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Agents for the Treatment of Overactive Detrusor. VII.[1a] Synthesis and Pharmacological Properties of 2,3- and 3,4-Diphenylcyclopentylamines, 2,3-Diphenyl-2-cyclopentenylamines, and Related Compounds

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As part of our search for new agents for the treatment of overactive detrusor, 2,3- and 3,4-diphenylcyclopentylamines (3), 2,3-diphenyl-2-cyclopentenylamines (4), and related compounds (5 and 18) were synthesized and evaluated for inhibitory activity (i.v.) against urinary bladder rhythmic contraction in rats. Among them, some compounds involving *N-tert*-butyl-2,3-diphenyl-2-cyclopentenylamine (4b) exhibited inhibitory activity against bladder contraction superior to that of terodiline (2). Mydriatic activity (i.v.) of compound 4b in rats, an index of its side effects due to antimuscarinic activity, was found to be relatively weak in comparison with its inhibitory activity against bladder contraction. The pharmacological profile of 4b was examined in comparison with that of terodiline.

Most of the objective amines (3, 4, 5) were synthesized by preparation of Schiff bases from the corresponding cyclic ketones (6, 7, 8) and amines in the presence of $TiCl_4$ in CH_2Cl_2 and subsequent reduction with $NaBH_4$ in the presence of MeOH in one pot (method A).

Keywords 2,3-diphenyl-2-cyclopentenylamine; bladder contraction inhibition; terodiline; detrusor contraction inhibition; antimuscarinic activity; diphenylcyclopentylamine

During the last decade, oxybutynin (**1**) and terodiline (**2**) have been shown to be effective in the treatment of patients suffering from urinary frequency and incontinence due to overactive detrusor (Fig. 1).[2a,b] Their pharmacological actions in the bladder are attributed to their muscarinic receptor antagonism and other action mechanisms such as calcium channel antagonistic, local anesthetic, and spasmolytic activities.[2b,c]

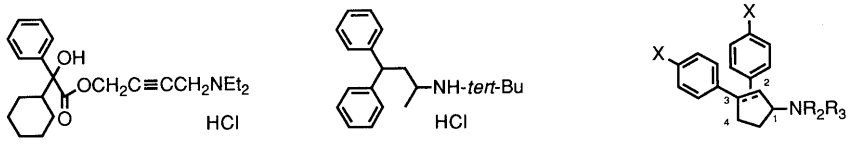
In the previous paper, we reported that structural modifications of oxybutynin could enhance the inhibitory activity against urinary bladder rhythmic contraction and decrease the mydriatic activity (an adverse effect) due to antimuscarinic activity.[1a] We selected terodiline as a lead compound with the aim of finding new agents for the treatment of overactive detrusor, because terodiline has an interesting clinical profile of longer duration of action and fewer side effects (mydriasis and dry mouth) due to antimuscarinic activity than oxybutynin. However its clinical effect on the bladder is weaker than that of oxybutynin.[2b,3] Thus we hoped to generate new agents superior to terodiline in regard to the effect on the bladder.

The pharmacological action of terodiline in the bladder is attributed to its antimuscarinic, calcium channel antagonistic, local anesthetic, and spasmolytic activities on the detrusor smooth muscle.[2b] We speculated that the two phenyl groups (lipophilic center) and the N atom (hydrophilic center) in terodiline might play important roles in the interaction with detrusor smooth muscle and that the optimum distances between the two centers might be different for each of its actions. In recent years, we have found that the cyclization of lead compounds (oxybutynin and terodiline) led to interesting changes in their pharmacological profiles.[1a–c] Thus, for generation of new agents by structural modification of terodiline, we adopted a combination of the following two methods. 1) The constraint of the distance between the two centers by cyclization. 2) The movement of one of the two phenyl groups at the same carbon to the adjacent carbon (a structural modification of the lipophilic center). We expected that these structural modifications might change the balance of the actions of terodiline and the intensity of interaction with detrusor smooth muscle. Thus, we synthesized 2,3- and 3,4-diphenylcyclopentylamines (**3**) and 2,3-diphenyl-2-cyclopentenylamines (**4**), illustrated in Fig. 1, and related compounds (**5**, **18**).

This article describes the synthesis, pharmacology, and structure–activity relationships of compounds **3**, **4**, **5** and **18** listed in Table I.

Synthesis

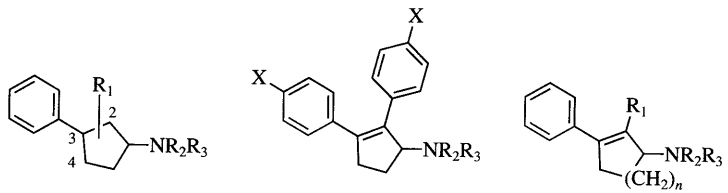
Most of the cyclopentyl, 2-cyclopentenyl, and 2-cyclohexenylamines (**3**, **4**, **5**) listed in Table I were synthe-



oxybutynin (**1**) terodiline (**2**) **3**, **4**

Fig. 1

TABLE I. Physical Properties of 2,3- and 3,4-Diphenylcyclopentylamines (**3**), 2,3-Diphenyl-2-cyclopentenylamines (**4**), and Related Compounds (**5**, **18**) and Their Effect on Urinary Bladder Rhythmic Contraction in Rats



