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Isoxazole Derivatives as Centrally Acting Muscle Relaxants. II.[1] Synthesis and Structure–Activity Relationship of 3-Amino-*N*-(3-phenyl-5-isoxazolyl)propanamides[2]

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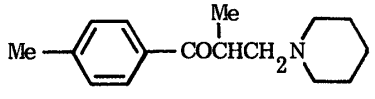
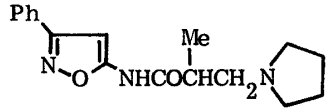
N-Substituted 3-amino-2-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamide derivatives (**5a—w**) were prepared, and their muscle relaxant and anticonvulsant activities were evaluated. Among the compounds with high potency, 3-diethylamino-2,*N*-dimethyl-*N*-(3-phenyl-5-isoxazolyl)propanamide (**5e**) was found to possess selective muscle relaxant and anticonvulsant activities. Compounds with carbon side chains other than the 2-methylpropanamide moiety did not give increased muscle relaxant activity. Optical isomers of **5e** were prepared from methyl (+)- and (−)-3-diethylamino-2-methylpropionates (**15a, b**), and the (+)-isomer (**5x**) was found to be twice as potent as the (−)-isomer (**5y**). The structure–activity relationship was studied with emphasis on the effects of the 3-amino moiety and of the substituent on the isoxazolyl 5-amino group. A good quadratic correlation equation was found between hydrophobicity and muscle relaxant activity.

Keywords——isoxazole derivative; muscle relaxant; propanamide; anticonvulsant; tolperisone; anemic decerebrate rigidity; hydrophobicity; optical resolution; structure–activity relationship

As described in the preceding paper, our studies to develop new types of muscle relaxant compounds led to the finding that 2-methyl-*N*-(3-phenyl-5-isoxazolyl)-3-pyrrolidinopropanamide (**5c**) exhibits activity as potent as that of tolperisone (**1**).[1] In an attempt to strengthen the muscle relaxant activity and selectivity relative to general central nervous system (CNS) depressant activity, we introduced an alkyl group onto the 5-amino group of the isoxazole ring. In the present paper, we describe the synthesis of *N*-substituted 3-amino-*N*-(3-phenyl-5-isoxazolyl)propanamides (**5, 12—14**), and their pharmacological activity, together with the result of a QSAR study of the synthesized compounds.



tolperisone (**1**)



5c

Chart 1

Chemistry

5-Monoalkylamino-3-phenylisoxazoles (**2b—f**) were synthesized by the acylation of 5-amino-3-phenylisoxazole (**2a**), followed by reduction of the resulting amides (**3b—f**) with lithium aluminum hydride, because **2b—f** were not obtained directly by the usual isoxazole formation. The aminoisoxazoles (**2a—h**) were then reacted with methacryloyl chloride under

basic conditions to give the 2-methyl-2-propenamides (**4a**—**h**), which were converted into the 3-amino-2-methylpropanamides (**5a**—**w**) by Michael addition reaction of various amines.

Compound **5i** could not be prepared by this route, due to the low reactivity of 2,5-dimethylpyrrolidine with **4b**. The magnesium salt of **2b**, formed by treatment with methylmagnesium bromide in tetrahydrofuran (THF), was subsequently heated with methyl 3-(2,5-dimethylpyrrolidino)-2-methylpropionate (**6**) in the same solvent to give **5i**.

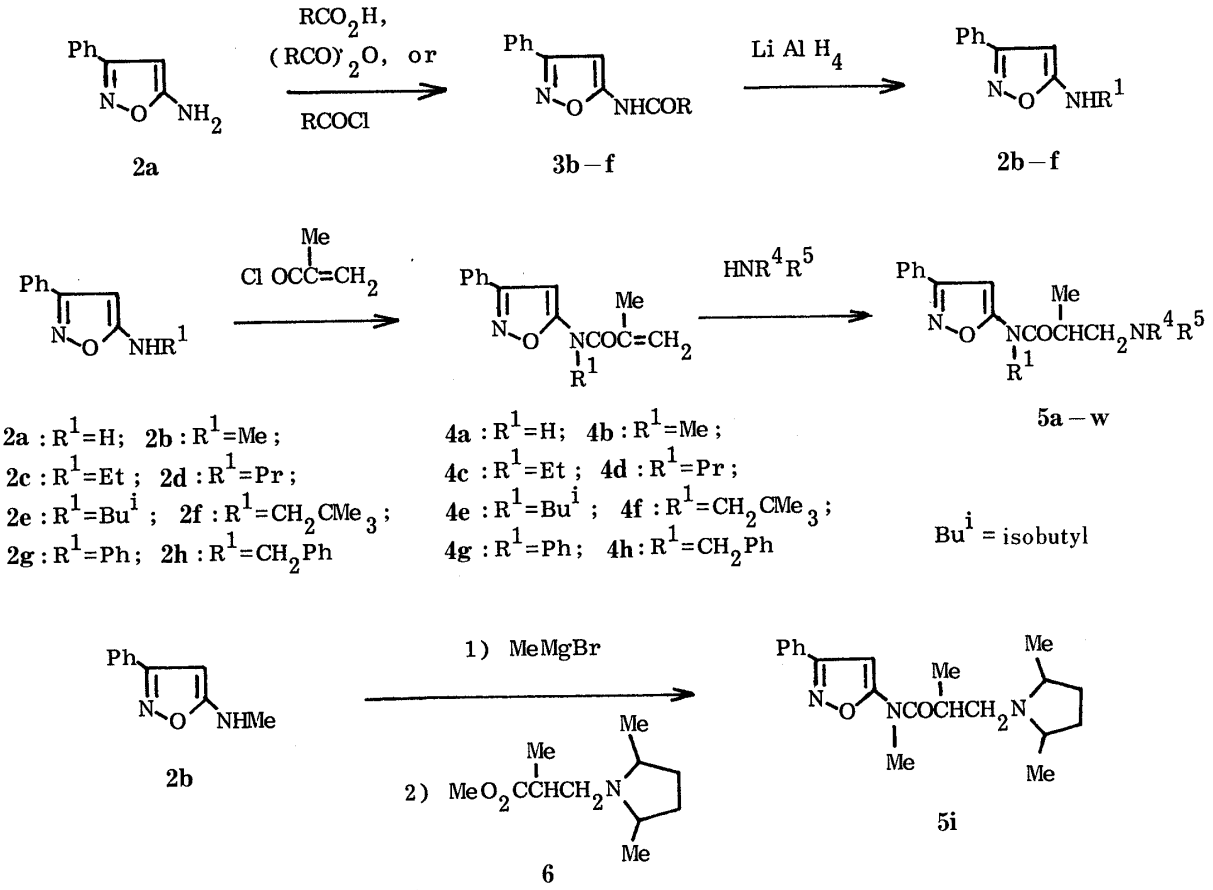


Chart 2

As an alternative route to prepare *N*-methyl-2-propenamides, *N*-methylation using methyl iodide and potassium fluoride-alumina in acetonitrile[3] was achieved in good yield. The 3-bromopropanamide (**7**)[1] was thus methylated with concomitant dehydrobromination to give *N*-methyl-2-propenamide (**8**), and similarly, the 2-butenamide (**9**)[1] gave *N*-methyl-2-butenamide (**10**).

