Synthesis of Novel 1,2,3,4-Tetrahydrobenzo[*c*]-1,5-naphthyridines from Pyrrolo[1,2-*b*]isoquinolines

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1,2,3,4-Tetrahydrobenzo[*c*]-1,5-naphthyridine (**5a**) was prepared by a novel synthetic route involving the rearrangement of (±)-(*Z*)-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione oxime to afford 1,4-dihydrobenzo[*c*]-1,5-naphthyridin-2(3*H*)-one, which was reduced to **5a**. The cholinomimetic activity observed with **5a** prompted the synthesis and biological evaluation of additional analogues.

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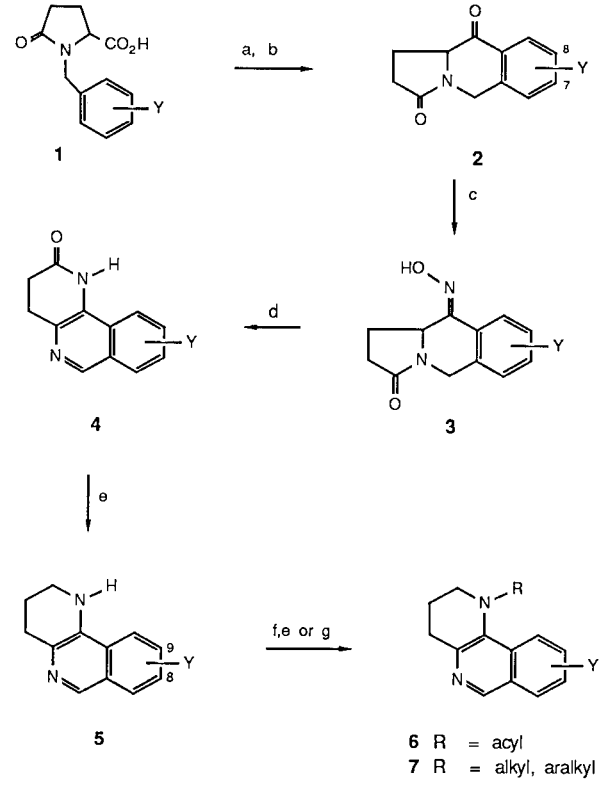
We recently reported a novel synthesis of 1,4-dihydrobenzo[*c*]-1,5-naphthyridin-2(3*H*)-one (**4a**) from (±)-(*Z*)-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione oxime (**3a**) and presented evidence which suggests that a Semmler-Wolff type aromatization reaction participates in the overall transformation [1]. Subsequent borane reduction of **4a** provided 1,2,3,4-tetrahydrobenzo[*c*]-1,5-naphthyridine (**5a**), which was evaluated for cholinomimetic properties based on perceived structural relationships to known cholinomimetic agents, *e.g.*, 1,2,3,4-tetrahydro-9-acridinamine [2] and the aminopyridines, including 4-aminopyridine and 3,4-diaminopyridine [3]. The encouraging biological activity observed with **5a** prompted the synthesis of additional analogues as potential agents for the treatment of diseases with associated cholinergic deficits, *e.g.*, Alzheimer's disease.



(a) $SOCl_2$, (b) $AlCl_3$, (c) NH_2OH, (d) polyphosphoric acid / 100°, (e) BH_3, (f) RCCl or $HCOCCH_3$, (g) KOH / DMSO / $C_6H_5CH_2Br$.

Scheme 1

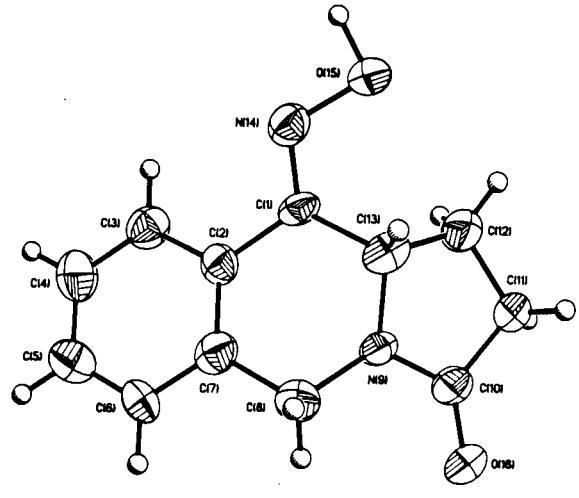


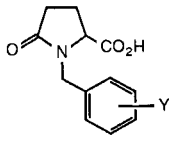
Figure 1. ORTEP view of the molecular structure of **3a** with anisotropic thermal ellipsoids.

As shown in Scheme 1, the required intermediates were prepared by Friedel-Crafts cyclization of (±)-5-oxo-1-(arylmethyl)proline) derivatives **1a-h** (Table 1) to give ketones **2a-h** (Table 2), which were converted to single oxime isomers **3a-h** (Table 3) by standard methods. The stereochemical assignment of **3a** as the *Z* isomer was previously based on steric arguments for the preferential formation of the *Z* oxime from the 9-chloro analogue of **2a** and on ^{13}C nmr comparison of **3a** and **3b** with the 9-chloro oxime

[1]. The assignment of **3a** as the *Z* isomer was subsequently confirmed by an X-ray structure determination (Figure 1, Tables 4-10). Based on these results, **3c-h** were also assigned as the *Z* oximes.