3 **4** **5**

No.	R_1	NR_2R_3	X	*n*	Form	Method[a]	Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibitory activity against bladder contraction[c] Dose (mg/kg i.v.)	Maximum inhibition (%) (duration, min)
3a[d]	4-Ph	NH-*tert*-Bu	—	—	MsOH	A_3	68.8	215—217 (EA–IE)	$C_{21}H_{27}N \cdot CH_3SO_3H$	67.83 (67.81)	8.02 8.11	3.60 3.61)	1	I.A.
3b[e]	4-Ph	NH-*tert*-Bu	—	—	MsOH	A_3	65.5	269—271 (IE)	$C_{21}H_{27}N \cdot CH_3SO_3H$	67.83 (67.71)	8.02 8.10	3.60 3.69)	1	22.2 (20)
3c[e]	4-Ph	NH-*tert*-Amyl	—	—	MsOH	A_3	35.2	180—182 (dec.) (EA–IE)	$C_{22}H_{29}N \cdot CH_3SO_3H$	68.45 (67.98)	8.24 8.24	3.47 3.87)	0.1 1	I.A. 100 (5)
3d[f]	2-Ph	NH-*tert*-Bu	—	—	HCl	[g]	94.6	253—255 (E)	$C_{21}H_{27}N \cdot HCl$	76.45 (76.04	8.55 8.55	4.25 4.69)	0.1 1	I.A. 100 (5)
4a	—	NH-iso-Pr	H	—	HCl	A_1	4.5	204—205 (dec.) (EA–IA)	$C_{20}H_{23}N \cdot HCl$	76.54 (76.01	7.71 7.63	4.46 4.39)	1 3.2	71.6 (10) 100 (10)
4b	—	NH-*tert*-Bu	H	—	HCl	A_1 A_3	4.3 34.4	261 (dec.) (E)	$C_{21}H_{25}N \cdot HCl$	76.92 (77.22	7.99 7.99	4.27 4.50)	0.1 1	I.A. 100 (10)
4c	—	NH-*n*-Bu	H	—	HCl	A_1	3.8	208—209 (EA–IA)	$C_{21}H_{25}N \cdot HCl$	76.92 (76.59	7.99 7.87	4.27 4.32)	3.2 1	100 (20) I.A.
4d	—	NH-*tert*-Amyl	H	—	HCl	A_2	4.6	190—191 [h]	$C_{22}H_{27}N \cdot HCl$	77.28 (77.40	8.25 8.45	4.10 3.91)	1	58.5 (10)
4e	—	NEt_2	H	—	HCl	[i]	1.7	122—124 [h]	$C_{21}H_{25}N \cdot HCl$	76.92 (77.05	7.99 8.12	4.27 4.40)	1	I.A.
4f	—	$NHCH_2Ph$	H	—	HCl	A_1	21.4	202—203 (dec.) (EA–IE)	$C_{24}H_{23}N \cdot HCl$	79.65 (79.34	6.68 6.71	3.87 3.97)	1	I.A.
4g	—	$NHCH_2Ph$–OMe-4	H	—	MsOH	A_3	45.1	211—212 (E–EA–IA)	$C_{25}H_{25}NO \cdot CH_3SO_3H$	69.15 (69.44	6.47 6.51	3.10 3.10)	1	I.A.
4h	—	$NHCH_2C{\equiv}CCH_2NMe_2$	H	—	2HCl	A_3	29.7	85 (dec.) (EE)	$C_{23}H_{26}N_2 \cdot 2HCl \cdot 1.7H_2O$	63.65 (63.60	7.29 7.53	6.45 6.97)	0.1 1	I.A. 100 (20)
4i	—	NH-*tert*-Bu	Me	—	HCl	A_2	39.3	238—248 (A–EA–IE)	$C_{23}H_{29}N \cdot HCl$	76.92 (77.22	7.99 7.99	4.27 4.50)	1 3.2	100 (10) 77.0 (10)
5a	Ph	NH-*tert*-Bu	—	2	HCl	A_3	28.3	224—226 (E–EA)	$C_{22}H_{27}N \cdot HCl$	77.28 (77.07	8.25 8.41	4.10 4.07)	0.1 1	I.A. 100 (10)
5b	H	NH-*tert*-Bu	—	1	HCl	A_3	24.3	209—211 (A–E)	$C_{15}H_{21}N \cdot HCl$	71.55 (71.60	8.81 8.95	5.56 5.49)	0.1 1	I.A. 100 (10)
5c	H	NH-*tert*-Bu	—	2	HCl	A_3	47.6	207 (E–EA)	$C_{16}H_{23}N \cdot HCl$	72.29 (72.34	9.10 9.30	5.27 5.23)	0.1 1	I.A. 100 (10)
18		 NH-*tert*-Bu			HCl	[i]	6.1	178—180 (dec.) (EA–IA)	$C_9H_{17}N \cdot HCl$	61.52 (61.31	10.33 10.42	7.97 7.95)	1	38.7 (10)
Terodiline (**2**)													0.1 1 3.2	I.A. 18.5 (10) 54.7 (>30)

a) Method A was subdivided to three methods, A_1, A_2, and A_3, which differ in the procedures for the addition of $NaBH_4$ and MeOH following the preparation of Schiff bases. A_1: $NaBH_4$ (1.5 eq) was added after addition of MeOH. A_2: A solution of $NaBH_4$ (1.5 eq) in MeOH was added. A_3: $NaBH_4$ (4.0 eq) was added and then MeOH was added. *b*) A = acetone, E = ethanol, EA = ethyl acetate, EE = diethyl ether, IA = isopropanol, IE = diisopropyl ether. *c*) I.A. = inactive. *d*) *r*-1, *c*-3, *t*-4 (The two phenyl groups are *trans* to each other). *e*) *r*-1, *c*-3, *c*-4 (The two phenyl groups and the amino group are *cis* to one another). *f*) *r*-1, *t*-2, *t*-3 (The phenyl groups and the amino group are *trans* to each other). *g*) Synthesized as shown in Chart 2. *h*) Purified by column chromatography ($CHCl_3$–MeOH). *i*) Synthesized as shown in Chart 3.

sized by preparation of Schiff bases from the corresponding cyclic ketones (**6**, **7**, **8**) and amines in the presence of $TiCl_4$ in CH_2Cl_2, followed by reduction with $NaBH_4$ in the presence of MeOH in one pot as shown in Chart 1 (method A). *c*-3,*t*-4-Diphenyl-*r*-1-cyclopentylamine (**3a**) was prepared by the reaction of *trans*-3,4-diphenylcyclopentanone (**6a**) with *tert*-butylamine by method A. The reaction of *cis*-3,4-diphenylcyclopentanone (**6b**) with *tert*-butyl or *tert*-amylamines by method A afforded *c*-3,*c*-4-diphenyl-*r*-1-cyclopentylamines (**3b** or **3c**, respectively), disclosing that reduction with $NaBH_4$ occurred from the less hindered side of the Schiff bases. The relative steric configuration of the *N*-*tert*-butyl derivative **3b** was determined by examination of the nuclear Overhauser effect two-dimensional (2D)-NMR (NOESY) spectrum. In this spectrum, NOEs were observed between the H-1 proton signal at δ 3.90 and the H-3 and H-4 proton signal at δ 3.61, disclosing that the amino group and the two phenyl groups are in a *cis* relationship to one another.

