Eur J Med Chem (1995) 30, 85–94

Short communication

Synthesis and activity of 2-methyl-3-aminopropiophenones as centrally acting muscle relaxants*

A Shiozawa, K Narita, G Izumi, S Kurashige, K Sakitama, M Ishikawa

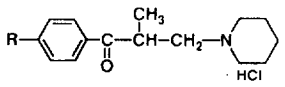
Research Laboratories, Pharmaceuticals Group, Nippon Kayaku Co Ltd, 31-12, Shimo 3-chome, Kita-ku, Tokyo 115, Japan

(Received 20 June 1994; accepted 3 October 1994)

Summary — Some novel 2-methyl-3-aminopropiophenones were synthesized and their centrally acting muscle relaxant activities were evaluated for an inhibitory effect on the flexor reflex in rats. The structure–activity relationships are discussed. In this series, 2-methyl-3-pyrrolidino-1-(4-trifluoromethylphenyl)-propan-1-one (**28**) showed significant centrally acting muscle relaxant activity. In addition, the activities of each enantiomer (**28**-(*S*) and (*R*)) were studied along with their acute toxicities. Compound **28**-(*R*) was found to exhibit more potent activity and weaker acute toxicity than **28**-(*S*). Accordingly, compound **28**-(*R*) (NK433) is under development as a novel centrally acting muscle relaxant.

centrally acting muscle relaxant / 2-methyl-3-aminopropiophenone / flexor reflex / optical resolution

Centrally acting muscle relaxants with few side effects have been an attractive target for drug research in recent years. Tolperisone **1** [1] and eperisone **2** [2] are a class of potent centrally acting muscle relaxants structurally characterized by a 2-methyl-3-aminopropiophenone moiety. They are of clinical importance in the treatment of gait or posture disturbance, hypertonea, cervicodynia, tremor caused by spasticity, and are also useful for lower back pain and shoulder stiffness.



1 Tolperisone R=Me
2 Eperisone R=Et

Despite showing lower potency than agents of other classes, such as baclofen [3], diazepam [4], and tizanidine [5], involved in centrally acting muscle relaxants, drugs such as **1** and **2** have been clinically preferred and widely used because of a lack of severe adverse effects.

As part of a program directed to the search for new highly potent centrally acting muscle relaxants with fewer side effects, our interest was focused on 2-methyl-3-aminopropiophenones. In the present study, we describe the synthesis of 2-methyl-3-aminopropiophenones (**33–35**) and the results obtained in the evaluation of their centrally acting muscle relaxant activities.

On the other hand, although the 2-methyl-3-aminopropiophenone structure has an asymmetric carbon at the 2-position of the propanone, drugs **1** and **2** are racemates. We were interested in the different biological activities of each enantiomer because there are few reports [5] dealing with centrally acting muscle relaxant activities of 2-methyl-3-aminopropiophenone enantiomers. We report the activities of each enantiomer of the most interesting compound in this series.

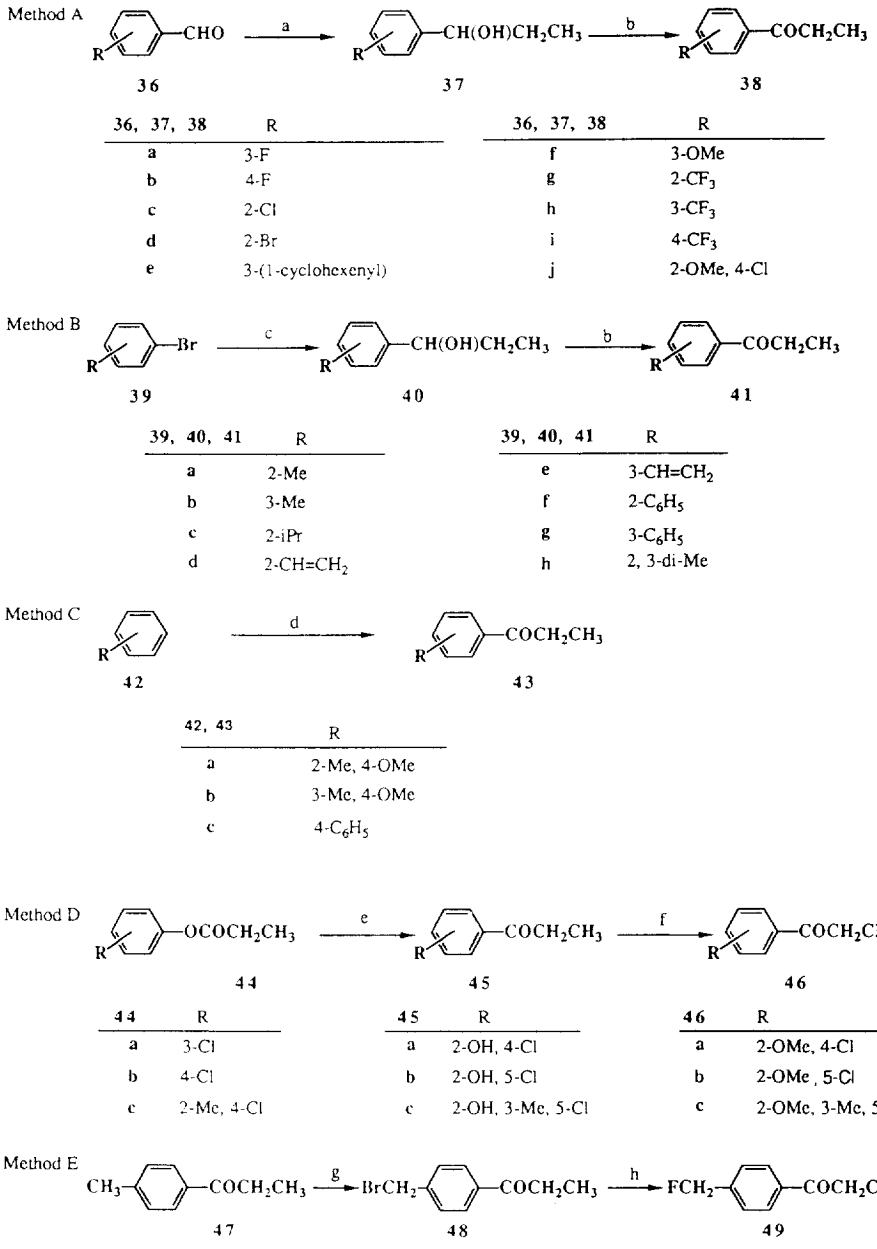
Chemistry

The 2-methyl-3-aminopropiophenones (**3–35**) were synthesized by the Mannich reaction [6] of the appropriate propiophenones with paraformaldehyde and pyrrolidine·HCl in the presence of a small amount of hydrochloric acid (scheme 1).

38, 41, 43, 46, 49 3-35

Scheme 1. Reagents: a) paraformaldehyde, pyrrolidine·HCl.

