Agents for the Treatment of Overactive Detrusor. VI.[1a] Synthesis and Pharmacological Properties of Acetamide Derivatives Bearing Cyclic Amines in *N*-Substituents

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With the aim of improving of the efficacy and decreasing the side effects of oxybutynin (1), *N*-[(tetrahydro-3- or 4-pyridyl)methyl]-, *N*-(4-piperidyl)-, and *N*-(3- or 4-piperidylalkyl)-2-hydroxyacetamides (3a—n, 4a—g) and the related carboxamides (3o—r, 4h—k, 13′, 17) were synthesized and evaluated for inhibitory activity against urinary bladder rhythmic contraction in rats and for mydriatic activity in rats. Some of these compounds were superior to oxybutynin in both inhibitory activity against bladder contraction and selectivity between inhibitory activity against bladder contraction and mydriatic activity. Among them, *N*-[(1,2,3,6-tetrahydro-4-pyridyl)methyl]- and *N*-[(1,2,3,6-tetrahydro-1-methyl-4-pyridyl)methyl]-2-hydroxy-2,2-diphenylacetamide (3e, 3f) exhibited the most potent inhibitory activity against bladder contraction (ED_{30} = 0.005 and 0.003 mg/kg i.v., respectively). Judging from the effect of 3e on detrusor contraction *in vitro* in guinea-pigs, it appeared that the inhibitory activity of 3e against bladder contraction *in vivo* was related mainly to its inhibitory activity against detrusor contraction *in vitro* induced with carbacol (antimuscarine-like activity). The selectivity (20-fold) of 3e between inhibitory activity against bladder contraction and mydriatic activity was greatly superior to that (0.48-fold) of oxybutynin.

Compound 3e was synthesized by debenzylation (method E or F) of the corresponding *N*-[[1-(4-methoxybenzyl)-tetrahydro-4-pyridyl]methyl] derivative (3k), which was prepared by acylation (method B) of the corresponding (tetrahydro-4-pyridyl)methylamine (7k) or by reduction (method D) of the corresponding pyridinium chloride (14k) with $NaBH_4$.

Keywords diphenylacetamide; bladder contraction inhibition; oxybutynin; overactive detrusor treatment; *N*-[(1,2,3,6-tetrahydro-4-pyridyl)methyl]acetamide; *N*-(4-piperidylalkyl)acetamide

Oxybutynin (**1**) is effective in the treatment of patients suffering from urinary frequency and incontinence due to an overactive detrusor.[2] However, it shows side effects of mydriasis and dry mouth.[2b,3] Its pharmacological action in the bladder is attributed to its antimuscarinic, spasmolytic, local anesthetic, and calcium channel antagonistic activities on the detrusor smooth muscle.[4a,b] Its nonselective muscarinic receptor antagonism in iris and salivary gland is considered to be responsible for the side effects.[4a]

In the preceding paper, we reported that the replacement of the ester function of oxybutynin with an amide function decreased the side effects (compounds **2** in Fig. 1).[1b] For the purpose of enhancing the efficacy and decreasing the side effects, so as to obtain new agents for the treatment of an overactive detrusor, we planned to generate new agents by further structural modifications of compounds **2**.

In recent years, we have found that the cyclization of prototype compounds, terodiline (an agent for overactive detrusor)[1a] and timegadine (an antiinflammatory agent),[5] led to interesting changes in the pharmacological profiles. Thus, we adopted the cyclization of compounds **2** as an approach for generation of new agents. Namely, we initially designed 2-hydroxyacetamides bearing cyclic amines such as tetrahydropyridine (**3a—n**) and piperidine (**4a—g**) in the *N*-substituents, as shown in Fig. 1. Although oxybutynin is characterized by several pharmacological

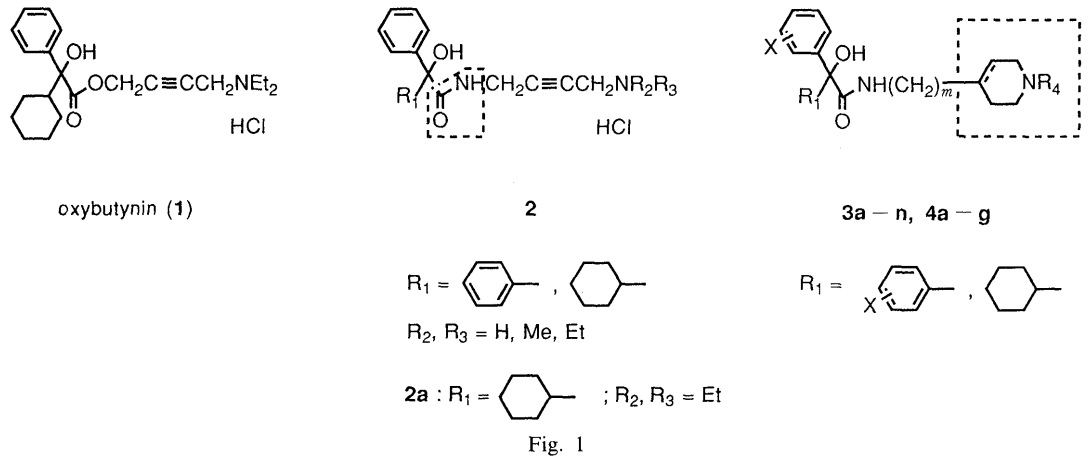


Fig. 1

actions, each of its actions may occur by interaction of different conformations with detrusor smooth muscle or muscarinic receptor subtypes. Therefore, in compounds **3** and **4** which are conformationally constrained (Tables I—III), the balance of the actions and the selectivity for muscarinic receptor subtypes were anticipated to be different from those of oxybutynin. Thus, we hoped that these compounds **3** and **4** might be superior to compounds **2** and oxybutynin in efficacy and in having lower side effects.

The compounds prepared in this study were first evaluated for inhibitory activity against urinary bladder rhythmic contraction in rats. Next, the selectivity between bladder contraction inhibitory activity and mydriatic activity in rats and the action mechanisms were examined for selected compounds. This paper describes the synthesis, pharmacology, and structure–activity relationships of compounds **3** and **4** and related compounds (**13′**, **17**) listed in Tables I—III.

Synthesis

N-[(Tetrahydropyridyl)methyl]carboxamides (**3**) listed in Tables I and II were synthesized according to three routes (routes 1, 2, and 3) as shown in Charts 1 and 2.

