[Chem. Pharm. Bull.
34(4)1634—1642(1986)]

Isoxazole Derivatives as Centrally Acting Muscle Relaxants. I. Synthesis and Activity of 5-(3-Aminopropyl)amino-3-phenylisoxazole Derivatives[1)]

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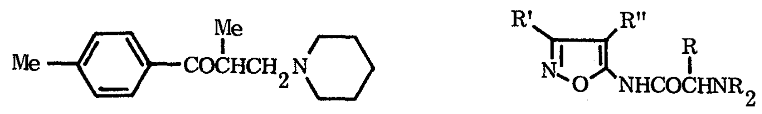
(Received September 3, 1985)

A series of 5-amino-3-phenylisoxazole derivatives was synthesized and evaluated as part of a search for new types of centrally acting muscle relaxants. The derivatives with an alkylaminopropyl moiety exhibited muscle relaxant activity comparable to that of tolperisone (**1**), but this activity was accompanied by strong general central nervous system (CNS) depressant and slight anticonvulsant activities.

On the other hand, the derivative with a propanamide moiety exhibited a favorable pharmacological profile for a selective muscle relaxant with little CNS depressant action.

Keywords——isoxazole derivative; muscle relaxant; propanamide; anticonvulsant; tolperisone; anemic decerebrate rigidity; propylenediamine; traction test; motor activity; optical resolution

In 1961, tolperisone (**1**), a Mannich base of *p*-methylpropiophenone, was reported to have muscle relaxant activity,[2)] and since 1973 it has been used clinically in Japan. Although no serious adverse effects have been found, further investigation is desirable to find a new muscle relaxant substance having less central nervous system (CNS) depressant activity.



tolperisone (**1**)

	R′	R″
2a:	Me	Me
2b:	Me	H
2c:	Ar	H

Chart 1

In connection with this, several studies on the pharmacology of isoxazole derivatives containing an α-aminoacetamide moiety at the 5-position have been reported, and Takahashi *et al.*[3)] and Uyeo *et al.*[4)] reported the analgesic activities of 2-amino-*N*-(3,4-dimethyl-5-isoxazolyl)acetamide (**2a**) and 2-amino-*N*-(3-methyl-5-isoxazolyl)acetamide (**2b**), respectively. Furthermore, muscle relaxant, antiinflammatory, and anticonvulsant activities were observed in similar isoxazole derivatives (**2a**) and (**2c**).[5)] Accordingly, we synthesized a series of *N*-substituted 5-amino-3-phenylisoxazole derivatives (**6**) containing an N–C–C–C–N moiety, instead of the known N–(C=O)–C–N type side chain, and found several derivatives to possess muscle relaxant activity as potent as that of **1**. A compound having an N–(C=O)–C–C–N moiety also exhibited similar potency in muscle relaxation and higher potency in anticonvulsant activity. In the present paper, we describe the synthesis of **6** and related compounds and their pharmacological activities.

Chemistry

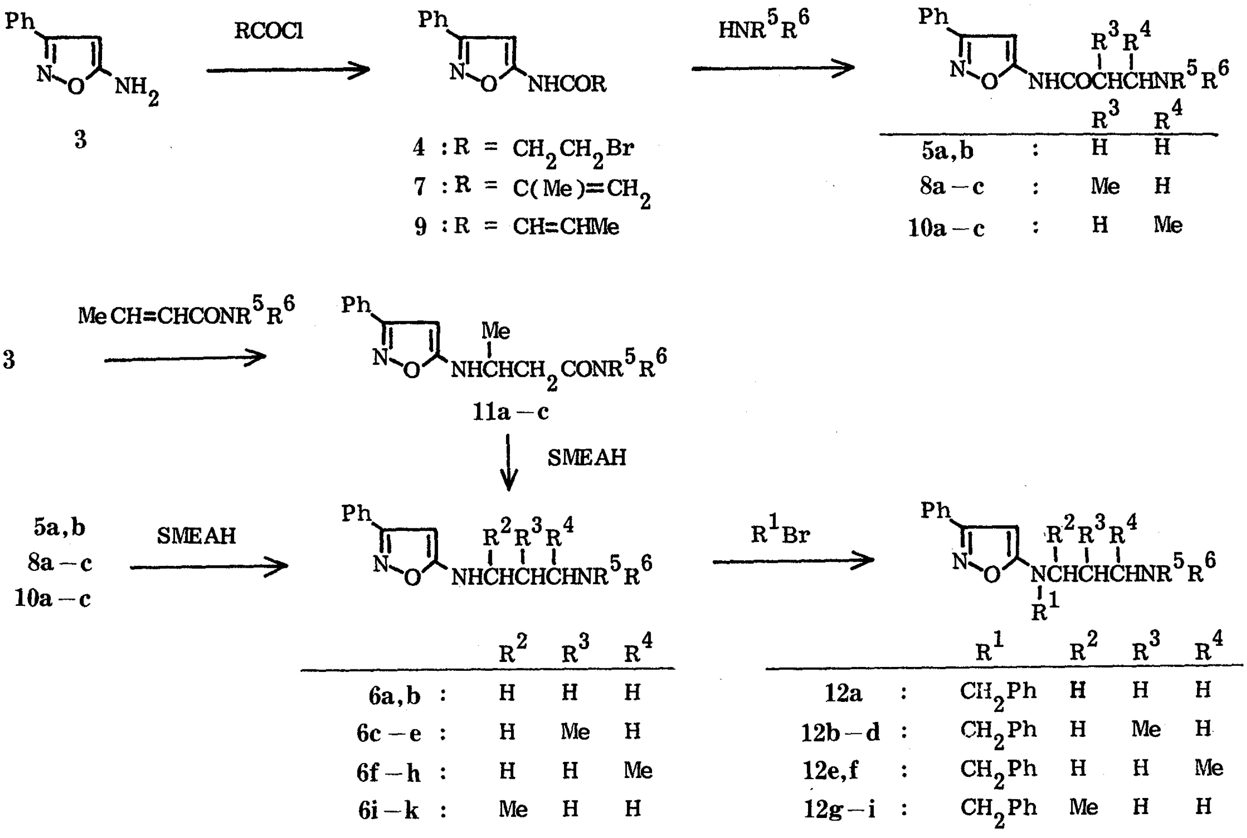
Isoxazole derivatives with a propylenediamine type side chain [N–C–C–C–N], or [N–(C=O)–C–C–N] at the 5-position were firstly synthesized by the acylation of 5-amino-3-phenylisoxazole (**3**) with an appropriate acid chloride, followed by reaction with amines, and the reduction of the resulting amino-amide by sodium bis-(2-methoxyethoxy)aluminum hydride (SMEAH).

