counts from the filters. Ligands were obtained from DuPont/New England Nuclear (Boston, MA). Haloperidol, poly(ethylenimine), and Tris were obtained from Sigma Chemicals (St. Louis, MO). Cyclazocine and levallorphan were obtained from the National Institute on Drug Abuse (Rockville, MD).

Behavioral Assays. Male Sprague-Dawley rats were placed individually into cages and allowed to acclimate to the new environment for at least 1 h. Drugs were dissolved in saline or sodium acetate buffer and administered such that 1 mL/kg was administered ip or sc, or 5 μL/rat was administered icv. The animals were rated by using a scale described by Sturgeon et al.,[35] and the ratings determined at the time of peak effect were used to generate dose-response curves. Briefly, the stereotyped behavioral rating is as follows: (0) inactive or in-place nonrepetitive activity, (1) sniffing, grooming, or rearing more frequently than the control; (2) nondirectional movements, occasional reciprocal forepaw treading, frequency of sniffing, rearing and grooming greater than (1); (3) turning or backpeddling; (4) rapid and continuous turning, backpeddling, assuming a praying posture and gagging; and (5) dyskinetic extension and flexion of limbs, head and neck, weaving greater than (4). The ataxial rating scale is as follows: (0) inactive or coordinated movements; (1) awkward or jerky movements or loss of balance while rearing; (2) moderate rate of falling; (3) frequent falling or partial impairment of antigravity reflexes; (4) cannot move beyond a small area, may support weight on stomach or haunches; and (5) unable to move except for twitching movements. A rating of 5 was considered a 100% response. Ratings for each animal were taken every 5 min after drug administration until ratings returned to control level. The ratings taken at the time of peak effect were used to evaluate the potency of each drug. ED_{50} values were determined by using a computerized Finney analysis.[36]

(35) Sturgeon, R. D.; Sessler, R.; Meltzer, H. Y. *Eur. J. Pharmacol.* **1979**, *59*, 169-179.

(36) Finney, D. J. *Statistical Methods in Biological Assay*, 2nd ed.; Hafner Publishing Co.: New York, 1964.

Potent Anticonflict Activity and Lessening of Memory Impairment with a Series of Novel [1]Benzothieno[2,3-*c*]pyridines and 1,2,3,4-Tetrahydro[1]benzothieno[2,3-*c*]pyridines†

Hiromu Kawakubo,*,‡ Katuya Okazaki,‡ Tadasi Nagatani,§ Katuyuki Takao,§ Shinichi Hasimoto,§ and Taisuke Sugihara§

Department of Medicinal Chemistry, Bioscience Laboratory, Institute of Life Science, Asahi Chemical Industry Company, Ltd., Asahi-Machi 6-2700, Nobeoka, Miyazaki 882, Japan. *Received August 14, 1989*

[1]Benzothieno[2,3-*c*]pyridines (**10a-c**, **11**, **12a-t**, and **13a,b**) and 1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridines (**3a-c**, **7**, **8a-c**, and **9**) were synthesized. The compounds are bioisosteres of β-carbolines and 1,2,3,4-tetrahydro-β-carbolines where the indole nitrogen is replaced by sulfur. Their pharmacological activity was evaluated in a water lick conflict test in rats and a passive avoidance test in mice. In the 1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridine series, the presence of ethyl ester (**3b**) or cyclohexyl carboxamide (**7**) groups at C-3 conferred good anticonflict activity and lessening of memory impairment, while N-acylation of **3b** abolished activity. In the [1]benzothieno[2,3-*c*]pyridine series, the aminoethyl carboxamide (**12a**) group at C-3 also conferred activity, but other amides studied were not active. The most potent compounds (**3b**, **7**, and **12a**) were also administered orally and had potent anticonflict and antiscopolamine amnesia-reversal activity. These compounds did not bind to the BZP receptor in spite of having structures similar to those of β-carbolines. Compound **7** bound strongly to 5-HT_{1A} receptors and would be expected to be a novel anxiolytic.

Introduction

Benzodiazepines have been widely used for the treatment of anxiety. They produce their pharmacological effects by interacting with central BZP receptors.[1] Whereas BZPs are safe and effective drugs, they produce sedation and muscle relaxation which may be undesirable in certain situations and potentiate the action of CNS depressants.[2] In addition, an amnesia[3,4] following their administration has been observed in men and experimental animals. Recently β-carbolines have been reported to be modulators[5,6] of anxiety states in the brain. β-Carboline methyl ester has been classified as an inverse agonist and reported to exert a proconflict effect.[7,8] In contrast, β-carbolines have been shown to produce a syndrome reminiscent of anxiety.[9,10]

In this paper, we report our successful efforts to design selective anxiolytics by structural modification of β-carboline to afford [1]benzothieno[2,3-*c*]pyridines. We describe the synthesis of novel [1]benzothieno[2,3-*c*]pyridines and 1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridines as well as their anticonflict activities, lessening of memory impairments, and structure-activity relationships. Interestingly the most potent compounds (**3b**, **7**, and **12a**) were different from BZP in that they did not bind to the

† Abbreviations: 5-HT, serotonin; BZP, benzodiazepine; CNS, central nervous system; DPPA, diphenyl phosphorazidate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

‡ Synthetic Section.

§ Pharmacological Section.

(1) Braestrup, C.; Squires, R. F. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 3805-3809.

(2) Malick, J. B. *Neuropsychopharmacological Drug Development in Drug Discovery and Development*; Williams, M., Malick, J. B., Eds.; 1987; pp 115-149.

(3) Ghoneim, M. M.; Mewaldt, S. P. *Psychopharmacologia* **1975**, *44*, 257-262.

(4) Komiskey, H. L.; Cook, T. M.; Lin, C. F.; Hayton, W. I. *Psychopharmacology* **1981**, *73*, 304-305.

(5) Prado de Carvalho, L.; Grecksch, G.; Chapouthier, G.; Rossier, J. *Nature* **1983**, *301*, 64-66.

(6) Petersen, E. N.; Jensen, L. H. *Eur. J. Pharmacol.* **1984**, *103*, 91-97.

(7) Nagatani, T.; Yamamoto, T.; Sugihara, T.; Ueki, S. *Jpn. J. Pharmacol.* **1988**, *46*, 267-274.

