Synthesis of 1-Azabicyclo[3.3.0]octane Derivatives and Their Effects as Piracetam-like Nootropics

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A useful pharmaceutical intermediate, 5-nitromethyl-1-azabicyclo[3.3.0]octane (1), was prepared in one step from 1,7-dichloro-4-heptanone (4) under mild conditions. Catalytic hydrogenation of 1 over Raney Ni in the presence of sodium hydroxide afforded 5-aminomethyl-1-azabicyclo[3.3.0]octane (2) in high yield. Piracetam analogues 20—23, which were pyrrolidine derivatives involving a 1-azabicyclo[3.3.0]octane ring, were synthesized. Pharmacological tests showed that *N*-[(1-azabicyclo[3.3.0]octan-5-yl)methyl]-2-oxo-1-pyrrolidineacetamide (20) improves cerebral function.

Key words 5-nitromethyl-1-azabicyclo[3.3.0]octane; piracetam-like nootropics; hydrogenation; cerebral function activator; 2-oxo-1-pyrrolidine

Senile dementia, which is increasingly becoming an object of public concern, is classified into the categories of multiinfarct dementia and Alzheimer-type dementia. As cerebral function activators have been used as therapeutic agents for the former, which is caused by cerebro-vascular accidents, we have become interested in piracetam analogues[1] such as piracetam, pramiracetam,[2] and aniracetam[3] (Chart 1).

Several kinds of compounds having the 1-azabicyclo[3.3.0]octane moiety have also shown good biological activity, however.[4] 1-Azabicyclo[3.3.0]octane has a unique alkaloid skeleton in which the lone pair on the bridgehead nitrogen atom is in the syn direction in relation to the substituent at the 5-position (Chart 1). It is therefore likely that the amine moiety acts differently on macromolecules than other amine moieties, and in some cases the action might be specific for enzymes or receptors.

In this study, we designed, prepared and assayed compounds having 5-aminomethyl- and 5-aminoethyl-1-azabicyclo[3.3.0]octane moieties in place of the amino group in piracetam analogues to improve the interaction with the binding site. We also describe here a novel synthesis of a useful intermediate, 5-aminomethyl-1-azabicyclo[3.3.0]octane (2).

Chemistry

Until now, 2 has been prepared only by the reduction of 5-cyano-1-azabicyclo[3.3.0]octane (3), obtained in four steps from 2-pyrrolidinone.[5] In the present study, however, we developed an alternative preparation method for 2.

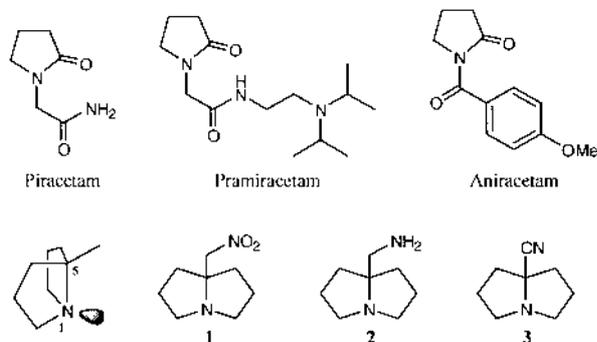We have already reported the synthesis of 3 from 4 by a nucleophilic attack of a cyanide anion on the iminium chloride 6.[6] Taking into account the pK_a values for a methyl group of nitromethane (10.2) and the ammonium ion (9.2), we expected the generation of nitromethyl anion from nitromethane in the presence of ammonia. Thus the reaction of four equivalents of nitromethane with one equivalent of 4 in the presence of 2.6 equivalents of ammonia in methanol afforded 1 in 66.5% yield[7] along with 10.8% of byproduct 10.[8] The proposed mechanism of the reaction is shown in Chart 2. The reaction of 4 with ammonia would initially provide the imine 5 and the enolate 7. The double cyclization of 5 gives 6, which is then attacked by the nitromethyl anion to give 1 (path A). At the same time, the enolate 7 undergoes cyclopropane formation to give 8, followed by dihydropyrrole ring formation to give 10 (path B).