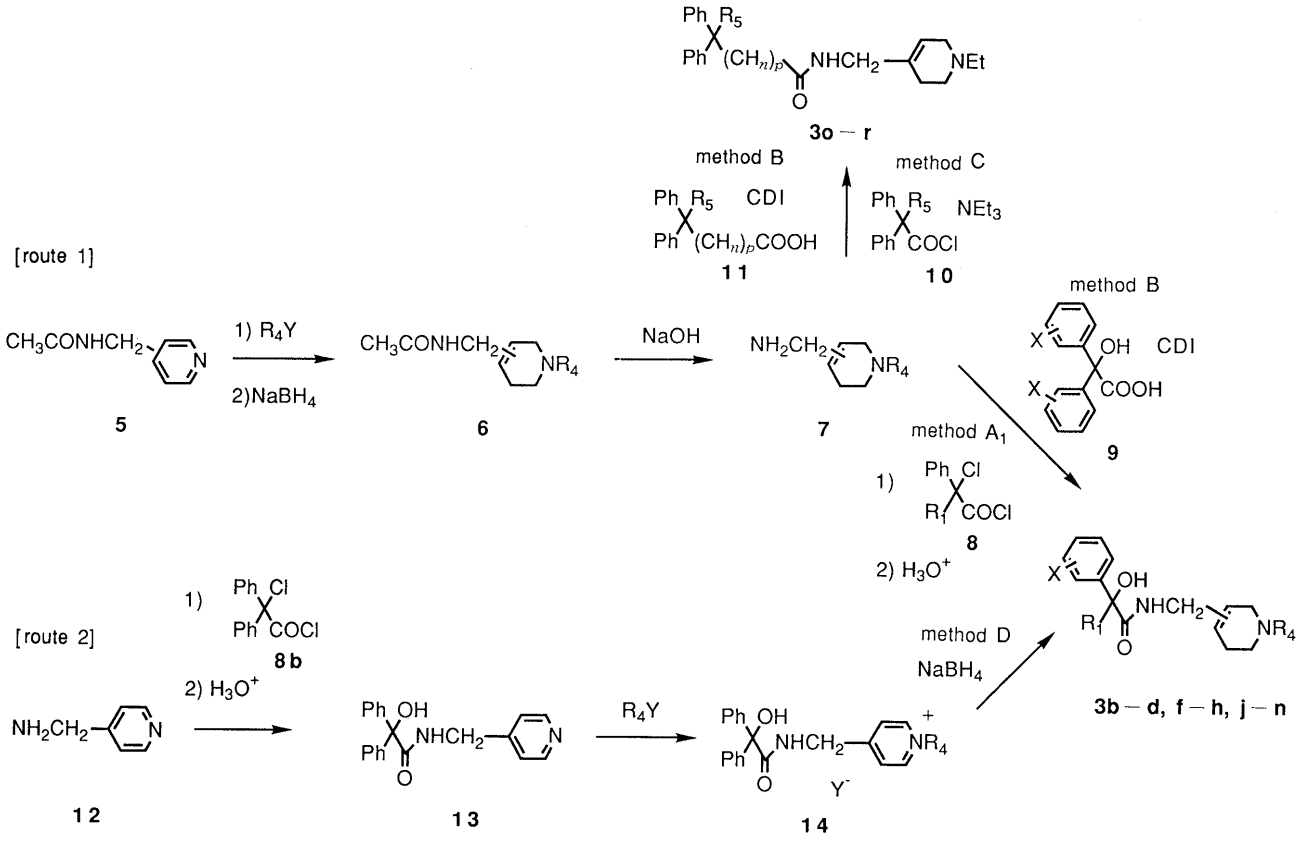


Chart 1

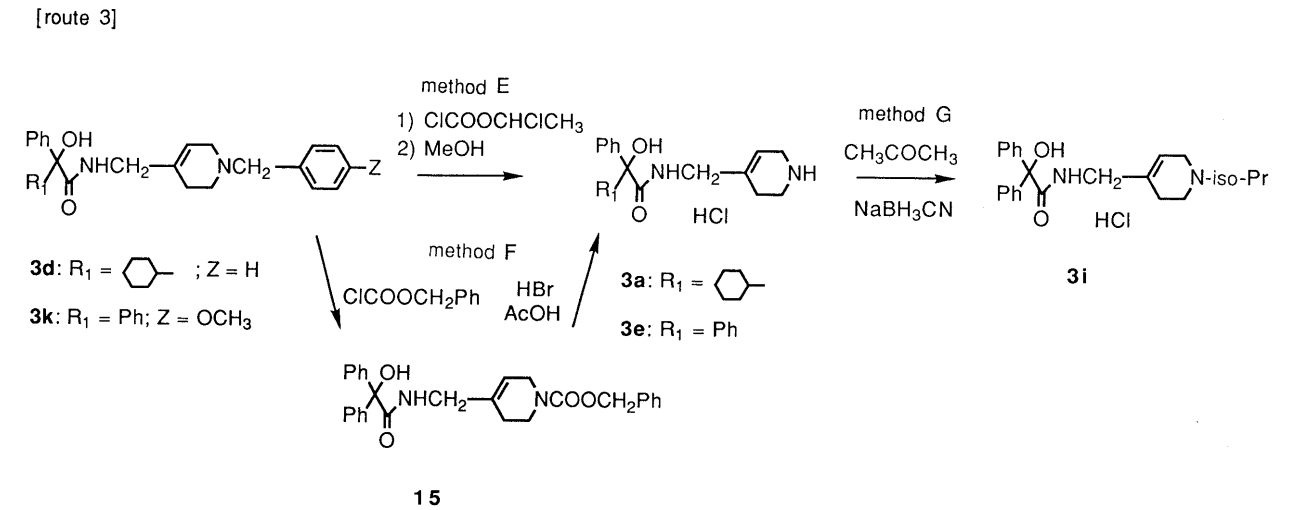
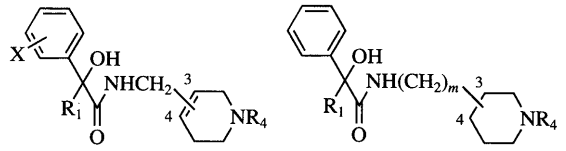
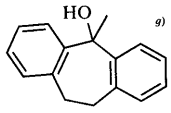


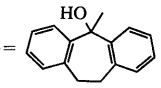
Chart 2

TABLE I. Physical Properties of *N*-(Tetrahydropyridylmethyl)-, *N*-(4-Piperidyl)-, and *N*-(Piperidylalkyl)-2-hydroxyacetamides (**3a—n** and **4a—g**) and Their Effect on Urinary Bladder Rhythmic Contraction in Rats



3a—n **4a—g**

No.	R_1	X	*m*	Position of $(CH_2)_m$	R_4	Form[a]	Route-method (Starting materials)	Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibitory activity against bladder contraction[c] Inhibition (%) (duration, min) 0.1 mg/kg i.v.	1 mg/kg i.v.
3a	Cyclohexyl	H	—	4	H	HCl	3-E (**3d**)	13.0	238—240 (M)	$C_{20}H_{28}N_2O_2 \cdot HCl$	65.83 (66.09	8.01 8.33	7.68 7.53)	32.7 (>30)	39.5 (>30)
3b	Cyclohexyl	H	—	4	Me	HCl	1-A_1	38.3	189—190 (IA–M)	$C_{21}H_{30}N_2O_2 \cdot HCl \cdot H_2O$	63.54 (63.33	8.38 8.58	7.06 6.96)	40.4 (20)	51.6 (>30)
3c	Cyclohexyl	H	—	4	Et	HCl	1-A_1	42.6	170—172 (EA)	$C_{22}H_{32}N_2O_2 \cdot HCl$	67.24 (67.10	8.46 8.75	7.13 7.03)	21.6 (10)	48.9 (>30)
3d	Cyclohexyl	H	—	4	CH_2Ph	HCl	1-A_1	22.6	133—136 (EA–IA)	$C_{27}H_{34}N_2O_2 \cdot HCl \cdot H_2O$	68.55 (68.38	7.88 7.71	5.92 5.67)	16.5 (20)	52.5 (>30)
3e	Ph	H	—	4	H	HCl	3-E (**3k**) 3-F (**3k**)	59.2 28.7	222—224 (E)	$C_{20}H_{22}N_2O_2 \cdot HCl$	66.94 (67.22	6.46 6.53	7.81 7.73)	52.2 (>30)	58.8 (>30)
3f	Ph	H	—	4	Me	HCl	1-B 2-D	31.1[d] 53.8[e]	173—174 (IA–M)	$C_{21}H_{24}N_2O_2 \cdot HCl$	67.64 (67.88	6.76 6.78	7.51 7.49)	61.3 (>30)	54.5 (>30)[d]
3g	Ph	H	—	4	Et	HCl	1-A_1 2-D	46.0 71.2	179—180 (IA)	$C_{22}H_{26}N_2O_2 \cdot HCl$	68.29 (68.31	7.03 7.13	7.24 7.34)	40.3 (>30)	48.8 (>30)
3h	Ph	H	—	4	*n*-Pr	HCl	1-B	34.6	96—98 (EA–IE–M)	$C_{23}H_{28}N_2O_2 \cdot HCl \cdot 7/10H_2O$	66.80 (66.77	7.41 7.76	6.77 6.44)	I.A.	32.6 (>30)
3i	Ph	H	—	4	iso-Pr	HCl	3-G	74.2	126—127 (DO)	$C_{23}H_{28}N_2O_2 \cdot HCl \cdot 1/2H_2O$	67.39 (67.40	7.38 7.84	6.83 6.58)	I.A.	28.9 (>30)
3j	Ph	H	—	4	CH_2Ph	HCl	1-B	60.1	139—141 (EA–IE–M)	$C_{27}H_{28}N_2O_2 \cdot HCl \cdot 4/5H_2O$	69.98 (69.94	6.66 6.67	6.05 5.94)	I.A.	46.1 (>30)
3k′	Ph	H	—	4	CH_2Ph–OMe-4	OA	1-B 2-D	68.4 99.2[f]	101—104 (EA–M)	$C_{28}H_{30}N_2O_3 \cdot C_2H_2O_4 \cdot H_2O$	65.44 (65.83	6.22 6.23	5.09 4.87)	I.A.	18.9 (10)
3l	Ph	H	—	3	Et	1/2FA	1-B	14.7	185—186 (IA)	$C_{22}H_{26}N_2O_2 \cdot 1/2C_4H_4O_4$	70.57 (70.36	6.91 7.11	6.86 6.72)	I.A.	25.7 (10)
3m	4-F–Ph	4-F	—	4	Et	HCl	1-B	3.9	155—157 (IE)	$C_{22}H_{24}F_2N_2O_2 \cdot HCl \cdot 1/3H_2O$	61.61 (61.69	6.03 6.09	6.53 6.54)	I.A.	37.1 (>30)
3n	 [g]	—		4	Et	HCl	1-B	35.7	158—159.5 (EA)	$C_{24}H_{29}ClN_2O_2 \cdot 3/2H_2O$	65.52 (65.68	7.27 7.27	6.37 6.38)	I.A.	I.A.
4a	Ph	H	0	4	H	HCl	4	30.3	193—195 (A)	$C_{19}H_{22}N_2O_2 \cdot HCl \cdot 1/3H_2O$	64.67 (64.79	6.76 6.93	7.94 7.92)	I.A.	100 (5)
4b	Ph	H	0	4	Et	1/2FA	4-G	13.2	197—199 (IA)	$C_{21}H_{26}N_2O \cdot 1/2C_4H_4O_4 \cdot 1/2H_2O$	68.13 (67.97	7.21 7.41	6.91 6.67)	I.A.	27.5 (5)
4c	Cyclohexyl	H	1	4	Et	HCl	A_1	4.6	222—223 (IA–IE–EA)	$C_{22}H_{34}N_2O_2 \cdot HCl \cdot 1/3H_2O$	66.90 (65.90	8.93 8.96	7.09 6.99)	I.A.	33.9 (20)
4d	Ph	H	1	4	H	HCl	H	34.8	251—253 (E)	$C_{20}H_{24}N_2O_2 \cdot HCl$	66.56 (67.04	6.98 7.09	7.76 7.76)	51.8 (>30)	N.T.
4e	Ph	H	1	4	Me	HCl	H	49.1	237—239 (E–M)	$C_{21}H_{26}N_2O_2 \cdot HCl$	67.28 (67.64	7.26 7.56	7.47 7.53)	I.A.	N.T.
4f	Ph	H	2	4	Me	FA	B	21.7	151—152 [h]	$C_{22}H_{28}N_2O_2 \cdot C_4H_4O_4$	66.65 (67.02	6.88 7.05	5.98 5.94)	I.A.	22.6 (5)
4g	Ph	H	1	3	Et	HCl	B	8.9	181—182 (IA)	$C_{22}H_{28}N_2O_2 \cdot HCl$	67.94 (67.76	7.52 7.68	7.20 7.15)	60.0 (10)	59.6 (>30)
Oxybutynin (**1**)														14.2 (5)	61.5 (>30)

a) FA = fumarate, OA = oxalate. *b*) A = acetone, DO = 1,4-dioxane, E = ethanol, EA = ethyl acetate, EE = diethyl ether, IA = isopropanol, IE = diisopropyl ether, M = methanol. *c*) I.A. = inactive, N.T. = not tested. *d*) Data for the oxalate: mp 185—190 °C (from iso-PrOH), *Anal.* Calcd for $C_{21}H_{24}N_2O_2 \cdot 1/2C_2H_2O_4 \cdot 1/2H_2O$: C, 67.67; H, 6.71; N, 7.17. Found: C, 67.16; H, 6.75; N, 7.12. *e*) Yield based on 2-hydroxy-2,2-diphenyl-*N*-(4-pyridylmethyl)acetamide (**13**). *f*) Yield of the free base. *g*) X–PhR_1C(OH)– =  *h*) Purified by column chromatography ($CHCl_3$–MeOH) over silica gel.