2-Ethyl-*N*-methyl-2-propenamide (**11**) was synthesized by the acylation of **2b** with 2-ethyl-2-propenoyl chloride.[12]

The unsaturated amides (**8**, **10**, **11**) were converted into 3-aminopropanamides (**12**—**14**) by Michael addition of amines.

In order to prepare optical isomers of **5e**, a resolution of methyl 3-diethylamino-2-methylpropionate (**15**) was performed using chiral α-methylbenzylamine. D(+)-α-methylbenzylamine was treated with ethylmagnesium bromide in THF and subsequently heated with **15** in the same solvent to form a diastereomeric mixture of amides (**16a**, **b**). Two triplet signals (δ 1.00 for **16a** and δ 0.92 for **16b**) due to methyls of the diethylamino groups were observed in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The mixture of amides (**16a**, **b**) was separated by silica gel column chromatography, but due to the marginal separation and the occurrence of tailing, only pure **16a**, which eluted first, was obtained.

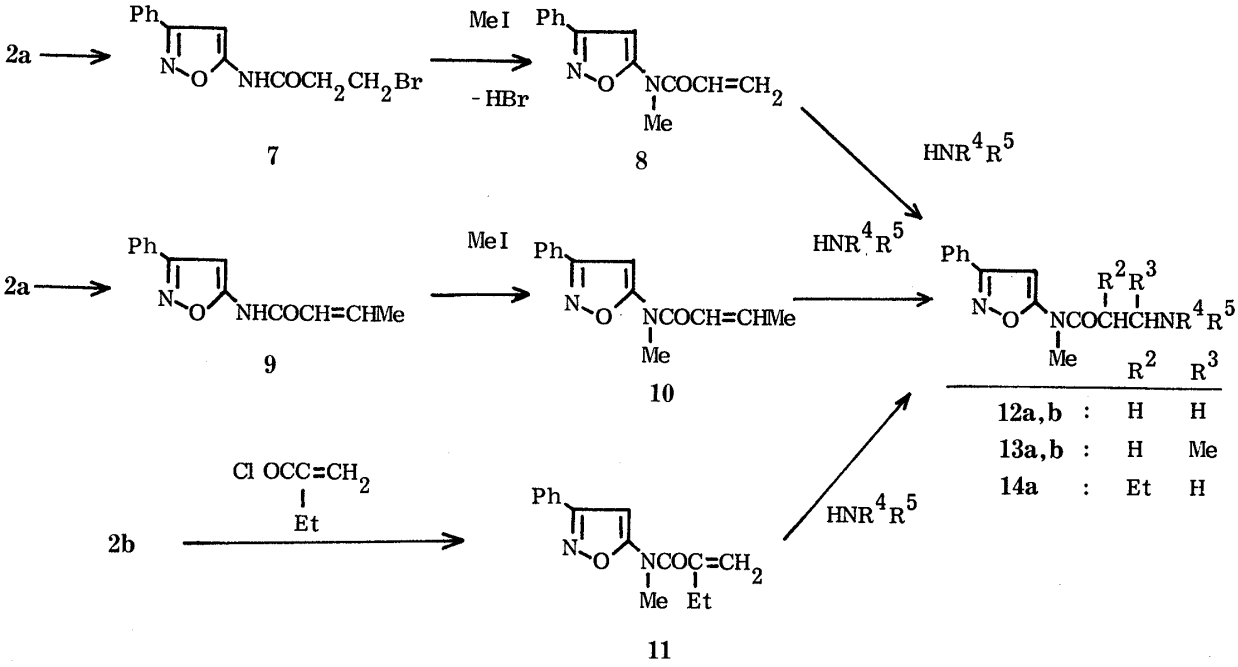


Chart 3

Similarly, the magnesium salt of L(−)-α-methylbenzylamine in THF was heated with **15** to give a diastereomeric mixture of **16c** and **16d**. Pure **16c** was obtained by column chromatography on silica gel.

Compound **16a** was smoothly reacted with boron trifluoride–methanol complex to give methyl (+)-3-diethylamino-2-methylpropionate (**15a**), which was heated with the magnesium salt of **2b** to form the (+)-isomer (**5x**). The (−)-isomer (**5y**) was obtained from the amide (**16c**) similarly, *via* the (−)-ester (**15b**).

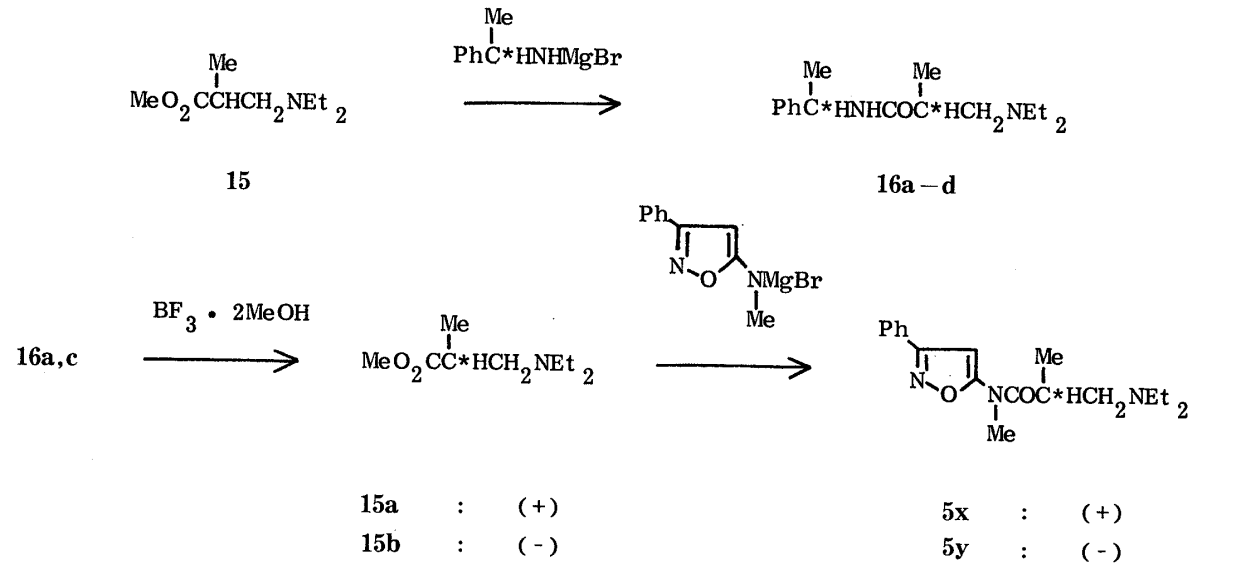
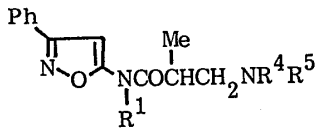


