manner as (2)-5·2HCl in 58% yield, mp 297–298 °C; $[\alpha]^{20}_D$ +66.0° (c 1, CH_3OH); ee > 96% (detection limit), determined with Yb(fod)$_3$ as chiral shift reagent; ^{1}H NMR (CD_3OD) δ 3.67 (m, 1 H), 3.12 (t, J = 9 Hz, 2 H), 1.99–3.24 (m, 6 H), 1.94 (m, 2 H), 1.06 (t, J = 8 Hz, 3 H), NH in the solvent blind peak. Anal. ($C_{10}H_{17}N_3S$·2HCl) C, H, Cl, N.

Pharmacology. DA Synthesis Rate. According to the method of Walters and Roth,[25] male rats (200–250 g) were injected with saline (0.9% NaCl, 1 mL/kg sc) or drugs at various doses. After 5 min GBL (750 mg/kg) and 5 min later the DOPA decarboxylase inhibitor NSD 1015 (100 mg/kg) were injected intraperitoneally. Forty minutes after drug administration, the rats were decapitated, and the corpus striatum was dissected on ice, weighed, and immediately homogenized in a mixture of 2 mL of 0.4 N perchloric acid, 0.05 mL of 5% $Na_2S_2O_5$, 0.1 mL of 10% Na_2EDTA, and 100 ng of 3,4-dihydroxybenzylamine as an internal standard. After homogenization of the tissue, the further clean-up procedure and the determination of the catechols by means of HPLC with electrochemical detection was performed as previously described.[10,26]

DA Utilization. For the estimation of the DA content following α-MT (250 mg/kg ip 4 h before killing) and the compounds (various doses sc 4 and 2 h before killing) total rat brain without cerebellum was investigated. It was treated and the DA content was measured as described above. In both experiments control values were obtained by giving saline (0.9%) instead of the drugs under investigation.

DA Receptor Binding. Dopamine receptor binding was performed as described[27] with [^{3}H]spiperone as radioactive ligand in a concentration of 0.5 nM.

Acknowledgment. We thank Hanfried Baltes, Rosemarie Korz, and Michael Lawall for chemical laboratory work and Stefan Balasus and Erich Dahlheimer for pharmacological evaluation of the compounds.

Registry No. (±)-4 (free base), 106006-79-5; (±)-4·2HCl, 106006-72-8; (+)-4 (free base), 106006-73-9; (+)-4 (L-tartrate), 106006-74-0; (+)-4·2HCl, 106006-75-1; (−)-4 (free base), 106006-76-2; (−)-4(D-tartrate), 106006-77-3; (−)-4·2HCl, 106006-78-4; (*R*)-5 (free base), 104632-28-2; (*R*)-5·2HCl, 104632-27-1; (*S*)-5 (free base), 104632-26-0; (*S*)-5·2HCl, 104632-25-9; 6, 106160-66-1; 6 (free base), 106092-08-4; (±)-7, 106006-80-8; (±)-8, 106006-83-1; (±)-8·2HBr, 106006-81-9; (±)-8·2HCl, 106006-82-0; (*S*)-8, 106092-09-5; (*S*)-8·(L-tartrate) (dihydrate), 106160-67-2; (*S*)-8·2HCl, 106092-10-8; (*R*)-8, 106092-11-9; (*R*)-9, 106006-85-3; (*S*)-9, 106006-84-2; 4-acetamidocyclohexanone, 27514-08-5; thiourea, 62-56-6; propionic anhydride, 123-62-6.

Supplementary Material Available: Atomic coordinates and geometrical data for compound (−)-8 (9 pages). Ordering information is given on any current masthead page.

(25) Walters, J. R.; Roth, R. H. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1976**, *296*, 5.
(26) Felice, L. J.; Felice, J. D.; Kissinger, P. T. *J. Neurochem.* **1978**, *31*, 1461.
(27) Creese, I.; Burt, D. R.; Snyder, S. H. *Science (Washington, D.C.)* **1975**, *188*, 1217.

Amnesia-Reversal Activity of a Series of Cyclic Imides†

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A series of dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-diones were synthesized and evaluated for their ability to reverse electroconvulsive shock (ECS) induced amnesia in mice. Among the structure–activity relationships explored were the effects of ring size, the presence of heteroatoms (sulfur) in the ring system, and the introduction of alkyl substituents. The optimal ring size for the bicyclic system was 5.5 with dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione (**3**), although some activity was present in the corresponding 5.6 [hexahydro-3,5-indolizinedione (**7**)] and 6.6 [tetrahydro-2*H*-quinolizine-4,6(3*H*,7*H*)-dione (**9**)] analogues. Replacement of the C-1 carbon atom in compound **3** with a sulfur [dihydropyrrolo[2,1-*b*]thiazole-3,5(2*H*,6*H*)-dione (**10**)] abolished activity, and the introduction of methyl groups resulted in poorer biological profiles except when the substitution was made at the 7a position [dihydro-7a-methyl-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione (**4**)]. In several instances, hydrolysis of the parent bicyclic compound was carried out to furnish the corresponding lactam acids, which were further derivatized. Several exhibited interesting activity, especially the 5-oxo-2-pyrrolidinepropanoic acid derivatives such as 5-oxo-2-pyrrolidinepropanoic acid (**12**), 5-oxo-2-pyrrolidinepropanoic acid phenylmethyl ester (**17**), 5-oxo-2-pyrrolidinepropanoic acid (3-chlorophenyl)methyl ester (**20**), *N*-4-pyridyl-5-oxo-2-pyrrolidinepropanoic acid amide (**25**), and *N*-(2,6-dimethylphenyl)-5-oxo-2-pyrrolidinepropanoic acid amide (**27**). Compound **3** (CI-911; rolziracetam) was also observed to improve performance on a delayed-response task in aged rhesus monkeys and was selected for evaluation in cognitively impaired human subjects on the basis of its biological profile and a wide margin of safety in animals.

