Agents for the Treatment of Overactive Detrusor. II.[1] Synthesis and Inhibitory Activity on Detrusor Contraction of 1,1′-Biphenyl-2,6-dicarboxylic Acid Diesters with an Aminoalkyl Group in the Ester Function

Kazuhiko TAKE,*[,a] Kazuo OKUMURA,[a] Koichi TAKIMOTO,[a] Minoru OHTSUKA,[b] and Youichi SHIOKAWA[a]

New Drug Research Laboratories[a] and Product Development Laboratories,[b] Fujisawa Pharmaceutical Co., Ltd., 1–6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532, Japan. *Received August 26, 1991*

A series of 1,1′-biphenyl-2,6-dicarboxylic acid diesters with an aminoalkyl group in the ester function were synthesized and examined for their inhibitory activity on detrusor contraction *in vitro* and *in vivo*. In the *in vivo* test, arrhythmia was observed as a side effect. Among those compounds synthesized, 2-methyl 6-[4-(1-methylpiperidinyl)] 3-hydroxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (18) showed strong inhibitory activity on detrusor contractions *in vivo* (ED_{50} = 0.54 mg/kg i.v., ED_{50} = 7.2 mg/kg i.d.) and good separation from the side effect. Compound 18 was chosen for further pharmacological evaluation as an agent for the treatment of overactive detrusor.

Keywords overactive detrusor; inhibitory activity; arrhythmia; 1,1′-biphenyl-2,6-dicarboxylic acid diester; aminoalkyl ester; FR75513

The overactive detrusor syndrome is a disease which makes the number of micturition extraordinarily large in a single day. Considering the properties of the disease, it is desirable that agents for the treatment of it are orally effective. In the previous paper we have already reported that 6-isopropyl 2-methyl 3-hydroxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (FR75513) had strong inhibitory activity on rat detrusor contractions in intravenous (i.v.) administration (IC_{50} = 0.04 mg/kg), but had less activity in intraduodenal (i.d.) administration.[1] The reason for its poor activity in i.d. administration was considered to be poor i.d. absorption, since this compound administered as a polyethyleneglycol suspension existed as a white solid in the duodenal lumen 2 h later. According to the structure–activity relationships of 1,1′-biphenyl derivatives, the inhibitory activity was relatively insensitive to changes in the ester function[1]; increasing the hydrophilicity of FR75513 by introducing a hydrophilic group such as an amino group into an alkyl part of the ester moiety would improve its i.d. absorption without loss of activity. On the

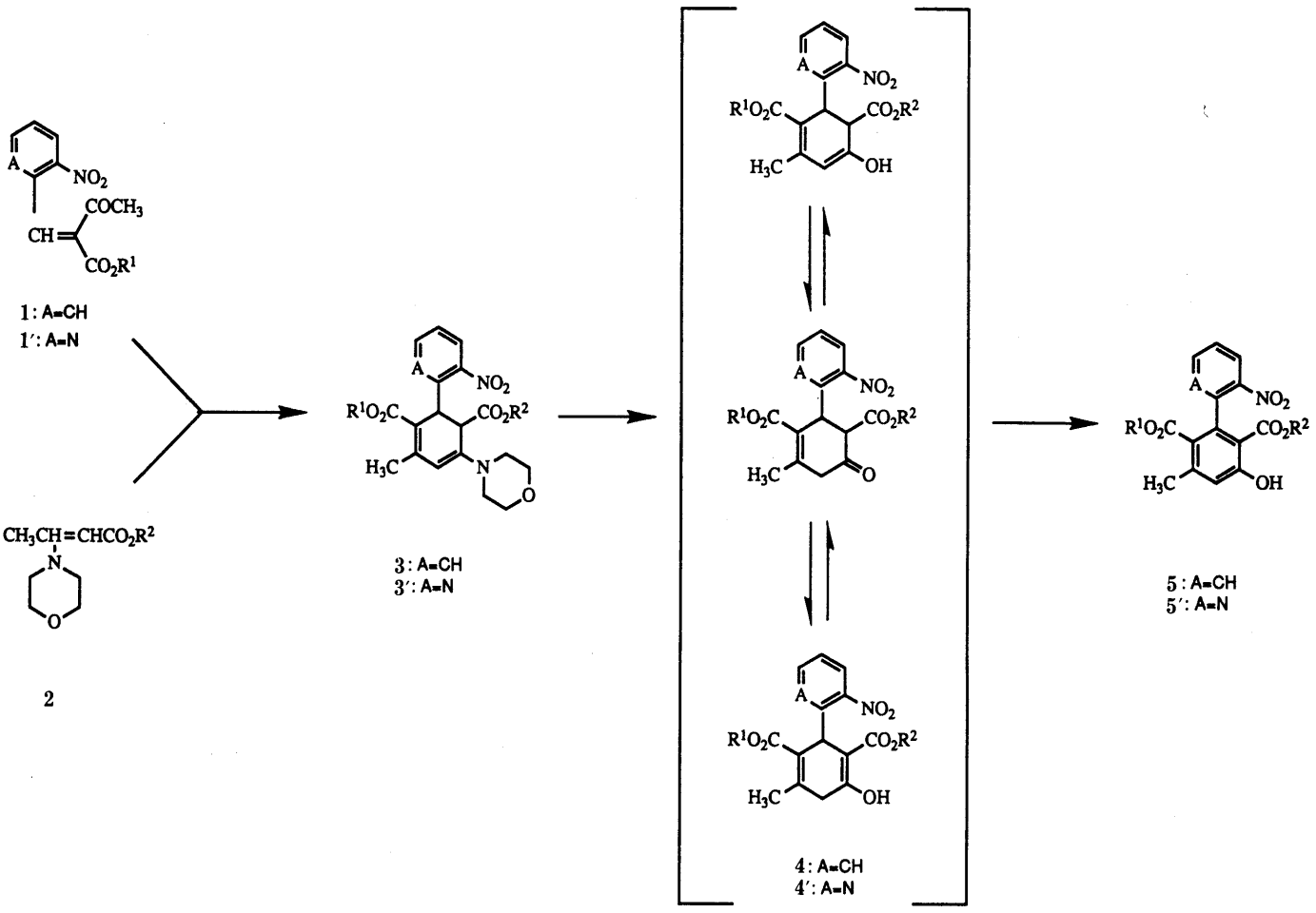


Chart 1

basis of this proposal, a series of 1,1′-biphenyl-2,6-dicarboxylic acid diesters with an aminoalkyl group in the ester function was synthesized, and each was examined for its inhibitory activity on detrusor contraction *in vitro* and *in vivo*. In the *in vivo* test, arrhythmia was observed as a side effect. Separation of the inhibitory activity on detrusor contraction and arrhythmic action was carried out by varying the alkyl substituents on the amino group in the ester function or by an introduction of a nitrogen atom into the basic skeleton (1,1′-biphenyl system) according to the previously reported structure–activity relationships as shown in Fig. 1.

