Notes

Synthesis and Anticholinergic Activity of the Four Stereoisomers of 4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide

Hitoshi Oyasu, Masanobu Nagano,† Atsushi Akahane,† Masaaki Tomoi,‡ Toshiji Tada,§ and Masaaki Matsuo*,†

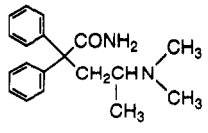
R & D Division, New Drug Research Laboratories, Pharmacological Research Laboratories, Analytical Research Laboratories, Fujisawa Pharmaceutical Company Ltd., 1-6, 2-Chome, Kashima, Yodogawa-ku, Osaka 532, Japan

Received December 13, 1993•

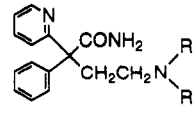
The four stereoisomers of 4-(dimethylamino)-2-phenyl-(2-pyridyl)pentanamide were synthesized, and the absolute configurations were determined by X-ray crystallography. Pharmacological testing for anticholinergic activity revealed great differences in potency among **10** (2*R*,4*R*, $IC_{50} = 0.40\ \mu M$), **11** (2*S*,4*S*, 31 μM), **12** (2*R*,4*S*, 170 μM), and **13** (2*S*,4*R*, 0.13 μM). A new drug application for the racemate **8** (FK176, vamicamide) has been filed in Japan for the treatment of overactive detrusor syndrome.

Anticholinergic agents which act on the muscarinic receptor have been utilized in the clinic, e.g., for treating spasm of internal organs. Terodiline and oxybutynin recently exploited a new clinical application of anticholinergics for the treatment of overactive detrusor syndrome associated with bladder muscle instability. The clinical effect of these drugs is mainly ascribed to antimuscarinic activity,[1,2] although both drugs bear additional pharmacological properties, i.e., calcium antagonism for terodiline[3-5] and local anesthetic and spasmolytic activities for oxybutynin.[6-8] Accordingly, some new types of anticholinergics have been discovered in the hope of finding a better treatment for overactive detrusor syndrome.[9-13]

We have paid attention to the following stereochemistry–activity relationships of aminopentamide (**1**) and disopyramide (**2**). The (−)-enantiomer of **1** having a *R* configuration at the asymmetric carbon[14] was 4 times as potent as the (+)-enantiomer,[15] and the (*S*)-(+)-enantiomer of **2** was 4 times more potent than the (*R*)-(−)-enantiomer[16] with respect to anticholinergic activity in isolated muscle strips. We thus introduced a methyl group at the methylene adjacent to the tertiary amino in compound **3**, the *N*,*N*-dimethyl analogue of **2**, in order to gain additional information concerning stereochemistry–activity relationships, as well as to discover a new compound with improved anticholinergic activity.



1 (aminopentamide)



2 R = $CH(CH_3)_2$ (disopyramide)
3 R = CH_3

We describe herein the synthesis and anticholinergic activity of the four stereoisomers of 4-(dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide (**10**–**13**).

Chemistry

Compound **7**, a mixture of A-racemate **8** and B-racemate **9**, was prepared via the route as shown in Scheme 1. Sperber *et al.*[17] reported the synthesis of the intermediate **6** by an alternative method: the reaction of 2-phenyl-2-(2-pyridyl)ethanenitrile (**4**) with 2-(dimethylamino)propyl chloride using a base. This reaction, however, yielded a mixture of **6** and its regioisomer, 3-((dimethylamino)-methyl)-2-phenyl-2-(2-pyridyl)butanenitrile. We thus employed a two-steps synthesis to obtain the desired regioisomer **6** in good yield. Alkylation of **4** with chloroacetone was efficiently achieved in the presence of powdered potassium hydroxide in dimethyl sulfoxide to give 4-oxopentanenitrile derivative **5** in 83% yield. Compound **5** was then converted to **6** in 75% yield by reductive amination, namely reaction with dimethylamine using titanium tetrachloride and successive reduction with sodium borohydride. The nitrile **6**, a mixture of two diastereoisomers, was hydrolyzed with concentrated sulfuric acid in acetic acid to give the objective pentanamide derivative **7**. This product **7** was indicated by HPLC analysis to be a mixture of two diastereoisomers, A-racemate **8** (48%) and B-racemate **9** (52%). Separation of **8** and **9** was accomplished by recrystallization of a mixture of their maleic acid salts.

