c** were prepared by acid-catalyzed cyclizations of the appropriate phenethyl isocyanate (prepared by a thermal Curtius rearrangement of the corresponding acyl azide). The cyclization of 2-(3-methoxyphenyl)ethyl isocyanate gave a mixture of regioisomers with the para-cyclized product predominating (ca. 3:1 for a stannic chloride catalyzed reaction and ca. 6:1 for a phosphoric acid catalyzed reaction).[7] Cyclization of 2-(3,4-dichlorophenyl)ethyl isocyanate with aluminum chloride gave a single regioisomer in 35–45% yield. Alkylation of the isoquinolone with ethyl bromoacetate and hydrolysis of the ethyl ester gave an α-amido acid **4**. The α-amido acid **4** was converted (acetic anhydride) to the mesoionic oxazolone which underwent 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) to give pyrrolo[2,1-*a*]isoquinolines **1**.

The pyrrolo[1,2-*a*]quinolines **5** and **8** were prepared from trifluoromethanesulfonate salts of 1,2-dihydro- and 1,2,3,4-tetrahydroquinoline Reissert compounds in 1,3-dipolar cycloaddition reactions with DMAD.[8] The overall





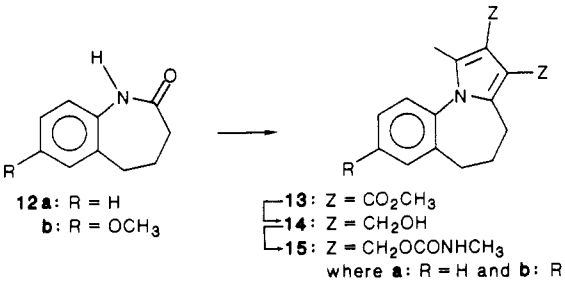
11a: R = H
b: R = OCH_3

5: Z = CO_2CH_3; X = CH_3
6: Z = CH_2OH; X = CH_3
7: Z = $CH_2OCONHCH(CH_3)_2$; X = CH_3
8: Z = CO_2CH_3 (4,5-dihydro); X = H
9: Z = CH_2OH (4,5-dihydro); X = H
10: Z = $CH_2OCONHCH(CH_3)_2$ (4,5-dihydro)
X = H where **a**: R = H and **b**: R = OCH_3

yields of **8a** and **8b** from quinoline and 6-methoxyquinoline were ca. 40% (three steps). An alternate route to **8** was also examined. This involved the synthesis of the carbostyryl precursors to **11a** and **11b**. 1,2,3,4-Tetrahydro-2-oxoquinoline was prepared from 3-chloropropionanilide in an aluminum chloride catalyzed Friedel–Craft reaction.[9] Cyclization of the 4-hydroxy analogue gave a mixture of two major products. The NMR spectrum of the crude mixture provided evidence that the major byproduct was a quinone imine.[10] Treatment of the crude mixture with HBr in acetic acid[11] gave a single major product that was selectively methylated (potassium carbonate and iodomethane) to give 6-methoxy-1,2,3,4-tetrahydro-2-oxoquinoline in ca. 35% yield. N-Alkylation of the carbostyryls with ethyl 2-bromopropionate, hydrolysis of the ethyl esters, and treatment of the resulting diacids **11** with DMAD and acetic anhydride gave **8a** and **8b** in yields of 62 and 36%, respectively.

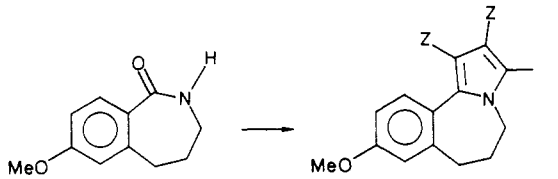
The diesters **5a** and **5b** were most conveniently prepared by the carbostyril (1,2-dihydro-2-oxoquinolines) route developed by Potts.[12] The carbostyrils are easily accessible from acetoacetanilides by a Knorr type cyclization or from quinoline *N*-oxides.[13,14] Subsequent alkylation of the carbostyril with ethyl 2-bromopropionate, hydrolysis of the ethyl ester, and treatment of the α-amido carboxylic acid with DMAD and acetic anhydride gave **5**. The initial alkylation of the carbostyril can occur on either nitrogen or oxygen. The solvent DMF and higher reaction temperatures gave the greatest amount of O-alkylation while anhydrous toluene as a solvent gave only N-alkylation.

The fused benzazepines **13a**, **13b**, and **17** were prepared from the corresponding lactams **12a**, **12b**, and **16**, respectively. The lactam **12a** was prepared via Beckmann rearrangement of 1-tetralone oxime using polyphosphoric acid.[15,16] The lactams **12b** and **16** were separated from the reaction of 6-methoxy-1-tetralone oxime with polyphosphoric acid.[17] The lactams **12a**, **12b**, and **16** were N-alkylated with ethyl 2-bromopropionate, the ethyl esters were hydrolyzed, and the resulting α-amido acids were treated with DMAD and acetic anhydride to give **13a**, **13b**, and **17**, respectively.



12a: R = H
b: R = OCH_3

13: Z = CO_2CH_3
14: Z = CH_2OH
15: Z = $CH_2OCONHCH_3$
where **a**: R = H and **b**: R = OCH_3



16

17: Z = CO_2CH_3
18: Z = CH_2OH
19: Z = $CH_2OCONHCH_3$

Biological Discussion

The bis(carbamates) were tested in vivo against P388 lymphocytic leukemia. The results are summarized in Table I. The pyrrolo[2,1-*a*]isoquinoline bis(carbamate) **3c** showed the best activity of the compounds tested. In the pyrrolo[2,1-*a*]isoquinoline series, the C-3 methyl group had a more pronounced effect on activity and toxicity than the C-7 methoxy group. There was a significant difference between the activities of **3c** and **3e**; addition of the C-3 methyl (**3c** → **3e**) caused a marked decrease in activity and a small decrease in potency. Addition of the C-3 methyl to **3a** yields **3b**; **3a** and **3b** are equiactive, but **3a** is more potent and, at equiactive doses, causes less animal weight loss.