Herein, we report the synthesis and pharmacological activity of 1,1′-biphenyl-2,6-dicarboxylic acid diesters with an aminoalkyl group in the ester function and related compounds.

Chemistry Charts 1 and 2 illustrate synthetic routes to the present 1,1′-biphenyl-2,6-dicarboxylic acid derivatives (**6**, **15**—**18**).

According to the previously reported methods[1] (Chart 1), the basic skeleton, 1,1′-biphenyl-2, 6-dicarboxylic acid diester (**5**) and related diester (**5′**) were synthesized. Ester exchange (aminoalcohol/*p*-toluenesulfonic acid cat.) afforded an aminoalkyl ester (**6**) (method A). In some cases, hydrolysis of the ester group instead of ester exchange had occurred. In such a case, activation of the obtained carboxylic acid with thionyl chloride, followed by esterification with aminoalcohol afforded the aminoalkyl ester (**6**). Introduction of an amino group into the ester moiety at the 6-position was carried out by the following methods: (B, C, D). At first the phenolic hydroxyl groups

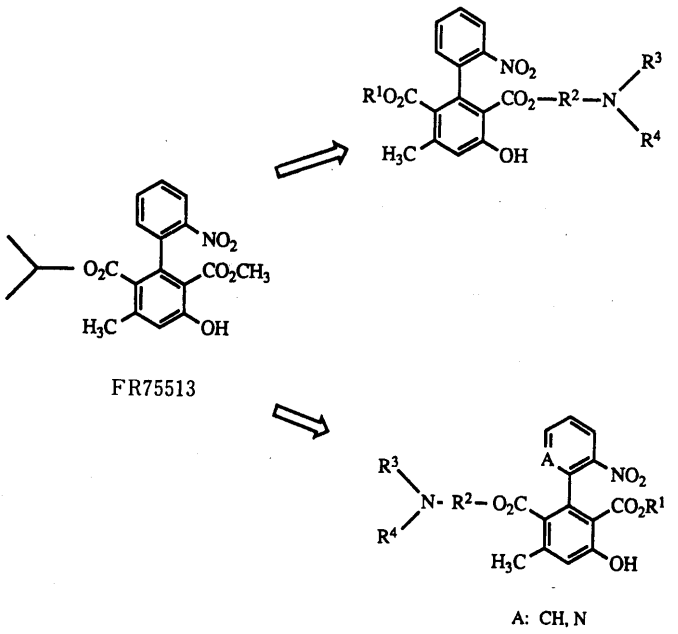


Fig. 1

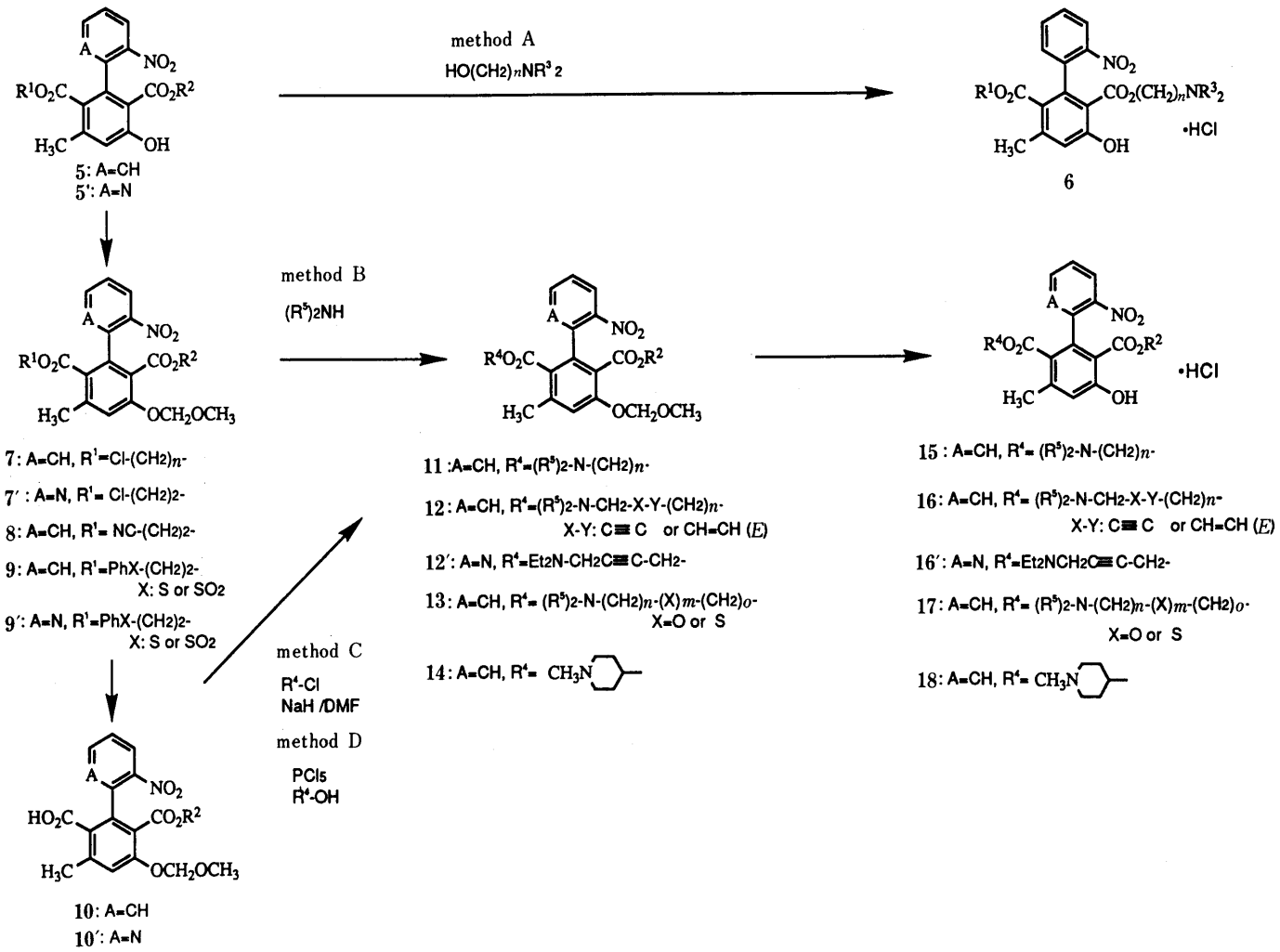


Chart 2

of (**5**, **5'**) were protected by methoxymethyl groups (**7**, **7'**, **8**). Amination of the chloroalkyl group in the ester moiety (**7**) afforded aminoalkyl ester (**11**) (method B). Treatment of the compound **8** or 2-phenylsulfonylethyl esters (**9**, **9'**), derived from the compounds **7**, **7'**, with aq. sodium hydroxide solution afforded the carboxylic acids (**10**, **10'**). Alkylation of the carboxylic acids (**10**, **10'**) (method C) or esterification after activation of the carboxylic acid (**10**) with PCl_5 (method D) afforded the aminoalkyl esters (**11**—**14**). Deprotection of the methoxymethyl group in the compounds **11**—**14** afforded the aminoalkyl esters at the 6-position (**15**—**18**).