Route 1 consisted of the synthesis of the corresponding [(1-alkyl-tetrahydropyridyl)methyl]amines (**7**) and acylation (methods A_1, B, and C) of **7** with acyl chlorides (**8**, **10**) or carboxylic acids (**9**, **11**). Method A_1 was acylation of **7** with the corresponding 2-chloroacetyl chlorides **8** in $CHCl_3$ or CH_2Cl_2 followed by treatment with heated dilute HCl. Method B was condensation of **7** with the corresponding carboxylic acids **9** and **11** in the presence of 1,1′-carbonyldiimidazole (CDI) in CH_2Cl_2. Method C was acylation of **7** with the corresponding acyl chlorides

10 in the presence of NEt_3 in CH_2Cl_2. Compounds **7** were synthesized according to Singh *et al.* with some modifications.[6] The starting materials, *N*-(3- or 4-pyridylmethyl)-acetamides (**5**), were converted to the corresponding 1-alkylpyridinium halides by alkylation, and the reduction of the pyridinium halides with $NaBH_4$ in MeOH afforded *N*-(1-alkyl-tetrahydro-3- or 4-pyridyl)acetamides (**6**), which were hydrolyzed to **7** with NaOH.

In route 2, the objective compounds **3** were synthesized by reduction of 1-alkyl-4-(acetylaminomethyl)pyridinium halides (**14**) with $NaBH_4$ in MeOH (method D). Compounds **14** were prepared by alkylation of *N*-(4-pyridylmethyl)acetamide (**13**), which was prepared by acylation of 4-pyridylmethylamine (**12**) with 2-chloroacetyl chloride (**8b**) and subsequent treatment with heated dilute HCl. Route 2 was superior to route 1 in terms of total yields.

Route 3 consisted of synthesis of *N*-[(1-unsubstituted-tetrahydro-4-pyridyl)methyl]acetamides (**3a**, **3e**) by debenzylation of *N*-[(1-benzyl-tetrahydro-4-pyridyl)methyl]-acetamides (**3d**, **3k**) (methods E and F) and alkylation of the obtained compound **3e** with ketone in the presence of $NaBH_3CN$ (method G). Method E was the reaction of **3d** and **3k** with 1-chloroethyl chloroformate followed by treatment with heated MeOH in one pot. With regard to the benzyl groups at the 1-position of the tetrahydropyridine, a 4-methoxybenzyl group (**3k**) afforded the corresponding objective debenzylated compound in better yield in comparison with an unsubstituted benzyl group (**3d**). In method F, **3k** was reacted with benzyl chloroformate to afford *N*-[(1-carbobenzyloxy-tetrahydro-4-pyridyl)methyl]acetamide (**15**), treatment of which with HBr–AcOH produced **3e**. Method E was superior to method F in terms of yields.

1-[(1-Ethyl-tetrahydro-4-pyridyl)methyl]pyrrolidinone (**17**) was synthesized by acylation of (1-ethyl-tetrahydro-4-pyridyl)methylamine (**7c**) with 4-bromobutanoyl chloride, followed by cyclization, as illustrated in Chart 3.

N-(4-Piperidyl)acetamides (**4a**, **4b**, Table I) were synthesized as shown in Chart 4 (route 4). The starting material, 1-carboethoxy-4-piperidylamine (**18**), was acylated with the corresponding acetic acid **9b** in the presence of CDI in CH_2Cl_2 to afford *N*-(1-carboethoxy-4-piperidyl)-acetamide (**19**). The use of KOH in refluxing 2-methoxyethanol hydrolyzed only the urethane function of **19** to afford **4a**, which was ethylated with acetaldehyde in the presence of $NaBH_3CN$ (method G) to afford *N*-(1-ethyl-4-piperidyl)acetamide (**4b**).

N-(3- or 4-Piperidylalkyl)acetamides (**4c—g**) listed in Table I were synthesized by catalytic hydrogenation of the

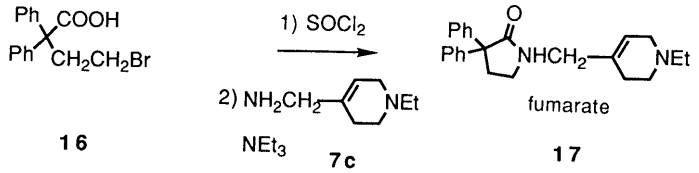
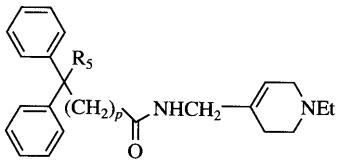


Chart 3

TABLE II. Physical Properties of *N*-[(1-Ethyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]carboxamides (**3o—r**) and a Related Compound (**17**) and Their Effect on Urinary Bladder Rhythmic Contraction in Rats



3o—r

No.	R_5	p	Form[a]	Route-method	Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibitory activity against bladder contraction[c] Inhibition (%) (duration, min) 0.1 mg/kg i.v.	1 mg/kg i.v.
3o	H	0	HCl	1-C	63.7	205—207 (E–IE)	$C_{22}H_{26}N_2O \cdot HCl$	71.24 (71.30	7.34 7.62	7.55 7.52)	100 (5)	27.8 (10)
3p	Me	0	HCl	1-C	8.4	93—94 (IA–IE)	$C_{23}H_{28}N_2O \cdot HCl$	68.56 (68.82	7.75 7.95	6.95 6.89)	I.A.	100 (5)
3q	H	1	OA	1-B	11.1	133—134 (IA–IE)	$C_{23}H_{28}N_2O \cdot C_2H_2O_4$	68.47 (68.46	6.90 6.97	6.39 6.31)	100 (5)	I.A.
3r	$Ph_2C{=}CH$[d]		OA	1-B	17.6	163—164 (EA–IA–M)	$C_{23}H_{26}N_2O \cdot C_2H_2O_4$	68.79 (69.21	6.47 6.53	6.42 6.40)	I.A.	I.A.
17	—	—	FA	[e]	24.1	90 (dec.) (H)	$C_{24}H_{28}N_2O \cdot C_4H_4O_4 \cdot 1.5H_2O$	66.78 (67.24	7.01 7.45	5.56 5.58)	I.A.	I.A.

a) FA = fumarate, OA = oxalate. *b*) E = ethanol, EA = ethyl acetate, H = *n*-hexane, IA = isopropanol, IE = diisopropyl ether, M = methanol. *c*) I.A. = inactive. *d*) $Ph_2CR_5(CH_2)_p = Ph_2C{=}CH$. *e*) Synthesized according to route shown in Chart 3.

[route 4]

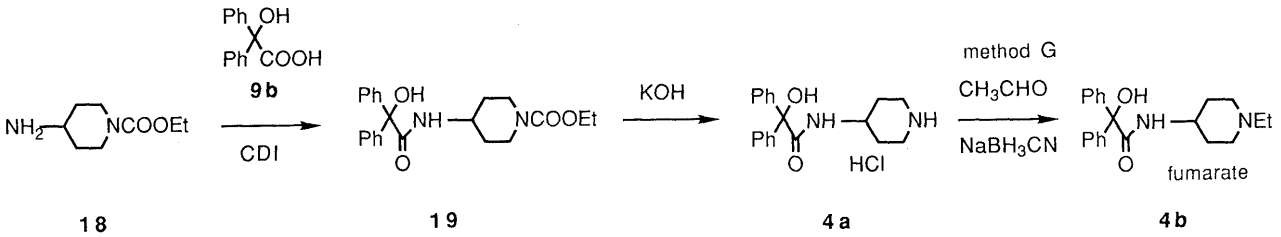


Chart 4

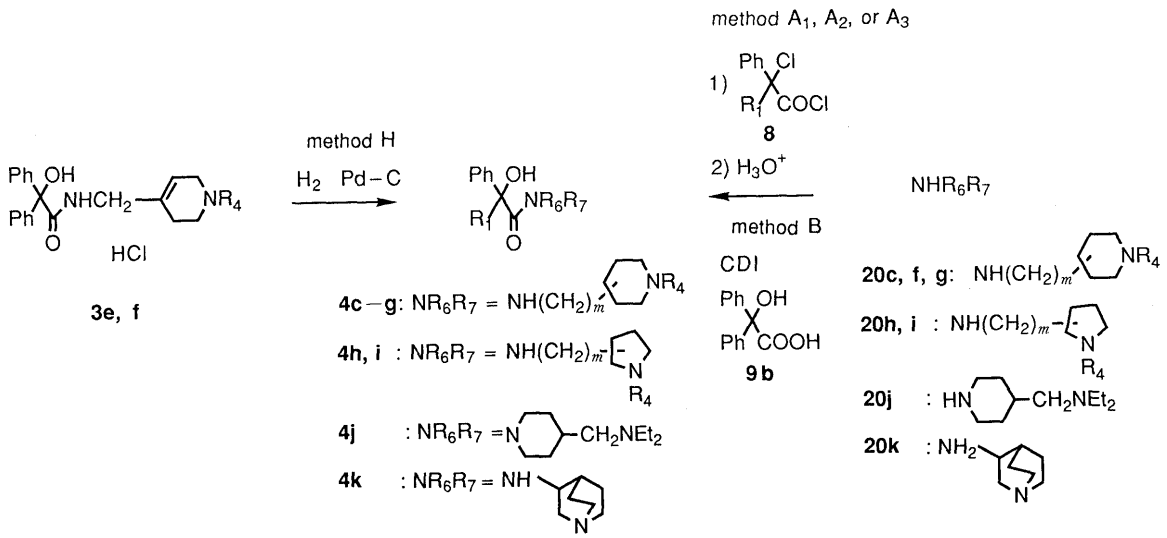
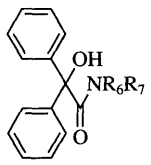
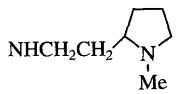
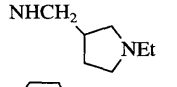
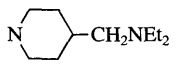
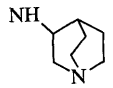
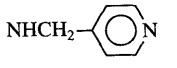


Chart 5

TABLE III. Physical Properties of 2-Hydroxy-2,2-diphenylacetamides (**4h—k** and **13′**) and Their Effect on Urinary Bladder Rhythmic Contraction in Rats



4h—k

No.	NR_6R_7	Form[a]	Method	Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibitory activity against bladder contraction[c] Inhibition (%) (duration, min) 0.1 mg/kg i.v.	1 mg/kg i.v.
4h		HCl	B	35.9	155—157 (E–EA)	$C_{21}H_{26}N_2O_2 \cdot HCl$	67.28 (67.29	7.26 7.53	7.47 7.46)	27.5 (20)	50.9 (>30)
4i		FA	B	6.5	128—129 (IA)	$C_{21}H_{24}N_2O_2 \cdot C_4H_4O_4 \cdot H_2O$	63.28 (63.55	6.40 6.83	5.55 5.93)	I.A.	35.6 (5)
4j		HCl	A_2	18.2	175—176 (IA)	$C_{24}H_{32}N_2O_2 \cdot HCl \cdot 1/2H_2O$	67.67 (67.62	8.04 8.08	6.58 6.51)	I.A.	42.5 (5)
4k		HCl	A_3	28.7	261—265 (E)	$C_{21}H_{24}N_2O_2 \cdot HCl$	67.64 (67.67	6.76 7.10	7.51 7.31)	59.9 (>30)	N.T.
13′		HCl	[d]	39.2	233—235 (IA–M)	$C_{20}H_{18}N_2O_2 \cdot HCl$	67.70 (67.96	5.40 5.46	7.89 7.97)	N.T.	64.4 (5)

a) F=fumarate. *b*) E=ethanol, EA=ethyl acetate, IA=isopropanol, M=methanol. *c*) I.A.=inactive, N.T.=not tested. *d*) Synthesized according to the synthetic route shown in Chart 1.

corresponding *N*-[(tetrahydro-4-pyridyl)methyl]acetamides (**3**) (method H) or by acylation of the corresponding amines (**20**) (methods A_1 or B) (Chart 5).