*Preliminary reports of our work were presented at the *XIIth International Symposium on Medicinal Chemistry*, Basel, Switzerland, September, 1992; Abstracts P-079 C.



36, 37, 38	R	36, 37, 38	R
a	3-F	f	3-OMe
b	4-F	g	2-CF_3
c	2-Cl	h	3-CF_3
d	2-Br	i	4-CF_3
e	3-(1-cyclohexenyl)	j	2-OMe, 4-Cl

39, 40, 41	R	39, 40, 41	R
a	2-Me	e	3-CH=CH_2
b	3-Me	f	2-C_6H_5
c	2-iPr	g	3-C_6H_5
d	2-CH=CH_2	h	2, 3-di-Me

42, 43	R
a	2-Me, 4-OMe
b	3-Me, 4-OMe
c	4-C_6H_5

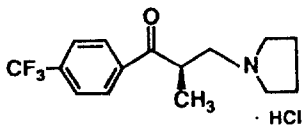
44	R	45	R	46	R
a	3-Cl	a	2-OH, 4-Cl	a	2-OMe, 4-Cl
b	4-Cl	b	2-OH, 5-Cl	b	2-OMe , 5-Cl
c	2-Me, 4-Cl	c	2-OH, 3-Me, 5-Cl	c	2-OMe, 3-Me, 5-Cl

Scheme 2. Reagents: a) EtMgBr; b) CrO_3, H_2SO_4; c) Mg, EtCHO; d) EtCOCl; e) $AlCl_3$; f) MeONa, MeI; g) NBS; h) KF.

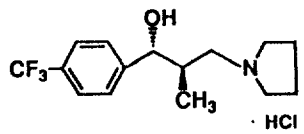
The Grignard reaction [7] of appropriate benzaldehydes (**36a–j**) with ethylmagnesium bromide gave the corresponding alcohols (**37a–j**), followed by oxidation with chromium trioxide [8] in dilute sulfuric acid to afford propiophenones **38a–j** in 35–88% yields from **36a–j**, respectively (scheme 2, *Method A*).

Propiophenones **41a–h** were prepared in 20–81% yields from **39a–h**, respectively (*Method B*), by the Grignard reaction of propionyl aldehyde with the phenylmagnesium bromide obtained from the appropriate phenyl bromide with magnesium, followed by oxidation with chromium trioxide. The Friedel–Crafts reaction [9] of appropriately substituted benzenes (**42a–c**) with propionyl chloride in the presence of aluminum chloride gave propiophenones **43a–c** in 20–81% yields, respectively (*Method C*). The Fries rearrangement [10] of propionates **44a–c** in the presence of aluminum chloride at 130°C gave the corresponding phenols (**45a–c**). The sodium salts of the phenols were then methylated with methyl iodide to give the required propiophenones (**46a–c**) in 54–88% yields (*Method D*). The bromination of 4-methylpropiophenone **47** with *N*-bromosuccinimide and perbenzoic acid gave 4-bromomethylpropiophenone **48**, which was converted into 4-fluoromethylpropiophenone **49** in a 15.5% yield from **47** (*Method E*).

Optical resolution of **28** into its enantiomers ((–) and (+)) was achieved by fractional crystallization of the salts prepared from the free base of **28** with (L)- and (D)-*N*-acetylphenyl glycine, respectively. The absolute configuration of (–)-**28** was determined on the basis of X-ray crystallographic analysis of its alcohol derivative (**50**) by Iidaka *et al* (unpublished results) to show unambiguously that (–)-**28** has an *R* configuration at C-2.



(-)-**28**



50

Pharmacological results and discussion

The centrally acting muscle relaxant activities 2-methyl-3-aminopropiophenones were evaluated for their inhibitory effects on the flexor reflex [11] in rats.

The activities were expressed as inhibitory percentages (%) and compared with the activities of tolperisone **1** and eperisone **2**. Table I shows the results obtained at a dose of 5 mg/kg intravenously administered in rats. The replacement of a piperidino group on the amine moiety of **1** or **2** with a pyrrolidino group (**12**) showed a more potent activity than **1**. Thus, a series of derivatives fixed with a pyrrolidino group as an amine moiety of 2-methyl-3-aminopropiophenones was examined. Table I indicates that the type and position of the substituents on the phenyl ring of the 2-methyl-3-pyrrolidinopropiophenones remarkably contributes to the activity. Introduction of a methyl group (**10**, **11**, and **12**) into the phenyl ring significantly enhanced the activities compared with the unsubstituted compound **3**, and the 2-methyl compound **10** was more potent than the 3- (**11**) and 4-isomers (**12**). The activities decreased in the order **10** > **11** > **12**. However, the replacement of the 2-methyl group (**10**) with a 2-ethyl group (**13**), a 2-isopropyl group (**14**), a 2-vinyl group (**15**), or a 2-phenyl group (**18**) decreased the activity in the order 2-methyl (**10**) > 2-vinyl (**15**) > 2-ethyl (**13**) > 2-phenyl (**18**).

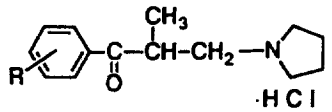
These results suggest that an increase in the bulkiness of the *ortho* substituents might lead to a decrease in the activity. Similarly, when the 3-methyl group (**11**) was replaced with a 3-vinyl group (**16**), a 3-(1-cyclohexenyl) group (**17**), or a 3-phenyl group (**19**), the activities decreased in the order 3-methyl (**11**) > 3-vinyl (**16**) > 3-(1-cyclohexenyl) (**17**) > 3-phenyl (**19**). The activity of the 4-phenyl compound **20** was also lower than that of the 4-methyl compound **12**.

In the series of methoxy derivatives, the 2- (**22**), 3- (**23**), and 4-methoxy (**24**) analogs were more potent than the unsubstituted compound **3**, but they were also less potent than the corresponding 2- (**10**), 3- (**11**), and 4-methyl (**12**) derivatives, respectively. The 2-hydroxy compound **21** had slightly enhanced activity compared with **22**.

When the halogenated analogs (**4–9** and **25–28**) were examined, the 3-fluoro compound **5** was more potent than the 2- (**4**) and 4-isomers (**6**), and **5** exhibited an approximately five times more potent activity than **3**. The activity of the 3-bromo compound **9** was slightly more potent than that of the 2-isomer **8**. The activity of the 2-chloro compound **7** was approximately comparable to those of the 2-fluoro (**4**) and 2-bromo (**8**) analogs. In addition, the trifluoromethyl analogs (**26–28**) were examined. The 4-trifluoromethyl compound **28** was considerably more potent in comparison to the 2- (**26**) and 3- (**27**) congeners and the activity decreased in the order **28** > **26** > **27**. The replacement of the 4-trifluoromethyl group (**28**) by a 4-fluoromethyl group (**25**) led to a dramatic decrease in the activity.