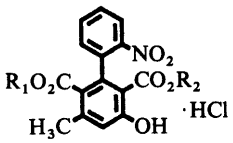
Pharmacological Activity and Discussion Pharmacological evaluations were carried out as follows: 1) *In vivo* tests were carried out if the compounds had over 50% inhibition at 1×10^{-5} g/ml in the *in vitro* assay (electrical field stimulation). 2) *In vivo* tests were performed on anesthetized rats at doses of 0.1 mg/kg and 1 mg/kg i.v.. If arrhythmia did not appear at 1 mg/kg i.v., tests at higher doses (3.2 mg/kg, 10 mg/kg i.v.) were carried out. 3) Tests in i.d. administration were carried out at dose of 10 mg/kg or 32 mg/kg. When arrhythmia would not appear at above mentioned doses, tests at 100 mg/kg were then carried out. The test procedures were performed as described in the preceding paper.[1] Tables I—III show the results.

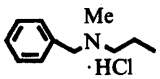
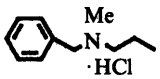
With the exception of the benzyl derivative (**6g**), compounds with an amino group in the ester moiety at the 2-position showed almost equipotent activity in the *in vitro* assay regardless of the type of alkyl group in the ester moiety at the 6-position (Table I). Although these compounds exhibited strong inhibitory activity on detrusor contraction in i.v. administration as expected, most of them showed undesirable arrhythmia at a dose of 1 mg/kg. Lengthening the alkylene chain in the aminoalkyl ester group from ethylene to propylene reduced the appearance of arrhythmia, but unfortunately, it led to a strongly toxic compound (**6d**). Also, replacement of the dimethylamino group with a diethylamino group in the ester moiety (**6e**) or introduction of amino groups into both of the ester moieties (**6i**, **j**) did not show significant improvement for reducing the appearance of arrhythmia.

On the other hand, in the case of introduction of an amino group into the ester moiety at the 6-position, the *in vitro* activity was dependent on the amino group and the length of the alkylene chain in the aminoalkyl ester moiety (Table II). Especially, with regard to the latter, an opposite trend in activity was observed in the case of dimethylamino groups (**15a**—**c**) and 4-methylpiperazino groups (**15g**—**i**).

In the *in vivo* test, many compounds showed strong inhibitory activity for detrusor contraction in i.v. ad-

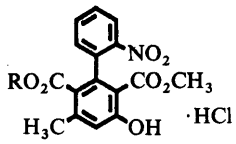
TABLE I. Pharmacological Properties of 1,1'-Biphenyl-2,6-dicarboxylic Acid Diesters·Hydrochloride



Compd. No.	R_1	R_2	*In vitro* IC_{50} (g/ml)	*In vivo* ED_{50} (mg/kg) i.v.	*In vivo* ED_{50} (mg/kg) i.d.	*In vivo* MED of arrhythmia (mg/kg) i.v.	*In vivo* MED of arrhythmia (mg/kg) i.d.	*In vivo* MLD (mg/kg) i.v.	*In vivo* MLD (mg/kg) i.d.	Safety margin MED/ED_{50} i.v.	Safety margin MED/ED_{50} i.d.	Safety margin MLD/ED_{50} i.v.	Safety margin MLD/ED_{50} i.d.
6a	Et	NMe_2	1.5×10^{-6}	0.45		1.0 (3/3)[e]		—		2.2			
6b	iso-Pr	NMe_2	2.9×10^{-6}	0.27	12	1.0 (1/3)[e]	10 (2/3)[e]	—	—	3.7	0.8		
6c	Cyclopentyl	NMe_2	1.3×10^{-6}	1.0	34	—	100 (1/2)[e]	10 (3/3)[e]	—		2.9	10	
6d	Cyclopentyl	NMe_2	7.9×10^{-7}	0.42		3.2 (2/2)[e]		3.2 (2/2)[e]		7.6		7.6	
6e	Cyclopentyl	NEt_2	6.4×10^{-7}	0.28		1.0 (2/3)[e]		—		3.6			
6f	Cyclohexyl	NMe_2	2.4×10^{-6}	0.22		1.0 (3/3)[e]		—		4.5			
6g	Ph-CH_2–	NMe_2	19.2%[a]										
6h	Ph-$(CH_2)_2$–	NMe_2	8.0×10^{-7}	66%[b]	59%[c]	1.0 (1/3)[e]	32 (2/2)[e]	—	—				
6i		NMe_2	4.4×10^{-6}	0.32	32	1.0 (2/2)[e]	32 (2/2)[e]	—	—	3.1	1.0		
6j		NMe_2	7.0×10^{-6}	NT	—		32 (1/1)[e]		—				
6k	Cyclopentyl	NEt_2	1.3×10^{-6}	NT	25%[c] 32%[d]		—		—				

Abbreviations: MED = minimum effective dose, MLD = minimum lethal dose, NT = not tested, — = no effect at the test doses. *a*) % inhibition at 10^{-5} g/ml. *b*) % inhibition at 1 mg/kg. *c*) % inhibition at 32 mg/kg. *d*) % inhibition at 100 mg/kg. *e*) Occurrence.