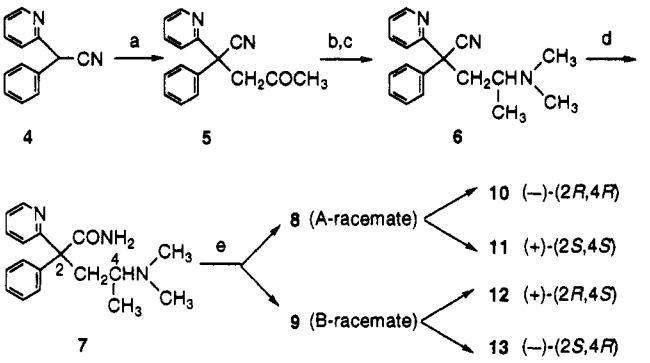
The two obtained racemates **8** and **9** were resolved by the classical recrystallization method. The (−)-enantiomer of **8** (compound **10**) was preferentially crystallized as a salt of (−)-dibenzoyl-L-tartaric acid. The corresponding (+)-enantiomer **11** was isolated from the mother liquor as a salt of (+)-dibenzolyl-D-tartaric acid. Recrystallization of the (−)-dibenzoyl-L-tartrate of **9** afforded (+)-enantiomer **12** as a crystalline salt, while (−)-enantiomer **13** was obtained from the mother liquor. The enantiomeric purities of these compounds were assessed by HPLC analyses using a chiral column and were >99% ee.

The absolute configurations of the isolated stereoisomers were confirmed by X-ray crystallography of (1*S*)-(+)-camphor-10-sulfonate of **10** (compound **14**) and (−)-dibenzoyl-L-tartrate of **12** (compound **15**). Compound **10** has *R* configurations at the 2- and 4-positions, whereas compound **12** possesses 2*R* and 4*S* configurations (Figure 1).

† New Drug Research Laboratories.
‡ Pharmacological Research Laboratories.
§ Analytical Research Laboratories.
• Abstract published in *Advance ACS Abstracts*, March 15, 1994.

0022-2623/94/1837-1378$04.50/0

Scheme 1[a]



[a] (a) $ClCH_2COCH_3$, KOH, DMSO; (b) $(CH_3)_2NH$, $TiCl_4$, CH_2Cl_2; (c) $NaBH_4$, MeOH; (d) concentrated H_2SO_4, AcOH; (e) recrystallization of maleate of 7.

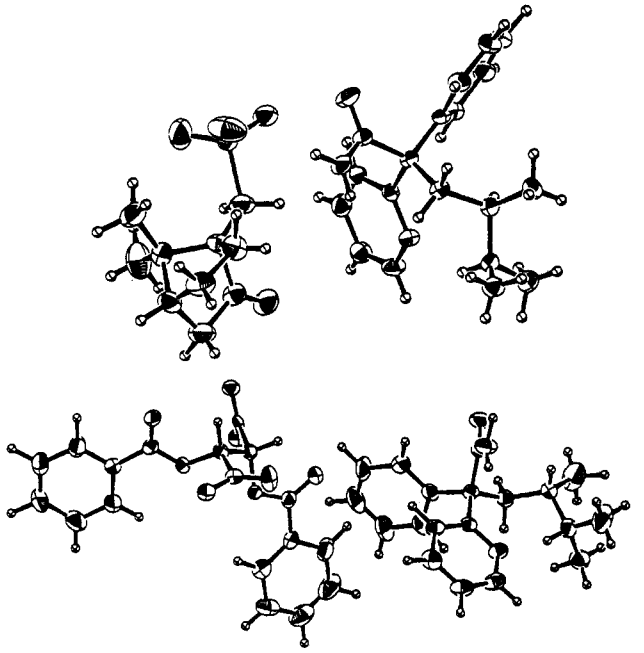


Figure 1. X-ray crystal structures: compound 14 (top), (1S)-(+)-camphor-10-sulfonate of 10; compound 15 (bottom), (−)-dibenzoyl-L-tartrate of 12.