When disubstituted compounds were examined, compound **34** (2,3-diMe) exhibited a more potent activity than **10** (2-Me) or **11** (3-Me). Compound **34** was found to have the most potent activity in this study. Introduction of a 4-methoxy group into the 2- (**10**) and 3-methyl (**11**) compounds decreased the activities as

Table I. The physical properties of 3-pyrrolidinopropiophenones and their centrally acting muscle relaxant activities.



3-35

Compd No.	R	Yield (%)	mp (℃)	Recrystn Solvent	Formula	FR[a] I(%)	LD_{50}[b] (mg/kg)
1	Tolperisone					31.3	
2	Eperisone					34.5	
3	H	80	148-149	CH_2Cl_2-CH_3COCH_3	$C_{14}H_{19}NO \cdot HCl$	7.7	
4	2-F	33	121-122	CH_3COCH_3	$C_{14}H_{18}FNO \cdot HCl$	23.2	
5	3-F	65	152-153.5	CH3COCH3	$C_{14}H_{18}FNO \cdot HCl$	41.5	41.2
6	4-F	23	148-149	Et_2O-CH_3COCH_3	$C_{14}H_{18}FNO \cdot HCl$	25.8	
7	2-Cl	62	163-164	CH_2Cl_2-AcOEt	$C_{14}H_{18}ClNO \cdot HCl$	24.1	
8	2-Br	14	134-136	MeOH-CH_3COCH_3	$C_{14}H_{18}BrNO \cdot HCl$	22.8	
9	3-Br	80	152.5-154	MeOH-CH_3COCH_3	$C_{14}H_{18}BrNO \cdot HCl$	29.9	
10	2-Me	73	144-145.5	MeOH-CH_3COCH_3	$C_{15}H_{21}NO \cdot HCl$	51.3	30.6
11	3-Me	98	166-168	MeOH-CH_3COCH_3	$C_{15}H_{21}NO \cdot HCl$	44.6	25.9
12	4-Me	90	168-169	MeOH-CH_3COCH_3	$C_{15}H_{21}NO \cdot HCl$	37.2	
13	2-Et	75	138-139	MeOH-CH_3COCH_3	$C_{16}H_{23}NO \cdot HCl$	33.7	
14	2-iPr	58	116-118	CH_3COCH_3	$C_{17}H_{25}NO \cdot HCl$	25.3	
15	2-CH=CH_2	73	143-144	MeOH-CH_3COCH_3	$C_{16}H_{21}NO \cdot HCl$	38.9	
16	3-CH=CH_2	68	151-153	MeOH-CH_3COCH_3	$C_{16}H_{21}NO \cdot HCl$	34.7	
17	3-(1-cyclohexenyl)	51	142-144	CH_3COCH_3	$C_{20}H_{27}NO \cdot HCl$	30.1	
18	2-Ph	51	138-139	MeOH-CH_3COCH_3	$C_{20}H_{23}NO \cdot HCl$	9.0	
19	3-Ph	48	157.5-158.5	MeOH-CH_3COCH_3	$C_{20}H_{23}NO \cdot HCl$	28.0	
20	4-Ph	61	156-158.5	MeOH-CH_3COCH_3	$C_{20}H_{23}NO \cdot HCl$	7.1	
21	2-OH	91	104-106	CH_3COCH_3	$C_{14}H_{19}NO_2 \cdot HCl$	26.3	
22	2-OMe	89	138-140	CH_2Cl_2-CH_3COCH_3	$C_{15}H_{21}NO_2 \cdot HCl$	20.4	
23	3-OMe	87	130-132	CH_3COCH_3	$C_{15}H_{21}NO_2 \cdot HCl$	10.8	
24	4-OMe	63	154-156	CH_3COCH_3	$C_{15}H_{21}NO_2 \cdot HCl$	22.8	
25	4-CH_2F	74	151-152	CH_2Cl_2-AcOEt	$C_{15}H_{20}FNO \cdot HCl$	15.5	
26	2-CF_3	19	148-149	MeOH-CH_3COCH_3	$C_{15}H_{18}F_3NO \cdot HCl$	32.8	
27	3-CF_3	33	144-145	CH_3COCH_3-Et_2O	$C_{15}H_{18}F_3NO \cdot HCl$	19.3	
28	4-CF_3	94	154-156	MeOH-CH_3COCH_3	$C_{15}H_{18}F_3NO \cdot HCl$	40.3	61.1
29	2-Me,4-OMe	52	142-143	CH_3COCH_3-AcOEt	$C_{16}H_{23}NO_2 \cdot HCl$	25.5	
30	3-Me,4-OMe	69	163-165	AcOEt	$C_{16}H_{23}NO_2 \cdot HCl$	29.4	
31	2-OMe,4-Cl	64	140-141.5	CH_3COCH_3-AcOEt	$C_{15}H_{20}ClNO_2 \cdot HCl$	16.0	
32	2-OMe,5-Cl	65	166-167	CH_3COCH_3	$C_{15}H_{20}ClNO_2 \cdot HCl$	33.1	
33	2-OMe,3-Cl	59	125-127	CH_3COCH_3	$C_{15}H_{20}ClNO_2 \cdot HCl$	26.7	
34	2,3-di-Me	52	149-151	MeOH-CH_3COCH_3	$C_{16}H_{23}NO \cdot HCl$	53.9	33.9
35	2-OMe,3-Me,5-Cl	64	149-150	CH_3COCH_3	$C_{16}H_{22}ClNO_2 \cdot HCl$	26.5	

[a]FR: flexor reflex. The compounds were intravenously administered at 5 mg/kg dose to rats (see *Experimental protocols*). [b]The values of LD_{50} were determined by the up-and-down method (*iv*, mice) (see *Experimental protocols*).

Table II. The inhibitory effects of **1**, **2**, **5**, **28** and **34** on anemic decerebrate rigidity and the flexor reflex, and their acute toxicities.

Compound	*Rigidity (iv)*[a] *I (%)*	*FR (po)*[b] *I (%)*	*LD_{50} (po)*[c] *mg/kg*
1	15.4	35.3	320
2	24.2	36.7	326
5	16.0		
28	23.6	72.9	800
34	53.9	58.1	280

[a]Rigidity means anemic decerebrate rigidity [13] and each compound was administered at 3.5 mg/kg dose to rats. [b]Each compound was orally administered at a dose of 50 mg/kg. [c]The LD_{50} value of each compound was determined by Van der Waerden's method in mice.

shown by a comparison of **29** (2-Me, 4-OMe) and **30** (3-Me, 4-OMe) with **10** and **11**, respectively. On the other hand, the introduction of a 3- or 5-chloro group into 2-methoxy compound **22** slightly increased the activity as shown by a comparison of **32** (2-OMe, 5-Cl) and **33** (2-OMe, 3-Cl) with **22** (2-OMe), but compound **31** (2-OMe, 4-Cl) with a 4-chloro group was less potent than **22**. Furthermore, when a 3-methyl group was introduced into compound **32**, compound **35** (2-OMe, 3-Me, 5-Cl) showed less potent activity.