N-(Pyrrolidylalkyl)acetamides (**4h**, **4i**, Table III) were also synthesized by method B (Chart 5).

4-(Diethylaminomethyl)piperidine (**20j**) and 1-azabicyclo[2.2.2]octan-3-ylamine (**20k**), hindered amines, were acylated with 2-chloroacetyl chloride (**8b**) in the absence of solvent (method A_2) and in benzene–*n*-hexane (method A_3), respectively, and then treated with heated dilute HCl to afford the corresponding acetamides (**4j**, **4k**, respectively) (Chart 5 and Table III). The starting material **20j** was prepared by reduction of *N*,*N*-diethyl-4-piperidinecarboxamide with $LiAlH_4$.

Pharmacological Results

N-[(Tetrahydro-3- or 4-pyridyl)methyl]-2-hydroxyacetamides **3a**—**n**, *N*-(4-piperidyl)- and *N*-(3- or 4-piperidylalkyl)-2-hydroxyacetamides **4a**—**g**, and the related carboxamides **3o**—**r**, **4h**—**k**, **13′** and **17** were evaluated for inhibitory activity against urinary bladder rhythmic contraction in rats. The results are listed in Tables I—IV in comparison with the data of oxybutynin **1** (Table I).

We first designed 2-cyclohexyl-*N*-[(1-ethyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]-2-hydroxy-2-phenylacetamide (**3c**) by cyclization of 2-cyclohexyl-*N*-[4-(diethylamino)-2-butynyl]-2-hydroxy-2-phenylacetamide (**2a**)[1b] bearing an amide function in place of the ester function in oxybutynin. Compound **3c** exhibited potent activity comparable to that of oxybutynin and **2a** (58.5% (>30 min) at 1 mg/kg i.v.[1b]). Hence, for further exploration of new lead compounds, modifications of the 2-cyclohexyl-2-hydroxy-2-phenylmethyl moiety in a prototype compound **3c** were carried out. Replacement of the cyclohexyl group in **3c** with a phenyl group (**3g**) enhanced the potency. The introduction of F atoms on the two phenyl groups in **3g** (**3m**) and the fixation of the two phenyl groups in **3g** as dibenzocycloheptene (**3n**) resulted in a decrease and complete loss of the activity, respectively. Removal of the 2-hydroxyl group in **3g** (**3o**—**r**, **17**) also resulted in a decrease or complete loss of the activity, showing the 2-hydroxyl group to be essential for the activity. To obtain more effective compounds we continued further structural modifications of **3c** and **3g**.

The weak activity of the *N*-(pyridylmethyl) derivative (**13′**, Table III) suggested that the N atom of the tetrahydropyridine plays an important role in the compound's biological actions. Thus, we tried optimization by changing the alkyl groups at the 1-position on the tetrahydropyridine moiety. 1-Unsubstituted (**3a**, **3e**) and 1-methyl (**3b**, **3f**) derivatives exhibited activity superior to that of the corresponding 1-ethyl derivatives (**3c**, **3g**, respectively) (Table IV). Larger groups such as *n*-propyl (**3h**), isopropyl (**3i**), benzyl (**3d**, **3j**) and 4-methoxybenzyl (**3k′**) mostly reduced the activity markedly. Diphenylacetamide derivatives (**3e**—**g**) were superior to the corresponding cyclohexylphenylacetamide derivatives (**3a**—**c**), unlike the *N*-(4-alkylamino-2-butynyl)acetamides series **2**.[1b] Movement of the substitution position on the tetrahydropyridine from the 4-position to the 3-position (**3l**) led to a decrease of the activity. Among the tetrahydropyridyl derivatives **3**, the 1-unsubstituted- and 1-methyl-2-hydroxydiphenylacetamide derivatives (**3e**, **3f**) exhibited the most potent activity, superior to that of oxybutynin.

Next, diphenylacetamide derivatives (**4a**—**g**) possessing piperidyl groups in place of the tetrahydropyridyl groups were evaluated. *N*-[(1-Unsubstituted-4-piperidyl)methyl]- and *N*-[(1-ethyl-3-piperidyl)methyl]-2-hydroxy-2,2-diphenylacetamide (**4d**, **4g**) exhibited potent activity, superior to that of oxybutynin. Interestingly, in the piperidylmethyl series (**4c**—**e**, **4g**), a structure–activity relationship different from that in the tetrahydropyridylmethyl series (**3c**, **3e**, **3f**, **3l**) was observed. Namely, the potency of 1-unsubstituted derivative **4d** was markedly different from that of the corresponding 1-methyl derivative **4e**, and the 3-piperidylmethyl derivative **4g** showed potent activity, in contrast with the weak activity of the corresponding (tetrahydro-3-pyridyl)methyl derivative **3l**. The activity of the *N*-(4-piperidyl) and *N*-[(4-piperidyl)ethyl] derivatives (**4a**, **4b**, **4f**) was weak. In the piperidyl series **4**, in terms of activity, no compound superior to **3e** and **3f** was obtained.

As a variation from the 4- and 3-piperidylmethyl groups (**4d**, **4g**), we considered alternative saturated cyclic amines. Among compounds **4h**—**k** (Table III), where the distance between the amide function and the N atom on the cyclic amines was similar to that in **4d** or **4g**, *N*-[(1-methylpyrrolidyl)ethyl] and *N*-(1-azabicyclo[2.2.2]octan-3-yl) derivatives (**4h**, **4k**) exhibited activity comparable and superior, respectively, to that of oxybutynin. The potency of the bridged bicyclic amine derivative **4k** was comparable to that of **3e** and **3f** (Table IV).

Six compounds **3a**, **3c**, **3e**, **3g**, **4d** and **4k** were selected for evaluation of selectivity between inhibitory activity against bladder contraction and mydriatic activity in rats (Table IV). Except for **4d**, these compounds exhibited the good selectivity superior to that of oxybutynin. In particular, **3e** exhibited the best selectivity (20-fold). *N*-[(Tetrahydro-4-pyridyl)methyl]diphenylacetamides **3e** and **3g** were superior to the corresponding cyclohexylphenylacetamides **3a** and **3c** in selectivity as well as in inhibitory activity against bladder contraction. *N*-(4-Piperidylmethyl)diphenylacetamide **4d** was markedly inferior to the corresponding *N*-[(tetrahydro-4-pyridyl)-methyl]acetamide **3e** in terms of selectivity.

Compound **3e** was further evaluated for inhibitory activity against detrusor contractions *in vitro* induced by electrical field stimulation, KCl, carbacol, $BaCl_2$, and ATP in guinea-pigs (Table IV). Compound **3e** exhibited a different pharmacological profile from that of oxybutynin. Namely, although oxybutynin inhibited all detrusor contractions, as shown in Table IV, **3e** inhibited only the contractions induced by electrical field stimulation and carbacol. The contraction by electrical field stimulation was inhibited completely by oxybutynin but only partially by **3e**, like atropine, a typical pure antimuscarinic agent.[7]

These results suggested that **3e** did not possess calcium channel antagonistic and spasmolytic actions, unlike oxybutynin, and that the inhibitory activity of **3e** against bladder contraction *in vivo* was related mainly to its inhibitory activity against detrusor contraction *in vitro* induced with carbacol, namely, its antimuscarine-like

TABLE IV. Effect of Selected Compounds on Urinary Bladder Rhythmic Contraction and Mydriasis in Rats and on Detrusor Contractions *in Vitro* Induced by Electrical Field Stimulation, KCl, Carbacol, $BaCl_2$, and ATP in Guinea-Pigs

No.	Inhibitory activity against bladder contraction ED_{30} mg/kg i.v.	Mydriatic activity MED[a] mg/kg i.v.	Selectivity MED/ED_{30}	Inhibitory activity against detrusor contraction IC_{50} g/ml *in vitro*				
				Electrical field stimulation	KCl	Carbacol	$BaCl_2$	ATP
3a	0.08	0.32	4.0					
3b	0.05							
3c	0.32	1.0	3.1					
3e	0.005	0.1	20	7.9×10^{-8} [b]	$>1.0\times10^{-4}$	5.3×10^{-8}	$>1\times10^{-4}$	$>1\times10^{-4}$
3f	0.003							
3g	0.05	0.32	6.4					
4d	0.013	<0.032	<2.5					
4h	0.13							
4k	0.007	0.1	14					
Oxybutynin (**1**)	0.21	0.1	0.48	5.8×10^{-7} [c]	2.2×10^{-5}	9.9×10^{-8}	2.3×10^{-5}	1.6×10^{-5}

a) MED = minimum effective dose. *b*) Partial inhibition. *c*) Complete inhibition.

activity. Muscarinic receptors have been pharmacologically classified into three major subtypes (M_1, M_2 and M_3) by the use of selective muscarinic receptor antagonists.[4a,c] Therefore, it is supposed that the good selectivity of **3e** between bladder and iris might be due to the difference of its affinity for the respective muscarinic receptors and/or the difference of its distribution (delivery) to the respective tissues. Further study is in progress.

