Spasmolytic Agents. 2.[1] 1,2,3,4-Tetrahydro-2-naphthylamine Derivatives

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N-[(Benzoyloxy)alkyl]-1,2,3,4-tetrahydro-2-naphthylamine derivatives were synthesized from 1,2,3,4-tetrahydro-2-naphthylamines and evaluated for their spasmolytic activity. Some of these compounds showed a nerve-selective effect on colon rather than stomach in anesthetized dogs and were found to be equal to or more active than the reference drug (mebeverine). The biological data have indicated some structure–activity relationships. Among these compounds, *N*-ethyl-*N*-[6-[(3,4-dimethoxybenzoyl)oxy]hexyl]-1,2,3,4-tetrahydro-6-methoxy-2-napththylamine hydrochloride (**63**) was found to be the most active spasmolytic agent.

A number of phenethylamine derivatives have various biological activities. Mebeverine,[2] which possesses a phenethylamine moiety, affects the colonic motility as well as the gastric motility and has been used for the treatment of irritable colon syndrome. It has been reported in the previous paper[1] that the phenethylamine moiety of mebeverine is presumed to take a transoid conformation, since *N*-ethyl-*N*-[4-[(3,4-dimethoxybenzoyl)oxy]butyl]-1,2,3,4-tetrahydro-2-naphthylamine, which is presumed to take a typical transoid conformation, shows more potent spasmolytic activity than 2-[4-[(3,4-dimethoxybenzoyl)-oxy]butyl]-1-methyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline which is presumed to take the typical cisoid comformation.

This paper deals with the synthesis and screening of a series of 1,2,3,4-tetrahydro-2-naphthylamine derivatives.

Chemistry. A large number of 1,2,3,4-tetrahydro-2-naphthylamine derivatives were prepared according to Scheme I.

Most of 2-tetralones, intermediates of 1,2,3,4-tetrahydro-2-naphtylamines (III), were prepared by the methods described in the literature.[3] New compounds, **1** and **2** (II, R^1 = 6-EtO and 6-*n*-PrO), were synthesized from phenylacetic acid derivatives (I) by Friedel–Crafts reaction. Similar reaction of compound **3** gave a mixture of compounds **4** (I, R^1 = 6,7-MeO) and **5**, which was used for the next ethylamination without separation to yield a mixture of **6** and **16** (Scheme II). The mixture was separated by chromatography on alumina.

The reductive amination of 2-tetralones was carried out according to the procedure described by Ames et al.[4] to yield 1,2,3,4-tetrahydro-2-naphthylamines (method A). PtO_2 and Raney Ni were used as the catalyst, and the reaction was carried out at atmospheric and elevated pressure, respectively.

N-Ethyl-1,2,3,4-tetrahydro-5,8-dimethoxy-2-naphthylamine (**21**) was prepared from *N*-acetyl-1,2,3,4-tetrahydro-5,8-dimethoxy-2-naphthylamine (**20**) by reduction with $LiAlH_4$. The compounds III are listed in Table I.

The compounds III were acylated with ω-(alkoxycarbonyl)alkylcarbonyl chlorides to give compounds IV, and the reduction of IV with $LiAlH_4$ gave *N*-(ω-hydroxyalkyl)-1,2,3,4-tetrahydro-2-naphthylamines (V) (method B). Treatment of V with benzoyl chloride (method C) gave the desired compounds VI which are listed in Table II.

Some of the compounds VI were also prepared from III by direct alkylation. This reaction was carried out by heating of III with ω-(benzoyloxy)alkyl chloride, sodium iodide, and sodium carbonate in methyl ethyl ketone (method D1). When ω-(benzoyloxy)alkyl iodide was used in this reaction, sodium iodide was omitted (method D2). These results are also listed in Table II.

Compound **57** was prepared by catalytic hydrogenation of its benzyl ether derivatives **56**. Compound **83** was prepared from compound **79** by the route described in Scheme III.

Pharmacology and Structure–Activity Relationships. The spasmolytic activity of 1,2,3,4-tetrahydro-2-naphthylamine derivatives was evaluated by measuring the effects on colonic contraction induced by pelvic nerve stimulation and on gastric contraction induced by vagas nerve stimulation in anesthetized dog. These results are listed in Table III.

The above biological data indicated that a series of 1,2,3,4-tetrahydro-2-naphthylamine derivatives has a spasmolytic effect on colonic contraction. In various series of 1,2,3,4-tetrahydro-2-naphthylamines, no well-defined relationships between structures and activities were obtained. However, these biological data indicate some relationships, as noted below.

A. Effects of the Alkyl Group (R^2) on Nitrogen. This alkyl group needs no less than two carbon atoms for activity. The spasmolytic activity of **44** was significantly decreased in comparison with **54**.

B. Effects of the Alkylene Side Chain. The spasmolytic activity and its selectivity for colonic motility increase with an increase of the number of carbon atoms in the side chain. The most effective number of carbon atoms may be in the vicinity of six. (Compare **63**, **54**, **46**, and **45**.)

C. Effects of the Ester Moiety. A number of 3,4-dimethoxybenzoic acid ester derivatives have intensive activities; however, the activities of non-3,4-dimethoxybenzoate esters are significantly decreased. When 3,4-dimethoxybenzoate esters were hydrolyzed to alcohols, their activities were decreased. (Compare **33** and **37** with **54** and **63**, respectively.) Furthermore, replacement of the benzoyloxy moiety by the benzyloxy moiety results in almost complete loss of activity. (Compare **83** with **54**.) These results suggest that the 3,4-dimethoxybenzoyloxy moiety is essential to the appearance of the activity.