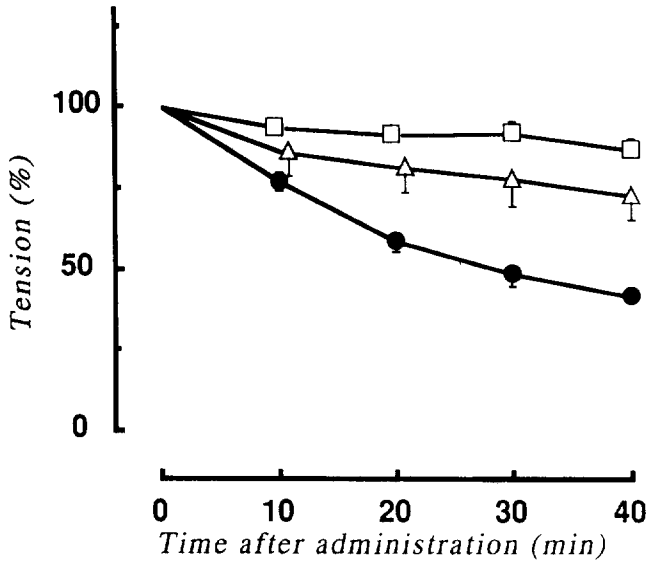


Fig 1. Effects of optical isomers and racemate (100 mg/kg, po) on anemic decerebrate rigidity in rats. The ordinate represents the mean amplitudes of the flexor reflex, as percentages of the value just prior to drug administration, with SEM indicated. ●: **28**-(*R*)(NK433); □: **28**-(*S*); △: racemate.

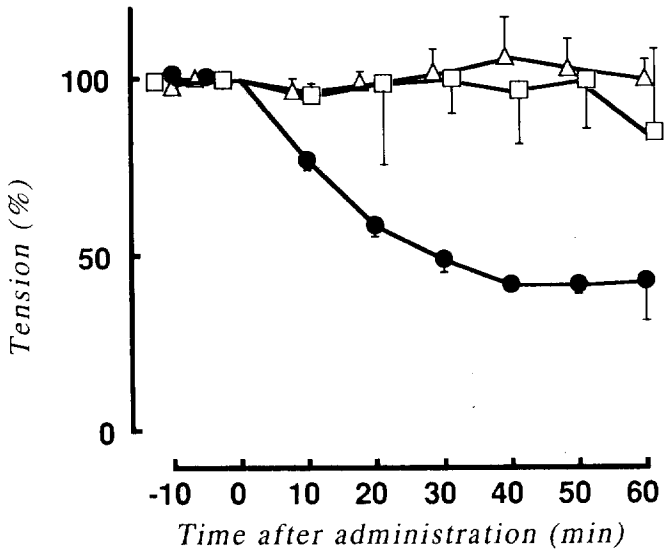


Fig 2. Effects of **1**, **2**, and NK433 (100 mg/kg, po) on anemic decerebrate rigidity in rats. The ordinate represents the mean amplitudes of the flexor reflex, as percentages of the value just prior to drug, administration, with SEM indicated. ●: NK433; □: **1** tolperisone; △: **2** eperisone.

Among the compounds described above, compounds **5**, **28** and **34**, which show the most potent activities and the lowest toxicity, were selected for further evaluation of centrally acting muscle relaxant activity. Thus, the inhibitory effects of the intravenously administered compounds on anemic decerebrate rigidity [12] and that of the orally administered compounds on the flexor reflex in rats were evaluated. Table II shows the results and LD_{50} (mg/kg) values. Compound **28** was selected on the basis of these pharmacological activities and safety evaluations.

As the compound **28** has an asymmetric carbon in the molecule, we were interested in the pharmacological action of each of enantiomer (**28**-(*S*) and -(*R*)). The activity of each of enantiomer (**28**-(*S*) and -(*R*)) was studied in relation to its acute toxicity. These results are shown in figure 1 and 2. Compound **28**-(*R*) exhibited a more potent activity and weaker acute toxicity than **28**-(*S*). Accordingly, compound **28**-(*R*) (NK433) has been selected for development as a centrally acting muscle relaxant.

Experimental protocols

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. The structures of all

compounds were supported by the infrared (IR), proton magnetic resonance (^{1}H-NMR), and mass spectra (MS). IR spectra were measured on a JASCO IR-G spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX60 spectrometer using Me_4Si as an internal standard. MS were determined with a Shimadzu GC MS-7000 Spectrometer (electron impact ionization mode). Elemental analysis (C, H, N and halogen) were in agreement with calculated values (within ±0.4%).

Chemistry

General procedures for the preparation of the propiophenones
Method A. A typical example: 4-trifluoromethylpropiophenone ***38i*** *[13].* A solution of ethyl bromide (37.6 g, 0.345 mol) in dry Et_2O (50 ml) was dropped into a suspension of Mg (10.1 g, 0.414 mol) in dry Et_2O (50 ml) under stirring to give a Grignard solution. To the Grignard solution, a solution of 4-trifluoromethylbenzaldehyde (20.0 g, 0.115 mol) in Et_2O (150 ml) was added, and the mixture was then stirred for 2 h at room temperature. Water was added to the mixture to decompose the Grignard reagent and the mixture was extracted with AcOEt three times. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a residual oil. The oil was purified by SiO_2 column chromatography using CH_2Cl_2/*n*-hexane (50:50) as an eluent to afford **37i** (22.0 g, 93.7%) as an oil. A solution of **37i** (22 g, 0.108 mol) in CH_3COCH_3 (70 ml) was added to a mixture of chromium trioxide [8] (22.0 g, 0.108 mol) and sulfuric acid (18.5 ml) in H_2O (205 ml) under ice cooling. The mixture was stirred for 2 h and then evaporated *in vacuo* to remove CH_3COCH_3. The mixture was then extracted with AcOEt and the AcOEt layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a residual oil. The oil was distilled to give **38i** (11.6 g, 53.1%) as an oil, bp 76°C (2 mmHg). IR ν ($CHCl_3$) cm^{-1}: 1690 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.2 (t, 3H; J = 7.0 Hz), 3.0 (q, 2H; J = 7.0 Hz), 7.7 (dd, 2H; J = 8.0 Hz), 8.0 (dd, 2H; J = 8.0 Hz).

Compounds **38a–h** and **j** were prepared by a similar method from appropriate benzaldehydes **36a–h** and **j**, respectively: **38a**: oil, bp 89°C (8 mmHg) [14]; **38b**: oil, bp 105–107°C (22 mmHg) [15]; **38c**: oil, bp 82–87°C (1.5 mmHg) [16]; **38d**: oil, bp 116–118°C (10–11 mmHg) [14]; **38e**: oil (the product was purified by chromatography on silica gel with CH_2Cl_2/*n*-hexane (50:50) as eluent); **38f**: oil, bp 129°C (14 mmHg) [17]; **38g**: oil, bp 55–58°C (0.5 mmHg) [18]; **38h**: oil, bp 100–102°C (16–18 mmHg) [19]; **38j**: oil, bp 170°C (50 mmHg) [20].