TABLE II. Pharmacological Properties of 1,1′-Biphenyl-2,6-dicarboxylic Acid Diesters·Hydrochloride



Compd. No.	R	*In vitro*	*In vivo*						Safety margin			
		IC_{50} (g/ml)	ED_{50} (mg/kg)		MED of arrhythmia (mg/kg)		MLD (mg/kg)		MED/ED_{50}		MLD/ED_{50}	
			i.v.	i.d.	i.v.	i.d.	i.v.	i.d.	i.v.	i.d.	i.v.	i.d.
15a	Me_2N	29.2%[a]										
15b	Me_2N	44.6%[a]										
15c	Me_2N	5.6×10^{-6}	1.0		3.2 (1/2)[f]		—		3.2			
15d	N	7.7×10^{-6}	NT	14.0%[c]		—		—				
15e	N	6.8×10^{-6}	NT	14.5		32		—		2.2		
15f	N	9.6×10^{-6}	NT	12.0%[c]		—		—				
15g	MeN N	4.2×10^{-6}	0.26	6.0	10 (1/1)[f]	32 (1/2)[f]	—	100 (2/2)[f]	38.5	5.3		16.7
15h	MeN N	46.7%[a]										
15i	MeN N	35.0%[a]										
15j	O N	31.0%[a]										
15k	Me N	2.2×10^{-6}	54.8%[b]	9.0%[c] 11%[e]	10 (2/2)[f]	—	10 (2/2)[f]	—				
15l	Et_2N	3.6×10^{-6}	0.28	42%[d]	—	100 (2/2)[f]	10 (2/2)[f]	100 (2/2)[f]			35.7	
16a	Et_2N	7.0×10^{-6}	0.51	NT	3.2 (3/3)[f]		10 (3/3)[f]		6.3		19.6	
16b	Me_2N	43.2%[a]	NT	11.2%[c]		—		—				
16c	N	9.6×10^{-6}	NT	13.9%[c]		—		—				
16d	MeN N	37.5%[a]										
16e	Et_2N	7.2×10^{-6}	100%[b]	15%[c]	1.0 (1/2)[f]	—	—	—				
16f	Et_2N	6.3×10^{-6}	NT	15%[c]		—		—				
17a	Et_2N O	8.0×10^{-6}	25.3%[b]	14.2	—	32 (2/2)[f]	—	—		2.3		
17b	Et_2N S	7.0×10^{-6}	10.8%[b]	NT	—		—					
18	MeN	6.9×10^{-6}	0.54	7.2	3.2 (1/3)[f]	100 (2/2)[f]	10 (1/3)[f]	100 (2/2)[f]	5.9	10.8	18.5	13.9

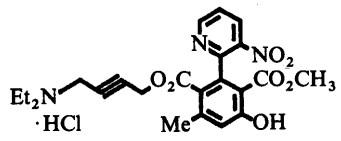
Abbreviations: MED = minimum effective dose, MLD = minimum lethal dose, NT = not tested, — = no effect at the test doses. Compounds (**15g**, **15h**, **15i**, **16d**) were dihydrochloride. *a*) % inhibition at 10^{-5} g/ml. *b*) % inhibition at 1 mg/kg. *c*) % inhibition at 10 mg/kg. *d*) % inhibition at 32 mg/kg. *e*) % inhibition at 100 mg/kg. *f*) Occurrence.

ministration and tended to have a weak influence on arrhythmia compared with the aminoalkyl ester series at the 2-position.

Introducing a nitrogen atom into the 1,1′-biphenyl skeleton (**16′**) caused loss of the activity. Among them, two compounds (**15g**, **18**) exhibited strong inhibitory activity in i.d. administration, suggesting that their intestinal absorption was greatly improved with an increase of solubility to water compared with that of the prototype compound FR75513. Compound **18** showed better separation between the inhibitory activity on detrusor contractions and induction of arrhythmia in i.d. administration than compound **15g**. Furthermore, like FR75513, compound **18** showed no anticholinergic activity ($IC_{50} > 1\times10^{-5}$ g/ml).

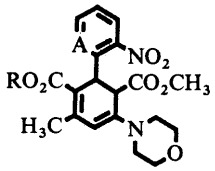
Agents for the treatment of an overactive detrusor on the market, that is terodiline[2] and oxybutynin,[3] have anticholinergic and other pharmacological activities and exhibit an inhibitory activity on detrusor contraction. Clinically, they frequently cause side effects such as mydriasis and dryness of the mouth based on their anticholinergic properties. Since the compound **18** exhibits an inhibitory activity on detrusor contractions without

TABLE III. Pharmacological Properties of 1,1′-Biphenyl-2,6-dicarboxylic Acid Related Compound

Compd. No.	Structure	*In vitro* % inhibition at 10^{-5} g/ml	*In vivo* ED_{50} (mg/kg) i.v.	*In vivo* ED_{50} (mg/kg) i.d.	*In vivo* MED of arrhythmia (mg/kg) i.v.	*In vivo* MED of arrhythmia (mg/kg) i.d.	*In vivo* MLD (mg/kg) i.v.	*In vivo* MLD (mg/kg) i.d.	Safety margin MED/ED_{50} i.v.	Safety margin MED/ED_{50} i.d.	Safety margin MLD/ED_{50} i.v.	Safety margin MLD/ED_{50} i.d.
16′		26.1%										

Abbreviations: MED = minimum effective dose, MLD = minimum lethal dose.

TABLE IV. Physical Properties of 1,2-Dihydrobenzene-1,3-dicarboxylic Acid Diesters



Compd. No.	A	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
3-1	CH	NC-$(CH_2)_2$-	119—120	44.9	$C_{23}H_{25}N_3O_7$	60.65	5.53	9.23	60.54	5.30	9.19
3-2	CH	Cl-$(CH_2)_3$-	161—167	33.3	$C_{23}H_{27}ClN_2O_7$	57.68	5.68	5.85	57.96	5.83	5.91
3-3	CH	Cyclohexyl	148—150	12.4	$C_{26}H_{32}N_2O_7$	64.45	6.66	5.78	64.14	6.57	5.94
3-4	CH	Ph-$(CH_2)_2$-	150.5—151	60.2	$C_{28}H_{30}N_2O_7$	66.39	5.97	5.76	66.13	5.76	5.50
3′	N	Cl-$(CH_2)_2$-	171—173	31.5	$C_{21}H_{24}ClN_3O_7$	54.14	5.19	9.02	54.33	5.18	8.84

anticholinergic activity and it is hoped that it will become a new type of agent for the disease, the compound **18** has been selected for further evaluation.

In conclusion, introduction of an amino group into the ester moiety of 1,1′-biphenyl-2, 6-dicarboxylic acid diester greatly improved intestinal absorption and exhibited a strong inhibitory activity on detrusor contractions in i.d. administration compared with the prototype compound FR75513.

Experimental

All melting points were determined in open glass capillaries on a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-90H NMR spectrometer with tetramethylsilane as an internal standard (δ value, ppm). Mass spectra (MS) were recorded on a JEOL JMS D-300 mass spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400CHN Elemental Analyzer. Yields are not optimized.