Table 1

(±)-5-Oxo-1-(arylmethyl)prolines

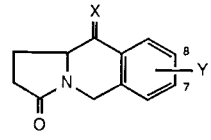


Compound No.	Y	Recrystallization Solvent [a]	Yield % [b]	Melting Point, °C
1a	H	B	90	118-120 [c]
1b	3-Cl	A	58	144-146
1c	3-F	A	66	114-117
1d	3-CH_3	A	77	142-145
1e	4-Br	A	64	138-139 [d]
1f	4-Cl	B	89	134-136 [e]
1g	4-OCH_3	A	48	103-105 [f]
1h	3,4-$(Cl)_2$	A	38	157-158 [g]

[a] A = toluene, B = benzene. [b] Saponification of the methyl esters provided **1a-h** in the indicated yields. [c] Lit [5] mp 122-123°. [d] Lit [6] mp 140°. [e] Lit [7] mp 133-134°. [f] Lit [6] mp 99.5°. [g] Lit [7] mp 160°.

Table 2

(±)-1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-diones and (±)-(*Z*)-1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione Oximes

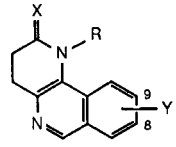


Compound No.	X	Y	Starting Material	Recrystallization Solvent [a]	Yield %	Melting Point, °C
2a	O	H	**1a**	C	82	105-110 [b]
2b	O	7-Cl	**1b**	C	51	151-154
2c	O	7-F	**1c**	C	62	160-163
2d	O	7-CH_3	**1d**	C	52	117-120
2e	O	8-Br	**1e**	C	54	147-148 [c]
2f	O	8-Cl	**1f**	C	67	130-136 [d]
2g	O	8-OCH_3	**1g**	C-D	24	106-107
2h	O	7,8-$(Cl)_2$	**1h**	C	45	189-192
3a	NOH	H	**2a**	G	61	214-216
3b	NOH	7-Cl	**2b**	E	67	249-252
3c	NOH	7-F	**2c**	F	53	237-245
3d	NOH	7-CH_3	**2d**	F	35	235-237
3e	NOH	8-Br	**2e**	G	56	241-242
3f	NOH	8-Cl	**2f**	E	64	229-235
3g	NOH	8-OCH_3	**2g**	F	44	229-230
3h	NOH	7,8-$(Cl)_2$	**2h**	G	79	245-246

[a] C = ethyl acetate, D = hexane, E = 1-propanol, F = absolute ethanol, G = 95% ethanol. [b] Lit [8] mp 107-108°. [c] Lit [8] mp 147-148°. [d] Lit [8] mp 125-126°.

Table 3

1,4-Dihydrobenzo[*c*]-1,5-naphthyridin-2(3*H*)-ones and 1,2,3,4-Tetrahydrobenzo[*c*]-1,5-naphthyridines



Compound No.	R	X	Y	Starting Material	Recrystallization Solvent [a]	Yield %	Melting Point, °C
4a	H	O	H	**3a**	G	52	224-225
4b	H	O	8-Cl	**3b**	E	64	281-284
4c	H	O	8-F	**3c**	F	44	266-267
4d	H	O	8-CH_3	**3d**	E	64	265-266
4e	H	O	9-Br	**3e**	E	44	300-302
4f	H	O	9-Cl	**3f**	E	63	285-286
4g	H	O	9-OCH_3	**3g**	E	44	254-256
4h	H	O	8,9-$(Cl)_2$	**3h**	E	60	349-350
5a	H	H_2	H	**4a**	H	80	125-128
5b	H	H_2	8-Cl	**4b**	H	68	169-170
5c	H	H_2	8-F	**4c**	H	86	189-191
5d	H	H_2	8-CH_3	**4d**	H	70	151-154
5e	H	H_2	9-Br	**4e**	H	62	181-183
5f	H	H_2	9-Cl	**4f**	H	65	185-187
5g	H	H_2	9-OCH_3	**4g**	H	61	116-119
5h	H	H_2	8,9-$(Cl)_2$	**4h**	H	56	248-251
6a	$C_6H_5C(=O)$	H_2	H	**5a**	A	75	208-210
6b	$C_6H_5CH_2C(=O)$	H_2	H	**5a**	I	51	89-90
6c	$C_6H_5(CH_2)_2C(=O)$	H_2	H	**5a**	I	72	89-92
6d	2-$FC_6H_4CH_2C(=O)$	H_2	H	**5a**	I	62	114-116
6e	2-$ClC_6H_4CH_2C(=O)$	H_2	H	**5a**	I	53	176-178
6f	2-$CH_3OC_6H_4CH_2C(=O)$	H_2	H	**5a**	I	37	108-111
6g	4-$ClC_6H_4CH_2C(=O)$	H_2	H	**5a**	I	80	114-116
6h	4-$CH_3OC_6H_4CH_2C(=O)$	H_2	H	**5a**	I	46	69-71
6i	2-thienyl$CH_2C(=O)$	H_2	H	**5a**	I	54	102-103
6j	3-thienyl$CH_2C(=O)$	H_2	H	**5a**	I	56	97-99
6k	$HC(=O)$	H_2	H	**5a**	A-J	53	85-88
7a	$C_6H_5CH_2$	H_2	H	**5a**	K	18	83-86
7b	$C_6H_5(CH_2)_2$	H_2	H	**6b**		40	Oil
7c	$C_6H_5(CH_2)_3$	H_2	H	**6c**	L-I	30	198-203
7d	2-$FC_6H_4(CH_2)_2$	H_2	H	**6d**	L-I	45	216-222
7e	2-$ClC_6H_4(CH_2)_2$	H_2	H	**6e**	L-I	42	216-220
7f	2-$CH_3OC_6H_4(CH_2)_2$	H_2	H	**6f**	L-I	50	200-202
7g	4-$ClC_6H_4(CH_2)_2$	H_2	H	**6g**	L-I	34	191-195
7h	4-$CH_3OC_6H_4(CH_2)_2$	H_2	H	**6h**	L-I	35	180-182
7i	2-thienyl$(CH_2)_2$	H_2	H	**6i**	G-I	42	191-195
7j	3-thienyl$(CH_2)_2$	H_2	H	**6j**	L-I	41	208-211
7k	CH_3	H_2	H	**6k**	F	20	261-274

[a] See corresponding footnote for Tables 1 and 2; H = acetonitrile, I = ether, J = cyclohexane, K = dimethylsulfoxide, L = methanol.