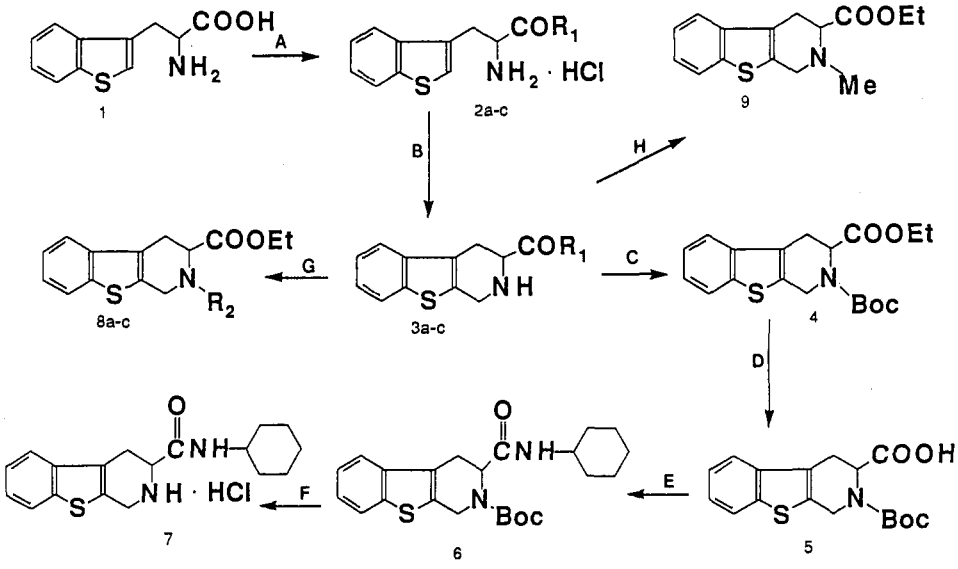
(8) Polc, P.; Bonetti, E. P.; Schaffner, R.; Haefely, W. *Arch. Pharmacol.* **1982**, *321*, 260-264.

(9) Ninan, P. T.; Insel, T. M.; Cohen, R. M.; Cook, J. M.; Skolnick, P.; Paul, S. M. *Science (Washington, D.C.)* **1982**, *218*, 1332-1334.

(10) Dorow, R.; Horowski, R.; Paschelke, G.; Amin, M.; Braestrup, C. *Lancet* **1983**, *2*, 98-99.

0022-2623/90/1833-3110$02.50/0

Scheme I[a]



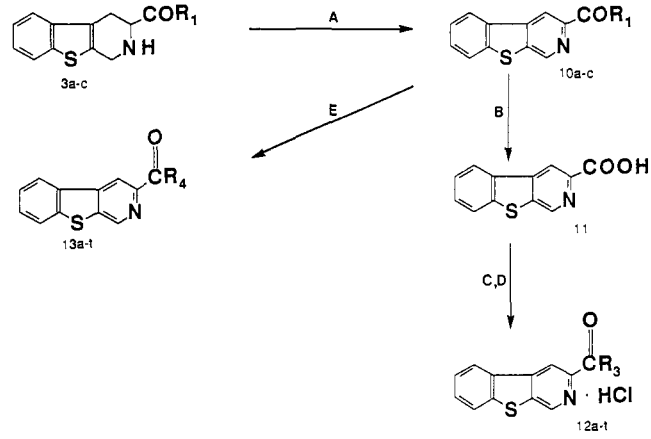
[a] (A) $SOCl_2/R_1H$, (B) 30% HCHO/EtOH-H_2O/$NaHCO_3$, (C) 2-[(*tert*-butoxycarbonyl)thio]-4,6-dimethylpyrimidine/THF, (D) NaOH/MeOH/H^+, (E) cyclohexylamine/DPPA/NEt_3-DMF, (F) 1 N HCl/AcOEt, (G) $R_2Cl/NEt_3/CHCl_3$, (H) MeI/DBU/THF.

central BZP receptor in spite of the structural similarities to β-carboline. Compound **7** bound strongly to the 5-HT_{1A} receptor. Compound **7** has a quite different chemical structure from those of buspirone[11] and ipsapirone[12] which bind to the 5-HT_{1A} receptor.

Chemistry

We synthesized novel 1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridines (**3a–c**, **7**, **8a–c**, and **9**) and [1]benzothieno[2,3-*c*]pyridines (**10a–c**, **11**, **12a–t**, and **13a,b**) which arre bioisosteres of the corresponding tetrahydro-β-carboline and β-carboline derivatives. The methods for preparation of 1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]-pyridines as well as some of their biochemical activities have been already reported.[13] Scheme I shows our synthetic routes to 3-substituted 1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridines (**3a–c** and **7**) and *N*-acyl (**8a–c**) and *N*-methyl (**9**) analogues of ethyl ester **3b**. The esters **2a–c** were synthesized by using the standard procedure[14,15] from amino acid **1**.[16] 1,2,3,4-Tetrahydro[1]benzothieno[2,3-*c*]pyridines **3a–c** were obtained from **2a–c** according to the standard procedure of Pictet–Spengler isoquinoline synthesis.[17-19] Treatment of **3b** with 2-[(*tert*-butoxycarbonyl)thio]-4,6-dimethylpyrimidine in THF gave **4**, which was hydrolyzed with NaOH solution in $CHCl_3$/EtOH to give *N*-Boc acid **5**. Acid **5** was converted to **6** by reaction with cyclohexylamine in the presence of DPPA/NEt_3. Cyclohexyl carboxamide **7** was obtained by treatment of **6** with 1 N HCl in AcOEt. Compounds **8a–c** were synthesized from **3b** with acyl halides and NEt_3 in $CHCl_3$. Compound **9** were synthesized from the reaction of **3b** with MeI. Scheme II illustrates our synthetic routes to novel 3-substituted [1]benzothieno[2,3-*c*]pyridines (**10a–c**, **11**, **12a–t**, and **13a,b**). Dehydrogenation[20] of **3a–c** with S in xylene produced **10a–c**. The ethyl ester **10b** was treated with 5 N NaOH and citric acid to give **11**. The reaction of **11** with the various amines DPPA followed by treatment with 1 N HCl in AcOEt gave **12a–t**. Carboxamide **13a** was synthesized from **10b** according to the standard amide synthesis.[21] Hydrazide **13b** was synthesized from the reaction of **10b** with NH_2NH_2·2HCl in MeOH.

Scheme II[a]



[a] (A) S/Xylene, (B) NaOH/MeOH/H^+, (C) R_3H/DPPA/NEt_3/DMF, (D) 1 N HCl/AcOEt, (E) R_4H/EtOH or MeOH.

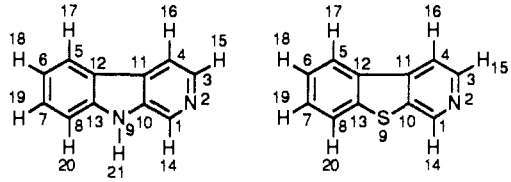
Pharmacological Methods

Anticonflict activity was evaluated with a water lick conflict test[22] using groups of six male Wistar rats. The procedure is described in the Experimental Section.