Some of these compounds have intensive spasmolytic activity for colonic motility. However, compounds (**71**, **75**, and **76**) having a methoxy group at the C-7 position of the

(1) For part 1 in this series, see Kanao, M.; Hashizume, T.; Ichikawa, Y.; Irie, K.; Satoh, Y.; Isoda, S. *Chem. Pharm. Bull.* **1982**, *30*, 180.
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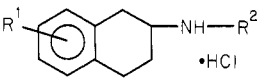
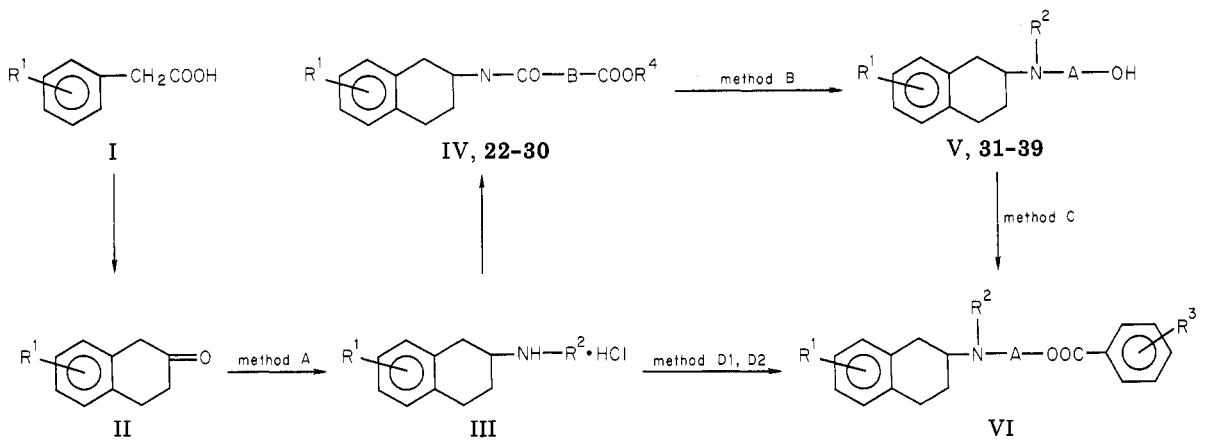
Table I. 1,2,3,4-Tetrahydro-2-naphthylamines III



compd	R^1	R^2	method	catalyst[a]	yield, %	mp, °C	formula[b]
7	H	Et	A	Ni	43.6	230-231	*c*
8	5-MeO	Et	A	Pt	61.9	255-256	*d*
9	6-MeO	Me	A	Pt	51.6	172-174	*e*
10	6-MeO	Et	A	Pt	86.5	230	$C_{13}H_{19}NO\cdot HCl$
11	6-MeO	*n*-Pr	A	Pt	82.7	249-251	$C_{14}H_{21}NO\cdot HCl$[f]
12	6-MeO	*i*-Pr	A	Pt	47.9	184-186	$C_{14}H_{21}NO\cdot HCl$
13	6-MeO	cyclohexyl	A	Pt	21.0	252-254	$C_{17}H_{25}NO\cdot HCl$
14	6-MeO	Et	A	Pt	10.1[g]	207-209	$C_{14}H_{21}NO\cdot HCl$
15	6-*n*-PrO	Et	A	Pt	8.3[g]	217-218	$C_{15}H_{23}NO\cdot HCl$[h]
16	6,7-$(MeO)_2$	Et	A	Pt	15.6	246-248	$C_{14}H_{21}NO_2\cdot HCl$
17	6,7-OCH_2O	Et	A	Pt	34.6	269.5-271	$C_{13}H_{17}NO_2\cdot HCl$[i]
18	7-MeO	Et	A	Pt	62.9	217-219	$C_{13}H_{19}NO\cdot HCl$
19	8-MeO	Et	A	Pt	60.5	237-238	*j*
21	5,8-$(MeO)_2$	Et			63.0	240-242	$C_{14}H_{21}NO_2\cdot HCl$[k]

[a] Pt/PtO_2 (Adams' catalyst), Ni/Raney Ni catalyst. [b] New compounds were analyzed for C, H and N, and analytical results obtained for these elements were within ±0.4% of the theoretical values unless otherwise noted. [c] See ref 5. [d] See ref 3a. [e] See ref 6. [f] C: calcd, 65.74; found, 66.25. [g] Calculated from acid I. [h] C: calcd, 66.77; found, 67.81. [i] C: calcd, 61.87; found, 61.46. [j] See ref 4. [k] C: calcd, 61.87; found, 61.28.

Scheme I



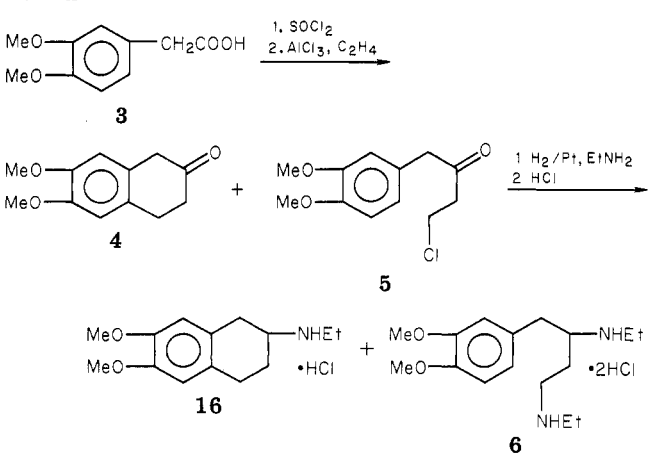
Formula IV

	R^1	R^2	B	R^4
22	H	Et	$(CH_2)_4$	Et
23	6-MeO	Et	$C(Me)_2$	Et
24	6-MeO	Et	$(CH_2)_2$	Me
25	6-MeO	*n*-Pr	$(CH_2)_2$	Me
26	6-MeO	*i*-Pr	$(CH_2)_2$	Me
27	6-MeO	cyclohexyl	$(CH_2)_2$	Me
28	6-MeO	Et	$(CH_2)_4$	Et
29	6-MeO	Et	$(CH_2)_6$	Et
30	6-MeO	Et	$(CH_2)_8$	Et