In conclusion, the cyclization of a 4-amino-2-butynyl moiety of compound **2a**, an amide congener of oxybutynin, generated a new compound **3e**, which was found to be superior to oxybutynin and compounds **2** both in inhibitory activity against urinary bladder rhythmic contraction and in selectivity between inhibitory activity against bladder contraction and mydriatic activity. Compound **3e** was selected as a candidate compound for further evaluation.

Experimental

The melting points were determined on a capillary melting point apparatus (BUECHI 530 or Electrothermal) and are uncorrected. The infrared (IR) spectra were measured on Shimadzu IR-408 and Hitachi 260-10 spectrometers. The ^{1}H-NMR spectra were recorded on Bruker AC200P and Varian EM-390 spectrometers using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, br = broad, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet. The mass (MS) spectra were recorded on a Hitachi M-80 mass spectrometer.

***N*-[[1,2,3,6-Tetrahydro-1-(4-methoxybenzyl)-4-pyridyl]methyl]acetamide (6k)** A solution of *N*-[4-pyridylmethyl]acetamide[6] (**5a**, 7.00 g) and 4-methoxybenzyl chloride (6.8 ml) in acetone (100 ml) was stirred under reflux for 4 h and cooled in an ice bath. The precipitated powder was collected by filtration and washed with acetone to afford 4-acetylaminomethyl-1-(4-methoxybenzyl)pyridinium chloride (10.88 g, 76.1%) as a hygroscopic powder, which was used for the next reaction without further purification.

$NaBH_4$ (5.73 g) was added portionwise to a stirred solution of the crude pyridinium chloride (10.88 g) in MeOH (200 ml) under ice cooling. The resulting solution was stirred at room temperature for 13 h, diluted with water, concentrated *in vacuo*, and extracted with AcOEt. The extract was washed with brine, dried, evaporated *in vacuo*, and chromatographed (CH_2Cl_2–MeOH) over silica gel to afford **6k** (7.27 g, 74.7%) as a pale yellow oil. IR (film): 3300, 1650, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.98 (3H, s, $NCOCH_3$), 2.10 (2H, br s, CH_2), 2.56 (2H, t, J = 5.7 Hz, CH_2N), 2.95 (2H, br s, NCH_2), 3.52 (2H, s, CH_2), 3.76 (2H, s, CH_2), 3.80 (3H, s, OCH_3), 5.53 (1H, t, J = 1.5 Hz, =CH), 5.95 (1H, br s, NH), 6.8—6.9 (2H, m, aromatic H), 7.2—7.3 (2H, m, aromatic H). MS *m/z*: 274 (M^+), 215, 121.

The following acetamides (**6**) were prepared in a similar manner.

***N*-[(1-Ethyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]acetamide (6c)** **6c** was prepared in 78.8% yield from **5a** and ethyl iodide. An oil: bp 143—145 °C (0.3 mmHg). IR (film): 3300, 3080, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J = 6.0 Hz, CH_3), 1.97 (3H, s, $NCOCH_3$), 1.85—2.35 (2H, m, CH_2), 2.35—2.75 (4H, m, CH_2NCH_2), 2.96 (2H, br s, NCH_2), 3.7—3.9 (2H, m, NCH_2), 5.53 (1H, m, =CH), 5.7—6.2 (1H, br s, NH). MS *m/z*: 182 (M^+), 167.

***N*-[(1-Benzyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]acetamide (6d)** **6d** was prepared in 94.9% yield from **5a** and benzyl bromide. A pale brown oil. IR (film): 3250, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.98 (3H, s, CH_3), 2.0—2.15 (2H, m, CH_2), 2.15—2.35 (2H, m, NCH_2), 2.97 (2H, br s, NCH_2), 3.45 (2H, s, NCH_2Ph), 3.95—4.0 (2H, m, CH_2N), 5.53 (1H, br s, =CH), 5.84 (1H, br s, NH), 7.2—7.4 (5H, m, aromatic H). MS *m/z*: 244 (M^+), 185, 172.

***N*-[(1,2,3,6-Tetrahydro-1-*n*-propyl-4-pyridyl)methyl]acetamide (6h)** **6h** was prepared in 69.0% yield from **5a** and *n*-propyl iodide. An oil. IR (film): 3300, 3050, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J = 7.3 Hz, CH_3), 1.58 (2H, tq, J = 7.3, 5.7 Hz, CH_2), 1.99 (3H, s, $NCOCH_3$), 2.23 (2H, br s, CH_2), 2.3—2.4 (2H, m, NCH_2), 2.56 (2H, t, J = 5.7 Hz, NCH_2), 2.95 (2H, d, J = 1.6 Hz, NCH_2C=), 3.79 (2H, d, J = 5.4 Hz, CH_2NCO), 5.54—5.57 (1H, m, =CH), 5.66 (1H, br s, NH). MS *m/z*: 196 (M^+), 167, 96.

***N*-[(1-Ethyl-1,2,5,6-tetrahydro-3-pyridyl)methyl]acetamide (6l)** **6l** was prepared in 74.7% yield from *N*-[3-pyridylmethyl]acetamide[8] (**51**) and ethyl iodide. An oil (purified by Kugelrohr distillation, 150 °C (0.3 mmHg)). IR (film): 3270, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J = 7.0 Hz, CH_3), 1.99 (3H, s, $NCOCH_3$), 2.19 (2H, m, CH_2), 2.49 (2H, q, J = 7.0 Hz, NCH_2), 2.52 (2H, t, J = 6.0 Hz, CH_2N), 2.72 (2H, d, J = 2.5 Hz, NCH_2C=), 3.78 (2H, d, J = 5.5 Hz, NCH_2), 5.65 (1H, m, =CH), 5.8 (1H, br s, NH). MS *m/z*: 182 (M^+), 123, 110, 108.

[[1,2,3,6-Tetrahydro-1-(4-methoxybenzyl)-4-pyridyl]methyl]amine (7k) A solution of **6k** (5.00 g) in 6 N NaOH and MeOH was refluxed for 23 h, evaporated *in vacuo*, and partitioned between AcOEt and 1 N NaOH. The organic layer was washed with brine, dried, and evaporated *in vacuo*, and the residue was chromatographed (CH_2Cl_2–MeOH) over silica gel to afford **7k** (2.31 g, 54.6%) as an oil. IR (film): 3370, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (2H, br s, NH_2), 2.13 (2H, br s, CH_2), 2.57 (2H, t, J = 5.8 Hz, NCH_2), 2.99 (2H, br s, NCH_2), 3.20 (2H, br s, NCH_2), 3.53 (2H, s, NCH_2Ar), 3.80 (3H, s, CH_3), 5.55 (1H, m, =CH), 6.8—6.9 (2H, m, aromatic H), 7.2—7.3 (2H, m, aromatic H). MS *m/z*: 232 (M^+), 202, 121.

The following (pyridylmethyl)amines (**7**) were prepared in a similar manner.

[(1-Ethyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]amine (**7c**): Yield 92.4%, an oil, bp 87 °C (19 mmHg). IR (film): 3360, 3270, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J = 6.0 Hz, CH_3), 0.95—1.4 (2H, m, NH_2), 2.0—2.3 (2H, m, CH_2), 2.3—2.7 (4H, m, $2NCH_2$), 2.85—3.05 (2H, m, NCH_2), 3.17 (2H, br s, NCH_2), 5.45—5.65 (1H, m, =CH). MS *m/z*: 140 (M^+), 123, 110.

[(1-Benzyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]amine (**7d**): Yield 58.0%, an oil. IR (film): 3370, 3270, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (2H, s, NH_2), 2.13 (2H, br s, CH_2), 2.58 (2H, t, J=5.8 Hz, NCH_2), 2.95—3.05 (2H, m, NCH_2), 3.20 (2H, br s, NCH_2), 3.59 (2H, s, NCH_2Ph), 5.5—5.55 (1H, m, =CH), 7.2—7.35 (5H, m, aromatic H). MS *m/z*: 202 (M^+), 172. 97.

[(1,2,3,6-Tetrahydro-1-*n*-propyl-4-pyridyl)methylamine (**7h**): Yield 51.2%, an oil (purified by Kugelrohr distillation, 140—150 °C (10 mmHg)). IR (film): 3270, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ; 0.92 (3H, t, J=7.3 Hz, CH_3), 1.1—1.7 (2H, br s, NH_2), 1.55 (2H, tq, J=7.3, 5.7 Hz, CH_2), 2.14 (2H, d, J=1.6 Hz, CH_2), 2.3—2.4 (2H, m, NCH_2), 2.57 (2H, t, J=5.7 Hz, NCH_2), 2.95—3.0 (2H, m, NCH_2), 3.10 (2H, s, NCH_2), 5.55 (1H, m, =CH). MS *m/z*: 154 (M^+), 125, 96.

[(1-Ethyl-1,2,5,6-tetrahydro-3-pyridyl)methyl]amine (**7l**): Yield 67.6%, an oil (purified by Kugelrohr distillation, 100—105 °C (8.5 mmHg)). IR (film): 3450, 3370, 3280, 3200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.0 Hz, CH_3), 1.61 (2H, s, NH_2), 2.21 (2H, m, CH_2), 2.47 (2H, q, J=7.0 Hz, NCH_2), 2.49 (2H, t, J=6.0 Hz, NCH_2), 2.93 (2H, m, NCH_2), 3.20 (2H, m, NCH_2), 5.62 (1H, m, =CH). MS *m/z*: 140 (M^+), 123, 110, 108.

[(1,2,3,6-Tetrahydro-1-methyl-4-pyridyl)methyl]amine (**7b**) was prepared according to the literature.[6]

2-Chloro-2-cyclohexyl-2-phenylacetyl chloride (**8a**), 2-chloro-2,2-diphenylacetyl chloride (**8b**), 10,11-dihydro-5-hydroxy-5*H*-dibenzo[*a*,*d*]-cycloheptene-5-carboxylic acid (**9n**), and 3,3-diphenyl-2-propenoic acid (**11d**) were prepared according to the literature.[9] 2-Hydroxy-2,2-diphenylacetic acid (**9b**), 2,2-bis(4-fluorophenyl)-2-hydroxyacetic acid (**9m**), diphenylacetic acid (**11a**), and 2,2- and 3,3-diphenylpropionic acid (**11b**, **11c**) were commercial products.