Compounds **3**, **3′**, **5**, **5′** in Tables IV and V were prepared by the previously reported procedure.[1)]

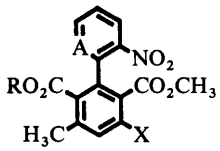
2-(2-*N*,*N*-Dimethylaminoethyl) 6-Ethyl 3-Hydroxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate·Hydrochloride (6a) Method A: A typical example is given to illustrate the general procedure.

A mixture of 6-ethyl 2-methyl 3-hydroxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (1.75 g), *N*,*N*-dimethylaminoethanol (5.8 ml) and *p*-toluenesulfonic acid monohydrate (29 mg) was heated at 80 °C for 5.5 h. After being cooled, EtOAc and water were added to the mixture, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (10 : 1) as an eluent to afford a free form of **6a** (1.0 g), which was dissolved in $CHCl_3$. To the solution was added 3 N HCl in MeOH (2 ml) and it was evaporated *in vacuo* to afford **6a** (1.1 g) as an oil. IR (neat) cm^{-1}: 3000—2300, 1715. NMR ($CDCl_3$–D_2O): 0.93 (3H, t, J=6 Hz), 2.35 (3H, s), 2.53 (6H, s), 2.60—2.86 (2H, m), 3.60—4.00 (2H, m), 4.15—4.50 (2H, m), 6.93 (1H, s), 7.13—7.73 (3H, m), 8.00—8.20 (1H, m). MS *m/z*: 416 (M^+), 371 ($M^+ - OEt$).

Other compounds **6b—j** in Table I were prepared in a similar manner. Table VI shows their physical data.

In the case of **6k**, hydrolysis of an ester group instead of an ester exchange had occurred to afford 3-hydroxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylic acid 6-cyclopentyl ester. mp 184—186 °C. IR (Nujol) cm^{-1}: 2800—2000, 1710, 1655. NMR ($CDCl_3$): 0.80—1.90 (8H, m), 2.30 (3H, s), 4.73—5.00 (1H, m), 6.90 (1H, s), 7.10—7.75 (3H, m), 8.06—8.30 (1H, m), 10.26 (2H, br s). Synthesis of **6k** was carried out as follows: To the above obtained compound (1.57 g) was added thionyl chloride (6 ml) and the mixture was heated at 50 °C for 4 h. After being cooled, the solution was evaporated *in vacuo*. To the residue were added ethylene glycol dimethyl ether (4.5 ml) and 4-diethylamino-2-butyn-1-ol (2.0 ml) and the mixture was heated at 50 °C for 11 h. After being cooled, EtOAc and aq. K_2CO_3 were added to the mixture. The organic layer was separated, washed with aq. NaOH, and evaporated *in vacuo*. The residue was acidified with 10% HCl and the acidic solution was washed with a mixture of EtOAc and diisopropyl ether. The acidic solution was made alkaline with aq. NaOH and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and EtOAc (5 : 1) as an eluent to afford a free form of **6k** (1.51 g), which was dissolved in $CHCl_3$. To the solution was added 3 N HCl in MeOH (2 ml) and the whole was evaporated *in vacuo* to afford **6k** (1.32 g) as an oil. IR (neat) cm^{-1}: 3400, 2800—2000, 1720, 1660. NMR ($CDCl_3$): 0.85—1.90 (14H, m), 2.33 (3H, s), 2.83—3.36 (4H, m), 3.83—4.03 (2H, m), 4.25 (2H, dt, J=16, 2 Hz), 4.75 (2H, dt, J=16, 2 Hz), 4.76—5.03 (1H, m), 6.96 (1H, s), 7.16—7.80 (3H, m), 8.15—8.30 (1H, m), 12.60 (1H, br s). MS *m/z*: 508 (M^+), 490 ($M^+ - 18$).

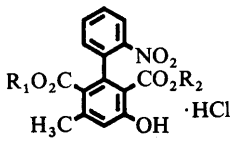
TABLE V. Physical Properties of 1,1′-Biphenyl-2,6-dicarboxylic Acid Diesters and Related Compounds



Compd. No.	A	R	X	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
5-1	CH	NC–$(CH_2)_2$–	OH	135—137	44.2	$C_{19}H_{16}N_2O_7$	59.38	4.20	7.29	59.22	4.02	7.29
5-2	CH	Cl–$(CH_2)_3$–	OH	108—112	49.0	$C_{19}H_{18}ClNO_7$	55.96	4.45	3.43	55.56	4.27	3.40
5-3	CH	Cyclohexyl	OH	122—124	63.4	$C_{22}H_{23}NO_7$	63.91	5.61	3.39	63.91	5.40	3.40
5-4	CH	Ph–$(CH_2)_2$–	OH	120—121	25.6	$C_{24}H_{21}NO_7$	66.20	4.86	3.22	66.08	4.76	3.27
5′	N	Cl–$(CH_2)_2$–	OH	80—83[a]	20.9							
7-1	CH	Cl–$(CH_2)_2$–	OCH_2OMe	88—89	82.7	$C_{20}H_{20}ClNO_8$	54.87	4.60	3.20	54.41	4.51	3.31
7-2	CH	Cl–$(CH_2)_3$–	OCH_2OMe	85—87	82.3	$C_{21}H_{22}ClNO_8$	55.82	4.91	3.10	55.97	4.86	3.09
7′	N	Cl–$(CH_2)_2$–	OCH_2OMe	Oil[b]	100							
8	CH	NC–$(CH_2)_2$–	OCH_2OMe	82.5—83.5	99.4	$C_{21}H_{20}N_2O_8$	58.88	4.71	6.54	58.79	4.44	6.54
9-1	CH	PhS–$(CH_2)_2$–	OCH_2OMe	Oil[c]	100							
9-2	CH	$PhSO_2$–$(CH_2)_2$–	OCH_2OMe	Oil[d]	91.0							
9′-1	N	PhS–$(CH_2)_2$–	OCH_2OMe	Oil[e]	98.4							
9′-2	N	$PhSO_2$–$(CH_2)_2$–	OCH_2OMe	Oil[f]	63.1							
10	CH	H	OCH_2OMe	150—151.5	98.0[g] 85.3[h]	$C_{18}H_{17}NO_8$	57.60	4.57	3.73	57.52	4.29	3.70
10′	N	H	OCH_2OMe	143—150[a]	83.7							

a) This compound was used for the next reaction without purification. *b*) MS *m/z*: 438 (M^+), 407 ($M^+ - OMe$). *c*) MS *m/z*: 511 (M^+), 480 ($M^+ - OMe$). *d*) MS *m/z*: 543 (M^+), 512 ($M^+ - OMe$). *e*) MS *m/z*: 512 (M^+), 481 ($M^+ - OMe$). *f*) MS *m/z*: 544 (M^+), 513 ($M^+ - OMe$). *g*) From compound (**8**). *h*) From compound (**9-2**).