We subsequently carried out the catalytic hydrogenation of 1 to 2. The reduction of 1 with Raney Ni in ethanol followed by treatment with HCl provided not only 2 dihydrochloride but also iminium chloride 6.[9] The ^{1}H-NMR spectrum showed a molar ratio of the dihydrochloride to 6 of 2.4 : 1 (Chart 3). On the other side, the ^{1}H-NMR spectrum of 1 in deuterated methanol showed that the methylene group at the α-position in relation to the nitro group was readily deuterated; surprisingly, however the protons on the methylene groups at the 4- and 6-positions were also deuterated at room temperature.[10] These results suggest that there was an equilibrium between 1 and 1-d$_6$, as shown in Chart 4. Interest-
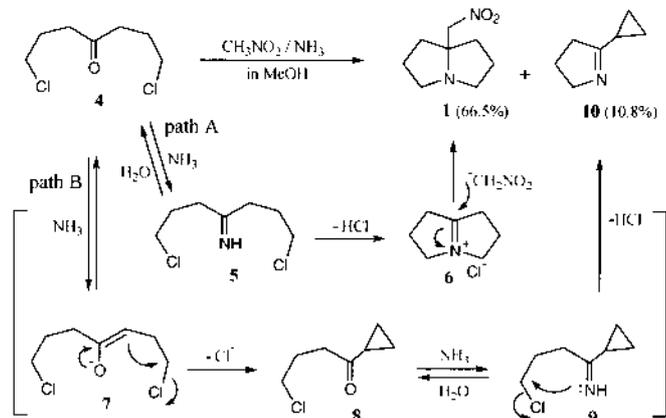

Chart 1

Chart 2

Chart 3

Chart 4

15

Table 1. Preparations of 2-Oxo-1-pyrrolidine Derivatives with 1-Azabicyclo[3.3.0]octane

16: R$_1$ = H, R$_2$ = Me
17: R$_1$ = Et, R$_2$ = Et
18: R$_1$ = Ph, R$_2$ = Me

2: n = 1
19: n = 2

90 °C, 6 h

20 - 23

Entry	Ester	Amine	Product	Yield (%)[a]
1	**16**	**2**	**20** (R$_1$=H, n=1)	73.4
2	**17**	**2**	**21** (R$_1$=Et, n=1)	69.3
3	**18**	**2**	**22** (R$_1$=Ph, n=1)	83.0
4	**16**	**19**	**23** (R$_1$=H, n=2)	69.3

a) Isolated yield.

Table 2. Effects of **20**—**23** on Cycloheximide-induced Passive Avoidance Deficit in ICR Mice[a]

Treatments	Dose (mg/kg, p.o.)	n	Latency in retention test (s)	% Retention[b]
Sham operation		20	223.4±23.3*	60[++]
Cycloheximide control		20	148.9±18.8	10
20	1	20	148.8±20.9	15
	10	20	237.1±21.1**	47[+]
21	1	20	155.6±24.6	30
	10	20	114.5±24.0	10
22	1	20	148.5±25.0	30
	10	20	135.9±25.3	20
23	1	20	121.2±22.7	15
	10	20	145.0±24.8	20
Piracetam	1	20	129.0±22.1	15
	10	20	206.8±27.5	55[++]
Pramiracetam	1	20	200.0±22.2	30
	10	20	223.5±20.3*	35