In the pyrrolo[1,2-*a*]quinoline series, the 4,5-dihydro compounds **10a** and **10b** are more potent than the fully unsaturated analogues **7a** and **7b** and also appear to be slightly more active. However, the differences in activity

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Table I. Activity of Tricyclic Bis(carbamates) against P388 Lymphocytic Leukemia[a]

compd	dose,[b] mg/kg	TDS[c]	wt change (T − C, g)[d]	% T/C[e]	KE[f]	compd	dose,[b] mg/kg	TDS[c]	wt change (T − C, g)[d]	% T/C[e]	KE[f]
3a	100	0/6				**7b**	240	6/6	−3.5	154	1.19
	50	3/6	−3.5				120	6/6	−0.6	131	−0.12
	25	4/6	−4.2				60	6/6	0.1	128	−0.3
	12.5	6/6	−3.1	188	3.84		30	6/6	0	112	−0.42
	6.25	6/6	−0.8	157	1.60		15	6/6	−0.1	109	−1.47
	3.12	6/6	−0.5	136	0.00	**10a**	15	0/6			
	1.56	6/6	−0.3	130	−0.38		7.5	6/6	−2.8	94	−1.64
3b	100	2/6	−3.8				3.75	6/6	−3.6	155	1.47
	50	6/6	−4.0	174	2.82		1.87	6/6	−1.5	134	−0.14
	25	6/6	−4.2	166	2.24	**10b**	60	0/6			
	12.5	6/6	−2.6	157	1.60		30	6/6	−4.2	160	1.51
	6.25	6/6	−0.9	153	1.28		15	4/4	−6.5	150	1.43
3c	60	4/6	−4.6				7.5	4/4	−2.9	116	−1.31
	30	4/6	−3.1				3.75	5/5	−0.8	105	−1.45
	15	5/5	−3.0	125	−1.07		1.87	5/5	−0.6	97	−1.56
	7.5	6/6	−4.8	232	5.83	**15a**	40	0/6			
	3.75	6/6	−3.4	194	3.46		20	6/6	−2.6		
	1.88	6/6	−1.8	174	2.18		10	6/6	−2.2	152	1.00
3d	480	6/6	−3.6	185	5.05		5	6/6	−0.9	147	0.55
	240	6/6	−2.3	137	0.10		2.5	6/6	−1.7	154	1.19
	120	6/6	−2.2	130	−0.68	**15b**	60	4/6	−2.8		
	60	6/6	−0.4	86	−1.54		30	4/6			
3e	100	3/6	−5.3				15	6/6	−1.2	144	0.27
	50	6/6	−6.6				7.5	6/6	−1.3	147	0.55
	25	6/6	−5.6	153	−1.29		3.75	6/6	−1.6	135	−0.06
	12.5	6/6	−3.0	153	−1.29		1.87	6/6	−1.0	125	−0.74
	6.25	6/6	−2.1	136	−1.51	**19**	60	5/6	−2.6		
	3.16	6/6	−1.1	142	−1.43		30	6/6	−2.2	133	−0.15
7a	240	6/6	−3.5	129	−0.5		15	6/6	−1.8	124	−0.88
	120	6/6	−1.8	106	−1.5						
	60	6/6	−1.1	139	0.47						
	30	6/6	−0.5	135	−0.53						

[a] Ascitic fluid containing ca. 10^6 cells was implanted intraperitoneally in CD_2F_1 mice. Antileukemic testing was conducted under the auspices of the National Cancer Institute. The protocol for the testing is described in NIH publication No. 84-2635, February 1984. [b] Suspensions of the drug were prepared fresh daily in saline with Tween 80. The suspensions were injected intraperitoneally beginning 24 h after tumor inoculation and at 24-h intervals thereafter for a total of five doses. [c] Toxicity day survivors expressed as number of animals that survived to day five/number of test animals. [d] Body weight change of test animals compared to control animals. [e] Percent test vs control of test animals compared to untreated tumor-bearing control animals (average life span 10–12 days). A % T/C ≥ 127 is considered statistically significant, and a reproducible T/C ≥ 175% is considered significant activity. [f] KE = net log cell kill.

are small, and neither series has activity comparable to that of **3c**. A comparison of comparably substituted pyrrolo[1,2-*a*]quinolines and pyrrolo[2,1-*a*]isoquinolines **10a** vs **3b** and **10b** vs **3e** does not show one series to be better than the other.

The pyrrolo[1,2-*a*]benzazepine bis(carbamates) **15a** and **15b** showed approximately equivalent activity to the comparable pyrrolo[1,2-*a*]quinolines **10a** and **10b**. The fused benzazepine **19** was less active and more toxic than the corresponding pyrrolo[2,1-*a*]isoquinoline **3e**.

In summary, ring fusion and ring substitution do alter the potency, activity, and toxicity of the bis(carbamates) tested. However, the present results do not offer any clear indications for the selection of an optimum ring system or substitution pattern. It appears likely that compounds with the phenyl ring attached directly to the pyrrole nitrogen will have different structure–activity requirements from the compounds in which the phenyl ring is attached to the pyrrole α-carbon. The present study did identify one compound, **3c**, with good in vivo activity against P388 leukemia.

Experimental Section

Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover Unimelt apparatus. IR spectra were determined as Nujol mulls (unless specified otherwise) with either a Perkin-Elmer 727B spectrophotometer or a Nicolet FT-IR interferometer. NMR spectra were determined as deuteriochloroform solutions containing 1% tetramethylsilane as an internal standard (unless otherwise specified) with either a Varian T-60A or a FT-80 spectrometer. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

Dimethyl 5,6-Dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (1a). Dimethyl acetylenedicarboxylate (7.5 mL, 0.061 mol) was added to a mixture of 2-(1,2,3,4-tetrahydro-1-oxoisoquinolin-2-yl)acetic acid (**4a**, 12.11 g, 0.059 mol) in acetic anhydride (80 mL), and the reaction mixture was heated at 90–110 °C (oil bath), for 3.5 h. The reaction mixture was then cooled and concentrated to dryness in vacuo. The residue was crystallyzed from methanol to give **1a** (9.22 g, 55%): mp 116–117 °C; IR 2929, 1710, 1527, 1463, 1449, 1379, 1301, 1217, 1175, 1069, 843, 780 cm^{-1}; ^1H NMR δ 3.00 (t, J = 5 Hz, 2 H), 3.80 (s, 3 H), 3.93 (s, 3 H) overlapping 4.06 (t, J = 5 Hz, 2 H), 7.22 (m, 4 H), 7.67 (m, 1 H). Anal. ($C_{16}H_{15}NO_4$) C, H, N.

Dimethyl 5,6-Dihydro-8-methoxypyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (1c). The diester **1c** (49% yield) was prepared as described for **1a** except the reaction mixture was heated at 80–90 °C for 6 h. The product had the following: mp 151–153 °C (dichloromethane–methanol); IR (KBr) 2992, 2964, 1709, 1618, 1575, 1519, 1484, 1442, 1392, 1301, 1287, 1202, 1061, 1026, 920, 836, 765 cm^{-1}; ^1H NMR δ 7.6 (d, J = 6 Hz, 1 H), 6.73 (dd, merging with the singlet at 7.03, J = 1 Hz, J = 6 Hz, 1 H), 7.03 (br s, 1 H), 3.95 (t, J = 6 Hz, 2 H), 3.86 (s, 3 H), 3.76 (s, 6 H), 2.93 (t, J = 6 Hz, 2 H). Anal. ($C_{17}H_{17}NO_5$) C, H, N.