Method B. A typical example: 2-methylpropiophenone ***41a*** *[21].* A solution of 2-tolylbromide (17.1 g, 0.10 mol) in dry THF (30 ml) was added to a suspension of Mg (2.92 g, 0.12 mol) in dry THF (15 ml). The mixture was stirred at room temperature for 2 h and then refluxed for 0.5 h to give a 2-tolylmagnesium bromide solution. To this Grignard solution, a solution of propionaldehyde (6.97 g, 0.12 mol) in dry THF (5 ml) was added under ice cooling, and the mixture was stirred for 1 h under ice cooling. The mixture was then poured into a saturated NH_4Cl aqueous solution (100 ml) and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried over $MgSO_4$. The Et_2O was then evaporated *in vacuo* to give a residual oil. The oil was distilled to give **40a** (12.3, 81.8%) as an oil, bp 107°C (15 mmHg). A solution of **40a** (10.5 g, 70 mmol) in CH_3COCH_3 (47 ml) was added dropwise under ice cooling into a mixture of chromium trioxide (7.70 g, 77 mmol) in sulfuric acid (10.7 ml) and H_2O (95.0 ml) over 0.5 h. The mixture was stirred for 2 h, and then evaporated *in vacuo* to remove CH_3COCH_3. The mixture was extracted with AcOEt. The organic layer was washed with H_2O three times, dried over $MgSO_4$, and then evaporated *in vacuo* to give a residual oil. The oil was distilled to give **41a** (8.22 g, 79.2%) as an oil, bp 70–72°C (3 mmHg). IR ν ($CHCl_3$) cm^{-1}: 1685 (C=O). ^{1}H-NMR δ ($CDCl_3$) 1.18 (t, 3H, J = 7.0 Hz), 2.46 (s, 3H), 2.90 (q, 2H, J = 7.0 Hz), 7.1–7.4 (m, 3H), 7.4–7.7 (m, 1H).

Compounds **41b–h** were prepared by a similar method from appropriate phenylbromides **39b–h**, respectively: **41b**; oil, bp 134°C (32 mmHg) [21]; **41c**: oil (the product was purified by chromatography on silica gel with *n*-hexane/AcOEt (50:50) as eluent); **41d**: oil, bp 74°C (5 mmHg) [22]; **41e**: oil (the product was purified by chromatography on silica gel with *n*-hexane/AcOEt (50:50) as eluent); **41f**: bp 120–121°C (6 mmHg) [23]; **41g**: bp 164–167°C (7 mmHg); **41h**: oil (the product was purified by chromatography on silica gel with *n*-hexane/AcOEt (50:50) as eluent) [24].

Method C. A typical example: 2-methyl-4-methoxypropiophenone ***43a*** *[25].* A solution of propionyl chloride (8.3 g, 90.0 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a mixture of aluminum chloride (13.1 g, 98.2 mmol) in CH_2Cl_2 (50 ml) under ice cooling and then stirred for 0.5 h. The mixture was added to a solution of 3-methylanisole (10.0 g, 81.9 mmol) in CH_2Cl_2 (50 ml) under ice cooling and then stirred for 1 h. This mixture was poured into aqueous ammonia solution (10%) under ice cooling and then extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and then dried over $MgSO_4$. The solution was evaporated *in vacuo* to give a residual oil. The oil was distilled to give **43a** (13.25 g, 74.3%) as an oil, bp 110–112°C (8 mmHg). IR ν (neat) cm^{-1}: 1680 (C=O). ^{1}H-NMR δ ($CDCl_3$),: 1.06 (t, 3H, J = 7.1 Hz), 2.33 (s, 6H), 3.00 (q, H, J = 7.0 Hz), 7.2 (d, 1H, J = 8.0 Hz); 7.7 (m, 2H).

Compounds **43b** and **43c** were prepared by a similar method from the appropriately substituted benzenes **41b** and **41c**, respectively: **43b**: colorless prisms, mp 50°C (pet ether) [15]; **43c**: mp 98°C (pet ether) [26].

Method D. A typical example: 4-chloro-2-hydroxypropiophenone ***45a***. A solution of propionyl chloride (9.25 g, 0.1 mol) in dry benzene (5 ml) was added dropwise to a mixture of 3-chlorophenol (12.9 g, 0.1 mol) and Mg (1.2 g, 0.1 mol) in dry benzene (25 ml) at room temperature and the mixture was stirred for 0.5 h. The mixture was then heated at 90°C for 2 h. The mixture was filtered and the filtrate was washed with 1% aqueous NaOH solution and then H_2O. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give 3-chlorophenyl propionate (16.4 g, 88.6%) as an oil, bp 90°C (0.8 mmHg). A mixture of 3-chlorophenyl propionate **44a** (5.53 g, 30 mmol) and $AlCl_3$ (6.67 g, 50 mmol) was heated at 140°C for 2 h. The resulting solid was decomposed with 3 N HCl and then extracted with Et_2O and AcOEt. The combined organic layers were dried over $MgSO_4$ and then evaporated *in vacuo* to give crude **45a** (4.96 g, 89.2%) as colorless prisms. IR ν ($CHCl_3$) cm^{-1}: 1680 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.23 (t, 3H, J = 8.0 Hz), 3.02 (q, 2H, J = 8.0 Hz), 6.95 (dd, 2H, J = 9.0 Hz, J = 2.0 Hz), 7.74 (d, 1H, J = 9.0 Hz), 10.0–11.5 (brs, 1H).

4-Chloro-2-methoxypropiophenone ***46a*** *[20].* A solution of **45a** (4.9 g, 26.7 mmol) in EtOH (10 ml) was added dropwise to a suspension of NaOMe (1.4 g, 26.7 mmol) in EtOH (100 ml) at room temperature for 0.5 h. Methyl iodide (4.54 g, 32 mmol) was added to the mixture. The mixture was stirred for 1 h at room temperature, and then warmed at 50°C for 6 h. The reaction mixture was evaporated *in vacuo* to give a residue, which was partitioned between H_2O and Et_2O. The Et_2O layer was dried over $MgSO_4$ and then evaporated *in vacuo* to give a resi-

due, which was chromatographed over silica gel using CH_2Cl_2/*n*-hexane (40:60) as an eluent solvent to give **46a** (3.21 g, 60.6%) as an oil. IR ν ($CHCl_3$) cm^{-1}: 1680. ^{1}H-NMR δ ($CDCl_3$): 1.13 (t, 3H, *J* = 7.8 Hz), 2.96 (q, 2H, *J* = 7.8 Hz), 3.93 (s, 3H), 6.7–7.2 (m, 2H), and 7.7 (d, 1H). Compounds **46b** and **46c** were prepared by a similar method using the appropriate phenol derivatives **44b** and **44c** respectively: **46b**: oil, bp 137°C (16.5 mm Hg) [27]; **46c**: oil, bp 139°C (8.0 mm Hg) [10].