Table 1. Inhibitory Effect on Acetylcholine-Induced Contraction of Guinea Pig Ileum

compound	IC_{50} (μM)[a]
8 (A-racemate)	1.5 ± 0.6
9 (B-racemate)	0.57 ± 0.07
10 (2R,4R)	0.40 ± 0.03
11 (2S,4S)	31 ± 7
12 (2R,4S)	170 ± 20
13 (2S,4R)	0.13 ± 0.01
3[b]	8.1 ± 0.3

[a] IC_{50} values were obtained according to the method of Litchfield and Wiloxon and are expressed as mean ± SEM. [b] Tested as a hydrochloride.

Pharmacological Results

We employed an *in vitro* assay, acetylcholine-induced contraction of isolated guinea pig ileum, to evaluate anticholinergic activity of 8–13. The results are summarized in Table 1, along with the data of compound 3.

Greater activity was seen with both racemates 8 and 9 in comparison with compound 3, suggesting that the introduction of a methyl group affected an increase of activity. Regarding the stereochemistry at the 2- and 4-positions, the 2S,4R-isomer (13) exhibited the most potent activity. The 2R,4R-isomer (10) was shown to be the second strongest, albeit with 3 times less activity. The isomers having an S configuration at the 4-position, however, exhibited dramatic attenuation of the activity, being 2 and 3 orders of magnitude less potent in 2S,4S-isomer (11) and 2R,4S-isomer (12), respectively. From these results, it is likely that the configuration of the 4-position plays a critical role in exerting biological activity rather than that of the 2-position, although the preferred configurations are R at the 4-position and S at the 2-position.

Compound 8 (FK176, vamicamide) was chosen as a candidate for clinical trials for the overactive detrusor syndrome associated with bladder muscle instability, and a new drug application has been filed in Japan. The detailed pharmacological properties and the results of clinical trials will be published elsewhere.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were taken with a Hitachi R-90H NMR spectrometer using tetramethylsilane as an internal standard. The values of optical rotation were measured at 25 °C with a DIP-360 (Nihon Bunkoh, Co. Ltd., Japan) polarimeter. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. Analytical results were within ±0.4% of the theoretical values unless otherwise noted. Organic extracts were dried over anhydrous $MgSO_4$.

4-Oxo-2-phenyl-2-(2-pyridyl)pentanenitrile (5). A mixture of powdered KOH (15.9 g, 0.28 mol) and dry DMSO (200 mL) was stirred vigorously at room temperature for 20 min under a nitrogen atmosphere, and 4[18,19] (50 g, 0.26 mol) was added. The mixture was stirred at room temperature for 50 min, and chloroacetone (35.7 g, 0.39 mol) was added. The resulting mixture was stirred at room temperature for 2 h and poured into ice–water. After the mixture was stirred for 1 h, the crystals that appeared were collected, washed with water, and air-dried. Recrystallization from EtOH afforded 5 (53.7 g, 83.0%) as colorless crystals: mp 121–122 °C; IR (Nujol) 2240, 1700, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (3 H, s), 3.35 (1 H, d, J = 18 Hz), 4.13 (1 H, d, J = 18 Hz), 7.0–7.9 (8 H, m), 8.43–8.70 (1 H, m). Anal. ($C_{18}H_{14}N_2O$) C, H, N.