When **3** was acylated with 3-bromopropionyl chloride in the presence of pyridine, 3-bromo-*N*-(3-phenyl-5-isoxazolyl)propanamide (**4**) was obtained in good yield. The bromo-amide (**4**) readily reacted with various *sec*-amines to give 3-dialkylamino-*N*-(3-phenyl-5-isoxazolyl)propanamides (**5a**, **b**), which were converted into 5-isoxazolylpropylenediamines (**6a**, **b**) by SMEAH reduction in benzene. This route is convenient for the preparation of the compounds having a straight side chain.

When methacryloyl chloride was used instead of 3-bromopropionyl chloride in the reaction of **3**, 2-methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (**7**) was obtained. The Michael addition of various amines to **7**, and the subsequent reduction of the resulting amides (**8a**—**c**) with SMEAH gave the *β*-branched 5-isoxazolylpropylenediamines (**6c**—**e**).

Similarly, the *γ*-methyl derivatives (**6f**—**h**) were synthesized by the acylation of **3** with crotonyl chloride, followed by Michael addition to the resulting aminoamides (**10a**—**c**) and SMEAH reduction.

The *α*-methyl derivatives (**6i**—**k**) were synthesized by the Michael addition of **3** to an appropriate *α*,*β*-unsaturated carboxamide in benzene in the presence of sodium amide,



4 : R = CH_2CH_2Br
7 : R = $C(Me)=CH_2$
9 : R = $CH=CHMe$

		R^3	R^4
5a,b	:	H	H
8a–c	:	Me	H
10a–c	:	H	Me

		R^2	R^3	R^4
6a,b	:	H	H	H
6c–e	:	H	Me	H
6f–h	:	H	H	Me
6i–k	:	Me	H	H

		R^1	R^2	R^3	R^4
12a	:	CH_2Ph	H	H	H
12b–d	:	CH_2Ph	H	Me	H
12e,f	:	CH_2Ph	H	H	Me
12g–i	:	CH_2Ph	Me	H	H

Chart 2

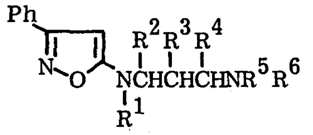
followed by the reduction of the resulting amino-amides (**11a**—**c**) with SMEAH in benzene.

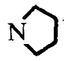
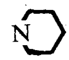
Compounds **12a**—**i** were prepared by the benzylation of **6** with benzyl bromide in the presence of sodium amide in benzene.

Optical isomers exist for the above compounds with a methyl group in the side chain. Among those having higher muscle relaxant activity, compound **8b** was resolved by the use of chiral tartaric acid, and gave the (+)-isomer (**8d**)·(+)-tartrate and the (−)-isomer (**8e**)·(−)-tartrate. The resolution of **12h** was also carried out in the same manner to afford the (+)-isomer (**12j**)·(+)-tartrate and the (−)-isomer (**12k**)·(−)-tartrate.

The yields, melting points, and results of elemental analysis of compounds **5**, **6**, **8**, **10**, **11**, **12** are listed in Tables III—V in the experimental section and pharmacological data are summarized in Tables I and II.