a) Each latency represents the mean±S.E. b) The percentage of good performers per group. * $p<0.05$, ** $p<0.01$: significantly different from control (Student's t-test). + $p<0.05$, ++ $p<0.01$: significantly different from control (Fisher's exact probability test).
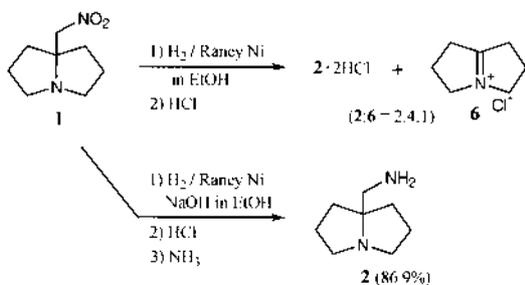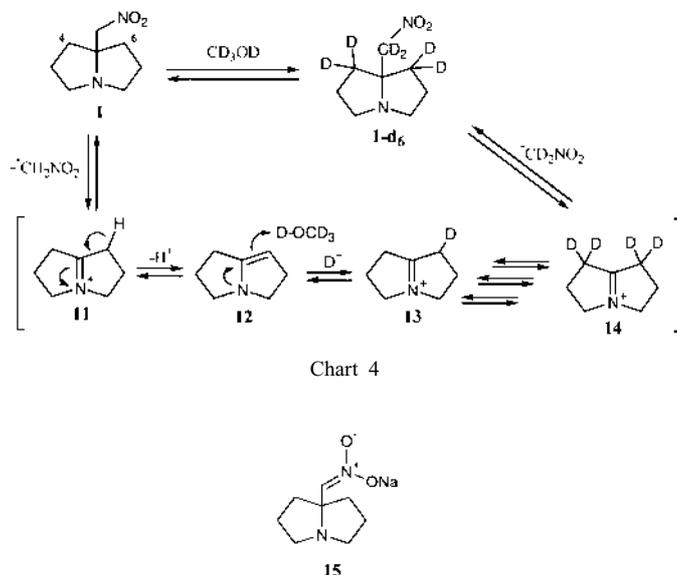
ingly, the reduction of **1** with Raney Ni in the presence of a stoichiometric amount of NaOH afforded **2** in high yield without the formation of **6** (Chart 3). We therefore presume that the conversion of **1** to the sodium salt **15**[11] by NaOH suppresses the shift to **11**. This reduction method using a base could also be applicable to β-aminonitroalkanes.
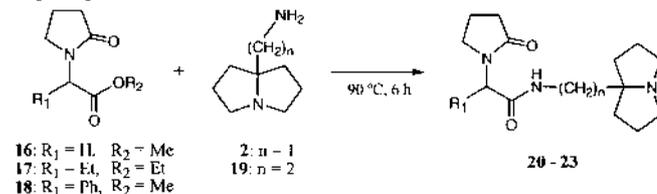
Compound **2** was allowed to react with the 2-oxopyrrolidone derivatives **16**, **17**,[12] and **18**[13] at 90 °C to give **20**, **21**, and **22**, respectively. Compound **23** was obtained by heating a mixture of **16** and **19**[14] (Table 1).

Pharmacological Results and Discussion

The step-through passive avoidance tests were performed with mice to determine the effects of the test compounds on memory retrieval (Table 2). Both latency and % retention in the test differed significantly between the sham operation group and the cycloheximide-treated control group. Both decreases were significantly reversed by the administration of 10 mg/kg of **20**. The administration of 10 mg/kg of piracetam reversed the % retention significantly, and that of pramiracetam reversed the latency, respectively. Compounds **21**, **22**, and **23** had no effect in this model.

Further, the effect of **20** on cerebral energy metabolism was clarified compared with that of pramiracetam, aniracetam, and piracetam using spontaneously hypertensive rats (SHR) exhibiting cerebral ischemia induced by bilateral carotid ligation (BLCL).[15] As shown in Table 3, the concentrations of ATP and the ratios of lactate concentration to pyruvate concentration (L/P) differed significantly between the sham operation group and the saline-treated control group with BLCL. The oral administration of 3 mg/kg or 10 mg/kg of **20** caused a significant increase in the concentrations of ATP compared with the control group. The concentrations of lactate and the L/P ratios in the **20**-treated group remained at lower levels than in the control group. In contrast, the administration of pramiracetam and aniracetam caused a slight increase in the concentrations of ATP and slight decreases in the L/P ratios. The administration of 10 mg/kg of piracetam was also not significantly effective in the same test (Table 4).