Chart 4

The yields, physical constants, and selected spectroscopic data of all the products (**2b—h**, **4b—h**, **5a—w**, **12a**, **b**, **13a**, **b**, **14a**) are listed in Tables VIII—XI in the experimental section, and the pharmacological data are summarized in Tables I—V.

TABLE I. Muscle Relaxant and Anticonvulsant Activities on 3-Amino-2-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamides (**5a—w**)



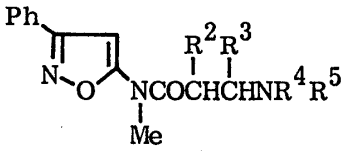
Compd. No.	R^1	NR^4R^5	R[a]		PTZ[b] ED_{50} (*i.p.*)[d]
			I[c]	ED_{50} (*i.v.*)[d]	
5a	H	NMe_2	*e*)	38.9	50
5b	H	NPr_2	5	12.0	79.3
5c	H		*e*)	10.0	17.7
5d	Me	NMe_2	*e*)	13.2	*e*)
5e	Me	NEt_2	63	3.0	14.0
5f	Me	N(Et)Pr	59	4.3	13.2
5g	Me	NPr_2	76	3.5	28.1
5h	Me		66	4.0	11.1
5i	Me		*e*)	2.5	8.1
5j	Me		67	3.6	*e*)
5k	Me		95	2.0	*e*)
5l	Et	NEt_2	78	3.6	12.5
5m	Et		73	3.8	22.3
5n	Pr	NEt_2	62	3.9	25—50
5o	Pr		35	10.5	25—50
5p	Bu^i	NMe_2	22	7.6	17.7
5q	Bu^i		58	4.2	28.1
5r	CH_2CMe_3	$NHPr^i$	59	4.1	*e*)
5s	CH_2CMe_3	NEt_2	39	6.5	*e*)
5t	Ph	NEt_2	90	3.0	14.0
5u	CH_2Ph	NMe_2	43	5.6	17.0
5v	CH_2Ph	NEt_2	45	5.4	35.4
5w	CH_2Ph		42	6.0	25
Tolperisone (**1**)			50	5.0	31.4

Dose was calculated as free base. *a*) Anemic decerebrate rigidity in rats. *b*) Anticonvulsant activity was examined against tonic extensor convulsion induced by pentylenetetrazole (PTZ). *c*) Inhibition ratio (%) at 5 mg/kg, *i.v.* *d*) ED_{50} is expressed as mg/kg. *e*) Not tested. Bu^i = isobutyl. Pr^i = isopropyl.

Pharmacology

Pharmacological data of compounds **5a—w** are shown in Table I. Muscle relaxant activity was tested in the anemic decerebrate rigidity model, and is shown as an inhibition ratio at 5 mg/kg *i.v.* and ED_{50} (*i.v.*). Anticonvulsant activity against pentylenetetrazole (PTZ)-induced seizure is shown as ED_{50} (*i.p.*). As regards R^1, replacement of hydrogen with a methyl group increased the potency for rigidity and anticonvulsion, but larger alkyl or aralkyl groups resulted in gradually decreased potency. Compounds **5e**, **i**, **k**, **t** exhibited muscle relaxant

TABLE II. Muscle Relaxant Activity of 3-Amino-*N*-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamides (**12a, b, 13a, b, 14a**)



Compd. No.	R^2	R^3	NR^4R^5	$R^{a)}$ $I^{a)}$
12a	H	H	NEt_2	26
12b	H	H	N⬡	4
13a	H	Me	NEt_2	30
13b	H	Me	N⬡	18
14a	Et	H	NEt_2	48[b)]

a) See footnote in Table I. *b*) Inhibition ratio at 2.5 mg/kg, *i.v.*

TABLE III. Muscle Relaxant, Anticonvulsant, and Central Depressant Activities of the Isoxazole Derivatives and Muscle Relaxants

Compound	$R^{a)}$	$A^{b)}$		$D^{c)}$
		PTZ	MES	
	i.v.	*i.p.*	*i.p.*	*i.p.*
5c	10.0	17.7	25.0	134
5e	3.0	14.0	25.0	56.1
Tolperisone (**1**)	5.0	31.4	61.5	63.0
Mephenesin	54.0	89.0	112	159
Baclofen	1.6	14.0	>50	5.3

Activity is expressed as ED_{50}. *a*) See footnote in Table I. *b*) Anticonvulsant activity against pentylenetetrazole (PTZ), or maximal electroshock (MES). *c*) Depression of motor activity determined by the revolving wheel method.

activity approximately twice as potent as that of tolperisone (**1**).

In order to identify the optimal propanamide moiety, muscle relaxant activity of **12a, b, 13a, b, 14a** was tested, and the results are shown in Table II. Compound **14a** (with an ethyl group as R^2) was twice as active as **1**, but other compounds were less potent than the corresponding 2-methylpropanamide derivatives.

For comparing the isoxazole derivatives tested with known muscle relaxant drugs (tolperisone, mephenesin, and baclofen), activity ratios (ED_{50} in depression of spontaneous motor activity/ED_{50} in muscle relaxant or anticonvulsant activity) were calculated as the protective index (PI) according to Share and McFarlane.[4)] Depression of spontaneous motor activity was used as an index of general CNS depression. Detailed data for **5c, e**, and the three muscle relaxant drugs are shown in Table III, and their PI values are given in Table IV. Baclofen showed the highest muscle relaxant activity among these five compounds, although its PI value was only three and PI values for anticonvulsant activity against PTZ and maximal electroshock (MES) were less than one. Compound **5c** showed the same PI value for rigidity as tolperisone (**1**), and **5e** showed a higher value than **1**. The PI values of **5c, e** for anticonvulsion were higher than those of the muscle relaxant drugs.