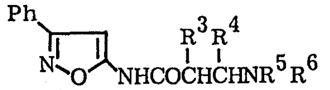
TABLE I. Pharmacological Data on 5-Isoxazolylpropylenediamines (**6a, c, d, f, h, j**, **12a**—**i**)



Compd. No.	R^1	R^2	R^3	R^4	NR^5R^6	R[a]	PTZ[b]	T[c]	D[d]	LD_{50}[e] (mg/kg)
						i.v.	*s.c.*	*i.p.*	*i.p.*	*i.p.*
6a	H	H	H	H		20	50	100	30	100—300
6c	H	H	Me	H		20	200	100	100	300—1000
6d	H	H	Me	H		10	50	30	30	100—300
6f	H	H	H	Me		20	300	100	30	100—300
6h	H	H	H	Me		6	[g]	30	10	30—100
6j	H	Me	H	H		5	50	10—30	30	100—300
12a	Bz[f]	H	H	H		5	[g]	30—100	30	100—300
12b	Bz	H	Me	H		20	200	300	30—100	300—1000
12c	Bz	H	Me	H		5	[g]	30	30	300
12d	Bz	H	Me	H		5	100	30—100	30	100—300
12e	Bz	H	H	Me		5	100	30	10—30	100—300
12f	Bz	H	H	Me		3	50	30	30	100
12g	Bz	Me	H	H		10	100	100	30—100	300—1000
12h	Bz	Me	H	H		5	100	10	30	100—300
12i	Bz	Me	H	H		6	[g]	30	10—30	100—300
1	Tolperisone					5	12.5	62.9	63.0	180

a—d) Activity is expressed as ED_{50} (mg/kg). *a*) Anemic decerebrate rigidity in rats. *b*) Anticonvulsant activity was examined against tonic extensor convulsion induced by pentylenetetrazole. *c*) Traction test in mice. *d*) Depression in motor activity determined by revolving wheel method. *e*) 50% lethal dose in mice. *f*) Bz: benzyl group. *g*) Not tested.

TABLE II. Pharmacological Data on 3-Amino-*N*-(3-phenyl-5-isoxazolyl)propanamides (**5a, b, 8a—c, 10a—c**)



Compd. No.	R^3	R^4	NR^5R^6	$R^{a)}$ *i.d.*	$PTZ^{b)}$ *i.p.*	$T^{c)}$ *i.p.*	$D^{d)}$ *i.p.*	$LD_{50}{}^{e)}$ (mg/kg) *i.p.*
5a	H	H		200	*f*)	100	30—100	300—1000
5b	H	H		*f*)	*f*)	30	30	300
8a	Me	H		140	300	100—300	30	1000
8b	Me	H		70	25	100	100	100—300
8c	Me	H		200	100—300	300	100	1000
10a	H	Me		320	300	300	10—30	1000
10b	H	Me		200	*f*)	30	100	100—300
10c	H	Me		*f*)	*f*)	300	100	1000
1	Tolperisone			70	31.4	62.9	63.0	180

a—e) See footnote to Table I. *f*) Not tested.

Pharmacology

Pharmacological data for the propylenediamines (**6a**, **c**, **d**, **f**, **h**, **j**, **12a—i**) are shown in Table I, along with those of tolperisone (**1**) for comparison. Rigidity produced by decerebration provides a good experimental model for spasticity. Anemic decerebrate rigidity in rats is thought to be due to hyperactivity of α-motoneurones, and this model was used in this study.[6] Togari *et al.* have recently investigated the action of centrally acting muscle relaxants on the decerebrate rigidity in rats.[7]

When evaluated in terms of the effect on anemic decerebrate rigidity, among the compounds **6** with a N–C–C–C–N moiety, compounds with a pyrrolidino or a piperidino group as the terminal amino group, and particularly compounds **12** with a benzyl group as R^1 showed muscle relaxant activity comparable to that of **1**, independently of the position of the methyl group in the carbon side chain (Table I). Compound **12f** showed higher activity than **1**. Compounds **6j**, **12a**, **c—e**, **h** were as potent as **1** in terms of activity on anemic decerebrate rigidity, but unfortunately all of these compounds were less potent than **1** against pentylenetetrazole (PTZ)-induced convulsion. Most of these compounds exhibited approximately similar or increased potency compared with **1** in the traction test and the depression in motor activity. Activities in these two tests are considered to be unfavorable for a selective muscle relaxant drug which has weak general CNS depressant activity.

On the other hand, among the compounds with the N–(C=O)–C–C–N moiety, compounds **8** with a methyl group as R^3 showed some muscle relaxant activity. In the anemic decerebrate rigidity model, when given intravenously, **8b** showed one-half of the activity of **1** ($ED_{50} = 10$ mg), but when injected intraduodenally, **8b** showed comparable activity to **1**. Table II shows these results together with the rigidity data (*i.d.*) for other compounds. Compound **8b** showed favorable results for a selective muscle relaxant; namely it showed higher anticonvulsant activity and lower activities in the traction test and the depression in motor activity, as compared with **1**. Compounds **8a**, and **10a**, with a morpholino group as the terminal amino group, showed higher potency in the depression in motor activity, and less muscle relaxant activity.

Compounds **11a**—**c** did not exhibit muscle relaxant or anticonvulsant activity, probably due to the absence of the basic amino group.

The traction test and anticonvulsant activity [PTZ and maximal electroshock seizure (MES)] tests were carried out on the optical isomers of **8b**, and no significant difference of activity was observed between **8d**·(+)-tartrate and **8e**·(−)-tartrate. In the case of the optical isomers of **12h**, **12j**·(+)-tartrate was as active as the racemic mixture of **12h**·fumarate at 5 mg/kg *i.v.* in the anemic decerebrate rigidity model, but **12k**·(−)-tartrate did not show activity at this dose.