Table 4

Crystals Parameters

Molecular Formula	$C_{12}H_{12}N_2O_2$
Molecular weight	216.3 g
Crystal color	Clear
Crystal size	.10 × .12 × .36 mm.
a	7.773(5) A°
b	15.371(9) A°
c	17.836(10) A°
V	2131(2) A°
Z	8
Space group	$P2_12_12_1$
ρ (calc)	1.35 g/cm^3
F (000)	912 e$^-$
μ (MoKα)	1.0 cm^{-1}

Table 5

Data Measurements

Diffractometer	Nicolet R3m
Radiation	MoKα
Monochromater	graphite single crystal
2 θ range	3°-50°
Scan type	ω
Scan speed	3.91-29.30°/minute
Scan width	1.00°
Reflections measured	+h+k+l
Unique reflections	2185
Observed reflections	1499
Parameters	291
R	0.081
R_w	0.071
GOF	1.12

Table 6

Atomic Coordinates (× 10^4) and Isotropic Thermal Parameters (A°^{2} × 10^3)

	x	y	z	U
C(1)	4702(8)	8656(3)	1715(3)	35(2)*
C(2)	3897(9)	8527(4)	966(3)	39(2)*
C(3)	3220(9)	7720(4)	769(4)	47(2)*
C(4)	2545(12)	7589(5)	68(4)	62(3)*
C(5)	2535(11)	8256(5)	−445(4)	60(3)*
C(6)	3175(11)	9055(4)	−257(3)	62(3)*
C(7)	3857(9)	9198(4)	445(3)	43(2)*
C(8)	4552(11)	10088(4)	644(3)	53(3)*
N(9)	4527(7)	10210(3)	1456(3)	37(2)*
C(10)	4095(9)	10958(4)	1793(3)	40(2)*
C(11)	4191(10)	10808(4)	2624(3)	50(3)*
C(12)	4506(11)	9858(4)	2714(3)	59(3)*
C(13)	5210(9)	9567(4)	1963(3)	44(2)*
N(14)	5042(7)	7966(3)	2091(3)	44(2)*
O(15)	5856(6)	8165(3)	2781(2)	48(2)*
O(16)	3692(7)	11635(3)	1475(3)	60(2)*
C(1')	9042(9)	1273(4)	1837(4)	42(2)*
C(2')	8900(9)	1194(4)	1011(4)	46(2)*
C(3')	9415(10)	434(5)	633(4)	62(3)*
C(4')	9129(12)	323(5)	−117(4)	78(3)*
C(5')	8345(11)	975(5)	−526(4)	69(3)*
C(6')	7914(11)	1744(5)	−180(4)	65(3)*
C(7')	8184(9)	1865(4)	567(4)	47(2)*
C(8')	7713(11)	2708(4)	944(4)	58(3)*
N(9')	8620(7)	2831(3)	1642(3)	46(2)*
C(10')	9360(8)	3576(4)	1858(4)	44(2)*
C(11')	10069(11)	3447(4)	2635(4)	56(3)*
C(12')	10081(10)	2463(4)	2738(4)	51(2)*
C(13')	8700(9)	2138(3)	2205(3)	43(2)*
N(14')	9306(8)	569(3)	2200(3)	49(2)*
O(15')	9274(7)	706(3)	2979(3)	60(2)*
O(16')	9412(7)	4235(3)	1465(3)	61(2)*

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table 7

Bond Lengths (A°)

C(1)-C(2)	1.488(8)	C(1)-C(13)	1.521(8)
C(1)-N(14)	1.283(7)	C(2)-C(3)	1.393(9)
C(2)-C(7)	1.389(8)	C(3)-C(4)	1.372(10)
C(4)-C(5)	1.374(11)	C(5)-C(6)	1.366(10)
C(6)-C(7)	1.378(9)	C(7)-C(8)	1.512(9)
C(8)-N(9)	1.461(7)	N(9)-C(10)	1.340(7)
N(9)-C(13)	1.441(7)	C(10)-C(11)	1.502(8)
C(10)-O(16)	1.226(7)	C(11)-C(12)	1.490(8)
C(12)-C(13)	1.514(9)	N(14)-O(15)	1.418(7)
O(15)-H(15)	1.029	C(1')-C(2')	1.482(9)
C(1')-C(13')	1.507(8)	C(1')-N(14')	1.278(8)
C(2')-C(3')	1.407(10)	C(2')-C(7')	1.415(9)
C(3')-C(4')	1.367(10)	C(4')-C(5')	1.381(11)
C(5')-C(6')	1.375(11)	C(6')-C(7')	1.362(9)
C(7')-C(8')	1.505(9)	C(8')-N(9')	1.443(9)
N(9')-C(10')	1.338(8)	N(9')-C(13')	1.466(7)
C(10')-C(11')	1.503(10)	C(10')-O(16')	1.233(7)
C(11')-C(12')	1.524(8)	C(12')-C(13')	1.519(10)
N(14')-O(15')	1.406(7)	O(15')-H(15')	1.156

Table 8

Bond Angles (°)