*Method E. Preparation of 4-bromomethylpropiophenone **48**.* A mixture of 4-methylpropiophenone **47** (21.7 g, 146.4 mmol), *N*-bromosuccimide (26.1 g, 146.4 mmol), and perbenzoic acid (0.25 g, 1.81 mmol) in CCl_4 (120 ml) was refluxed for 1 h. After the mixture was filtered, the filtrate was evaporated *in vacuo* to give a residue. The residue was chromatographed over SiO_2 using *n*-hexane/AcOEt (90:10) as an eluent solvent to give **48** (10.2 g, 31%) as an oil. IR ν (KBr) cm^{-1}: 1685 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.27 (t, 3H, *J* = 7.0 Hz), 3.03 (q, 2H, *J* = 7.0 Hz), 4.56 (s, 2H), 7.56 (d, 2H, *J* = 8.0 Hz), 8.05 (d, 2H, *J* = 8.0 Hz).

*4-Fluoromethylpropiophenone **49** [28].* A mixture of **48** (10.0 g, 44.0 mmol) and KF (12.7 g, 219 mmol) in diethyleneglycol (25 ml) was heated at 140°C for 1 h. Water was added to the mixture and then the mixture was extracted with Et_2O. The Et_2O layer was washed with H_2O and dried over $MgSO_4$, then evaporated *in vacuo* to give a residue, which was distilled to give **49** (3.62 g, 50.0%) as an oil, bp 99–102°C (6 mmHg). IR ν (neat) cm^{-1}: 1690 (C=O). ^{1}H-NMR δ ($CDCl_3$): 1.22 (t, 3H, *J* = 0.7 Hz); 3.03 (t, 2H, *J* = 7.0 Hz), 5.46 (d, 2H, *J* = 56 Hz), 7.46 (d, 2H, *J* = 8.0 Hz), 8.01 (d, 2H, *J* = 8.0 Hz).

*2-Methyl-3-pyrrolidinopropiophenones **3–35**. A typical example: 2-methyl-3-pyrrolidino-1-(4-trifluoromethylphenyl)-propan-1-one hydrochloride **28**.* A mixture of 4-trifluoromethylpropiophenone (4.0 g, 20 mmol), paraformaldehyde (1.8 g, 60 mmol), pyrrolidine hydrochloride (3.2 g, 30 mmol), and HCl (0.2 ml) in *i*PrOH (35 ml) was refluxed for 7 h. The reaction mixture was evaporated *in vacuo*. The residue was made alkaline with a saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with toluene. The extract was dried over $MgSO_4$, and evaporated *in vacuo* to afford the free base of **28** (5.4 g, 94%) as an oil. IR ν (neat): 1690 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (d, 3H, *J* = 7.0 Hz), 1.4–2.1 (m, 4H), 2.3–3.2 (m, 6H),3.65 (m, 1H), 7.70 (d, 2H, *J* = 8.0 Hz), 8.05 (d, 2H, *J* = 8.0 Hz). Mass m/z (relative intensity %): 285 (2.21, M^+), 214 (100), 173 (100), 145 (100), 95 (29.7), 84 (100).

This free base was converted into its hydrochloride with dry HCl gas in Et_2O. The resulting salt was recrystallized from MeOH/CH_3COCH_3 to give **28** as colorless prisms, mp 154–156°C. Anal ($C_{15}H_{18}F_3NO$ HCl) C, H, N, Cl, F. Compounds **3–27**, **29–35** were prepared by a method similar to that described above. Yields were calculated on the basis of propiophenones. The yields, recrystallization solvents, and melting points are listed in table I. The ^{1}H-NMR spectral data are shown in table III.

*Optical resolution. (+)-(R)-2-Methyl-3-pyrrolidino-1-(4-trifluoromethylphenyl)-propan-1-one hydrochloride **28**-(R) (NK433)*

(*RS*)-2-Methyl-3-pyrrolidino(4-trifluoromethylphenyl)propan-1-one (30.6 g, 107 mmol) and (L)-*N*-acetylphenylglycine (21.0 g, 109 mmol, $[\alpha]_D^{20}$ +212.8°, c = 1.0, MeOH) were dissolved in AcOEt. The solution was allowed to stand overnight at room temperature, and then was stirred at about 5°C for 3 h. The resulting precipitate was filtered off as first crude crystals (21.9 g). The filtrate was then reduced in weight to 5.74 g *in vacuo*, allowed to stand at room temperature for 2 d, and then stirred at *ca* 5°C for 3 h. The deposited crystals were filtered off as second crude crystals (17.5 g).

The first and second crude crystals prepared above were mixed and added to a mixture of 10% aqueous NaCl solution (63 ml) and AcOEt (95 ml). The mixture was made alkaline with saturated aqueous ammonia solution (28%) and then the AcOEt was extracted. The AcOEt was washed with 10% aqueous NaCl solution and then dried over $MgSO_4$. Dry HCl gas (2.9 g) was introduced to the AcOEt solution below 25°C and then the solution was stirred at 5°C for 2 h. The crystals were filtered off and washed with cold AcOEt (37 ml) to give (*R*)-2-methyl-3-pyrrolidino-1-(4-trifluoromethylphenyl)propan-1-one hydrochloride (21.5 g, optical purity 97%). The crude salts were added to a mixture of 10% aqueous NaCl solution (32 ml) and AcOEt (48 ml) similar to the previous treatment. The mixture was made alkaline with saturated aqueous ammonia solution (28%) and then the AcOEt was extracted. The AcOEt was washed with 10% aqueous NaCl solution and then dried over $MgSO_4$. Dry HCl gas (2.9 g) was introduced to the AcOEt solution below 25°C and then the solution was stirred at 5°C for 2 h to give (*R*)-2-methyl-3-pyrrolidino-1-(4-trifluoromethylphenyl)-1-propanone hydrochloride (17.4 g, optical purity 99.5%), $[\alpha]_D^{20}$ = 1.0, –45°(c = 1.0, MeOH); mp 156–159°C.

Pharmacology

Flexor reflex inhibitory action

The flexor reflex was recorded according to the methods of Sakitama and Ishikawa [11]. In brief, animals (male Wistar rats) were anesthetized with urethane and α-chloralose, and the tibial nerve was dissected and stimulated (0.1 ms, 0.1 Hz, supra-maximum stimulation) by a stimulator (Model MSE-3; Nihon Kohden). The evoked electromyogram (EMG) recorded through a silver ball electrode placed on the ipsilateral muscle tibialis anterior was amplified and displayed on a memory-oscilloscope (VC-10; Nihon Kohden). The amplitude of this evoked EMG was recorded on a pen recorder through a peak holder. The activity of each of the compounds was expressed by the flexor reflex inhibition rate. The flexor reflex inhibition rate was calculated from the following equation:

$$\text{Inhibition rate} = (A - B)/A \times 100\ (\%)$$

where *A* is the average amplitude of the EMG in the period of 10 min before the administration of one of the above-mentioned compounds, and *B* is the average amplitude of the EMG in the period of 30 min after intravenous (iv) administration of 5 mg/kg of the compound dissolved in physiological saline solution. In the case of the *per os* (*po*) study, *B* is the average amplitude of the EMG in the period of 60 min after the administration of 50 mg/kg of the compound dissolved in distilled water.

