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Spasmolytic Agents. I.[1] Aminoalcohol Esters having a Phenethylamine-Like Moiety

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A series of semi-rigid analogs of phenethylamine was prepared as fixed transoid and cisoid analogs of mebeverine, and tested for spasmolytic activity *in vitro*. The fixed transoid analogs were more potent than the corresponding cisoid analogs. In this series, tetrahydro-2-napthylamine derivative (**2a**) which is presumed to take transoid conformation had the most potent activity, and tetrahydroisoquinoline derivatives (**2g** and **2h**) which are presumed to take typical cisoid conformations were less active. These results suggested that the phenethylamine moiety of mebeverine takes the transoid conformation for the manifestation of the spasmolytic activity.

Keywords—phenethylamine; transoid conformation; cisoid conformation; spasmolytic activity; mebeverine; 1,2,3,4-tetrahydro-2-naphthylamine; 1,2,3,4-tetrahydroisoquinoline

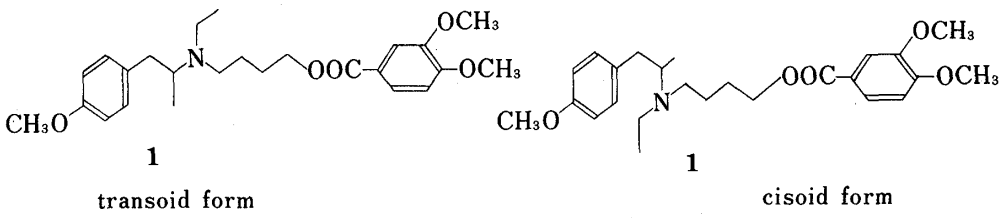
Various compounds having a β-phenethylamine moiety as the essential structure for their biological activities are known. The phenethylamine moiety is flexible and can take a variety of conformations, though some are restricted by a substituent group. Considerable research effort has been made to identify specific conformations which are favorable for interaction with receptor sites.

As part of our continuing search for new musculotropic agents, mebeverine (**1**),[2] a phenethylamine derivative, was selected for study, since **1** exerts a spasmolytic effect on colonic as well as gastric contraction,[3] and **1** has been used for the treatment of irritable colon syndrome.[4] In order to clarify which conformer of **1** exerts the spasmolytic activity, eight compounds (**2a**—**h**) were synthesized and their activities were evaluated. Both **2a** and **2b** take typical transoid conformations with respect to the phenyl ring and the amino group.[5] On the other hand, **2g** and **2h** take typical cisoid conformations, and **2f** takes an approximate cisoid conformation.

The six compounds **2a**—**f** were prepared by methods similar to that used for the synthesis of **1**:[6] acylation of the phenethylamine derivatives (**3a**—**f**) with 3-methoxycarbonylpropionyl chloride (**4**), reduction of the amido ester derivatives (**5a**—**f**) with $LiAlH_4$, and esterification of the butanolamine derivatives (**6a**—**f**) with 3,4-dimethoxybenzoyl chloride.

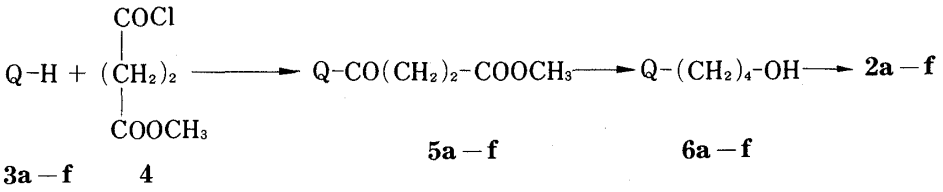
The starting materials **3a**—**f** were prepared by the routes shown in Chart 2. *N*-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine (**3a**), 3-(4-methoxyphenyl)piperidine (**3b**),[7] 2-(4-methoxybenzyl)pyrrolidine (**3c**) and *N*-ethyl-5-methoxy-2-indanylamine (**3e**) were synthesized by means of $LiAlH_4$ reduction of compounds (**8**) [obtained by hydrogenation of (**7**)[8]], (**9**),[9] (**10**),[10] and (**13**) [obtained by acetylation of (**12**)[11]], respectively.

Hydrogenation of compound (**11**)[12] in the presence of Pt[13] gave 2-(4-methoxybenzyl)-piperidine (**3d**). 1,2,4,5-Tetrahydro-7-methoxy-3*H*-3-benzazepine (**3f**)[14] was obtained as follows. Friedel–Crafts cyclization of *N*-[2-(3-methoxyphenyl)ethyl]-*N*-(*p*-toluenesulfonyl)-glycine (**15**)[15] [which was obtained from compound (**14**)[16]] with $AlCl_3$ in CH_2Cl_2 gave 1,2,4,5-tetrahydro-7-methoxy-3-(*p*-toluenesulfonyl)-3*H*-3-benzazepine-1-one (**16**) and its 9-methoxy isomer (**17**) in a ratio of about 1.6: 1. Reaction of **16** with $NaBH_4$ followed by dehydration with *p*-TsOH, hydrogenation over PtO_2, and then detosylation in liq. NH_3 with $NaNH_2$ gave (**3f**) *via* **18**, **19**, and **20**.