Many substances are known to affect intellectual performance in humans, usually producing an impairment of cognition. Several of these have been used by neurobiologists to study the brain systems responsible for cognitive functions in animals.[1] Unfortunately, no drugs have been identified yet that are useful in the prevention or treatment of the most prominent human cognitive disorders such as mental retardation, learning disabilities, or the dementias [primary degenerative dementia (PDD); Alzheimer's disease].[2]

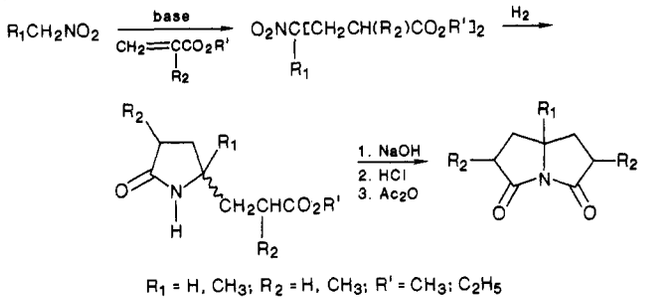
We previously reported on the cognition-activating effects of 3-phenoxypyridine (CI-844, compound **1**).[3] This compound improved performance in a single-trial passive

† Portions of this material were presented at the 188th National Meeting of the American Chemical Society, Philadelphia, PA, Aug 1984, Medicinal Chemistry Division, Paper 109.
‡ Chemistry Department.
§ Pharmacology Department.

(1) See, for example: Busby, J.; Bonelli, A.; Vargas, L.; Stirna, J.; Caranasos, G. *J. Am. Geriatri. Soc.* **1985**, *33*, 366. Olton, D. S.,, Gamzu, E., Corkin, S., Eds. *Ann. N.Y. Acad. Sci.* **1985**, *444*. Roth, M., Iversen, L. L,, Eds. *Br. Med. Bull.* **1986**, *42*(1). Hershenson, F. M.; Marriott, J. G.; Moos, W. H. *Annu. Rep. Med. Chem.* **1986**, *21*, 31.
(2) Hershenson, F. M.; Moos, W. H. *J. Med. Chem.* **1986**, *29*, 1125.
(3) Butler, D. E.; Poschel, B. P. H.; Marriott, J. G. *J. Med. Chem.* **1981**, *24*, 346.

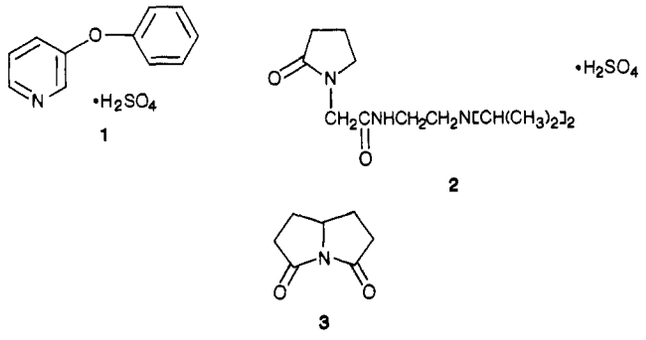
0022-2623/87/1830-0498$01.50/0

Scheme I



R_1 = H, CH_3; R_2 = H, CH_3; R' = CH_3; C_2H_5

avoidance test in mice and displayed positive effects in several additional animal models. A second compound



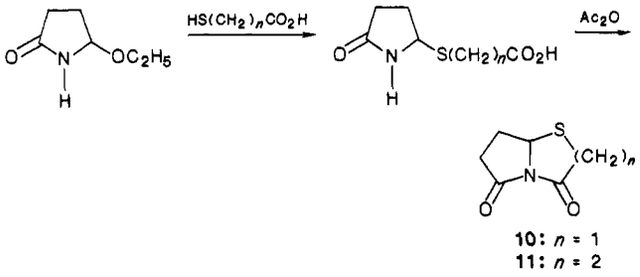
1 2 3

from our laboratories, pramiracetam (CI-879, compound **2**), was discovered to reverse electroconvulsive shock (ECS) induced amnesia in rodents and was found to possess cognition-enhancing activity in other paradigms.[4,5] Open-label clinical studies with pramiracetam noted an increase in goal-directed behaviors and a reduction in the degree of confusion in certain patients with Alzheimer's disease.[6]

We have continued our search for new agents to improve impaired cognitive function, and this paper will describe the biological test methods used, along with the chemistry and structure–activity relationships pertaining to a series of cyclic imides.

In the course of evaluating a number of pyrrolidone derivatives for their ability to reverse ECS-induced amnesia in rodents, the known compound dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione (**3**) was selected for study. Although a number of reports have appeared on the chemical properties of **3**,[7-9] there were no publications on its biological profile prior to our investigation. It was found that compound **3** reversed the effects of ECS in mice over an extraordinarily broad dose range (0.63 to 320 mg/kg, po). This finding prompted us to investigate the structure–activity relationships that existed for compounds related to **3** in the ECS-induced mouse amnesia model and then to evaluate the best candidates from this study in additional paradigms, including short-term memory tests in aged monkeys.

Scheme II



10: n = 1
11: n = 2

Chemistry. Compound **3** had been synthesized previously by the hydrogenation of 4-nitroheptanedioic acid diethyl ester[7] or by a ring-closure procedure beginning with esters of 4-oximinopimelic acid.[8] Our synthetic methodology was modeled after these earlier approaches along with modifications reported more recently.[9] Among the structure–activity relationships examined were the effects of ring size, the inclusion of a sulfur atom in the ring system, and the introduction of alkyl substituents. For compound **3** and simple alkylated analogues, the synthetic sequence employed is outlined in Scheme I.

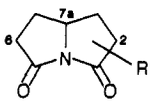
The indolizine and quinolizine analogues of compound **3** (compounds **7** and **9**) along with the corresponding pyrrolo[1,2-*a*]azepine (compound **8**) were prepared by using methods described by Flitsch.[10] Analogues of **3** and **7** where the C-1 carbon atom has been replaced by a sulfur (i.e., compounds **10** and **11**, respectively) were prepared from 5-ethoxy-2-pyrrolidinone by the sequence described in Scheme II.