Dimethyl 5,6-Dihydro-8,9-dichloropyrrolo[2,1-*b*]isoquinoline-1,2-dicarboxylate (1d). The diester **1d** was prepared as described for **1a** except the reaction was run at 100 °C for 6 h. The product was crystallized from methanol (42% yield): mp 155–156 °C; IR (KBr) 3140, 3027, 2999, 2950, 1724, 1696, 1597, 1520, 1463, 1435, 1393, 1294, 1245, 1189, 1062, 977, 928, 766 cm^{-1}; ^1H NMR δ 7.8 (s, 1 H), 7.3 (d, 2 H), 4.1 (t, 2 H), 3.95 (s, 3 H), 3.80 (s, 3 H), 3.10 (t, 2 H). Anal. ($C_{16}H_{13}NO_4Cl_2$) C, H, N.

5,6-Dihydro-1,2-bis(hydroxymethyl)pyrrolo[2,1-*a*]isoquinoline (2a). A solution of the diester **1a** (5.00 g, 0.018 mol) in anhydrous dichloromethane (40 mL) was added dropwise to a stirred suspension of lithium aluminum hydride 1.66 g, 0.044

mol) in anhydrous diethyl ether (50 mL). The stirred suspension (protected from moisture) was heated under reflux for 2 h after the addition was completed. The mixture was cooled on an ice bath and excess hydride was destroyed by the sequential addition of water (1.5 mL), 15% aqueous NaOH (1.5 mL), and water (3 mL). The mixture was filtered, the solid residue was washed with hot THF (300 mL), and the combined filtrate was concentrated to dryness in vacuo. The residue was crystallized from dichloromethane–petroleum ether to give **2a** (3.52 g, 88%) as a white crystalline solid: mp 104–105 °C; IR 3366, 2914, 1604, 1596, 1527, 1463, 1379, 1315, 1189, 1146, 1013, 977, 766 cm^{-1}; ^1H NMR δ 3.00 (t, J = 5 Hz, 2 H) overlapping (br s, 2 OH), 4.02 (t, J = 5 Hz, 2 H), 4.60 (s, 2 H), 4.83 (s, 2 H), 6.63 (s, 1 H), 7.02–7.63 (m, 3 H); 7.66–7.90 (m, 1 H).

5,6-Dihydro-8-methoxy-1,2-bis(hydroxymethyl)pyrrolo[2,1-*a*]isoquinoline (2c). Lithium aluminum hydride (1.42 g, 40 mmol) was added in portions to a stirred solution of the diester **1c** (3.3 g, 10.47 mmol) in anhydrous THF (50 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 6 h (the disappearance of starting material was monitored by TLC). Excess hydride was destroyed by the dropwise addition of water and the 20% NaOH solution (30 mL) was added. The mixture was stirred for a few minutes and extracted with dichloromethane. The organic solution was dried ($MgSO_4$) and concentrated to dryness in vacuo. The residue was crystallized from ethyl acetate–hexanes to give **2c** (2.0 g, 74%): mp 115–117 °C; IR (KBr) 3288, 2957, 2872, 1611, 1492, 1463, 1337, 1245, 970 cm^{-1}; ^1H NMR (CD_3CN–Me_4Si + D_2O) δ 7.7 (d, J = 10 Hz, 1 H), 6.9 (m, 2 H), 6.7 (s, 1 H), 4.6 (s, 2 H), 4.45 (s, 2 H), 4.0 (t, J = 6 Hz, 2 H), 3.8 (s, 3 H), 3.0 (t, J = 6 Hz, 2 H). Anal. ($C_{15}H_{17}NO_3$) C, H, N.

5,6-Dihydro-8,9-dichloro-1,2-bis(hydroxymethyl)pyrrolo[2,1-*a*]isoquinoline (2d). The reduction of **1d** was carried out as described for **2c** except the reaction mixture was extracted with ether after the excess hydride had been destroyed. The product **2d** (100% yield) was analytically pure but could be crystallized from benzene: mp 125–126 °C; IR (KBr) 3401, 3330, 2943, 2879, 1724, 1703, 1597, 1520, 1463, 1386, 1337, 1203, 1160, 1062, 1013, 998, 991, 886, 822, 787, 667 cm^{-1}; ^1H NMR (CD_3CN–Me_4Si + D_2O) δ 7.8 (s, 1 H), 7.35 (s, 1 H), 6.85 (s, 1 H), 4.60 (s, 2 H), 4.47 (s, 2 H). Anal. ($C_{14}H_{13}NO_2Cl_2$) C, H, N.

5,6-Dihydro-1,2-bis(hydroxymethyl)pyrrolo[2,1-*a*]isoquinoline Bis[*N*-(2-propyl)carbamate] (3a). The bis(carbamate) **3a** was prepared as described for **3c** except the reaction mixture was heated at reflux for 1.5 h and the product was crystallized from anhydrous ethyl acetate to give **3a** (97%): mp 152–153 °C; IR 3324, 2922, 1682, 1541, 1463, 1259, 1252, 1083, 935, 766 cm^{-1}; ^1H NMR δ 1.22 (d, J = 5 Hz, 12 H), 3.10 (m, 2 H), 3.73–4.33 (m, 4 H), 4.57 (br s, 2 H), 5.13 (s, 2 H), 5.33 (s, 2 H), 6.70 (s, 1 H), 7.03–7.83 (m, 3 H), 7.83–7.90 (m, 1 H). Anal. ($C_{22}H_{29}N_3O_4$) C, H, N.

5,6-Dihydro-8-methoxy-1,2-bis(hydroxymethyl)pyrrolo[2,1-*a*]isoquinoline Bis[*N*-(2-propyl)carbamate] (3c). A solution of diol **2c** (0.92 g, 3.5 mmol) in anhydrous dichloromethane (10 mL) was treated with 2-propyl isocyanate (0.85 g, 10 mmol) followed by one drop of di-*n*-butyltin diacetate. The mixture was stirred at ambient temperature for 3 h under a nitrogen atmosphere and then it was concentrated to dryness in vacuo. The residue was crystallized from isopropyl ether–ethyl acetate to give **3c** (1.277 g, 85%): mp 164–165 °C; IR nKBr) 3323, 2971, 1675, 1534, 1245, 1088 cm^{-1}; ^1H NMR δ 7.6 (dm, 1 H), 6.8 (m, 2 H), 5.25 (s, 2 H), 5.15 (s, 2 H), 4.6 (br m, 2 H), 4.0 (m, 4 H), 3.0 (t, 2 H), 3.8 (s, 3 H), 1.25 (dd, 12 H). Anal. ($C_{23}H_{31}N_3O_5$) C, H, N.