Formula V

	R^1	R^2	A
31	H	Et	$(CH_2)_6$
32	6-MeO	Et	$CH_2C(Me)_2CH_2$
33	6-MeO	Et	$(CH_2)_4$
34	6-MeO	*n*-Pr	$(CH_2)_4$
35	6-MeO	*i*-Pr	$(CH_2)_4$
36	6-MeO	cyclohexyl	$(CH_2)_4$
37	6-MeO	Et	$(CH_2)_6$
38	6-MeO	Et	$(CH_2)_8$
39	6-MeO	Et	$(CH_2)_{10}$

Scheme II



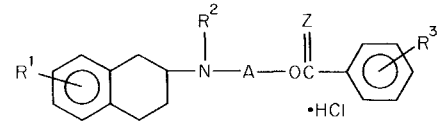
naphthalene ring have spasmolytic activity for colonic and gastric motility. Especially **76** was recognized to have a stronger spasmolytic activity for gastric motility than for colonic motility.

Among these compounds, *N*-ethyl-*N*-[6-[(3,4-dimethoxybenzoyl)oxy]hexyl]-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine hydrochloride (**63**) was found to be the most active spasmolytic agent having a selective effect on the colonic motility.

Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micro melting point apparatus MP-1 and are uncorrected. IR spectra were recored on a Hitachi Perkin-Elmer 285 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ or CCl_4 solution on a Hitachi Perkin-Elmer R20B (60 MHz) instrument, and Me_4Si was used as an internal standard. The elemental analyses were carried out for C, H, and N, and the analytical

Table II. *N*-[ω-(Benzoyloxy)alkyl]-1,2,3,4-tetrahydro-2-naphthylamines VI



compd	R^1	R^2	A	Z	R^3	method	yield, %	mp, °C	formula[a]
40	H	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D2	39.4	119–121	$C_{25}H_{33}NO_4 \cdot HCl \cdot 0.5H_2O$
41	H	Et	$(CH_2)_6$	O	3,4-$(MeO)_2$	C	69	oil[b]	$C_{27}H_{37}NO_4 \cdot HCl$[c]
42	5-MeO	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	47	162–164	$C_{26}H_{35}NO_5 \cdot HCl$
43	6-MeO	H	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	14.6	220–224 dec	$C_{24}H_{31}NO_5 \cdot HCl$
44	6-MeO	Me	$(CH_2)_4$	O	3,4-$(MeO)_2$	D2	44.9	oil[b]	$C_{25}H_{33}NO_5 \cdot HCl \cdot H_2O$
45	6-MeO	Et	$(CH_2)_2$	O	3,4-$(MeO)_2$	D2	65.5	100–101	$C_{24}H_{31}NO_5 \cdot HCl \cdot 0.5H_2O$
46	6-MeO	Et	$(CH_2)_3$	O	3,4-$(MeO)_2$	D2	62.5	146–148	$C_{25}H_{33}NO_5 \cdot HCl$
47	6-MeO	Et	$CH_2C(CH_3)_2CH_2$	O	3,4-$(MeO)_2$	C	25	165–168	$C_{27}H_{37}NO_5 \cdot HCl$
48	6-MeO	Et	$(CH_2)_4$	O	H	C	23.2	114–116	$C_{24}H_{31}NO_3 \cdot HCl$
49	6-MeO	Et	$(CH_2)_4$	O	3-MeO	C	35.1	139–140	$C_{25}H_{33}NO_4 \cdot HCl$
50	6-MeO	Et	$(CH_2)_4$	O	4-MeO	D1	34.9	120–121	$C_{25}H_{33}NO_4 \cdot HCl$
51	6-MeO	Et	$(CH_2)_4$	O	4-EtO	C	54	119–120	$C_{26}H_{35}NO_4 \cdot HCl$
52	6-MeO	Et	$(CH_2)_4$	O	4-*n*-PrO	C	67	123–124	$C_{27}H_{37}NO_4 \cdot HCl$
53	6-MeO	Et	$(CH_2)_4$	O	4-Me	C	49.2	138–140	$C_{25}H_{33}NO_3 \cdot HCl$
54	6-MeO	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	C	41.8	134–135	$C_{26}H_{35}NO_5 \cdot HCl$
55	6-MeO	Et	$(CH_2)_4$	O	3,4-OCH_2O	C	35.2	118–120	$C_{25}H_{31}NO_5 \cdot HCl$
56	6-MeO	Et	$(CH_2)_4$	O	3,4-$(PhCH_2O)_2$	C	66	139–140	$C_{38}H_{45}NO_5 \cdot HCl$
57	6-MeO	Et	$(CH_2)_4$	O	3,4-$(HO)_2$		70	oil[b]	$C_{24}H_{31}NO_5 \cdot HCl \cdot H_2O$
58	6-MeO	Et	$(CH_2)_4$	O	3-MeO-4-EtO	C	15	oil[b]	$C_{27}H_{37}NO_5 \cdot HCl \cdot 0.5H_2O$
59	6-MeO	Et	$(CH_2)_4$	O	2,6-$(MeO)_2$	C	31.9	oil[b]	$C_{26}H_{35}NO_5 \cdot HCl \cdot 0.5H_2O$
60	6-MeO	Et	$(CH_2)_4$	O	3,4-Cl_2	C	43	117–118	$C_{24}H_{29}Cl_2NO_3 \cdot HCl$
61[d]	6-MeO	Et	$(CH_2)_4$	O	3,4,5-$(MeO)_3$	D2	38	oil[b]	$C_{27}H_{37}NO_6 \cdot CH_3SO_3H \cdot 2H_2O$
62	6-MeO	Et	$(CH_2)_4$	O	3,4,5-$(EtO)_3$	C	50	118–120	$C_{30}H_{43}NO_6 \cdot HCl$
63	6-MeO	Et	$(CH_2)_6$	O	3,4-$(MeO)_2$	D2	44	116–118	$C_{28}H_{39}NO_5 \cdot HCl$
64	6-MeO	Et	$(CH_2)_8$	O	3,4-$(MeO)_2$	C	58	oil[b]	$C_{30}H_{43}NO_5 \cdot HCl \cdot 0.5H_2O$
65	6-MeO	Et	$(CH_2)_{10}$	O	3,4-$(MeO)_2$	C	70	oil[b]	$C_{32}H_{47}NO_5 \cdot HCl \cdot 0.5H_2O$
66	6-MeO	*n*-Pr	$(CH_2)_4$	O	3,4-$(MeO)_2$	C	82.2	oil[b]	$C_{27}H_{37}NO_5 \cdot HCl \cdot 0.5H_2O$
67	6-MeO	*i*-Pr	$(CH_2)_4$	O	3,4-$(MeO)_2$	C	76	172–174	$C_{27}H_{37}NO_5 \cdot HCl$
68	6-MeO	cyclohexyl	$(CH_2)_4$	O	3,4-$(MeO)_2$	C	57.8	oil[b]	$C_{30}H_{41}NO_5 \cdot HCl \cdot 0.5H_2O$
69	6-EtO	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	30.6	129–131	$C_{27}H_{37}NO_5 \cdot HCl \cdot 0.5H_2O$
70	6-*n*-PrO	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	31.4	112–114	$C_{28}N_{39}NO_5 \cdot HCl \cdot 0.5H_2O$
71	7-MeO	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	48	160–161.5	$C_{26}H_{35}NO_5 \cdot HCl$
72	8-MeO	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	30.6	133–135	$C_{26}H_{35}NO_5 \cdot HCl$
73	8-MeO	Et	$(CH_2)_6$	O	3,4-$(MeO)_2$	D1	60[e]	oil[b]	$C_{28}H_{39}NO_5 \cdot HCl \cdot H_2O$
74	5,8-$(MeO)_2$	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	24.7	oil[b]	$C_{27}H_{37}NO_6 \cdot HCl \cdot 2H_2O$
75	6,7-$(MeO)_2$	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	57[e]	107–109	$C_{27}H_{37}NO_6 \cdot HCl$
76	6,7-$(MeO)_2$	Et	$(CH_2)_6$	O	3,4-$(MeO)_2$	D1	59[e]	102–105	$C_{29}H_{41}NO_6 \cdot HCl$
77	6,7-OCH_2O	Et	$(CH_2)_4$	O	3,4-$(MeO)_2$	D1	31.2	151.5–153	$C_{26}H_{33}NO_6 \cdot HCl$
78	6-MeO	Et	$(CH_2)_2O(CH_2)_2$	O	3,4-$(MeO)_2$	D1	41[e]	oil[b]	$C_{26}H_{33}NO_6 \cdot HCl \cdot 0.5H_2O$
83	6-MeO	Et	$(CH_2)_4$	H_2	3,4-$(MeO)_2$		16.8[e]	oil[b]	$C_{26}H_{37}NO_4$