The hydrogenation of *N*-*tert*-butyl-2,3-diphenyl-2-cyclopentenylamine (**4b**) over Pd on carbon in EtOH afforded the corresponding *t*-2,*t*-3-diphenyl-*r*-1-cyclopentylamine (**3d**), the relative steric configuration of which was determined by X-ray crystallography (Chart 2, Fig. 2). Interestingly, this hydrogenation was shown to occur from the more hindered side (the side of the *tert*-butylamino group on the cyclopentenyl ring). So the orientation of this hydrogenation seemed to depend on the stability of the product.

N,*N*-Diethyl-2,3-diphenyl-2-cyclopentenylamine (**4e**) and *N*-*tert*-butyl-2-cyclopentenylamine (**18**) were synthesized by methanesulfonylation of the corresponding 2-cyclopenten-1-ol (**9**, **17**, respectively) and subsequent substitution reaction with the corresponding amines in one pot (Chart 3). The 2-cyclopenten-1-ols **9** and **17** were prepared by reduction of the corresponding 2-cyclopenten-1-ones (**7a**, **16**, respectively) with $LiAlH_4$ and diisobutylaluminum hydride (DIBAL), respectively.

2,3-Diphenyl-2-cyclopenten-1-one (**7a**), a key inter-

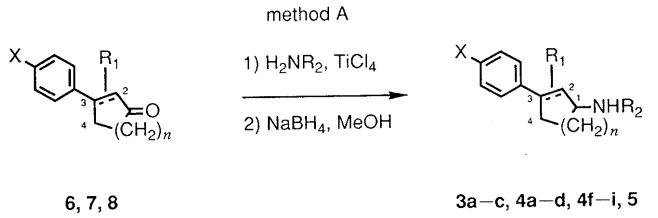


Chart 1

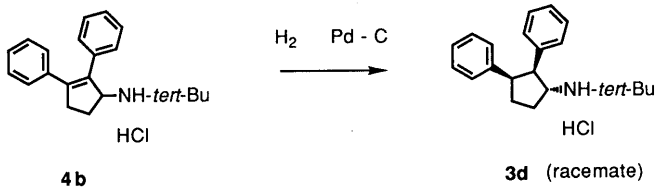


Chart 2

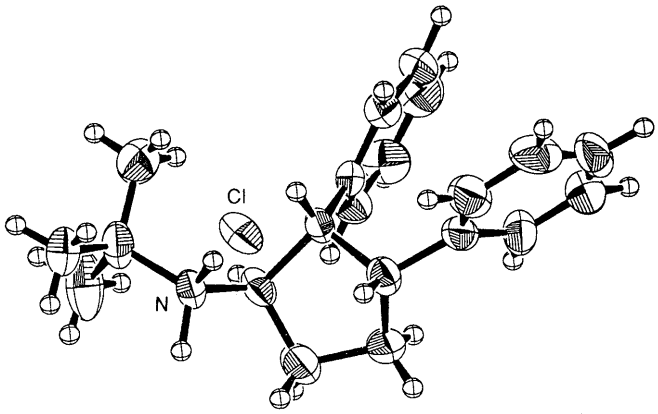
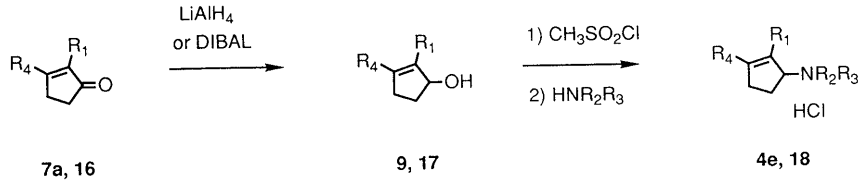


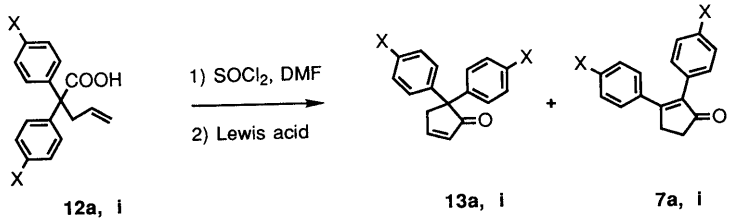
Fig. 2. ORTEP Drawing of the Crystal Structure of **3d** (Racemate) Determined by X-Ray Crystallographic Analysis



7a, **9**, **4e**: $R_1 = R_4$ = Ph, $NR_2R_3 = NEt_2$

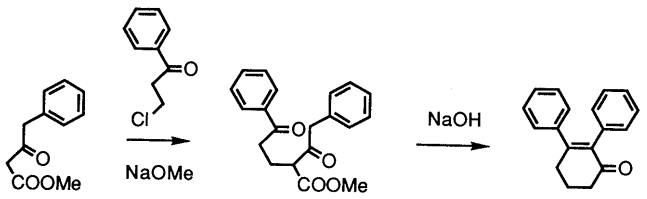
16, **17**, **18**: $R_1 = R_4$ = H, NR_2R_3 = NH-*tert*-Bu

Chart 3



a: X = H
i: X = CH_3

Chart 4



14 15 8a

Chart 5

mediate for the synthesis of 2,3-diphenyl-2-cyclopentenylamines (**4a**—**h**), was obtained as a by-product in the cyclization reaction of the acyl chloride of 2,2-diphenyl-4-pentenoic acid (**12a**) to 5,5-diphenyl-2-cyclopenten-1-one (**13a**) by use of Lewis acids such as $SnCl_4$, $AlCl_3$, $EtAlCl_2$, and $TiCl_4$ as described in the previous paper (Chart 4).[1b] The use of $TiCl_4$ at $-3\,°C$ and then room temperature afforded **13a** and **7a** in 32.4% and 22.6% yields, respectively.