TABLE IV. Protective Index (PI)[a] of the Isoxazole Derivatives and Muscle Relaxants

Compound	R[b]	A[b]	
		PTZ	MES
5c	13	7.6	5.4
5e	19	4.0	2.2
Tolperisone (**1**)	13	2.0	1.0
Mephenesin	2.9	1.8	1.4
Baclofen	3.3	0.4	<0.1

a) PI = ED_{50} in depression in motor activity/ED_{50} in each test. *b*) See footnote in Table III.

TABLE V. Muscle Relaxant and Anticonvulsant Activities, and Acute Toxicities of Optically Resolved Isomers

Compound No.	R[a] *i.v.*	PTZ[a]			LD_{50} (mg/kg)[b]	
		i.p. (30 min)[c]	*p.o.* (10 min)	*p.o.* (60 min)	*i.v.*	*p.o.*
5e	3.4	8.5	42.2	46.5	31.0	367.7
5x	2.9	7.3	45.9	44.1	22.3	341.0
5y	6.9	14.7	42.2	34.2	50.0	367.7

Dose was calculated as fumarate. *a*) See footnote in Table I. Activity is expressed as ED_{50} (mg/kg). *b*) The 50% lethal dose in mice. *c*) Test compound was administered intraperitoneally 30 min before the injection of PTZ.

The muscle relaxant and anticonvulsant activities of **5e**, **x**, **y** are shown in Table V. The (+)-isomer (**5x**) was as potent as the racemic mixture (**5e**), and approximately twice as potent as the (−)-isomer (**5y**) in rigidity-reducing and anticonvulsant activities (*i.p.*), but when orally administered, these three showed identical anticonvulsant activity.

Structure–Activity Relationship

The pED_{50} values of compounds **5a**—**w** are shown in Table VI together with the hydrophobic parameters[5] of substituents, R^1 and NR^4R^5, used for calculation. Although π value is best established for aromatic substituents, it is available for a wide range of substituents and its additive nature is established, so the π value was used as a hydrophobic parameter. We considered π_1, π_2, the sum of π_1 and π_2, and quadratic terms of these three. Significant correlation equations are shown in Table VII.[6]

Equations 1—6 showed that no one linear or quadratic term of each parameter or their sum could account for the activity. Equation 7 indicated that a quandratic equation using $\pi_1 + \pi_2$ could give a reliable equation in terms of the F and t test, but the correlation coefficient was not satisfactory. With two more terms, an equation with improved r and identical F values was obtained as Eq. 8.

As this Eq. 8 was not easy to understand, it was plotted on a two-dimensional plane with π_1 on the horizontal axis and π_2 on the vertical axis, as shown in Fig. 1.[7] The π values of **5a**—**w** were also plotted on the same plane. This figure showed that potency is more dependent upon π_2, and is less sensitive to the increase of π_1. As the partition coefficient (log P) can be calculated by adding π values to the parent molecule, Eq. 7 showed a correlation between activity and partition coefficient of compounds **5a**—**w**.

The preference for Eq. 8 over Eq. 7 indicated that the hydrophobicity of the terminal amino moiety (NR^4R^5) has a greater influence on the activity than that of the substituent (R^1)

TABLE VI. Hydrophobic Parameters and Activity of Compounds **5a**—**w** in the Anemic Decerebrate Rigidity Test, Used in Regression Analysis

Compound No.	π_1[a]	π_2[a]	pED_{50} (μmol/kg) Observed	Calcd[b]	Observed − calcd
5a	0	0.18	−2.16	−1.94	−0.22
5b	0	2.3[c]	−1.56	−1.30	−0.26
5c	0	0.4[c]	−1.52	−1.69	0.17
5d	0.56	0.18	−1.66	−1.65	−0.01
5e	0.56	1.18	−0.98	−1.01	0.03
5f	0.56	1.7[c]	−1.12	−1.00	−0.12
5g	0.56	2.3[c]	−1.01	−1.31	0.30
5h	0.56	0.4[c]	−1.11	−1.27	0.16
5i	0.56	1.5[c]	−0.87	−0.97	0.10
5j	0.56	0.85	−1.04	−1.12	0.08
5k	0.56	1.3[c]	−0.80	−0.96	0.16
5l	1.02	1.18	−1.04	−0.97	−0.07
5m	1.02	0.85	−1.05	−1.03	−0.02
5n	1.55	1.18	−1.06	−0.98	−0.08
5o	1.55	0.85	−1.47	−1.01	−0.46
5p	2.1[c]	0.18	−1.36	−1.28	−0.08
5q	2.1[c]	0.4[c]	−1.07	−1.18	0.11
5r	2.5[c]	0.6[c]	−1.06	−1.16	0.10
5s	2.5[c]	1.18	−1.24	−1.18	−0.06
5t	1.96	1.18	−0.90	−1.05	0.15
5u	2.01	0.18	−1.19	−1.30	0.11
5v	2.01	1.18	−1.14	−1.07	−0.07
5w	2.01	0.4[c]	−1.19	−1.19	0

a) π_1 and π_2 are hydrophobic parameters for R^1 and NR^4R^5, respectively. *b*) Calcd from Eq. 8 in Table VII. *c*) Estimated from π and f values in ref. 5.

TABLE VII. Correlation Equations between Muscle Relaxant Activity (pED_{50}) and Hydrophobic Parameters of *N*-Isoxazolylpropanamides (**5a**—**w**)

Equation No.	pED_{50} =	n	r	s	F
(1)	$0.105\pi_1 - 1.322$ (± 0.159)[a] (± 0.226)	23	0.287	0.300	$F^1_{21} = 1.88$
(2)	$0.023(\pi_1)^2 - 1.246$ (± 0.064) (± 0.186)	23	0.159	0.309	$F^1_{21} = 0.55$
(3)	$0.179\pi_2 - 1.368$ (± 0.206) (± 0.231)	23	0.367	0.291	$F^1_{21} = 3.27$
(4)	$0.040(\pi_2)^2 - 1.250$ (± 0.091) (± 0.176)	23	0.194	0.307	$F^1_{21} = 0.82$
(5)	$0.184(\sum\pi)^{b} - 1.591$ (± 0.131) (± 0.301)	23	0.537	0.264	$F^1_{21} = 8.49$
(6)	$0.034(\sum\pi)^2 - 1.379$ (± 0.037) (± 0.231)	23	0.387	0.289	$F^1_{21} = 3.69$
(7)	$-0.154(\sum\pi)^2 + 0.759(\sum\pi) - 2.001$ (± 0.105) (± 0.409) (± 0.380)	23	0.717	0.224	$F^2_{20} = 10.55$
(8)	$-0.139(\sum\pi)^2 - 0.299(\pi_2)^2 + 1.388(\sum\pi) - 0.742\pi_1 - 2.172$ (± 0.090) (± 0.193) (± 0.529) (± 0.480) (± 0.338)	23	0.834	0.186	$F^4_{18} = 10.32$

a) The figures in parenthesis are for the construction of 95% confidence limits of the coefficient in the t test. *b*) $\sum\pi = \pi_1 + \pi_2$.