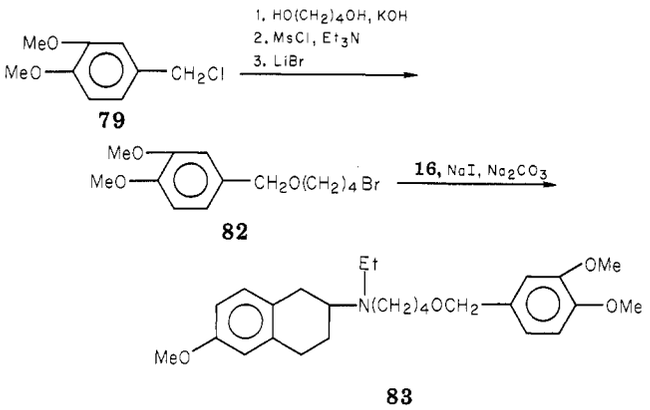
[a] All compounds were analyzed for C, H, and N, and analytical results obtained for those elements were within ±0.4% of the theoretical values unless otherwise noted. [b] These compounds did not crystallize. [c] H: calcd, 7.48; found, 8.16. [d] Methanesulfonate. [e] These indicate the yields of the free base of the desired amines.

Table III. Antispasmodic Activities of 2-Aminotetralin Derivatives

compd	stomach[a]	colon[b]	compd	stomach[a]	colon[b]
33	<5.0	2.6	**62**	<5.0	−6.8
37		5.2	**63**	<5.0	54.7
40	<5.0	27.9	**65**	<5.0	13.7
41	31.3	56.0	**66**	<5.0	22.4
42	<5.0	13.3	**67**	<5.0	19.6
44	<5.0	−4.9	**69**	<5.0	7.4
45	<5.0	11.4	**70**	<5.0	1.4
46	<5.0	−1.0	**71**	18.1	30.9
47	<5.0	15.8	**72**	21.3	40.0
48	<5.0	−2.6	**74**	<5.0	9.2
50	<5.0	8.1	**75**	11.8	63.8
51	<5.0	−2.5	**76**	64.5	54.2
52	<5.0	10.2	**77**	<5.0	13.4
54	6.6	20.0	**78**	<5.0	0.0
55	<5.0	1.3	**83**	<5.0	−4.3
59	<5.0	−8.7	mebeverine	2.6	22.0
61	<5.0	1.1			

[a] Effect on stomach contraction caused by stimulation of vagus nerve: dog, 0.1 mg/kg (iv). [b] Effect on colonic contraction caused by stimulation of pelvic nerve: dog, 0.1 mg/kg (iv).

Scheme III



results were within ±0.4% of the theoretical values unless otherwise noted. The compounds synthesized were assigned on the basis of various spectral data and elementa analyses.