5,6-Dihydro-8,9-dichloro-1,2-bis(hydroxymethyl)pyrrolo[2,1-*a*]isoquinoline Bis[*N*-(2-propyl)carbamate] (3d). The carbamoylation was carried out as described for **3c** except the entire reaction was run at 0 °C for 4 h. The product was crystallized from ethyl acetate to give 2.95 g (81%) of **3d**: mp 199–200 °C; IR (KBr) 3337, 2971, 1675, 1597, 1569, 1527, 1463, 1386, 1372, 1322, 1245, 1139, 1069, 935, 851, 787, 780, 667 cm^{-1}; ^1H NMR δ 7.7 (s, 1 H), 7.3 (s, 1 H), 6.85 (s, 1 H), 5.25 (s, 2 H), 5.15 (s, 2 H), 4.5 (br m, 2 H), 4.0 (t, 2 H), 3.7 (m, 2 H), 3.0 (t, 2 H), 1.2 (d, 6 H), 1.1 (d, 6 H). Anal. ($C_{22}H_{27}N_3O_4Cl_2$) C, H, N.

2-(1,2,3,4-Tetrahydro-1-oxoisoquinolin-2-yl)acetic Acid (4a). A mechanically stirred solution of 1,2,3,4-tetrahydro-1-oxoisoquinole[6] (17.9 g, 0.12 mol) in anhydrous toluene (250 mL) carefully was treated with sodium hydride (60% oil dispersion, 5.00 g, 0.14 mol) at 0 °C. After the addition was completed, the stirred mixture was heated at reflux for 1 h and then cooled. Neat ethyl bromoacetate (15.5 mL, 0.14 mol) was added dropwise (caution), and the resulting mixture was heated at reflux for 5 h. The reaction mixture was cooled and filtered, the salts were washed with toluene, and the combined filtrate was concentrated to dryness in vacuo. The residue was dissolved in ethanol (200 mL) and treated with a solution of sodium hydroxide (12 g) in water (20 mL). The mixture was heated at reflux for 45 min and then concentrated to dryness in vacuo. The residue was dissolved in water (500 mL) and extracted with dichloromethane (3 × 200 mL). The aqueous layer was acidified (pH 2) with concentrated HCl and extracted with dichloromethane (3 × 300 mL). The combined extracts were washed with water (2 × 200 mL), dried (Na_2SO_4), and concentrated to dryness in vacuo to give an off-white solid (14.11 g, 57%): mp 180–182 °C; IR 2934 (br), 1776, 1755, 1621, 1600, 1571, 1458, 1409, 1331, 1303, 1205, 1190, 1007, 873, 724 cm^{-1}; NMR (Me_2SO-d_6–Me_4Si) δ 2.90 (t, J = 5 Hz, 2 H), 3.53 (t, J = 5 Hz, 2 H), 4.07 (s, 2 H), 6.96–7.99 (m, 4 H). Anal. ($C_{11}H_{11}NO_3$) C, H, N.

2-(1,2,3,4-Tetrahydro-1-oxo-6-methoxyisoquinolin-2-yl)acetic Acid (4b). A solution of 3-(3-methoxyphenyl)propionic acid (18.0 g, 100 mmol) in anhydrous toluene was treated with thionyl chloride (17.85 g, 150 mmol) and the mixture was stirred at 55–60 °C for 3 h. Volatiles were removed in vacuo to give a red liquid acid chloride (19.6 g, 100%). A solution of the acid chloride (19.6 g, 100 mmol) in anhydrous acetone (250 mL) was vigorously stirred at 0 °C and treated dropwise with a solution of sodium azide (13.0 g, 200 mmol) in water (20 mL). The mixture was stirred at 0 °C for 0.5 h after the addition was completed and then it was diluted with water and extracted with toluene. The organic solution was dried ($MgSO_4$) and filtered. The solution was then heated at 80 °C for 0.5 h. The reaction mixture was concentrated to dryness in vacuo and a red liquid isocyanate (16.0 g, 100%) was obtained. The isocyanate was dissolved in anhydrous acetone (50 mL), and the solution was added slowly to ice-cold polyphosphoric acid with vigorous mechanical stirring at 24 °C. The reaction mixture became a thick semisolid mass after ca. 0.5 h and could not be stirred so it was shaken manually every 15 min for 2 h. Ice-cold water was added to the reaction mixture, and the mixture was stirred for 0.5 h to give a homogeneous solution. The mixture was extracted with dichloromethane. The organic phase was washed sequentially with water, saturated sodium carbonate, water, and brine solution, and then it was dried ($MgSO_4$) and concentrated to dryness in vacuo. The pale yellow solid residue was crystallized twice from benzene–hexane to give 6-methoxy-2,3,4-tetrahydro-1-oxoisoquinoline (6.5 g, 37%) as a white solid: mp 133–135 °C.

The isoquinoline was alkylated with ethyl bromoacetate as described for **4a** to give **4b** (73%): mp 191–192 °C (ethyl acetate); IR (KBr) 3457, 3330, 2971, 2922, 2717, 2583, 2513, 1731, 1597, 1632, 1604, 1484, 1456, 1407, 1351, 1322, 1252, 1189, 1097, 1020, 935, 914, 865, 780 cm^{-1}; ^1H NMR (CD_3CN–Me_4Si–Me_2SO-d_6) δ 7.9 (d, J = 7 Hz, 1 H), 6.8 (d, J = 7 Hz, 1 H), 6.75 (s, 1 H), 4.2 (s, 2 H), 3.8 (s, 3 H), 3.6 (t, J = 6 Hz, 2 H), 3.0 (t, J = 6 Hz, 1 H). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

2-(6,7-Dichloro-1,2,3,4-tetrahydro-1-oxoisoquinolin-2-yl)acetic Acid (4c). A mixture of 3,4-dichloroaniline (162 g, 1.0 mol), acetone (2 L), and 48% HBr (320 mL) was stirred at −5 °C and was treated over 0.5 h with a solution of sodium nitrite (84 g, 1.22 mol) in water (200 mL). Methyl acrylate (860 g, 10 mol) and cuprous bromide (0.15 g, 0.5 mmol) were added. The internal temperature was allowed to rise in a carefully controlled manner; at 7 °C the nitrogen evolution was vigorous. When the rate of nitrogen evolution decreased, the mixture was stirred at 25 °C for 0.5 h to complete the reaction. The mixture was evaporated and the residue was partitioned between water and toluene; the organic phase was dried and concentrated in vacuo to give methyl 2-bromo-3-(3,4-dichlorophenyl)propionate (312 g, 99%).