C(2)-C(1)-C(13)	119.6(5)	C(2)-C(1)-N(14)	116.4(5)
C(13)-C(1)-N(14)	123.8(5)	C(1)-C(2)-C(3)	120.3(5)
C(1)-C(2)-C(7)	120.7(5)	C(3)-C(2)-C(7)	118.9(6)
C(2)-C(3)-C(4)	120.4(6)	C(3)-C(4)-C(5)	120.0(7)
C(4)-C(5)-C(6)	120.3(7)	C(5)-C(6)-C(7)	120.5(6)
C(2)-C(7)-C(6)	119.9(6)	C(2)-C(7)-C(8)	120.4(5)
C(6)-C(7)-C(8)	119.7(5)	C(7)-C(8)-N(9)	110.1(5)
C(8)-N(9)-C(10)	123.9(5)	C(8)-N(9)-C(13)	122.0(5)
C(10)-N(9)-C(13)	113.5(5)	N(9)-C(10)-C(11)	107.4(5)
N(9)-C(10)-O(16)	125.8(6)	C(11)-C(10)-O(16)	126.8(5)
C(10)-C(11)-C(12)	105.4(5)	C(11)-C(12)-C(13)	104.7(5)
C(1)-C(13)-N(9)	110.6(5)	C(1)-C(13)-C(12)	115.8(5)
N(9)-C(13)-C(12)	102.7(5)	C(1)-N(14)-O(15)	111.5(4)
N(14)-O(15)-H(15)	92.9	C(2')-C(1')-C(13')	119.5(5)
C(2')-C(1')-N(14')	116.5(5)	C(13')-C(1')-N(14')	123.7(6)
C(1')-C(2')-C(3')	121.5(6)	C(1')-C(2')-C(7')	121.7(6)
C(3')-C(2')-C(7')	116.7(6)	C(2')-C(3')-C(4')	121.7(7)
C(3')-C(4')-C(5')	119.9(7)	C(4')-C(5')-C(6')	119.6(7)
C(5')-C(6')-C(7')	121.3(7)	C(2')-C(7')-C(6')	120.5(6)
C(2')-C(7')-C(8')	118.3(6)	C(6')-C(7')-C(8')	121.2(6)
C(7')-C(8')-N(9')	112.3(6)	C(8')-N(9')-C(10')	124.8(5)
C(8')-N(9')-C(13')	121.1(5)	C(10')-N(9')-C(13')	113.9(5)
N(9')-C(10')-C(11')	108.1(5)	N(9')-C(10')-O(16')	123.5(6)
C(11')-C(10')-O(16')	128.4(6)	C(10')-C(11')-C(12')	104.2(5)
C(11')-C(12')-C(13')	104.2(5)	C(1')-C(13')-N(9')	110.5(5)
C(1')-C(13')-C(12')	116.0(5)	N(9')-C(13')-C(12')	102.7(5)
C(1')-N(14')-O(15')	111.8(5)	N(14')-O(15')-H(15')	97.7

Table 9

Anisotropic Thermal Parameters ($A^{\circ 2} \times 10^3$)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	43(4)	23(3)	39(4)	8(3)	8(3)	−1(3)
C(2)	45(5)	41(4)	31(3)	−2(3)	9(4)	−0(3)
C(3)	44(4)	43(4)	54(4)	−0(3)	−2(4)	−1(4)
C(4)	72(6)	59(5)	56(4)	−12(4)	−16(5)	−11(5)
C(5)	71(6)	64(5)	47(4)	4(4)	−12(4)	8(5)
C(6)	106(7)	52(4)	26(4)	−2(3)	2(4)	4(5)
C(7)	46(5)	38(3)	44(4)	−0(3)	12(4)	3(4)
C(8)	77(6)	43(4)	39(4)	6(3)	2(4)	−8(4)
N(9)	53(4)	25(2)	33(3)	2(2)	4(3)	5(3)
C(10)	45(4)	33(3)	43(4)	9(3)	−1(4)	−16(3)
C(11)	72(6)	32(3)	46(4)	−4(3)	−14(4)	7(4)
C(12)	97(7)	39(4)	40(4)	−1(3)	1(4)	3(4)
C(13)	37(4)	36(3)	59(4)	4(3)	1(4)	1(3)
N(14)	50(4)	36(3)	45(3)	−0(3)	3(3)	−2(3)
O(15)	62(3)	33(2)	49(3)	5(2)	−12(3)	3(2)
O(16)	97(4)	29(2)	55(3)	2(2)	−9(3)	−0(3)
C(1')	43(4)	26(3)	56(4)	4(3)	−4(4)	−0(3)
C(2')	42(5)	45(4)	52(4)	−9(3)	12(4)	−9(4)
C(3')	65(6)	60(5)	61(5)	−3(4)	−1(5)	12(5)
C(4')	96(8)	73(5)	66(5)	−19(4)	7(5)	13(6)
C(5')	77(6)	82(6)	48(5)	6(4)	3(5)	7(5)
C(6')	68(6)	76(5)	50(5)	6(4)	5(4)	−3(5)
C(7')	41(4)	48(4)	53(4)	11(4)	13(4)	−7(4)
C(8')	72(6)	24(3)	78(5)	1(4)	6(5)	7(4)
N(9')	47(4)	38(3)	52(3)	−3(3)	−14(3)	−2(3)
C(10')	39(4)	27(3)	64(5)	−6(3)	5(4)	3(3)
C(11')	48(5)	43(4)	76(6)	−7(4)	−0(5)	−5(4)
C(12')	63(5)	28(3)	64(5)	−4(3)	−9(5)	−9(3)
C(13')	51(5)	22(3)	57(4)	8(3)	5(4)	1(3)
N(14')	63(4)	37(3)	45(3)	1(3)	3(3)	−3(3)
O(15')	89(4)	33(2)	57(3)	1(2)	−2(3)	4(3)
O(16')	80(4)	28(2)	73(3)	7(2)	8(3)	−4(3)

The anisotropic temperature factor exponent takes the form:
$-2\pi^2(h^2a^{\cdot 2}U_{11} + \ldots + 2hka{\cdot}b{\cdot}U_{12})$