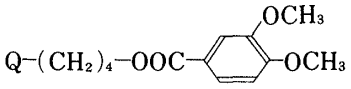


1
transoid form

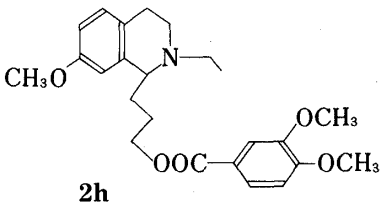
1
cisoid form



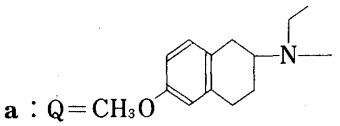
3a—f 4 5a—f 6a—f



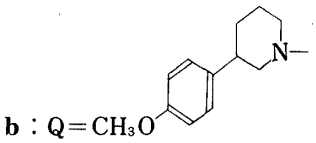
2a—g



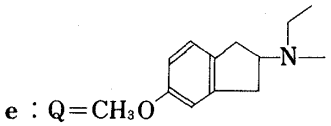
2h



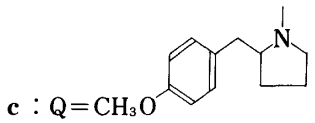
a : Q=CH3O



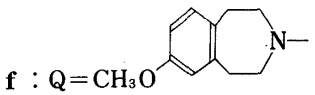
b : Q=CH3O



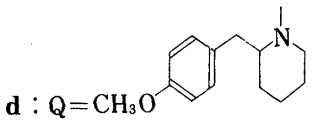
e : Q=CH3O



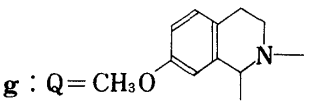
c : Q=CH3O



f : Q=CH3O



d : Q=CH3O



g : Q=CH3O

Chart 1

The intermediates **5a**—**f** and **6a**—**f** did not crystallize, and their structures were confirmed by analysis of their spectral data, which are shown in Table II. They were used for the next steps without further purification.

7-Methoxy-1-methylisoquinoline (**22**)[17] [prepared from Reissert compound (**21**)[18]] was heated with 4-iodobutyl 3,4-dimethoxybenzoate to give the isoquinolinium derivative (**23**). Reduction of **23** with $NaBH_4$ gave 1,2,3,4-tetrahydro-2-[4-(3,4-dimethoxybenzoyloxy)butyl]-7-methoxy-1-methylisoquinoline (**2g**). The compound (**21**) was treated with 3-iodopropyl benzyl ether to give 1-(3-benzyloxypropyl)-7-methoxyisoquinoline (**24**). Ethylation of **24** with ethyl iodide, successive reduction with $NaBH_4$ and hydrogenolysis over Pd-carbon gave 3-(2-ethyl-1,2,3,4-tetrahydro-7-methoxy-1-isoquinolyl)propanol (**6h**). This was acylated in a manner similar to that described above.

Table I shows the spasmolytic activities of **2a**—**h**. The musculotropic spasmolytic activities of **2a**, **2b** and **2d** measured with $BaCl_2$ were superior to that of **1**, and that of **2c** was equal to that of **1** at low concentrations (10^{-6}—10^{-8} g/ml). At a high concentration (10^{-5}

