[Chem. Pharm. Bull. 35(9)3676—3690(1987)]

Isoxazole Derivatives as Centrally Acting Muscle Relaxants. III.[1] Synthesis and Activity of Conformationally Restricted Analogs[2]

TOCHIRO TATEE,*,[a] KAZUHISA NARITA,[a] SHUJI KURASHIGE,[a] SHINJI ITO,[a] HIROSHI MIYAZAKI,[a] HIROSHI YAMANAKA,[b] MICHINAO MIZUGAKI,[b] TAKAO SAKAMOTO,[b] and HIDEOMI FUKUDA[c]

Research Laboratories of Pharmaceuticals Group, Nippon Kayaku Co., Ltd.,[a] Shimo, Kita-ku, Tokyo 115, Japan, Pharmaceutical Institute, Tohoku University,[b] Aobayama, Sendai 980, Japan, and Faculty of Pharmaceutical Sciences, The University of Tokyo,[c] Hongo, Bunkyo-ku, Tokyo 113, Japan

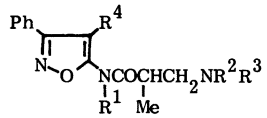
(Received December 23, 1986)

Conformationally restricted analogs of muscle-relaxant 3-amino-2-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamides (**1**) and 5-(3-aminopropylamino)-3-phenylisoxazoles (**2**) were prepared, and their muscle-relaxant and other pharmacological activities were tested and compared with those of the corresponding acyclic derivatives. 7-(3-Diethylamino-2-methylpropanoyl)-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (**8**) exhibited muscle-relaxant and anticonvulsant activities comparable with those of corresponding acyclic derivatives, *i.e.* 3-diethylamino-2-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamides (**1e—g**), but other types of compounds showed decreased activities. The preferred conformation of the present isoxazole derivatives for muscle-relaxant activity is discussed.

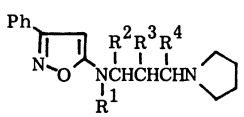
7-Benzyl-6-methyl-3-phenyl-4-pyrrolidino-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (**3d**) showed moderate central nervous system-depressant activity.

Keywords——muscle relaxant; isoxazole derivative; isoxazolo[5,4-*b*]pyridine; structure–activity relationship; conformation; conformationally restricted analog; tolperisone; anticonvulsant; anemic decerebrate rigidity

In the previous papers,[1] we reported the preparation, pharmacological activity, and quantitative structure–activity relationships (QSAR) of 5-aminoisoxazole derivatives (**1**, **2**) containing a 3-aminopropanamide or 3-aminopropylamino side chain as centrally acting muscle relaxants. Both types of isoxazole derivatives (**1**, **2**) have significant muscle-relaxant activities. However, the derivatives with a 3-aminopropylamino side chain showed weaker anticonvulsant activity and higher depressant action on spontaneous motor activity than the derivatives with a 3-aminopropanamide side chain. Among the derivatives with a 3-aminopropanamide side chain synthesized, 3-diethylamino-2,*N*-dimethyl-*N*-(3-phenyl-5-isoxazolyl)propanamide (**1a**) was obtained as an optimized derivative with selective action, namely potent muscle-relaxant and anticonvulsant activities with reduced central nervous system (CNS)-depressant activity.

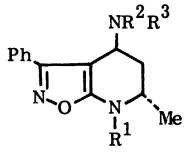


1

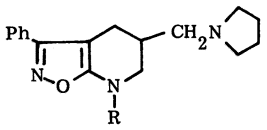


2

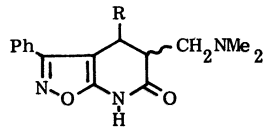
Chart 1



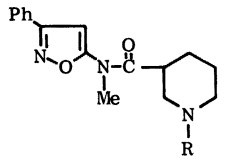
	R^1	NR^2R^3
3a	H	
3b	H	
3c	H	
3d	CH_2Ph	



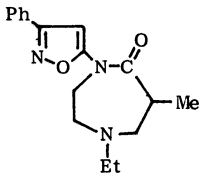
4a : R = H
4b : R = *p*-Ts
4c : R = COPh
4d : R = CH_2Ph



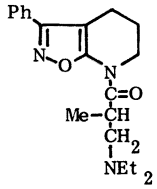
5a : R = H
5b : R = Me



6a : R = Me
6b : R = Et
6c : R = Pr
6d : R = iso-Pr



7



8

Chart 2

In these 3-amino-*N*-(5-isoxazolyl)-2-methylpropanamides (**1**) and 5-[(3-aminopropyl)-amino]isoxazoles (**2**), the 3-aminopropanamide and 3-aminopropylamino side chains can rotate freely. Recently, conformationally restricted analogs of pharmacologically active compounds were prepared and their activities were examined in order to identify the preferred conformation at the site of action.[3] The compounds with one of the carbon atoms on the side chain connected with the isoxazolyl ring carbon, or another carbon atom on the side chain, or the amide nitrogen atom should have comparable activities with their corresponding acyclic derivatives, if they have the spatial interrelationship of functional groups that is necessary for activity. A side effect can be eliminated if it is caused by a conformation different from that required for the principal effect.[3e] From this point of view, we synthesized conformationally restricted analogs (**3**—**8**) of the previously reported isoxazole derivatives, and compared their muscle-relaxant and anticonvulsant activities with those of the corresponding acyclic analogs. We found compound **8** to possess a muscle-relaxant activity comparable with those of the corresponding acyclic derivatives. Compound **3d** exhibited moderate CNS-depressant activity instead of the muscle-relaxant activity. In the present paper, we describe the synthesis of **3**—**8** and their pharmacological activities. The preferred conformation of muscle-relaxant isoxazole derivatives at the site of action is discussed.

Synthesis

4-Substituted isoxazolo[5,4-*b*]pyridines (**3a**—**c**) were synthesized by reductive cyclization of the 3-(5-isoxazolylamino)butanamides (**9a**—**c**) with sodium bis-(2-methoxyethoxy)-aluminum hydride (SMEAH) in toluene. Compound **3c** was reacted with benzyl chloride

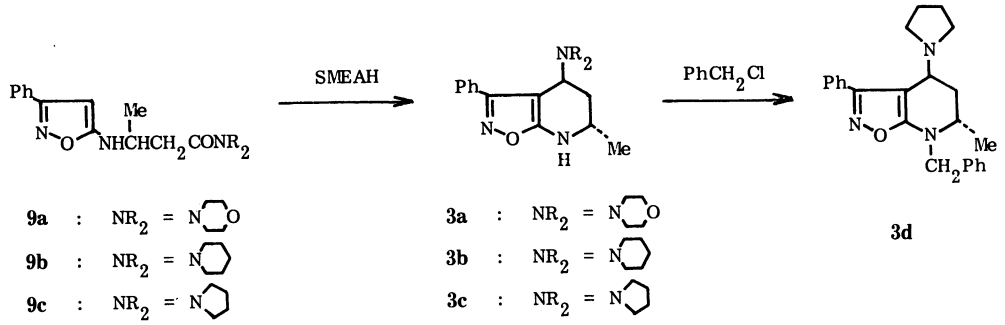


Chart 3

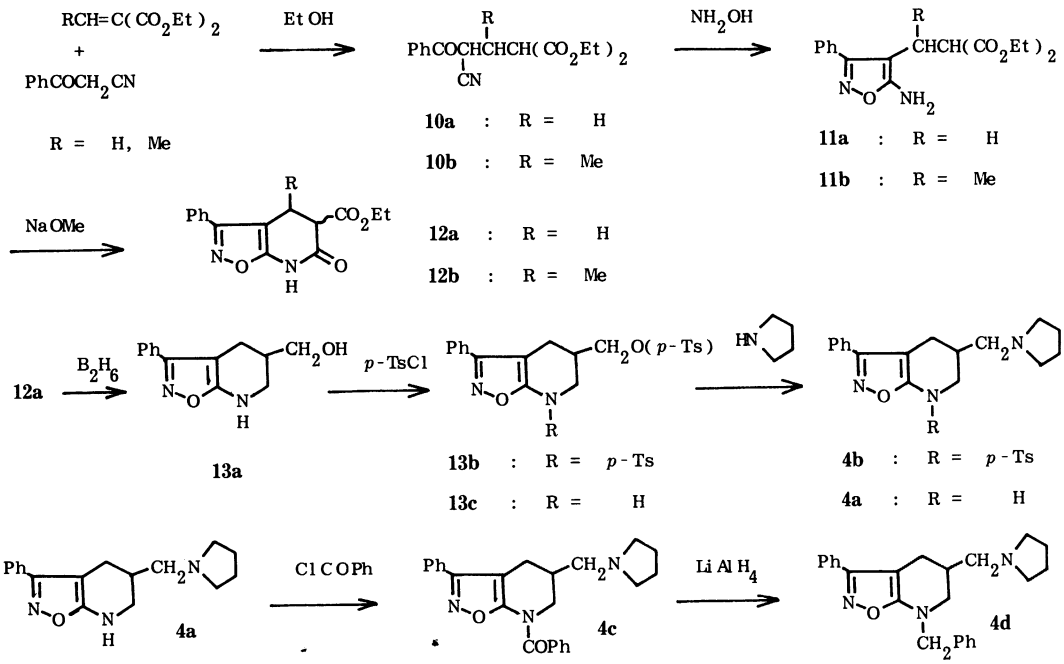


Chart 4

in the presence of sodium amide in toluene to give a benzylated derivative (**3d**). The 400 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3d** is best interpreted on the basis of a *trans* stereostructure of the 4-pyrrolidino group and 6-methyl group; J (4-H, 5-axial H) = 3.4 Hz, J (4-H, 5-equatorial H) = 3.4 Hz, J (5-axial H, 5-equatorial H) = 14.4 Hz, J (5-axial H, 6-H) = 11.2 Hz, J (5-equatorial H, 6-H) = 2.9 Hz.