These results suggest that **8b** may have potential as a selective muscle relaxant drug with weak CNS depressant action.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured on a JASCO model IR-G or a JASCO model A-202 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured using a JEOL JNM-PMX60 (60 MHz) spectrometer. Chemical shifts are expressed downfield from tetramethylsilane as an internal standard, and coupling constants are given in Hz. Mass spectra (MS) were taken on a Shimadzu 7000 mass spectrometer operating at 70 eV. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. The structures of all compounds are consistent with the IR, ^{1}H-NMR, and MS. For column chromatography, Merck Kieselgel 60 and Sumitomo Active Alumina KCG-30 were used.

Chemistry

3-Bromo-*N*-(3-phenyl-5-isoxazolyl)propanamide (4)——A solution of 3-bromopropionyl chloride (445.9 g, 2.6 mol) in $CHCl_3$ (500 ml) was added to a solution of 5-amino-3-phenylisoxazole (**3**, 320.4 g, 2 mol) and pyridine (210.3 ml, 2.6 mol) in $CHCl_3$ (3 l) below 5 °C. After being stirred for 3.5 h at room temperature, the reaction mixture was quenched with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give an oil (603 g), which solidified and was recrystallized from PhH–AcOEt to afford **4** (436 g, 74%), mp 149—150 °C. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.05 (2H, t, J=7 Hz), 3.73 (2H, t, J=7 Hz), 6.73 (1H, s), 7.3—8.0 (5H, m), 12.2 (1H, s). MS m/z (relative intensity): 296 (M^+, 9), 294 (M^+, 9), 160 (100), 144 (47), 132 (31), 77 (32). *Anal.* Calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.83; H, 3.76; N, 9.49. Found: C, 48.65; H, 4.10; N, 9.33.

***N*-(3-Phenyl-5-isoxazolyl)-3-pyrrolidinopropanamide (5b)**——A mixture of **4** (29.5 g, 0.1 mol) and pyrrolidine (21.3 g, 0.3 mol) in anhydrous EtOH was heated under reflux for 2 h. The reaction mixture was evaporated under reduced pressure, diluted with H_2O, and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and evaporated, and the residue (29.6 g) was separated on a column of Al_2O_3 using PhH as an eluent to give a crude solid. Recrystallization gave **5b** (23.8 g). IR (KBr): 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.2 (4H, m), 2.3—3.1 (8H, m), 6.65 (1H, s), 7.3—8.0 (5H, m), 9.5—11.5 (1H, br s). MS m/z (relative intensity): 285 (M^+, 6), 105 (31), 104 (31), 103 (100), 97 (30).

Compound **5a** was prepared in the same manner as described above from **4** and *N*-methylpiperazine (see Table III).

2-Methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (7)——A solution of methacryloyl chloride (282 g, 2.7 mol) in $CHCl_3$ (300 ml) was added dropwise to a solution of **3** (320 g, 2 mol) and pyridine (243 ml, 3 mol) in $CHCl_3$ (2 l) at −10—−5 °C. After being stirred at −5 °C for 2 h, the reaction mixture was quenched with H_2O, and extracted with AcOEt. The organic layer was dried over $MgSO_4$, and evaporated to give a crude solid, which was recrystallized from AcOEt–MeOH to afford **7** (329 g, 72%), mp 180—183 °C. IR (Nujol): 1695, 1615 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.0 (3H, br s), 5.7 (1H, br s), 6.0 (1H, br s), 6.78 (1H, s), 7.3—8.0 (5H, m). MS m/z (relative intensity): 228 (M^+, 9), 117 (32), 102 (32), 69 (95), 41 (100), 39 (38). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.26; H, 5.24; N, 12.05.

2-Methyl-*N*-(3-phenyl-5-isoxazolyl)-3-pyrrolidinopropanamide (8b)——A mixture of **7** (27.4 g, 0.12 mol) and pyrrolidine (17.1 g, 0.24 mol) in EtOH (100 ml) was heated under reflux for 8 h. The reaction mixture was evaporated under reduced pressure, and the residue was diluted with H_2O and extracted with AcOEt. The organic layer was dried over Na_2SO_4, evaporated under reduced pressure, and recrystallized to give **8b** (31.5 g). IR (Nujol): 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, d, J=7 Hz), 1.7—2.1 (4H, m), 2.3—3.1 (7H, m), 6.68 (1H, s), 6.68 (1H, s), 7.2—8.0 (5H, m). MS m/z (relative intensity): 299 (M^+, 7), 85 (27), 84 (100), 70 (35), 55 (28), 42 (54).

Compounds **8a**, **c** were prepared in the same manner from **7** with morpholine and piperidine, respectively (see Table III).