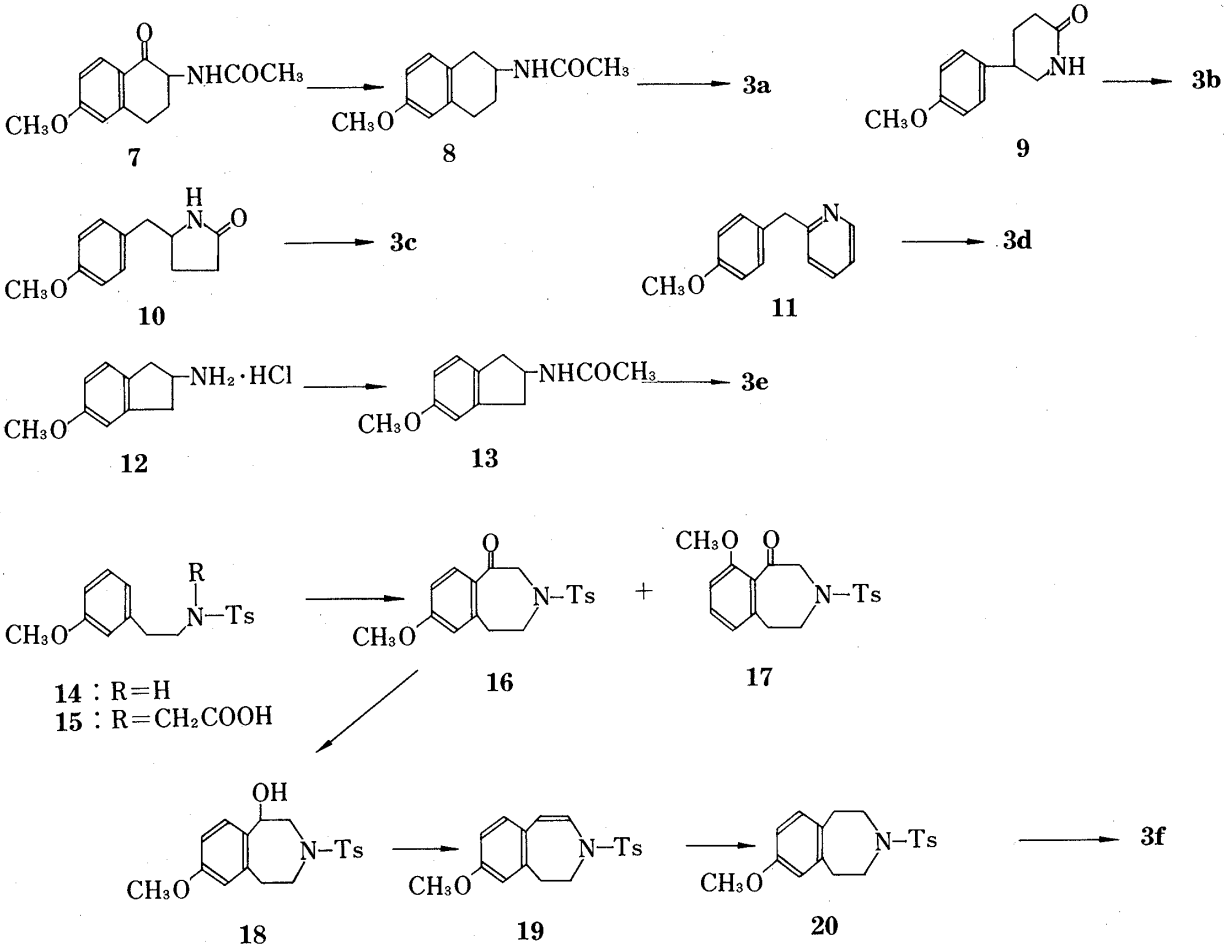


Chart 2

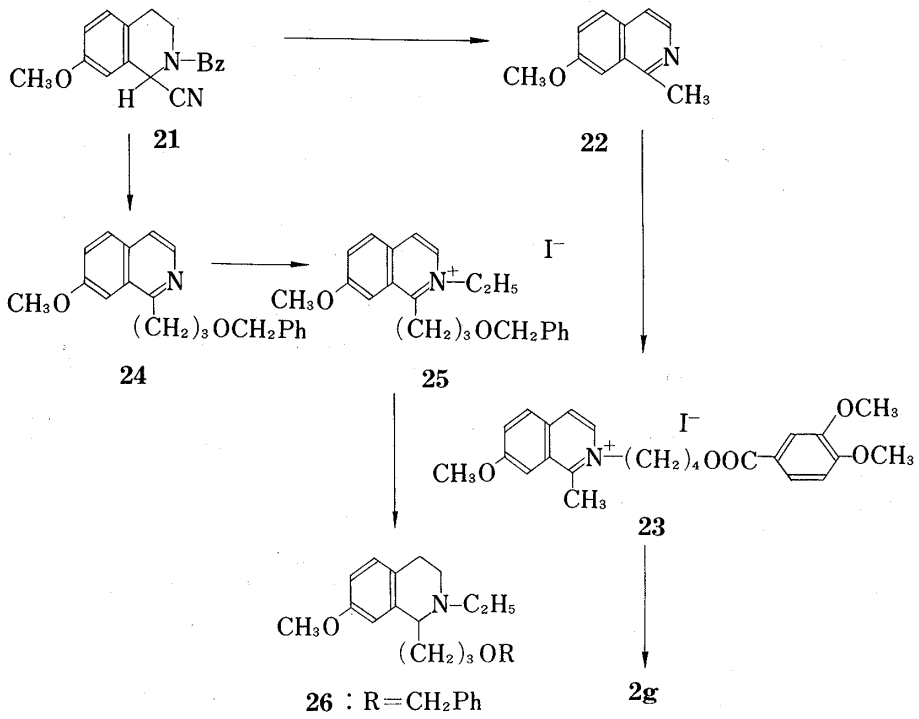


Chart 3

Table I. Spasmolytic Activities of Aminoester Derivatives

Compd. No.	Spasmogen	Inhibition of contraction (%) Concentration (g/ml) 10^{-5}	10^{-6}	10^{-7}	10^{-8}
1	Ach	90—100	50—60	20—30	0
(Mebeverine)	$BaCl_2$	50—60	20—30	0	
2a	Ach	100	70—80	30—40	10—20
	$BaCl_2$	50—60	30—40	10—20	0
2b	Ach	90—100	60—70	20—30	0—10
	$BaCl_2$	40—50	20—30	10—20	0
2c	Ach	80—90	20—30	0	
	$BaCl_2$	50—60	20—30	0	
2d	Ach	100	70—80	20—30	0
	$BaCl_2$	50—60	20—30	10—20	
2e	Ach	100	40—50	20—30	0
	$BaCl_2$	80—90	20—30	0	
2f	Ach	60—70	0		
	$BaCl_2$	10—20	0		
2g	Ach	80—90	30—40	0	
	$BaCl_2$	70—80	10—20	0	
2h	Ach	50—60	20—30	0	
	$BaCl_2$	60—70	0		

g/ml), **2a**—**d** were as potent as **1**, **2f** was less potent and **2f**, **g** and **h** were more potent than **1** against $BaCl_2$-induced contraction. With regard to anticholinergic activity, **2a**, **b**, **d** and **2e** had almost equal potencies and **2c**, **f**, **g** and **h** had lower potencies as compared with **1**. From these results, it is presumed that the phenethylamine moiety of **1** takes a transoid conformation when **1** interacts with the drug receptor site as a spasmolytic agent.

Experimental

The following instruments were used. Melting points, a Yanagimoto MP-1 melting point apparatus; infrared (IR) spectra, a Hitachi 285 spectrometer; nuclear magnetic resonance (NMR) spectra, a Hitachi Perkin-Elmer R-20B spectrometer with tetramethylsilane as an internal standard. All melting points are uncorrected.

General Procedure for Syntheses of 3-Methoxycarbonylpropionyl Derivatives (5)——A solution of **4** (2.86 g, 19 mmol) in benzene (10 ml) was added to an ice-cooled solution of **3** (17 mmol) and triethylamine (2.63 g, 26 mmol) in benzene (30 ml) with stirring. After being stirred for 1 h at room temperature, the solution was refluxed for 2 h, washed with 2 N HCl, 2 N NaOH and H_2O successively, dried over Na_2SO_4, and concentrated *in vacuo* to give **5** as a syrup. The syrup was used for the next step without further purification.

General Procedure for Syntheses of Butanolamine Derivatives (6)——A solution of **5** (15.5 mmol) in tetrahydrofuran (THF) (20 ml) was added to a suspension of $LiAlH_4$ (3.04 g, 80 mmol) in THF (50 ml). After being stirred for 0.5 h at room temperature, the mixture was refluxed for 4 h, and worked up in the usual manner to give **6** as an oil. The oil was used for the next step without further purification. The physical data of **5** and **6** are listed in Table II.

General Procedure for Syntheses of 2——A solution of 3,4-dimethoxybenzoyl chloride (3.81 g, 19 mmol) in benzene (20 ml) was added dropwise to a solution of **6** (14 mmol) and triethylamine (3.04 g, 30 mmol) in benzene (40 ml). After being heated under reflux for 3 h, the reaction mixture was washed with H_2O, 2 N NaOH and H_2O successively, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel (150 g) chromatography. The fraction eluted with benzene–acetone (5 : 1) was concentrated. The residue was dissolved in HCl–MeOH and the solution was concentrated. The residue was recrystallized from a suitable solvent, when it was a solid. The physical data of **2** are listed in Table III.