4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanenitrile (6). To a stirred solution of 5 (25.0 g, 0.10 mol) and anhydrous dimethylamine (45.0 g, 1.0 mol) in CH_2Cl_2 (200 mL) was added dropwise a solution of titanium tetrachloride (6.6 mL, 0.06 mol) in CH_2Cl_2 (25 mL) over 30 min under a nitrogen atmosphere while maintaining the temperature below 5 °C, and the resulting mixture was stirred at 5 °C for 0.5 h. To the reaction mixture were added MeOH (300 mL) and subsequently sodium borohydride (3.78 g, 0.10 mol) at 10 °C. The mixture was stirred at 10 °C for 20 min and then at room temperature for 30 min. After evaporation of the solvent, the residue was poured into a mixture of water (180 mL) and EtOAc (150 mL). Insoluble materials were filtered off, and the filtrate was adjusted to pH 4.0 with concentrated HCl. The aqueous layer was separated and adjusted to pH 8.5 with 6 N NaOH. The alkaline solution was extracted twice with EtOAc. The extracts were combined, washed with brine, dried, and evaporated to give crude crystals, which were recrystallized from petroleum ether to give 6 (20.8 g, 75%): mp 65.5–67 °C; IR (Nujol) 2235, 1580, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.05 (3 H, m), 2.04 (3 H, s), 2.08 (3 H, s), 2.3–3.0 (3 H, m), 7.0–7.85 (8 H, m), 8.5–8.77 (1 H, m). Anal. ($C_{18}H_{21}N_3$) C, H, N.

4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide (7). To a stirred solution of 6 (20.0 g, 72 mmol) in AcOH (20 mL) was added dropwise concentrated H_2SO_4 (40 mL) over 10 min while maintaining the temperature below 65 °C. The mixture was stirred at 90 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into a mixture of crushed ice and 24% NaOH (165 mL). The resulting solution was adjusted to

Table 2. Crystal Data of Compounds 14 and 15

	14	15
mol formula	$C_{18}H_{23}N_3O \cdot C_{10}H_{16}O_4S \cdot H_2O$	$C_{18}H_{23}N_3O \cdot C_{18}H_{14}O_8 \cdot 2H_2O$
mol weight	547.72	673.73
crystal system	triclinic	orthorhombic
space group	$P1$	$P2_12_12_1$
cell dimension: a (Å)	11.378(1)	30.003(2)
b (Å)	8.967(1)	14.598(1)
c (Å)	7.603(1)	7.993(1)
α (deg)	76.69(1)	
β (deg)	105.77(1)	
γ (deg)	103.78(1)	
V (Å^3)	713.6(2)	3500.8(5)
density (g cm^{-1})	D_x = 1.274	D_x = 1.278
number of formula units, Z	1	4
number of unique reflections	2350	2559
final R value	0.053	0.057

pH 7.4 with 6 N NaOH and washed with EtOAc. The aqueous solution was adjusted to pH 12 with 6 N NaOH and extracted twice with EtOAc. The extracts were combined, washed with brine, dried, and evaporated to give crude **7** (18.9 g), a mixture of two diastereoisomers **8** and **9** in 48:52 ratio from HPLC analysis: column, Nucleosil 50-5 (250 mm × 4 mm); eluent, $CHCl_3$–MeOH–NH_4OH (900:100:2); detection, 254 nm; flow rate, 1.5 mL/min; retention times, 13.4 min for **8** and 9.3 min for **9**. This crude substance was recrystallized from 40% aqueous EtOH to give **7** (14.9 g, 70.0%, a mixture of **8** and **9** in 50:50 ratio): mp 134–136 °C; IR (Nujol) 3200, 1635, 1630, 1585, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (3 H, d, J = 6.5 Hz), 2.17 (6 H, s), 2.0–3.46 (3 H, m), 6.92–7.83 (8 H, m), 8.47–8.76 (1 H, m). Anal. ($C_{18}H_{23}N_3O$) C, H, N.