Similarly, cyclization reaction of the acyl chloride of 2,2-bis(4-methylphenyl)-4-pentenoic acid (**12i**) to 5,5-bis(4-methylphenyl)-2-cyclopenten-1-one (**13i**) by use of $AlCl_3$ afforded 2,3-bis(4-methylphenyl)-2-cyclopenten-1-one (**7i**), a key intermediate for synthesis of 2,3-bis(4-methylphenyl)-2-cyclopentenylamine (**4i**), as a by-product in 6.8% yield (Chart 4). The pentenoic acid **12i** was prepared by migration of the allyl group of bis(4-methylphenyl)acetic acid allyl ester (**11i**) in the presence of NaH in toluene. The ester **11i** was prepared from the corresponding acid (**10i**) and allyl alcohol.

2,3-Diphenyl-2-cyclohexen-1-one (**8a**) was synthesized by intramolecular condensation reaction and decarboxylation of 5-oxo-5-phenyl-2-(phenylacetyl)pentanoic acid ester (**15**) in the presence of NaOH in 1,4-dioxane–water as depicted in Chart 5. The ester **15** was prepared by reaction of 3-oxo-4-phenylbutyric acid ester (**14**) with 3-chloropropiophenone in the presence of NaOMe in MeOH.

Pharmacological Results

The 2,3- and 3,4-diphenylcyclopentylamines (**3**), 2,3-diphenyl-2-cyclopentenylamines (**4**), and related compounds (**5**, **18**) were evaluated for inhibitory activity (i.v.) against urinary bladder rhythmic contraction in rats.[1d] The results are listed in Tables I and II in comparison with the data for terodiline **2**.

In this study, we first designed *N-tert*-butyl-3,4- and 2,3-diphenylcyclopentylamines (**3a**, **b**, **d**). Among them, the 2,3-diphenyl derivative **3d** exhibited the most potent inhibitory activity, which was superior to that of terodiline, but its duration of action was short. *N-tert*-Butyl-2,3-diphenyl-2-cyclopentenylamine (**4b**), a dehydro derivative of **3d**, exhibited potent inhibitory activity superior to that of **3d** or terodiline. These results indicated that the cyclic forms, such as cyclopentylamine and cyclopentenylamine, are able to inhibit bladder contraction and that the two phenyl groups were not necessarily required to exist on the same carbon in the cyclic form. In addition, the relative steric configuration of the two phenyl groups and the *tert*-butylamino group was found to be important for the expression of inhibitory activity against bladder contraction. We selected compound **4b** as a new prototype compound for further modifications.

The modification of the *N*-alkyl group of compound **4b** led to marked changes in the potency of inhibitory activity against bladder contraction. Isopropyl (**4a**) and *tert*-amyl (**4d**) groups, both nearly as bulky as a *tert*-butyl group, slightly reduced the inhibitory activity. A *n*-butyl group (**4c**), a less hindered group, and benzyl groups (**4f**, **g**), bulkier groups, resulted in complete loss of the inhibitory activity. A diethylamino group (**4e**) also caused complete loss of the inhibitory activity. Interestingly, the compound with a 4-amino-2-butynyl group (**4h**) exhibited inhibitory activity comparable to that of **4b**, showing that investigation of alternative *N*-substituent groups to the *tert*-butyl group could be an effective approach.

The introduction of a substituent (Me group) on the two phenyl groups in **4b** (**4i**) slightly decreased the inhibitory activity against bladder contraction. A cyclohexenyl analogue of **4b** (**5a**) also exhibited inhibitory activity comparable to that of **4b**.

Removal of the 2-phenyl group of **4b** and **5a** (**5b**, **c**) did not decrease the inhibitory activity against bladder contraction, while removal of both the 2- and 3-phenyl groups of **4b** (**18**) reduced the inhibitory activity. This result revealed that the 2-phenyl group might not necessarily be essential, but the 3-phenyl group might play an important role in the expression of the inhibitory activity.

The inhibitory profiles of the potent compounds (**3c**, **d**, **4a**, **b**, **d**, **h**, **i**, **5**) against bladder contraction were different from that of terodiline. Namely, these compounds had a tendency to decrease the contraction frequency, while terodiline had a tendency to increase it.

Compound **4b**, one of compounds exhibiting efficacy superior to that of terodiline in terms of inhibitory activity against bladder contraction in this study, was further evaluated for mydriatic activity in rats (i.v.),[4] an index of side effects due to antimuscarinic activity, and for inhibitory activity against detrusor contractions *in vitro* induced by electrical field stimulation, KCl, carbacol, and ATP in guinea-pigs.[1d] These results are listed in Table II. Mydriatic activity of compound **4b** was found to be relatively weak in comparison with its inhibitory activity against bladder contraction. Compound **4b** exhibited a different pharmacological profile from that of terodiline. Namely, although **4b** was inferior to terodiline in inhibitory activity against detrusor contractions induced with carbacol and particularly KCl, it was superior to terodiline in inhibitory activity against detrusor contractions induced by electrical field stimulation and ATP. Judging from these results, in comparison with terodiline, its superior inhibitory activity against bladder contraction *in vivo* in rats may be related to its more potent inhibitory activity against detrusor contraction *in vitro* induced by electrical field stimulation. On the other hand, its good bladder selectivity over iris may be related to its weaker antimuscarinic activity in comparison with terodiline. Further pharmacological evaluation of compound **4b** is in progress.