6-Ethoxy-3,4-dihydro-2(1*H*)-naphthalenone (1). A solution of *p*-ethoxyphenylacetyl chloride, prepared by treating *p*-ethoxyphenylacetic acid (5 g, 27 mmol) with PCl_5 (7 g, 33 mmol) in CH_2Cl_2 (10 mL), was added dropwise with stirring to a suspension of $AlCl_3$ (7.3 g) in CH_2Cl_2 (80 mL) cooled in a dry ice–acetone bath. Ethylene was bubbled vigorously into this mixture for 15 min. After stirring for 4 h at room temperature, the mixture was added to ice–water (80 mL). The organic layer was separated, washed with 2 N HCl, 5% $NaHCO_3$, and water, dried (anhydrous N_2SO_4), and concentrated in vacuo to give a syrup (5.3 g, quantitatively yield) of **1**: NMR ($CDCl_3$) δ 1.39 (t, 3 H, OCH_2CH_3), 2.50 (m, 2 H, C3 H), 2.96 (m, 2 H, C4 H), 3.48 (s, 2 H, C1 H), 4.00 (q, 2 H, OCH_2CH_3), 6.6–7.2 (m, 3 H, aromatic H).

This syrup was used for the next reaction without further purification. Similarly, **2** was obtained from *p*-propoxyphenylacetic acid.

6,7-Dimethoxy-3,4-dihydro-2(1*H*)-naphthalenone (4). Treatment of 3,4-dimethoxyphenylacetic acid (**3**; 6 g, 30.6 mmol) in a manner similar to that described for **1** afforded a syrup of a mixture of **4** and 1-(3,4-dimethoxyphenyl)-4-chloro-2-butanone (**5**).

Reductive Ethylamination of the Mixture of 4 and 5. The mixture of **4** and **5** was added to a mixture of PtO_2 (0.25 g) and 14% $EtNH_2$ in EtOH (35 mL). The mixture was hydrogenated under atmospheric pressure. After cessesion of H_2 uptake, the catalyst was filtered off. The filtrate was concentrated in vacuo. The residue was dissolved in 18% HCl–EtOH, and the solution was concentrated in vacuo. The residue was crystallized from acetone to give white crystals (3.5 g). This material was added in 2 N NaOH, and the solution was extracted with $CHCl_3$. The extract was washed with water, dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography over alumina. Elution with benzene gave a colorless oil (1.21 g, 15.6% from **3**): NMR (CCl_4) δ 0.57 (broad, 1 H, NH), 1.06 (t, J = 7 Hz, 3 H, NCH_2CH_3), 3.17 (s, 6 H, 2 OMe), 6.41 (s, 2 H, aromatic H).

This oil was treated with HCl–EtOH, and the mixture was concentrated to dryness. The residue was recrystallized from EtOH–*i*-PrOH to give colorless needles of **16**: mp 246–248 °C; mass spectrum, m/e 235 (M^+, as free base), 220, 206. Anal. ($C_{14}H_{21}NO_2$·HCl) H, N; C: calcd, 61.87; found, 61.46.

Further elution with benzene and acetone (1:1) gave a colorless oil (1.05 g, 12.2% from **3**): NMR (CCl_4) δ 0.87 (broad, 2 H, 2 NH), 0.98 and 1.02 (each t, J = 7 Hz, NCH_2CH_3), 3.75 and 3.77 (each s, 6 H, 2 OMe), 6.55 (m, 3 H, aromatic H).

This oil was treated with HCl–EtOH, and the mixture was concentrated to dryness. The residue was recrystallized from EtOH–ether to give white needles of **6**: mp 222–224 °C; mass spectrum, m/e 281 (M^+ as free base), 208, 152, 129. Anal. ($C_{16}H_{28}N_2O_2$·2HCl) H, N; C: calcd, 54.39; found, 54.89.

Method A. *N*-Ethyl-6-methoxy-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (10). Hydrogenation of a mixture of 6-methoxy-3,4-dihydro-2(1*H*)-naphthalenone (16 g, 91 mmol)e, PtO_2 (0.6 g), and 19% $EtNH_2$ in EtOH (150 mL) gave a dark red oil of the free base of **10**: NMR ($CDCl_3$) δ 1.2 (broad, 1 H, NH), 1.10 (t, 3 H, $NHCH_2CH_3$), 1.7–2.1 (m 2 H, methyene H), 3.1–3.4 (m, 7 H, C2 H, methyene H), 3.72 (s, 3 H, OMe), 6.6–7.1 (m, 3 H, aromatic H).

This oil was teated with HCl–EtOH, and the mixture was concentrated in vacuo. The residue was recrystallized from EtOH–ether to give colorless crystals (19.0 g, 87%) of **10**, mp 230 °C. Anal. ($C_{13}H_{19}NO$·HCl) C, H, N.

5,8-Dimethoxy-*N*-ethyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (21). A solution of *N*-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthylamine (**20**; 2 g, 8.02 mmol) in THF (7 mL) was added dropwise to a suspension of $LiAlH_4$ (1 g) in THF (20 mL) and refluxed for 2.5 h. To this solution was added dropwise a mixture of water (1 mL) and THF (10 mL), followed by the addition of 15% NaOH (1 mL) and H_2O (3 mL). The precipitate was filtered off, and the filtrate was concentrated in vacuo. The residue was extracted with $CHCl_3$, and the extract was washed with water, dried (anhydrous Na_2SO_4), and concentrated in vacuo to give an oil: NMR ($CDCl_3$) δ 1.12 (t, 3 H, NCH_2CH_3), 1.3 (broad, 1 H, NH), 1.9 (m, 2 H, methyene H), 2.3–3.1 (m, 7 H, C2 H, methyene H), 3.73 (s, 6 H, 2 OMe), 6.60 (s, 2 H, C6 H, C7 H).

This oil was treated with HCl–EtOH, and the mixture was concentrated in vacuo. The residue was recrystallized from EtOH–ether to yield colorless needles (1.3 g, 63%) of **21**: mp 240–242 °C. Anal. ($C_{14}H_{21}NO_2$·HCl) C, H, N.