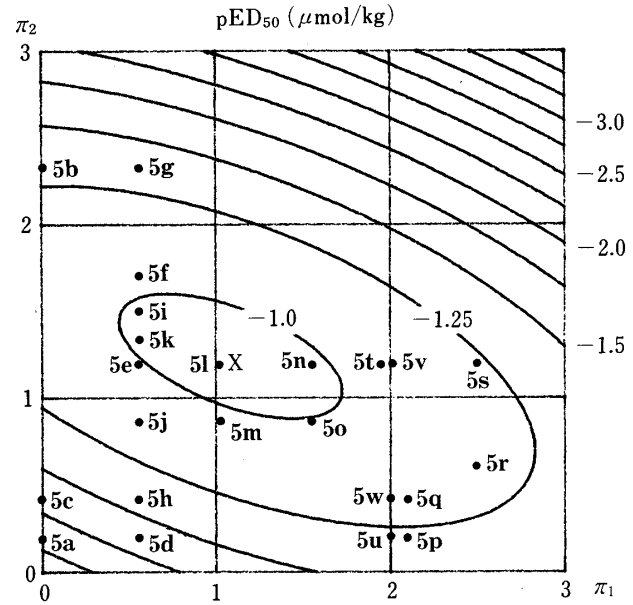


Fig. 1. Effect of Hydrophobic Parameters (π_1 and π_2) on Muscle Relaxant Activity of Propanamides (**5a**—**w**)

Muscle relaxant activity [pED$_{50}$ (μmol/kg)] was calculated from Eq. 8 in Table VII.

on the isoxazolyl 5-amino group. Equation 8 indicated that the optimal π values of R^1 and NR^4R^5 were 1.11 and 1.25, and the corresponding pED$_{50}$ was −0.96. It was plotted as X in Fig. 1. Although less than 70% of the variance of potency was explained by this equation, compounds of high activity (pED$_{50} > -1$, **5e**, **i**, **k**) were located close ot the optimal position. In spite of its high potency, however, compound **5t** was located far from the optimal position. This might be due to the influence of the aromatic phenyl group.

Calculated optimum pED$_{50}$ of −0.96 was realized in these four compounds, and this potency may be optimal in this series of alkylated derivatives of *N*-isoxazolylpropanamides **5**.

The present study suggests that compound **5e** may be more potent and selective than currently used muscle relaxant drugs.

Experimental

Melting points were determined on a Sibata apparatus and are not corrected. Boiling points are uncorrected. Infrared (IR) spectra were recorded using a JASCO model IR-G, or a JASCO model A-202 instrument. Data are presented in reciprocal centimeters, and only the important diagnostic bands are reported. ^{1}H-NMR spectra were determined on a JEOL model JNM-PMX60 (60 MHz) spectrometer. Chemical shifts are reported in parts per million downfield from a tetramethylsilane internal standard (δ scale) and coupling constants in Hz. Mass spectra (MS) were taken on a Shimadzu 7000 mass spectrometer operating at 70 eV; only major ion fragments are reported in the form of *m*/*z* (relative intensity). High-resolution MS were measured using a VG Analytical MM ZAB 2F-HF spectrometer. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. The structures and purities of all compounds are supported by the IR, ^{1}H-NMR, and MS data. For column chromatography, Merck Kieselgel 60 and Sumitomo Active Alumina KCG-30 were used.

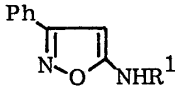
Chemistry

5-Formylamino-3-phenylisoxazole (3b)[8]——A mixture of 5-amino-3-phenylisoxazole (**2a**, 48.0 g, 0.3 mol) and HCO_2H (250 ml) was stirred at 100 °C for 1 h and poured into H_2O (1 l). The resulting precipitate was dissolved in AcOEt and washed with H_2O. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from $CHCl_3$ to give **3b** (38.4 g, 83%), mp 112 °C (lit.,[8] mp 115—117 °C as the hemihydrate recrystallized from H_2O).

N-(3-Phenyl-5-isoxazolyl)acetamide (**3c**) and *N*-(3-phenyl-5-isoxazolyl)propanamide (**3d**) were prepared in a usual manner from **2a**, the corresponding acid anhydride, and pyridine. 2-Methyl-*N*-(3-phenyl-5-isoxazolyl)-propanamide (**3e**) and 2,2-dimethyl-*N*-(3-phenyl-5-isoxazolyl)propanamide (**3f**) were prepared in a usual manner from **2a**, the corresponding acid chloride, and Et_3N in $CHCl_3$. The products were used in the next step without purification.

5-Methylamino-3-phenylisoxazole (2b)——Compound **3b** (145 g, 0.771 mol) was added portionwise under N_2 to

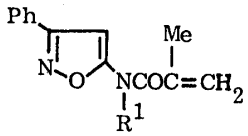
TABLE VIII. 5-*N*-Substituted Amino-3-phenylisoxazoles (**2b—h**)



Compd. No.	R^1	Yield[a]	mp (°C)	Recrystn. solvent	IR ν (cm^{-1})	^{1}H-NMR[b] δ	MS m/z (M^+)
2b	Me	71	110—112	PhH	3230, 1625 (Nujol)	5.28	174
2c	Et	40	115—116	Hexane–PhMe	3230, 1610 (Nujol)	5.27	188
2d	Pr	86	107—109	PhMe	3240, 1615 (Nujol)	5.27	202
2e	Bu^i	45	46—47	Hexane–Et_2O	3240, 1615 (KBr)	5.23	216
2f	CH_2CMe_3	47	102—104	PhH	3280, 3200, 1625 (KBr)	5.25	230
2g	Ph	35[c]	131—133[d]	MeOH	3280, 3190, 1650 (Nujol)	5.83	236
2h	CH_2Ph	37	83—84[e]	EtOH–H_2O	3430, 1610 (KBr)	5.30	250

a) Yield from 5-amino-3-phenylisoxazole (**2a**). *b*) Chemical shift of the C-4 proton of the isoxazole ($CDCl_3$). *c*) Yield from 1-morpholino-1-phenylethylene. *d*) Lit.,[9a] mp 143—144 °C (MeOH); Lit.,[9b] mp 136—137 °C (EtOH). *e*) Lit.,[10] 91—92 °C (EtOH).