A solution of methyl 2-bromo-3-(3,4-dichlorophenyl)propionate (312 g, 1 mol) in acetic acid (1325 mL) was stirred and treated with zinc dust (135 g, 2 mol) in portions over 30 min. The mixture was stirred for an additional 30 min and filtered, and the filter cake was washed with acetic acid. The filtrate was evaporated,

the residue was partitioned between chloroform and water, and the organic phase was dried and concentrated in vacuo to give crude methyl 3-(3,4-dichlorophenyl)propionate (233 g, 99%). The ester was heated at reflux with 10% aqueous sodium hydroxide (1.6 L) for 2 h, cooled, treated with decolorizing carbon, and filtered. The filtrate was acidified with 3 N HCl and filtered. The dry filter cake was crystallized from toluene to give 93.3 g (43%) of 3-(3,4-dichlorophenyl)propionic acid (mp 92–94 °C) and 54.6 g (25%) of a second crop (mp 86–90 °C).

In an alternate synthesis of 3-(3,4-dichlorophenyl)propionic acid, a solution of 3,4-dichlorobenzaldehyde (16.75 g, 96 mmol) and malonic acid (10 g, 100 mmol) in pyridine (25 mL) was treated with piperidine (0.5 mL). The stirred reaction mixture was heated for 1 h at 80 °C, for 1 h at 100 °C, and then at reflux for 0.5 h. The mixture was poured into ice–water and acidified with 6 N HCl. The precipitate was collected, washed with water, and crystallized from aqueous ethanol to give 3,4-dichlorocinnamic acid (18.5 g, 89%): mp 215–216 °C.

The cinnamic acid was reduced at 50 psi of hydrogen pressure (Adam's catalyst, 0.15 g) to give 3-(3,4-dichlorophenyl)propionic acid (100%): mp 92–94 °C (toluene–petroleum ether); ^{1}H NMR δ 2.8 (m, 4 H), 7.2 (m, 3 H), 8.7 (br s, 1 H).

3-(3,4-Dichlorophenyl)propionic acid was converted to the acid chloride and then to the isocyanate by the procedure described for **4b**. The crude isocyanate (ca. 28 g) was dissolved in tetrachloroethylene (200 mL), aluminum chloride (21.2 g, 224 mmol) was added, and the mechanically stirred mixture was heated at 60–65 °C for 0.5 h. The mixture was cooled, quenched with 6 N HCl, and extracted with dichloromethane. The organic solution was washed sequentially with 6 N HCl, water, and aqueous sodium carbonate; the solution was dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed (silica gel–ethyl acetate) to give 6,7-dichloro-1,2,3,4-tetrahydro-1-oxoisoquinoline (7.65 g, 28%): mp 183–184 °C (ethyl acetate); IR (KBr) 3555, 3485, 3408, 3316, 2985, 2879, 1675, 1590, 1477, 1456, 1407, 1337, 1294, 1210, 900 cm^{-1}; ^{1}H NMR δ 8.18 (s, 1 H), 7.30 (d, 2 H), 7.15 (br m, 1 H), 3.60 (m, 2 H), 3.0 (t, 2 H). Anal. ($C_9H_7NOCl_2$) C, H, N.

6,7-Dichloro-1,2,3,4-tetrahydro-1-oxoisoquinoline was alkylated with ethyl bromoacetate as described for **4a** to give **4c** (71%): mp 214–216 °C (ethanol); IR (KBr) 3443, 3098, 2985, 2576, 1738, 1625, 1583, 1548, 1477, 1449, 1344, 1280, 1210, 1175, 1020 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 7.9 (s, 1 H), 7.5 (s, 1 H), 4.25 (s, 2 H), 3.7 (t, 2 H), 3.1 (t, 2 H). Anal. ($C_{11}H_9NO_3Cl_2$) C, H, N.

Dimethyl 1,5-Dimethylpyrrolo[1,2-*a*]quinoline-2,3-dicarboxylate (5a). 2-Oxo-1,2-dihydroquinoline[13b] was alkylated with ethyl 2-bromopropionate by using the method described for the preparation of **4a** to give 2-(4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)propionic acid (82%): mp 154–155 °C; IR (KBr) 3467, 2946, 1716, 1621, 1421, 1237, 1167, 1135, 1036, 828 cm^{-1}; ^{1}H NMR (Me_4SO-d_6–Me_4Si) δ 1.53 (d, J = 6 Hz, 3 H), 2.37 (s, 3 H), 5.02 (q, J = 6 Hz, 1 H), 6.62 (s, 1 H), 7.00–7.55 (m, 4 H). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

The diester **5a** was prepared from 2-(4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)propionic acid as described for **1a** except the reaction mixture was heated at 70–80 °C for 24 h. The diester was chromatographed (silica gel–ethyl acetate) and crystallized (methanol) to give **5a** as colorless needles (38%): mp 151–152 °C; IR 2960, 1717, 1689, 1379, 1224, 1069, 738, 808 cm^{-1}; ^{1}H NMR δ 2.37 (s 3 H), 2.77 (s, 3 H), 3.88 (s, 3 H), 3.95 (s, 3 H), 7.18–8.24 (m, 5 H). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

Dimethyl 7-Methoxy-1,5-dimethylpyrrolo[1,2-*a*]quinoline-2,3-dicarboxylate (5b). 2-(6-Methoxy-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)propionic acid was prepared from 6-methoxy-4-methyl-2-oxo-1*H*-quinoline[13a] with ethyl 2-bromopropionate and by using the method described for **4a**. The product (79%) had the following: mp 131–133 °C; IR (KBr) 3457, 2945, 1752, 1632, 1562, 1442, 1386, 1210, 1050, 850 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 1.45 (d, J = 6 Hz, 3 H), 2.42 (s, 3 H), 3.90 (s, 3 H), 5.17 (q, J = 6 Hz, 1 H), 6.54 (s, 1 H), 6.75–7.80 (m, 3 H). Anal. ($C_{14}H_{15}NO_4$) C, H, N.

The diester **5b** was prepared from 2-(6-methoxy-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)propionic acid by the method described from **5a**. The diester **5b** (39%) had the following: mp 171–172 °C; IR 2930, 1722, 1700, 1683, 1540, 1300, 1250, 1210, 1096, 880, 810 cm^{-1}; ^{1}H NMR δ 2.42 (s, 3 H), 2.82 (s, 3 H), 3.78 (s, 3 H), 3.95 (s, 6 H), 7.15 (s, 1 H), 7.95 (s, 1 H), 8.09 (s, 1 H), 8.17 (s, 1 H). Anal. ($C_{19}H_{19}NO_5$) C, H, N.

1,5-Dimethyl-2,3-bis(hydroxymethyl)pyrrolo[1,2-*a*]quinoline (6a). The diester **5a** was reduced by using the method described for **2a** except that the reaction mixture was not heated at reflux; instead it was stirred at 24 °C for 3 h. The diol **6a** had the following: mp 136–137 °C; IR 3341, 2922, 1457, 1450, 1379, 985 cm^{-1}; ^{1}H NMR (CD_3OD–$CDCl_3$–Me_4Si) δ 2.25 (s, 3 H), 2.70 (s, 3 H), 4.53 (s, 2 H), 4.62 (s, 2 H), 6.95–8.11 (m, 5 H).