5-Substituted isoxazolo[5,4-*b*]pyridines (**4**, **5**) were synthesized *via* 5-ethoxycarbonyl derivatives (**12a**, **b**). Namely, benzoylacetonitrile was heated with diethyl alkylidenemalonates in ethanol to give Michael adducts (**10a**, **b**), which were converted into isoxazole diesters (**11a**, **b**) by reaction with hydroxylamine hydrochloride and pyridine in ethanol. Compounds **12a**, **b** were synthesized by refluxing **11a**, **b** with sodium methoxide in methanol.

When the amido-ester (**12a**) was treated with borane in tetrahydrofuran (THF), the amino alcohol (**13a**) was obtained. The amino alcohol (**13a**) reacted readily with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine to afford the ditosylate (**13b**) and the monoto-

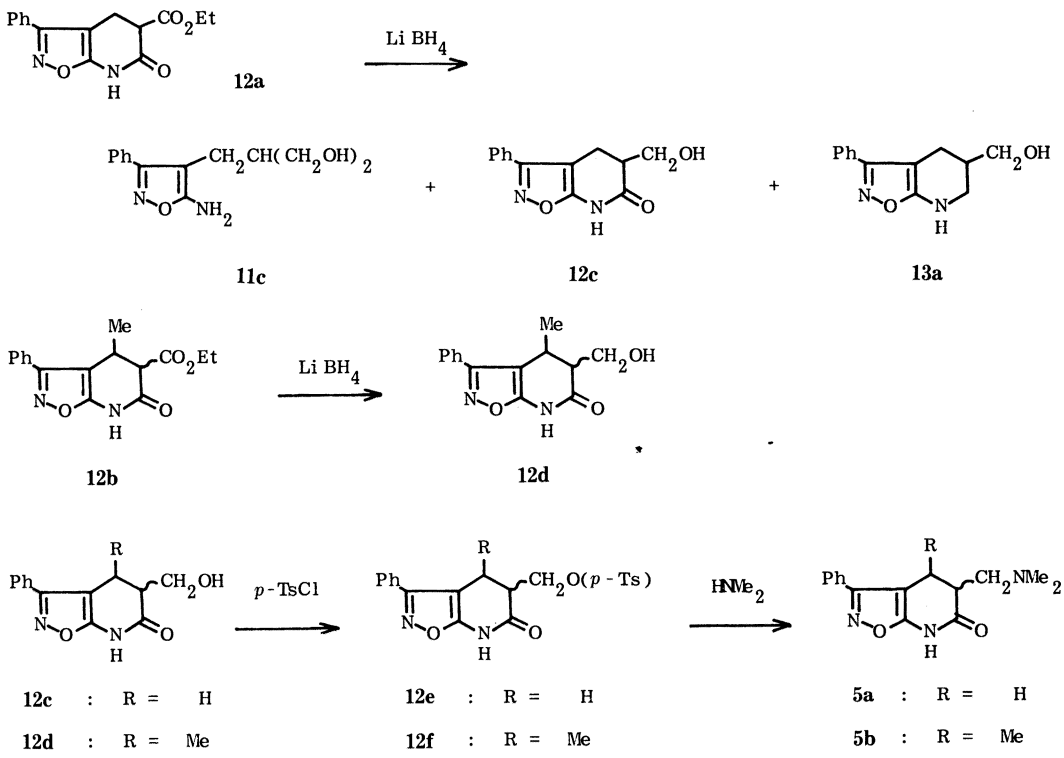
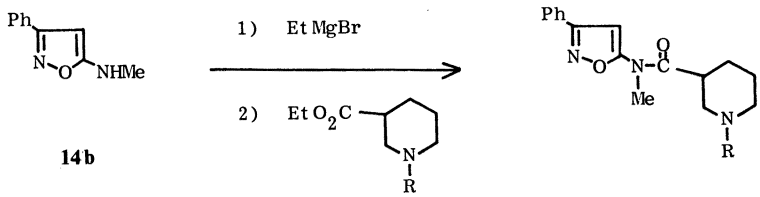


Chart 5



6a: R = Me
6b: R = Et
6c: R = Pr
6d: R = iso-Pr

Chart 6

sylate (**13c**), which were converted into **4b** and **4a**, respectively, by reaction with pyrrolidine.

When the amido-ester (**12a**) was treated with lithium borohydride in 1,2-dimethoxyethane, the diol (**11c**) was obtained as a major product along with the amido-alcohol (**12c**) and the amino alcohol (**13a**). When the 4-methylated amido-ester (**12b**) was reacted with the same reagent, the amido-alcohol (**12d**) was obtained as a sole product. In a 4-methylated isoxazolo[5,4-*b*]pyridine ring system such as that of **12b**, the methyl group at position 4 may be oriented quasi-axial due to repulsion of the phenyl group at position 3 and thus protect the amide function from hydride attack. Therefore, the amidoalcohols (**12c**, **d**) were tosylated with *p*-TsCl in pyridine, followed by reaction with dimethylamine to give **5a**, **b**, respectively.

N-(5-Isoxazolyl)nipecotamides (**6a**—**d**) were synthesized by the reaction of the corresponding *N*-substituted nipecotates[4] with the magnesium salt of 5-methylamino-3-phenylisoxazole (**14b**).

Among unsymmetrically *N,N'*-disubstituted hexahydro-1*H*-1,4-diazepin-5-ones, the preparation of 4-cyclohexyl-1-(1,2-diphenylethyl)hexahydro-1*H*-1,4-diazepin-5-one has been reported.[5] A similar scheme was devised to prepare a 4-(5-isoxazolyl)hexahydro-1*H*-1,4-diazepin-5-one (**7**). The chloroacetamide derivative (**14c**) was reacted with ethylamine to give the 2-ethylaminoacetamide derivative (**14d**), which was then converted into 5-(2-ethylaminoethyl)amino-3-phenylisoxazole (**14e**) by reduction with lithium aluminum hydride in THF. Compound **14e** was reacted with an equimolar amount of *tert*-butyl *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate and triethylamine in chloroform to give a *tert*-butoxycarbonyl (Boc) derivative (**14f**), which was acylated to yield a 2-propenamide (**14g**) by the use of methacryloyl chloride and triethylamine. The Boc group of **14g** was eliminated by treatment with trifluoroacetic acid to give the 2-propenamide derivative (**14h**), which was cyclized to **7** by heating with acetic acid in benzene.

3-Phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (**13d**) was synthesized by hydrolysis and concomitant decarboxylation of the amido-ester (**12a**) with potassium carbonate in ethanol, followed by the reduction of the resulting amide (**12g**) with lithium aluminum