TABLE IX. 2-Methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamides (**4b—h**)



Compd. No.	R^1	Yield	mp (°C)	Recrystn. solvent	IR (Nujol) ν (cm^{-1})	^{1}H-NMR[a] δ	MS m/z (M^+)
4b	Me	70	60—61	Et_2O	1675, 1615	6.50	242
4c	Et	88	Oil	—	—	6.39	256
4d	Pr	91	Oil	—	—	6.35	270
4e	Bu^i	87	43—44	Hexane–Et_2O	1660, 1610	6.33	284
4f	CH_2CMe_3	72	75—77	Hexane–Et_2O	—	6.25	298
4g	Ph	68	83—84	Et_2O	1675	6.60	304
4h	CH_2Ph	74	95—97	Et_2O	1675, 1600	6.15	318

a) Chemical shift of the C-4 proton of the isoxazole ($CDCl_3$).

a stirred suspension of $LiAlH_4$ (38.0 g, 1 mol) in anhydrous THF (1.4 l). The reaction muxture was stirred at room temperature for 4 h, and excess $LiAlH_4$ was decomposed with H_2O. The THF layer was dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure, and the residue was recrystallized to afford **2b** (114 g, 85%). ^{1}H-NMR ($CDCl_3$) δ: 2.93 (3H, d, J=5 Hz), 4.7 (1H, br s), 5.28 (1H, s), 7.3—8.0 (5H, m). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.67; H, 5.56; N, 15.84.

Compounds **2c—f** were prepared in the same manner from **3c—f**, respectively. Compounds **2g**[9a] and **2h**[10] were prepared according to the reported methods.

Typical Example of the Preparation of *N*-Substituted 2-Methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamides (4b—h): 2,*N*-Dimethyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (4b)——A solution of methacryloyl chloride (19.2 g, 184 mmol) in $CHCl_3$ (20 ml) was added dropwise to a solution of **2b** (16.0 g, 92 mmol) and Et_3N (18.6 g, 184 mmol) in $CHCl_3$ (100 ml) below 5 °C. The reaction mixture was stirred at room temperature for 12 h, and quenched with H_2O. After being washed with dilute HCl, the $CHCl_3$ layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified on a column of silica gel (1.25 kg) using $CHCl_3$ as an eluent. The crude product from the $CHCl_3$ eluate was recrystallized from Et_2O to give **4b** (15.5 g). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, m), 3.47 (3H, s), 5.28 (2H, m), 6.50 (1H, s), 7.3—7.9 (5H, m). MS m/z (relative intensity): 242 (M^+, 16), 158 (28), 117 (87), 77 (24), 69 (100), 41 (79).

Compounds **4c—h** were prepared in the same manner as described above from **2c—h**, respectively.

Preparation of 2-methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (**4a**) was described previously.[1]

Typical Example of the Preparation of *N*-Substituted 3-Amino-2-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamides

TABLE X. 3-Amino-2-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamides (**5a**—**w**)

Compd. No.	Yield[a]	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
5a	85	HCl	85—87	Et_2O	$C_{15}H_{20}ClN_3O_2$	58.15	6.51	13.57
						(57.96	6.53	13.44)
5b	58	f	79—82	CH_3COCH_3	$C_{23}H_{31}N_3O_6$	62.00	7.01	9.43
						(62.14	6.75	9.50)
5c	88	—	107—108	Hexane–AcOEt	$C_{17}H_{21}N_3O_2$	68.20	7.07	14.04
						(68.55	6.91	13.88)
5d	83	f	108—109	CH_3COCH_3	$C_{20}H_{25}N_3O_6$	59.54	6.25	10.42
						(59.62	6.11	10.72)
5e	72	f	113—114	CH_3COCH_3	$C_{22}H_{29}N_3O_6$	61.24	6.77	9.74
						(60.88	6.70	9.71)
5f	34	f	79—81	CH_3COCH_3	$C_{23}H_{31}N_3O_6$	62.00	7.01	9.43
						(61.83	6.94	9.59)
5g	27	t	55—57	CH_3COCH_3	$C_{24}H_{35}N_3O_8$	58.40	7.15	8.51
						(58.60	7.13	8.73)
5h	95	f	144—145	CH_3COCH_3	$C_{22}H_{27}N_3O_6$	61.52	6.34	9.79
						(61.35	6.72	9.52)
5i	3[c]	—	Oil	—	$C_{20}H_{27}N_3O_2$	Calcd: 341.2103.[d]		
						Found: 341.2096.		
5j	69	f	115—117	CH_3COCH_3	$C_{23}H_{29}N_3O_6$	62.29	6.59	9.48
						(62.31	6.44	9.56)
5k	45	f	144—147	CH_3COCH_3–MeOH	$C_{24}H_{31}N_3O_6$	63.00	6.83	9.19
						(62.85	6.72	8.97)
5l	56	f	99—101	CH_3COCH_3	$C_{23}H_{31}N_3O_6$	62.00	7.01	9.43
						(62.17	7.15	9.27)
5m	76	f	131—133	CH_3COCH_3	$C_{24}H_{31}N_3O_6$	63.00	6.83	9.19
						(62.83	6.68	8.83)
5n	52	f	115—117	CH_3COCH_3	$C_{24}H_{33}N_3O_6$	62.72	7.24	9.14
						(62.65	7.05	8.94)
5o	75	f	123—125	CH_3COCH_3	$C_{25}H_{33}N_3O_6$	63.67	7.05	8.91
						(63.50	6.83	8.74)
5p	84	f	90—93	CH_3COCH_3	$C_{23}H_{31}N_3O_6$	62.00	7.01	9.43
						(62.27	7.22	9.51)
5q	83	—	75—76	Hexane–Et_2O	$C_{21}H_{29}N_3O_2$	70.95	8.22	11.82
						(71.09	7.87	12.03)
5r	87	—	80—82	Hexane–Et_2O	$C_{21}H_{31}N_3O_2$	70.55	8.74	11.76
						(70.68	8.64	11.88)
5s	68	—	80—82	Hexane–Et_2O	$C_{22}H_{33}N_3O_2$	71.12	8.95	11.31
						(70.87	9.14	11.27)
5t	98	t	76—78	Hexane	$C_{27}H_{33}N_3O_8$	61.47	6.31	7.97
						(61.29	6.50	8.03)
5u	99	t	82—85	Hexane–Et_2O	$C_{26}H_{31}N_3O_8$	60.81	6.08	8.18
						(60.95	5.99	8.35)
5v	41	t	54—55	Hexane–Et_2O	$C_{28}H_{35}N_3O_8$	62.09	6.51	7.76
						(62.22	6.47	7.65)
5w	82	f	118—120	CH_3COCH_3	$C_{28}H_{31}N_3O_6$	66.52	6.18	8.31
						(66.45	6.07	8.24)

a) Yield of free base from *N*-isoxazolylpropenamides (**4a**—**h**), except **5i**. *b*) f, fumarate; t, tartrate. *c*) Yield of free base from methyl 3-(2,5-dimethyl-pyrrolidino)-2-methylpropionate (**6**). *d*) High MS Calcd for $C_{20}H_{27}N_3O_2$.