Since we were concerned about the stability of cyclic imides, such as compound **3**, in biological fluids under physiological conditions, we decided to prepare a number of pyrrolidone derivatives where one of the five-membered rings of the pyrrolizidine system had been hydrolytically opened. These were obtained by converting **3**, under acidic conditions, to 5-oxo-2-pyrrolidinepropanoic acid (**12**) and subsequently preparing several esters by standard methods. Amides were synthesized by reaction of **3** with amines. A number of lactam alkanoic acids related to compound **12** were also synthesized by literature methods and then derivatized.

Pharmacology. The rationale, test sequence, and methodology used to identify and characterize the cognition-activating properties of novel compounds have been described earlier.[4] New chemical entities were first tested for gross central nervous system (CNS) activity in mice by using a general observational procedure. Those compounds devoid of significant CNS activity in the observational screen were then submitted for further behavioral evaluation. The single-trial, inhibitory avoidance learning task was similar to that developed by Essman and Alpern.[11] Others have employed similar ECS-induced impairments to study drug effects upon memory in rodents.[12]

(4) Butler, D. E.; Nordin, I. C.; L'Italien, Y. J.; Zweisler, L.; Poschel, B. P. H.; Marriott, J. G. *J. Med. Chem.* **1984**, *27*, 684.
(5) Poschel, B. P. H.; Marriott, J. G.; Gluckman, M. I. *Drugs Exp. Clin. Res.* **1983**, *9*, 853.
(6) Branconnier, R. J.; Cole, J. O.; Dessain, E. C.; Spera, K. F.; Ghazvinian, S.; DeVitt, D. *Psychopharmacol. Bull.* **1983**, *19*, 726.
(7) Leonard, N. J.; Hruda, L. R.; Long, F. W. *J. Am. Chem. Soc.* **1947**, *69*, 690.
(8) Lukes, R.; Sorm, F. *Collect. Czech. Chem. Commun.* **1947**, *12*, 278.
(9) More recent references to **3** include the following: Scipioni, A. *Ann. Chim. (Rome)* **1952**, *42*, 53. Micheel, F.; Albers, H. Justus Liebigs *Ann. Chem.* **1953**, *581*, 225. Micheel, F.; Flitsch, W. *Chem. Ber.* **1955**, *88*, 509. Micheel, F.; Flitsch, W. *Chem. Ber.* **1956**, *89*, 129. Micheel, F.; Flitsch, W. *Chem. Ber.* **1961**, *94*, 1749. Cologne, J.; Pouchol, J.-M. *Bull. Soc. Chim. Fr.* **1962**, 598. Flitsch, W. *Chem. Ber.* **1964**, *97*, 1548. Fayat, C.; Foucaud, A. *C. R. Seances Acad. Sci., Ser. C* **1967**, *265*, 345. Mackay, R. A.; Poziomek, E. J. *Spectrochim. Acta, Part A*, **1969**, *25*, 283. Aasen, A. J.; Culvenor, C. C. J.; Willing, R. I. *Aust. J. Chem. 1971*, *24*, 2575. Van Binst, G.; Steger, Y.; Flitsch, W. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1975**, *30B*, 591. Buchs, P.; Brossi, A.; Flippen-Anderson, J. L. *J. Org. Chem.* **1982**, *47*, 719.
(10) Flitsch, W. *Chem. Ber.* **1964**, *97*, 1542.
(11) Essman W. B.; Alpern, H. *Psychol. Rep.* **1964**, *14*, 731.

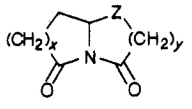
Table I. Dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-diones



no.	R	mp, °C	yield, %	emp formula	synth scheme	purifn method	amnesia-reversal dose, mg/kg, po							
							320	160	80	20	5	2.5	1.25	0.63
3	H	179–181	43.7[a]	$C_7H_9NO_2$	I[b]	*c*	85	62	63[d]	31	69	25	27	73[e]
4	7a-CH_3	162–165	78[f]	$C_8H_{11}NO_2$	I	*c*			85	77	31			
5	2-CH_3	110–111	8.5[a]	$C_8H_{11}NO_2$	I	*g*			30	0	50	50	20	
6	2,6-$(CH_3)_2$	113–125[h]	62[a]	$C_9H_{13}NO_2$	I[h]	*c*			20	20	0			

[a] Including reduction, hydrolysis, neutralization, and ring closure. [b] Leonard, N. J.; Hruda, L. R.; Long, F. W. *J. Am. Chem. Soc.* **1947**, *69*, 690. Lukes, R.; Sorm, F.; *Collect. Czech. Chem. Commun.* **1947**, *12*, 278. [c] Sublimed. [d] 92% amnesia reversal at 40 mg/kg. [e] 19% amnesia reversal at 0.31 mg/kg. [f] From crude penultimate acid. [g] Recrystallization—toluene. [h] Mixture of exo and endo isomers. Cologne and Pouchol (Cologne, J.; Pouchol, J.-M. *Bull. Soc. Chim. Fr.* **1962**, 508) report mp 103 °C.

Table II. Dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-diones



no.	*x*	*y*	Z	mp, °C	yield, %	emp formula	anal.	synth scheme or ref	purifn method	amnesia-reversal dose, mg/kg, po							
										100	80	20	10	5	2.5	1.25	1.0
7	1	2	CH_2	149–151	85[a]	$C_8H_{11}NO_2$	C,H,N	*b*	*c*		64	50		29	56	18	
8	1	3	CH_2	111–113	73[a]	$C_9H_{13}NO_2$	C,H,N	*b*	*d*		36	9		14			
9	2	2	CH_2	110–111	58[a]	$C_9H_{13}NO_2$	C,H,N	*b*	*e*		55	44		33			
10	1	1	S	126–127	45[a]	$C_6H_7NO_2S$	C,H,N	II	*f*	0			0				31
11	1	2	S	95–97	56[a]	$C_7H_9NO_2S$	C,H,N	II	*c*	55			51				19

[a] From pure penultimate acid. [b] Flitsch, W. *Chem. Ber.* **1964**, *97*, 1548. [c] Recrystallization—toluene. [d] Recrystallization—ethyl acetate/ligroin. [e] Recrystallization—toluene/ligroin. [f] Sublimed.

This test system was found to be generally insensitive to the activity of many other classes of CNS drugs, including psychomotor stimulants, antidepressants, anxiolytics, or neuroleptics.