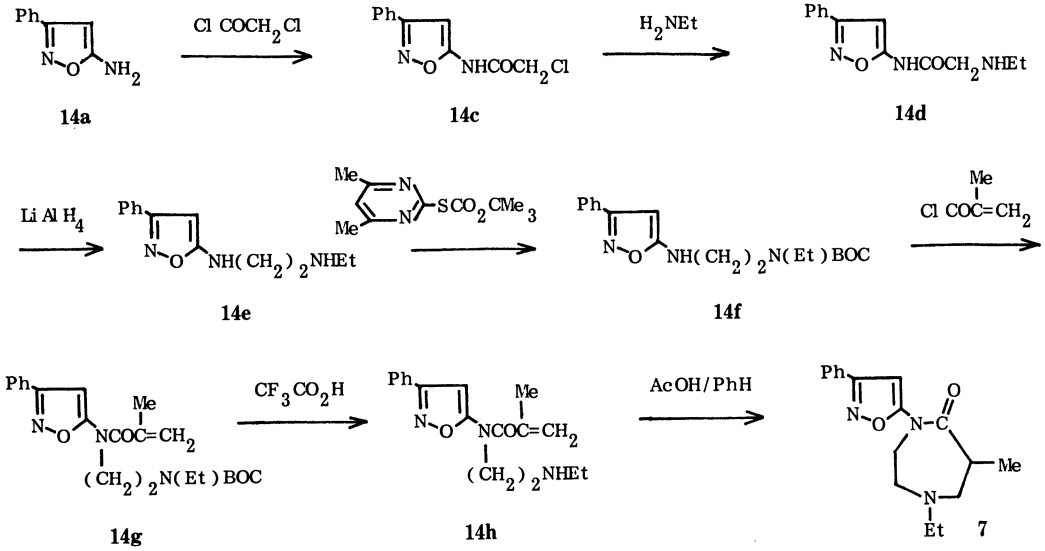


Chart 7

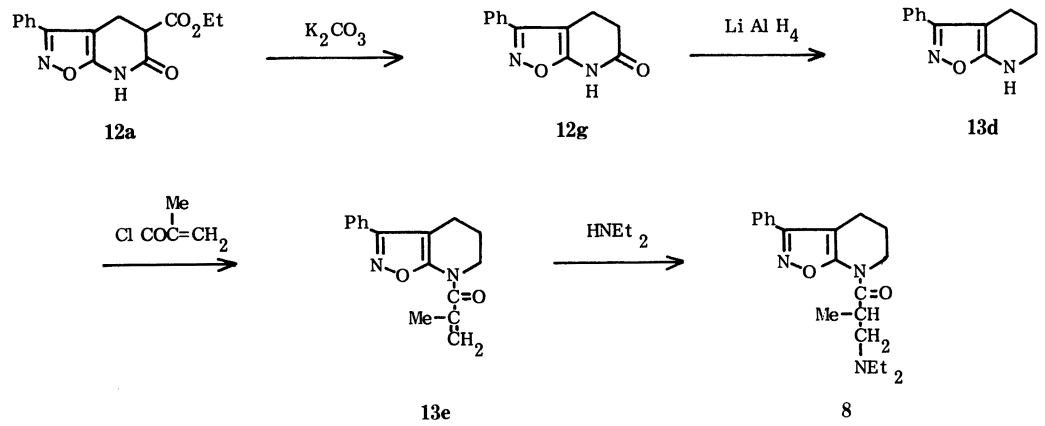


Chart 8

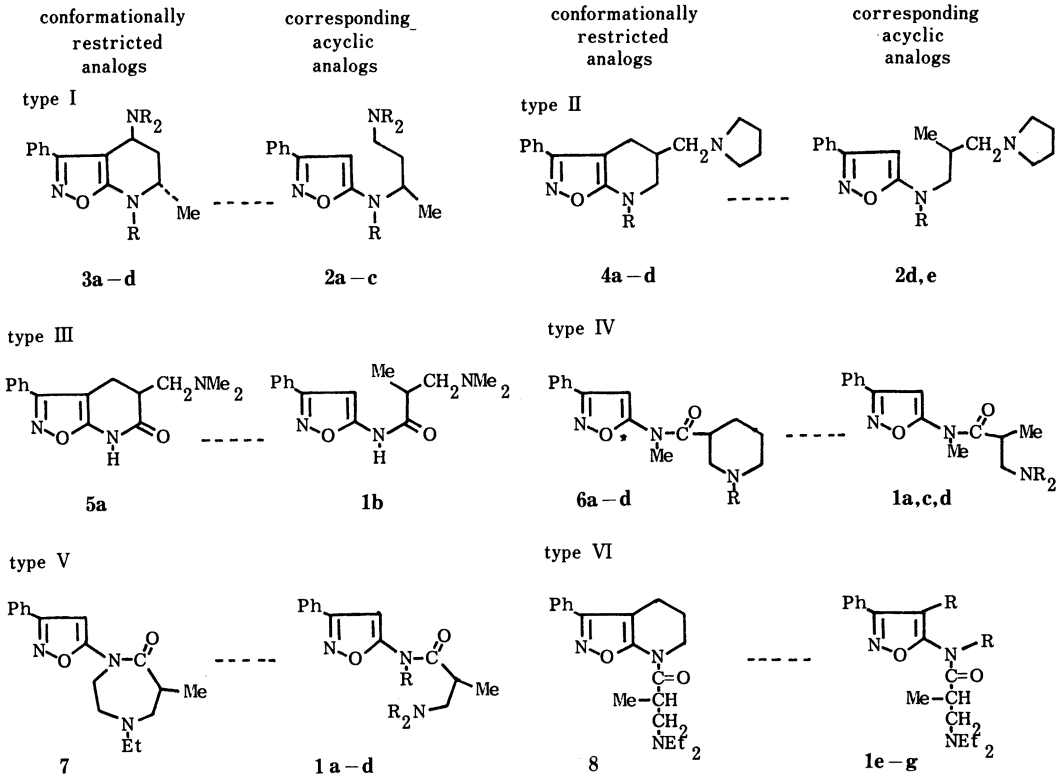


Chart 9

hydride. Compound **13d** reacted readily with methacryloyl chloride under basic conditions to give the 2-propenamide (**13e**), which was converted to the 3-diethylamino-2-methylpropanamide (**8**) by Michael addition with diethylamine.

The yields, melting points, selected spectroscopic data, and the results of elemental analysis of compounds **3a**—**d**, **15a**—**f**, and of the free bases or fumarates of compounds **1e**, **f** are listed in Tables V and VI in the experimental section.

Pharmacology

Six types of conformationally restricted analogs were thus prepared and their activities were compared with those of the corresponding acyclic analogs.

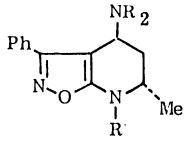
Pharmacological and toxicological data for compounds **3a**—**d**, as well as the corresponding acyclic analogs (**2a**—**c**) are shown in Table I. Muscle-relaxant and anticonvulsant activities of **2a**—**c** and **3a**—**d** were tested by means of the traction test, and the pentylenetetrazole (PTZ) test, respectively. The results for **3a**—**c** indicated that derivatives with a hydrogen as R did not show any muscle-relaxant activity. Compound **3d** (with a benzyl group as R) exhibited higher potency than **3c**. Muscle-relaxant and anticonvulsant activities of these bicyclic isoxazole derivatives were compared with those of the corresponding acyclic compounds **2a**—**c**. Compounds **3c** and **3d** are rigid analogs of **2a** and **2b**, respectively; namely, the carbon atom at the 3-position of the 3-aminopropylamino side chain of compounds **2a** and **2b** is connected with the isoxazolyl 4-position in compounds **3c** and **3d**. Although **3c** and **3d** showed moderate anticonvulsant activities, both derivatives showed decreased potency in muscle relaxation.

CNS-depressant activity was evaluated by the effect on the conditioned-avoidance

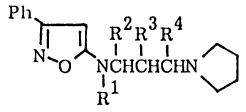
response and the depression of spontaneous motor activity determined by the revolving wheel method. The rigid compounds (**3c**, **d**) showed an increased CNS-depressant activity. Compound **3c** showed weak potency in the depression in motor activity and the benzylated derivative (**3d**) exhibited increased potency in the conditioned avoidance response and motor activity. Acyclic compounds (**2a**, **b**) showed less CNS-depressant activity.

The isoxazolopyridine derivatives **4a** and **4d** are also rigid analogs of **2d** and **2e**, respectively; namely, the carbon atom of the methyl group on the 3-aminopropylamino side chain of compounds **2d** and **2e** is connected with the isoxazolyl 4-position in compounds **4a**

TABLE I. Pharmacological Data on Isoxazolopyridines (**3a—d**) and the Corresponding Acyclic Analogs (**2a—c**)



3a—d

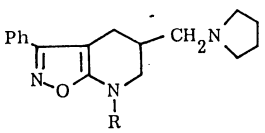


2a—c

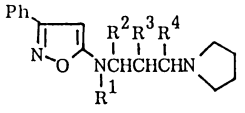
Compd. No.	T[a] i.p.	PTZ[b] s.c.	C[c] i.p.	D[d] s.c.	LD_{50}[e] i.p.
3a	>300	f)	>100	f)	>1000
3b	>300	f)	>300	f)	>1000
3c	100	50—100	>30	10—30	84.5
3d	50	25—50	10—30	3	126
2a	10—30	>50	f)	f)	100—300
2b	10	>100	100	30	100—300
2c	30	>100	>100	f)	100—300
Tolperisone	100	13.7	100	30	180
Chlorpromazine	f)	f)	3—10	0.5—1.0	108

a—d) Activity is presented as ED_{50}. *a*) Traction test in mice. *b*) Anticonvulsant activity was examined against tonic extensor convulsion induced by PTZ. *c*) Conditioned avoidance response. *d*) Depression in motor activity determined by the revolving wheel method. *e*) 50% lethal dose in mice. *f*) Not tested.

TABLE II. Pharmacological Data on Isoxazolopyridines (**4a—d**) and the Corresponding Acyclic Analogs (**2d, e**)



4a—d



2d, e

Compd. No.	T[a] i.p.	MES[b] i.p.	C[a] i.p.	D[a] i.p.	LD_{50}[a] i.p.
4a	>50	>50	>30	>30	72.6
4b	>300	c)	>300	300	1000
4c	>300	100—300	>100	100	c)
4d	>50	>50	>10	>30	49.5
2d	>30	c)	c)	>30	100—300
2e	30	c)	c)	30	300
Tolperisone	50—100	50—100	100	63	100—300
Chlorpromazine	c)	c)	3—10	1—2	108

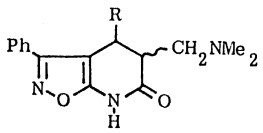
a) See footnote to Table I. *b*) Anticonvulsant activity was examined against maximal electroshock (MES). *c*) Not tested.

and **4d**. Anticonvulsant activity was tested by means of the maximal electroshock (MES) test. These compounds (**4a** and **4d**) did not show any significant pharmacological activity. Even the benzylated compound (**4d**) was less active than the corresponding acyclic compound (**2e**) in terms of the traction test.

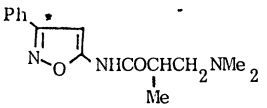
The 6-oxoisoxazolopyridine derivative (**5a**) corresponds to the propanamide (**1b**); namely, the carbon atom of the methyl group on the 3-aminopropanamide side chain of compound **1b** is connected with the isoxazolyl 4-position in compound **5a**. The pharmacological data are shown in Table III. Compound **5a** showed less than half of the muscle-relaxant and anticonvulsant activities of **1b**. The 4-methyl homolog (**5b**) exhibited decreased effects.