Action on anemic decerebrate rigidity of rats

This rigidity is caused by hyperactivity of α-motoneurons, and is considered a good experimental model for spasticity in humans. Anemic decerebrate rigidity was produced according to the method of Fukuda *et al* [12]. A tracheal cannula was inserted into an animal under ether anesthesia. Both of the common carotid arteries were ligated and the basilar artery was cauterized with a bipolar coagulator to block blood circulation to produce rigidity. The rigidity was recorded as described below. A rat was fixed on its back on a fixing stand and its

Table III. ^{1}H-NMR spectra of 3-pyrrolidinopropiophenones (**3–27**, **29–35**).

Compd No	*δ (CDCl$_3$)*
3	1.23 (d, 3H, *J* = 7.0 Hz), 1.4-2.1 (m, 4H), 2.1-3.2 (m, 6H), 3.3.-4.1 (m, 1H), 7.2-7.7 (m, 3H), 7.7-8.2 (m, 2H)
4	1.23 (d, 3H, *J* = 7.0Hz), 1.3-2.1 (m, 4H), 2.0-3.2 (m, 6H), 3.2-3.8 (m, 1H), 6.8-8.0 (m, 4H)
5	1.22 (d, 3H, *J* = 7.0Hz), 1.4-2.1 (m, 4H), 2.1-3.2 (m, 6H), 3.3-3.9 (m, 1H), 7.0-7.9 (m, 4H)
6	1.21 (d, 3H, *J* = 7.0Hz), 1.4-2.1 (m, 4H), 2.1-3.2 (m, 6H), 3.3-4.0 (m, 1H), 6.9-7.4 (m, 2H), 7.8-8.3 (m, 2H)
7	1.23 (d, 3H, *J* = 7.0Hz), 1.4-2.0 (m, 4H), 2.1-3.2 (m, 6H), 3.2-3.8 (m, 1H), 7.1-7.6 (m, 4H)
8	1.25 (d, 3H, *J* = 7.0Hz), 1.4-2.1 (m, 4H), 2.2-3.1 (m, 6H), 3.2-3.8 (m, 1H), 7.0-7.8 (m, 4H)
9	1.20 (d, 3H, *J* = 7.0Hz), 1.4-2.0 (m, 4H), 2.1-3.1 (m, 6H), 3.2-3.9 (m, 1H), 7.2-8.2 (m, 4H)
10	1.20 (d, 3H, *J* = 7.0Hz), 1.4-2.0 (m, 4H), 2.2-3.1 (m, 6H), 2.43 (s, 3H), 3.2-3.9 (m, 1H), 7.0-7.4 (m, 3H), 7.4-7.7 (m, 1H)
11	1.20 (d, 3H, *J* = 7.0Hz), 1.5-2.1 (m, 4H), 2.2-3.2 (m, 6H), 2.42 (s, 3H), 3.2-3.9 (m, 1H), 7.3-7.6 (m, 2H), 7.6-8.0 (m, 2H)
12	1.22 (d, 3H, *J* = 7.0Hz), 1.5-2.1 (m, 4H), 2.2-3.2 (m, 6H), 2.40 (s, 3H), 3.3-4.0 (m, 1H), 7.0-7.4 (m, 2H), 7.7-8.1 (m, 2H)
13	1.20 (d, 3H, *J* = 7.0Hz), 1.25 (t, 3H, J = 8.0Hz), 1.4-1.9 (m, 4H), 2.2-3.1 (m, 8H), 3.1-3.8 (m, 1H), 7.1-7.7 (m, 4H)
14	1.22 (d, 3H, *J* = 7.0Hz), 1.25 (d, 6H, *J* = 7.0Hz), 1.4-2.0 (m, 4H), 2.2-3.7 (m, 8H), 7.1-7.5 (m, 4H)
15	1.18 (d, 3H, *J* = 7.0Hz), 1.2-2.0 (m, 4H), 2.2-3.1 (m, 6H), 3.2-3.8 (m, 1H), 5.1-5.8 (m, 2H), 6.7-7.2 (m, 1H), 7.2-7.8 (m, 4H)
16	1.23 (d, 3H, *J* = 7.0 Hz), 1.4-2.0 (m, 4H), 2.2-3.2 (m, 6H), 3.3-4.0 (m, 1H), 5.2-6.0 (m, 2H), 6.5-7.1 (m, 1H), 7.2-8.1 (m, 4H)
17	1.22 (d, 3H, *J* = 7.0Hz), 1.3-2.1 (m, 8H), 2.1-3.2 (m, 10H), 3.3-4.1 (m, 1H), 6.0-6.3 (m, 1H), 7.2-8.1 (m, 4H)
18	0.88 (d, 3H, *J* = 7.0Hz), 2.3-2.9 (m, 4H), 2.9-3.0 (m, 7H), 7.1-7.6 (m, 9H)
19	1.22 (d, 3H, *J* = 7.0Hz), 1.4-1.9 (m, 4H), 2.1-3.2 (m, 6H), 3.3-4.0 (m, 1H) 7.1-8.3 (m, 9H)
20	1.26 (d, 3H, *J* = 7.0Hz), 1.5-2.1 (m, 4H), 2.2-3.2 (m, 6H), 3.4-4.1 (m, 1H), 7.2-8.3 (m, 9H)
21	1.25 (d, 3H, *J* = 7.0Hz), 1.5-2.1 (m, 4H), 2.3-3.2 (m, 6H), 3.4-4.3 (m, 1H), 6.7-8.0 (m, 4H), 10.0-11.5 (brs, 1H)

Table III. Continued.