Lessening of memory impairment was evaluated with a passive avoidance test[3,4] using groups of 10 male ddy

(11) Hibert, M. F.; Mcdermott, I.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *Eur. J. Med. Chem.* **1989**, *24*, 31-37.
(12) Dompert, W. U.; Glaser, T.; Traber, J. *Arch. Pharmacol.* **1985**, *328*, 467-470.
(13) Clineschmidt, B. V.; Reiss, D. R.; Pettibone, D. J.; Robinson, J. L. *Pharmacol. Exp. Ther.* **1985**, *235* (*3*), 696-708.
(14) Weissberger, A.; Kibler, C. J. *Organic Syntheses* Wiley: New York, Collect. Vol. 4., p 610.
(15) Peterson, M. L.; Way, J. W. *Ind. Eng. Chem.* **1958**, *50*, No. 9, 1335.
(16) Yabe, Y.; Muira, C.; Horikoshi, H.; Baba, Y. *Chem. Pharm. Bull.* **1976**, *24* (*12*), 3149.
(17) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.
(18) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151.
(19) Ong, H. H.; May, E. L. *J. Heterocycl. Chem.* **1971**, *8*, 1007.
(20) Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Crawley, J. N.; Paul, S. M.; Skolnick, P. *J. Med. Chem.* **1982**, *25*, 1081.
(21) Aspinall, S. R. *J. Am. Chem. Soc.* **1941**, *63*, 852.
(22) Vogel, J. R.; Beer, B.; Clody, D. E. *Psychopharmacologia* **1971**, *21*, 1-7.

Table I. Physical Properties[a] of the Skeleton for β-CCP and 10c



	atomic posn	β-CCP	10c
ionization energy (eV)		7.9385	7.8003
total energy (e)		-1910	-1888
dipole moment (debye)		2.824	2.154
electron density (eV)	1	0.0334	0.1118
	2	-0.1398	-0.1549
	3	0.0533	0.0964
	4	-0.0236	-0.0415
	5	0.0122	-0.0054
	6	-0.0329	0.0067
	7	0.0195	0.0010
	8	-0.0620	0.0164
	9	-0.0933	-0.1393
	10	0.1017	-0.0169
	11	0.0054	0.0821
	12	-0.0233	0.0502
	13	0.1339	0.0150
	14	-0.0125	-0.0068
	15	-0.0118	-0.0072
	16	-0.0032	-0.0019
	17	-0.0040	-0.0025
	18	-0.0087	-0.0044
	19	-0.0088	-0.0031
	20	-0.0010	0.0041
	21	0.0705	

[a] The computer used was a VAX-11/780. The calculated method was the CNDO method. The software used was CHEMLAB-II.

mice. The procedure is described in the Experimental Section.

BZP receptor affinity[23] was measured with [^{3}H]flunitrazepam and a receptor preparation obtained from cerebral cortex of Wistar rats. The procedure is described in the Experimental Section.

Result and Discussion

Structure–Activity Relationships. Tables II–IV show melting points, yields, structural formulas, and synthetic routes as well as anticonflict activities and lessening of memory impairments of our compounds. Table II lists 1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridines having an ester or *N*-cyclohexylamide group at C-3. Table III lists *N*-acyl and *N*-methyl analogues of the ethyl ester **3b**. Table IV lists all of the [1]benzothieno[2,3-*c*]pyridines. The biological results show that the activity is strongly dependent on the chemical structure of the compounds. This is summarized below.

(1) In a series of 3-substituted 1,2,3,4-tetrahydro[1]-benzothieno[2,3-*c*]pyridines, the ethyl ester **3b** and cyclohexyl carboxamide **7** were the most potent compounds while the methyl (**3a**) and propyl (**3c**) esters were not active (Table II). (2) Several *N*-acyl derivatives **8a–c** of ethyl ester **3b** were inactive while the *N*-methyl derivative **9** appeared to have slight anticonflict activity (Table III). (3) In the 3-substituted [1]benzothieno[2,3-*c*]pyridine series, several esters **10a–c** and carboxylic acid **11** were virtually inactive (Table IV). (4) In the same series, aminoethyl carboxamide **12a** was very active. However, aminopropyl carboxamide **12b** and (dimethylamino)ethyl carboxamide **12c** were not active (Table IV). (5) In the same series, among amides **12d–l** derived from diazacycloalkanes, only **12g** and **12i** had anticonflict activities (Table IV). (6) In the same series, amides obtained from piperidines (**12m,o**), morpholine (**12n**), or simple alkyl amines (**12p–t** and **13a,b**) were virtually inactive (Table IV).

The most active compounds (**3b**, **7**, and **12a**) were examined following oral administration for anticonflict activity in the water lick conflict test where they were as effective but somewhat less potent than diazepam (Table V). In addition, the ability of compounds (**3b**, **7**, and **12a**) to reverse scopolamine-induced amnesia in a passive avoidance test used to assess memory impairment was also determined. While the compounds were active and increased latency over that seen with diazepam or scopolamine, they did not return latency to that seen in control animals (Table VI).

As shown in Table I, theoretically calculated values of the ionization energy, the total energy, the dipole moment, and the electron density for the skeleton of **10c** are different from those for β-CCP, which is a ligand of the BZP receptor. Ethyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate (TH-β-CCE),[24] **3b**, **7**, **12a**, and **10c** had no affinity for the BZP receptor, while diazepam and propyl β-carboline-3-carboxylate (β-CCP) showed the expected high affinity (Table VII). This difference in binding potential for the BZP receptor may be a partial reason why the most active compounds (**3b**, **7**, and **12a**) were quite different from diazepam in the pharmacological mechanism. Compound **7** was the safest in oral toxicity among the most active compounds (**3b**, **7**, and **12a**). Two main metabolites of **7**, M_1 (1,2,3,4-tetrahydro[1]benzothieno-[2,3-*c*]pyridine-3-carboxylic acid) and M_2 [*N*-([1]benzothieno[2,3-*c*]pyridin-3-ylcarbonyl)glycine] also had no affinity for the BZP receptor (Table VII). The mechanism of action cannot be shown clearly at present. However, it is interesting to note that **7** showed a high affinity for the 5-HT_{1A} receptor ($K_i = 2.8 \times 10^{-7}$ M) in the ordinary measurement method.[25] This characteristic is similar to that of buspirone which was recently known to be a 5-HT_{1A} receptor agonist.[11] Our separate, preliminary study showed that compound **7** tended to increase 5-hydroxyindoleacetic acid, which is a metabolite of 5-HT in the brain of rats. This suggests that compound **7** seems to be a 5-HT_{1A} receptor agonist. Further investigations to elucidate the mechanism are currently in progress.