Method B. *N*-Ethyl-1,2,3,4-tetrahydro-*N*-[3-(methoxycarbonyl)propionyl]-6-methoxy-2-naphthylamine (24). The free base (8.8 g, 42.9 mmol) of **10**, prepared from its hydrochloride in the usual manner, was dissolved in a solution of triethylamine (6.1 g, 60.3 mmol) in benzene (10 mL). To this solution was added

a mixture of 3-(methoxycarbonyl)propionyl chloride (7.1 g, 47.1 mmol) and benzene (10 mL), and the mixture was refluxed for 2.5 h and allowed to stand overnight at room temperature. The reaction mixture was washed with 2 N HCl, 2 N NaOH, and water, dried (anydrous Na_2SO_4), and then concentrated in vacuo to give a pale yellow oil (12.5 g, 91.3%) of **24**. This oil was used for the next reaction without further purification.

Compounds **22**, **23**, **25–29**, and **30** were obtained in 87–99% yield by this method.

***N*-Ethyl-1,2,3,4-tetrahydro-*N*-(4-hydroxybutyl)-6-methoxy-2-naphthylamine Hydrochloride (33).** Treatment of **24** (14.5 g, 45.9 mmol) with $LiAlH_4$ (8.3 g, 21.9 mmol) under conditions similar to those described for the preparation of **21** gave a pale yellow oil (10.8 g, 86.6%): NMR ($CDCl_3$) δ 1.09 (t, 3 H, NCH_2CH_3), 1.3–2.2 (m, 6 H, methyene H), 2.3–3.2 (m, 9 H, C2 H, methyene H), 3.55 (m, 2 H, CH_2OH), 3.73 (s, 3 H, OMe), 5.3 (broad, 1 H, OH), 6.6–7.1 (m, 3 H, aromatic H).

This oil was treated with HCl–EtOH, and the mixture was concentrated in vacuo. The residue was recrystallized from methyl ethyl ketone (MEK) and ether to give colorless needles of **33**: mp 124–126 °C. Anal. ($C_{17}H_{27}NO_2$·HCl) C, H, N.

Compounds **31**, **32**, **34–38**, and **39** were obtained in 78–98% yield by this method.

Method C. *N*-Ethyl-*N*-[4-[(3,4-dimethoxybenzoyl)oxy]butyl]-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine Hydrochloride (54). A solution of 3,4-dimethoxybenzoyl chloride, prepared from 3,4-dimethoxybenzoic acid (10.35 g, 56.8 mmol) and $SOCl_2$ (15 mL), in benzene (100 mL) was added dropwise to a solution of **33** (14.3 g, 51.6 mmol) and triethylamine (10 g) in benzene (250 mL). The mixture was refluxed for 3.5 h. The cooled reaction mixture was washed with water, 2 N NaOH, and water, dried (anhydrous Na_2SO_4), and concentrated in vacuo to give an oil. Purification of the residue by silica gel chromatography with $CHCl_3$ as eluent gave a colorless oil: NMR ($CDCl_3$) δ 1.04 (t, 3 H, NCH_2CH_3), 1.3–2.2 (m, 6 H, methylenic H), 2.3–3.1 (m, 9 H, C2 H, methylenic H), 3.75 (s, 3 H, OMe), 3.91 (s, 6 H, 2 OMe), 4.32 (m, 2 H, CH_2OCO), 6.5–7.1 (m, 4 H, aromatic H), 7.5–7.8 (m, 2 H, aromatic H).

This oil was treated with HCl–EtOH, and the mixture was concentrated to dryness. The residue was recrystallized from acetone to give colorless prisms (10.3 g, 41.8%) of **54**, mp 134–135 °C. Anal. ($C_{26}H_{35}NO_5$·HCl) C, H, N.

Method D1. *N*-Ethyl-*N*-[6-[(3,4-dimethoxybenzoyl)oxy]hexyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-naphthylamine Hydrochloride (76). The free base (6 g, 22.1 mmol) of **16**, prepared from its hydrochloride, was dissolved in a solution of 6-chlorohexyl 3,4-dimethoxybenzoate (9.2 g, 27.6 mmol), NaI (4.6 g, 30.7 mmol), and Na_2CO_3 (3.3 g, 31.1 mmol) in MEK (150 mL). The mixture was refluxed for 96 h. The reaction mixture was concentrated in vacuo. The residue was extracted with $CHCl_3$, and the extract was washed with water, dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel, and the elution with $CHCl_3$ gave a pale yellow oil (7.5 g, 59%) of the free base of **76**: NMR δ 1.09 (t, 3 H, NCH_2CH_3), 3.82 and 3.91 (each s, 12 H, 4 OMe), 4.15–4.45 (m, 2 H, CH_2OCO), 6.56 (s, 2 H, C5 H, C8 H), 6.85 (d, J = 8 Hz, 1 H, C5′ H), 7.53 (d, J = 2 Hz, 1 H, C2′ H), 7.68 (dd, J = 2 and 8 Hz, 1 H, C6′ H).

This oil was treated with HCl–EtOH, and the mixture was concentrated in vacuo. The residue was recrystallized from EtOAc to give colorless prisms of **76**, mp 102–105 °C. Anal. ($C_{29}H_{41}NO_6$·HCl) C, H, N.

Method D2. *N*-Ethyl-*N*-[(3,4-dimethoxybenzoyl)oxy]hexyl]-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine Hydrochloride (63). The free base of **10** was obtained from its hydrochloride (2.5 g, 10.3 mmol) in the usual manner and dissolved in a solution of 6-iodohexyl 3,4-dimethoxybenzoate (4.0 g, 10.1 mmol) and Na_2CO_3 (1.15 g) in MEK (60 mL). The mixture was refluxed for 40 h. The reaction mixture was worked up in the same procedure described for the preparation of **76** (method D1) to give a pale yellow oil: NMR ($CDCl_3$) δ 1.02 (t, 3 H, HCH_2CH_3), 3.72 (s, 3 H, OMe), 3.88 (s, 6 H, 2 OMe), 4.29 (m, 2 H, CH_2OCO), 6.5–7.1 (m, 3 H, C5 H, C7 H, C8 H), 6.83 (d, 1 H, C5′ H), 7.53 (d, 1 H, C2′ H), 7.66 (dd, 1 H, C6′ H). This oil was treated with HCl–EtOH, and the mixture was concentrated. The residue was recrystallized from EtOAc to give colorless needles (2.0 g, 44%) of **63**, mp 119–120 °C. Anal. ($C_{28}H_{39}NO_5$·HCl) C, H, N.