2-Hydroxy-2,2-diphenyl-*N*-(4-pyridylmethyl)acetamide (13) A solution of (4-pyridylmethyl)amine (**12**, 94.7 g) in toluene (100 ml) was added dropwise to a stirred solution of 2-chloro-2,2-diphenylacetyl chloride[9a] (**8b**, 257.0 g) in toluene (1.00 l) at room temperature over 20 min. The resulting mixture was stirred at room temperature for 30 min and diluted with acetone (1.00 l). The precipitated powder was collected by filtration to afford 2-chloro-2,2-diphenyl-*N*-(4-pyridylmethyl)acetamide hydrochloride as a crude powder, a solution of which in water (1.00 l) and 1 N HCl (800 ml) was stirred at 45 °C for 30 min. The reaction mixture was cooled to room temperature and basified with 6 N NaOH with stirring. The precipitated powder was collected by filtration and washed with water and Et_2O to afford **13** (201.76 g, 72.3%) as a colorless powder, mp 149—151 °C. IR (Nujol): 3380, 3350, 1650, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.33 (2H, d, J=6.3 Hz, CH_2), 6.85 (1H, s, OH), 7.15—7.2 (2H, m, aromatic H), 7.25—7.4 (10H, m, aromatic H), 8.4—8.45 (2H, m, aromatic H), 8.84 (1H, t, J=6.3 Hz, NH). MS *m/z*: 183, 105.

The free base **13** was converted to the hydrochloride (**13'**) in a usual manner and its physical data are listed in Table I.

4-[(2-Hydroxy-2,2-diphenylacetyl)aminomethyl]-1-(4-methoxybenzyl)-pyridinium Chloride (14k) A solution of **13** (80.0 g) and 4-methoxybenzyl chloride (47.2 g) in *N*, *N*-dimethylformamide (DMF) (120 ml) was stirred at 65 °C for 1 h, diluted with acetone (500 ml) and Et_2O (100 ml), and stirred under ice cooling for 20 min. The precipitated powder was collected by filtration to afford **14k** (107.57 g, 90.1%) as a colorless powder: 205—208 °C. *Anal.* Calcd for $C_{28}H_{27}ClN_2O_3$: C, 70.80; H, 5.73; N, 5.90. Found: C, 70.47; H, 5.75; N, 5.95. IR (Nujol): 3250, 3160, 1660, 1640, 1610, 1250 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.76 (3H, s, CH_3), 4.55 (2H, d, J=5.9 Hz, CH_2), 5.72 (2H, s, CH_2), 6.99 (2H, d, J=8.6 Hz, aromatic H), 7.00 (1H, s, OH), 7.25—7.4 (10H, m, aromatic H), 7.53 (2H, d, J=8.6 Hz), 7.87 (2H, d, J=6.7 Hz, aromatic H), 9.11 (1H, t, J=5.9 Hz, NH), 9.13 (2H, d, J=6.7 Hz, aromatic H). MS *m/z*: 183, 93.

The following pyridinium halides (**14**) were prepared in a similar manner.

1-Ethyl-4-[(2-Hydroxy-2,2-diphenylacetyl)aminomethyl]pyridinium Iodide (14g) **14g** was prepared in 93.3% yield from **13** and EtI, and then used for the next reaction without further purification. A pale yellow powder, mp 123—124 °C. IR (Nujol): 3350, 3250, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.52 (3H, t, J=7.2 Hz, CH_3), 4.57 (2H, q, J=7.2 Hz, CH_2), 4.60 (2H, d, J=6.0 Hz, CH_2), 7.00 (1H, s, OH), 7.2—7.5 (10H, m, aromatic H), 7.85 (2H, d, J=6.6 Hz, aromatic H), 9.01 (2H, d, J=6.6 Hz, aromatic H), 9.13 (1H, t, J=6.0 Hz, NH). MS *m/z*: 183, 105.

4-[(2-Hydroxy-2,2-diphenylacetyl)aminomethyl]-1-methylpyridinium iodide (**14f**) was prepared from **13** and MeI and used for the next reaction without further purification and characterization.

1-[(1-Ethyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]-3,3-diphenyl-2-pyrrolidinone Fumarate (1:1) (17) A solution of 4-bromo-2,2-diphenylbutanoic acid[10] (**16**, 1.50 g) and $SOCl_2$ (1.37 ml) in $CHCl_3$ (20 ml) was refluxed for 4 h and evaporated *in vacuo* to afford the butanoyl chloride. A solution of the butanoyl chloride in CH_2Cl_2 (15 ml) was added slowly to a stirred solution of **7c** (0.73 g) and NEt_3 (2.6 ml) in CH_2Cl_2 (15 ml) at room temperature and the resulting mixture was stirred at the same temperature overnight. The reaction mixture was evaporated *in vacuo* and partitioned between AcOEt and 1 N NaOH. The organic layer was separated, washed with water (three times) and brine, dried, and evaporated *in vacuo*. The residue was chromatographed (CH_2Cl_2–MeOH) over silica gel. The eluate was evaporated *in vacuo*. The residue was chromatographed (*n*-hexane–AcOEt) over alumina, and the product was treated with fumaric acid in a usual manner. The obtained fumarate was washed with *n*-hexane to afford **17** (0.54 g) as a powder. IR (Nujol): 2500, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.11 (3H, t, J=7.2 Hz, CH_3), 2.17 (2H, br s, CH_2), 2.73 (2H, q, J=7.2 Hz, NCH_2), 2.8—2.9 (4H, m, $2CH_2$), 3.24 (2H, br s, CH_2), 3.86 (2H, s, CH_2), 4.11 (2H, t, J=6.4 Hz, CH_2), 5.53 (1H, s, =CH), 6.52 (2H, s, HC=CH), 7.1—7.4 (10H, m, aromatic H). MS *m/z*: 360 (M^+), 238, 165, 123. The other physical data are listed in Table II.

***N*-(1-Carboethoxy-4-piperidyl)-2-hydroxy-2,2-diphenylacetamide (19)** **19** was prepared in 92.5% yield from **9b** and 1-carboethoxy-4-piperidylamine (**18**) by method B and used for the next step without purification. A colorless powder, mp 128—131 °C (from *n*-hexane). IR (Nujol): 3300, 1650, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.4 (2H, m, 2CH), 1.23 (3H, t, J=7.1 Hz, CH_3), 1.7—2.0 (2H, m, 2CH), 2.75—3.0 (2H, m, CHNCH), 3.9—4.2 (3H, m, NCH, CHNCH), 4.08 (2H, q, J=7.1 Hz, OCH_2), 6.67 (1H, d, J=8.0 Hz, NH), 6.93 (1H, s, OH), 7.2—7.5 (10H, m, aromatic H). MS *m/z*: 382 (M^+), 370, 216, 183.

2-Hydroxy-2,2-diphenyl-*N*-(4-piperidyl)acetamide Hydrochloride (4a) A solution of **19** (4.00 g) and KOH (2.00 g) in 2-methoxyethanol (30 ml) was refluxed for 4.5 h, cooled to room temperature, diluted with water, and extracted three times with AcOEt. The combined extracts were washed with brine, dried, and evaporated *in vacuo*. The residue was washed with acetone to afford **4a** (1.10 g) as a powder. Its physical data are listed in Tables I and V.

4-(Diethylaminomethyl)piperidine (20j) A mixture of *N*,*N*-diethyl-4-piperidinecarboxamide hydrochloride[11a] (6.0 g) and $LiAlH_4$ (2.06 g) in tetrahydrofuran (60 ml) was stirred under reflux, cooled, and diluted successively with water (2.1 ml), 5% NaOH (4.2 ml), and water (6.3 ml). The resulting mixture was filtered. The filtrate was evaporated *in vacuo* and the residue was distilled to afford **20j** (3.55 g, 76.6%) as a colorless oil, bp 108—113 °C (20 mmHg). IR (film): 3290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95—1.15 (8H, m, $2CH_3$, 2CH), 1.53 (1H, m, CH), 1.74 (2H, br d, J=12.6 Hz, 2CH), 1.93 (1H, s, NH), 2.20 (2H, d, J=6.9 Hz, NCH_2), 2.48 (4H, q, J=7.1 Hz, $2CH_2N$), 2.58 (2H, dt, J=12.1, 2.6 Hz, 2CHN), 3.07 (2H, m, 2CHN). MS *m/z*: 170 (M^+), 86.

[(1-Ethyl-4-piperidyl)methyl]amine (**20c**), [2-(1-methyl-4-piperidyl)-ethyl]amine (**20f**), [(1-ethyl-3-piperidyl)methyl]amine (**20g**), [(1-ethyl-3-pyrrolidyl)methyl]amine (**20i**), and 1-azabicyclo[2.2.2]octan-3-yl-amine (**20k**) were prepared according to literature.[11b,c] 1-Carboethoxy-4-piperidylamine (**18**) and [2-(1-methyl-2-pyrrolidyl)ethyl]amine (**20h**) were commercial products.

Method A_1. *N*-[(1-Ethyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]-2-hydroxy-2,2-diphenylacetamide Hydrochloride (3g) A solution of **8b** (2.50 g) in $CHCl_3$ (10 ml) was added dropwise to a stirred solution of **7c** (1.45 g) in $CHCl_3$ (5 ml) under ice cooling. The resulting mixture was stirred at the same temperature for 30 min and at room temperature for 4 h, and then washed with aqueous $NaHCO_3$ and brine. The organic layer was dried and evaporated *in vacuo*. The residue was dissolved in a mixture of 1,4-dioxane (30 ml) and 1 N HCl (15 ml), and then the solution was heated at 90 °C for 1 h. The reaction mixture was evaporated *in vacuo* and partitioned between AcOEt and aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and evaporated *in vacuo*, then the residue was chromatographed ($CHCl_3$–MeOH) over silica gel to afford an oil, which was recrystallized from AcOEt–iso-Pr_2O to afford the free base of **3g** (1.96 g, 59.3%). The free base (2.09 g) was converted to the hydrochloride in a usual manner and the hydrochloride was recrystallized from iso-PrOH to afford **3g** (1.79 g). Its physical data are listed in Tables I and V.