In compounds **6a**—**d**, the carbon atom of the methyl group on the 3-aminopropanamide

TABLE III. Pharmacological Data on Isoxazolopyridines (**5a, b**) and the Corresponding Acyclic Analogs (**1b**)



5a, b

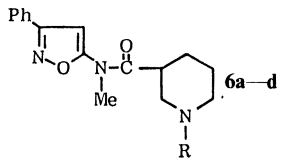


1b

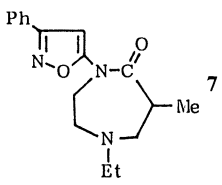
Compd. No.	T[a] i.p.	PTZ[a] i.p.	MES[b] i.p.	C[a] i.p.	LD_{50}[a] i.p.
5a	>200	>200	>200	c)	c)
5b	>400	>400	>400	>100	600
1b	100	50	50—100	c)	300—1000

a) See footnote to Table I. *b*) See footnote to Table II. *c*) Not tested.

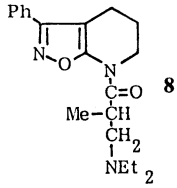
TABLE IV. Pharmacological Data on Conformationally Restricted Analogs (**6a—d, 7, 8**) and the Corresponding Acyclic Analogs (**1a, c—g**)



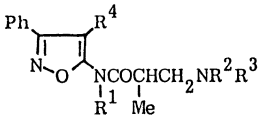
6a—d



7



8



1a, c—g

Compd. No.	R[a] Inhibition ratio (%) at 2.5 mg/kg i.v.	5 mg/kg i.v.	PTZ ED_{50} (mg/kg) i.p.
6a	17	b)	b)
6b	16	b)	50
6c	5	b)	b)
6d	8	b)	b)
7	b)	6	56.1
8	28	52	12.5
1a	46	63	14.0
1c	20	59	13.2
1d	26	76	28.1
1e	28	76	12.5
1f	29	65	50
1g	28	62	25—50

a) Muscle relaxant activity was tested in the anemic decerebrate rigidity model. *b*) Not tested.

side chain in compounds **1a**, **c**, **d** is connected with the carbon atom of the alkyl substituent on the 3-amino group. In compound **7**, the carbon atom of the alkyl substituent on the 3-amino group of the 3-aminopropanamide side chain of compounds **1a—d** is connected with the amide nitrogen, or the carbon atom of the alkyl substituent on the amide nitrogen. In compound **8**, the carbon atom of the alkyl substituent on the amide nitrogen of compounds **1e—g** is connected with the isoxazolyl 4-position. Pharmacological data on **6a—d**, **7**, and **8** are shown in Table IV. Muscle-relaxant activities were tested in the anemic decerebrate rigidity model,[1a] and are shown as an inhibition ratio at 2.5 mg/kg or 5 mg/kg i.v.

Compounds **6b** and **6c** showed decreased potency at 2.5 mg/kg i.v. in the rigidity model, compared with their acyclic derivatives (**1a** and **1c**), respectively. The isoxazolyl diazepinone (**7**) inhibited the tension of rigid forelimbs by only 6% at 5 mg/kg in the rigidity model,[1a] and showed weak anticonvulsant activity. The isoxazolopyridine derivative (**8**) showed muscle-relaxant and anticonvulsant activities comparable with those of the corresponding acyclic compound **1e** or **1g**.

Discussion

Derivatives of types I—V showed decreased potency compared with the corresponding acyclic analogs, and only compound **8** showed comparable activity. As mentioned in the previous paper, a good correlation equation was obtained between potency and hydrophobic parameters, but the equation can only explain less than 70% of the variance of activity.[1b] We were therefore interested in the activity-determining factors other than the hydrophobic parameter. The mechanisms of action of centrally acting muscle relaxants are still uncertain, and the nature of the preferred conformation of the present isoxazole derivatives at the site of action is not known. However, the spatial interrelationships of the terminal amino group, the 5-isoxazolyl amino or amide group, the isoxazole ring, and the phenyl group are expected to play an important role in the activity.[3]

Among compounds of types I—VI, type I had the least freedom of interrelationship of these four groups, and in types II and III, the terminal amino group can rotate only in a limited area. In types IV and V, alkyl substituents on the terminal amino group are conformationally fixed. The decreased potency of the rigid analogs of these types indicates that other conformations than types I—V are desirable for activity.

In type VI, the terminal amino group can move freely except in the area that is occupied by the 4,5,6-positions of the isoxazolo[5,4-*b*]pyridine ring system, where the terminal amino groups of the compounds of types I—III are located, and only the alkyl group on the amide nitrogen is fixed *cis* to the isoxazolyl 4-hydrogen.

The present results suggest that the preferred conformation of the isoxazole derivatives as muscle relaxants may be close to type VI, and the terminal amino group may not be located near the isoxazolyl 4-position.

Experimental

Melting points were measured on a Sibata apparatus and are not corrected. Infrared (IR) spectra were determined on a JASCO model IR-G or a JASCO model A-202 spectrometer, taken as neat film, Nujol mull, or KBr disc as indicated in parentheses. Data are presented in reciprocal centimeters and only the important diagnostic bands are reported. ^{1}H-NMR spectra were obtained with a JEOL JNM-PMX60 (60 MHz) spectrometer, unless otherwise noted. The 400 MHz ^{1}H-NMR spectra were measured on a JEOL JNM-GX 400 spectrometer. Chemical shifts are expressed downfield from tetramethylsilane (TMS) as an internal standard. Data are presented in the form: value of signal (integrated number of protons, peak multiplicity, coupling constant (if any)). Mass spectra (MS) were taken on a Shimadzu 7000 mass spectrometer operating at 70 eV unless otherwise indicated. High-resolution MS were taken on a VG Analytical MM ZAB 2F-HF.

Unless otherwise stated, the reaction mixture was quenched with H_2O, and thoroughly extracted with organic

solvent. The extract was washed with saturated brine, dried, and filtered. The solvent was removed by rotary evaporation. The extraction solvent and drying agent are indicated in parenthesis. For column chromatography, Merck Kieselgel 60 (No. 7734) was used. For alumina dry column chromatography, Sumitomo Active Alumina KCG-30 was uniformly mixed with Merck Fluorescent-indicator F_{254} (No. 9182). For silica gel dry column chromatography, Woelm Pharma No. 4526 was used. For preparative thin layer chromatography, Merck Kieselgel 60 F_{254} No. 5717 was used. The chromatographic solvent is presented in parenthesis.

Synthesis

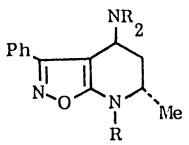
6-Methyl-3-phenyl-4-pyrrolidino-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (3c)——An excess of 70% solution of SMEAH in PhMe (500 ml) was added dropwise at room temperature to a suspension of *N*-[3-(3-phenyl-5-isoxazolyl)aminobutanoyl]pyrrolidine (**9c**, 230 g, 1.3 mol) in PhMe (1.5 l). The reaction mixture was stirred at room temperature for 12 h, then quenched with H_2O. Usual product isolation (PhMe, $MgSO_4$) gave an oil, which crystallized, and was recrystallized to afford **3c** (78.3 g) as a colorless powder. MS *m/z*: 283 (M^+). Compounds **3a**, **b** were obtained as colorless powders in the same manner from **9a**, **b**, respectively.

7-Benzyl-6-methyl-3-phenyl-4-pyrrolidino-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (3d)——Compound **3c** (28.34 g, 100 mmol) was added in portions to a suspension of $NaNH_2$ (5.85 g) in anhydrous PhMe (300 ml). The reaction mixture was heated under reflux for 1 h, then cooled to room temperature, and benzyl chloride (15.43 g, 122 mmol) was added dropwise. Stirring was continued at room temperature for 12 h, and product isolation (PhMe, $MgSO_4$) gave an oil which was purified on a column of silica gel ($CHCl_3$–MeOH, 10 : 1) to afford **3d** (10.95 g) as colorless needles, mp 95—98 °C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=7 Hz), 1.35 (10H, m), 3.4—3.9 (2H, m), 4.59 (2H, AB quartet, J=15.4 Hz), 7.1—7.9 (10H, m). MS *m/z*: 373 (M^+), 202, 189, 186, 92. *Anal.* Calcd for $C_{24}H_{27}N_3O$: C, 77.18; H, 7.29; N, 11.25. Found: C, 76.94; H, 7.33; N, 11.06. Compound **3d** was converted into the hydrochloride in a usual manner to give **3d**·HCl as a colorless powder. IR (KBr) *v*: 2580, 2500, 1615 cm^{-1}

5-Ethoxycarbonyl-4-methyl-6-oxo-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (12b)——A mixture of benzoylacetonitrile (3 g, 20.7 mmol) and diethyl ethylidenemalonate (4 g, 21.5 mmol) in EtOH (70 ml) was heated under reflux for 8 h. The reaction mixture was evaporated to give an oil (7.1 g), which was purified by dry column chromatography on silica gel (400 g, hexane–Et_2O, 2 : 1 followed by 1 : 1) to afford diethyl 3-cyano-2-methyl-4-oxo-4-phenylbutan-1,1-dicarboxylate (**10b**, 5.01 g, 73%) as an oil. IR (neat) *v*: 2250, 2200, 1755, 1745, 1740, 1730, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7 Hz), 1.33 (3H, t, J=7 Hz), 1.33 (3H, d, J=7 Hz), 2.8—3.9 (2H, m), 4.27 (2H, q, J=7 Hz), 4.33 (2H, q, J=7 Hz), 5.15 (1H, d, J=4 Hz), 7.3—8.2 (5H, m). MS *m/z* (20 eV, relative intensity): 331 (M^+, 1.3), 141 (22), 115 (19), 106 (28), 105 (100).