Table 10

H-Atom Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($A^{\circ} \times 10^3$)

	x	y	z	U
H(3)	3232	7252	1125	55
H(4)	2079	7032	−65	75
H(5)	2075	8157	−938	68
H(6)	3147	9518	−618	74
H(8A)	3844	10524	414	68
H(8B)	5711	10142	463	68
H(11A)	3138	10978	2864	63
H(11B)	5131	11132	2835	63
H(12A)	5327	9750	3105	79
H(12B)	3447	9565	2829	79
H(13)	6442	9524	1981	51
H(15)	6088	7521	2901	108(27)
H(3')	9970	−22	910	73
H(4')	9478	−206	−360	101
H(5')	8104	893	−1050	80
H(6')	7422	2206	−472	71
H(8'A)	6500	2706	1045	69
H(8'B)	7982	3182	613	69
H(11'A)	11201	3690	2680	69
H(11'B)	9319	3713	2996	69

Table 10 (continued)

	x	y	z	U
H(12'A)	9848	2301	3248	69
H(12'B)	11174	2228	2589	69
H(13')	7646	2042	2473	51
H(15')	9508	−6	3162	108(26)

Table 11

Elemental Analysis [a]

Compound No.	Molecular Formula	% Calculated/(% Found) C	H	N
1b	$C_{12}H_{12}ClNO_3$	56.79	4.77	5.53
		57.05	4.80	5.49
1c	$C_{12}H_{12}FNO_3$	60.73	5.10	5.91
		60.51	5.20	5.77
1d	$C_{13}H_{15}NO_3$	66.92	6.49	6.01
		67.16	6.50	5.94
2b	$C_{12}H_{10}ClNO_2$	61.16	4.28	5.94
		60.79	4.41	5.89
2c	$C_{12}H_{10}FNO_2$	65.70	4.60	6.39
		65.60	4.68	6.27
2d	$C_{13}H_{13}NO_2$	72.52	6.09	6.51
		72.26	6.11	6.54
2g	$C_{13}H_{13}NO_3$	67.50	5.67	6.06
		67.47	5.78	5.95
2h	$C_{12}H_9Cl_2NO_2$	53.36	3.36	5.19
		53.16	3.52	5.12
3a	$C_{12}H_{12}N_2O_2$	66.65	5.60	12.95
		66.36	5.59	12.93
3b	$C_{12}H_{11}ClN_2O_2$	57.50	4.42	11.17
		57.33	4.51	11.11
3c	$C_{12}H_{11}FN_2O_2$	61.51	4.74	11.97
		61.50	4.81	11.98
3d	$C_{13}H_{14}N_2O_2$	67.79	6.13	12.18
		67.67	6.12	12.13
3e	$C_{12}H_{11}BrN_2O_2$	48.83	3.76	9.49
		48.70	3.91	9.37
3f	$C_{12}H_{11}ClN_2O_2$	57.50	4.42	11.17
		57.18	4.41	11.21
3g	$C_{13}H_{14}N_2O_3$	63.38	5.73	11.38
		63.40	5.79	11.38
3h	$C_{12}H_{10}Cl_2N_2O_3$	50.55	3.54	9.83
		50.57	3.45	9.74
4a	$C_{12}H_{10}N_2O$	72.69	5.08	14.13
		72.53	5.26	14.14
4b	$C_{12}H_9ClN_2O$	61.89	3.90	12.04
		62.00	3.97	12.00
4c	$C_{12}H_9FN_2O$	66.64	4.20	12.97
		66.64	4.27	13.01
4d	$C_{13}H_{12}N_2O$	73.54	5.70	13.21
		73.62	5.89	13.24
4e	$C_{12}H_9BrN_2O$	52.01	3.27	10.11
		51.83	3.38	10.12
4f	$C_{12}H_9ClN_2O$	61.95	3.90	12.04
		61.97	3.92	11.99
4g	$C_{13}H_{12}N_2O_2$	68.39	5.30	12.28
		68.48	5.42	12.35
4h	$C_{12}H_8Cl_2N_2O$	53.96	3.02	10.49
		53.85	2.92	10.34
5a	$C_{12}H_{12}N_2$	78.23	6.57	
		78.32	6.58	
5b	$C_{12}H_{11}ClN_2$	65.86	5.07	12.82
		65.46	4.98	12.70
5c	$C_{12}H_{11}FN_2$	71.25	5.49	13.86
		71.20	5.44	13.99
5d	$C_{13}H_{14}N_2$	78.75	7.12	
		78.70	7.07	
5e	$C_{12}H_{11}BrN_2$	54.77	4.21	10.65
		54.40	4.44	10.77
5f	$C_{12}H_{11}ClN_2$	65.91	5.07	12.81
		65.88	5.19	12.90
5g	$C_{13}H_{14}N_2O$	72.85	6.59	13.09
		73.09	6.74	13.04
5h	$C_{12}H_{10}Cl_2N_2$	56.94	3.98	11.07
		56.48	3.90	11.02
6a	$C_{19}H_{16}N_2O$	79.14	5.59	9.71
		79.08	5.82	9.58
6b	$C_{20}H_{18}N_2O$	79.50	6.00	9.26
		79.45	6.10	9.25
6c	$C_{21}H_{20}N_2O$	79.72	6.37	8.85
		79.91	6.31	8.92
6d	$C_{20}H_{17}FN_2O$	74.98	5.35	8.74
		74.91	5.56	8.66
6e	$C_{20}H_{17}ClN_2O$	71.32	5.09	8.32
		71.29	5.09	8.42
6f	$C_{21}H_{20}N_2O_2$	75.88	6.06	8.43
		75.71	6.11	8.63
6g	$C_{20}H_{17}ClN_2O$	71.32	5.09	8.32
		70.92	5.29	8.15
6h	$C_{21}H_{20}N_2O_2$	75.88	6.06	8.43
		75.83	6.09	8.37
6i	$C_{18}H_{16}N_2OS$	70.10	5.23	9.08
		70.04	5.34	9.00
6j	$C_{18}H_{16}N_2OS$	70.10	5.23	9.08
		69.98	5.44	8.99
6k	$C_{13}H_{12}N_2O$	73.57	5.70	13.20
		73.88	5.99	13.19
7a	$C_{14}H_{18}N_2$	83.18	6.61	
		83.19	6.59	
7b	$C_{20}H_{20}N_2$	83.30	6.99	
		83.08	7.06	
7c	$C_{21}H_{22}N_2 \cdot 2HCl$	67.20	6.44	7.46
		66.93	6.36	7.48
7d	$C_{20}H_{19}FN_2 \cdot HCl$	70.07 [b]	5.88	8.17
		69.48	5.96	8.03