TABLE VI. Physical Properties of 1,1′-Biphenyl-2,6-dicarboxylic Acid Diesters·Hydrochloride



Compd. No.	mp (°C) (Recryst. solv.)	Yield (%)	MS *m/z*
6a	Oil	49.5	416 (M^+), 371 ($M^+ - OEt$)
6b	Oil	39.5	430 (M^+)
6c	Oil	33.9	456 (M^+), 371 (M^+ – O-cyclopentyl)
6d	152—154 (dec.)[a] (IPA)	27.0	470 (M^+), 453 ($M^+ - OH$)
6e	Oil	74.0	484 (M^+), 467 ($M^+ - OH$)
6f	Oil	74.2	470 (M^+), 453 ($M^+ - OH$)
6g	Oil	46.0	478 (M^+), 461 ($M^+ - OH$)
6h	Oil	39.3	492 (M^+), 374
6i	Oil	45.7	535 (M^+), 518 ($M^+ - OH$)
6j	Oil	37.6	549 (M^+), 532 ($M^+ - OH$)
6k	Oil	51.2	508 (M^+), 490 ($M^+ - 18$)

a) *Anal.* Calcd for $C_{25}H_{30}N_2O_7 \cdot HCl \cdot 0.5H_2O$: C, 58.19; H, 6.25; N, 5.43. Found: C, 58.22; H, 6.38; N, 5.39. IPA, isopropyl alcohol.

6-(2-Chloroethyl) 2-Methyl 3-Methoxymethoxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (7-1) To a solution of 6-(2-chloroethyl) 2-methyl 3-hydroxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (17.16 g) in dimethylformamide (DMF) (85 ml) was added K_2CO_3 (6.24 g) and chloromethyl methyl ether (5.8 ml). The mixture was then stirred at room temperature for 19 h. The mixture was poured into ice-water and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was triturated with diisopropyl ether to afford **7-1** (16.05 g), mp 88—89 °C (recrystallized from a mixture of *n*-hexane and EtOAc). *Anal.* Calcd for $C_{20}H_{20}ClNO_8$: C, 54.87; H, 4.60; N, 3.20. Found: C, 54.41; H, 4.51; N, 3.31. IR (Nujol) cm^{-1}: 1720. NMR ($CDCl_3$): 2.50 (3H, s), 3.33 (2H, t, $J=6$ Hz), 3.43 (3H, s), 3.46 (3H, s), 4.00—4.25 (2H, m), 5.15—5.40 (2H, m), 7.10 (1H, s), 7.20—7.70 (3H, m), 8.10—8.30 (1H, m).

Compounds **7-2**, **7′**, **8** in Table V were prepared in a similar manner.

2-Methyl 6-(2-Piperidinoethyl) 3-Methoxymethoxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (11d) Method B: A typical example is given to illustrate the general procedure.

A mixture of **7-1** (2.0 g), piperidine (2.26 ml) and KI (0.91 g) in DMF (5 ml) was stirred at 100 °C for 4 h. After being cooled, EtOAc and water were added to the mixture. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (10:1) as an eluent to afford **11d** (2.10 g) as an oil. IR (Nujol) cm^{-1}: 1720, 1680. NMR ($CDCl_3$): 1.25—1.80 (6H, m), 2.10—2.45 (4H, m), 2.46 (3H, s), 3.20—3.50 (2H, m), 3.75—4.30 (2H, m), 3.43 (3H, s), 3.46 (3H, s), 5.13—5.35 (2H, m), 7.10 (1H, s), 7.20—8.30 (4H, m). MS *m/z*: 486 (M^+).

2-Methyl 6-(2-Phenylthioethyl) 3-Methoxymethoxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (9-1) To a solution of **7-1** (6.93 g), thiophenol (1.83 g) and NaI (0.23 g) in DMF (7 ml) was added K_2CO_3 (4.37 g) at 22—28 °C under a nitrogen atmosphere. After being stirred for 3 h, EtOAc and water were added to the mixture. The organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to afford **9-1** (8.10 g) as an oil. IR (neat) cm^{-1}: 1730. NMR ($CDCl_3$): 2.46 (3H, s), 2.73 (2H, t, $J=7$ Hz), 3.47 (3H, s), 3.50 (3H, s), 4.04 (2H, t, $J=7$ Hz), 5.26 (2H, s), 7.13 (1H, s), 7.29 (5H, s), 7.20—7.73 (3H, m), 8.06—8.28 (1H, m). MS *m/z*: 511 (M^+), 480 ($M^+ - OMe$).

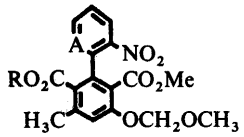
Compound **9′-1** in Table V was similarly prepared.

2-Methyl 6-(2-Phenylsulfonylethyl) 3-Methoxymethoxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (9-2) To a solution of **9-1** (8.15 g) in $CHCl_3$ (80 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (6.70 g) in $CHCl_3$ (24 ml) at 1—4 °C and stirred for 1 h. The solution was made alkaline with sat.$NaHCO_3$ solution and the organic layer was separated. The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to afford **9-2** (8.55 g) as an oil. IR (neat) cm^{-1}: 1730. NMR ($CDCl_3$): 2.35 (3H, s), 3.08 (2H, t, $J=7$ Hz), 3.46 (3H, s), 3.50 (3H, s), 3.91—4.43 (2H, m), 5.26 (2H, s), 7.09 (1H, s), 7.17—7.35 (1H, m), 7.41—7.74 (5H, m), 7.80—7.97 (2H, m), 8.06—8.21 (1H, m). MS *m/z*: 543 (M^+), 512 ($M^+ - OMe$).

Compound **9′-2** in Table V was prepared in a similar manner.