7-Methoxy-1,5-dimethyl-2,3-bis(hydroxymethyl)pyrrolo[1,2-*a*]quinoline (6b). The diester **5b** was reduced as described for the preparation of **6a** to give **6b**. The unstable diol **6b** was dried in vacuo for 0.5 h and used immediately in the next step. The diol **60b** had the following: 154–155 °C; IR 3288, 2929, 1562, 1160, 1034, 984, 970 cm^{-1}; ^{1}H NMR (CD_3OD–Me_4Si) δ 2.40 (s, 3 H), 2.77 (s, 3 H), 3.85 (s, 3 H), 4.71 (s, 2 H), 4.75 (s, 2 H), 6.90 (s, 1 H), 7.10 (m, 2 H), 8.05 (1 H).

1,5-Dimethyl-2,3-bis(hydroxymethyl)pyrrolo[1,2-*a*]quinoline Bis[*N*-(2-propyl)carbamate] (7a). The diol **6a** was converted to **7a** (93%) by the method described for **3c** except the reaction mixture was heated at reflux for 0.5 h. Compound **7a** had the following: mp 167–168 °C (dichloromethane–petroleum ether); IR 3338, 2929, 1682, 1527, 1457, 1253, 1076, 1062, 942, 759 cm^{-1}; ^{1}H NMR δ 1.13 (d, J = 5 Hz, 12 H), 2.46 (s, 3 H), 2.90 (s, 3 H), 3.48–4.0 (m, 2 H), 4.25–4.77 (br s, 2 H), 7.24–8.26 (m, 4 H). Anal. ($C_{24}H_{31}N_3O_4$) C, H, N.

7-Methoxy-1,5-dimethyl-2,3-bis(hydroxymethyl)pyrrolo[1,2-*a*]quinoline Bis[*N*-(2-propyl)carbamate] (7b). The diol **6b** was converted to **7b** (95%) by the method described for **7a**. Compound **7b** had the following: mp 178–180 °C; IR 3323, 2922, 1682, 1534, 1456, 1253, 1083, 1041, 844 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 1.17 (d, J = 5 Hz, 12 H), 2.43 (s, 3 H), 2.87 (s, 3 H), 3.45–4.80 (m, 4 H), 3.91 (s, 3 H), 5.21 (s, 2 H), 5.28 (s, 2 H), 7.24–8.24 (m, 3 H). Anal. ($C_{25}H_{33}N_3O_5$) C, H, N.

Dimethyl 1-Methyl-4,5-dihydropyrrolo[1,2-*a*]quinoline-2,3-dicarboxylate (8a). 1,2,3,4-Tetrahydro-2-oxoquinoline was alkylated with ethyl 2-bromopropionate by using the procedure described for **4a** to give 2-(1,2,3,4-tetrahydro-2-oxoquinolin-1-yl)propionic acid (**11a**, 77%): mp 165–167 °C; IR 3436, 2929, 1738, 1626, 1590, 1414, 1231, 1210, 1196, 1119, 900, 766 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 1.48 (d, J = 6 Hz, 3 H), 2.35–3.00 (m, 4 H), 5.02 (q, J = 6 Hz, 1 H), 6.97–7.33 (m, 1 H). Anal. ($C_{12}H_{13}NO_3$) C, H, N.

The acid **11a** was converted to **8a** (80%) by the method described for **1a** (85 °C for 2 h). Compound **8a** had the following: mp 72–73 °C (methanol–water); IR 2922, 1724, 1696, 1534, 1499, 1372, 1203, 1153, 1090, 752 cm^{-1}; ^{1}H NMR δ 2.63 (s, 3 H), 2.73–3.22 (m, 4 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 7.17–7.50 (m, 4 H). Anal. ($C_{17}H_{17}NO_4$) C, H, N.

Dimethyl 7-Methoxy-1-methyl-4,5-dihydropyrrolo[1,2-*a*]quinoline-2,3-dicarboxylate (8b). 6-Hydroxy-1,2,3,4-tetrahydro-2-oxoquinoline[9] (5.0 g, 0.031 mol) was added to a mixture of anhydrous DMF (50 mL) and potassium carbonate (4.20 g, 0.032 mol). Iodomethane (2 mL, 0.032 mol) was then added, and the reaction mixture was stirred overnight at room temperature. The reaction was found (by TLC) to be incomplete so the mixture was treated with an additional 0.5 equiv of both potassium carbonate and methyl iodide. The mixture was allowed to stand for an additional 24 h and then poured into water, and the black gum was filtered. Large, colorless needlelike crystals formed when the mixture stood overnight; they were collected and dried to give 6-methoxy-1,2,3,4-tetrahydro-2-oxoquinoline (3.40 g, 62%): mp 135–136 °C; IR 3197, 2936, 1661, 1506, 1499, 1463, 1386, 1238, 1182, 1041, 802 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 2.10–3.14 (m, 4 H), 3.60 (s, 3 H), 6.65–7.38 (m, 3 H), 10.73 (br s, 1 H). Anal. ($C_{10}H_{11}NO_2$) C, H, N.

6-Methoxy-1,2,3,4-tetrahydro-2-oxoquinoline was alkylated with ethyl 2-bromopropionate by using the procedure described for the synthesis of **4a** to give 2-(1,2,3,4-tetrahydro-2-oxo-6-methoxyquinolin-1-yl)propionic acid (**11b**; 53%): mp 123–125 °C; IR 3476, 2929, 1738, 1619, 1456, 1238, 1048, 851 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 1.65 (d, J = 5 Hz, 3 H), 2.45–3.29 (m, 4 H), 3.93 (s, 3 H), 5.20 (q, J = 5 Hz, 1 H), 6.87–7.33 (m, 3 H).

The acid **11b** was converted to **8b** (68%) by the method described for **1a** (80–85 °C for 4 h). Compound **8b** had the following: mp 145–147 °C (ethyl acetate); IR 2922, 1717, 1696, 1506, 1443,

1196, 1175, 1083, 1034, 872 cm^{-1}; ^{1}H NMR δ 2.67 (s, 3 H), 2.67–3.30 (m, 4 H), 3.85 (s, 9 H), 6.70–7.00 (m, 1 H), 7.20–7.65 (m, 2 H). Anal. ($C_{18}H_{19}NO_5$) C, H, N.

1-Methyl-2,3-bis(hydroxymethyl)-4,5-dihydropyrrolo[1,2-*a*]quinoline (9a). The diester **8a** was reduced by the procedure described for **2a** (24 °C for 3 h). The crude product, a light yellow glass that could not be induced to crystallize, was used directly in the next step.