Method A_2. 4-(Diethylaminomethyl)-1-(2-hydroxy-2,2-diphenylacetyl)piperidine Hydrochloride (4j) A mixture of **8b** (0.80 g) and **20j** (0.51 g) was stirred at room temperature for some time and suspended

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

No.	IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ (J, Hz)	MS m/z
3a	3330, 2670, 2570, 2480, 1650	0.9—1.8 (10H, m), 2.0—2.15 (2H, br s), 2.2—2.4 (1H, br s), 3.06 (2H, t, 5.9), 3.44 (2H, s), 3.5—3.75 (2H, m), 5.28 (1H, s), 5.56 (1H, s), 7.2—7.4 (3H, m), 7.55—7.65 (2H, m), 7.98 (1H, t, 6.4), 8.95 (2H, s)	328 (M^+), 309 216, 189
3b	3460, 3350, 3270, 2670, 2600, 1640	0.85—1.85 (10H, m), 2.0—2.35 (3H, m), 2.71 (3H, s), 2.9—3.4 (2H, br s), 3.45—3.8 (4H, m), 5.24 (1H, s), 5.58 (1H, s), 7.1—7.4 (3H, m), 7.5—7.65 (2H, m), 8.02 (1H, t, 5.9), 10.57 (1H, br s)	342 (M^+), 189
3c	3400, 2480, 1660	0.85—1.95 (10H, m), 1.20 (3H, t, 7.0), 1.95—2.45 (3H, m), 2.75—3.85 (8H, m), 5.27 (1H, m), 5.50 (1H, s), 7.15—7.45 (3H, m), 7.45—7.75 (2H, m), 7.95 (1H, t, 5.0), 10.20 (1H, br s)	356 (M^+), 189
3d	3300, 2570, 1650	0.8—1.6 (10H, m), 1.75—2.15 (3H, m), 2.45—3.35 (6H, m), 4.28 (2H, s), 5.24 (1H, br s), 5.55 (1H, s), 6.3—6.75 (10H, m), 8.00 (1H, br s), 10.42 (1H, s)	418 (M^+), 327, 282, 189, 172, 91
3e	3350, 3270, 2800—2400, 1650	2.15 (2H, br s), 3.10 (2H, t, 5.9), 3.34 (2H, br s), 3.70 (2H, d, 5.5), 5.41 (1H, br s), 6.82 (1H, s), 7.2–7.45 (10H, m), 8.34 (1H, t, 5.5), 9.15 (2H, br s)	322 (M^+), 183, 95
3f	3340, 3200, 2670, 2610, 2550, 1660	2.0—2.5 (2H, m), 2.73 (3H, s), 2.8—3.9 (4H, m), 3.72 (2H, d, 6.1), 5.38 (1H, s), 6.82 (1H, s), 7.2—7.4 (10H, m), 8.37 (1H, t, 6.1), 10.77 (1H, br s)	336 (M^+), 183, 109
3g	3310, 3230, 2550, 1660	1.23 (3H, t, 7.2), 2.05—2.4 (2H, m), 3.07 (2H, q, 7.2), 3.25—3.8 (4H, m), 3.73 (2H, d, 6.0), 5.39 (1H, br s), 6.81 (1H, br s), 7.2—7.45 (10H, m), 8.37 (1H, t, 6.0)	350 (M^+), 335, 302, 183
3h	3250, 1660	0.89 (3H, t, 7.3), 1.6—1.8 (2H, m), 2.0—2.55 (2H, m), 2.9—4.25 (8H, m), 5.89 (1H, br s), 6.82 (1H, s), 7.2—7.45 (10H, m), 8.37 (1H, t, 6.1), 10.50 (1H, br s)	364 (M^+), 335, 183, 137
3i	3250, 1660	1.26 (6H, d, 6.6), 2.05—2.25 (1H, m), 2.3—2.6 (1H, m), 2.75—3.1 (1H, m), 3.25—3.5 (2H, m), 3.58 (2H, br s), 3.73 (2H, d, 6.0), 5.42 (1H, s), 6.83 (1H, br s), 7.15—7.6 (10H, m), 8.36 (1H, t, 6.0), 10.30 (1H, br s)	
3j	3450, 3200, 2570, 1660	2.0—2.5 (2H, m), 2.7—3.5 (2H, m), 3.50 (2H, br s), 3.72 (2H, d, 6.0), 4.30 (2H, s), 5.38 (1H, s), 6.81 (1H, s), 7.25—7.65 (15H, m), 8.36 (1H, t, 6.0), 10.92 (1H, br s)	
3k′	3400–3180, 2730—2300, 1725, 1660, 1610, 1250	2.16 (2H, m), 3.03 (2H, m), 3.36 (2H, br s), 3.72 (2H, d, 6.0), 3.77 (3H, s), 4.05 (2H, s), 5.37 (1H, br s), 6.4 (1H, br), 6.97 (2H, d, 8.5), 7.2—7.45 (12H, m), 8.32 (1H, t, 6.0)	442 (M^+), 215, 202, 183, 121
3l	3400, 2750—2600, 1675, 1590	1.02 (3H, t, 7.0), 2.09 (2H, m), 2.45—2.65 (4H, m), 2.92 (2H, s), 3.68 (2H, m), 5.52 (1H, br s), 6.51 (2H, s), 7.25—7.4 (10H, m), 8.21 (1H, br s)	350 (M^+), 183, 124, 105
3m	3350, 3270, 2500, 1660, 1600	1.24 (3H, t, 7.2), 2.0—2.45 (2H, m), 2.85—3.8 (6H, m), 3.09 (2H, q, 7.2), 5.39 (1H, s), 6.96 (1H, s), 7.1—7.2 (4H, m), 7.35—7.45 (4H, m), 8.46 (1H, br s), 10.21 (1H, br s)	386 (M^+), 371, 219, 123, 110
3n	3420, 3330, 2730—2000, 1655	1.23 (3H, t, 7.0), 1.95—2.45 (2H, m), 2.75—3.15 (5H, m), 3.3—3.45 (4H, m), 3.35—3.65 (3H, m), 5.30 (1H, br s), 6.89 (1H, s), 7.05—7.25 (6H, m), 7.75—7.85 (3H, m), 10.5 (1H, br)	376 (M^+), 209, 123, 110
3o	3270, 2670, 2550, 2470, 1640	1.23 (3H, t, 7.2), 2.0—2.4 (2H, m), 2.8—3.0 (4H, m), 3.04 (2H, q, 7.2), 3.6—3.8 (2H, m), 5.06 (1H, s), 5.39 (1H, s), 7.1—7.35 (10H, m), 8.67 (1H, t, 5.7), 10.43 (1H, br s)	334 (M^+), 167, 123
3p	3450, 3350, 2670, 2600, 1630	1.24 (3H, t, 7.2), 1.89 (3H, s), 2.0—3.7 (8H, m), 3.06 (2H, q, 7.2), 5.31 (1H, br s), 7.1—7.4 (10H, m), 7.64 (1H, br s), 10.08 (1H, br s)	
3q	3330, 2600, 1720, 1640, 1600	1.18 (3H, t, 7.2), 1.95 (2H, br s), 2.89 (2H, d, 8.2), 3.01 (2H, q, 7.2), 2.95—3.10 (2H, m), 3.39 (2H, br s), 3.54 (2H, br s), 4.47 (1H, t, 8.2), 4.88 (1H, s), 7.1—7.3 (10H, m), 8.13 (1H, br s)	348 (M^+), 333, 167, 123
3r	3330, 2720, 1720, 1640	1.20 (3H, t, 7.3), 2.11 (2H, br s), 3.08 (2H, q, 7.3), 3.0—3.2 (2H, m), 3.51 (2H, br s), 3.55—3.7 (2H, m), 4.40 (2H, br s), 5.22 (1H, s), 6.50 (1H, s), 7.1—7.4 (10H, m), 8.15—8.2 (1H, m)	346 (M^+), 207, 123
4a	3300, 2700, 2600, 2470, 1660	1.6—2.0 (4H, m), 2.75—3.05 (2H, m), 3.05–3.3 (2H, m), 3.75—4.0 (1H, m), 6.77 (1H, s), 7.2—7.95 (10H, m), 8.15 (1H, d, 7.7), 8.94 (1H, br s), 9.10 (1H, br s)	183, 105
4b	3420, 2350, 1670	1.05 (3H, t, 7.2), 1.45—1.65 (4H, m), 2.15—2.4 (2H, m), 2.54 (2H, q, 7.2), 2.85—3.05 (2H, m), 3.55—3.75 (1H, m), 6.5 (1H, s), 7.2—7.4 (11H, m), 7.96 (1H, d, 8.0)	
4c	3400, 3250, 2650, 2600, 2400, 1640	0.85—1.85 (15H, m), 1.20 (3H, t, 7.2), 2.1—2.35 (1H, m), 2.6—3.15 (6H, m), 3.25—3.5 (2H, m), 5.48 (1H, s), 7.15—7.4 (3H, m), 7.55—7.65 (2H, m), 7.9—8.05 (1H, m), 9.75 (1H, br s)	358 (M^+), 343, 329, 275, 189
4d	3360, 2470, 1650	1.1—1.4 (2H, m), 1.5—1.8 (3H, m), 2.65—2.9 (2H, m), 2.9—3.1 (2H, m), 3.1—3.3 (2H, m), 6.75 (1H, s), 7.2—7.45 (10H, m), 8.28 (1H, br s), 8.69 (2H, br s)	324 (M^+), 183, 105
4e	3430, 3150, 1670	1.2—1.5 (1H, m), 1.6—1.8 (2H, m), 2.2—3.2 (8H, m), 2.68 (3H, s), 6.73 (1H, s), 7.2—7.35 (10H, m), 8.3 (1H, br s), 9.7—9.9 (1H, br s)	338 (M^+), 183, 105
4f	3360, 3250, 3200, 2740—2100, 1700, 1670	1.15—1.45 (5H, m), 1.7 (2H, m), 2.35 (2H, m), 2.45 (3H, s), 3.0—3.2 (4H, m), 6.50 (2H, s), 7.2—7.4 (11H, m), 8.15 (1H, t, 6.0)	352 (M^+), 337, 183
4g	3360, 3220, 2660, 2570, 1655	1.05 (1H, m), 1.16 (3H, t, 7.0), 1.75 (3H, m), 2.1 (1H, m), 2.45 (1H, m), 2.7 (1H, m), 2.95—3.35 (6H, m), 6.79 (1H, s), 7.2—7.45 (10H, m), 8.40 (1H, t, 6.0), 10.2 (1H, br)	352 (M^+), 337, 183, 105
4h	3400, 3180, 2620, 1660	1.4—1.95 (4H, m), 1.95—2.25 (2H, m), 2.64 (3H, s), 2.75—3.1 (2H, m), 3.1—3.25 (2H, m), 3.35—3.55 (1H, m), 6.76 (1H, s), 7.2—7.5 (10H, m), 8.38 (1H, br s), 10.36 (1H, br s)	338 (M^+), 323, 183, 155, 84
4i	3400, 2750—2300, 1700, 1660	1.10 (3H, t, 7.0), 1.61 (1H, m), 1.87 (1H, m), 2.4—3.2 (10H, m), 6.52 (2H, s), 7.2—7.4 (10H, m), 8.42 (1H, t, 5.5)	338 (M^+), 323, 183, 155, 105
4j	3400, 3160, 2760—2300, 1610	0.7 (1H, m), 1.05 (1H, m), 1.18 (6H, t, 7.0), 1.45 (1H, m), 1.9 (2H, m), 2.65 (2H, m), 2.8 (2H, m), 3.05 (4H, m), 4.15 (1H, m), 4.4 (1H, m), 6.92 (1H, s), 7.3 (10H, m), 9.9 (1H, br)	380 (M^+), 183, 86
4k	3300, 2800—2300, 1660	1.6—2.1 (5H, m), 3.05—3.6 (6H, m), 4.15 (1H, m), 6.87 (1H, s), 7.25—7.45 (10H, m), 8.59 (1H, d, 7.0), 10.36 (1H, br s)	336 (M^+), 183, 105