***N*-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)acetamide (8)**——A solution of **7**[8] (1.0 g, 4 mmol) in AcOH (15 ml) and $HClO_4$ (1.0 ml) was hydrogenated over 15% Pd-C (0.5 g). After the theoretical amount of H_2 had been absorbed, the catalyst was filtered off. The filtrate was treated with AcOK (1.1 g), and the precipitate was filtered off. The filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with H_2O, 2 N NaOH and H_2O successively, dried, and concentrated *in vacuo* to

Table II.

Q–CO–$(CH_2)_2$–$COOCH_3$ **5**

Compd. No.	Yield %	IR ν_{max}^{neat} cm^{-1}	NMR δ ($CDCl_3$)
a	91.3		1.16 (3H, t, J=7), 2.0 (4H, m), 3.0 (6H, m), 3.35 (2H, q, J=7), 3.68 (3H, s), 3.75 (3H, s), 4.0 (1H, m), 6.8 (3H, m).
b	69.4	1730, 1640, 1505, 1430, 1240, 1020	1.0—3.3 (13H, m), 3.69 (3H, s), 3.78 (3H, s), 6.85 (2H, d, J=9), 7.15 (2H, d, J=9).
c	72.0		1.8 (6H, m), 2.6 (6H, m), 3.4 (1H, m), 3.68 (3H, s), 3.75 (3H, s), 6.78 (2H, d, J=9), 7.12 (2H, d, J=9).
d	92.3	1730, 1630, 1500, 1240, 1160, 1020	1.7 (4H, m), 2.2—3.4 (10H, m), 4.1 (1H, m), 3.72 (3H, s), 3.83 (3H, s), 6.83 (2H, d, J=9), 7.15 (2H, d, J=9).
e	97.4	1730, 1640, 1580, 1240, 1020	1.1 (3H, t, J=7), 2.65 (4H, s), 3.0 (5H, m), 3.30 (2H, d, J=7), 3.68 (3H, s), 3.75 (3H, s), 6.6 (1H, dd, J=2, J=9), 6.76 (1H, d, J=2), 7.10 (1H, d, J=9).
f	95.0	1730, 1640, 1600, 1250, 1160	2.5—3.4 (8H, m), 2.70 (4H, s), 3.69 (3H, s), 3.78 (3H, s), 6.70 (2H, m), 7.01 (1H, d, J=8).

Q–$(CH_2)_4$–OH **6**

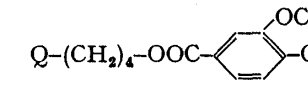
Compd, No.	Yield %	IR ν_{max}^{neat} cm^{-1}	NMR δ ($CDCl_3$)
a	85.8	3350, 1600, 1490, 1260, 1230, 1030	1.09 (3H, t, J=7), 1.3—2.2 (6H, m), 2.3—3.2 (9H, m), 3.55 (2H, m), 3.74 (3H, s), 5.25 (1H, br), 6.5—7.1 (3H, m).
b	81.2	3350, 1600, 1500, 1240, 1170, 1020	1.4—2.2 (10H, m), 2.2—2.6 (2H, m), 2.6—3.3 (3H, m), 3.4—3.7 (2H, m), 3.78 (3H, s), 5.7 (1H, br), 6.84 (2H, d, J=9), 7.15 (2H, d, J=9).
c	65.5		1.2—2.1 (6H, m), 2.1—3.4 (9H, m), 3.61 (2H, m), 3.77 (3H, s), 5.0 (1H, br), 6.80 (2H, d, J=9), 7.11 (2H, d, J=9).
d	84.3	3350, 1605, 1505, 1240, 1170, 1030	1.0—2.0 (8H, m), 2.1—3.2 (5H, m), 3.55 (2H, m), 3.76 (3H, s), 6.2 (1H, br), 6.78 (2H, d, J=9), 7.07 (2H, d, J=9).
e	70.6	3380, 1610, 1580, 1490, 1290, 1240, 1140	1.06 (3H, t, J=7), 1.7 (4H, m), 3.1 (7H, m), 3.6 (2H, m), 3.85 (3H, s), 5.2 (1H, br), 6.63 (1H, d, J=2), 6.65 (1H, dd, J=9, J=2), 7.08 (1H, d, J=9).
f	95.0	1600, 1500, 1025	1.45—1.95 (4H, m), 2.25—3.15 (10H, m), 3.50—3.75 (2H, m), 3.77 (3H, s), 4.80—5.70 (1H, br), 6.68 (2H, m), 6.99 (1H, d, J=8).

give **8** as pale yellow prisms, mp 112°C (0.9 g, 95.7%). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.97; H, 7.91; N, 6.60. IR ν_{max}^{KBr} cm^{-1}: 3300, 2930, 1630, 1500, 1260, 1240, 1030, 790. NMR ($CDCl_3$) δ: 1.5—2.0 (2H, m, C3–H), 1.95 (3H, s, CH_3CO–), 2.5—3.0 (4H, m, C1–H, C4–H), 3.75 (3H, s, OMe), 4.21 (1H, m, C2–H), 6.0 (1H, broad s, –NHCO–), 6.5—7.5 (3H, m, aromatic H).

***N*-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine Hydrochloride (3a)·HCl**——A solution of **8** (11.6 g, 53 mmol) in THF (100 ml) was added dropwise to a suspension of $LiAlH_4$ (5.3 g, 0.14 mmol) in THF (200 ml). After being heated under reflux for 4 h, the mixture was treated in the usual manner to give **3a** as a pale red oil (10.6 g, 97.6%). NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz, $-NCH_2\underline{C}H_3$), 1.22 (1H, s, –NH–), 1.5—3.2 (9H, m, C2–H, methylene-H), 3.72 (3H, s, OMe), 6.60—6.68 (3H, m, aromatic H).