Table 11 (continued)

Compound No.	Molecular Formula	% Calculated/(% Found) C	H	N
7e	$C_{20}H_{19}ClN_2 \cdot HCl$	66.86	5.61	7.80
		66.89	5.72	7.75
7f	$C_{21}H_{22}N_2O \cdot HCl \cdot 0.5H_2O$	69.30	6.65	7.70
		69.61	6.45	7.69
7g	$C_{20}H_{19}ClN_2 \cdot HCl$	66.82	5.61	7.80
		66.97	5.87	7.78
7h	$C_{21}H_{22}N_2O \cdot HCl \cdot 0.5H_2O$	69.30 [c]	6.65	7.70
		69.71	6.45	7.69
7i	$C_{18}H_{18}N_2S \cdot HCl$	65.32	5.79	8.47
		65.20	5.93	8.44
7j	$C_{18}H_{18}N_2S \cdot HCl$	65.32	5.79	8.47
		65.36	5.83	8.47
7k	$C_{13}H_{14}N_2 \cdot 2HCl$	57.58	5.95	10.33
		57.52	6.25	10.23

[a] Analytical results within ± 0.4% of theoretical values unless otherwise noted. Compounds **1a**, **1e**, **1f**, **1h**, **2a**, **2e** and **2f** are reported in the references cited in Tables 1-3. [b]C, Calcd: 70.07. Found: 69.48. [c] C, Calcd: 69.30. Found: C, 67.71.

Treatment of **3a-h** under Beckmann conditions (hot polyphosphoric acid) afforded lactams **4a-h** in good yields. The reduction of **4a-h** was performed with excess borane, and the borane complex of each product was conveniently isolated and decomposed with concentrated hydrochloric acid to afford the naphthyridines **5a-h** (Table 3). For the synthesis of the tertiary amines **7a-k**, **5a** was acylated to give the tertiary amides **6a-k** which were reduced with excess borane as previously described. The tertiary amines were each contaminated with the amide cleavage product **5a**, and the mixtures were separated by preparative hplc. The amide cleavage reaction predominated in the case of **6a**, and the preparation of **7a** was achieved by the direct *N*-benzylation of **5a**.

All compounds listed in Tables 1-3 were evaluated in a battery of assays to detect biological activity. For many of the compounds in Table 3, most notably **4b**, **5a** and **7b**, significant cholinomimetic-like activity was observed, as evidenced by their ability to stimulate the contraction of the isolated guinea pig ileum longitudinal muscle [4], which was antagonized by atropine.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds are supported by their ir (Pye Unicam SP3-200), ^{1}H-nmr (Varian XL 200, chemical shifts are reported in δ units downfield relative to tetramethylsilane as internal standard), and ms (Finnigan 4023) spectra. Reactions were generally conducted under a dry nitrogen atmosphere with exclusion of moisture. Preparative hplc separations were performed on silica gel with a Waters Associates Prep LC/System 500 equipped with a Gow Mac model 80-800 UV detector. Elemental analyses were performed by Micro Tech Laboratories, Skokie, IL, and results (Table 11) are within ± 0.4% of the theoretical values unless otherwise noted. The X-ray crystal structure determination was performed by D. Van Engen, Princeton University.

(±)-5-Oxo-1-(phenylmethyl)proline (**1a**).

This material was prepared from (±)-glutamic acid monohydrate as previously described [1]. Compounds **1b-h** were prepared in a similar manner and the properties of these compounds are included in Table 1.

(±)-1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)dione (**2a**).

This compound was prepared by Friedel-Crafts cyclization of the acid chloride of **1a** as previously described [1]. The properties of **2a**, and of **2b-h** which were prepared in a similar manner, are included in Table 2.

(±)-(*Z*)-1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10-(2*H*,5*H*)-dione 10-Oxime (**3a**).

This compound was prepared from **2a** as previously described [1]. The properties of **3a**, and of **3b-h** which were prepared in a similar manner, are included in Table 2.

1,4-Dihydrobenzo[*c*]-1,5-naphthyridin-2(3*H*)-one (**4a**).

This compound was prepared by adding **3a** to hot (100°) polyphosphoric acid as previously described [1]. The properties of **4a**, and of **4b-h** which were prepared in a similar manner, are included in Table 3.

1,2,3,4-Tetrahydrobenzo[*c*]-1,5-naphthyridine (**5a**).

A stirred solution of **4a** (19.83 g, 0.1 mole) and sieve dried tetrahydrofuran (1500 ml) was treated over 15 minutes with 1 *M* borane in tetrahydrofuran (430 ml). During addition of the borane solution a colorless precipitate formed and then dissolved to give an amber solution. After stirring overnight at room temperature, the solution was treated over 15 minutes with 2.5 *N* sodium hydroxide solution (250 ml, gas evolution occurs) under a nitrogen purge. The mixture was concentrated to remove the tetrahydrofuran and the resultant suspension of yellow crystalline material was filtered. A stirred suspension of the filter cake (a borane complex) and glacial acetic acid (100 ml) was treated with concentrated hydrochloric acid (100 ml) under a nitrogen purge. After stirring for two hours at room temperature, the bright yellow solution was decanted over crushed ice, diluted with water and basified with 50% sodium hydroxide solution. The mixture was extracted with dichloromethane (2 × 700 ml), and the dried (sodium sulfate) organic phase was filtered and evaporated to give a yellow solid (22.2 g). Recrystallization of the solid from acetonitrile (45 ml) gave 14.7 g (80%) of **5a** as yellow crystals, mp 125-128°; ir (chloroform): 3450, 3075, 3030 (sh), 2960, 2850, 1625, 1580, 1515, 1480, 1450, 1420, 1400, 1360, 1340, 1310, 1280, 1135 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.02-2.14 (m, 2H), 3.12 (t, 2H, J = 8 Hz), 3.44 (t, 2H, J = 7 Hz), 4.44 (s, 1H, exchangeable with deuterium oxide), 7.44-7.68 (m, 3H), 7.86 (d, 1H), 8.66 (s, 1H); ms m/e (%): 184 (M$^+$, 100), 183 (63), 156 (21). Properties of **5b-h**, which were prepared in a similar manner, are included in Table 3.