***N*-Ethyl-*N*-[4-[(3,4-dihydroxybenzoyl)oxy]butyl]-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine Hydrochloride (57).** A mixture of **56** (2.5 g, 4.0 mmol) and 5% Pd/C (0.5 g) in EtOH (70 mL) and water (70 mL) was hydrogenated under atmospheric pressure at room temperature. After cessation of H_2 uptake, the catalyst was filtered off, and the filtrate was concentrated in vacuo to give a colorless oil (1.3 g, 70%) of **57**: NMR as free base ($CDCl_3$) δ 1.03 (t, 3 H, NCH_2CH_3), 3.72 (s, 3 H, OMe), 4.0–4.45 (broad, 2 H, CH_2OCO), 6.60–7.05 (m, 4 H, aromatic H), 7.30–7.70 (m, 2 H, aromatic H), 9.10 (broad, 2 H, aromatic H). Anal. ($C_{24}H_{31}NO_5$·HCl·H_2O) C, H, N.

4-[(3,4-Dimethoxybenzyl)oxy]-1-butanol (80). Potassium hydroxide (8.88 g, 0.158 mol) was dissolved in 1,4-butanediol (29.51 g, 0.327 mol), and a small amount of water contained in this solution was evaporated off in vacuo. To this mixture was added dropwise 3,4-dimethoxybenzyl chloride (24.29 g, 0.13 mol) at 90 °C, and then the mixture was heated at 130 °C for 2 h. The mixture was diluted with H_2O (65.3 mL) and extracted with $CHCl_3$. The extract was washed with water, dried (anhydrous Na_2SO_4), and concentrated in vacuo to give a colorless oil (28.17 g, 90.1%) of **80**: NMR ($CDCl_3$) δ 1.65 (m, 4 H, methylenic H), 2.5 (broad, 1 H, OH), 3.2–3.7 (m, 4 H, methylenic H), 3.85 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.45 (s, 2 H, OCH_2Ph), 6.85 (s, 3 H, aromatic H).

4-[(3,4-Dimethoxybenzyl)oxy]butyl Methanesulfonate (81). Methanesulfonyl chloride (3.44 g, 26.3 mmol) was added to an ice-cooled solution of **80** (6.0 g, 25.0 mmol) and triethylamine (3.40 g, 30.0 mmol) in THF (50 mL), and the mixture was stirred for 24 h at room temperature. To the reaction mixture was added $CHCl_3$, and the organic layer was washed with HCl and water. The extract was dried (anhydrous Na_2SO_4) and concentrated to give a pale yellow oil (8.55 g, quantitatively) of **81**: NMR ($CDCl_3$) δ 1.7–1.9 (m, 4 H, methylenic H), 2.98 (s, 3 H, OMe), 4.45 (s, 2 H, CH_2Ph), 6.88 (s, 3 H, aromatic H).

4-[(3,4-Dimethoxybenzyl)oxy]butyl Bromide (82). A mixture of **81** (8.41 g, 26.4 mmol), $LiBr·H_2O$ (9.75 g, 93.0 mmol), and DMF (110 mL) was heated for 2 h at 60 °C. The mixture was treated with benzene. The organic layer was washed with water, dried (anhydrous Na_2SO_4), and concentrated in vacuo to give a pale yellow oil (6.03 g, 75.1%) of **82**: NMR ($CDCl_3$) δ 1.7–1.9 (m, 4 H, methlenic H), 3.85 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 4.42 (s, 2 H, OCH_2Ph), 6.85 (s, 3 H, aromatic H).

***N*-Ethyl-*N*-[(3,4-Dimethoxybenzyl)oxy]butyl]-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine (83).** The free base of **10**, prepared from its hydrochloride (3.36 g, 13.9 mmol) in the usual manner, was added to a mixture of **82** (4.64 g, 15.3 mmol), NaI (2.29 g, 15.3 mmol), and Na_2SO_3 (1.62 g) in MEK (10 mL) and refluxed for 41 h. The organic layer was concentrated in vacuo and extracted with $CHCl_3$. The organic layer was washed with water, dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with a mixture of benzene and acetone (20:1) to give a colorless oil (1.0 g, 16.8%) of **83**: NMR ($CDCl_3$) δ 1.01 (t, 3 H, NCH_2CH_3), 1.3–2.0 (m, 6 H, methlenic H), 2.4–3.0 (m, 9 H, C2 H, methylenic H), 3.3–3.6 (m, 2 H, CH_2Ph), 3.72 (s, 3 H, OMe), 3.83 (s, 6 H, 2 OMe), 4.40 (s, 2 H, $PhCH_2O$), 6.5–7.0 (m, 6 H, aromatic H); mass spectrum, m/e 428 (M + 1), 427 (M^+), 277, 276, 219, 161, 112.