Experimental Section

All melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. Elemental analyses performed by Yanagimoto MT-3 were obtained for all new compounds and were within ±0.4% of the theoretical values unless otherwise noted. IR spectra were determined with a Hitachi IR-260-10 spectrometer. NMR spectra were recorded on a NEC JMX GX-400 instrument with tetramethylsilane as an internal standard. MS spectra were measured with an NEC 01-SG mass spectrometer. Column chromatography was carried out on silica gel 60 (0.063–0.200 mm, Wako Pure Chemical Industry, Ltd.).

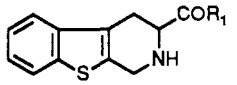
Synthetic Methods. Scheme I. α-Amino-3-[1]benzothiophenepropionic Acid Ethyl Ester Hydrochloride (2b). Thionyl chloride (260 mL, 1.32 mol) was gradually added to dry EtOH (1.5 L) at -10 °C. The mixture was stirred for 30 min at -10 °C. Compound **1** (221.3 g, 1.00 mol) was added to the mixture and stirred for 2 days at room temperature. After EtOH was removed under reduced pressure, Et_2O (500 mL) was added to

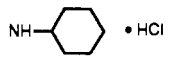
(23) Mohler, H.; Okada, T. *Science (Washington, D.C.)* **1977**, *198*, 849.

(24) Claus, B.; Mogens, N.; Carl, E. O. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2288–2292.

(25) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 301–314.

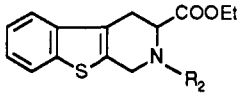
Table II. 3-Substituted 1,2,3,4-Tetrahydro[1]benzothieno[2,3-c]pyridines[a]

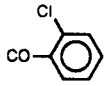
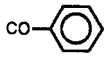


no.	R_1	mp, °C	% yield	formula[b]	synthetic route in Scheme I	anticonflict activity,[c,f]	lessening of memory impairment[d,f]
3a	OCH_3	127–129	64	$C_{13}H_{13}NO_2S$	A, B	17.9 ± 5.1	64.5 ± 11.1
3b	OC_2H_5	163–166	63	$C_{14}H_{15}NO_2S$	A, B	27.2 ± 4.7**	90.5 ± 12.6**
3c	OC_3H_7	208–211	67	$C_{15}H_{17}NO_2S$	A, B	14.5 ± 4.0	57.2 ± 18.7
7		274	30	$C_{18}H_{22}N_2OS$·HCl	C, D, E, F	36.9 ± 7.7**	120.4 ± 32.2**
control						12.6 ± 3.5	43.3 ± 5.0
diazepam[e]						39.4 ± 5.9**	25.1 ± 8.4*

[a] All compounds were racemates. [b] Analyses for C, H, N, S were within ±0.4% of the theoretical values unless otherwise noted. [c] Number of shocks received in 5 min at a dose of 10 mg/kg iv. [d] Time of latency in seconds at a dose of 10 mg/kg iv. [e] Dose of compound in the anticonflict activity and lessening of memory impairment was 3 mg/kg ip. [f] $*p < 0.05$; $**p < 0.01$ (Student's t test).

Table III. 2-Substituted 1,2,3,4-Tetrahydro[1]benzothieno[2,3-c]pyridines[a]



no.	R_2	mp, °C	% yield	formula[b]	synthetic route in Scheme I	anticonflict activity[c,g]	lessening of memory impairment[d,g]
8a		175–176	67	$C_{21}H_{18}ClNO_3S$	G	2.5 ± 0.5	28.1 ± 9.0
8b		125–126	80	$C_{21}H_{19}NO_3S$	G	6.3 ± 2.0	35.1 ± 17.9
8c	$COCH_3$	oil	85	$C_{16}H_{17}NO_3S$	G	NT[e]	37.3 ± 14.7
9	CH_3	147–151	69	$C_{15}H_{17}NO_2S$	H	22.0 ± 3.9*	32.9 ± 11.1
control						12.6 ± 3.5	43.3 ± 5.0
diazepam[f]						39.4 ± 5.9**	25.1 ± 8.4*

[a] All compounds were racemates. [b] Analyses for C, H, N, S were within ±0.4% of the theoretical values unless otherwise noted. [c] Number of shocks received in 5 min at a dose of 10 mg/kg iv. [d] Time of latency in seconds at a dose of 10 mg/kg iv. [e] Not tested. [f] Dose of compound in the anticonflict activity and lessening of memory impairment was 3 mg/kg ip. [g] $*p < 0.05$; $**p < 0.01$ (Student's t test).

the residue. Compound **2b** (259.8 g, 910 mmol) was obtained by filtration in a yield of 91%. MP: 175–175.5 °C. IR (KBr): 1740 cm^{-1}. Anal. ($C_{13}H_{15}NO_2S$·HCl): C, H, N, S.

1,2,3,4-Tetrahydro[1]benzothieno[2,3-*c*]pyridine-3-carboxylic Acid Ethyl Ester (3b). Compound **2b** (116.2 g, 407 mmol) and 30% HCHO (51 mL, 510 mmol) were dissolved in a mixture of EtOH (1 L) and H_2O (1 L) and stirred at 80 °C for 5 h. The reaction mixture was concentrated to about $^1/_2$ its original volume. The pH was adjusted to 10 with $NaHCO_3$. The mixture was extracted with $CHCl_3$ (100 mL × 3). The $CHCl_3$ layer was washed with saturated aqueous brine (50 mL × 2) and dried on Na_2SO_4. $CHCl_3$ was removed under reduced pressure. The residue was recrystallized from a mixture of $CHCl_3$ (100 mL) and Et_2O (100 mL) to provide **3b** (74.2 g, 284 mmol) in a yield of 69%. MP: 163–166 °C. IR (KBr): 2970, 2900, 1720, 1430, 1195, 760, 740 cm^{-1}. NMR (δ, $CDCl_3$): 1.35 (t, J = 5 Hz, 3 H), 2.25 (s, 2 H), 3.10 (d, J = 2.5 Hz, 2 H), 3.70–4.00 (m, 1 H), 4.30 (q, J = 5 Hz, 2 H), 7.30–8.00 (m, 4 H). Anal. ($C_{14}H_{15}NO_2S$): C, H, N, S.