3-Methoxymethoxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylic Acid 2-Methyl Ester (10) To a solution of **8** (14.1 g) in a mixture of MeOH (70 ml) and THF (35 ml) was added 1 N NaOH solution (36 ml) and the

TABLE VII. Physical Properties of 1,1′-Biphenyl-2,6-dicarboxylic Acid Diesters and Related Compound



Compd. No.	A	R	mp (°C)	Method	Yield (%)	MS *m/z*
11a	CH	Me_2N	Oil	C	53.4	445 (M^+-1), 429 (M^+-OH), 415 (M^+-OMe)
11b	CH	Me_2N	Oil	C	55.4	460 (M^+), 443 (M^+-OH), 429 (M^+-OMe)
11c	CH	Me_2N	Oil	D	75.0	328 ($M^+-Me_2N-(CH_2)_4-$), 313, 298
11d	CH	N	Oil	B	94.6	486 (M^+)
11e	CH	N	Oil	B	70.0	500 (M^+), 483 (M^+-OH), 469 (M^+-OMe)
11f	CH	N	Oil	D	82.7	514 (M^+)
11g	CH	MeN N	Oil	B	62.0	500 (M^+-1), 484 (M^+-OH), 470 (M^+-OMe)
11h	CH	MeN N	Oil	B	56.8	498 (M^+-OH), 483 (M^+-OMe)
11i	CH	MeN N	Oil	D	23.6	529 (M^+), 512 (M^+-OH), 499 (M^+-OMe)
11j	CH	O N	Oil	B	53.2	487 (M^+-1), 456 (M^+-OMe)
11k	CH	Me N	Oil	B	38.5	522 (M^+), 505 (M^+-OH), 491 (M^+-OMe)
11l	CH	Et_2N	Oil	B	51.5	474 (M^+), 457 (M^+-OH), 443 (M^+-OMe)
12a	CH	Et_2N	Oil	C	62.3	498 (M^+), 481 (M^+-OH)
12b	CH	Me_2N	Oil	C	29.8	470 (M^+), 453 (M^+-OH), 439 (M^+-OMe)
12c	CH	N	Oil	D	15.1	510 (M^+), 493 (M^+-OH), 489 (M^+-OMe)
12d	CH	MeN N	Oil	D	24.3	525 (M^+), 507 (M^+-18)
12e	CH	Et_2N	Oil	C	50.7	513 (M^+), 495 (M^+-18)
12f	CH	Et_2N	Oil	C	86.0	500 (M^+), 483 (M^+-OH), 469 (M^+-OMe)
12′	N	Et_2N	Oil	C	75.0	499 (M^+), 482 (M^+-OH)
13a	CH	Et_2N O	Oil	D	32.8	517 (M^+-1), 503 (M^+-15), 487 (M^+-OMe)
13b	CH	Et_2N S	Oil	C	41.6	535 (M^+)
14	CH	MeN	104—105[a]	D	70.1	

a) *Anal.* Calcd for $C_{24}H_{28}N_2O_8$: C, 61.01; H, 5.97; N, 5.93. Found: C, 61.24; H, 5.92; N, 5.91.

mixture was stirred at room temperature for 30 min and then evaporated *in vacuo*. The alkaline solution was washed with EtOAc, acidified with 1 N HCl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residual solid was recrystallized from a mixture of EtOH and diisopropyl ether to afford **10** (8.08 g) as a powder. The second crop of **10** (0.62 g) was obtained by a similar treatment of the mother liquor. mp 150—151.5 °C. *Anal.* Calcd for $C_{18}H_{17}NO_8$: C, 57.60; H, 4.57; N, 3.73. Found: C, 57.52; H, 4.29; N, 3.70. IR (Nujol) cm^{-1}: 1730, 1700, 1685. NMR ($CDCl_3$): 2.50 (3H, s), 3.43 (3H, s), 3.50 (3H, s), 5.25—5.40 (2H, m), 7.06 (1H, s), 7.10—7.70 (3H, m), 7.95—8.15 (1H, m).

Compound **10** was also prepared from compound **9**-2 and the compound **10′** in Table V was similarly prepared from compound **9′**-2.

6-(*N*,*N*-Dimethylaminoethyl) 2-Methyl 3-Methoxymethoxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (11a) Method C: A typical example is given to illustrate the general procedure.

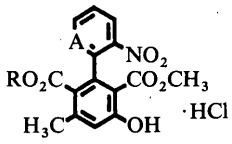
To a solution of **10** (1.50 g) in DMF (15 ml) was added NaH (60%, 155 mg) and the whole was stirred at room temperature for 20 min. To the suspension was added Et_3N (1.67 ml) and 2-chloroethyldimethylamine hydrochloride (1.73 g) and the mixture was heated at 100 °C for 13 h. After being cooled, ice water was added to the mixture and extracted with EtOAc. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (10 : 1) as an eluent to afford **11a** (0.95 g) as an oil. IR (neat) cm^{-1}: 1710. NMR ($CDCl_3$):2.13 (6H, s), 2.20 (2H, t, J=6 Hz), 2.46 (3H, s), 3.45 (3H, s), 3.50 (3H, s), 3.70—4.10 (2H, m), 5.10—5.33 (2H, m), 7.05 (1H, s), 7.15—7.65 (3H, m), 8.00—8.20 (1H, m). MS *m/z*: 445 (M^+-1), 429 (M^+-OH), 415 (M^+-OMe).

2-Methyl 6-[4-(1-Methylpiperidinyl)] 3-Methoxymethoxy-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate (14) Method D: A typical example is given to illustrate the general procedure.

Phosphorous pentachloride (2.72 g) was added portionwise to a solution of **10** (2.42 g) in $CHCl_3$ (75 ml) at 1.5 to 2.5 °C. The mixture was stirred below 5 °C for 30 min and then a solution of 4-hydroxy-1-methylpiperidine (15.0 g) in $CHCl_3$ (25 ml) was added dropwise thereto at −8 to −4 °C. After being stirred at room temperature for 8 d, the mixture was evaporated *in vacuo*. To the residue was added water, followed by extraction with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (100 : 1) as an eluent to afford **14** (2.55 g), which was recrystallized from diisopropyl ether to afford pure **14** (2.10 g). The filtrate was evaporated *in vacuo*, and the residue afforded the second crop of **14** (0.06 g). mp 104—105 °C. *Anal.* Calcd for $C_{24}H_{28}N_2O_8$: C, 61.01; H, 5.97; N, 5.93. Found: C, 61.24; H, 5.92; N, 5.91. IR (Nujol) cm^{-1}: 1730, 1700. NMR ($CDCl_3$): 1.03—2.80 (8H, m), 2.20 (3H, s), 2.46 (3H, s), 3.45 (3H, s), 3.50 (3H, s), 4.40—4.80 (1H, m), 5.10—5.33 (2H, m), 7.06 (1H, s), 7.15—7.66 (3H, m), 8.00—8.20 (1H, m).

Compounds in Table VII were prepared by methods B, C, and D.