These results indicate that **20** ameliorates memory disturbance and that the effects on energy metabolism in cases of cerebro-vascular accident are superior to those of pramiracetam, aniracetam, and piracetam. Compound **20** can therefore be expected to function as a therapeutic agent for multiinfarct dementia.

In conclusion, we have developed a convenient synthetic method for the novel compound **1**. The reduction of **1** to **2** was improved based on the observation of the deuteration of **1**. This method may be readily applicable to large-scale pro-

Table 3. Effects of **20** on Cerebral Metabolism in SHR with Brain Ischemia Induced by Bilateral Common Carotid Artery Ligation (BLCL)[a]

Treatments	Dose (mg/kg, *p.o.*)	n	ATP (μmol/g)	Lactate (μmol/g)	Pyruvate (μmol/g)	Ratio (L/P)
Sham operation		5	1.54±0.09**	2.04±0.79	365.5±8.4	5.68±2.17*
Control		6	0.65±0.23	10.50±4.26	351.9±30.1	41.07±14.26
20	3	6	1.35±0.18*	7.54±2.96	308.9±30.4	21.68±7.80
	10	6	1.53±0.14**	2.47±0.75	408.1±65.5	6.27±1.63
Pramiracetam	3	5	1.21±0.30	6.87±1.77	360.9±31.8	18.25±3.46
	10	5	1.11±0.25	6.04±2.63	410.1±37.9	13.80±5.64
Aniracetam	10	6	0.89±0.19	6.77±2.04	320.6±45.7	23.49±8.10
	30	5	1.07±0.25	9.23±1.91	351.7±21.7	25.88±4.77

a) Each value represents mean±S.E. * $p < 0.05$, ** $p < 0.01$: significantly different from control (Student's *t*-test).

Table 4. Test for Piracetam on Cerebral Metabolism in SHR with Brain Ischemia Induced by Bilateral Common Carotid Artery Ligation (BLCL)[a]

Treatments	Dose (mg/kg, *p.o.*)	n	ATP (μmol/g)	Lactate (μmol/g)	Pyruvate (μmol/g)	Ratio (L/P)
Sham operation		5	1.88±0.02**	1.80±0.14***	379.8±8.2**	4.75±0.44**
Control		4	0.70±0.24	29.04±2.01	543.7±36.1	54.65±6.99
Piracetam	1	5	1.38±0.34	20.35±6.40	412.2±95.0	44.53±6.95
	10	6	1.37±0.31	16.03±5.26	341.0±99.7	62.68±29.78

a) Each value represents mean±S.E. ** $p < 0.01$, *** $p < 0.001$: significantly different from control (Student's *t*-test).

duction. Piracetam analog **20** involving **2** showed satisfactory bioactivity. The 1-azabicyclo[3.3.0]octane moiety might therefore successfully interact with the biopolymer. Additional applications of intermediate **2** to various bioactive substances might cause increases in the activities of these substances.

Experimental

Melting points were measured on a Yanagimoto micromelting point apparatus and were uncorrected. Infrared (IR) spectra were obtained on a JASCO FT/IR-8000, ^{1}H-NMR spectra on a JEOL JNM-GSX 270 spectrometer (270 MHz for ^{1}H and 68 MHz for ^{13}C) using tetramethylsilane as an internal standard; mass spectra were obtained on a JEOL JMS-DX 300 spectrometer; and elemental analyses for C, H, and N were obtained on a Yanaco CHN Analyzer MT-5.