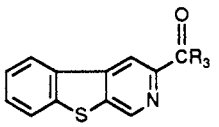
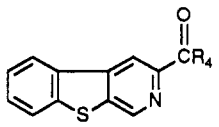
2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridine-3-carboxylic Acid Ethyl Ester (4). Compound **3b** (6.0 g, 23.0 mmol) and 2-[(*tert*-butoxycarbonyl)-thio]-4,6-dimethylpyrimidine (6.63 g, 27.6 mmol) were dissolved in dry THF (30 mL) and stirred at 70 °C for 1 h. The THF solution was concentrated under reduced pressure. The residue was dissolved in AcOEt (300 mL) and the solution was washed with aqueous 10% citric acid solution (50 mL × 2), aqueous 5% $NaHCO_3$ solution (50 mL × 2), and saturated brine (50 mL × 2) and dried on Na_2SO_4. AcOEt was removed under reduced pressure and compound **4** (6.18 g, 17.1 mmol) was recrystallized from a mixture of $CHCl_3$ (60 mL) and petroleum ether (30 mL) in a yield of 74%. MP: 191–194 °C. IR (KBr): 1720, 1695 cm^{-1}. Anal. ($C_{19}H_{23}NO_4S$): C, H, N, S.

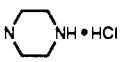
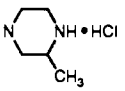
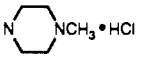
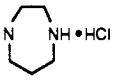
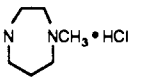
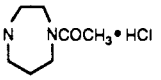
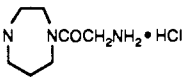
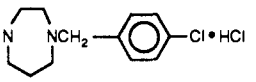
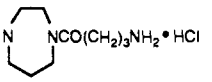
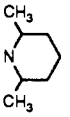
2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridine-3-carboxylic Acid (5). Compound **4** (6.0 g, 16.6 mmol) and 5 N NaOH (6.6 mL, 33 mmol) were dissolved in MeOH (50 mL), stirred at 100 °C for 1 h, and concentrated under reduced pressure. Aqueous 5% citric acid (300 mL) and $CHCl_3$ (300 mL) were added to the residue and shaken. The $CHCl_3$ extract was dried on Na_2SO_4, concentrated, and recrystallized in a mixture of $CHCl_3$ (30 mL) and hexane (30 mL) to give **5** (4.15 g, 12.5 mmol) in a yield of 75%. MP: 210–214 °C. IR (KBr): 1700, 1695 cm^{-1}. Anal. ($C_{17}H_{19}NO_4S$): C, H, N, S.

***N*-Cyclohexyl-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridine-3-carboxamide (6).** Compound **5** (0.33 g, 1.00 mmol) and cyclohexylamine (0.11 g, 1.11 mmol) were dissolved in DMF (5 mL). A solution of DPPA (0.33 g, 1.20 mmol) in DMF (5 mL) and a solution of NEt_3 (0.17 mL, 2.32 mmol) in DMF (2 mL) were added to the solution under cooling and stirred at 0 °C for 1 h and further at 20 °C for 12 h. AcOEt (50 mL) was added to the reaction mixture. The mixture was washed with aqueous 5% citric acid (20 mL × 2), aqueous Na_2CO_3 (20 mL × 2), and saturated brine (20 mL × 2). The AcOEt extract was dried on Na_2SO_4, concentrated, and purified through a silica gel column ($CHCl_3$) to give **6** (0.27 g, 0.65 mmol) in a yield of 65%. MP: 199–201 °C. IR (KBr): 1700, 1680 cm^{-1}. Anal. ($C_{23}H_{30}N_2O_3S$): C, H, N, S.

***N*-Cyclohexyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (7).** Compound **6** (4.30 g, 10.4 mmol) and 1 N HCl in AcOEt solution (10.4 mL) were dissolved in AcOEt (20 mL) and stirred at 80 °C for 1 h. The

Table IV. 3-Substituted [1]Benzothieno[2,3-*c*]pyridines

no.	R_3	R_4	mp, °C	% yield	formula[a]	synthetic route in Scheme II	anticonflict activity[b,i]	lessening of memory impairment[c,i]
10a	OCH_3	–	146–147	89	$C_{13}H_9NO_2S$	A	8.5 ± 3.2	31.6 ± 12.5
10:	OC_2H_5	–	129–130	86	$C_{14}H_{11}NO_2S$	A	10.7 ± 0.8	11.3 ± 3.8
10c	OC_3H_7	–	140–142	86	$C_{15}H_{13}NO_2S$	A	9.6 ± 2.5	22.1 ± 6.6
11	OH	–	227–230	90	$C_{12}H_7NO_2S$	B	4.0 ± 1.1	55.8 ± 22.4
12a	$NH(CH_2)_2NH_2 \cdot HCl$	–	260	64	$C_{14}H_{13}N_3OS \cdot HCl$	B, C, D	37.2 ± 6.9**	103.9 ± 32.0**
12b	$NH(CH_2)_3NH_2 \cdot HCl$	–	265–269	69	$C_{15}H_{15}N_3OS \cdot HCl$	B, C, D	15.2 ± 5.4	37.7 ± 14.1
12c	$NH(CH_2)_2N(CH_3)_2 \cdot HCl$	–	257–259	72	$C_{16}H_{17}N_3OS \cdot HCl$[d]	B, C, D	9.6 ± 1.6	64.5 ± 21.3
12d		–	276–278	69	$C_{16}H_{15}N_3OS \cdot HCl$	B, C, D	17.8 ± 4.0	40.7 ± 7.3
12e		–	241–243	72	$C_{17}H_{17}N_3OS \cdot HCl$	B, C, D	7.6 ± 1.9	40.3 ± 17.3
12f		–	264–266	71	$C_{17}H_{17}N_3OS \cdot HCl$	B, C, D	3.3 ± 1.4	44.2 ± 7.4
12g		–	242–244	80	$C_{17}H_{17}N_3OS \cdot HCl$	B, C, D	21.8 ± 6.2*	38.9 ± 13.2
12h		–	234–238	81	$C_{18}H_{19}N_3OS \cdot HCl$	B, C, D	3.5 ± 1.1	40.3 ± 10.1
12i		–	oil	82	$C_{19}H_{19}N_3O_2S \cdot HCl$[e]	B, C, D	22.2 ± 7.4*	55.0 ± 18.1
12j		–	227–231	83	$C_{19}H_{20}N_4O_2S \cdot HCl$	B, C, D	14.1 ± 6.1	NT[f]
12k		–	164–168	71	$C_{24}H_{22}ClN_3OS \cdot HCl$	B, C, D	12.8 ± 3.8	34.7 ± 7.6
12l		–	210–211	62	$C_{21}H_{24}N_4O_2S \cdot HCl$	B, C, D	NT[f]	51.9 ± 13.4
12m		–	153–154	78	$C_{17}H_{16}N_2OS$	B, C	5.0 ± 1.6	60.2 ± 16.5
12n		–	158–159	82	$C_{16}H_{14}N_2O_2S$	B, C	8.2 ± 2.7	52.9 ± 19.2
12o		–	156–158	61	$C_{19}H_{20}N_2OS$[g]	B, C	4.5 ± 1.0	NT[f]
12p	$NHCH_3$	–	128–130	81	$C_{13}H_{10}N_2OS$	B, C	8.4 ± 2.8	28.6 ± 6.7
12q	NHC_2H_5	–	124–126	77	$C_{14}H_{12}N_2OS$	B, C	8.5 ± 2.1	36.3 ± 10.6
12r	NHC_3H_7	–	114–115	79	$C_{15}H_{14}N_2OS$	B, C	17.3 ± 5.0	42.0 ± 9.5
12s	NHC_6H_{13}	–	89–92	70	$C_{18}H_{20}N_2OS$	B, C	10.5 ± 3.2	62.3 ± 12.1
12t	$NH(CH_2)_3CO_2CH_3$	–	83–84	65	$C_{17}H_{16}N_2O_3S$	B, C	9.9 ± 3.4	NT[f]
13a	–	NH_2	267–269	96	$C_{12}H_8N_2OS$	E	17.0 ± 4.3	24.7 ± 2.5
13b	–	$NHNH_2$	350	35	$C_{12}H_9N_3OS$	E	11.2 ± 1.8	20.4 ± 4.5
control							12.6 ± 3.5	43.3 ± 5.0
diazepam[h]							39.4 ± 5.9**	25.1 ± 8.4*