in CH_2Cl_2, and the suspension was stirred at the same temperature for some time. The reaction mixture was partitioned between AcOEt and water. The AcOEt layer was washed with aqueous NaOH and water, dried, and evaporated *in vacuo*. The residue was dissolved in 1,4-dioxane (7.4 ml) and 1 N HCl (3.7 ml). The solution was stirred at 90 °C for 1.5 h, evaporated *in vacuo*, and extracted with AcOEt. The extract was washed with aqueous NaOH and water, dried, and evaporated *in vacuo*, and then the residue was chromatographed ($CHCl_3$–MeOH) over silica gel to afford an oil, which was converted to the hydrochloride in a usual manner. The hydrochloride was recrystallized from iso-PrOH to afford **4j** (0.20 g) as a powder. Its physical data are listed in Tables III and V.

Method A_3. *N*-(1-Azabicyclo[2.2.2]octan-3-yl)-2-hydroxy-2,2-diphenylacetamide Hydrochloride (4k) A solution of 1-azabicyclo[2.2.2]-octan-3-ylamine[11c] (**20k**, 3.00 g) in benzene (12 ml) was added dropwise to a stirred solution of **8b** (6.30 g) in benzene (17 ml) and *n*-hexane (11 ml) at room temperature. The resulting mixture was stirred at room temperature for 3.5 h and partitioned between toluene and water. The organic layer was extracted twice with 1 N HCl. The aqueous layers were combined, washed with Et_2O, stirred at 70 °C for 1 h, cooled with ice-water, basified with 5% NaOH, and extracted twice with AcOEt. The AcOEt extracts were combined, washed with brine, dried, and evaporated *in vacuo*. The residue was washed with iso-Pr_2O to afford a colorless powder, which was converted to the hydrochloride in a usual manner. The hydrochloride was recrystallized from EtOH to afford **4k** (2.55 g) as a colorless powder. Its physical data were listed in Tables III and V.

Method B. 2-Hydroxy-2,2-diphenyl-*N*-[[1,2,3,6-tetrahydro-1-(4-methoxybenzyl)-4-pyridyl]methyl]acetamide (3k) A mixture of 2-hydroxy-2,2-diphenylacetic acid (**9b**, 2.21 g) and 1,1′-carbonyldiimidazole (1.73 g) in CH_2Cl_2 (45 ml) was stirred at room temperature for 2.5 h, and then a solution of **7k** (2.25 g) in CH_2Cl_2 (20 ml) was added dropwise to the mixture over 20 min. The resulting mixture was stirred at the same temperature for 45 min, evaporated *in vacuo*, and dissolved in a mixture of AcOEt and 1 N NaOH. The organic layer was separated, washed twice with water, dried, and evaporated *in vacuo*. The residue was chromatographed (CH_2Cl_2–MeOH) over silica gel to afford **3k** (3.47 g, 81.0%) as an amorphous powder, mp 56—61 °C. *Anal.* Calcd for $C_{28}H_{30}N_2O_3 \cdot 1/2H_2O$: C, 74.48; H, 6.92; N, 6.20. Found: C, 74.10; H, 6.82; N, 5.97. IR (film): 3370, 1660, 1610, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.02 (2H, br s, CH_2), 2.52 (2H, t, J=5.8 Hz, NCH_2), 2.91 (2H, br s, NCH_2), 3.50 (2H, s, NCH_2Ar), 3.80 (3H, s, OCH_3), 3.87 (2H, d, J=5.6 Hz, $CONCH_2$), 4.1 (1H, br s, OH), 5.39 (1H, br s, =CH), 6.41 (1H, t, J=5.6 Hz, NH), 6.85 (2H, d, J=8.6 Hz, aromatic H), 7.2—7.5 (12H, m, aromatic H). MS *m/z*: 442 (M^+), 202, 121.

Compound **3k** was converted to the oxalate (1 : 1) (**3k′**) in a usual manner and its physical data are listed in Tables I and V.

Method C. *N*-[(1-Ethyl-1,2,3,6-tetrahydro-4-pyridyl)methyl]-2,2-diphenylpropionamide hydrochloride (3p) A solution of 2,2-diphenylpropionic acid (**11p**, 0.70 g) in thionyl chloride (2.3 ml) was refluxed for 2 h and evaporated *in vacuo* to afford 2,2-diphenylpropionyl chloride (**10p**). A solution of **7c** (0.43 g) and NEt_3 (1.5 ml) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of **10p** in CH_2Cl_2 (10 ml) at room temperature. The resulting mixture was stirred at the same temperature for 3 h, washed successively with water (four times), 1 N NaOH, and brine, dried, and evaporated *in vacuo*, and then the residue was chromatographed (CH_2Cl_2–MeOH) over silica gel. The eluate was treated with 4 N HCl in AcOEt and evaporated *in vacuo*. The residue was recrystallized from iso-Pr_2O–iso-PrOH to afford **3p** (0.10 g) as a powder. Its physical data are listed in Tables II and V.

Method D. 3k: $NaBH_4$ (2.70 g) was added portionwise to a solution of **14k** (8.28 g) in MeOH (66 ml) under ice cooling over 1 h. The resulting solution was stirred at room temperature for 30 min, evaporated *in vacuo*, diluted with water, and extracted with AcOEt. The extract was washed with water and brine, dried, and evaporated *in vacuo* to afford **3k** (7.64 g, 99.2%).

Method E. 2-Hydroxy-2,2-diphenyl-*N*-[(1,2,3,6-tetrahydro-4-pyridyl)-methyl]acetamide Hydrochloride (3e) A mixture of **3k** (2.77 g) and 1-chloroethyl chloroformate (0.75 ml) in CH_2ClCH_2Cl (55 ml) was refluxed for 30 min. After addition of MeOH (50 ml) to the reaction mixture, the resulting mixture was refluxed for 1 h, and evaporated *in vacuo*. The residue was treated with 4 N HCl in AcOEt. The precipitated powder was collected by filtration and recrystallized from EtOH to afford **3e** (1.33 g) as a colorless powder. Its physical data are listed in Tables I and V.

Method F. 3e: A solution of **3k** (1.03 g) and benzyl chloroformate (0.437 g) in CH_2ClCH_2Cl (10 ml) was stirred at room temperature for 4 h, diluted with water, and extracted with CH_2Cl_2. The extract was dried and evaporated *in vacuo*, and the residue was chromatographed (CH_2Cl_2–MeOH) over silica gel to afford *N*-[(1-carbobenzyloxy-1,2,3,6-tetrahydro-4-pyridyl)methyl]-2-hydroxy-2,2-diphenylacetamide (**15**, 0.797 g, 74.9%) as an oil. *Anal.* Calcd for $C_{28}H_{28}N_2O_4 \cdot 1/2H_2O$: C, 72.24; H, 6.28; N, 6.02. Found: C, 72.03; H, 6.30; N, 5.53. IR (film): 3390, 1690, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.99 (2H, br s, CH_2), 3.52 (2H, t, J=5.5 Hz, CH_2N), 3.76 (1H, s, OH), 3.90 (4H, m, $2CH_2N$), 5.13 (2H, s, OCH_2), 5.37 (1H, br s, =CH), 6.49 (1H, m, NH), 7.3—7.5 (15H, m, aromatic H). MS *m/z*: 183, 105, 91, 77.

A solution of **15** (186 mg) in 25% HBr in AcOH (1.86 ml) was stirred under ice cooling for 30 min and at room temperature for 3 h, and then evaporated *in vacuo*. The residue was partitioned between iso-Pr_2O and water. The aqueous layer was separated, basified with 1 N NaOH, and extracted CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried, and evaporated *in vacuo*, and the residue was chromatographed (CH_2Cl_2–MeOH) over silica gel. The obtained powder was converted to the hydrochloride in a usual manner to afford **3e** (56 mg, 38.3%).

Method G. 2-Hydroxy-2,2-diphenyl-*N*-[(1,2,3,6-tetrahydro-1-isopropyl-4-pyridyl)methyl]acetamide Hydrochloride (3i) A mixture of **3e** (0.70 g), acetone (5 ml), and $NaBH_3CN$ (0.18 g) in MeOH (15 ml) was stirred at room temperature for 4 d and then evaporated *in vacuo*. The residue was partitioned between AcOEt and 1 N NaOH. The organic layer was separated, washed with brine, dried, and evaporated *in vacuo*. The residue was treated with 4 N HCl in AcOEt and crystallized from 1,4-dioxane to afford **3i** (0.58 g) as a powder. Its physical data are listed in Tables I and V.

N-(1-Ethyl-4-piperidyl)-2-hydroxy-2,2-diphenylacetamide fumarate (2 : 1) (**4b**) was also prepared from **4a** and acetaldehyde by method G. Its physical data are listed in Tables I and V.

Method H. 2-Hydroxy-2,2-diphenyl-*N*-(4-piperidylmethyl)acetamide Hydrochloride (4d) **3e** (1.00 g) was catalytically hydrogenated in MeOH at atmospheric pressure at room temperature using 10% Pd on carbon (0.20 g). After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* and the residue was recrystallized from EtOH to afford **4d** (0.35 g). Its physical data are listed in Tables I and V.

Compounds **3** and **4** prepared by methods A—H are listed in Tables I—III and their spectral data are listed in Table V.

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.[12]

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