A mixture of **10b** (500 mg, 1.51 mmol), NH_2OH·HCl (114 mg, 1.64 mmol), and pyridine (300 mg, 3.79 mmol) was heated under reflux for 3 h. NH_2OH·HCl (230 mg, 3.31 mmol) and pyridine (200 mg, 2.53 mmol) were added, and the refluxing was continued for another 1 h. The reaction mixture was quenched with H_2O and product isolation

TABLE V. 4-Amino-6-methyl-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridines (**3a**—**d**)



Compd. No.	R	NR_2	Recrystn. solvent	mp (°C)	Yield	Formula	Analysis (%) Calcd (Found) C	H	N
3a	H		Et_2O	152—154	20[a]	$C_{17}H_{21}N_3O_2$	67.88 (68.20	7.20 7.07	14.25 14.04)
3b	H		Et_2O	137—140	27[a]	$C_{18}H_{23}N_3O$	72.62 (72.69	7.66 7.80	14.04 14.13)
3c	H		MeOH	157—158	36[a]	$C_{17}H_{21}N_3O$	72.33 (72.05	7.15 7.47	15.08 14.83)
3d	$PhCH_2$		EtOH[b]	138—140[b]	29[c]	$C_{24}H_{27}N_3O$·HCl[b]	70.12 (70.31	7.20 6.88	10.14[b] 10.25)

a) Yield of cyclization. *b*) As the hydrochloride. *c*) Yield of 7-benzylation.

(AcOEt, $MgSO_4$) gave an oil (507 mg), which was purified by silica gel preparative thin layer chromatography (PhMe–Et_3N, 3:1) to afford diethyl 2-methyl-2-(5-amino-3-phenyl-4-isoxazolyl)ethan-1,1-dicarboxylate (**11b**, 265 mg, 51%) as an oil. IR (Nujol) ν: 3380, 3150, 1745, 1680, 1653 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=7 Hz), 1.17 (3H, t, J=7 Hz), 1.23 (3H, t, J=7 Hz), 3.2—3.8 (2H, m), 4.10 (2H, q, J=7 Hz), 4.15 (2H, q, J=7 Hz), 4.8 (2H, br s), 7.45 (5H, s). MS m/z (relative intensity): 346 (M^+, 24), 188 (12), 187 (100), 159 (12), 69 (11).

A mixture of **11b** (230 mg, 0.665 mmol) and NaOMe (50 mg, 0.93 mmol) in MeOH (8 ml) was heated under reflux for 1.5 h. The reaction mixture was evaporated and the residue was diluted with H_2O and acidified with dilute HCl. Product isolation (AcOEt, $MgSO_4$) gave an oil (206 mg), which was purified by silica gel preparative thin layer chromatography (hexane–Et_2O, 1:2) to afford **12b** (185 mg, 93%) as colorless plates, mp 145—146 °C (hexane–AcOEt). IR (Nujol) ν: 1740, 1690, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz), 1.25 (3H, d, J=7 Hz), 3.4—4.0 (2H, m), 4.17 (2H, q, J=7 Hz), 7.3—7.9 (5H, m), 9.4 (1H, br s). MS m/z (relative intensity): 300 (M^+, 10), 227 (100), 105 (24), 77 (30), 51 (23). *Anal.* Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.59; H, 5.15; N, 9.17.

5-Ethoxycarbonyl-6-oxo-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (12a)——Compound **12a** was obtained as colorless needles in the same manner in 24% yield from benzoylacetonitrile, mp 179—180 °C (hexane–AcOEt). IR (Nujol) ν: 1740, 1690, 1660 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 1.20 (3H, t, J=7 Hz), 3.1—4.3 (3H, m), 4.27 (2H, q, J=7 Hz), 7.4—8.2 (5H, m). MS m/z (relative intensity): 286 (M^+, 10), 215 (50), 214 (54), 213 (100), 105 (77), 104 (35). *Anal.* Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.05; H, 4.70; N, 9.75.

5-Hydroxymethyl-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (13a)——A solution of 1 M borane–THF complex (130 ml) was added dropwise to a solution of **12a** (25 g, 88 mmol) in anhydrous THF (600 ml) under N_2 and ice cooling. The mixture was stirred at room temperature for 3 h, then another 130 ml of the same borane complex was added under cooling, and stirring was continued for 17 h. The mixture was quenched with H_2O and product isolation (AcOEt, $MgSO_4$) afforded the residue (26.3 g), which was purified by silica gel dry column chromatography (500 g, Et_2O) to give unreacted **12a** (1.53 g, 6.1%), and **13a** (9.93 g, 52% yield from the reacted material) as colorless plates, mp 144—145 °C (EtOH). IR (Nujol) ν: 3300, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.6—2.2 (1H, m), 2.2—2.7 (2H, m), 2.7—3.7 (5H, m), 4.6 (1H, br s), 7.3—7.8 (5H, m). MS m/z (20 eV, relative intensity): 230 (M^+, 100), 127 (20), 99 (32).

3-Phenyl-5-pyrrolidinomethyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (4a) and 3-Phenyl-5-pyrrolidinomethyl-7-(*p*-toluenesulfonyl)-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (4b)——*p*-TsCl (12.0 g, 62.9 mmol) was added to a solution of **13a** (11.1 g, 48.2 mmol) in anhydrous pyridine (50 ml) under ice cooling. The mixture was stirred at room temperature for 13 h, then *p*-TsCl (3.0 g, 15.8 mmol) was added and the stirring was continued for another 24 h. The mixture was evaporated and the residue (41.2 g) was separated by dry column chromatography on silica gel (1 kg, CH_2Cl_2) to afford 3-phenyl-7-(*p*-toluenesulfonyl)-5-(*p*-toluenesulfonyloxymethyl)-4,5,6,7-tetrahydroisoxazolo-[5,4-*b*]pyridine (**13b**, 5.62 g, 21.7%) as an oil, and 3-phenyl-5-(*p*-toluenesulfonyloxymethyl)-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (**13c**, 10.48 g, 56.6%) as an oil. Then, compound **13b** (5.62 g, 10.4 mmol) was mixed with pyrrolidine (50 ml) and heated under reflux for 3 h. The mixture was evaporated and the product was isolated (CH_2Cl_2, $MgSO_4$) as a colorless powder, which was recrystallized from $CHCl_3$–EtOH to give **4b** (3.34 g, 15.9% from **13a**) as colorless needles, mp 177—179 °C (AcOEt). IR (Nujol) ν: 1620, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.0 (5H, m), 2.2—2.7 (7H, m), 2.40 (3H, s), 3.0—3.5 (2H, m), 4.25 (1H, m), 7.2—8.0 (5H, m). MS m/z (20 eV, relative intensity): 437 (M^+, 1), 282 (19), 103 (8), 85 (10), 84 (100). *Anal.* Calcd for $C_{24}H_{27}N_3O_3S$: C, 65.88; H, 6.22; N, 9.60; S, 7.33. Found: C, 65.65; H, 6.00; N, 9.31; S, 7.29. Compound **4b** was converted into the hydrochloride in a usual manner to give **4b**·HCl as colorless needles, mp 208—209 °C (EtOH). IR (Nujol) ν: 2450, 1635 cm^{-1}. *Anal.* Calcd for $C_{24}H_{28}ClN_3O_3S$: C, 60.81; H, 5.95; Cl, 7.48; N, 8.87; S, 6.76. Found: C, 60.45; H, 5.71; Cl; 7.73; N, 8.58; S, 6.70.

Compound **13c** (10.48 g, 27.3 mmol) was mixed with pyrrolidine (70 ml) and refluxed for 3 h. The mixture was evaporated, and a usual product isolation gave the residue (16.93 g), which was purified by dry column chromatography on Al_2O_3 (400 g, CH_2Cl_2) to afford **4a** (6.08 g, 44.6% from **13a**) as colorless plates, mp 124—127 °C (PhH). IR (Nujol) ν: 3150, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.0 (4H, m), 2.0—2.8 (9H, m), 2.8—3.8 (2H, m), 4.7 (1H, br s), 7.2—7.9 (5H, m). MS m/z (relative intensity): 283 (M^+, 3), 225 (10), 214 (11), 212 (15), 84 (100). *Anal.* Calcd for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.47; N, 14.83. Found: C, 71.95; H, 7.66; N, 15.14. Compound **4a** was converted into the hydrochloride in a usual manner to give **4a**·HCl as a colorless powder, mp 175—178 °C (MeOH). IR (Nujol) ν: 2580, 2480, 1650 cm^{-1}.

7-Benzoyl-3-phenyl-5-pyrrolidinomethyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (4c)——A mixture of **4a** (10.05 g, 35.5 mmol), PhCOCl (7.50 g, 53.4 mmol), and pyridine (30 ml) was allowed to stand overnight at room temperature. The product was filtered off, and washed with $CHCl_3$, AcOEt, 5% aqueous $KHCO_3$, 1 N HCl, and H_2O to give **4c**·HCl (6.08 g, 40.4%) as colorless plates, mp 217—219 °C. IR (Nujol) ν: 2600, 2500, 1660, 1620 cm^{-1}. MS m/z (relative intensity): 387 (M^+ of **4c** as a free base, 4), 213 (5), 105 (8), 85 (7), 84 (100). *Anal.* Calcd for $C_{24}H_{26}ClN_3O_2$: C, 67.99; H, 6.18; N, 9.91. Found: C, 67.84; H, 6.04; N, 10.00. The combined aqueous layer was basified with dilute NaOH, the product was isolated ($CHCl_3$, $MgSO_4$) and the residue (9.04 g) was purified by dry column chromatography on Al_2O_3 (500 g, light petroleum–CH_2Cl_2, 2:1) to give **4c** (2.26 g, 16.4%) as an oil. IR (neat)

v: 1710, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.1 (5H, m), 2.3—2.9 (5H, m), 3.2—3.8 (5H, m). MS *m/z* (relative intensity): 387 (M^+, 4), 225 (4), 213 (4), 105 (8), 85 (7), 84 (100).