TABLE III. 3-Amino-*N*-(3-phenyl-5-isoxazolyl)propanamides (**5a, b, 8a—c, 10a—c**)

Compd. No.	Yield[a]	mp (°C)[b]	Recrystn.[b] solvent	Formula	Analysis (%) Calcd (Found) C	H	N
5a	71	157—159	Hexane–PhH	$C_{17}H_{22}N_4O_2$	64.94	7.05	17.82
					(64.70	7.23	17.60)
5b	84	81—82	Hexane–AcOEt	$C_{16}H_{19}N_3O_2$	67.34	6.71	14.73
					(67.12	6.85	14.67)
8a	84	148—149	Hexane–PhH	$C_{17}H_{21}N_3O_3$	64.74	6.71	13.33
					(65.03	6.82	12.95)
8b	88	107—108	Hexane–AcOEt	$C_{17}H_{21}N_3O_2$	68.20	7.07	14.04
					(68.55	6.91	13.88)
8c	82	115—116	Et_2O	$C_{18}H_{23}N_3O_2$	68.98	7.40	13.41
					(69.22	7.30	13.55)
10a	74	101—102	Hexane–PhH	$C_{17}H_{21}N_3O_3$	64.74	6.71	13.33
					(64.52	6.94	12.99)
10b	69	170—172[c]	Et_2O–AcOEt[c]	$C_{17}H_{21}N_3O_2 \cdot HCl$	60.80	6.60	12.51
					(60.53	6.64	12.86)
10c	90	94—95	Hexane–AcOEt	$C_{18}H_{23}N_3O_2$	68.98	7.40	13.41
					(68.67	7.32	13.24)

a) Yield of free base from **4**, **7**, or **9**. *b*) Melting point and recrystn. solvent are for the free base unless otherwise noted. *c*) Hydrochloride.

***N*-(3-Phenyl-5-isoxazolyl)-2-butenamide (9)**——A solution of crotonyl chloride (251 g, 2.4 mol) in $CHCl_3$ (800 ml) was added dropwise under cooling in an ice bath to a mixture of **3** (320 g, 2 mol) and Na_2CO_3 (276 g, 2.6 mol) in $CHCl_3$ (6 l). The reaction mixture was refluxed for 7 h, quenched with H_2O, and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized from PhH–AcOEt to give **9** (187 g, 44%), mp 155—157 °C. IR (KBr): 1680, 1640, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, dd, J=7, 1.5 Hz), 6.0 (1H, dq, J=15, 1.5 Hz), 6.73 (1H, s), 6.8—8.0 (6H, m), 9.3 (1H, br s). MS *m/z* (relative intensity): 228 (M^+, 17), 131 (18), 103 (36), 70 (14), 69 (100). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.32; H, 5.13; N, 11.98.

***N*-(3-Phenyl-5-isoxazolyl)-3-pyrrolidinobutanamide (10b)**——A mixture of **9** (27.4 g, 0.12 mol) and pyrrolidine (17.1 g, 0.24 mol) in EtOH (100 ml) was refluxed for 30 h. The reaction mixture was evaporated under reduced pressure, and the residue was diluted with H_2O and acidified with dilute HCl. The aqueous layer was washed with AcOEt, basified with aqueous Na_2CO_3, and extracted with AcOEt. The organic layer was evaporated, and the residue (36.2 g) was purified on a column of Al_2O_3 using PhH as an eluent to afford **10b** (24.6 g) as an oil. IR (neat): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=7 Hz), 1.5—2.1 (4H, m), 2.4—3.2 (7H, m), 6.56 (1H, s), 7.2—7.9 (5H, m). MS *m/z* (relative intensity): 299 (M^+, 20), 146 (43), 124 (88), 110 (71), 105 (76), 104 (100).

Compound **10b** was converted into the hydrochloride in a usual manner to give **10b**·HCl.

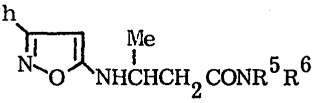
Compounds **10a, c** were prepared in the same manner from **9** with morpholine and piperidine, respectively. The products were purified by recrystallization as free bases.

4-[3-(3-Phenyl-5-isoxazolyl)aminobutanoyl]morpholine (11a)——Compound **3** (19.0 g, 119 mmol) was added in portions to a suspension of $NaNH_2$ (4.60 g, 118 mmol) in anhydrous PhH (200 ml). After dropwise addition of 4-(2-butenoyl)morpholine [bp 100—104 °C (0.2 mmHg), 18.4 g, 119 mmol] in anhydrous PhH (50 ml), the reaction mixture was refluxed for 16 h, then cooled to room temperature and quenched with H_2O. The mixture was extracted with PhH, dried over $MgSO_4$, and evaporated under reduced pressure. The residue (40.5 g) was purified on a column of Al_2O_3 using PhH as an eluent and recrystallized from Et_2O to give **11a** (23.4 g). IR (KBr): 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, J=7 Hz), 2.4—2.7 (2H, m), 3.1—4.2 (9H, m), 5.27 (1H, s), 5.50 (1H, d, J=9 Hz), 7.2—7.9 (5H, m). MS *m/z* (relative intensity): 315 (M^+, 3), 146 (100), 144 (82), 114 (88), 103 (58).