5-Nitromethyl-1-azabicyclo[3.3.0]octane (1) and 5-cyclopropyl-3,4-dihydro-2H-pyrrole (10) A solution of **4** (4.79 g, 26.2 mmol) and nitromethane (6.40 g, 0.105 mol) in MeOH (2.8 ml) was saturated with ammonia gas at 20 °C, followed by stirring for 24 h. The reaction mixture was concentrated, made basic with 0.1 N NaOH, and extracted with methylene chloride. The organic extract was dried over sodium sulfate and concentrated *in vacuo*. Chromatography of the residue on silica gel (CH$_2$Cl$_2$/MeOH=30 : 1) afforded 2.94 g (66.0%) of **1** and 0.307 g (10.8%) of **10** as pale yellow oils, respectively. **1**: ^{1}H-NMR (CDCl$_3$) δ: 1.59—1.96 (6H, m, 3, 7-CH$_2$ and two protons of 4, 6-CH$_2$), 2.10—2.19 (2H, m, two protons of 4, 6-CH$_2$), 2.56—2.66 and 3.01—3.09 (4H, m, 2, 8-CH$_2$), 4.27 (2H, s, CH$_2$NO$_2$). ^{13}C-NMR (CDCl$_3$) δ: 25.33 (C3, C7), 36.00 (C4, C6), 55.48 (C2, C8), 72.75 (C5), 82.96 (CH$_2$NO$_2$). IR (neat) cm^{-1}: 2958 (C-H), 1547 (NO$_2$). MS (EI) *m/z*: 170 (M$^+$). HRMS (EI) Calcd for C$_8$H$_{14}$N$_2$O$_2$ (M$^+$) *m/z*: 170.1055. Found 170.1071. **10**: ^{1}H-NMR (CDCl$_3$) δ: 0.82—0.87 (4H, m, CH$_2$ of cyclopropane), 1.77—1.91 (3H, m, 3-CH$_2$ and CH of cyclopropane), 2.32—2.38 (2H, m, 4-CH$_2$), 3.75—3.80 (2H, m, 2-CH$_2$). ^{13}C-NMR (CDCl$_3$) δ: 7.16 (CH$_2$ of cyclopropane), 14.06 (CH of cyclopropane), 22.35 (C3), 34.68 (C4), 60.45 (C2), 179.72 (C5). IR (neat) cm^{-1}: 1460 (C=N). MS (EI) *m/z*: 109 (M$^+$). HRMS (EI) Calcd for C$_7$H$_{11}$N (M$^+$) *m/z*: 109.0891. Found 109.0880.

5-Aminomethyl-1-azabicyclo[3.3.0]octane (2) To a solution of **1** (1.00 g, 5.88 mmol) and NaOH (0.235 g, 5.88 mmol) in ethanol (5 ml), was added 0.40 g of Raney nickel and the mixture was placed under hydrogen at 20 °C for 12 h. After filtration, the filtrate was poured into 5.0 ml of 33% HCl-isopropanol solution below 20 °C. The mixture was concentrated, and the HCl salt of **2** was recrystallized from the mixed solvent of ethanol and isopropanol. Excess ammonia gas was introduced into the suspension of the salt in ether, and the solution was then stirred at 20 °C for a few hours. The precipitate was filtered off, and the filtrate was concentrated to afford 716 mg

(86.9%) of **2** as a colorless oil. ^{1}H-NMR (CDCl$_3$) δ: 1.40 (2H, br, NH$_2$), 1.49—1.82 (8H, m, 3, 4, 6, 7-CH$_2$), 2.53 (2H, s, CH$_2$NH$_2$), 2.53—2.65 and 2.93—3.01 (4H, m, 2, 8-CH$_2$). ^{13}C-NMR (CDCl$_3$) δ: 24.93 (C3, C7), 35.90 (C4, C6), 51.10 (CH$_2$NH$_2$), 55.49 (C2, C8), 73.98 (C5). IR (neat) cm^{-1}: 3380 (N-H), 2950 (C-H). MS (CI) *m/z*: 141 (M+H)$^+$. Calcd for C$_{18}$H$_{16}$N$_2$·2HCl: C, 45.08; H, 8.51; N, 13.14. Found: C, 45.22; H, 8.39; N, 13.38.