Results and Discussion

Amnesia Reversal. Structure–Activity Relationships. The compounds considered to have the greatest therapeutic potential were those producing (1) the greatest degree of amnesia-reversal activity as measured by the percent amnesia-reversal score and (2) the broadest active dose range. Under these criteria, the most promising compounds to emerge from the amnesia-reversal screen included compounds **3**, **4**, **12**, **13**, **20**, **25**, and **27** (see Tables I–IV).

In early tests for amnesia-reversal activity, several compounds were found to be active over a broad, 16-fold dose range (5–80 mg/kg). To better determine the limits of the effective dose range, many compounds were subsequently evaluated over an even broader dose range (1–100 mg/kg). The results shown in Tables I–IV reflect these differing ranges.

Table I details the effects of alkyl substitution on the parent dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione structure (compound **3**). Table II describes the effects of ring size on activity and includes the two examples (compounds **10** and **11**) where a sulfur atom has replaced the carbon at C-1 of the pyrrolizidine (compound **3**) and indolizidine (compound **8**), respectively. Table III includes lactam acids, as well as related esters and amides. Finally, Table IV includes data on a miscellaneous group of compounds.

With compound **3** as a point of reference, several SAR generalizations can be made from the data contained in Tables I–IV:

1. Methyl substitution at any ring position, with the exception of the 7a position (compound **4**), resulted in lowered activity. The presence of one methyl substituent adjacent to a carbonyl group (compound **5**) diminished activity, while the presence of methyls next to both carbonyls (compound **6**) completely abolished it.

2. Altering the ring system, i.e., the indolizidine (compound **7**) or quinolizidine (compound **9**), furnished analogues that retained amnesia-reversal activity, while the pyrroloazepine derivative (compound **8**) was virtually inactive.

3. Replacement of the C-1 carbon atom with a sulfur gave mixed results. In the case of compound **10**, it provided an inactive compound. Although compound **11** exhibited activity in the amnesia-reversal screen, it was inactive in a rodent model of short-term memory.[13]

4. Partial reduction of one of the carbonyl groups of the cyclic imide in compound **3** furnished an analogue (compound **39**) with little activity.

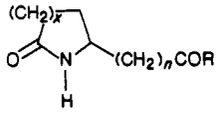
5. The lactam alkanoic acids, related esters, and amides were usually active in the amnesia-reversal test (see Tables III and IV). Among the structural variations studied within this group of compounds, the following SAR was noted:

a. Alterations of the length of the acidic side chain produce moderate changes in activity (i.e., in Table III, compare compounds **31**, **12**, and **29**, where n = 1, 2, and 3, respectively). Inclusion of a trans double bond (compound **35** compared to the corresponding ester, **17**) or a

(12) For example: Cumin, R.; Bandle, E. F.; Gamzu, E.; Haefely, W. E. *Psychopharmacology (Berlin)* **1982**, *78*, 104. Pfeifer, W. D.; Bookin, H. B. *Pharmacol. Biochem. Behav.* **1978**, *9*, 261. Dall'Olio, R.; Gandolfi, O.; Montanaro, N. *Pharmacol. Res. Commun.* **1978**, *10*, 851. Sara, S. J.; Remac, J.-F. *Behav. Biol. (U.S.A.)* **1977**, *19*, 465.

(13) Marriott, J. G., Warner-Lambert/Parke-Davis, personal communication.

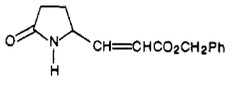
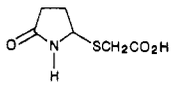
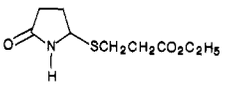
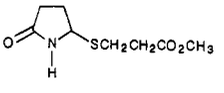
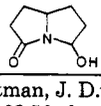
Table III. Lactam Alkane Carboxylic Acids, Esters, and Amides



no.	x	n	R	mp, °C	yield, %	emp formula	anal.	synth scheme or ref	purifn method	amnesia-reversal dose, mg/kg, po 100	80	20	10	5	2.5	1.25	1.0	0.6
12	1	2	OH	127–129[a]	92[a]	$C_7H_{11}NO_3$	C,H,N	*b*	*c*		67	100		89	91	83		58
13	1	2	OCH_3	67–69	30[d]	$C_8H_{13}NO_3$	C,H,N	*f*	*g*		75	100		75				
14	1	2	OC_2H_5	60–62	65[e]	$C_9H_{15}NO_3$	C,H,N	*b*	*h*		27	0		10				
15	1	2	$OCH(CH_3)_2$	65–68	70[a]	$C_{10}H_{17}NO_3$	C,H,N	*a*	*i*	16		42					42	
16	1	2	O-*t*-Bu	75–78.5	5	$C_{11}H_{19}NO_3$	C,H,N	*j*	*k*									
17	1	2	OCH_2Ph	79–82	61[a]	$C_{14}H_{17}NO_3$	C,H,N	*a,j*	*l*		71	64		64	67	56		44
18	1	2	$OCH(CH_3)Ph$	87–89	30[a]	$C_{15}H_{19}NO_3$	C,H,N	*a*	*m*	16			60				13	
19	1	2	$OCH_2C_6H_4$-2-Cl	99–100	63[a]	$C_{14}H_{16}ClNO_3$	C,H,N	*a*	*n*	70			80				30	
										31			85				15	
20	1	2	$OCH_2C_6H_4$-3-Cl	90–91	67[a]	$C_{14}H_{16}ClNO_3$	C,H,N	*a*	*n*	90			30				100	
21	1	2	$OCH_2C_6H_4$-4-Cl	63–64	71[a]	$C_{14}H_{16}ClNO_3$	C,H,N	*a*	*n*	42			25				0	
22	1	2	NH_2	177.5–178	61	$C_7H_{12}N_2O_2$	C,H,N	*p,o*	*q*	64			33				64	
23	1	2	$NHCH_2Ph$	140–142	79[q]	$C_{14}H_{18}N_2O_2$	C,H,N	*p*	*r*		50	62		0				
24	1	2	$NHCH_2CH_2C_6H_4OH$	185–187	52[q]	$C_{15}H_{20}N_2O_3$	C,[s]H,N	*p*	*t*	0			0				20	
25	1	2	NH-4-Py	188–190[h]	93[q]	$C_{12}H_{16}N_3O_2$	C,H,N	*p*	*u*	53			59				64	
26	1	2	NH-Ad[v]	188–190	36[l]	$C_{17}H_{26}N_2O_2$	C,H,N	*p*	*w*	57			40				57	
27	1	2	NH-2,6-$(CH_3)_2C_6H_3$	206–208	61	$C_{15}H_{20}N_2O_2$	C,H,N	*p*	*x*	50			56				49	
28	1	2	$NHCH_2CH_2N(i\text{-}Pr)_2$	62–65	16	$C_{15}H_{29}N_3O_2$	C,H,N	*p*	*m*		17	33		17				
29	1	3	OH	125–127	77	$C_8H_{13}NO_3$	C,H,N	*y,z*	*aa*	100			50				34	
30	1	3	OCH_2Ph	oil	53	$C_{15}H_{19}NO_3$	C,H,N	*y*	*ab*	43			24				70	
31	1	1	OH	121–123	20	$C_6H_9NO_3$	C,H,N	*ac*	*ad*	42			0				2	
32	2	2	OH	157–158	59	$C_8H_{13}NO_3$	C,H,N	*ac*	*aa*		8	70		86	60	56	67	
33	2	3	OH	143–145	40	$C_9H_{15}NO_3$	C,H,N	*ae*	*aa*		0	100		67				
34	3	2	OH	152–153	66	$C_{10}H_{17}NO_3$	C,H,N	*ae*	*aa*	67			38				0	