7-Methoxy-1-methyl-2,3-bis(hydroxymethyl)-4,5-dihydropyrrolo[1,2-*a*]quinoline (9b). The diester **8b** was reduced as described for **2a** (4.5 h at 24 °C) to give **9b** (94%): mp (dichloromethane–petroleum ether) 136–137 °C; IR 3190, 2922, 1506, 1456, 1436, 1245, 1005, 865 cm^{-1}; ^{1}H NMR δ 2.50 (s, 3 H), 2.81 (m, 4 H), 3.83 (s, 3 H), 4.67 (m, overlapping s, 4 H), 6.67–7.56 (m, 3 H). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

1-Methyl-2,3-bis(hydroxymethyl)-4,5-dihydropyrrolo[1,2-*a*]quinoline Bis[*N*-(2-propyl)carbamate] (10a). The diol **9a** was converted to **10a** (97%) by the procedure described for **3c** (reflux 30 min). Compound **10a** had the following: mp (dichloromethane–petroleum ether) 181–182 °C; IR 3330, 2922, 1675, 1534, 1463, 1253, 1083, 760 cm^{-1}; ^{1}H NMR δ 1.11 (d, 12 H), 2.50 (s, 3 H), 2.87 (m, 4 H), 3.46–4.17 (m, 2 H), 4.37–4.78 (br m, 2 H), 5.07 (s, 2 H), 5.10 (s, 2 H), 6.97–7.50 (m, 4 H). Anal. ($C_{23}H_{31}N_3O_4$) C, H, N.

7-Methoxy-1-methyl-2,3-bis(hydroxymethyl)-4,5-dihydropyrrolo[1,2-*a*]quinoline Bis[*N*-(2-propyl)carbamate] (10b). The diol **9b** was converted to **10b** (81%) by the procedure described for **3c** (reflux 2 h). Compound **10b** had the following: mp (anhydrous dichloromethane–petroleum ether) 165–167 °C; IR 3324, 2922, 1675, 1541, 1506, 1463, 1323, 1259, 1076, 935, 851 cm^{-1}; ^{1}H NMR δ 1.10 (d, J = 6 Hz, 12 H), 2.50 (s, 3 H), 2.79 (s, 4 H), 3.47–4.15 (m, 2 H), 3.80 (s, 3 H), 4.37–4.80 (br s, 2 H), 5.07 (s, 2 H), 5.10 (s, 2 H), 6.60–7.50 (m, 3 H). Anal. ($C_{24}H_{33}N_3O_5$) C, H, N.

Dimethyl 1-Methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]benzazepine-2,3-dicarboxylate (13a). The lactam **12a**[15,16] was converted to 2-(1,2,3,4-tetrahydro-2-oxo-5*H*-benzazepin-1-yl)-propionic acid by the procedure described for **4a**. The acid (63% yield) had the following: IR 2933, 2855, 1746, 1647, 1626 1598, 1493, 1458, 1324, 1212, 916, 762 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 1.40 (d, J = 6 Hz, 3 H), 2.02–2.98 (m, 6 H), 4.56 (q, J = 6 Hz, 1 H), 7.23 (s, 4 H).

The acid was treated with acetic anhydride and dimethyl acetylenedicarboxylate as described for **1a** to give **13a** (83%): mp 83–85 °C; IR 2957, 1710, 1569, 1379, 1210, 1019, 840, 769 cm^{-1}; ^{1}H NMR δ 1.98–2.79 (m, 6 H), 2.48 (s, 3 H), 3.83 (s, 3 H), 7.36 (m, 4 H). Anal. ($C_{18}H_{19}NO_4$) C, H, N.

Dimethyl 1-Methyl-8-methoxy-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]benzazepine-2,3-dicarboxylate (13b). The lactam **12b**[17] was converted to 2-(1,2,3,4-tetrahydro-2-oxo-7-methoxy-5*H*-benzazepin-1-yl)propionic acid (67% yield) by the procedure described for **4a**. The acid had the following: IR 1747, 1630, 1623, 1596, 1473, 1459, 1377, 1212, 1117, 1048, 987, 911, 767 cm^{-1}; ^{1}H NMR (Me_2SO-d_6–Me_4Si) δ 1.32 (d, J = 6 Hz, 3 H), 1.96–2.95 (m, 6 H), 3.85 (s, 3 H), 4.37 (q, J = 6 Hz, 1 H), 6.96–7.55 (m, 3 H).

The acid was treated with acetic anhydride and dimethyl acetylenedicarboxylate as described for **1a** to give **13b** (81%): mp 126–128 °C; IR 2956, 1718, 1569, 1380, 1218, 1020, 840, 780 cm^{-1}; ^{1}H NMR δ 1.99–2.82 (m, 6 H), 2.42 (s, 3 H), 3.85 (s, 9 H), 6.93–7.40 (m, 3 H). Anal. ($C_{19}H_{21}NO_5$) C, H, N.

1-Methyl-2,3-bis(hydroxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]benzazepine Bis[*N*-(2-propyl)carbamate] (15a). The diester **13a** was reduced as described for **2a** to give **14a** (87%): mp 109–111 °C (90% ethanol); IR 3267, 2930, 1597, 1463, 1010, 770 cm^{-1}; ^{1}H NMR δ 1.98–2.96 (m, 6 *H*), 2.25 (s, 3 H), 4.63 (m, 4 H), 7.27 (m, 4 H). Anal. ($C_{16}H_{19}NO_2$) C, H, N.

The diol **14a** was treated with methyl isocyanate under conditions described for **3c** except the reaction proceeded for 30 min at reflux to give **15a** (72% yield): mp 120–122 °C (acetone or chloroform–petroleum ether); IR (KBr) 3328, 2950, 1689, 1555, 1513, 1273, 1088, 991, 970, 865 cm^{-1}; ^{1}H NMR δ 1.98–2.65 (m, 6 H), 2.28 (s, 3 H), 2.78 (s, 3 H), 2.82 (s, 3 H), 4.62 (br s, 2 H), 5.16 (s, 2 H), 5.18 (s, 1 H), 7.30 (m, 4 H). Anal. ($C_{20}H_{25}N_3O_4$) C, H, N.

1-Methyl-8-methoxy-2,3-bis(hydroxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]benzazepine Bis[*N*-(2-propyl)carbamate] (15b). The diester **13b** was reduced by the procedure described for **2a** to give **14b** (67% yield): mp 162–164 °C; IR 3280, 2930, 1440, 1400, 1211, 990, 785 cm^{-1}; ^{1}H NMR δ 1.95–2.99 (m, 6 H), 2.18 (s, 3 H), 3.86 (s, 3 H), 4.67 (m, 4 H), 6.87–7.43 (m, 3 H). Anal. ($C_{17}H_{21}NO_3$·0.5H_2O) C, H, N.