(5d—w): 2,*N*-Dimethyl-*N*-(3-phenyl-5-isoxazolyl)-3-pyrrolidinopropanamide (5h)——A mixture of **4b** (4 g, 16.5 mmol) and pyrrolidine (1.4 g, 19.9 mmol) in PhH (80 ml) was refluxed for 24 h. The mixture was evaporated, and the residue was purified on a column of silica gel using $CHCl_3$–MeOH (10 : 1) as an eluent to give **5h** (4.91 g) as an oil. IR (neat):

1680, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7 Hz), 1.75 (4H, m), 2.2—3.1 (7H, m), 3.43 (3H, s), 6.52 (1H, s), 7.3—7.9 (5H, m). MS m/z (relative intensity): 313 (M^+, 2), 112 (1), 103 (1), 85 (13), 84 (100), 83 (1), 70 (2).

Compounds **5d—g, j—w** were prepared in the same manner as described above from **4b—h**. When the reaction was too slow, particularly in the case of the addition of diethylamine, a small amount of AcOH was used to accelerate the reaction.[11] Compounds **5a—c** were prepared according to the reported method.[1]

Compound **5a** was converted into the hydrochloride, compounds **5b, d—f, h, j—p, w** were converted into the fumarates and compounds **5g, t—v** were converted into the tartrates in a usual manner, and the resulting salts were recrystallized from an appropriate solvent.

2,*N*-Dimethyl-3-(2,5-dimethylpyrrolidino)-*N*-(3-phenyl-5-isoxazolyl)propanamide (5i)——A 1 M MeMgBr solution (21 ml, 21 mmol) in anhydrous THF was added dropwise to a solution of **2b** (3 g, 17.2 mmol) in anhydrous THF (30 ml) at room temperature. The mixture was stirred for 30 min, then methyl 3-(2,5-dimethylpyrrolidino)-2-methylpropionate [**6**, 3.43 g, 17.2 mmol, bp 107—109 °C (20 mmHg), lit.,[11] bp 95 °C (18 mmHg)] in anhydrous THF (10 ml) was added dropwise and the resulting mixture was heated under reflux for 1 h. After cooling, the mixture was quenched with aqueous NH_4Cl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated, and the residue was purified on a column of silica gel using $CHCl_3$–MeOH (10 : 1) as an eluent to afford **5i** (176 mg) as an oil. IR (neat): 1680, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7 Hz), 1.00 (3H, d, J=7 Hz), 1.16 (3H, d, J=7 Hz), 1.3—2.0 (4H, m), 2.2—3.2 (5H, m), 3.45 (3H, s), 6.53 (1H, s), 7.3—8.0 (5H, m). MS m/z (relative intensity): 341 (M^+, 0.2), 325 (4), 113 (8), 112 (100), 96 (4), 55 (4).

***N*-Methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (8)**——KF-Al_2O_3 (Type B,[3] 4 g) and MeI (1.4 g, 9.86 mmol) were added to a solution of 3-bromo-*N*-(3-phenyl-5-isoxazolyl)propanamide[1] (**7**, 1.5 g, 5.08 mmol) in CH_3CN (20 ml), and the resulting reaction mixture was stirred at room temperature for 22 h. The mixture was filtered and the filtrate was evaporated. The residue was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated, and the residue was purified on a column of Al_2O_3 using hexane–CH_2Cl_2 (1 : 1) as an eluent to give **8** (0.76 g, 66%) as an oil. IR (neat): 1685, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (3H, s), 5.77 (1H, t, J=6 Hz), 6.45 (1H, s), 6.50 (2H, d, J=6 Hz), 7.3—7.9 (5H, m). MS m/z (relative intensity): 228 (M^+, 5), 144 (28), 117 (56), 102 (28), 77 (25), 55 (100). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.52; H, 5.33; N, 12.06.

N-(3-Phenyl-5-isoxazoyl)-2-butenamide (**9**)[1] was treated in the same manner to give *N*-methyl-*N*-(3-phenyl-5-isoxazolyl)-2-butenamide (**10**, 92%) as an oil. IR (neat): 1680, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, dd, J=7, 2 Hz), 3.43 (3H, s), 6.18 (1H, dq, J=15, 2 Hz), 6.43 (1H, s), 6.95 (1H, dd, J=15, 7 Hz), 7.3—7.9 (5H, m). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.27; H, 5.73; N, 11.70.

Compound **2b** was treated with 2-ethyl-2-propenoyl chloride [bp 121—124 °C (lit.,[12] bp 117—119 °C)] and Et_3N in $CHCl_3$ in the same manner as described for **4b** to afford 2-ethyl-*N*-methyl-*N*-(3-phenyl-5-isoxazolyl)-2-propenamide (**11**, 61%) as an oil. IR (neat): 1680, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 2.35 (2H, dq, J=7, 1 Hz), 3.43 (3H, s), 5.25 (2H, m), 6.50 (1H, s), 7.3—7.9 (5H, m). MS m/z (relative intensity): 256 (M^+, 3), 117 (61), 102 (30), 83 (94), 77 (18), 55 (100). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.04; H, 6.52; N, 11.20.

Compounds **12a, b**, compounds **13a, b**, and compound **14a** were prepared in the same manner as described for **5h** from **8**, **10**, and **11**, respectively. All of these products were converted into the fumarates in a usual manner.