This oil was treated with HCl–MeOH and the mixture was concentrated to dryness *in vacuo*. Recrystallization of the residue from EtOH–Et_2O gave **3a**·HCl as colorless needles, mp 231—231.5°C. *Anal.* Calcd for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.34; Cl, 14.67; N, 5.79. Found: C, 64.62; H, 8.55; Cl, 14.44; N, 6.04. IR ν_{max}^{KBr} cm^{-1}: 2940, 2880, 2460, 1605, 1580, 1500, 1300, 1270, 1015, 800.

TABLE III.



Compd. No.	HX	Yield (%)	mp (°C) (Recryst. solvent)	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N	Cl	S
a	HCl	41.8	134—135 (MEK–Et_2O)	Prisms	$C_{26}H_{35}NO_5\cdot HCl$	65.34 (65.84	7.59 7.46	2.93 2.97)		
b	*p*-TsOH	63.1	118 (EtOH–Et_2O)	Powder	$C_{25}H_{33}NO_5\cdot C_7H_8O_3S$	64.08 (63.79	6.89 6.97	2.34 2.55		5.35 5.56)
	MsOH			Syrup	$C_{25}H_{33}NO_5\cdot CH_4O_3S$	59.64 (59.22	7.12 7.02	2.68 2.77)		
c		77.8		Syrup	$C_{25}H_{33}NO_5$	70.23 (70.26	7.78 7.47	3.28 2.93)		
d	HCl	58.0		Syrup	$C_{26}H_{35}NO_5\cdot HCl$	65.33 (64.90	7.59 7.49	2.93 2.87)		
e	HCl	42.6		Syrup	$C_{25}H_{33}NO_5\cdot HCl$	64.71 (64.53	7.39 7.22	3.02 2.99)		
f	HCl	20.6	167—168 (Me_2CO)	Prisms	$C_{24}H_{31}NO_5\cdot HCl$	64.06 (64.14	7.17 7.47	3.11 2.98	7.88 7.68)	
g	HCl	60.7		Syrup	$C_{24}H_{31}NO_5\cdot HCl$	64.06 (64.46	7.17 7.33	3.11 2.77)		
h	HCl	79.2	184—185 (MEK–EtOH–Et_2O)	Needles	$C_{24}H_{31}NO_5\cdot HCl$	64.06 (63.51	7.17 7.22	3.11 3.23	7.88 7.75)	

3-(4-Methoxyphenyl)piperidine (3b)——Reduction of **9**[9] was achieved by the same method as described for the syntheses of **6** to give **3b** as a pale yellow oil (98%). NMR ($CDCl_3$) δ: 1.3—2.2, 2.4—3.4 (9H, m), 2.11 (1H, s), 3.79 (3H, s, OMe), 6.84 (2H, d, J=9 Hz), 7.16 (2H, d, J=9 Hz). Its hydrochloride was obtained in the usual manner: mp 143—145°C (reported[11] mp 145°C).

2-(4-Methoxybenzyl)pyrrolidine (3c)——Similarly, **3c** was obtained by the reduction of **10**[10] as a pale red oil (99%). IR ν_{max}^{neat} cm^{-1}: 2940, 1600, 1500, 1240, 1170, 1020. NMR ($CDCl_3$) δ: 1.3—2.0 (4H, m), 2.4 (1H, broad, –NH), 2.5—3.1 (4H, m), 3.6 (1H, m), 3.78 (3H, s, OMe), 6.84 (2H, d, J=9 Hz), 7.15 (2H, d, J=9 Hz).

2-(4-Methoxybenzyl)piperidine (3d)——A solution of **11**[12] (3 g, 15 mmol) in AcOH (25 ml) was hydrogenated over PtO_2 (0.45 g). After the theoretical amount of H_2 had been absorbed, the catalyst was filtered off. The filtrate was made basic with 2 N NaOH and extracted with benzene. The extract was washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to give **3d** as a colorless oil (2.7 g, 87.4%). IR ν_{max}^{neat} cm^{-1}: 2920, 2850, 1610, 1580, 1510, 1440, 1300, 1240, 1170, 1030, 740. NMR ($CDCl_3$) δ: 1.00—1.93 (7H, m), 2.53—3.13 (5H, m), 3.73 (3H, s, OMe), 6.78 (2H, d, J=9 Hz), 7.09 (2H, d, J=9 Hz).

***N*-(5-Methoxy-2-indanyl)acetamide (13)**——Acetic anhydride (8 ml) was added to a solution of **12**[11] (2.3 g, 14 mmol) in AcOH (5 ml) and H_2O (5 ml). After standing at room temperature for 80 min, the mixture was concentrated *in vacuo*. The residue was crystallized from Et_2O to give white prisms, mp 100—102°C (1.82 g, 62.9%), which were collected and used for the next step without further purification. IR ν_{max}^{KBr} cm^{-1}: 3300, 3100, 3000, 2840, 1640, 1550, 1490, 1370, 1250, 1030, 870, 790, 600. NMR ($CDCl_3$) δ: 1.90 (3H, s, $-NHCOCH_3$), 2.8 (2H, m), 3.2 (2H, m), 3.76 (3H, s, OMe), 4.6 (1H, m, C2–H), 6.2 (1H, broad, NH), 6.7—7.2 (3H, m).

***N*-Ethyl-5-methoxy-2-indanylamine Hydrochloride (3e)·HCl**——Compound **3e**·HCl was prepared from **13** by a method similar to that described for the synthesis of **6** as colorless prisms (60.1%), mp 190—194°C. *Anal.* Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.96; N, 6.15. Found: C, 63.02; H, 8.13; N, 6.19. IR ν_{max}^{KBr} cm^{-1}: 2950, 1610, 1490, 1300, 1250. NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7 Hz, $NCH_2\underline{CH_3}$), 1.70 (1H, broad, NH), 2.4—3.2 (5H, m), 3.60 (2H, q, J=7 Hz, $-NH\underline{CH_2}CH_3$), 3.77 (3H, s, OMe), 6.7—7.2 (3H, m, aromatic H).