The diol **14b** was treated with methyl isocyanate as described for **15a** to give **15b** (74% yield): mp 135.5–137.5 °C (acetone); IR (KBr) 3330, 2943, 1689, 1545, 1502, 1440, 1272, 1088, 990, 970, 868 cm^{-1}; ^{1}H NMR δ 1.98–2.60 (m, 6 H), 2.57 (s, 3 H), 2.60 (s, 3 H), 3.82 (s, 3 H), 4.48 (br s, 2 H), 5.00 (s, 4 H), 7.00 (m, 4 H). Anal. ($C_{21}H_{27}N_3O_5$) C, H, N.

Dimethyl 3-Methyl-8-methoxy-5,6-dihydro-4*H*-pyrrolo[2,1-*a*]isobenzazepine-1,2-dicarboxylate (17). The lactam **16**[17] was alkylated as described for **4a** to give 2-(1,2,3,4-tetrahydro-1-oxo-7-methoxy-5*H*-isobenzazepin-2-yl)propionic acid (64% yield): IR 2911, 1719, 1609, 1589, 1459, 1377, 1322, 1219, 1028, 890, 850 cm^{-1}; ^{1}H NMR (DMSO-d_6–Me_4Si) δ 1.48 (d, J = 5 Hz, 3 H), 1.75–3.60 (m, 6 H), 3.86 (s, 3 H), 4.76–5.21, 6.85–7.65 (m, 3 H).

The acid was treated with acetic anhydride and dimethyl acetylenedicarboxylate as described for **1a** to give **17** (70% yield): mp 136–138 °C; IR 2930, 1710, 1703, 1457, 1320, 1092, 960, 822 cm^{-1}; ^{1}H NMR δ 1.98–3.08 (m, 6 H), 2.28 (s, 3 H), 3.82 (s, 3 H), 3.88 (s, 6 H), 6.95–7.74 (m, 3 H). Anal. ($C_{19}H_{21}NO_5$) C, H, N.

3-Methyl-8-methoxy-1,2-bis(hydroxymethyl)-5,6-dihydro-4*H*-pyrrolo[2,1-*a*]isobenzazepine Bis[*N*-(2-propyl)carbamate] (19). The diester **17** was reduced by the procedure described for **2a** to give **18** (98% yield): mp 136–137.5 °C; IR 3253, 2925, 1565, 1466, 1377, 1294, 1164, 1062, 979, 836 cm^{-1}; ^{1}H NMR δ 1.99–2.99 (m, 6 H), 2.15 (s, 3 H), 3.33 (br s, 4 H), 4.58 (m, 4 H), 6.58–7.42 (m, 3 H). Anal. ($C_{17}H_{21}NO_3$) C, H, N.

The diol **18** was treated with methyl isocyanate as described for **15a** to give **19** (67% yield): mp 148–150 °C (chloroform–petroleum ether); IR (KBr) 3337, 2943, 1689, 1547, 1500, 1440, 1280, 870 cm^{-1}; ^{1}H NMR δ 1.83–2.80 (m, 4 H), 2.58 (s, 3 H), 2.67 (s, 3 H), 3.43–3.60 (m, 2 H), 3.67 (s, 3 H), 4.55–4.91 (br s, 2 H), 5.27 (s, 2 H), 5.33 (s, 2 H), 6.68–7.33 (m, 4 H). Anal. ($C_{21}H_{27}N_3O_5$) C, H, N.

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Registry No. **1a**, 115706-09-7; **1c**, 115706-10-0; **1d**, 115706-11-1; **2a**, 115706-12-2; **2c**, 115706-13-3; **2d**, 115706-14-4; **3a**, 115706-15-5; **3b**, 115706-44-0; **3c**, 104156-70-9; **3d**, 104156-71-0; **3e**, 91523-55-6; **4a**, 101301-18-2; **4b**, 115706-07-5; **4c**, 115706-08-6; **5a**, 115706-20-2; **5b**, 115706-21-3; **6a**, 115706-22-4; **6b**, 115706-23-5; **7a**, 115706-24-6; **7b**, 115706-25-7; **8a**, 94620-36-7; **8b**, 94620-37-8; **9a**, 115706-26-8; **9b**, 115706-27-9; **10a**, 115706-28-0; **10b**, 115706-29-1; **11a**, 115706-37-1; **11b**, 115706-38-2; **12a**, 4424-80-0; **12b**, 22245-89-2; **13a**, 115706-30-4; **13b**, 115706-31-5; **14a**, 115706-41-7; **14b**, 115706-42-8; **15a**, 115706-32-6; **15b**, 115706-33-7; **16**, 3648-86-0; **17**, 115706-34-8; **18**, 115731-81-2; **19**, 115706-35-9; 1,2,3,4-tetrahydro-1-oxoisoquinoline, 1196-38-9; 3-(3-methoxyphenyl)propionic acid, 10516-71-9; 3-(3-methoxyphenyl)propionic acid chloride, 40478-49-7; 1-isocyano-2-(3-methoxyphenyl)ethane, 62334-10-5; 6-methoxy-1,2,3,4-tetrahydro-1-oxoisoquinoline, 22246-12-4; 3,4-dichloroaniline, 95-76-1; methyl 2-bromo-3-(3,4-dichlorophenyl)propionate, 115706-16-6; methyl 3-(3,4-dichlorophenyl)-propionate, 115706-17-7; 3-(3,4-dichlorophenyl)propionic acid, 25173-68-6; 3,4-dichlorobenzaldehyde, 6287-38-3; 3,4-dichlorocinnamic acid, 1202-39-7; 3-(3,4-dichlorophenyl)propionic acid chloride, 90273-67-9; 1-isocyano-2-(3,4-dichlorophenyl)ethane, 115706-18-8; 6,7-dichloro-1,2,3,4-tetrahydro-1-oxoquinoline, 115706-19-9; 2-oxo-1,2-dihydroquinoline, 59-31-4; 2-(4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)propionic acid, 103368-26-9; 6-methoxy-4-methyl-2-oxo-1*H*-quinoline, 5342-23-4; 2-(6-methoxy-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)propionic acid, 115706-36-0; 1,2,3,4-tetrahydro-2-oxoquinoline, 553-03-7; 2-(1,2,3,4-tetrahydro-2-oxo-5*H*-benzazepin-1-yl)propionic acid, 115706-39-3; 6-hydroxy-1,2,3,4-tetrahydro-2-oxoquinoline, 54197-66-9; 6-methoxy-1,2,3,4-tetrahydro-2-oxoquinoline, 54197-64-7; 2-(1,2,3,4-tetrahydro-2-oxo-7-methoxy-5*H*-benzapin-1-yl)propionic acid, 115706-40-6; 2-(1,2,3,4-tetrahydro-1-oxo-7-methoxy-5*H*-isobenzpin-5-yl)propionic acid, 115706-43-9.