Compounds **11b, c** were prepared in the same manner as described above using *N*-(2-butenoyl)pyrrolidine [bp 75—78 °C (0.4 mmHg)] and *N*-(2-butenoyl)piperidine [bp 81—87 °C (0.7 mmHg)], respectively, instead of 4-(2-butenoyl)morpholine (see Table IV).

Typical Example for Preparation of 5-[(3-Aminopropyl)amino]-3-phenylisoxazoles (6)——5-[3-(4-Morpholinyl)-butyl]amino-3-phenylisoxazole (**6f**): A 70% toluene solution of SMEAH (43.2 g, 150 mmol) in anhydrous PhH (250 ml) was added dropwise to a solution of 3-(4-morpholinyl)-*N*-(3-phenyl-5-isoxazolyl)butanamide (**10a**, 21.4 g, 68 mmol) in anhydrous PhH (250 ml) at 5—10 °C. The reaction mixture was stirred at room temperature for 12 h,

TABLE IV. 3-(3-Phenyl-5-isoxazolyl)aminobutanamides (**11a**—**c**)



Compd. No.	NR^5R^6	Yield	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
11a		63	100—103	Et_2O	$C_{17}H_{21}N_3O_3$	64.74	6.71	13.33
						(64.52	6.68	13.15)
11b		89	156—158	Et_2O	$C_{17}H_{21}N_3O_2$	68.20	7.07	14.04
						(68.03	7.10	13.97)
11c		73	104—106	Et_2O	$C_{18}H_{23}N_3O_2$	68.98	7.40	13.41
						(68.86	7.46	13.11)

quenched with H_2O, and extracted with PhH. The organic layer was evaporated, and the residue was purified on a column of Al_2O_3 using PhH as an eluent to give a crude solid (17.8 g). Recrystallization from Et_2O afforded **6f** (11.9 g).

IR (Nujol): 3130, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, $J=7$ Hz), 2.3—3.2 (7H, m), 3.6—3.9 (4H, m), 6.56 (1H, s), 7.2—7.9 (5H, m). MS *m/z* (relative intensity): 301 (M^+, 5), 146 (49), 126 (100), 115 (34), 114 (100).

Compounds **6a**—**e**, **g**—**k** were prepared in the same manner as described above from **5a**, **b**, **8a**—**c**, **10b**, **c**, **11a**—**c**, respectively (see Table V).

Compounds **6h**, **i**, **k** were converted into the oxalate or the citrate, and the resulting salts were recrystallized from an appropriate solvent.

Typical Example for Preparation of 5-[*N*-(3-Aminopropyl)-*N*-benzyl]amino-3-phenylisoxazoles (12)——5-[*N*-Benzyl-*N*-(3-pyrrolidinobutyl)]amino-3-phenylisoxazole (**12e**): 5-(3-Pyrrolidinobutyl)amino-3-phenylisoxazole (**6g**, 7.38 g, 25.9 mmol) was added in portions to a suspension of $NaNH_2$ (1.51 g, 38.7 mmol) in anhydrous PhH (150 ml), and the reaction mixture was refluxed for 1.5 h. After cooling, benzyl bromide (5.51 g, 32.2 mmol) was added dropwise and the whole was stirred at 50 °C for 12 h. The reaction mixture was quenched with H_2O and extracted with PhH. The organic layer was dried over $MgSO_4$ and evaporated, and the residue was purified on a column of silica gel using hexane–acetone–NH_4OH (350 : 150 : 2) as an eluent to give **12e** (4.5 g, 46%) as an oil. IR (neat): 1605, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, $J=7$ Hz), 1.6—2.0 (6H, m), 2.3—2.7 (5H, m), 3.2—3.6 (2H, m), 4.50 (2H, s), 5.17 (1H, s), 6.9—7.8 (10H, m). MS *m/z* (relative intensity): 375 (M^+, 36), 263 (58), 231 (38), 230 (100), 167 (62), 160 (50).

Compound **12e** was converted into the fumarate in a usual manner to give **12e**·fumarate.

Compounds **12a**—**d**, **f**—**i** were prepared in the same manner as described above from **6b**—**e**, **h**—**k**, respectively (see Table V).

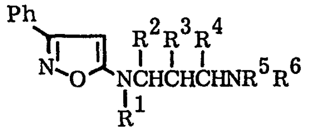
Compound **12g** was purified by recrystallization as the free base.

Optical Resolution of 2-Methyl-*N*-(3-phenyl-5-isoxazolyl)-3-pyrrolidinopropanamide (8b)——Compound **8b** (29.24 g, 97.7 mmol) was added to a solution of *d*-(+)-tartaric acid (15.0 g, 100 mmol) in EtOH, and the solution was stirred at room temperature. The resulting precipitate was filtered to give the (+)-isomer (**8d**)·(+)-tartrate (13.3 g, 30%), mp 157—158 °C. MS *m/z*: 299 (M^+). $[\alpha]_D^{25}$ +84.0° ($c=1$, MeOH). The combined mother liquor was evaporated under reduced pressure to give an oil, which was dissolved in H_2O, neutralized with Na_2CO_3, and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give an oil (149 g, 498 mmol). $[\alpha]_D^{25}$ −61.8° ($c=1$, MeOH). The oil (12.86 g, 43.0 mmol) was mixed with *l*-(−)-tartaric acid (6.45 g, 43.0 mmol) in EtOH (65 ml), and the resulting mixture was allowed to stand at room temperature to give a crude solid. Recrystallization from MeOH gave the (−)-isomer (**8e**)·(−)-tartrate (14.55 g, 33%), mp 157—158 °C. MS *m/z*: 299 (M^+). $[\alpha]_D^{25}$ −83.2° ($c=1$, MeOH). The free base was obtained by treating the tartrate with dilute NH_4OH, and extracted with Et_2O. The organic layer was recrystallized from Et_2O to give the (−)-isomer (**8e**), mp 78—80 °C. $[\alpha]_D^{23}$ −81.0° ($c=1$, MeOH).