In conclusion, some of the 2-cyclopentenyl and

TABLE II. Effect of **4b** on Urinary Bladder Rhythmic Contraction and Mydriasis in Rats and on Detrusor Contractions *in Vitro* Induced by Electrical Field Stimulation, KCl, Carbacol, and ATP in Guinea-Pigs

No.	Inhibitory activity against bladder contraction		Mydriatic activity MED[a] (mg/kg i.v.)	Inhibitory activity against detrusor contraction IC_{50} (g/ml) *in vitro*				
	Dose (mg/kg i.v.)	Inhibition (%) (duration (min))		Electrical field stimulation	KCl	Carbacol	ATP (g/ml)	ATP Inhibition (%)
4b	0.32	I.A.[b]	>3.2	6.0×10^{-6}	4.2×10^{-5}	2.4×10^{-5}	1.0×10^{-5}	I.A.[b]
	1	100 (10)					1.0×10^{-4}	93.2
	3.2	100 (20)						
Terodiline (**2**)	1	18.5 (10)	10	1.4×10^{-5}	7.9×10^{-6}	9.8×10^{-6}	1.0×10^{-5}	I.A.[b]
	3.2	54.7 (>30)					1.0×10^{-4}	56.3

a) MED = minimum effective dose. *b*) Inactive.

2-cyclohexenylamines **4** and **5** exhibited efficacy superior to that of terodiline in terms of inhibition (i.v.) of bladder contraction. In particular, the mydriatic activity (i.v.) of compound **4b** was found to be relatively weak in comparison with its inhibitory activity against bladder contraction. The pharmacological profile of **4b** appeared to be different from that of terodiline.

Experimental

The melting points were determined on a capillary melting point apparatus (Büchi 530 and Electrothermal) and are uncorrected. The infrared (IR) spectra were measured on Shimadzu IR-408 and Hitachi 260-10 spectrometers. The ^{1}H-NMR spectra and the 2D-NMR (NOESY) spectrum were recorded on a Bruker AC200P spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, br = broad, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet. The MS were recorded on Hitachi M-80 and M1000H mass spectrometers.

2,3-Diphenyl-2-cyclopenten-1-one (7a)[1b] A solution of 2,2-diphenyl-4-pentenoyl chloride[1b] (1.53 g) in CH_2Cl_2 (10 ml) was added dropwise to a stirred mixture of 1 N $TiCl_4$ in CH_2Cl_2 (6.79 ml) and CH_2Cl_2 (10 ml) at −3—2 °C over 15 min and the resulting mixture was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo* and partitioned between AcOEt and 1 N HCl. The AcOEt layer was washed with brine, dried, evaporated *in vacuo*, and chromatographed (*n*-hexane–AcOEt) over silica gel. The first eluate afforded 5,5-diphenyl-2-cyclopentenone (**13a**, 0.43 g, 32.4%)[1b] and the second eluate afforded **7a** (0.30 g, 22.6%) as a powder: mp 95—97 °C (from iso-Pr_2O–AcOEt) (lit.[5] mp 95—96 °C). *Anal.* Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.17; H, 6.04. IR (Nujol): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.61—2.78 (2H, m, CH_2), 2.92—3.10 (2H, m, CH_2), 7.08—7.42 (10H, m, aromatic H). EI-MS *m/z*: 234 (M^+), 191.

Allyl 2,2-Bis(4-methylphenyl)acetate (11i) A mixture of 2,2-bis(4-methylphenyl)acetic acid[6] (**10i**, 8.52 g), allyl alcohol (6.6 ml), and 4-TosOH·H_2O in toluene (25 ml) was refluxed with continuous removal of water for 20 h, cooled to room temperature, poured into 1 N NaOH, and extracted with AcOEt. The extract was washed successively with 1 N NaOH, 1 N HCl, and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (CH_2Cl_2) over silica gel to afford **11i** (8.09 g, 81.4%) as an oil. IR (film): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (6H, s, $2CH_3$), 4.60—4.70 (2H, m, CH_2), 4.98 (1H, s, CH), 5.15—5.30 (2H, m, $=CH_2$), 5.80—6.00 (1H, m, CH=), 6.95—7.36 (8H, m, aromatic H). EI-MS *m/z*: 280 (M^+) 195.

2,2-Bis(4-methylphenyl)-4-pentenoic Acid (12i) A solution of **11i** (8.00 g) in toluene (40 ml) was added dropwise to a stirred suspension of 60% NaH (1.60 g) in toluene (30 ml) at 130 °C under an N_2 atmosphere and the resulting mixture was refluxed for 6 h. After cooling, the reaction mixture was poured into 1 N HCl in an ice bath and extracted with AcOEt. The extract was washed with brine, dried, and evaporated *in vacuo* to afford **12i** (5.58 g, 69.7%) as a crude solid, which was used for the next reaction without further purification. IR (Nujol): 2500—2750, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (6H, s, $2CH_3$), 3.12 (2H, d, J = 6.9 Hz, CH_2), 4.92 (1H, d, J = 11.2 Hz, =CH), 4.94 (1H, d, J = 16.4 Hz, =CH), 5.48—5.68 (1H, m, CH=), 6.90—7.25 (8H, m, aromatic H). EI-MS *m/z*: 280 (M^+), 239, 193.

2,3-Bis(4-methylphenyl)-2-cyclopenten-1-one (7i) A solution of **12i** (8.17 g) in *N,N*-dimethylformamide (DMF, 1.0 ml) and CH_2Cl_2 (45 ml) was treated with $SOCl_2$ (3.2 ml). The resulting solution was stirred at room temperature for 1 d and evaporated *in vacuo* to afford the acyl chloride of **12i** as a crude oil. A solution of the acyl chloride in CH_2Cl_2 (50 ml) was added dropwise to a stirred suspension of $AlCl_3$ (4.66 g) in CH_2Cl_2 (50 ml) under dry ice–acetone cooling and an N_2 atmosphere. The resulting mixture was stirred at room temperature overnight, poured into 1 N HCl, and extracted with AcOEt. The extract was washed successively with 1 N HCl, water, 1 N NaOH, and brine, dried, evaporated *in vacuo*, and chromatographed (*n*-hexane–AcOEt) over silica gel. The first eluate afforded 5,5-bis(4-methylphenyl)-2-cyclopenten-1-one (**13i**, 2.30 g, 30.1%) as a powder: mp 61—63 °C. *Anal.* Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 87.18; H, 6.87. IR (Nujol): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (6H, s, $2CH_3$), 3.47 (2H, m, CH_2), 6.20—6.35 (1H, m, =CH), 7.10 (8H, s, aromatic H), 7.75—7.90 (1H, m, =CH). EI-MS *m/z*: 262 (M^+). The second eluate afforded **7i** (0.52 g, 6.8%), mp 119—121 °C. *Anal.* Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.78; H, 6.98. IR (Nujol): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.65—2.70 (2H, m, CH_2), 3.00—3.05 (2H, m, CH_2), 7.05—7.30 (8H, m, aromatic H). EI-MS *m/z*: 262 (M^+), 205.