[a] Analyses for C, H, N, S were within ±0.4% of the theoretical values unless otherwise noted. [b] Number of shocks received in 5 min at a dose of 10 mg/kg iv. [c] Time of latency in seconds at a dose of 10 mg/kg iv. [d] N: calcd, 12.51; found, 12.99. [e] N: calcd, 10.78; found, 11.35. [f] Not tested. [g] S: calcd, 9.88; found, 9.39. [h] Dose of compound in the anticonflict activity and lessening of memory impairment was 3 mg/kg ip. [i] $*p < 0.05$ $**p < 0.01$ (Student's *t* test).

reaction mixture was allowed to stand overnight in a refrigerator, and the precipitated crystals were collected by filtration to give **7** (3.0 g, 8.55 mmol) in a yield of 82%. MP: 293 °C. IR (KBr): 3300, 2940, 2860, 1700, 1680, 1540, 760, 730 cm^{-1}. NMR (δ, $CDCl_3$): 0.90–2.20 (m, 10 H), 1.50 (s, 9 H), 2.80–3.20 (m, 1 H), 3.50–3.90 (m, 2 H), 4.10–4.50 (m, 1 H), 4.90–5.30 (m, 2 H), 5.70–6.00 (m, 1 H), 7.10–7.50 (m, 2 H), 7.50–7.80 (m, 2 H). Anal. ($C_{18}H_{22}N_2OS \cdot HCl$): C, H, N, S.

2-(2-Chlorobenzoyl)-1,2,3,4-tetrahydro[1]benzothieno-[2,3-*c*]pyridine-3-carboxylic Acid Ethyl Ester (8a). Compound **3b** (600 mg, 2.30 mmol), 2-chlorobenzoyl chloride (523 mg, 2.99 mmol), and NEt_3 (220 μL, 3.00 mmol) were dissolved in $CHCl_3$ (30 mL) and stirred at room temperature for 1 h. The reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with aqueous $NaHCO_3$ (20 mL) and with H_2O (20 mL × 2). The $CHCl_3$ solution was dried on Na_2SO_4, concentrated, and purified through a silica

Table V. Anticonflict Activity on Water Lick Conflict Test in Rats

compound (mg/kg po)	no. shocks of 5 min (no. of rats)[a]	no. rats showing anticonflict activity[b]
control	11.1 ± 0.9 (90)	
diazepam (10)	22.7 ± 2.1*** (43)	25/43
3b (5)	16.1 ± 3.9 (10)	3/10
3b (20)	29.3 ± 5.5* (10)	6/10
3b (40)	30.2 ± 4.0* (10)	8/10
7 (5)	15.5 ± 4.0 (10)	3/10
7 (20)	28.1 ± 5.8* (10)	5/10
7 (40)	26.9 ± 4.2** (9)	6/9
12a (20)	9.3 ± 2.3 (8)	2/8
12a (40)	22.0 ± 5.2* (7)	4/7

[a] $*p < 0.05$; $**p < 0.01$; $***p < 0.005$ (Student's t test). [b] Number of rats which received shocks more than twice vs shocks received in control rats/number of rats tested.

Table VI. Effect of Compounds on Passive Avoidance Test in Scopolamine-Induced Amnesia in Mice

compound (mg/kg po)	latency to step through, s (no. of mice)	no. mice showing antiamnesic activity[a]
control	295.0 ± 6.2 (16)	
scopolamine (3)	45.0 ± 7.5*** (18)	0/18
diazepam (5)	30.0 ± 10.0	1/10
3b (5)	68.8 ± 17.7 (8)	2/8
3b (20)	110.1 ± 19.2* (8)	4/8
3b (40)	129.9 ± 30.2* (8)	6/8
7 (5)	67.5 ± 25.0* (8)	1/8
7 (20)	85.0 ± 22.5* (8)	3/8
12a (5)	65.5 ± 18.7 (8)	4/8
12a (20)	106.7 ± 18.7* (8)	4/8
12a (40)	125.1 ± 31.8* (8)	6/8

[a] $*p < 0.05$; $**p < 0.01$; $***p < 0.005$ (Student's t test). [b] Number of mice which prolonged latency more than twice the duration of mice administered scopolamine singly/number of mice tested.

Table VII. IC_{50} Values of **3b**, **7**, **10c**, **13a**, β-CCP, M_1, M_2, and Diazepam for the Benzodiazepine Receptor

compounds	IC_{50}, μM	compounds	IC_{50}, μM
3b	1499 ± 331	β-CCP	0.0625 ± 0.0085
7	1597 ± 471	M_1	1675 ± 456
10c	1529 ± 412	M_2	1463 ± 395
13a	1560 ± 459	diazepam	0.0514 ± 0.0074

gel column ($CHCl_3$/MeOH 50:1) to give **8a** (614 mg, 1.54 mmol) in a yield of 67%. MP: 175–176 °C. IR (KBr): 1712, 1638 cm^{-1}. Anal. ($C_{21}H_{18}ClNO_3S$): C, H, N, S.