1-Benzoyl-1,2,3,4-tetrahydrobenzo[*c*]-1,5-naphthyridine (**6a**).

A stirred solution of **5a** (4.6 g, 0.025 mole) and potassium hydroxide-dried pyridine (50 ml) was treated dropwise over one minute with benzoyl chloride (8.4 g, 0.06 mole) to afford a suspension, which was heated for 1.25 hours on a steam bath. The solution was then stirred overnight at room temperature, during which a crystalline precipitate formed. The suspension was decanted into excess 2.5 *N* sodium hydroxide solution and the mixture was extracted with dichloromethane. The dried (sodium sulfate) organic phase was filtered and concentrated to afford a tan solid, which was recrystallized from toluene to give 6.25 g (75%) of **6a**, mp 208-210°; ir (chloroform): 3030, 2970, 1645, 1580, 1500, 1460, 1400, 1375, 1350, 1270, 1250, 1160, 990 cm^{-1}; ^{1}H nmr: Only poorly resolved spectra were obtained with this compound despite several attempts using various solvents (deuteriochloroform, dimethylsulfoxide-d_6, trifluoroacetic acid); ms: m/e (%) 288 (M$^+$, 100) 181 (6), 105 (55).

1-(Phenylacetyl)-1,2,3,4-tetrahydrobenzo[*c*]-1,5-naphthyridine (**6b**).

Powdered **5a** (3.22 g, 0.018 mole) was rapidly treated with cold phenylacetyl chloride (35 ml) to give a solution from which a precipitate rapidly separated. After stirring overnight at room temperature, the suspension was diluted with ether (50 ml), the precipitate was collected by vacuum filtration, and the filter cake was thoroughly washed with ether. A solution of the filter cake and water (100 ml) was basified with 2.5 *N* sodium hydroxide solution, and extracted with dichloromethane. The dried (sodium sulfate) organic phase was filtered and concentrated to an oil (5.4 g) which was purified by preparative hplc (eluted with ethyl acetate, flow rate 150 ml/minute). The appropriate fractions were concentrated to an oil, which crystallized on trituration with ether to give 2.7 g (51%) of **6b**, mp 89-90°; ir (chloroform): 3050, 2960, 1640, 1580, 1490, 1450, 1390, 1360 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.84-2.00 (m, 1H), 2.04-2.28 (m, 1H), 2.48-2.68 (m, 1H), 2.84-3.04 (m, 2H), 3.52 (q_{ab}, 2H), 4.80-4.96 (m, 1H), 6.60-6.72 (m, 2H), 7.04-7.20 (m, 3H), 7.66 (t, 1H, J = 7 Hz), 7.82 (t, 1H, J = 7 Hz), 7.96 (d, 1H, J = 7 Hz), 8.06 (d, 1H, J = 7 Hz), 9.12 (s, 1H); ms m/e (%): 302 (M^+, 5), 185 (13), 184 (79), 183 (32), 128 (13), 91 (100). The properties of **6c-j**, which were prepared in a similar manner, are included in Table 3.

1-Formyl-1,2,3,4-tetrahydrobenzo[*c*]-1,5-naphthyridine (**6k**).

Powdered **5a** (5.0 g, 0.027 mole) was added to formic-acetic anhydride (prepared from 13.5 ml of 96% formic acid and 30 ml of acetic anhydride) and the solution was heated on a steam for 3.5 hours. The cooled solution was decanted into ice water and basified with 50% sodium hydroxide solution. After extraction with dichloromethane, the dried (sodium sulfate) organic phase was filtered and concentrated to an oil. Thin layer analysis (silica gel, 10% methanol in ethyl acetate) indicated the presence of starting material and the oil was treated again with formic-acetic anhydride. Thin layer analysis of the crude product now indicated the absence of starting material. The crude oil (5.2 g) was dissolved in hot toluene (10 ml) and the solution was gradually diluted with cyclohexane (45 ml) to give 3.02 g (53%) of **6k** as tan crystals, mp 85-88°; ir (chloroform): 3000, 2980, 1670, 1620, 1580, 1450, 1380, 1355, 1325, 1250 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.08-2.32 (m, 2H), 3.20 (t, 2H, J = 8 Hz), 3.98 (t, 2H, J = 8 Hz), 7.52-7.80 (m, 2H), 7.88-8.08 (m, 2H), 8.70 (s, 1H), 9.08 (s, 1H); ms m/e (%): 212 (M^+, 100), 184 (45), 183 (87), 156 (30).

1-Phenylmethyl-1,2,3,4-tetrahydrobenzo[*c*]-1,5-naphthyridine (**7a**).