Methyl 5-Oxo-5-phenyl-2-(phenylacetyl)pentanoate (15) A 28% solution of MeONa in MeOH (7.3 ml) was added slowly to a stirred solution of methyl 3-oxo-4-phenylbutyrate[7] (**14**, 5.99 g) and 3-chloropropiophenone (5.00 g) in MeOH (50 ml) at room temperature over 10 min. The resulting mixture was stirred at the same temperature for 3.5 h and filtered. The filtrate was evaporated *in vacuo*, and partitioned between AcOEt and brine. The AcOEt layer was washed successively with 1 N HCl, 1 N NaOH, and brine, dried, evaporated *in vacuo*, and chromatographed (*n*-hexane–AcOEt) over silica gel to afford **15** (8.57 g, 58.4%) as a crude oil, which was used for the next step without further purification. IR (film): 1730, 1710, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15—3.3 (4H, m, $2CH_2$), 3.71 (2H, s, CH_2Ph), 3.84 (3H, s, CH_3), 4.47 (1H, m, CH), 6.9—8.1 (10H, m, aromatic H). EI-MS *m/z*: 324 (M^+).

2,3-Diphenyl-2-cyclohexen-1-one (8a) A solution of **15** (6.25 g) in 2% NaOH (116 ml) and 1,4-dioxane (100 ml) was refluxed for 1 h, cooled to room temperature, evaporated *in vacuo*, and partitioned between AcOEt and brine. The AcOEt layer was washed with 1 N HCl and brine, dried, and chromatographed (*n*-hexane–AcOEt) over silica gel to afford a yellow powder (4.64 g), which was recrystallized from AcOEt–iso-Pr_2O to afford **8a** (2.49 g, 52.0%) as crystals: mp 78—82 °C. *Anal.* Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.59; H, 6.49. IR (Nujol): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (2H, quin, J = 6.8 Hz, CH_2), 2.68 (2H, t, J = 6.8 Hz, CH_2), 2.85 (2H, t, J = 6.8 Hz, CH_2), 6.93 (2H, m, aromatic H), 7.02 (2H, m, aromatic H), 7.13 (6H, m, aromatic H). EI-MS *m/z*: 248 (M^+), 220, 205, 192, 191, 178, 165, 115, 77.[8]

trans- and *cis*-3,4-Diphenylcyclopentanone (**6a**, **b**), 3-phenyl-2-cyclopenten-1-one (**8b**), and 3-phenyl-2-cyclohexen-1-one (**8c**) were prepared according to the literature.[9]

Preparation of Cyclopentylamines (3a—c), 2-Cyclopentenylamines (4a—d, 4f—i, 5b), and 2-Cyclohexenylamines (5a, c) Method A was subdivided into three methods, A_1, A_2 and A_3, which differ in the procedures for the addition of $NaBH_4$ and MeOH following the preparation of Schiff bases.

Method A_1. *N*-Isopropyl-2,3-diphenyl-2-cyclopentenylamine Hydro-

TABLE III. IR, ^{1}H-NMR, and MS Spectral Data for Compounds **3**, **4**, **5**, and **18**