Separation of (±)-(2*R,4*R**)-4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide (8) and (±)-(2*R**,4*S**)-4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide (9).** A mixture of **7** (25.0 g, 84 mmol) and maleic acid (9.7 g, 84 mmol) in EtOH (175 mL) was stirred at 50 °C for 30 min. The resulting solution was cooled to room temperature. The colorless crystals that appeared were collected by filtration (as described later, **8** was isolated from this filtrate) and recrystallized twice from EtOH to give the maleate of **9** (12.5 g, 35.9%). This maleate was suspended in water, and the mixture was made alkaline with 2 N NaOH and extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried, and concentrated under reduced pressure. The residue was recrystallized from 40% aqueous EtOH to give **9** (8.5 g, 34%): mp 151–153 °C; IR (Nujol) 3220, 1635, 1590, 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (3 H, d, J = 6.5 Hz), 2.17 (6 H, s), 2.18 (1 H, dd, J = 15, 4 Hz), 2.42 (1 H, m, CH at C4), 3.24 (1 H, dd, J = 15, 6 Hz), 5.74 (1 H, m), 6.92–7.73 (8 H, m), 8.62 (1H, dd, J = 5, 2 Hz). Anal. ($C_{18}H_{23}N_3O$) H, N; C: calcd 72.69; found 72.26.

The filtrate, which was obtained above, was concentrated under reduced pressure. The residue was diluted with 2 N NaOH and extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried, and evaporated. The residual crystals (15.0 g) were dissolved in a mixed solvent of acetone (105 mL) and isopropyl alcohol (45 mL) at 50 °C. To the solution was added concentrated HCl (1.38 g), and the resulting mixture was allowed to cool to room temperature. The colorless crystals that appeared were collected by filtration and suspended in water. The mixture was made alkaline with 2 N NaOH and extracted twice with CH_2Cl_2. The combined organic layer was washed with brine, dried, and concentrated under reduced pressure. The residue was recrystallized from 40% aqueous EtOH to give **8** (7.3 g, 29.2%): mp 156–157 °C; IR (Nujol) 3220, 1630, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (3 H, d, J = 6.5 Hz), 2.18 (6 H, s), 2.28 (1 H, dd, J = 13.5, 4 Hz), 2.53 (1 H, m, CH at C4), 2.84 (1 H, dd, J = 13.5, 6 Hz), 5.76 (1 H, m), 7.08–7.48 (6 H, m), 7.56–7.83 (2 H, m), 8.67 (1H, dd, J = 5, 2 Hz). Anal. ($C_{18}H_{23}N_3O$) C, H, N.

(−)-(2*R*,4*R*)-4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide (10). A hot solution of **8** (12.1 g, 40.7 mmol) and (−)-dibenzoyl-L-tartaric acid (15.3 g, 40.7 mmol) in a mixed solvent of EtOH (24 mL) and acetonitrile (121 mL) was allowed to stand at room temperature overnight. The crystals that appeared were collected by filtration (as described later, **11** was isolated from this filtrate), washed with acetonitrile (10 mL), and dried at 50 °C to give crude (−)-dibenzoyl-L-tartrate of **10** (12.5 g): mp 92–95 °C; $[\alpha]_D$ −92.6° (c = 0.5, MeOH) as a free base. The crude crystals were recrystallized three times from a mixed solvent of EtOH and acetonitrile (1:5) to give pure (−)-dibenzoyl-L-tartrate of **10** (8.91 g): mp 114–116 °C; $[\alpha]_D$ −98.7° (c = 0.5, MeOH) as a free base. These pure salts (8.4 g) were added to 1 N NaOH (50 mL), and the mixture was extracted with EtOAc (40 mL × 3). The combined extracts were washed with brine (40 mL), dried, and evaporated to give crystals, which were recrystallized from a mixed solvent of EtOAc and isopropyl ether to give **10** (2.35 g, 38.8% of the theoretical yield) as prisms: mp 104 °C; $[\alpha]_D$ −103.1° (c = 0.5, MeOH). The optical purity was >99% ee from HPLC analysis: column, CHIRAL AGP (100 mm × 4 mm); eluent, CH_3CN–0.02 M phosphate buffer (pH 6.3) (1:20); detection, 254 nm; flow rate, 0.9 mL/min; retention time, 8.1 min. IR (Nujol) 3250, 1665, 1580 cm^{-1}. The ^{1}H NMR spectrum was identical with that of **8**. Anal. ($C_{18}H_{23}N_3O$) C, H, N.