7-Benzyl-3-phenyl-5-pyrrolidinomethyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (4d)——$LiAlH_4$ (1.50 g, 39.5 mmol) was added in portions to a solution of **4c**·HCl (2.8 g, 6.6 mmol) in anhydrous THF (150 ml) under N_2 and ice cooling. The mixture was stirred at room temperature for 5 h, the reaction mixture was quenched with H_2O, and the product was isolated (AcOEt, $MgSO_4$). HCl gas was passed through a solution of the residue (3.20 g) in AcOEt (25 ml) and the product was recrystallized to give **4d**·HCl (2.02 g, 74.6%), mp 170—172 °C (AcOEt–MeOH) as a colorless powder. IR (Nujol) *v*: 2600, 1650, 1605 cm^{-1}. *Anal.* Calcd for $C_{24}H_{28}ClN_3O$: C, 70.31; H, 6.88; Cl, 8.65; N, 10.25. Found: C, 70.22; H, 6.96; Cl, 8.71; N, 10.20. Compound **4d**·HCl was dissolved in H_2O, basified with $NaHCO_3$, and extracted with AcOEt. The organic layer was dried over $MgSO_4$, evaporated, and recrystallized from hexane–AcOEt to give **4d** as colorless needles, mp 121—123 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.2 (5H, m), 2.2—3.0 (4H, m), 3.0—3.9 (6H, m), 4.65 (2H, s), 7.2—7.9 (10H, m). MS *m/z* (relative intensity): 225 (11), 214 (9), 212 (11), 180 (7), 152 (7), 84 (100). *Anal.* Calcd for $C_{24}H_{27}N_3O$: C, 77.18; H, 7.29; N, 11.25. Found: C, 77.31; H, 7.24; N, 10.89.

5-Hydroxymethyl-6-oxo-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (12c)——$NaBH_4$ (9.20 g, 243 mmol) and LiBr (20.00 g, 230 mmol) were added in portions to a solution of **12a** (30.1 g, 105 mmol) in 1,2-dimethoxyethane (550 ml) under ice cooling, and the stirring was continued at room temperature for 5 h. The reaction mixture was quenched with H_2O, and neutralized with dilute HCl. Product isolation (AcOEt, $MgSO_4$) gave an oil, which crystallized, and was recrystallized from CH_2Cl_2 to afford **12c** (4.26 g, 16.6%). The mother liquor was evaporated and the residue (25.68 g) was separated by column chromatography on silica gel (1 kg, hexane–AcOEt, 1 : 1, next AcOEt alone) to give **13a** (2.81 g, 11.6%) and **12c** (2.15 g, 8.4%) as colorless plates, mp 196—197 °C (EtOH). IR (Nujol) *v*: 3400, 1690, 1655 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 3.22 (3H, br s), 4.3—4.5 (2H, m), 7.3—8.2 (5H, m). MS *m/z* (relative intensity): 244 (M^+, 7), 169 (25), 105 (100), 104 (28), 77 (25). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.91; H, 4.91; N, 11.39. Further elution with AcOEt, and then with AcOEt–acetone (1 : 1) gave **11c** (12.66 g, 48.5%) as an oil. IR (Nujol) *v*: 3300, 1645 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 2.0—2.6 (1H, m), 2.92 (2H, d, J=7 Hz), 4.05 (4H, d, J=5 Hz), 5.7 (4H, br s), 7.2—8.2 (5H, m). MS *m/z* (relative intensity): 248 (M^+, 25), 173 (79), 145 (38), 119 (38), 105 (100), 104 (67).

5-Dimethylaminomethyl-6-oxo-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4,-*b*]pyridine (5a)——A mixture of **12c** (196 mg, 0.803 mmol), *p*-TsCl (600 mg, 3.15 mmol), and anhydrous pyridine (3 ml) was stirred at room temperature for 2 h. The mixture was quenched with H_2O and evaporated, and the residue (1.47 g) was purified by dry column chromatography on silica gel (30 g, CH_2Cl_2–Et_2O, 10 : 1) to afford 6-oxo-3-phenyl-5-*p*-toluenesulfonyloxymethyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (**12e**, 260 mg) as an oil. Me_2NH gas was passed through a solution of **12e** (260 mg, 0.653 mmol) in pyridine (3 ml) for 10 min under ice cooling. The mixture was stirred at room temperature overnight, and evapoated. Recrystallization of the crystalline residue from EtOH gave **5a** (152 mg, 70% from **12c**) as colorless plates, mp 154—160 °C (EtOH). IR (Nujol) *v*: 1700, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15 (6H, s), 2.3—3.2 (6H, m), 7.4—7.9 (5H, m). MS *m/z* (20 eV, relative intensity): 271 (M^+, 11), 226 (28), 168 (37), 105 (53), 59 (61), 58 (100). *Anal.* Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.51; H, 6.23; N, 15.32.

Compound **5b** was obtained as colorless plates in the same manner in 51% yield from **12d**, mp 151—153 °C (EtOH–H_2O). IR (Nujol) *v*: 1700, 1640 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, d, J=7 Hz), 2.15 (6H, s), 2.1—2.7 (4H, m), 3.27 (1H, q, J=7 Hz), 7.3—7.9 (5H, m). MS *m/z* (20 eV, relative intensity): 285 (M^+, 0.7), 226 (5), 225 (19), 105 (6), 59 (7), 58 (100). *Anal.* Calcd for $C_{16}H_{19}N_3O_2$: C, 67.34; H, 6.71; N, 14.73. Found: C, 67.29; H, 6.60; N, 14.45.

***N*-Methyl-*N*-(3-phenyl-5-isoxazolyl)-1-methylnipecotamide (6a)**——A solution of EtMgBr, freshly prepared from Mg (0.85 g, 35.0 mmol) and EtBr (2.82 g, 25.9 mmol) in anhydrous THF (25 ml), was added dropwise to a solution of 5-methylamino-3-phenylisoxazole (**14b**, 6.10 g, 35.0 mmol) in anhydrous THF (35 ml) under ice cooling. The mixture was stirred at room temperature for 30 min, then ethyl 1-methylnipecotate (3.00 g, 17.5 mmol) in anhydrous THF (7 ml) was added and the whole was stirred at room temperature for 30 min, and heated under reflux for another 3 h. The reaction mixture was quenched with H_2O and evaporated. The residue was dissolved in Et_2O and filtered. The filtrate was extracted with 2 N HCl, and the aqueous layer was washed with Et_2O and basified with 7% NH_4OH. Extraction with Et_2O and evaporation of the solvent gave **6a** (3.87 g, 73.8% from ethyl 1-methylnipecotate) as an oil. IR (neat) *v*: 1685, 1620, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.4 (6H, m), 2.27 (3H, s), 2.6—3.1 (3H, m), 3.42 (3H, s), 6.48 (1H, s), 7.3—7.9 (5H, m). MS *m/z* (relative intensity): 299 (M^+, 3), 282 (13), 126 (49), 124 (33), 98 (100), 97 (29), 70 (33), 58 (36).

Compound **6a** was converted into the fumarate in a usual manner to give **6a**·fumarate as colorless plates, mp 210—213 °C (CH_3COCH_3). *Anal.* Calcd for $C_{21}H_{25}N_3O_6$: C, 60.71; H, 6.07; N, 10.12. Found: C, 60.52; H, 6.09; N, 9.95.

Compound **14b** and ethyl 1-ethylnipecotate were treated in the same manner to give *N*-methyl-*N*-(3-phenyl-5-isoxazolyl)-1-ethylnipecotamide (**6b**, 81.2%) as an oil. MS *m/z* (relative intensity): 313 (M^+, 14), 298 (39), 140 (70), 138 (45), 112 (100), 84 (38), 72 (37). Compound **6b**·fumarate as colorless plates, mp 183—184 °C (CH_3COCH_3). *Anal.* Calcd for $C_{22}H_{27}N_3O_6$: C, 61.52; H, 6.34; N, 9.79. Found: C, 61.81; H, 6.10; N, 9.45.

Compound **14b** and ethyl 1-propylnipecotate were treated in the same manner to give *N*-methyl-*N*-(3-phenyl-5-isoxazolyl)-1-propylnipecotamide (**6c**, 57.2%) as an oil. MS *m/z* (relative intensity): 327 (M^+, 5), 298 (100), 157 (17),

155 (21), 144 (20), 126 (23). Compound **6c**·fumarate as colorless plates, 139—140 °C (CH_3COCH_3). *Anal.* Calcd for $C_{23}H_{29}N_3O_6$: C, 62.29; H, 6.59; N, 9.48. Found: C, 62.15; H, 6.71; N, 9.20.