2-Methyl-1,2,3,4-tetrahydro[1]benzothieno[2,3-c]pyridine-3-carboxylic Acid Ethyl Ester (9). Compound **3b** (392 mg, 1.50 mmol), methyl iodide (170 mg, 1.50 mmol), and DBU (251 mg, 1.63 mmol) were dissolved in THF (30 mL) and stirred at room temperature for 12 h. The reaction mixture was diluted with AcOEt (20 mL) and washed with aqueous $NaHCO_3$ (20 mL) and with H_2O (20 mL × 2). The AcOEt solution was dried on Na_2SO_4, concentrated, and purified through a silica gel column ($CHCl_3$/MeOH 50:1) to give **9** (284 mg, 1.03 mmol) in a yield of 69%. MP: 147–151 °C. IR (KBr): 1740 cm^{-1}. Anal. ($C_{15}H_{17}NO_2S$) C, H, N, S.

Scheme II. [1]Benzothieno[2,3-c]pyridine-3-carboxylic Acid Ethyl Ester (10b). Compound **3b** (15.5 g, 59.3 mmol) and S (41 g, 1.28 mol) were dissolved in xylene (1 L) at 110 °C for 1 day. After the solution was concentrated, the residue was washed with MeOH (100 mL × 2) to remove S. After the MeOH solution was concentrated, $CHCl_3$ (100 mL) was added to the residue. After washing with aqueous 5% citric acid (30 mL × 2), aqueous $NaHCO_3$ (30 mL × 2), and saturated brine (20 mL × 2), the $CHCl_3$ solution was dried on Na_2SO_4, concentrated, and recrystallized to give **10b** (13.1 g, 51.0 mmol) in a yield of 86%. MP: 129–130 °C. IR (KBr): 1700 cm^{-1}. Anal. ($C_{14}H_{11}NO_2S$): C, H, N, S.

[1]Benzothieno[2,3-c]pyridine-3-carboxylic Acid (11). A solution of compound **10b** (12.7 g, 49.4 mmol) in a mixture of 1 N NaOH (55 mL) and MeOH (200 mL) was stirred at room temperature. After 1 h, the then homogeneous solution was heated with H_2O (50 mL). The pH of mixture was adjusted to 3 with 1 N HCl and the mixture was stirred at room temperature for 1.5 days. Precipitates formed were collected by filtration to provide **11** (10.2 g, 44.5 mmol) in a yield of 90%. MP: 227–230 °C. Anal. ($C_{12}H_7NO_2S$): C, H, N, S.

***N*-(2-Aminoethyl)[1]benzothieno[2,3-c]pyridine-3-carboxamide Hydrochloride (12a).** Compound 11 (487 mg, 2.13 mmol), *N*-(benzyloxycarbonyl)ethylenediamine (428 mg, 2.21 mmol), DPPA (660 mg, 2.40 mmol), and NEt_3 (336 μL, 4.58 mmol) were added in DMF (10 mL) under ice cooling for 1 h and at room temperature overnight. AcOEt (100 mL) was added to the reaction mixture, which was washed with aqueous 5% citric acid (20 mL × 2), aqueous $NaHCO_3$ (20 mL × 2), and saturated brine (20 mL × 2). The AcOEt extract was dried on Na_2SO_4, concentrated, and purified through a silical gel column ($CHCl_3$) to give *N*-[2-[[(benzyloxy)carbonyl]amino]ethyl][1]benzothieno[2,3-c]-pyridine-3-carboxamide (758 mg, 1.87 mmol) as an oil in a yield of 88%. IR (KBr): 1700, 1680 cm^{-1}. Anal. ($C_{22}H_{19}N_3O_3S$): C, H, N, S. *N*-[2-[[(Benzyloxy)carbonyl]amino]ethyl][1]benzothieno[2,3-c]pyridine-3-carboxamide (700 mg, 1.73 mmol) and a solution of HBr (25%) in CH_3CO_2H (5 mL) were dissolved in CH_3CO_2H (10 mL) and stirred at 50 °C for 1 h. H_2O (100 mL) was added to the reaction solution. The aqueous layer was separated and washed with Et_2O (50 mL × 2). The pH of an aqueous solution was adjusted to 10 with NaOH and extracted with $CHCl_3$ (100 mL × 2). The $CHCl_3$ extract was dried on Na_2SO_4 and concentrated. MeOH (50 mL) and a MeOH solution containing 1 N HCl (2 mL) were added to the residue. Precipitated crystals were collected by filtration to provide **12a** (430 mg, 1.40 mmol) in a yield of 81%. MP: 260 °C. IR (KBr): 3320, 2950, 2900, 1650, 1520, 1240, 760, 740 cm^{-1}. NMR (δ, $CDCl_3$): 2.90–3.40 (m, 2 H), 3.50–3.90 (m, 2 H), 7.50–7.90 (m, 4 H), 8.10–8.30 (m, 1 H), 8.30–8.70 (m, 2 H), 9.30 (s, 1 H), 8.50 (s, 1 H). Mass spectra (m/z): 271 (M^+), 252, 242, 229, 185, 140. Anal. ($C_{14}H_{13}N_3OS$·HCl): C, H, N. S.

***N*-[2-(Dimethylamino)ethyl][1]benzothieno[2,3-c]-pyridine-3-carboxamide Hydrochloride (12c).** Compound 11 (487 mg, 2.13 mmol), *N,N*-dimethylethylenediamine (212 mg, 2.40 mmol), DPPA (660 mg, 2.40 mmol), and NEt_3 (335 μL, 4.58 mmol) were dissolved in DMF (10 mL) with ice cooling and stirred overnight at room temperature. The reaction mixture was diluted with AcOEt (100 mL), washed with aqueous NaOH (50 mL × 2), and dried on Na_2SO_4. The AcOEt extract was concentrated and purified through a silical gel column ($CHCl_3$). The product was diluted with AcOEt (50 mL) and 1 N HCl in AcOEt solution (2 mL) to give **12c** (570 mg, 1.70 mmol) as crystals in a yield of 80%. MP: 257–259 °C. IR (KBr): 1660, 1600 cm^{-1}. Anal. ($C_{16}H_{17}N_3OS$·HCl) N: calcd, 12.51; found, 12.99.