[a] From acid-catalyzed solvolysis of **3**. [b] Lukes, R.; Sorm, F.; *Collect. Czech. Chem. Commun.* **1947**, *12*, 278. [c] Recrystallization—water. [d] Isolated by chromatography of the reduction mixture. [e] 75% by acid-catalyzed ethanolysis of **3**. [f] Leonard, N. J.; Hruda, L. R.; Long, F. W. *J. Am. Chem. Soc.* **1947**, *69*, 690. [g] Recrystallization—methanol/diethyl ether. [h] Recrystallization—di-2-propyl ether. [i] Recrystallization—diethyl ether at −70 °. [j] Synthesis described in Experimental Section. [k] Triturated di-2-propyl ether. [l] Recrystallization—cyclohexane/dichloromethane. [m] Chromatography on SiO_2; dichloromethane/2-propanol, 9:1. [n] Recrystallization—toluene/diethyl ether. [o] Michael, F.; Flitsch, W. *Chem. Ber.* **1956**, *89*, 129. [p] Solvolysis of compound **3** in excess amine. [q] Recrystallization—1-butanol. [r] Chromatography on SiO_2; chloroform/methanol, 95:5. [s] Calcd, 68.27; found, 67.52. [t] Chromatography on SiO_2; 2-propanol. [u] Recrystallization—acetonitrile. [v] Ad = 1-adamantyl. [w] Chromatography on SiO_2; dichloromethane/methanol, 7:3. [x] Chromatography on SiO_2; 2-propanol/methanol, 1:1. [y] From acid-catalyzed solvolysis of **7**. [z] Birkofer, L.; Barnikel, C. *Chem. Ber.* **1958**, *91*, 1996. [aa] Freeze dried. [ab] Chromatography on SiO_2; ethyl acetate/methanol, 95:5. [ac] Evans, G. L.; Gray, H. W.; Jacobson, H. W. *J. Am. Chem. Soc.* **1950**, *72*, 2727. [ad] Recrystallization—acetone/acetonitrile/diethyl ether. [ae] Flitsch, W. *Chem. Ber.* **1964**, *97*, 1548.

Table IV. Miscellaneous Structures

no.	structure	mp, °C	yield, %	emp formula	anal.	synth scheme or ref	purifn method	amnesia-reversal dose, mg/kg, po 100	10	1.0
35		oil	*a*	$C_{14}H_{15}NO_3$	C,[b] H, N	*a*	*c*	17	31	0
36		147–149	70	$C_6H_9NO_3S$	C, H, N	*d*	*e*	31	21	64
37		58–59	60	$C_8H_{13}NO_3S$	C, H, N	*d*	*f*	44	66	49
38		oil	82	$C_8H_{13}NO_3S$	C, H, N	*d*	*g*	87	25	53
39		95–97	30	$C_7H_{11}NO_2$	C, H, N	*h*	*i*	17	27	19

[a] Hartman, J. D.; Dodd, J. H.; Hicks, J. L.; Hershenson, F. M.; Huang, C. C.; Butler, D. E. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 583. [b] Calcd, 68.56; found, 67.71. [c] Chromatography on SiO_2; ethyl acetate. [d] Synthesis described in Experimental Section. [e] Trituration with diethyl ether. [f] Chromatography on SiO_2; diethyl ether. [g] Chromatography on SiO_2; ethyl acetate/hexane, 1:9. [h] Buchs, P.; Brossi, A.; Flippen-Anderson, J. L. *J. Org. Chem.* **1982**, *47*, 719. [i] Recrystallization—ethyl acetate.

sulfur atom (compound **36**) reduced amnesia-reversal effects.

b. Variations in the ring size of the lactam (i.e., in Table III, compare compounds **12**, **32**, and **34**, where $x = 2$, 3, and 4, respectively) suggest that the five-membered-ring compounds gave the best activity over the broadest dose range.

c. Conversion of the free carboxylic acids to esters or amides did not generally diminish activity and in some

instances provided compounds with interesting profiles, for example, compounds **13**, **17**, **20**, and **25**.

In subsequent tests, compound **3** was found to enhance delayed-response performance of aged monkeys following acute and subacute oral dosing.[13] This suggested that **3** may be effective in treating short-term memory impairments. After completing toxicological studies of **3** and finding a wide margin of safety in animal species, phase 1 clinical evaluation, carried out in healthy volunteers, revealed that the compound was well-tolerated. As a result, **3** (CI-911; rolziracetam) has been the subject of a multicenter, phase 2 clinical study in memory-impaired elderly patients, as well as individuals with PDD. The results of these studies will be reported in the near future.