Pharmacology. Measurement Method of Spasmolytic Activity on Colonic Contraction Induced by Pelvic Nerve Stimulation. The assay was carried out according to a method described by Goldenberg et al.[7] Mongrel dogs of either sex, weighing 8–15 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv), and supplementary doses were given as required. The trachea was cannulated, and the animal was allowed to breathe spontaneously. The left pelvic nerve was exposed through lower abdominal incisions and cut, and its peripheral end was stimulated every 3 min via bipolar platinum electrodes. The stimulation parameters were as follows: frequency, 50 Hz; duration, 1 ms; voltage, 4 V. A water-filled balloon connected to a low-pressure transducer was inserted into the distal colon via the anus, and elevation in intraluminal pressure induced by the

(7) Goldenberg, M. M.; Burns, R. H. *Eur. J. Pharmacol.* **1972**, *18*, 1.

nerve stimulation was recorded on a polygraph. A dose of 0.1 mg/kg of each compound was injected into the cannulated femoral vein. Spasmolytic activity (percent inhibition of the contraction) was calculated from the following formula:

100 – (av contraction ht during 30-min period after drug injn/av contraction ht before drug injn) × 100

Measurement Method of Spasmolytic Activity on Gastric Contraction Induced by Vagus Nerve Stimulation. The assay was measured by the method described above. Mongrel dogs of either sex, weighing 8–15 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv). The left cervical vagus nerve was exposed through upper abdominal incisions and cut, and its peripheral end was stimulated every 3 min via platinum electrodes. The stimulation parameters were as follows: frequency, 20 Hz; duration, 1 ms; voltage, 8 V. A water-filled balloon connected to a low-pressure transducer was inserted into the stomach through the small incised corpus, and elevation in intraluminal pressure induced by the vagus nerve stimulation was recorded on a polygraph. A dose of 0.1 mg/kg of each compound was injected into the cannulated femoral vein. Spasmolytic activity (percent inhibition of the contraction) was calculated from the formula shown above.

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Synthesis and Comparison of Some Cardiovascular Properties of the Stereoisomers of Labetalol[1]

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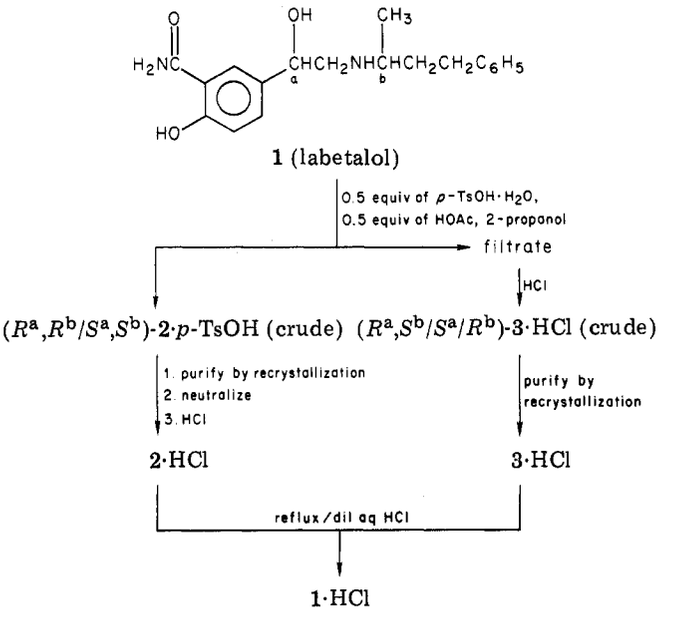
A useful method for the separation of labetalol into its two racemic diastereomers, as well as a stereoselective synthesis of its four stereoisomers, is described. The absolute stereochemistry of each isomer was determined by analysis of the CD spectra and confirmed by X-ray analysis. The α- and β_1-adrenergic blocking properties, as well as the relative antihypertensive activities, have been measured in rats. The *R,R* isomer, **2a** (SCH 19927), possesses virtually all of the β_1-blocking activity elicited by labetalol and displays little α-blocking activity. In contrast, the *S,R* isomer, **3a**, has most of the α-blocking activity. Of the four isomers, only **2a** has antihypertensive potency comparable to that of labetalol. These findings, coupled with published data showing that labetalol possesses β-adrenergic mediated peripheral vasodilating activity deriving essentially from its *R,R* isomer, lead to the following conclusion: The antihypertensive activity of labetalol can be ascribed to at least three identified complementary mechanisms, β-adrenergic blockade, β-adrenergic mediated vasodilatation, and α-adrenergic blockade, whereas the antihypertensive activity of **2a** derives from the first two mechanisms only.

The synthesis[3] and the pharmacological[4] and clinical[5] properties, as well as the metabolism,[6] of the new antihypertensive agent labetalol (**1**) are well documented. The novelty of this agent has been ascribed to its property of being both an α- and β-adrenergic receptor blocker, the ratio of α/β blockade, in a variety of animal and isolated tissue studies, being in the range of 1:4–16.[7] Recently several other arylethanolamines have also been shown to have combined α- and β-adrenergic blocking properties,[8] including an analogue of labetalol, the biology of which has been investigated in some detail.[8a,b] Labetalol consists of an approximately equicomponent mixture of its four optical isomers, and several recent reports have described some of their adrenoceptor properties. Thus, in isolated tissue, the α- and β-blocking properties have been shown to each derive from a different racemic diastereomer.[9] Other studies in anesthetized dogs[3b,10,26] ascribe these activities respectively to the *S,R* (**3a**) and *R,R* (**2a**) isomers. Finally, several of us have reported some comparative adrenoceptor properties of labetalol and its *R,R* isomer (**2a**, SCH 19927) in dogs and rats.[11]

This paper describes the synthesis and characterization of all four isomers and compares their relative blocking activity at adrenoceptors and their blood-pressure lowering properties in rats.[3b]

Separation of Labetalol into Its Racemic Diastereomers (2 and 3). After many attempts with various acid salts, including our inability to readily repeat the published procedure,[3] we easily effected the fractional crystallization

Scheme I



of **1** by taking advantage of the extreme insolubility of the *p*-TsOH salt of diastereomer **2** (*R,R/S,S*) and the solubility

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(1) This paper has been presented, see E. H. Gold, T. Baum, W. Chang, M. Cohen, S. Ehrreich, G. Johnson, N. Prioli, and E. J. Sybertz, "Abstracts of Papers", 183rd National Meeting of the American Chemical Society, Las Vegas, NV, Mar 1982, American Chemical Society, Washington, DC, 1982, Abstr MEDI 36.

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