***N*-[2-(3-Methoxyphenyl)ethyl]-*N*-(*p*-toluenesulfonyl)glycine (15)**——Ethyl bromoacetate (74.0 g, 0.44 mol) was added to a refluxing solution of **14**[16] (88.6 g, 0.29 mol) and K_2CO_3 (276 g, 2.0 mol) in acetone (1.5 l), and the mixture was refluxed for 20 h. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in a solution of NaOH (52 g, 1.3 mol) in 50% EtOH (1.0 l). After the mixture had been refluxed for 5 h, EtOH was evaporated off *in vacuo*. The residue was diluted with H_2O (1.0 l). After extraction with ether, the aqueous solution was made acidic with conc. HCl and extracted with ether. The latter extract was shaken with 5% $NaHCO_3$. The aqueous extract was made acidic with conc. HCl, and reextracted with ether. Removal of the ether gave crude **15**, mp 81—86°C (102 g, 97%).

Recrystallization from benzene–hexane gave **15** as colorless needles, mp 96—97.5°C. *Anal.* Calcd for $C_{18}H_{21}NO_5S$: C, 59.48; H, 5.83; N, 3.86; S, 8.82. Found: C, 59.41; H, 5.85; N, 3.91; S, 8.74. IR ν_{max}^{KBr} cm^{-1}: 1710, 1350, 1250, 1150. NMR ($CDCl_3$) δ: 2.39 (3H, s, Me), 2.61—3.02 (2H, m), 3.22—3.64 (2H, m), 3.76 (3H, s, OMe), 4.00 (2H, s), 6.60—7.88 (8H, m), 10.73 (1H, s, -COOH).

Cyclization of 15——A mixture of **15** (94.5 g, 0.26 mol) and $SOCl_2$ (60 g, 0.50 mol) in benzene (300 ml) was heated under reflux for 8 h, then concentrated *in vacuo*. A solution of the residue in CH_2Cl_2 (300 ml) was added dropwise to a suspension of $AlCl_3$ (43.0 g, 0.32 mol) in CH_2Cl_2 (800 ml) at −65°C with stirring over a 3 h period. After being stirred at −65°C for a further 5 h and then at room temperature for 12 h. the mixture was poured into a solution of conc. HCl (200 ml) and ice-water (2 l). The whole was stirred for 2 h, then the organic layer was separated, washed with H_2O, 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with benzene–acetone (99: 1) gave **16** as colorless needles (37.0 g, 42%), mp 169—170°C. *Anal.* Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.96; H, 5.67; N, 3.97; S, 9.54. IR ν_{max}^{KBr} cm^{-1}: 1670, 1600, 1360, 1270, 1160. NMR ($CDCl_3$) δ: 2.36 (3H, s, Me), 2.91 (2H, t, J=7 Hz), 3.62 (2H, t, J=7 Hz), 3.81 (3H, s, OMe), 4.17 (2H, s, C2–H), 6.61 (1H, d, J=2.5 Hz, C6–H), 6.72 (2H, dd, J=2.5 and 8 Hz, C8–H), 7.44 (1H, d, J=8 Hz, C9–H), 7.10 (2H, d, J=8 Hz), 7.41 (2H, d, J=8 Hz). Further elution gave **17** as a pale yellow oil (23 g, 26%). NMR ($CDCl_3$) δ: 2.37 (3H, s, Me), 3.52 (2H, t, J=6.5 Hz), 3.73 (3H, s, OMe), 4.08 (2H, s, C2–H), 6.50—6.90 (2H, m), 6.90—7.85 (5H, m).

1,2,4,5-Tetrahydro-7-methoxy-3-(*p*-toluenesulfonyl)-3*H*-3-benzazepin-1-ol (18)——$NaBH_4$ (5.3 g, 140 mmol) was added portionwise to a suspension of **16** (24.2 g, 70 mmol) in MeOH (350 ml) with stirring. The mixture was stirred for 1 h at room temperature, refluxed for 0.5 h, and concentrated *in vacuo*. The residue was diluted with H_2O (200 ml), and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The residue was treated with ether, and solidified by scratching. Recrystallization from ether gave **18** as colorless needles, mp 97—99°C (16.5 g, 68%). *Anal.* Calcd for $C_{18}H_{21}NO_4S$: C, 62.22; H, 6.09; N, 4.03; S, 9.23. Found: C, 62.51; H, 6.44; N, 3.74; S, 9.08. IR ν_{max}^{KBr} cm^{-1}: 3400, 1610, 1490, 1300, 1250, 1150. NMR ($CDCl_3$) δ: 2.40 (3H, s, Me), 2.65—3.70 (6H, m), 3.76 (3H, s, OMe), 4.83 (1H, m, C1–H), 6.64 (2H, m), 7.29 (3H, d, J=8 Hz), 7.64 (2H, d, J=8 Hz).

1,2-Dihydro-8-methoxy-3-(*p*-toluenesulfonyl)-3*H*-3-benzazepine (19)——A solution of **18** (14.0 g, 40 mmol) and *p*-TsOH (50 mg) in benzene (150 ml) was refluxed for 2 h. The H_2O formed during the reaction was absorbed with molecular sieves in a Soxhlet apparatus. The mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with benzene to give **19** as colorless prisms, (9.5 g, 72%), mp 116—117°C. *Anal.* Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found: C, 65.80; H, 6.07; N, 4.38; S, 9.67. IR ν_{max}^{KBr} cm^{-1}: 1640, 1600, 1490, 1350, 1150. NMR ($CDCl_3$) δ: 2.38 (3H, s, Me), 2.25—2.95 (4H, m), 3.73 (3H, s, OMe), 5.63 (1H, d, J=11 Hz), 6.45—7.15 (4H, m), 7.31 (2H, d, J=8 Hz), 7.70 (2H, d, J=8 Hz).