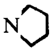
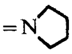
Optical Resolution of 5-[*N*-Benzyl-*N*-(1-methyl-3-pyrrolidinopropyl)]amino-3-phenylisoxazole (12h)——A solution of **12h** (22.35 g, 59.6 mmol) and *d*-(+)-tartaric acid (8.93 g, 59.5 mmol) in EtOH (80 ml) was stirred overnight. The precipitate was washed with a small amount of cold EtOH and recrystallized from EtOH, and then from PrOH to afford the (+)-isomer (**12j**)·(+)-tartrate (10.88 g, 34.8%), mp 120—121 °C, $[\alpha]_D^{25}$ +10.5° ($c=1$, MeOH). The free base was obtained by treating the tartrate with dilute NH_4OH and extracted with AcOEt. Evaporation of the solvent gave **12j** as an oil, $[\alpha]_D^{25}$ +3.10° ($c=1.1$, CH_3COCH_3).

Compound **12j** was converted into the fumarate in a usual manner to give **12j**·fumarate, mp 140—142 °C, $[\alpha]_D^{25}$ +1.8° ($c=1$, CH_3COCH_3).

TABLE V. 5-Isoxazolylpropylenediamines (**6a**—**k**, **12a**—**i**)



Compd. No.	Yield[a)]	Salt[b)]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
6a	69	—	101—103	PhH–THF	$C_{17}H_{24}N_4O$	67.97 (67.88	8.05 8.27	18.65 18.51)
6b[c)]	94	—	77—80	Hexane–Et_2O	$C_{16}H_{21}N_3O$	70.82 (70.53	7.80 7.89	15.49 15.40)
6c	89	—	145—147	Et_2O	$C_{17}H_{23}N_3O_2$	67.75 (67.82	7.69 7.95	13.94 13.58)
6d	77	—	79—82	Et_2O	$C_{17}H_{23}N_3O$	71.54 (71.76	8.12 8.15	14.73 14.65)
6e[d)]	96	—	99—100	Hexane–Et_2O	$C_{18}H_{25}N_3O$	72.20 (72.32	8.42 8.43	14.04 14.12)
6f	58	—	76—77	Et_2O	$C_{17}H_{23}N_3O_2$	67.75 (68.10	7.69 7.52	13.94 13.74)
6g[e)]	81	—	64—67	PhH–AcOEt	$C_{17}H_{23}N_3O$	71.54 (71.48	8.12 8.35	14.73 14.96)
6h	81	o	152—153	PhH–MeOH	$C_{20}H_{27}N_3O_5$	61.68 (61.44	6.99 7.12	10.79 10.70)
6i[f)]	88	c	75	Et_2O–AcOEt	$C_{23}H_{31}N_3O_9$	55.97 (56.11	6.33 6.42	8.52 8.38)
6j	79	—	88—89	Et_2O–AcOEt	$C_{17}H_{23}N_3O$	71.54 (71.68	8.12 8.10	14.73 14.54)
6k[g)]	95	c	66	Et_2O–AcOEt	$C_{24}H_{33}N_3O_8$	58.64 (58.45	6.77 6.83	8.55 8.49)
12a	56	HCl	157	Et_2O–AcOEt	$C_{23}H_{28}ClN_3O$	69.42 (69.52	7.09 6.97	10.56 10.34)
12b	75	c	80	Et_2O–AcOEt	$C_{30}H_{37}N_3O_9$	61.34 (60.98	6.39 6.26	7.20 7.15)
12c	94	c	60	Et_2O–AcOEt	$C_{30}H_{37}N_3O_8$	63.48 (63.54	6.57 6.63	7.40 7.08)
12d	97	f	55	Et_2O–AcOEt	$C_{29}H_{35}N_3O_5$	68.89 (68.77	6.98 6.90	8.31 8.24)
12e	46	f	157	CH_3COCH_3	$C_{28}H_{33}N_3O_5$	68.41 (68.32	6.77 6.89	8.55 8.65)
12f	85	o	146—147	PhH–MeOH	$C_{27}H_{33}N_3O_5 \cdot$ $1/2\,H_2O$	66.38 (66.20	7.01 7.13	8.60 8.48)
12g	27	—	130—133	Et_2O–CH_3COCH_3	$C_{24}H_{29}N_3O_2$	73.62 (73.28	7.47 7.30	10.73 10.51)
12h	41	f	142	Et_2O	$C_{28}H_{33}N_3O_5$	68.41 (68.53	6.77 6.74	8.55 8.71)
12i	36	HCl	52	Et_2O	$C_{25}H_{32}ClN_3O$	70.48 (70.16	7.57 7.72	9.87 10.09)