N-[(1-Azabicyclo[3.3.0]octan-5-yl)methyl]-2-oxo-1-pyrrolidineacetamide (20) A mixture consisting of **16** (14.1 g, 89.6 mmol) and **2** (11.4 g, 81.4 mmol) was stirred under argon at 90 °C for 6 h. The resulting mixture was concentrated and then purified by chromatography on aluminum oxide (CH$_2$Cl$_2$/MeOH) to give an oil. The oil was converted to the terephthalate by heating with terephthalic acid (13.5 g, 81.4 mmol) in EtOH (2000 ml). EtOH was removed until the solution reached a volume of approximately 700 ml. The precipitate was dissolved in NaOH solution and extracted with dichloromethane. The organic layer was dried over MgSO$_4$, and the solvent was evaporated to give 15.5 g (73.4%) of **20** as a pale yellow oil. ^{1}H-NMR (CDCl$_3$) δ: 1.5—1.9 (8H, m, 3, 4, 6, 7-CH$_2$ of azabicyclooctane), 2.10 (2H, quintet, $J=7.8$ Hz, 4-CH$_2$ of oxopyrrolidine), 2.45 (2H, t, $J=7.8$ Hz, 3-CH$_2$ of oxopyrrolidine), 2.57—2.66 and 2.95—3.01 (each 2H, m, 2, 8-CH$_2$ of azabicyclooctane), 3.19 (2H, d, $J=5.4$ Hz, CONHCH$_2$), 3.50 (2H, t, $J=7.8$ Hz, 5-H of oxopyrrolidine), 3.94 (2H, s, NCH$_2$CONH), 6.65 (1H, brs, NH). IR (neat) cm^{-1}: 3308 (N-H), 1669 (C=O). MS (CI) *m/z*: 266 (M+H)$^+$. *Anal.* Calcd for C$_{14}$H$_{23}$N$_3$O$_2$·C$_8$H$_6$O$_4$ (terephthalate): C, 61.24; H, 6.77; N, 9.74. Found: C, 61.19; H, 6.91; N, 9.58.

N-[(1-Azabicyclo[3.3.0]octan-5-yl)methyl]-α-ethyl-2-oxo-1-pyrrolidineacetamide (21) By using a similar procedure as described for **20**, compound **21** was prepared from **17** and **2** as a pale yellow oil. ^{1}H-NMR (CDCl$_3$) δ: 0.89 (3H, t, $J=7.3$ Hz, CH$_3$CH$_2$), 1.52—1.83 (10H, m, 3, 4, 6, 7-CH$_2$ of azabicyclooctane and CH$_3$CH$_2$), 1.94—2.08 (2H, m, 4-CH$_2$ of oxopyrrolidine), 2.38 (2H, m, 3-CH$_2$ of oxopyrrolidine), 2.54—2.61 and 2.92—3.00 (each 2H, m, 2, 8-CH$_2$ of azabicyclooctane), 3.13 (2H, d, $J=5.4$ Hz, CONHCH$_2$), 3.38—3.49 (2H, m, 5-CH$_2$ of oxopyrrolidine), 4.43 (H, dd, $J=8.8$, 6.8 Hz, NCHCONH), 6.49 (1H, brs, NH). IR (neat) cm^{-1}: 3316 (NH), 1658 (C=O). MS (CI) *m/z*: 294 (M+H)$^+$. *Anal.* Calcd for C$_{16}$H$_{27}$N$_3$O$_2$·C$_8$H$_6$O$_4$ (terephthalate): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.49; H, 7.41; N, 9.18.

N-[(1-Azabicyclo[3.3.0]octan-5-yl)methyl]-α-phenyl-2-oxo-1-pyrrolidineacetamide (22) By using a similar procedure as described for **20**, compound **22** was prepared from **18** and **2** as colorless prisms. mp: 110—112 °C. ^{1}H-NMR (CDCl$_3$) δ: 1.45—1.81 (8H, m, 3, 4, 6, 7-CH$_2$ of azabicyclooctane), 1.81—2.13 (2H, m, 4-CH$_2$ of oxopyrrolidine), 2.31—2.52 (2H, m, 3-CH$_2$ of oxopyrrolidine), 2.31—2.50 and 3.73—3.82 (each 1H, m, 5-CH$_2$ of oxopyrrolidine), 2.50—2.70 and 2.88—3.07 (each 2H, m, 2, 8-CH$_2$ of azabicyclooctane), 3.13 and 3.24 (each 1H, dd, $J=13.2$, 5.9 Hz, CONHCH$_2$), 5.81 (1H, s, NCHCONH), 6.32 (1H, brs, NH), 7.36 (5H, s, aro-