***N*-Methyl[1]benzothieno[2,3-c]pyridine-3-carboxamide (12p).** Compound 11 (459 mg, 2.0 mmol), methylamine hydrochloride (162 mg, 2.40 mmol), and NEt_3 (307 μL, 4.20 mmol) were dissolved in DMF (5 mL). To this solution was added DPPA (660 mg, 2.40 mmol) dropwise under ice cooling. The mixture was stirred at room temperature for 3 h and diluted with AcOEt (100 mL). The AcOEt layer was washed according to the conventional procedures, concentrated, and purified through a silica gel column ($CHCl_3$/MeOH 30:1) to give **12p** (434 mg, 1.79 mmol) in a yield of 90%. MP: 128–130 °C. IR (KBr): 1660 cm^{-1}. Anal. ($C_{13}H_{10}N_2OS$): C, H, N, S.

[1]Benzothieno[2,3-c]pyridine-3-carboxamide (13a). Ammonia gas was slowly bubbled into EtOH (30 mL) containing **10b** (487 mg, 1.89 mmol) for 15 min under ice cooling. After the solution was allowed to stand for 3 days at room temperature, precipitated crystals were collected to provide **13a** (410 mg, 1.81 mmol) in a yield of 96%. MP: 267–269 °C. IR (KBr): 1685 cm^{-1}. Anal. ($C_{12}H_8N_2OS$): C, H, N, S.

[1]Benzothieno[2,3-c]pyridine-3-carboxylic Acid Hydrazide (13b). A mixture of **10b** (515 mg, 2 mmol), NH_2NH_2·2HCl (252 mg, 2.4 mmol), and NEt_3 (700 μL, 9.57 mmol) in dry MeOH (20 mL) was stirred at room temperature for 2 days and heated at refluxing temperature for 2 h. Precipitated crystals were collected to provide **13b** (169 mg, 0.70 mmol) in a yield of 35%. MP: 350 °C. IR (KBr): 1690 cm^{-1}. Anal. ($C_{12}H_9N_3OS$): C, H, N, S.

Water Lick Conflict Test.[22] Male Wistar rats (170–200 g) were used. Rats were deprived of water for 24 h prior to the test.

The rats were placed in a test chamber and allowed to locate a drinking spout which gave off mild electric shocks (1.0 mA). Only rats making between 3 and 10 licks during a total of 30 s in this presession were used for the animal test. The rats were removed from the chamber, administered compounds and were returned to the home cage for 60 min. The rats were then returned to the test chamber for the 5-min test session. During the 5-min test session, the rats were delivered a shock (2.5 mA) for every drop they drank. The number of shocks received during the 5-min session was recorded automatically.

Passive Avoidance Test.[3,4] Male ddy mice (20–25 g) were kept in a plastic cage in groups of 10 and allowed free access to dry food pellets and water. The mice were trained in a one-trial step-through passive avoidance task. The apparatus consisted of a small white box (15 cm × 10 cm × 9 cm) and a black shock box (15 cm × 15 cm × 14 cm) with a hall at the bottom and a grillotine door. During the acquisition test, they were placed in a small, lighted compartment. Five seconds later, the door was opened. The mice received a 1 mA foot shock after entering the dark compartment and they were then returned to their home cage. Twenty-four hours later, after the acquisition test, mice were placed in the small, lighted box again. Time latency to enter the dark compartment was recorded (maximum = 300 s). Compounds were administered 60 min prior to the acquisition. For evaluation of the effect on scopolamine-induced amnesia, scopolamine 3 mg/kg was administered intraperitoneally 15 min prior to the acquisition test. Compounds were administered 45 min prior to the administration of scopolamine.

BZP Receptor Binding Assays.[23] Wistar rats were decapitated, and the cerebral cortex was dissected. The cortex was homogenized in 20 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.4) with a Physcotron (15 s, setting 60, NITI-ON Medical Instruments) and centrifuged (4 °C) for 20 min at 50000*g*. The tissue was resuspended in an equal volume of buffer and recentrifuged. This procedure was repeated two more times. The final pellet was resuspended, frozen in a liquid nitrogen bath, and stored at −80 °C. For the binding assay, the frozen membrane preparations were thawed and centrifuged. The pellet was resuspended in 100 volumes (protein concentrations, 0.5–0.6 mg/mL) of ice-cold 50 mM Tris-HCl buffer containing 100 mM NaCl and 5 mM KCl, and 0.5-mL aliquots of this homogenate were added to 0.1 mL of a solution of [^{3}H]flunitrazepam (final concentration, 56.6 pM) and varying amounts of the test compounds. The mixture was incubated at 0 °C for 20 min, and the incubations were terminated by addition of 2.5 mL of ice-cold incubation buffer, followed by rapid filtration through Whatman GF/C filters. The filters were washed three times with 2.5 mL of the buffer and placed in minivials containing 5 mL of Clear-sol I. After 12 h, the radioactivity was counted with an Aloka LSC-673 liquid-scintillatin counter. Nonspecific binding was determined by parallel experiments with nonradioactive diazepam (final concentration, 100 μM) and accounted for less than 10% of total binding. Each value was determined in duplicate, and IC_{50} values were calculated from semilogarithmic plots. The data are means of at least three individual determinations.

Acknowledgment. We thank Dr. K. Komatu for helpful discussion and encouragement during the course of the study. We also acknowledge the excellent technical support of members of the synthetic section. We are very grateful to Prof. K. Fujita of Nagasaki University, Faculty of Pharmaceutical Sciences, for proofreading of our manuscript and helpful discussions.

Additions and Corrections

1990, Volume 33

James L. Kelley,* Ed W. McLean, Naomi K. Cohn, Mark P. Edelstein, David S. Duch, Gary K. Smith, Mary H. Hanlon, and Robert Ferone*: Synthesis and Biological Activity of an Acyclic Analogue of 5,6,7,8-Tetrahydrofolic Acid, *N*-[4-[[3-(2,4-Diamino-1,6-dihydro-6-oxo-5-pyrimidinyl)propyl]amino]benzoyl]-L-glutamic Acid.

Page 561. The following should be inserted after the introduction: E. C. Taylor and coworkers recently reported the synthesis of *N*-[4-[4-(2,4-diamino-6(1*H*)-oxopyrimidin-5-yl)butyl]benzoyl]-L-glutamic acid (7-DM-DDATHF) (Taylor, E. C.; Harrington, P. M.; Shih, C. *Heterocycles* **1989**, *28*, 1169), an open-chain analogue of DDATHF and 5-DATHF (Taylor, E. C.; Hamby, J. M.; Shih, C.; Grindey, G. B.; Rinzel, S. M.; Beardsley, G. P.; Moran, R. G. *J. Med. Chem.* **1989**, *32*, 1517), which possesses structural features similar to 5-DACTHF reported by us (Kelley, J. L.; McLean, E. W.; Cohn, N. K.; Edelstein, M. P.; Duch, D. S.; Smith, G. K.; Hanlon, M. H.; Ferone, R. *J. Med. Chem.* **1990**, *33*, 561).