a) For compound **6**, yield of the free base in the reduction with SMEAH, and for compound **12**, yield of the free base in the benzylation are presented. *b*) o, oxalate; c, citrate; f, fumarate. *c*) $R^1=R^2=R^3=R^4=H$, $NR^5R^6=$N  *d*) $R^1=R^2=R^4=H$, $R^3=Me$, $NR^5R^6=$N  *e*) $R^1=R^2=R^3=H$, $R^4=Me$, $NR^5R^6=$N . *f*) $R^1=R^3=R^4=H$, $R^2=Me$, $NR^5R^6=$N O . *g*) $R^1=R^3=R^4=H$, $R^2=Me$, $NR^5R^6=$N 

The combined mother liquor was evaporated, and the residue was dissolved in H_2O, basified with $NaHCO_3$, and extracted with Et_2O. The organic layer was dried over $MgSO_4$, and evaporated to give a residue (12.87 g, 34.3 mmol), $[\alpha]_D^{25}$ $-2.52°$ ($c=1$, CH_3COCH_3). The residue was dissolved in PrOH (100 ml) and the solution was stirred after being mixed with *l*-(−)-tartaric acid (5.15 g, 34.3 mmol). The precipitate was filtered, and washed with PrOH. Recrystallization from PrOH gave the (−)-isomer (**12k**)·(−)-tartrate (11.27 g, 36%, mp 121—122 °C, $[\alpha]_D^{25}$ $-9.6°$ ($c=1$, MeOH).

Pharmacology

All doses were calculated as free bases. The test compounds were dissolved in saline or suspended in 0.5% carboxymethyl cellulose (CMC) solution.

Muscle Relaxant Activities——1) Effect on Anemic Decerebrate Rigidity in Rats: Male Wistar rats, weighing 350—450 g, were used in groups of at least three animals per dose. Under ether anesthesia, the animal was fixed on its back. The trachea was exposed and cut, and a plastic cannula was inserted. Esophagectomy was carried out. The rigidity model was prepared by ligations of the bilateral common carotid arteries and by cauterization of the basilar artery using the bipolar pincette electrode of a coagulator (Mizuho Ika Kogyo, MICRO-1C) according to the method described by Fukuda *et al.*[6] The anemic decerebrated rat was placed on its back with the hindlimbs and the head fixed. One end of a celluloid bar with a strain gauge (Shinko, M102) was put on the forelimps. The other end of the bar was pushed up by the rigid forelimbs. The output of the strain gauge (directly proportional to the force) was detected through a bridge circuit and recorded on a servocorder (Shimadzu, R-12M).

Inhibition ratio was calculated according to the following formula: Inhibition ratio (%) = [100 − (average tension (g) for 10 min at peak period)/(average tension (g) for 10 min before administration) × 100]. The 50% effective dose (ED_{50}) was calculated from the dose-dependent inhibition data.

2) Effect on Skeletal Muscle Tone: Traction Test[8]: Male ICR mice (6 weeks) were used in groups of ten animals. The animals were suspended by their forelimbs on a horizontal wire with a diameter of 2 mm. Normal animals could draw their hindlimbs up and hang from the wire within 10 s. The number of animals which failed to draw their hindlimbs up or dropped off the wire within 30 s was counted. The test compound was injected intraperitoneally, and ED_{50} values were calculated according to the Van der Waerden method.

Anticonvulsant Activities——1) Effect on Seizures Induced by PTZ: Six male ICR mice (8 weeks) per dose were used. PTZ (170 mg/kg) was injected intraperitoneally. The test compound was subcutaneously or intraperitoneally administered 30 min before the injection of the convulsant drug.

2) Effect on MES: Six male ICR mice (8 weeks) per dose were used. Electroshock (60 Hz, 50 mA, 2000 V for 0.2 s) was applied to the eyeballs using corneal electrodes. The test compound was intraperitoneally administered 30 min before the application of electroshock.

In both tests, the ability of the test compounds to abolish the hindlimb tonic extensor seizure was measured. ED_{50} was calculated from the dose-dependent inhibition data.

Depression in Motor Activity: Revolving Wheel Method[9]——Six male ICR mice weighing 28—30 g per dose were used. The test compound was injected intraperitoneally in a volume of 0.1 ml/10 g body weight, either dissolved in 0.9% w/v saline or suspended in 0.5% CMC solution. Saline or 0.5% CMC solution was given to control animals. Immediately after the administration, mice were put into activity cages, and the number of revolutions was measured and recorded every 10 min, for 2 h. ED_{50} was defined as the dose reducing the motor-activity level to below the mean −1.65 s.d. of the control, in half of the treated mice during the maximum-effect period.

The experiments were carried out between 9:00 a.m. and 4:00 p.m. in a sound-proof room at a temperature of 22 to 24 °C and a relative humidity of 60 to 70%.

Acute Toxicity——Four male ICR mice per dose were used. The test compound was intraperitoneally administered. The animals were observed for 72 h after the injection.

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

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