(+)-(2*S*,4*S*)-4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide (11). The filtrate, which was obtained in the isolation of **10**, was concentrated under reduced pressure. The residual oil was diluted with 1 N NaOH (150 mL), extracted with EtOAc (50 mL × 3), washed with brine, dried, and evaporated to give crude **11** (6.50 g), $[\alpha]_D$ +78.6° (c = 0.5, MeOH). A hot solution of this crude substance and (+)-dibenzoyl-D-tartaric acid (8.23 g, 21.9 mmol) in a mixed solvent of EtOH (15 mL) and acetonitrile (74 mL) was allowed to stand at room temperature overnight. The crystals that appeared were filtered, washed with acetonitrile (10 mL), and dried to give crude (+)-dibenzoyl-L-tartrate of **11** (10.2 g): mp 111–114 °C; $[\alpha]_D$ +101.7° (c = 0.5, MeOH) as a free base. The crude crystals were recrystallized three times from a mixed solvent of EtOH and acetonitrile (1:5) to give pure (+)-dibenzoyl-L-tartrate of **11** (8.86 g): mp 114–116 °C; $[\alpha]_D$ +102.5° (c = 0.5, MeOH) as a free base. These pure salts were added to 1 N NaOH (50 mL), and the mixture was extracted with EtOAc (40 mL × 3). The combined extracts were washed with brine (40 mL), dried, and evaporated to give crystals, which were recrystallized from a mixed solvent of EtOAc and isopropyl ether (1:4) to give **11** (3.05 g, 50.4% of the theoretical yield) as prisms: mp 103–104 °C; $[\alpha]_D$ +103.3° (c = 0.5, MeOH). The optical purity was >99% ee from HPLC analysis using the same conditions as for **10**: retention time 5.5 min; IR (Nujol) 3250, 1665, 1580 cm^{-1}. The ^{1}H NMR spectrum was identical with that of **8**. Anal. ($C_{18}H_{23}N_3O$) C, H, N.

(+)-(2*R*,4*S*)-4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)pentanamide (12). A hot solution of **9** (13.4 g, 45.1 mmol) and (−)-dibenzoyl-L-tartaric acid (17.0 g, 45.1 mmol) in a mixed solvent of isopropyl alcohol (180 mL) and water (30 mL) was allowed to stand at room temperature overnight. The crystals that appeared were collected by filtration (as described later, **13** was isolated from this filtrate) and dried at 50 °C to give crude (−)-dibenzoyl-L-tartrate of **12** (10.2 g): mp 129–131 °C; $[\alpha]_D$ +48.6° (c = 0.5, MeOH) as a free base. The crude crystals were recrystallized twice from a mixed solvent of isopropyl alcohol and water (6:1) to give the pure (−)-dibenzoyl-L-tartrate of **12** (8.40 g): mp 135–137 °C; $[\alpha]_D$ +52.0° (c = 0.5, MeOH) as a free base. These pure salts were added to 1 N NaOH (50 mL), and the mixture was

extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine (50 mL), dried, and evaporated to give crystals, which were recrystallized from EtOAc to give **12** (2.92 g, 43.6% of the theoretical yield) as needles: mp 167–168 °C; $[\alpha]_D$ +51.7° (c = 0.5, MeOH). The optical purity was >99% ee from HPLC analysis using the same conditions as for **10**: retention time 7.1 min; IR (Nujol) 3240, 1665, 1625, 1580 cm^{-1}. The ^{1}H NMR spectrum was identical with that of **9**. Anal. ($C_{18}H_{23}N_3O$) C, H, N.