(+)-3-Diethylamino-2-methyl-*N*-[(+)-1-phenylethyl]propanamide (16a)——A solution of D(+)-α-methylbenzylamine (175 g, 1.44 mol) in anhydrous THF (270 ml) was added dropwise below 15 °C to a solution of EtMgBr freshly prepared from EtBr (188 g, 1.73 mol) and Mg (35 g, 1.44 mol) in anhydrous THF (1070 ml). After stirring at room temperature for 30 min, a solution of **15** [125 g, 0.72 mol, bp 75—76 °C (12 mmHg) [lit.,[13a] bp 77—79 °C (15 mmHg),[13b] bp 98—99 °C (35 mmHg)]] in THF (140 ml) was added dropwise below 10 °C. The mixture was stirred at room temperature for 30 min and refluxed for 4.5 h. The reaction mixture was quenched with H_2O and extracted with PhMe. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated under reduced pressure to give a crude mixture of (+)- and (−)-3-diethylamino-2-methyl-*N*-[(+)-1-phenylethyl]propanamides (**16a** and **16b**, 168 g), $[\alpha]_D^{25}$ +27.9° (c=0.62, $CHCl_3$), which was separated on a column of silica gel (8 kg) using $CHCl_3$–EtOH–28% NH_4OH (600 : 20 : 1) as an eluent to afford **16a** (24.5 g, 13.0% yield from **15**) as an oil. IR (neat): 3300, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (6H, t, J=7 Hz), 1.10 (3H, d, J=7 Hz), 1.43 (3H, d, J=7 Hz), 1.8—3.1 (7H, m), 4.8—5.3 (1H, m), 7.25 (5H, s), 9.15 (1H, br s). MS m/z (relative intensity): 262 (M^+, 0.8), 105 (7), 87 (7), 86 (100), 72 (6), 58 (7), $[\alpha]_D^{25}$ +81.6° (c=0.711, $CHCl_3$).

The purity was determined to be >99% by GLC analysis [column: 1.5% FFAP (Carbowax 20M terminated with 2-nitroterephthalic acid) on chromosorb WHP, 2 m, 210 °C, retention times of 3.8 min and 4.3 min for **16b** and **16a**, respectively].

L(−)-α-Methylbenzylamine and **15** were treated in the same manner as described above to afford (−)-3-diethylamino-2-methyl-*N*-[(−)-1-phenylethyl]propanamide (**16c**, 24.6% yield from **15**) as an oil (99% pure by gas-liquid chromatography (GLC) analysis). $[\alpha]_D^{25}$ −83.1° (c=0.603, $CHCl_3$). IR, ^{1}H-NMR, and MS data were identical with those of **16a**.

Methyl (+)-3-Diethylamino-2-methylpropionate (15a)——Boron trifluoride–methanol complex ($BF_3 \cdot 2MeOH$,

TABLE XI. 3-Amino-*N*-methyl-*N*-(3-phenyl-5-isoxazolyl)propanamides (**12a, b, 13a, b, 14a**)

Compd. No.	Yield[a]	mp (°C)[b]	Formula	Analysis (%) Calcd (Found)		
				C	H	N
12a	88	96—98	$C_{21}H_{27}N_3O_6$	60.42 (60.54	6.52 6.43	10.07 9.92)
12b	70	144—145	$C_{21}H_{25}N_3O_6$	60.71 (60.80	6.07 5.82	10.12 10.33)
13a	94	118—120	$C_{22}H_{29}N_3O_6$	61.24 (61.08	6.77 6.83	9.74 9.85)
13b	86	146—148	$C_{22}H_{27}N_3O_6$	61.52 (61.47	6.34 6.25	9.79 9.55)
14a	37	112—114	$C_{23}H_{31}N_3O_6$	62.00 (62.21	7.01 6.84	9.43 9.26)

a) Yield of free base from **8**, **10**, or **11**. *b*) mp of fumarate (recrystallized from acetone).

128 ml) was slowly added dropwise to **16a** (24 g, 91.5 mmol) under cooling in an ice bath. The mixture was stirred at 100 °C for 3 h, and poured into ice-water. Conc. NH_4OH was added to adjust the pH to 8 and the mixture was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure, and the residue (21.2 g) was purified on a column of silica gel using CH_2Cl_2–MeOH (10 : 1) as an eluent to afford **15a** (4.63 g, 29.2%). IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (6H, t, J=7 Hz), 1.13 (3H, d, J=5 Hz), 2.2—3.0 (7H, m), 3.67 (3H, s). MS *m/z* (relative intensity): 173 (M^+, 0.6), 144 (7), 87 (10), 86 (100), 58 (69), 43 (32). $[\alpha]_D^{25}$ +28.2° (c=0.621, $CHCl_3$).

Methyl (−)-3-diethylamino-2-methylpropionate (**15b**) was obtained in the same manner in 49.2% yield. $[\alpha]_D^{25}$ −28.4° (c=0.828, $CHCl_3$). IR, ^{1}H-NMR, and MS data were identical with those of **15a**.

(+)-3-Diethylamino-2,*N*-dimethyl-*N*-(3-phenyl-5-isoxazolyl)propanamide (5x)——A solution of **2b** (9.25 g, 53.1 mmol) in anhydrous THF (30 ml) was added dropwise to a solution of EtMgBr freshly prepared from EtBr (4.76 ml, 63.7 mmol) and Mg (1.29 g, 53.1 mmol) in anhydrous THF (60 ml). The mixture was stirred for 30 min, then **15a** (4.60 g, 26.6 mmol) in anhydrous THF (30 ml) was added and the whole was refluxed for 3 h, quenched with H_2O and extracted with PhMe. The organic layer was extracted with 1 N HCl and the aqueous extract was basified with conc. NH_4OH and extracted with PhMe. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated under reduced pressure to give **5x** (6.60 g, 78.8% yield from **15a**) as an oil. IR (neat): 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, t, J=7 Hz), 1.13 (3H, d, J=7 Hz), 2.2—3.1 (7H, m), 2.44 (3H, s), 7.3—7.9 (5H, m). $[\alpha]_D^{25}$ +63.4° (c=0.708, $CHCl_3$).

Compound **5x** was converted into the fumarate in a usual manner, mp 106.5—107.5 °C. $[\alpha]_D^{25}$ +51.4° (c=0.432, CH_3COCH_3).

(−)-3-Diethylamino-2,*N*-dimethyl-*N*-(3-phenyl-5-isoxazolyl)propanamide (**5y**) was prepared in the same manner in 82.9% yield from **15b**. Compound **5y** gave IR, ^{1}H-NMR, MS data identical with those of **5x**. $[\alpha]_D^{25}$ −64.6° (c=0.608, $CHCl_3$).

Compound **5y** was converted into the fumarate in a usual manner, mp 107.5—108.5 °C. $[\alpha]_D^{25}$ −48.1° (c=0.563, CH_3COCH_3).

Pharmacology

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

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