matic H). IR (neat) cm^{-1}: 3318 (NH), 1660 (C=O). MS (CI) *m/z*: 342 (M+H)$^+$. *Anal.* Calcd for $C_{20}H_{27}N_3O_2 \cdot 2/3(C_8H_6O_4)$ (terephthalate): C, 67.28; H, 6.91; N, 9.29. Found: C, 67.23; H, 7.11; N, 9.33.

***N*-[2-(1-Azabicyclo[3.3.0]octan-5-yl)ethyl]-2-oxo-1-pyrrolidineacetamide (23)** By using a similar procedure as described for **20**, compound **23** was prepared from **16** and **19** as a pale yellow oil. ^{1}H-NMR (CDCl$_3$) δ: 1.58—1.82 (10H, m, 3, 4, 6, 7-CH$_2$ of azabicyclooctane and CONHCH$_2$CH$_2$), 2.09 (2H, quintet, *J*=7.8 Hz, 4-CH$_2$ of oxopyrrolidine), 2.44 (2H, t, *J*=7.8 Hz, 3-CH$_2$ of oxopyrrolidine), 2.55—2.63 and 2.90—2.98 (each 2H, m, 2, 8-CH$_2$ of azabicyclooctane), 3.35—3.40 (2H, m, CONHCH$_2$CH$_2$), 3.47 (2H, t, *J*=7.8 Hz, 5-CH$_2$ of oxopyrrolidine), 3.92 (2H, s, NCH$_2$CONH), 8.83 (1H, brs, NH). IR (neat) cm^{-1}: 3294 (NH), 1668 (C=O). MS (CI) *m/z*: 280 (M+H)$^+$. *Anal.* Calcd for $C_{15}H_{25}N_3O_2 \cdot C_6H_3N_3O_7$ (picrate): C, 49.60; H, 5.55; N, 16.53. Found: C, 49.51; H, 5.54; N, 16.53.

Reference Compounds Pramiracetam and aniracetam were synthesized at our laboratory, and piracetam was purchased from Sigma-Aldrich.

Step-through Passive Avoidance Tests in Mice ICR mice weighing 24—40 g were used for the passive avoidance cycloheximide model. The training apparatus consisted of two compartments (light and dark) with a small gateway between them. The floor of the dark compartment was made of a grid through which a foot shock was delivered with a shock generator-scrambler. Mice were placed in the light compartment. Immediately after a mouse would step through to the dark compartment, a foot shock would be delivered until the mouse returned to the light compartment (acquisition trial). Twenty-four hours after the training, the mice were again placed into the light compartment, and the latency period for the mice to enter the dark compartment (step-through latency) was recorded up to 300 seconds (retention test). Compounds **20**—**23** with equimolar fumaric acid were dissolved in saline and administered *p.o.* (1 or 10 mg/kg) 30 minutes before the acquisition trial, respectively. Piracetam and pramiracetam dissolved in saline were administered in the same manner, respectively. Cycloheximide was administered i.p. (120 mg/kg) 15 minutes before the acquisition trial. The sham operation group received two injections of saline.

Measurement of Cerebral Metabolites in Rats Spontaneously hypertensive rats, each of which weighed 340 to 410 g, were anesthetized with ether. Bilateral common carotid arteries were exposed and simultaneously double-ligated. One hour after the operation, oral administrations (5 ml/kg) were performed. Compound **20** with equimolar fumaric acid dissolved in water was administered; pramiracetam and piracetam dissolved in water were administered, respectively; or aniracetam dissolved in 5% gum arabic solution was administered. For the sham-operated group and the control group, saline was administered. Four hours after the administrations, each of the animals was irradiated with microwaves (Toshiba Microwave Applicator, 5.0 kW output for 1.5 sec). The cortex portion of each brain was isolated and used for the measurement of concentrations of ATP, lactate, and pyruvate. The concentrations of ATP, lactate, and pyruvate were determined by an ATP test, Lactate test, and Pyruvate test (Boehringer Mannheim), respectively.