No.	IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ ppm (J=Hz)	EI-MS m/z
3a	2750—2300, 1595, 1155, 1040	1.34 (9H, s), 1.94—2.1 (1H, m), 2.17—2.43 (1H, m), 2.36 (3H, s), 2,51—2.69 (1H, m), 3.14—3.28 (1H, m), 3.35—3.50 (2H, m), 4.03 (1H, br), 7.10—7.28 (10H, m), 8.50 (2H, br s)	293 (M^+), 278
3b	2750—2300, 1595, 1150, 1040	1.40 (9H, s), 2.15—2.35 (2H, m), 2.36 (3H, s), 2.45—2.6 (2H, m), 3.61 (2H, m), 3.90 (1H, br), 6.93—7.10 (10H, m), 8.62 (2H, br s)	293 (M^+), 278, 189
3c	2700—2400, 1595, 1155. 1030	0.95 (3H, t, 7.4), 1.34 (6H, s), 1.74 (2H, q, 7.4), 2.15—2.35 (2H, m), 2.33 (3H, s), 2.5—2.60 (2H, m), 3.62 (2H, m), 3.92 (1H, br), 6.92—7.07 (10H, m), 8.53 (2H, br s)	307 (M^+), 292, 278
3d	2800-2300, 1590	1.34 (9H, s), 2.04—2.33 (3H, m), 2.65—2.85 (1H, m), 3.61—3.80 (2H, m), 4.10—4.24 (1H, m), 6.80—7.11 (10H, m)[a]	293 (M^+), 278, 112, 56
4a	2800—2300, 1580	1.16 (6H, d, 6.5), 2.15—2.3 (1H, m), 2.35—2.5 (1H, m), 2.55—2.75 (1H, m), 2.95—3.15 (1H, m), 3.25—3.45 (1H, m), 4.85—5.0 (1H, m), 7.05—7.4 (10H, m), 8.15 (1H, br), 8.95 (1H, br)	277 (M^+), 219, 200
4b	2800—2400, 1580	1.24 (9H, s), 2.25—2.4 (2H, m), 2.55—2.7 (1H, m), 3.3—3.5 (1H, m), 5.0—5.1 (1H, m), 7.1—7.4 (10H, m), 8.75—9.0 (1H, br)	291 (M^+), 276, 218
4c	2800—2300, 1600, 1580	0.76 (3H, t, 7.5), 1.15 (2H, sep, 7.5), 1.45 (2H, quin, 7.5), 2.15—2.3 (1H, m), 2.35—2.55 (1H, m), 2.55—2.75 (3H, m), 3.25—3.45 (1H, m), 4.8—4.95 (1H, m), 7.05—7.4 (10H, m), 8.75 (2H, br)	291 (M^+), 219, 214
4d	2750—2400, 1580	0.69 (3H, t, 7.3), 1.16 (3H, s), 1.19 (3H, s), 1.45—1.70 (2H, m),2.25—2.45 (2H, m), 2.45—2.70(1H, m), 3.35—3.65 (1H, m), 5.02 (1H, br s), 7.00—7.30 (10H, m), 9.15 (2H, br s)	305 (M^+), 276, 234, 219
4e	2580, 2490, 1630	1.12 (3H, t, 7.2), 1.26 (3H, t, 7.2), 2.30—2.55 (2H, m), 2.55—2.80 (2H, m), 2.90—3.20 (3H, m), 3.20—3.50 (1H, m), 5.25—5.40 (1H, m), 7.05—7.15 (2H, m), 7.15—7.45 (8H, m), 9.19 (1H, br s)	291 (M^+), 219
4f	2800—2200, 1600, 1560	2.25—2.45 (2H, m), 2.6—2.75 (1H, m), 3.35—3.5 (1H, m), 3.94 (2H,br q), 4.82 (1H, m), 7.05—7.6 (15H, m), 9.2 (1H, br), 9.4 (1H, br)	325 (M^+), 248, 91
4g	2800, 2750, 2640, 2490, 1610, 1240, 1145, 1035	2.2 (1H, m), 2.30 (3H, s), 2.4 (1H, m), 2.7 (1H, m), 3.35 (1H, m), 3.75 (3H, s), 3.92 (2H, m), 4.83 (1H, m), 6.95 (2H, d, 9), 7.11 (2H, m), 7.2—7.4 (10H, m), 8.8 (2H, br s)	356 (M^++1), 219[b]
4h	2750—2300, 1640, 1570	2.25—2.45 (2H, m), 2.6—2.75 (1H, m), 2.79 (6H, s), 3.3—3.45 (1H, m), 3.66 (1H, br d, 14), 3.88 (1H, br d, 14), 4.12 (2H, s), 5.08 (1H, m), 7.05—7.35 (10H, m), 9.35 (1H, br), 10.05 (1H, br), 11.45 (1H, br)	331 (M^++1)[b]
4i	2750, 1580	1.24 (9H, s), 2.26 (3H, s), 2.29 (3H, s), 2.09—2.30 (2H, m), 2.30—2.50 (1H, m), 3.30—3.50 (1H, m), 4.99 (1H, br s), 7.00—7.20 (8H, m), 8.80—9.00 (2H, br)	319 (M^+), 246
5a	2750—2350, 1575	0.98 (9H, s), 1.85—2.35 (6H, m), 4.37 (1H, m), 6.93—7.25 (10H, m), 7.93 (1H, br), 8.19 (1H, br)	305 (M^+), 290, 277, 262, 248, 233, 232
5b	2750, 1580	1.37 (9H, s), 2.05—2.30 (1H, m), 2.30—2.55 (1H, m), 2.55—2.80 (1H, m), 2.80—3.10 (1H, m), 4.52 (1H, br s), 6.35 (1H, s), 7.30—7.50 (3H, m), 7.50—7.60 (2H, m), 8.80 (2H, br s)	215 (M^+), 143
5c	2800—2350, 1585	1.40 (9H, s), 1.65—2.05 (4H, m), 2.43 (2H, m), 4.15 (1H, m), 6.19 (1H, br s), 7.18—7.52 (5H, m), 8.73 (2H, br)	229 (M^+), 214, 201, 186, 157, 144
18	2770, 2650, 2500, 2440	1.52 (9H, s), 2.20—2.64 (3H, m), 2.64—2.90 (1H, m), 4.24 (1H, br s), 6.00—6.18 (2H, m), 9.24 (2H, br s)[c]	

a) Measured in CD_3OD. *b*) (+)APCI MS. *c*) Measured in $CDCl_3$.

chloride (4a) A 1 M solution of $TiCl_4$ in CH_2Cl_2 (8.54 ml) was added dropwise to a stirred solution of 2,3-diphenyl-2-cyclopenten-1-one (**7a**, 1.00 g) and isopropylamine (1.82 ml) in CH_2Cl_2 (7 ml) at −70——65 °C over 15 min. The mixture was stirred at the same temperature for 3 h and then MeOH (25 ml) was added dropwise at −70——55 °C over 10 min. Then, $NaBH_4$ (0.25 g) was added at the same temperature. After being stirred at the same temperature for 2 h, the mixture was allowed to stand at room temperature overnight and poured into a mixture of AcOEt and aqueous $NaHCO_3$. After filtration, the organic layer was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH, treated with ethanolic HCl, crystallized from AcOEt–iso-Pr_2O, and recrystallized from EtOH to afford **4a** (0.060 g) as crystals. The physical data are listed in Tables I and III.

Method A_2. *N*-*tert*-Butyl-2,3-bis(4-methylphenyl)-2-cyclopentenylamine Hydrochloride (4i) A 1 M solution of $TiCl_4$ in CH_2Cl_2 (4.58 ml) was added dropwise to a stirred solution of **7i** (0.60 g) and *tert*-butylamine (1.82 ml) in CH_2Cl_2 (7 ml) at −70——65 °C over 15 min. The mixture was stirred at the same temperature for 1.5 h and then a solution of $NaBH_4$ (0.13 g) in MeOH (20 ml) was added dropwise at −70——55 °C over 10 min. Stirring was continued at the same temperature for 2 h, then the mixture was worked up according to the procedure in method A_1 to afford **4i** (0.32 g) as a powder. Its physical data are listed in Tables I and III.