1,2,4,5-Tetrahydro-7-methoxy-3-(*p*-toluenesulfonyl)-3*H*-3-benzazepine (20)——A solution of **19** (7.5 g, 23 mmol) in AcOH (250 ml) was hydrogenated over PtO_2 (0.25 g). After the theoretical amount of H_2 had been absorbed, the catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from MeOH to give **20** as colorless scales, (7.0 g, 92%), mp 129—130°C. *Anal.* Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; S, 9.67. Found: C, 65.28; H, 6.59; N, 4.44; S, 9.67. IR ν_{max}^{KBr} cm^{-1}: 1610, 1490, 1330, 1250, 1150. NMR ($CDCl_3$) δ: 2.39 (3H, s, Me), 2.75—3.50 (8H, m), 3.75 (3H, s, OMe), 6.66 (2H, m), 6.97 (1H, d, J=8 Hz), 7.28 (2H, d, J=8 Hz), 7.63 (2H, d, J=8 Hz).

1,2,4,5-Tetrahydro-7-methoxy-3*H*-3-benzazepine (3f)——Sodium (1.0 g, 0.043 g atom) was added portionwise to a solution of **20** (6.6 g, 20 mol) in liq. NH_3 (200 ml) with stirring. After being stirred for 0.5 h, the reaction mixture was treated with NH_4Cl (10 g), and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and concentrated *in vacuo* to give **3f** as a pale yellow oil (3.3 g, 92%). NMR ($CDCl_3$) δ: 2.08 (1H, br, -NH), 2.88 (8H, m), 3.74 (3H, s, OMe), 6.66 (2H, m), 6.97 (1H, d, J=8 Hz).

Treatment of this oil with HCl–MeOH gave pale yellow needles, mp 231—233°C (reported[15] mp 231—234°C). *Anal.* Calcd for $C_{11}H_{16}ClNO$: C, 61.82; H, 7.55; Cl, 16.59; N, 6.56. Found: C, 61.37; H, 7.85; Cl, 16.45; N, 6.71. IR ν_{max}^{KBr} cm^{-1}: 1580, 1490, 1260.

7-Methoxy-1-methylisoquinoline (22)——A mixture of **21**[18] (10 g, 34 mmol) and MeI (10 g, 70 mmol) in DMF (60 ml) was treated with 50% NaH (2.2 g, 46 mmol) under an N_2 atmosphere with ice-cooling. The whole was stirred for 4 h at room temperature, then a small volume of EtOH was added to decompose excess NaH, and the mixture was extracted with benzene. The extract was washed with water, dried and concentrated *in vacuo*. A mixture of KOH (30 g, 0.53 mol), H_2O (40 ml) and EtOH (300 ml) was added to this residue, and the mixture was refluxed for 3.5 h. The mixture was concentrated *in vacuo*, and the residue was extracted with benzene. The organic layer was extracted with 10% HCl. This aqueous layer was made basic with 2 N NaOH and reextracted with benzene. This extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **22** as colorless prisms, mp 32—34°C (reported[17] mp 32—34°C) (4.4 g, 73.5%). NMR ($CDCl_3$) δ: 2.90 (3H, s, Me), 3.92 (3H, s, OMe), 7.2—8.2 (5H, m).

7-Methoxy-1-methyl-2-[4-(3,4-dimethoxybenzoyloxy)butyl]isoquinolinium Iodide (23)——A mixture of **22** (2.1 g, 12 mmol) and 4-iodobutyl 3,4-dimethoxybenzoate (10.1 g, 28 mmol) was heated at 100°C for 3.5 h, then cooled. Ether was added to the mixture, and the precipitate was collected. Recrystallization from

EtOH–ether gave **23** as pale yellow prisms, mp 218—220°C (dec.). *Anal.* Calcd for $C_{23}H_{28}INO_5$: C, 53.64; H, 5.25; N, 2.61. Found: C, 53.34; H, 5.46; N, 2.73. IR ν_{max}^{KBr} cm^{-1}: 3000, 2930, 1700, 1590, 1500, 1450, 1410, 1260, 1010, 760.

1,2,3,4-Tetrahydro-7-methoxy-1-methyl-2-[4-(3,4-dimethoxybenzoyloxy)butyl]isoquinoline Hydrochloride (2g)·HCl——$NaBH_4$ (5.5 g, 0.14 mol) was added portionwise to a suspension of **23** (6.1 g, 11 mmol) in 85% aqueous MeOH (250 ml) at room temperature. After being stirred for 2 h, the mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (100 g), eluting with benzene–acetone (5: 1) to give a colorless oil. Treatment of this oil with HCl–MeOH gave **2g**·HCl (3.1 g, 60.7%). Physical date are listed in Table II.

1-(3-Benzyloxypropyl)-7-methoxyisoquinoline (24)——An ice-cooled solution of **21**[17] (11.5 g, 39.5 mmol) and 3-benzyloxypropyl iodide (19 g, 69 mmol) in DMF (100 ml) was treated with 50% NaH (2.8 g, 0.57 mol) under an N_2 atmosphere. After being stirred for 4.5 h, the mixture was worked up as described above for the preparation of **22** to give **24** as a pale yellow oil (11.2 g, 92.0%). NMR ($CDCl_3$) δ: 2.3 (2H, m), 3.41 (2H, t, J=6 Hz), 3.67 (2H, t, J=6 Hz), 3.85 (3H, s, OMe), 4.56 (2H, s, Ph–CH_2O–), 7.2—7.5 (8H, m), 7.74 (1H, d, J=8.5 Hz), 8.36 (1H, d, J=6 Hz).