TABLE VIII. Physical Properties of 1,1′-Biphenyl-2,6-dicarboxylic Acid Diesters·Hydrochloride and Related Compound



Compd. No.	mp (°C)	Recryst. solv.	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
15a	183—185 (dec.)	EtOH	78.2	$C_{20}H_{22}N_2O_7$ ·HCl	54.74 (54.95)	5.28 (5.28)	6.38 (6.40)
15b	193 (dec.)	EtOH–MeOH	71.1	$C_{21}H_{24}N_2O_7$ ·HCl	55.69 (55.69)	5.56 (5.38)	6.19 (6.22)
15c	146 (dec.)	EtOH–ether	80.3	$C_{22}H_{26}N_2O_7$ ·HCl	56.59 (56.28)	5.83 (5.80)	6.00 (5.93)
15d	203 (dec.)	MeOH	58.5	$C_{23}H_{26}N_2O_7$ ·HCl	57.68 (57.47)	5.68 (5.55)	5.85 (5.91)
15e	163—165 (dec.)	MeOH–ether	90.0	$C_{24}H_{28}N_2O_7$ ·HCl	58.48 (58.13)	5.93 (5.99)	5.68 (5.78)
15f	Oil[a]		100				
15g	196—197 (dec.)	MeOH–ether	72.4	$C_{23}H_{27}N_3O_7$ ·2HCl	52.08 (51.87)	5.51 (5.40)	7.92 (7.58)
15h	181—184 (dec.)	EtOH	90.9	$C_{24}H_{29}N_3O_7$ ·2HCl·0.5H_2O	52.09 (51.83)	5.83 (5.80)	7.59 (7.40)
15i	141—142 (dec.)	EtOAc–ether[h]	61.4	$C_{25}H_{31}N_3O_7$ ·2HCl·1.5H_2O	51.29 (51.15)	6.20 (6.55)	7.18 (7.22)
15j	197—198 (dec.)	EtOH–MeOH	84.6	$C_{22}H_{24}N_2O_8$ ·HCl	54.95 (54.87)	5.40 (5.03)	5.83 (5.77)
15k	Amorphous[b]		83.6				
15l	145 (dec.)	EtOH–EtOAc	84.6	$C_{22}H_{26}N_2O_7$ ·HCl·0.25H_2O	56.05 (56.04)	5.88 (5.50)	5.94 (5.99)
16a	119—121 (dec.)	Acetone[h]	79.2	$C_{24}H_{26}N_2O_7$ ·HCl·0.25H_2O	58.18 (58.30)	5.59 (5.49)	5.65 (5.69)
16b	Oil[c]		93.9				
16c	Oil[d]		100				
16d	135—136 (dec.)	EtOAc–ether[h]	92.6	$C_{25}H_{27}N_3O_7$ ·2HCl·H_2O	52.46 (52.40)	5.46 (5.34)	7.34 (7.15)
16e	Oil[e]		92.2				
16f	186 (dec.)	EtOH	96.5	$C_{24}H_{28}N_2O_7$ ·HCl	58.48 (58.51)	5.93 (5.87)	5.68 (5.57)
16′	157—158 (dec.)	EtOH–ether	98.4	$C_{23}H_{25}N_3O_7$ ·HCl	56.16 (55.91)	5.33 (5.37)	8.54 (8.42)
17a	Oil[f]		100				
17b	Oil[g]		100				
18	124 (dec.)	Ether[h]	76.1	$C_{22}H_{24}N_2O_7$ ·HCl·H_2O	54.73 (54.46)	5.64 (5.42)	5.80 (5.64)

a) MS *m/z*: 470 (M^+), 453 ($M^+ - OH$). *b*) MS *m/z*: 461 (M^+), 477 ($M^+ - OMe$). *c*) MS *m/z*: 426 (M^+), 409 ($M^+ - OH$). *d*) MS *m/z*: 466 (M^+), 449 ($M^+ - OH$). *e*) MS *m/z*: 469 (M^+), 451 ($M^+ - 18$). *f*) MS *m/z*: 474 (M^+). *g*) MS *m/z*: 491 (M^+). *h*) Crystallizing solvent.

2-Methyl 6-[4-(1-Methylpiperidinyl)] 3-Hydroxyl-5-methyl-2′-nitro-1,1′-biphenyl-2,6-dicarboxylate Hydrochloride (18) To a solution of **14** (1.47 g) in $CHCl_3$ (5 ml) was added HCl in MeOH (0.15 g/ml, 1 ml), and the solution was refluxed for 1.5 h. After being cooled, the solution was evaporated *in vacuo* and the residue was triturated with diethyl ether to afford **18** (0.35 g), mp 124 °C (dec.). *Anal.* Calcd for $C_{22}H_{24}N_2O_7 \cdot HCl \cdot H_2O$: C, 54.73; H, 5.64; N, 5.80. Found: C, 54.46; H, 5.42; N, 5.64. IR (Nujol) cm^{-1}: 1720, 1700. NMR ($CDCl_3$): 1.10—3.50 (4H, m), 2.33 (3H, s), 2.73 (3H, s), 3.45 (3H, s), 4.75—5.05 (1H, m), 7.00 (1H, s), 7.15—8.30 (4H, m), 11.40 (1H, s).

Other compounds in Table II and compound **16′** were prepared in a similar manner. Table VIII shows their physical data.

Acknowledgment We wish to thank the staff of the Division of Analytical Research Laboratories for elemental analyses and spectral measurements.

References and Notes

1) Part I: K. Take, K. Okumura, K. Takimoto, M. Kato, M. Ohtsuka, and Y. Shiokawa, *Chem. Pharm. Bull.*, **39**, 2915 (1991).
2) *a*) K.-E. Andersson, B. Ekstrom, and A. Mattiason, *Pharmacol. Toxicol.*, **37**, 148 (1988); *b*) T. C. Gerstemberg, P. Klarskov, D. Ramirez, and T. Hald, *Br. J. Urol.*, **58**, 129 (1986); *c*) J. F. Ostergaard, K. Ostergaard, K.-E. Andersson, and L. Sommer, *Acta Pharmacol. Toxicol.*, **46**, 12 (1980); *d*) S. Husted, K.-E. Andersson, L. Sommer, and J. R. Ostergaard, *ibid.*, **46**, 20 (1980).
3) *a*) G. F. Anderson and C. M. Fredericks, *Pharmacology* (Basal), **15**, 31 (1977); *b*) P. M. Lish, J. A. LaBudde, E. L. Peters, and S. I. Robbins, *Arch. Int. Pharmacodyn.*, **156**, 467 (1965); *c*) M. Tonini, C. A. Rizzi, E. Perucca, F. DePonti, L. D'Angelo, A. DelVecchio, and A. Crema, *J. Pharm. Pharmacol.*, **39**, 103 (1987).