Compound **14b** and ethyl 1-isopropylnipecotate were treated in the same manner to give *N*-methyl-*N*-(3-phenyl-5-isoxazolyl)-1-isopropylnipetamide (**6d**, 77.3%) as an oil. MS *m/z* (relative intensity): 327 (M^+, 14), 312 (100), 126 (23), 110 (36), 84 (31), 56 (26). Compound **6d**·fumarate as colorless plates, mp 144—146 °C (CH_3COCH_3). *Anal.* Calcd for $C_{23}H_{29}N_3O_6$: C, 62.29; H, 6.59; N, 9.48. Found: C, 62.33; H, 6.54; N, 9.60.

2-Ethylamino-*N*-(3-phenyl-5-isoxazolyl)acetamide (14d)——Chloroacetyl chloride (10.64 g, 94.2 mmol) was added to a mixture of 5-amino-3-phenylisoxazole (**14a**, 5.68 g, 35.5 mmol), Et_3N (8.93 g, 88.2 mmol), and CH_2Cl_2 (60 ml) under ice cooling and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with H_2O under ice cooling, and washed with aqueous Na_2CO_3, and H_2O. The organic layer was dried over $MgSO_4$, and evaporation of the solvent gave crude 2-chloro-*N*-(3-phenyl-5-isoxazolyl)acetamide (**14c**, 12.14 g). A solution of $EtNH_2$ (9.5 g, 211 mmol) and Et_3N (21 g, 208 mmol) in $CHCl_3$ (35 g) was added to a suspension of **14c** (12.14 g) in $CHCl_3$ (130 ml) under ice cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated and the residue was dissolved in 0.2 N HCl. The aqueous layer was washed with AcOEt, basified with aqueous Na_2CO_3, and extracted with AcOEt. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to give **14d** (6.16 g, 70.7% from **14a**) as an oil. IR (neat) *v*: 3200, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz), 2.73 (2H, q, J=7 Hz), 3.45 (2H, s), 4.8 (2H, br s), 6.70 (1H, s), 7.3—8.0 (5H, m).

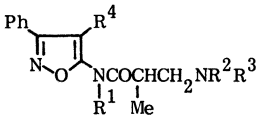
5-[2-(*N*-*tert*-Butoxycarbonyl-*N*-ethyl)aminoethyl]amino-3-phenylisoxazole (14f)——A solution of **14d** (49.91 g, 204 mmol) in anhydrous THF (400 ml) was added dropwise to a suspension of $LiAlH_4$ (30 g, 791 mmol) in anhydrous THF (800 ml) under N_2 with ice cooling. The reaction mixture was stirred at room temperature for 6 h, then quenched with H_2O (100 ml) under ice cooling. The organic layer was dried over $MgSO_4$, and evaporated to afford 5-(2-ethylaminoethyl)amino-3-phenylisoxazole (**14e**, 43.74 g) as an oil. IR (neat) *v*: 3280, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 2.2—3.0 (5H, m), 3.1—3.5 (2H, m), 5.25 (1H, s), 5.3 (1H, br s), 7.2—7.9 (5H, m). A solution of **14e** (43.74 g) in $CHCl_3$ (270 ml) was mixed with Et_3N (22.4 g, 221 mmol) and a solution of *tert*-butyl S-(4,6-dimethylpyrimidin-2-yl)thiocarbonate (50 g, 208 mmol) in $CHCl_3$ (110 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 h, then quenched with H_2O, and product isolation (CH_2Cl_2, $MgSO_4$) gave a residue (98 g), which was purified by column chromatography on silica gel (1 kg, CH_2Cl_2, then CH_2Cl_2–Et_2O, 10 : 1, and finally CH_2Cl_2–AcOEt, 10 : 1) to afford **14f** (42.42 g, 62.9% from **14d**) as an oil. IR (neat) *v*: 3300, 1680, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 1.48 (9H, s), 3.25 (2H, q, J=7 Hz), 3.43 (4H, s), 5.25 (1H, s), 5.3 (1H, br s), 7.2—7.9 (5H, m). MS *m/z* (relative intensity): 331 (M^+, 0.2), 146 (43), 106 (36), 105 (38), 58 (88), 57 (100).

1-Ethyl-6-methyl-4-(3-phenyl-5-isoxazolyl)hexahydro-1*H*-1,4-diazepin-5-one (7)——A solution of freshly distilled methacryloyl chloride (60 g, 574 mmol) in $CHCl_3$ (200 ml) was added dropwise over 1 h under ice cooling to a solution of **14f** (47.29 g, 143 mmol) and Et_3N (150 g, 1.48 mol) in $CHCl_3$ (600 ml). The reaction mixture was stirred at room temperature overnight and quenched with H_2O. The organic layer was washed with aqueous Na_2CO_3, dried over $MgSO_4$, and evaporated to give crude *N*-[2-(*N'*-*tert*-butoxycarbonyl-*N'*-ethyl)aminoethyl]-2-methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (**14g**, 104.26 g) as an oil. Compound **14g** (102.26 g) was dissolved in CF_3CO_2H (200 ml) under ice cooling and the reaction mixture was stirred at room temperature for 3 h. The mixture was evaporated, and the residue was dissolved in AcOEt, and washed with aqueous NaOH and H_2O. This solution was dried over $MgSO_4$ and evaporated to give crude *N*-(2-ethylaminoethyl)-2-methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (**14h**, 71.60 g) as an oil. A mixture of **14h** (69.60 g) and AcOH (30 g) in PhH (1 l) was heated under reflux overnight. The reaction mixture was evaporated, and the residue was diluted with AcOEt, and extracted with 0.2 N HCl. The aqueous layer was basified with aqueous NaOH, and extracted with AcOEt, The organic layer was dried over $MgSO_4$, and evaporation of the solvent gave a residue (9.40 g), which was purified by column chromatography on silica gel (500 g, hexane–Et_2O–Et_3N, 2 : 1 : 1) to afford **7** (2.94 g, 7.3% from **14f**) as an oil. IR (neat) *v*: 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 1.27 (3H, d, J=7 Hz), 1.9—3.5 (5H, m), 2.57 (2H, q, J=7 Hz), 3.5—4.8 (2H, m), 6.85 (1H, s), 7.3—7.9 (5H, m). MS *m/z* (relative intensity): 299 (M^+, 7), 195 (46), 127 (71), 103 (100), 71 (46). Compound **7**·HCl as colorless plates, mp 205—208 °C (MeOH). IR (Nujol) *v*: 2400—2300, 1700 cm^{-1}. *Anal.* Calcd for $C_{17}H_{22}ClN_3O_2$: C, 60.80; H, 6.60; Cl, 10.56; N, 12.51. Found: C, 61.02; H, 6.65; Cl, 10.56; N, 12.70.

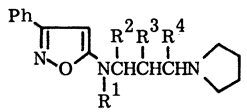
6-Oxo-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (12 g)——A mixture of **12a** (2.00 g, 6.99 mmol) and K_2CO_3 (2.00 g, 14.5 mmol) in BuOH (30 ml) was heated under reflux for 18 h. The reaction mixture was evaporated, and the residue was diluted with H_2O and acidified with 1 N HCl. Product isolation (AcOEt, $MgSO_4$) gave a residue (1.33 g), which was purified by column chromatography on silica gel (160 g, CH_2Cl_2, then CH_2Cl_2–AcOEt, 9 : 1) to afford **12g** (0.84 g, 56.1%) as colorless plates, mp 216—218 °C (THF). IR (Nujol) *v*: 1690, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.5—3.1 (4H, m), 3.4 (1H, br s), 7.4—7.9 (5H, m). MS *m/z* (20 eV, relative intensity): 214 (M^+, 75), 170 (15), 169 (79), 143 (26), 105 (100). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.08; H, 4.51; N, 12.92.

3-Phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (13d)——$LiAlH_4$ (100 mg, 2.64 mmol) was added in portions to a solution of **12g** (200 mg, 0.935 mmol) in anhydrous THF (10 ml) under ice cooling, and the reaction mixture was stirred at room temperature for 3 h. The mixture was quenched with H_2O, with cooling, and product isolation

(AcOEt, $MgSO_4$) gave a residue (174 mg), which was purified by silica gel thin layer chromatography (PhMe–Et_2O, 3 : 1) to afford **13d** (113 mg, 60.4%) as colorless plates, mp 112—115 °C (hexane–PhH). IR (Nujol) ν: 3200, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.2 (2H, m), 2.67 (2H, t, J=6 Hz), 3.2—3.6 (2H, m), 4.6 (1H, br s), 7.3—7.9 (5H, m). MS m/z (20 eV, relative intensity): 200 (M^+, 100), 199 (24), 105 (37), 69 (18), 68 (19). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C,

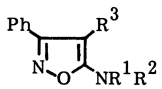


	R^1	NR^2R^3	R^4
1a	Me	NEt_2	H
1b	H	NMe_2	H
1c	Me	N(Et)Pr	H
1d	Me	NPr_2	H
1e	Me	NEt_2	Et
1f	Me	NEt_2	iso-Pr
1g	Pr	NEt_2	H



	R^1	R^2	R^3	R^4
2a	H	Me	H	H
2b	CH_2Ph	Me	H	H
2c	CH_2Ph	H	H	Me
2d	H	H	Me	H
2e	CH_2Ph	H	Me	H

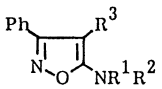
Chart 10



	R^1	R^2	R^3
15a	H	H	Et
15b	H	H	iso-Pr
15c	Me	H	Et
15d	Me	H	iso-Pr
15e	Me	$COC(Me)=CH_2$	Et
15f	Me	$COC(Me)=CH_2$	iso-Pr