Experimental Section

Chemistry. Melting points were determined in a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. The structures of the compounds were confirmed by elemental analysis, infrared spectrometry, and NMR spectrometry. Infrared spectra were recorded on a Digilab FTP-14 infrared spectrometer. NMR spectra were obtained on a Varian EM 390 or Bruker WH 90 spectrometer, and chemical shifts are reported in ppm (δ) from the specified internal standard. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. TLC was carried out with 0.25-mm silica gel 60 F254 (E. Merck) glass plates. Vapor-phase chromatography was carried out with a Shimadzu GC Mini 2 or a Perkin-Elmer Model 910 gas chromatograph equipped with FID.

All compounds that were synthesized from compound **3** were routinely analyzed by HPLC for the absence of **3** since low-level contamination by this compound would result in a false positive rating at one or more of the standard test doses.

All concentrations were performed at reduced pressure on a rotary evaporator, and the temperature and approximate final pressure are indicated in parentheses. Chromatography was carried out on silica gel, and elution solvents for chromatographic purification are indicated in parentheses.

The following compounds were prepared by the literature references indicated and unless otherwise noted have physical and spectral properties comparable to those cited: hexahydro-3,5-indolizinedione (**7**), mp 149–151 °C (lit.[10] mp 152 °C); tetrahydro-1H-pyrrolo[1,2-*a*]azepine-3,5(2*H*,6*H*)-dione (**8**), mp 111–113 °C (lit.[10] mp 114.5 °C); tetrahydro-2*H*-quinolizine-4,6(3*H*,7*H*)-dione (**9**), mp 110–111 °C (lit.[10] mp 111 °C); 5-oxo-2-pyrrolidinepropanamide (**22**), mp 177.5–178 °C (lit.[14] mp 173 °C); 5-oxo-2-pyrrolidinebutyric acid (**29**), mp 125–127 °C (lit.[10] mp 130 °C); 5-oxo-2-pyrrolidineacetic acid (**31**), mp 121–123 °C (lit.[15] mp 120.5–122.2 °C); 6-oxo-2-piperidinepropanoic acid (**32**), mp 157–158 °C (lit.[10] mp 161.5 °C); 6-oxo-2-piperidinebutyric acid (**33**), mp 143–145 °C (lit.[10] mp 143 °C); hexahydro-7-oxo-1*H*-azepine-2-propanoic acid (**34**), mp 152–153 °C (lit.[10] mp 103 °C); hexahydro-5-hydroxy-3*H*-pyrrolizin-3-one (**39**), mp 95–97 °C (lit.[16] mp 93–95 °C). 3-(5-Oxo-2-pyrrolidinyl)-2-propenoic acid phenylmethyl ester (**35**) was synthesized as described by Hartman et al. as an oil with the following physical characteristics.[17] Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56. Found: C, 67.71; H; N. NMR ($CDCl_3$, Me_4Si): δ 7.3 (s, 5 H), 6.7–7.0 (m, 2 H), 5.9 (dd, 1 H, J = 10 Hz, 1.0 Hz), 5.1 (s, 2 H), 4.3 (q, 1 H, J = 4 Hz), 1.7–2.5 (m, 4 H). IR (film): cm^{-1} 3220, 1720, and 1700.

Synthetic Scheme I. Synthesis of Dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione (3). A solution of 4-nitroheptanedioic acid dimethyl ester (744 g, 3.2 mol) in methanol (3.78 L) was hydrogenated at 50 psi in the presence of 20% Pd/C (15 g). When hydrogen uptake was completed, the mixture was filtered to remove the catalyst. The filtrate was concentrated (45 °C, 12 mm) until no more distillate was observed. The bath temperature was raised to 100 °C to remove the remaining volatiles and to promote ring closure of any amino ester present.

The resulting oil consisted principally of 5-oxo-2-pyrrolidinepropanoic acid methyl ester (**13**) and of the partially hydrolyzed 5-oxo-2-pyrrolidinepropanoic acid (**12**). (The latter appears to arise from the intermediate formation of tetrahydro-6-oxo-2*H*-1,2-oxazine-3-propanoic acid methyl ester followed by hydrogenolysis of the N–O bond and ring reclosure.) The mixture was dissolved in methanol (600 mL) and water (400 mL). Sodium hydroxide solution (50%, 296 g, 3.8 mol) and water (200 mL) were added, and the solution was refluxed overnight.

After the mixture was cooled, it was concentrated (45 °C, 12 mm) and concentrated hydrochloric acid (330 mL, 3.8 mol) diluted with water (300 mL) was added. The volatiles were removed (60 °C, 12 mm). The thick, pasty residue of wet 5-oxo-2-pyrrolidinepropanoic acid (**12**) was treated slowly with acetic anhydride (500 mL). (**Caution**: This may become exothermic if large amounts of water remain.)

Additional acetic anhydride (1000 mL) was added, and the resulting suspension was stirred and heated (95 °C, 18 h). The suspension was cooled to 60 °C and filtered through filter aid. The salt cake was washed with hot (60 °C) acetic anhydride. The filtrate was concentrated (60 °C, 12 mm), and toluene (1 L) was added. A further 150 mL of volatiles was removed (45 °C, 12 mm) and the solution chilled to 5 °C. The crystalline product was collected by filtration and the filter cake pressed dry with a rubber dam and then washed with anhydrous diethyl ether (500 mL). The yield of crude dihydro-1*H*-pyrrolizine-3,5(2*H*,6*H*)-dione (**3**) was 211 g (48% overall yield), mp 178–182 °C (lit. mp 176–177 °C,[7] 181 °C[8]).

Crude **3** was dissolved in 2-propanol (2.5 L) at 95 °C. Fifteen grams of activated charcoal (Darco G-60) was added, and the mixture was filtered by using filter aid in a heated sintered-glass funnel. The filtrate was cooled to 5 °C and the crystalline **3** removed by filtration. The crystals were washed with cold (5 °C) 2-propanol (200 mL) and dried in vacuo at 50 °C to yield pure **3**, 192 g (43.7% overall yield), mp 180–183 °C. Anal. ($C_7H_9NO_2$) C, H, N.