A solution of **5a** (11.21 g, 0.061 mole) and sieve dried dimethylsulfoxide was treated with powdered 85% potassium hydroxide (0.12 mole potassium hydroxide) and stirred until most of the solid had dissolved. The red solution was treated dropwise over 20 minutes with benzyl bromide (12.49 g, 0.073 mole). After stirring overnight at room temperature, the solution was diluted with water and extracted with ethyl acetate (2 × 300 ml). The organic phase was washed with water and saturated brine, dried (sodium sulfate), filtered and concentrated to an oil (19.9 g). Thin layer analysis (silica gel, ethyl acetate) indicated a multicomponent mixture, which included the product (R_f = 0.31) and starting material (R_f = 0.21). Multiple preparative hplc separations (ethyl acetate, 150 ml/minute flow rate) afforded **7a** as an oil which crystallized. Recrystallization from dimethylsulfoxide afforded 3.0 g (18%) of **7a**, mp 83-86°; ir (chloroform): 3075, 3030 (sh), 2960, 2850, 1625, 1580, 1500, 1460, 1400, 1370, 1340, 1260, 1180, 1120, 1070, 1030, 950 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.92-2.08 (m, 2H), 3.04-3.20 (m, 4H), 4.38 (s, 2H), 7.32-7.72 (m, 7H), 7.94 (d, 1H, J = 8 Hz), 8.08 (d, 1H, J = 8 Hz), 8.94 (s, 1H); ms m/e (%): 274 (M^+, 82), 183 (100), 182 (24), 91 (36).

1-(2-Phenylethyl)-1,2,3,4-tetrahydrobenzo[*c*]-1,5-naphthyridine (**7b**).

A stirred solution of **6b** (5.11 g, 0.017 mole) and sieve dried tetrahydrofuran (300 ml) was rapidly treated with 1.0 *M* borane in tetrahydrofuran (68 ml, 0.068 mole borane). After stirring overnight at room temperature, the yellow solution was treated dropwise under a nitrogen purge with 2.5 *N* sodium hydroxide solution (60 ml, gas evolution occurs) and then concentrated to remove the tetrahydrofuran. The residual yellow oil-water mixture was diluted with water (100 ml) and extracted with dichloromethane (2 × 200 ml). The dried (sodium sulfate) organic phase was filtered and concentrated to an oil, which consisted of a mixture of borane complexes. A stirred solution of the oil and glacial acetic acid (30 ml) was cautiously treated under a nitrogen purge with concentrated hydrochloric acid (15 ml). After one hour, the solution was decanted into ice water (500 ml) and basified with 50% sodium hydroxide solution. The turbid mixture was extracted with dichloromethane (2 × 250 ml), and the dried (sodium sulfate) organic phase was filtered and concentrated to an oil (4.72 g). Thin layer analysis (silica gel, ethyl acetate) indicated the oil was a mixture of **5a** (from acyl cleavage, R_f = 0.21) and the desired product (R_f = 0.37). The mixture was separated by preparative hplc (ethyl acetate, 150 ml/minute flow rate) to afford 1.92 g (40%) of **7b** as a yellow oil; ir (chloroform): 3080, 3030 (sh), 2960, 2875, 1625, 1580, 1500, 1450, 1400, 1370, 1170, 1110, 1040, 950, 920 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.96-2.12 (m, 2H), 3.04-3.20 (m, 4H), 3.22-3.40 (m, 4H), 7.20-7.36 (m, 5H), 7.40-7.64 (m, 2H), 7.78 (d, 1H, J = 8 Hz), 7.88 (d, 1H, J = 8 Hz), 8.84 (s, 1H); ms m/e (%): 288 (M^+, 4), 198 (15), 197 (100). The properties of **7c-k**, which were prepared in a similar manner, are included in Table 3.

X-Ray Determination of **3a**.

A single crystal of $C_{12}H_{12}N_2O_2$ measuring 0.10 × 0.12 × 0.36 mm was mounted on a glass fiber and centered on a Nicolet R3m diffractometer. Cell constants and their esd's were determined by a least-squares fit of 22 diffractometer-measured reflections with 20° ≤ 2θ ≤ 25°. The material belongs to the orthorhombic crystal class, space group $P2_12_12_1$, with a = 7.773(5)A°, b = 15.371(9)A° and c = 17.836(10)A°. A density of 1.35 g/cm^3 was calculated for Z = 8, mw = 216.3 g and a unit cell volume of 2131(2)$A°^3$.

All intensity measurements were made at room temperature using graphite-monochromated MoKα radiation (λ = 0.71069A°) and an ω-scan technique with a variable scan rate of 3.91-29.30°/minute. Background counts were taken for half the scan time at each extreme of the scan range. All data (2185) having h,k,l ≥ 0 with 3° ≤ 2θ ≤ 50° were measured in this manner. Crystal decomposition was monitored throughout data collection by remeasuring two standard reflections after every 50 data measurements; no significant variations were recorded. The intensities were reduced by applying Lorentz polarization corrections after which 1499 were considered to be observed [$|F_o| > 2\sigma(F_o)$].

The structure was solved by direct methods using the SHELXTL software. There are two independent molecules per asymmetric unit representing both enantiomers. Following refinement of the nonhydrogen atoms with anisotropic temperature factors, a difference map showed peaks at plausible hydrogen positions. The oxime hydrogens were held fixed; all other hydrogen atoms were included in refinement in ideal positions (C-H 0.96A°, CCH 120° or 109.5°). In the final cycles of blocked-cascade least-squares refinement, the nonhydrogen atoms were refined with anisotropic temperature factors and the hydrogens were varied using a riding model. Refinement converged (shift/error ≤ 0.1) at R = 0.081, R_w = 0.071 ($R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$; $Rw = \Sigma[w(|F_o|-|F_c|)^2]^{1/2}/\Sigma(w|F_o|^2)^{1/2}$). A final difference map was featureless with a maximum peak of 0.29e $-/A°^3$. The quantity minimized by the least-squares program was $\Sigma\, w(|F_o|-|F_c|)^2$ where w is the weight of a given observation ($w^{-1} = \sigma^2(|F_o|) + g|F_o|^2$; the final value of g = 0.00097). The analytical forms for the scattering factors of the neutral atoms were used [9].

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