(−)-(2*S*,4*R*)-4-(Dimethylamino)-2-phenyl-2-(2-pyridyl)-pentanamide (13). The filtrate, which was obtained in the isolation of **12**, was concentrated under reduced pressure. The residual oil was diluted with 1 N NaOH, extracted with EtOAc (70 mL × 3), washed with brine (70 mL), dried, and evaporated to give crude **13** (7.0 g). This crude substance was recrystallized twice from EtOAc to give **13** (4.28 g, 63.9% of the theoretical yield) as needles: mp 167–168 °C; $[\alpha]_D$ −51.6° (c = 0.5, MeOH). The optical purity was >99% ee from HPLC analysis using the same conditions as for **10**: retention time 13.4 min; IR (Nujol) 3240, 1665, 1625, 1580, 1560 cm^{-1}. The ^{1}H NMR spectrum was identical with that of **9**. Anal. ($C_{18}H_{23}N_3O$) C, H, N.

X-ray Crystallography. Lattice constants and intensity data were measured using graphite-monochromated Cu Kα (λ = 1.541 78 Å) radiation on a Rigaku AFC-5 diffractometer. Unique reflections with $|F_o| \geq 3\sigma(F_o)$ were obtained using the 2θ–ω scanning method within $5° \leq 2\theta \leq 130°$. The structures were solved by MULTAN 84 based on direct methods. Crystal data of **14** and **15** are listed in Table 2, and the ORTEP drawings are shown in Figure 1.

Acetylcholine-Induced Contraction of Isolated Guinea Pig Ileum. Male Hartley strain guinea pigs weighing 340–400 g were used in this study. They were fasted but allowed free access to tap water for 24 h prior to the start of the experiments. An ileal strip approximately 1.5 cm long was suspended in an organ bath containing 25 mL of Tyrode's solution under an initial tension of 0.5 g. The bath solution was maintained at 27 °C and aerated with a gas mixture of 95% O_2–5% CO_2. Contraction was induced several times by addition of 2.0 × 10^{-7} g/mL of acetylcholine chloride. After the contraction became constant, the test compound was added to the bath and an agonist was added 3 min after dosing. The effect was evaluated as percentage of contraction before and after dosing. Three preparations from different animals were used for each concentration of the test compound.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, and anisotropic displacement parameters for compounds **14** and **15** (11 pages). Ordering information is given on any current masthead page.

References

(1) Noronha-Blob, L.; Lowe, V. C.; Peterson, J. S.; Hanson, R. C. The Anticholinergic Activity of Agents Indicated for Urinary Incontinence is an Important Property for Effective Control of Bladder Dysfunction. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 586–593.

(2) Gerstenberg, T. C.; Klarskov, P.; Ramirez, D.; Hald, T. Terodiline in the Treatment of Women with Urgency and Motor Urge Incontinence. A Clinical and Urodynamic Double-blind Crossover Study. *Br. J. Urol.* **1986**, *58*, 129–133.

(3) Andersson, K.-E.; Ekström, B.; Mattiasson, A. Actions of Terodiline, its Isomers and Main Metabolite on Isolated Detrusor Muscle from Rabbit and Man. *Pharmacol. Toxicol.* **1988**, *63*, 390–395.

(4) Østergaard, J. R.; Østergaard, K.; Andersson, K.-E.; Sommer, L. Calcium Antagonistic Effects of Terodiline in Rabbit Aorta and Human Uterus. *Acta Pharmacol. Toxicol.* **1980**, *46*, Suppl. I, 12–19.

(5) Husted, S.; Andersson, K.-E.; Sommer, L.; Østergaard, J. R. Anticholinergic and Calcium Antagonistic Effects of Terodiline in Rabbit Urinary Bladder. *Acta Pharmacol. Toxicol.* **1980**, *46*, Suppl. I, 20–30.

(6) Anderson, G. F.; Fredericks, C. M. Characterization of the Oxybutynin Antagonism of Drug-Induced Spasms in Detrusor. *Pharmacology* **1977**, *15*, 31–39.

(7) Lish, P. M.; Labudde, J. A.; Peters, E. L.; Robbins, S. I. Oxybutynin—A Musculotropic Antispasmodic Drug with Moderate Anticholinergic Action. *Arch. Int. Pharmacodyn.* **1965**, *156*, 467–488.