The final recrystallization works well from toluene if the filter funnel is heated at 110 °C. Compound **3** reacts quite rapidly with methanol or ethanol, particularly in dilute solution, and this probably explains some of the literature melting points below 179 °C. When a sample was prepared for GC analysis in chloroform, the GC showed the presence of 5-oxo-2-pyrrolidinepropanoic acid ethyl ester (**14**) from reaction with the ethanol used as a chloroform stabilizer.

Synthetic Scheme II. Synthesis of Dihydropyrrolo[2,1-*b*]thiazole-3,5(2*H*,6*H*)-dione (10) and [(5-Oxo-2-pyrrolidinyl)thio]acetic Acid (36). A mixture of 5-ethoxy-2-pyrrolidinone[18] (6.24 g, 0.0484 mol) and mercaptoacetic acid (Aldrich) (4.51 g, 0.049 mol) was heated at 70 °C for 24 h. Upon cooling, a crystalline solid was obtained. This material was triturated with anhydrous diethyl ether and filtered to yield [(5-oxo-2-pyrrolidinyl)thio]acetic acid (**36**), 5.5 g, 51%, mp 147–150 °C. Anal. ($C_6H_{13}NO_3S$) C, H, N. NMR (Me_2SO, Me_4Si): δ 8.3 (1 H), 4.9 (dd, 1 H), 3.4 (s, 2 H), 1.8–2.6 (m, 5 H). IR (KBr): cm^{-1} 3310, 1690, and 1640.

Compound **36** (2.5 g, 0.0143 mol) was suspended in glacial acetic acid (10 mL) and acetic anhydride (10.2 g, 0.1 mol). The solution was heated to 100 °C over 30 min and held at 100 °C for 1 h. The mixture was concentrated to yield dihydropyrrolo[2,1-*b*]thiazole-3,5(2*H*,6*H*)-dione (**10**), 1.9 g, as a light brown solid. The solid was recrystallized from toluene and sublimed (110 °C at 0.1 mm) to afford pure **10**, 1.0 g, 11.9%, mp 126–127 °C. Anal. ($C_6H_7NO_2S$) C, H, N, S. NMR ($CDCl_3$, Me_4Si): δ 5.5 (dd, 1 H), 3.5–4.1 (two sets of doublets, 2 H), 2.0–3.0 (m, 4 H). IR ($CHCl_3$): cm^{-1} 1782 and 1720.

[(5-Oxo-2-pyrrolidinyl)thio]acetic acid ethyl ester (37) was synthesized in the same manner as **36** by using thioacetic acid

(14) Scipioni, A. Ital. Patent 482946, July 14, 1953; *Chem. Abstr.* **1955**, *49*, 15952*d*.
(15) Evans, G. L.; Gray, H. W.; Jacobson, H. W. *J. Am. Chem. Soc.* **1950**, *72*, 2727.
(16) See ref 9, Buchs et al.
(17) Hartman, J. D.; Dodd, J. H.; Hicks, J. L.; Hershenson, F. M.; Huang, C. C.; Butler, D. E. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 583.
(18) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

ethyl ester (60% yield, mp 58–59 °C). Anal. ($C_8H_{13}NO_3S$) C, H, N. NMR ($CDCl_3$, Me_4Si): δ 7.5 (1 H), 5.1 (m, 1 H), 4.3 (q, 2 H), 3.4 (s, 2 H), 2.2–2.7 (m, 4 H), 1.3 (t, 3 H). IR ($CHCl_3$): cm^{-1} 3175, 3100, and 1730.

Dihydro-2*H*-pyrrolo[2,1-*b*][1,3]thiazine-4,6(3*H*,7*H*)-dione (11) and 3-[(5-Oxo-2-pyrrolidinyl)thio]propanoic Acid (40). A mixture of 5-ethoxy-2-pyrrolidine[18] (9.4 g, 0.0734 mol) and 3-mercaptopropanoic acid (7.04 mL, 0.0808 mol) was heated at 60 °C for 16 h. Upon cooling, a crystalline product was obtained. Trituration with anhydrous diethyl ether (3 × 75 mL) yielded 3-[(5-oxo-2-pyrrolidinyl)thio]propanoic acid (**40**), 10.5 g, 76%, mp 108–110 °C. Anal. ($C_7H_{11}NO_3S$) C, H, N. NMR (Me_2SO, Me_4Si): δ 8.3 (m, 1 H), 4.9 (m, 1 H), 1.7–2.9 (m, 9 H). IR ($CHCl_3$): cm^{-1} 3305, 1707, and 1665.

Compound **40** (4.2 g, 0.022 mol) was suspended in acetic anhydride (25 mL) and the mixture heated at 100 °C for 2 h. The resulting solution was concentrated and chromatographed (diethyl ether/dichloromethane, 5:95). Recrystallization from toluene provided pure dihydro-2*H*-pyrrolo[2,1-*b*][1,3]thiazine-4,6-(3*H*,7*H*)-dione (**11**), 2.1 g, 56%, mp 95–97 °C. Anal. ($C_7H_9NO_2S$) C, H, N. NMR ($CDCl_3$, Me_4Si): δ 5.2 (m, 1 H), 1.8–3.3 (m, 8 H). IR (KBr): cm^{-1} 1758 and 1637.

3-[(5-Oxo-2-pyrrolidinyl)thio]propanoic acid methyl ester (38) was synthesized in the same manner as **37** by using 3-mercaptopropanoic acid methyl ester and was obtained in 82% yield as an oil purified by flash chromatography (ethyl acetate/hexane, 1:10). Anal. ($C_8H_{13}NO_3S$) C, H, N. NMR ($CDCl_3$, Me_4Si): δ 6.9 (m, 1 H), 4.8 (m, 1 H), 3.7 (s, 3 H), 1.9–3.0 (m, 8 H).

5-Oxo-2-pyrrolidinepropanoic Acid (12). A solution of **3** (25 g, 0.18 mol) in deionized water (150 mL) was treated with concentrated hydrochloric acid (0.1 mL), and the solution was refluxed for 80 h. Activated charcoal (Darco G-60, 1 g) was added, and the suspension was filtered. Concentration (60 °C, 12 mm) yielded 5-oxo-2-pyrrolidinepropanoic acid (**12**) as a crystalline solid, which after drying in vacuo weighed 25.9 g, 92%, mp 127–129 °C (lit.[8] mp 128 °C). Anal. ($C_7H_{11}NO_3$) C, H, N.