1-(3-Benzyloxypropyl)-2-ethyl-7-methoxyisoquinolinium Iodide (25)——A mixture of **24** (10.5 g, 34 mmol) and EtI (120 ml, 1.5 mol) was heated at 100°C for 4.5 h in a sealed tube. The reaction mixture was treated with EtOH, and the precipitate was recrystallized from EtOH–ether to give **25** as pale yellow needles, mp 119—120°C (15.2 g, 96.0%). *Anal.* Calcd for $C_{22}H_{26}INO_2$: C, 57.03; H, 5.66; N, 3.02. Found: C, 56.97; H, 5.79; N, 3.05. IR ν_{max}^{KBr} cm^{-1}: 3440, 1615, 1430, 1340, 1100, 860, 740. NMR ($CDCl_3$) δ: 1.72 (3H, t, J= 7.5 Hz, $N^+-CH_2CH_3$), 2.0—2.6 (2H, m), 3.78 (3H, s, OMe), 3.8—4.1 (4H, m), 4.58 (2H, s, Ph–CH_2–O–), 5.10 (2H, q, J=7.5 Hz, $N^+-CH_2CH_3$), 7.38 (5H, s), 7.68 (1H, d, J=9 Hz), 7.76 (1H, s), 8.12 (1H, d, J=9 Hz), 8.26 (1H, d, J=6 Hz), 8.90 (1H, d, J=6 Hz).

1-(3-Benzyloxypropyl)-2-ethyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline (26)——The reduction of **25** (12 g, 26 mmol) with $NaBH_4$ (10 g, 0.26 mol) was achieved by the same procedure as described for the synthesis of **2g** to give **26** as a colorless oil (8.1 g, 92.1%), NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7.5 Hz, NCH_2CH_3), 1.5—2.0 (4H, m), 2.3—3.2 (6H, m), 3.4—3.7 (3H, t), 3.70 (3H, s, OMe), 4.45 (2H, s, Ph–CH_2–O–), 6.55—7.1 (3H, m), 7.25 (5H, s).

3-(2-Ethyl-1,2,3,4-tetrahydro-7-methoxy-1-isoquinolyl)propanol (6h)——A mixture of **26** (8.0 g, 23 mmol), 25% Pd-C (3 g) and 10% HCl (12 ml) in EtOH (100 ml) was hydrogenated. After the theoretical amount of H_2 had been absorbed, the catalyst was filtered off. The filtrate was concentrated *in vacuo*. The residue was made alkaline with 2 N NaOH, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give **6h** as a colorless oil (5.41 g, 92.1%). IR ν_{max}^{KBr} cm^{-1}: 3350, 2900, 1605, 1490, 1260, 1230, 1030. NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz, NCH_2CH_3), 1.5—2.2 (4H, m), 2.5—3.4 (7H, m), 3.6 (3H, m), 3.78 (3H, s, OMe), 6.62 (1H, d, J=2 Hz), 6.73 (1H, dd, J=8.5, 2 Hz), 7.40 (1H, d, J=8.5 Hz).

Spasmolytic Activity——A segment of the ileum, 2 to 3 cm in length, was removed from a guinea pig and suspended in a 50 ml bath containing Tyrode solution of the following composition: NaCl, 8.0; KCl, 0.2; $CaCl_2$, 0.2; $MgCl_2$, 0.1; NaH_2PO_4, 0.05; $NaHCO_3$, 1.0; and glucose, 1.0 (in g/l of distilled water). The solution was bubbled through with air and maintained at 37°C. A drug was applied to the bath 30 sec before the addition of acetylcholine and $BaCl_2$ at final concentrations of 10^{-8} and 10^{-4} g/l, respectively. The longitudinal muscle contraction was monitored isotonically on a recorder by means of a force displacement transducer (Model ME-4031). Percent reduction of the contraction by a drug was regarded as percent inhibition.

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References and Notes

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2) A. Lindner, V. Classen, T.W.J. Hendriksen, and T. Kralt, *J. Med. Chem.*, **6**, 97 (1693).
3) A. Kasahara, A. Akashi, T. Hashizume, K. Yamaguchi, Y. Shiraishi, and Y. Oshima, *Nippon Yakurigaku Zasshi*, **64**, 589 (1968).
4) C.V. Perrier and L. Sitavanc, *Helv. Med. Acta*, **36**, 123 (1972).
5) P.H. Volkamn, J.D. Kohli, L.J. Goldberg, J.G. Cannon, and T. Lee, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 3602 (1977).
6) T. Kralt, H.D. Moed, A. Lindner, and W.J. Asma, Ger. Patent 1126889 (1962) [*C. A.*, **58**, 4525(1963)].
7) A.V. El'tsov, A.G. Chigarev, and N.T. Starykh, *Biol. Aktivn. Soedin., Akad. Nauk SSR*, **1965**, 109 [*C.A.*, **63**, 16299 (1965)].
8) T. Chiemprast, H.J. Rimek, and F. Zymalkowski, *Ann.*, **685**, 141 (1965).

9) M. Julia, O. Siffert, and J. Bagot, *Bull. Soc. Chim. Fr.*, **1968**, 1000.
10) K. Yamada, Y. Togawa, T. Kato, and Y. Hirata, *Tetrahedron*, **27**, 5445 (1971).
11) H. Richter and M. Schenk, Ger. Patent, 952441 (1956) [*C. A.*, **53**, 2190(1959)].
12) H. Sperber, D. Papa, E. Schwenk, and M. Sherlock, *J. Am. Chem. Soc.*, **73**, 3856 (1951).
13) R.J. Wolters, A.J. Bej, and N.S. Tanner, *J. Pharm. Sci.*, **63**, 1379 (1974).
14) *a*) B. Pecherer, R.C. Sunburg, and A. Brossi, *J. Heterocycl. Chem.*, **8**, 779 (1971); *b*) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Am. Chem. Soc.*, **90**, 776 (1968).
15) B.V. Shetty and T.A. Davidson, Ger. Patent Offen, 1934150 (1970) [*C. A.*, **72**, 90331(1970)].
16) K. Ito and H. Tanaka, *Chem. Pharm. Bull.*, **25**, 1732 (1977).
17) E. Schlittler and J. Müller, *Helv. Chim. Acta*, **31**, 914 (1949).
18) R.M. Coomes, J.R. Falck, D.D. Williams, and F.R. Stermitz, *J. Org. Chem.*, **38**, 3701 (1973).