(8) Tonini, M.; Rizzi, C. A.; Perucca, E.; De Ponti, F.; D'Angelo, L.; Del Vecchio, A.; Crema, A. Depressant Action of Oxybutynin on the Contractility of Intestinal and Urinary Tract Smooth Muscle. *J. Pharm. Pharmacol.* **1987**, *39*, 103–107.

(9) Kaiser, C.; Spagnuolo, C. J.; Adams, T. C., Jr.; Audia, V. H.; Dupont, A. C.; Hatoum, H.; Lowe, V. C.; Prosser, J. C.; Sturm, B. L.; Noronha-Blob, L. Synthesis and Antimuscarinic Properties of Some *N*-Substituted 5-(Aminomethyl)-3,3-diphenyl-2(3*H*)-furanones. *J. Med. Chem.* **1992**, *35*, 4415–4424.

(10) Take, K.; Okumura, K.; Takimoto, K.; Kato, M.; Ohtsuka, M.; Shiokawa, Y. Agents for the Treatment of Overactive Detrusor. I. Synthesis and Structure-Activity Relationships of 1,1'-Biphenyl Derivatives. *Chem. Pharm. Bull.* **1991**, *39*, 2915–2923.

(11) Take, K.; Okumura, K.; Takimoto, K.; Ohtsuka, M.; Shiokawa, Y. Agents for the Treatment of Overactive Detrusor. II. Synthesis and Inhibitory Activity on Detrusor Contraction of 1,1'-Biphenyl-2,6-dicarboxylic Acid Diesters with an Aminoalkyl Group in the Ester Function. *Chem. Pharm. Bull.* **1992**, *40*, 899–906.

(12) Take, K.; Okumura, K.; Tsubaki, K.; Terai, T.; Shiokawa, Y. Agents for the Treatment of Overactive Detrusor. III. Synthesis and Structure-Activity Relationships of *N*-(4-Amino-2-butynyl)acetamide Derivatives. *Chem. Pharm. Bull.* **1992**, *40*, 1415–1423.

(13) Take, K.; Okumura, K.; Tsubaki, K.; Terai, T.; Shiokawa, Y. Agents for the Treatment of Overactive Destrusor. IV. Synthesis and Structure-Activity Relationships of Cyclic Analogues of Terodiline. *Chem. Pharm. Bull.* **1993**, *41*, 507–515.

(14) Beckett, A. H.; Casy, A. F. Configurational Studies in Synthetic Analgesics. *J. Chem. Soc.* **1955**, 900–904.

(15) Wheatley, W. B.; Minor, W. F.; Byrd, W. M.; Fitzgibbon, W. E., Jr.; Speeter, M. E.; Cheney, L. C.; Binkley, S. B. Basic Amides as Antispasmodic Agents. II. *J. Org. Chem.* **1954**, *19*, 794–801.

(16) Giacomini, K. M.; Cox, B. M.; Blaschke, T. F. Comparative Anticholinergic Potencies of R- and S-Disopyramide in Longitudinal Muscle Strips from Guinea Pig Ileum. *Life Sci.* **1980**, *27*, 1191–1197.

(17) Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M.; Fricano, R. Histamine Antagonists. γ,γ-Disubstituted *N,N*-Dialkylpropylamines. *J. Am. Chem. Soc.* **1951**, *73*, 5752–5759.

(18) Moon, M. P.; Komin, A. P.; Wolfe, J. F. Photostimulated Reactions of 2-Bromopyridine and 2-Chloroquinoline with Nitrile-Stabilized Carbanions and Certain Other Nucleophiles. *J. Org. Chem.* **1983**, *48*, 2392–2399.

(19) Kawano, T.; Kurimoto, M.; Hatanaka, M.; Ueda, I. Reaction of 4-(*N,N*-Dimethylamino)-2-phenyl-2-(2-pyridyl)butanenitrile and Related Compounds with Ethyl Chloroformate; Formation of Indolizinium and Quinolizinium Chlorides. *Chem. Pharm. Bull.* **1992**, *40*, 3067–3071.