Chart 11

TABLE VI. 4-Substituted 5-Amino-3-phenylisoxazoles (**15a—f**, **1e**, **f**)



Compd. No.	R^1	R^2	R^3	Yield	mp (°C)	Recrystn. solvent	IR (cm^{-1})	MS m/z (M^+)
15a	H	H	Et	37[a]	Oil	—	[b]	188
15b	H	H	iso-Pr	37[a]	Oil	—	1646, 1635 (neat)	202
15c	Me	H	Et	60[c]	103—105[h]	PhMe	[b]	202
15d	Me	H	iso-Pr	50[c]	102—103[i]	Hexane–AcOEt	[b]	216
15e	Me	$COC(Me)=CH_2$	Et	86	Oil	—	1675, 1635 (neat)	270
15f	Me	$COC(Me)=CH_2$	iso-Pr	77	Oil	—	[b]	284
1e	Me	$COCH(Me)CH_2NEt_2$	Et	28[d]	92—96[e,j]	CH_3COCH_3	1685, 1640 (neat)	343
1f	Me	$COCH(Me)CH_2NEt_2$	iso-Pr	25[d]	119—120[e,k]	CH_3COCH_3	1690, 1635 (neat)	357

a) Yield from benzonitrile. *b*) Not determined. *c*) Yield from **15a**, or **15b**, respectively. *d*) Yield of the free base. *e*) Fumarate. *f*) **15a**: ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz), 2.32 (2H, q, J=7 Hz), 4.60 (2H, br s), 7.2—7.7 (5H, m). **15b**: ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, d, J=7 Hz), 2.80 (1H, quintet, J=7 Hz), 4.33 (2H, br s), 7.46 (5H, s). **15c**: ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7 Hz), 2.32 (2H, q, J=7 Hz), 3.07 (3H, d, J=6 Hz), 4.20 (1H, br s), 7.2—7.7 (5H, m). **15d**: ^{1}H-NMR ($CDCl_3$) δ: 1.15 (6H, d, J=7 Hz), 2.75 (1H, quintet, J=7 Hz), 3.05 (3H, d, J=6 Hz), 4.05 (1H, br s), 7.42 (5H, s). **15e**: ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7 Hz), 1.92 (3H, t, J=1.5 Hz), 2.47 (2H, q, J=7 Hz), 3.32 (3H, s), 5.17 (2H, t, J=1.5 Hz), 7.2—7.8 (5H, m). **15f**: ^{1}H-NMR ($CDCl_3$) δ: 1.10 (6H, d, J=7 Hz), 1.93 (3H, br s), 2.82 (1H, quintet, J=7 Hz), 3.30 (3H, s), 5.23 (2H, br s), 7.45 (5H, s). *g*) **1e**·fumarate: *Anal.* Calcd for $C_{24}H_{33}N_3O_6$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.50; H, 7.22; N, 8.87. **1f**·fumarate: *Anal.* Calcd for $C_{25}H_{35}N_3O_6$: C, 63.40; H, 7.45; N, 8.87. Found: C, 63.53; H, 7.56; N, 8.59. *h*) Obtained as colorless plates. *i*) Obtained as colorless plates. *j*) Obtained as colorless plates. *k*) Obtained as colorless plates.

71.98; H, 6.04; N, 13.99. Found: C, 72.00; H, 6.07; N, 13.70.

7-(2-Methyl-2-propenoyl)-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (13e)——A solution of methacryloyl chloride (0.71 ml, 7.27 mmol) in $CHCl_3$ (3 ml) was added dropwise to a mixture of **13d** (960 mg, 4.80 mmol) and Et_3N (1.00 ml, 7.17 mmol) in $CHCl_3$ (15 ml) under ice cooling. The mixture was stirred at room temperature for 15 h, then Et_3N (1.00 ml, 7.17 mmol) and methacryloyl chloride (0.71 ml, 7.27 mmol) were added and the stirring was continued for another 4 h. The product was isolated ($CHCl_3$, $MgSO_4$) and the residue (2.74 g) was purified by column chromatography on silica gel (200 g, $CHCl_3$–AcOEt, 50 : 1) to afford **13e** (848 mg, 65.9%) as colorless plates, mp 106—107 °C. IR (KBr) *v*: 1660, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.1 (5H, br s), 2.75 (2H, t, J=7 Hz), 3.7—4.0 (2H, m), 5.32 (2H, d, J=7 Hz), 7.3—7.9 (5H, m).

7-(3-Diethylamino-2-methylpropanoyl)-3-phenyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridine (8)——A mixture of **13e** (800 mg, 2.98 mmol), Et_2NH (20 ml), and AcOH (0.1 ml) was heated under reflux for 17 h. The reaction mixture was evaporated, and the residue was dissolved in PhMe, and extracted with 0.4 N HCl. The aqueous layer was washed with PhMe, basified with conc. NH_4OH to pH 9, and extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to give **8** (964 mg, 94.7%) as colorless plates, mp 55—57 °C. IR (Nujol) *v*: 1685, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, t, J=7 Hz), 1.22 (3H, d, J=7 Hz), 1.7—3.0 (6H, m), 2.48 (4H, q, J=7 Hz), 3.4—4.0 (2H, m), 4.0—4.5 (1H, m), 7.3—7.9 (5H, m). MS *m/z* (relative intensity): 341 (M^+, 3), 105 (7), 87 (13), 86 (100), 58 (10). M_r (high-resolution MS). Calcd for $C_{20}H_{27}N_3O_2$: 341.2102. Found: 341.2090.

The syntheses of **1a**—**d**, **1g**, and **2a**—**e** were previously described.[1a,b]

3-Diethylamino-2,*N*-dimethyl-*N*-(4-ethyl-3-phenyl-5-isoxazolyl)propanamide (**1e**) and 3-diethylamino-2,*N*-dimethyl-*N*-(4-isopropyl-3-phenyl-5-isoxazolyl)propanamide (**1f**) were prepared in the same manner as described previously,[1b] from 5-amino-4-ethyl-3-phenylisoxazole (**15a**) and 5-amino-4-isopropyl-3-phenylisoxazole (**15b**), respectively, *via* compounds **15c**—**f**. The yields, physical constants, selected spectroscopic data, and the results of elemental analysis of **15a**—**f**, and of the free bases or fumarates of **1e**, **f** are listed in Table VI.

Pharmacology

Effects on the Conditioned-Avoidance Response in Rats——An automatic shuttle box designed in our laboratories was used as the testing apparatus. The conditioned stimuli (60 W light bulbs) were presented for 10 s, and an unconditioned stimulus (a scrambled electric shock of 100 V) was delivered to the grid floor for 3 s from 7 s after the onset of the conditioned stimuli. The intertrial interval was 60 s. Well trained and conditioned rats were given intraperitoneal doses of the test compounds. Three to six animals were used for each treatment. At 0.5, 1, 2, 4, 6, and 8 h after the administration, the response of each animal to the light was determined by 10 successive trials. The ED_{50} was defined as the dose suppressing the mean conditioned rate by 50% at the time of peak compound activity.

Other pharmacological procedures described in this report were carried out in the manner previously reported.[1]

Acknowledgement The authors wish to thank Dr. W. Tanaka, Research Laboratories, Nippon Kayaku Co., for encouragement throughout this work.

References and Notes

1) *a*) Part I: T. Tatee, S. Kurashige, A. Shiozawa, K. Narita, M. Takei, S. Ito, H. Miyazaki, H. Yamanaka, M. Mizugaki, T. Sakamoto, and H. Fukuda, *Chem. Pharm. Bull.*, **34**, 1634 (1986); *b*) Part II: T. Tatee, K. Narita, S. Kurashige, S. Ito, H. Miyazaki, H. Yamanaka, M. Mizugaki, T. Sakamoto, and H. Fukuda, *ibid.*, **34**, 1643 (1986).
2) This work was presented in part at the 3rd Symposium on Medicinal Chemistry, Osaka, Nov. 1981.
3) *a*) G. L. Olson, H. C. Cheung, K. D. Morgan, J. F. Blount, L. Todaro, L. Berger, A. B. Davidson, and E. Boff, *J. Med. Chem.*, **24**, 1026 (1981); *b*) A. R. Martin, S. H. Kim, H. I. Yamamura, and A. S. Horn, *ibid.*, **23**, 938 (1980); *c*) C. J. Grol, D. Dijkstra, W. Schunselaar, B. H. C. Westerink, and A. R. Martin, *ibid.*, **25**, 5 (1982); *d*) A. J. Elliott and H. Guzik, *J. Heterocycl. Chem.*, **18**, 861 (1981); *e*) M. J. Kukla, J. L. Bloss, and L. R. Brougham, *J. Med. Chem.*, **22**, 401 (1979); *f*) J. G. Cannon, T. Lee, H. D. Goldman, J. P. Long, J. R. Flynn, T. Verimer, B. Costall, and R. J. Naylor, *ibid.*, **23**, 1 (1980); *g*) Y. C. Clement-Cormier, L. R. Meyerson, H. Phillips, and V. E. Davis, *Biochem. Pharmacol.*, **28**, 3123 (1979).
4) D. L. Lee, C. J. Morrow, and H. Rapoport, *J. Org. Chem.*, **39**, 893 (1974).
5) M. Hori and H. Fujimura, Japan. Patent 130776 (1975) [*Chem. Abstr.*, **85**, 5705*y* (1976)].