Method A_3. *N*-(4-Methoxybenzyl)-2,3-diphenyl-2-cyclopentenylamine Methanesulfonate (4g) A 1 M solution of $TiCl_4$ in CH_2Cl_2 (14.0 ml) was added dropwise to a stirred solution of **7a** (1.64 g) and 4-methoxybenzylamine (4.80 g) in CH_2Cl_2 (41 ml) at −70——65 °C over 30 min. The mixture was stirred at the same temperature for 2 h and then $NaBH_4$ (1.06 g) was added. Stirring was continued at the same temperature for 2.5 h, then MeOH (30 ml) was added dropwise at the same temperature over 20 min and the resulting mixture was stirred at the same temperature for 2.5 h and at room temperature for 2 h. The reaction mixture was worked up according to the procedure in method A_1 to afford the free base of **4g** (1.77 g, 71.0%) as an oil, 0.150 g of which was converted to the methanesulfonate in a usual manner. The methanesulfonate was recrystallized from AcOEt–iso-PrOH–EtOH to afford **4g** (0.121 g). The physical data are listed in Tables I and III.

Compounds **3**, **4** and **5** prepared by methods A_1—A_3 are listed in Table I and their spectral data are listed in Table III.

***N-tert*-Butyl-*t*-2,*t*-3-diphenyl-*r*-1-cyclopentylamine Hydrochloride (3d)** *N-tert*-Butyl-2,3-diphenyl-2-cyclopentenylamine hydrochloride (**4b**, 0.82 g) was hydrogenated at 43 °C in the presence of 10% Pd on carbon (0.20 g) and H_2 at a pressure of 2.6 atm in EtOH (25 ml) for 2.5 h. After removal of the catalyst, the solution was evaporated *in vacuo* and the residue was recrystallized from EtOH to afford **3d** (0.78 g) as colorless prisms. Its physical data are listed in Tables I and III. X-Ray crystallographic analysis: the crystal data of **3d** were as follows: $C_{21}H_{27}N \cdot HCl$, monoclinic, $P2_1/a$(#14), $a=12.753$ (3) Å, $b=11.830$ (5) Å, $c=13.209$ (5) Å, $\beta=102.82$ (2)°, $V=1943$ (1) Å^3, $Z=4$, $D_{calcd}=1.128$ g/cm^3, $\mu(CuK_\alpha)=17.25$ cm^{-1}, $F(000)=712.00$. Intensities were collected on a Rigaku AFC5R diffractometer with graphite-monochromated CuK_α radiation ($\lambda=1.54178$ Å), and 3392 unique reflections with $I_O \geqq 3\sigma_I$ were obtained using the ω–2θ scanning method within $5° \leqq 2\theta \leqq 130°$. The structure was solved by using MULTAN 84 based on direct methods, and refined. The final R value was 0.076. An ORTEP drawing of **3d** is shown in Fig. 2.

2,3-Diphenyl-2-cyclopenten-1-ol (9) $LiAlH_4$ (0.50 g) was added to a stirred solution of 2,3-diphenyl-2-cyclopenten-1-one (**7a**, 10.0 g) in tetrahydrofuran (THF) (50 ml) at room temperature over 30 min. The resulting mixture was stirred at the same temperature for a while, then poured into 1 N HCl, and extracted with AcOEt. The extract was washed with brine, dried, evaporated *in vacuo*, and chromatographed (*n*-hexane–AcOEt) over silica gel to afford **9** (8.23 g, 81.6%) as a colorless oil. IR (film): 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (1H, br s, OH), 1.94—2.04 (1H, m, CH), 2.40—2.50 (1H, m, CH), 2.66—2.79 (1H, m, CH), 3.03—3.23 (1H, m, CH), 5.22 (1H, br s, OCH), 7.00—7.31 (10H, m, aromatic H). EI-MS m/z: 236 (M^+), 219, 159.

***N,N*-Diethyl-2,3-diphenyl-2-cyclopentenylamine Hydrochloride (4e)** CH_3SO_2Cl (0.6 ml) was added to a solution of **9** (1.50 g) in acetone (15 ml) under ice cooling. The mixture was stirred for 5 min, and a solution of NEt_3 (1.1 ml) in acetone (83 ml) was added to the mixture at the same temperature, then $HNEt_2$ (3.3 ml) was added dropwise thereto. The resulting mixture was stirred at room temperature for 21 h and evaporated *in vacuo*. The residue was partitioned between 1 N NaOH and AcOEt. The AcOEt layer was separated, washed with brine, dried, evaporated *in vacuo*, chromatographed (CH_2Cl_2–MeOH) over silica gel, and treated with ethanolic HCl to afford **4e** (35 mg) as a powder. Its physical data are listed in Tables I and III.

***N-tert*-Butyl-2-cyclopentenylamine Hydrochloride (18)** A 0.94 M solution of DIBAL in *n*-hexane (28.5 ml) was added to a stirred solution of 2-cyclopenten-1-one (**16**, 2.0 g) in Et_2O (20 ml) under an N_2 atmosphere at −70—−60 °C. The mixture was stirred for 1 h, then AcOEt (11.9 ml) was added thereto, and the resulting solution was acidified with dilute HCl and extracted with AcOEt. The extract was washed with brine, dried, and evaporated *in vacuo* to afford crude 2-cyclopenten-1-ol (**17**). This was dissolved in acetone (50 ml) and treated with CH_3SO_2Cl (1.88 ml) and NEt_3 (3.39 ml) under ice cooling. The mixture was stirred for 10 min, then NaI (3.63 g) was added thereto, and the resulting mixture was stirred for 10 min. Then *tert*-butylamine (49 ml) was added, and the reaction mixture was stirred at room temperature overnight, evaporated *in vacuo*, and partitioned between water and AcOEt. The AcOEt layer was treated with ethanolic HCl and evaporated *in vacuo*. The residue was suspended in Et_2O–iso-PrOH and filtered. The filtrate was evaporated *in vacuo*, and the residue was crystallized from Et_2O–AcOEt and recrystallized from iso-PrOH–AcOEt to afford **18** (0.26 g). Its physical data are listed in Tables I and III.

Biological Tests Inhibitory activities against urinary bladder rhythmic contraction in rats and against detrusor contractions *in vitro* induced by electrical field stimulation, KCl, carbacol, $BaCl_2$, and ATP were examined as described previously.[1c]

Mydriatic activity in rats was examined by the methods of Parry and Heathcote.[4]

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