Compd No	*δ (CDCl$_3$)*
22	1.18 (d, 3H, *J* = 7.0Hz), 1.3-2.1 (m, 4H), 2.2-3.1 (m, 6H), 3.1-3.9 (m, 1H), 3.90 (s, 3H), 6.7-7.7 (m, 4H)
23	1.23 (d, 3H, *J* = 7.0Hz), 1.4-2.1 (m, 4H), 2.1-3.2 (m, 6H), 3.3-4.0 (m, 1H), 3.87 (s, 3H), 6.9-7.7 (m, 4H)
24	1.23 (d, 3H, *J* = 7.0 Hz), 1.4-2.0 (m, 4H), 2.2-3.2 (m, 6H), 3.3-3.9 (m, 1H), 3.86 (s, 3H), 6.97 (d, 2H, *J* = 8.0Hz), 8.03 (d, 2H, *J* = 8.0Hz)
25	1.10 (d, 3H, *J* = 7.0Hz), 1.2-2.0 (m, 4H), 2.1-2.9 (m, 6H), 3.0-3.9 (m, 1H), 4.90 (d, 2H, J = 43.0 Hz), 6.5-6.9 (m, 2H), 7.0-7.5 (m, 2H)
26	1.18 (d, 3H, *J* = 7.0Hz), 1.5-2.0 (m, 4H), 2.2-3.1 (m, 6H), 3.1-3.7 (m, 1H), 7.4-7.9 (m, 4H)
27	1.22 (d, 3H, *J* = 7.0Hz), 1.3-2.1 (m, 4H), 2.2-3.1 (m, 6H), 3.2-4.0 (m, 1H), 7.5-8.0 (m, 2H), 8.0-8.4 (m, 2H)
28	1.25 (d, 3H, *J* = 7.0 Hz), 1.4-2.1 (m, 4H), 2.3-3.2 (m, 6H), 3.3-4.0 (m, 1H), 7.5-7.9 (m, 2H), 7.9-8.3 (m, 2H)
29	1.16 (d, 3H, *J* = 7.0 Hz), 1.4-1.9 (m, 4H), 2.1-3.2 (m, 6H), 2.47 (s, 3H), 3.2-3.9 (m, 1H), 3.85 (s, 3H), 6.6-6.9 (m, 2H), 7.4-7.8 (m, 1H)
30	1.20 (d, 3H, *J* = 7.0Hz), 1.5-2.1 (m, 4H), 2.1-3.2 (m, 6H), 2.25 (s, 3H), 3.3-4.1 (m, 1H), 3.90 (s, 3H), 6.7-7.1 (m, 1H), 7.6-8.1 (m, 2H)
31	1.15 (d, 3H, *J* = 7.0Hz), 1.4-2.0 (m, 4H), 2.1-3.1 (m, 6H), 3.2-4.2 (m, 1H), 3.88 (s, 3H), 6.7-7.3 (m, 2H), 7.3-7.8 (m, 1H)
32	1.18 (d, 3H, J = 7.0 Hz), 1.4-2.0 (m, 4H), 2.1-3.1 (m, 6H), 3.3-4.2 (m, 1H), 3.88 (s, 3H), 6.8-7.1 (m, 1H), 7.2-7.8 (m, 2H)
33	1.17 (d, 3H, *J* = 7.0Hz), 1.4-2.0 (m, 4H), 2.1-3.1 (m, 6H), 3.2-3.8 (m, 1H), 3.86 (s, 3H), 6.8-7.7 (m, 3H)
34	1.20 (d, 3H, *J* = 7.0Hz), 1.5-2.0 (m, 4H), 2.1-3.1 (m, 6H), 2.66 (s, 6H), 3.1-3.8 (m, 1H), 6.9-7.5 (m, 3H)
35	1.18 (d, 3H, *J* = 7.0Hz), 1.5-2.1 (m, 4H), 2.2-3.1 (m, 6H), 2.30 (s, 3H), 3.3-4.0 (m, 1H), 3.73 (s, 3H), 7.2-7.5 (m, 2H)

forepaws were allowed to grasp an end of a celluloid plate provided with strain gauges on both sides. A change of the resistance observed when the celluloid plate was forced up by the rigidity of the forepaws was recorded as a tension through a bridge circuit on a recorder. A rigidity inhibition rate was calculated according to the following equation:

$$\text{Rigidity inhibition rate} = (C - D) / C \times 100\ (\%)$$

where C represents the average tension (g) for 10 min before the administration of one of the above-mentioned compounds, and D represents the average for 10 min at peak period tension after iv administration of 3.5 mg/kg of the compound. The results are shown in table II.

Acknowledgments

We thank Y Iidaka and H Nakamura for the X-ray analysis of compound **50**.

References

1 Černalcèk J, JaLgr J (1966) *In: IV Conferentia Hungarica pro Therapia et investigatione in Pharmacologia*, Akado, Kiado, Budapest, Hungary, 557–561
2 Kuroiwa Y, Sobue I, Tazaki Y, Nakanishi T, Ohtomo E, Itahara K (1981) *Clin Eval* 9, 391 (abstract in English)
3 Hudgson P, Weightman D (1971) *Br Med J* IV, 15–17
4 Kaurimsky ZF, Fassbender HM (1981) *J Int Med Res* 9, 501–505

5 Nippon Kayaku Co Ltd (1978) Jpn Kokai 7840779; *Chem Abstr* (1978) 109128m
6 Blicke FF (1942) *In: Organic Reactions* (Adams R, ed) John Wiley & Sons Inc, New York, USA, vol 1, Ch 10, 303–341
7 Ropp GA, Coyner EC (1950) *J Am Chem Soc* 72, 3960–3963
8 Bull JR (1972) *J Chem Soc Perkin Trans* 1, 627–632
9 Olah GA (1964) *In: Friedel Crafts and Related Reactions*, John Wiley & Sons Inc, New York, USA, Part 1, 2;
10 Chakravarti, Dutta (1940) *J Ind Chem Soc* 17, 65–71
11 Sakitama K, Ishikawa M (1992) *Jpn J Pharmacol* 60, 127–131
12 Fukuda H, Ito T, Hashimoto S, Kudo Y (1974) *Jpn J Pharmacol* 24, 810–813
13 Capillon J, Guétté JP (1979) *Tetrahedron* 35, 1817–1820
14 Zenitz BL, Hartung WL (1946) *J Org Chem* 11, 444–450
15 Kindler K, Trauping Li (1941) *Chem Ber* 74, 321–324
16 Jensen BL, Burke SE, Thomas SE (1978) *Tetrahedron* 34, 1627–1631
17 Johnson WS, Erickson CA, Ackerman J (1952) *J Am Chem Soc* 74, 2251–2253
18 Mc Neil Lab (1967) US Pat No 3308121; *Chem Abstr* 67, 32693
19 Eistert B, Schade W, Meck N (1968) *Justus Liebigs Ann Chem* 717, 80–90
20 Sen AB, Tiwari SS (1952) *J Ind Chem Soc* 29, 419–424
21 Birch SF, Dean RA, Fidler FA, Lowry RA (1949) *J Am Chem Soc* 71, 1362–1369
22 Reid AA, Sharp JT, Sood HR, Thorogood PB (1973) *J Chem Soc Perkin Trans* 1, 2543–2551
23 Stiles M, Sisti AJ (1961) *J Org Chem* 26, 3639–3644
24 Leont'eva LI, Yuldashev KhY, Sidorova NG (1971) *Uzb Khim Zh* 15, 54–57
25 Miquel JF, Buu-Hoï NP, Royer R (1955) *J Chem Soc* 3417–3420
26 Mann N, Back W, Mutscher E (1973) *Arch Pharm* 306, 625–631
27 Chakravarti D, Majumdar B (1938) *J Ind Chem Soc* 15, 136–138
28 Hokuriku Pharmaceutical Co Ltd (1985) Jpn Kokai Tokkyo Koho JP 59 190 982; *Chem Abstr* (1985) 102, 166464d