5-Oxo-2-pyrrolidinepropanoic Acid 1,1-Dimethylethyl Ester (16). A suspension of **12** (15.4 g, 0.1 mol) in dichloromethane (300 mL), 2-methylenepropane (168 g, 3 mol), and concentrated sulfuric acid (2.2 mL) was shaken at 25 °C and 150 psi for 12 h. The resulting mixture was poured into a 2.5% sodium bicarbonate solution (1 L). The organic layer was separated, and the aqueous solution was extracted with dichloromethane (3 × 500 mL). The combined extracts were dried ($MgSO_4$) and concentrated to yield an oil that crystallized. Trituration of the solid with di-2-propyl ether afforded 5-oxo-2-pyrrolidinepropanoic acid 1,1-dimethylethyl ester (**16**), 1.1 g, 5%, mp 75–78 °C. Anal. ($C_{11}H_{19}NO_3$) C, H, N.

5-Oxo-2-pyrrolidinepropanoic Acid Phenylmethyl Ester (17). Compound **3** (28 g, 0.2 mol) was dissolved in benzenemethanol (76 g, 0.7 mol), and a catalytic amount of concentrated hydrochloric acid (0.2 mL) was added. The solution was heated (98 °C, 104 h) [until **3** could no longer be detected by TLC (dichloromethane/diethyl ether, 9:1)]. The solvolysis was faster if run at high dilution but was inefficient in time when the solvent was high boiling. The mixture was cooled slightly, and excess benzenemethanol was distilled at 0.1 mm until the external oil bath temperature was 100 °C. The residual oil was dissolved in anhydrous diethyl ether (1 L), activated charcoal (1 g) added, and the suspension filtered through filter aid. The filtrate was partially concentrated at reduced pressure and cooled. The crystalline product, 5-oxo-2-pyrrolidinepropanoic acid phenylmethyl ester (**17**) was isolated by filtration, 42 g, 85%, mp 79–80 °C. Recrystallization (cyclohexane/dichloromethane, 9:1) furnished pure **17**, 32 g, 65%, mp 79–82 °C. Anal. ($C_{14}H_{17}NO_3$) C, H, N.

5-Oxo-*N*-4-pyridinyl-2-pyrrolidinepropanoic Acid Amide (25). An intimate mixture of **3** (15 g, 0.108 mol) and 4-aminopyridine (Aldrich) (11.4 g, 0.12 mol) was heated in a Woods metal bath at 150 °C for 24 h. The solid residue was chromatographed (dichloromethane/methanol, 9:1) and yielded pure **25**, 18 g, 70%, mp 184–186 °C (acetonitrile). Anal. ($C_{12}H_{15}N_3O_2$) C, H, N.

5-Oxo-2-pyrrolidinebutanoic acid phenylmethyl ester (30) was synthesized by acid-catalyzed solvolysis of **7** in benzenemethanol in 53% yield after purification by chromatography (dichloromethane/methanol, 98:2) as an oil. Anal. ($C_{15}H_{19}NO_3$) C, H, N.

Pharmacology. Amnesia-Reversal Testing.[4] Male CF-1 mice (Charles River Laboratories) were assigned randomly to groups (20 animals in each group). With footshock (0.58 mA, 3-s duration) as punishment, these animals were trained to avoid a dark compartment when placed on a shelf outside this area. Two hours after training, groups received either ECS (20 mA for 1 s) or sham ECS treatment (non-ECS control) through electrodes attached to the ears. Two hours after ECS or sham treatment, animals received the test compound or vehicle (non-ECS control and ECS control) orally via gastric gavage. One hour after drug or vehicle treatment, animals were tested for retention of the inhibitory avoidance response by placing animals on the shelf outside the compartment and recording the latency to reentry. The percentage of animals entering the dark compartment within 60 s served as the measure of amnesia.

Data were analyzed by using the normal approximation to the binomial distribution. According to screening criteria, 75% of the ECS-control animals must demonstrate amnesia and there must be at least a 50% difference between non-ECS and ECS controls. With these constraints, 40% or greater amnesia reversal was significantly different ($p < 0.05$) from ECS control and was rated as active. The equation employed was as follows: % amnesia reversal = [(drug group − base-line control group)/(ceiling control group − base-line control group)] × 100.

Registry No. **3**, 18356-28-0; **4**, 106039-89-8; **5**, 106039-90-1; **6**, 90643-39-3; **7**, 69498-64-2; **8**, 5779-53-3; **9**, 91240-16-3; **10**, 106039-91-2; **11**, 106039-92-3; **12**, 7766-86-1; **13**, 81980-11-2; **14**, 89317-07-7; **15**, 106039-93-4; **16**, 106039-94-5; **17**, 89317-06-6; **18**, 106039-95-6; **19**, 89317-08-8; **20**, 89317-09-9; **21**, 89317-10-2; **22**, 89317-13-5; **23**, 89317-14-6; **24**, 106039-96-7; **25**, 89317-17-9; **26**, 106039-97-8; **27**, 89317-18-0; **28**, 89317-15-7; **29**, 90088-23-6; **30**, 106039-98-9; **31**, 86976-29-6; **32**, 90088-17-8; **33**, 90942-98-6; **34**, 93387-52-1; **35**, 106039-99-0; **36**, 106040-00-0; **37**, 106040-01-1; **38**, 106040-02-2; **39**, 106040-03-3; **40**, 106040-04-4; 4-nitroheptanedioic acid dimethyl ester, 7766-83-8; 5-ethoxy-2-pyrrolidinone, 39662-63-0; mercaptoacetic acid, 68-11-1; thioacetic acid ethyl ester, 625-60-5; 4-aminopyridine, 504-24-5; 3-mercaptopropanoic acid, 107-96-0; 3-mercaptopropanoic acid methyl ester, 2935-90-2; 2-methylenepropane, 115-11-7; benzenemethanol, 100-51-6.