References and Notes
1) Gouliaev A. H., Senning A., *Brain Res. Rev.*, **19**, 180—222 (1994).
2) L'Italien Y. J., Nordin I. C., *Ger. Offen.*, DE 2808067 (1978) [*Chem. Abstr.*, **90**, 22798*b* (1979)].
3) Hoffmann-La Roche, F. und Co. A.-G., *Jpn. Kokai*, 79 117468 (1979) [*Chem. Abstr.*, **92**, 41755*t* (1980)].
4) Miyano S., Shima K., Hayashimatsu M., Satoh F., Sumoto K., *J. Pharm. Sci.*, **76**, 416—418 (1987); Kakigami T., Usui T., Ikami T., Tsukamoto K., Miwa Y., Taga T., Kataoka T., *Chem. Pharm., Bull.*, **46**, 1039—1043 (1998); Suzuki T., Oka M., Maeda K., Furusawa K., Uesaka H., Kataoka T., *Chem. Pharm., Bull.*, **47**, 28—36 (1999).
5) Miyano S., Fujii S., Yamashita O., Toraishi N., Sumoto K., *J. Heterocyclic Chem.*, **19**, 1465—1468 (1982); Miyano S., Yamashita O., Sumoto K., Shima K., Hayashimatsu M., Satoh F., *J. Heterocyclic Chem.*, **24**, 47—49 (1987).
6) Oka M., Matsumoto Y., Unno R., *Heterocycles*, **45**, 1447—1450 (1997).
7) Our unpublished data suggest that the reaction time is related to the ammonia concentration, while the yield of byproduct **10** is related to the ratio of nitromethane to ammonia. The optimum conditions for mass production are shown in the experimental section.
8) Bradford P. M., Kenneth B. L., Marc L., Brent R. L., *J. Org. Chem.*, **39**, 1963—1965 (1963).
9) Iminium chloride **6** was identified by a comparison of the ^{1}H-NMR spectrum of the mixture with that of already-known iminium perchlorate: Miyano S., Somehara T., Nakao M., Sumoto K., *Synthesis*, **1978**, 701—702.
10) The peak area for the methylene group at the α-position in relation to the nitro group was reduced by approximately half immediately after the dissolution of **1** in deuterated methanol, and disappeared after 24 h. The signals at 2.08—2.18 ppm corresponding to 2.10—2.19 ppm in CDCl$_3$ disappeared, and the area of signals in 1.65—1.97 ppm corresponding to 1.59—1.96 ppm in CDCl$_3$ was decreased enough for two protons after 24 h.
11) Sodium salts of nitroalkanes appear as intermediates in the Nef Reaction: Pinnick H. W., *Org. React.*, **38**, 655—792 (1990).
12) Valenta V., Sindelar K., Holubek J., Ryska M., Krejci I., Dlabac A., Protiva M., *Collect. Czech. Chem. Commun.*, **55**, 1613—1629 (1990).
13) Ichikawa K., Ito T., *Jpn. Kokai*, 76 41353 (1976) [*Chem. Abstr.*, **85**, 159870*k* (1976)].
14) Oka M., Baba K., Suzuki T., Matsumoto Y., *Heterocycles*, **45**, 2317—2320 (1997); Suzuki T., Usui T., Oka M., Suzuki T., Kataoka T., *Chem. Pharm. Bull.*, **46**, 1265—1273 (1998).
15) Fujishima M., Sugi T., Omae T., *The Japanese Journal of Clinical and Experimental Medicine*, **51**, 3532—3536 (1974).