Journal of Medicinal Chemistry, 1973, Vol. 16, No. 1 49

Synthetic Antidiarrheal Agents. 1. An Approach to the Separation of Antidiarrheal Activity from Narcotic Analgesic Activity

Donald E. Butler,* Robert F. Meyer, Susan M. Alexander, Paul Bass, and John A. Kennedy

Chemistry Department, Research and Development Division, Parke, Davis and Company, Ann Arbor, Michigan 48106.
Received May 23, 1972

A series of 1-(disubstituted amino)-3-(dialkylaminoalkyl)-3-phenyloxindoles was found in which analgesic or dependence liability as measured by the Straub tail effect in mice could be separated from a constipating effect. The best separation of effects was found in the 1-[(substituted benzyl)methylamino]-3-(dialkylaminoalkyl)-3-phenyloxindoles. Of a number of substitutions on the benzyl group, an *o*-chloro resulted in consistent separation of the biological activities. The nmr spectra of 1-[(1-substituted benzyl)methylamino]-3-phenyloxindoles demonstrate restricted rotation around the N–N bond.

In certain diseases, diarrhea can be the cause of a high degree of morbidity and even mortality.[1] The narcotic analgesics remain the drugs of choice for the treatment of diarrhea and dysentery. This group of drugs has the disadvantage of possessing narcotic and dependence liabilities. In man the parallelism of narcotic and constipating properties in any series of analgesics has not been systematically explored. It is apparent that morphine and methadone which have similar narcotic properties do not appear to have similar constipating effects[2] and morphine and codeine do not possess the same degree of addiction liability.[3]

Clinically, *increased colonic contractile activity is associated with the constipating effect.*[4] The ideal constipating drug would increase colonic circular muscle activity without stimulation of the longitudinal muscle and without other pharmacological actions. Narcotic analgesics have the general property of increasing intestinal activity *in vivo*[5-9] but with many other undesirable effects for a constipating drug.

Janssen and Jageneau[10] have previously noted the poor correlation between "analgesic" and "constipating" activity in a series of analgesically active meperidine derivatives. Evaluation of a series of chemicals led to the introduction of diphenoxylate into the therapeutic regimen of diarrhea control.[11,12] This agent possesses morphine-like as well as anticholinergic properties, both of which may be responsible for its antidiarrheal action. Diphenoxylate, because of its narcotic properties, is capable of supporting morphine physical dependence in man[12] and the monkey;[13] overdose in children has led to symptoms and fatalities that were characteristic of the narcotics, *e.g.*, respiratory depression and narcosis (reversed by Nalorphine).[14,15]

We considered that a chemical could be found that would have antidiarrheal activity without dependence liability or other significant side effects. Janssen, Jageneau, and Huygens[11] had used the mouse hot plate[16] and the charcoal meal in the development of diphenoxylate. Since morphine-dependent monkeys can be supported by diphenoxylate, we felt that a different approach was needed. Shemano and Wendel[17] had compared the pharmacological profile of *N*-allylnormorphine (Nalorphine), a nonaddicting compound, with that of morphine and had noted that Nalorphine lacks certain central stimulatory effects of morphine, namely, excitation of the cat and a Straub tail effect[18-20] in mice. A general relationship has been found between the cat excitatory effect and human addiction liability of morphine-like drugs, but the correlation was not clear-cut.[21] We decided to use the Straub tail effect as one of our primary tests because of its simplicity and because Juul[22] had shown that codeine was approximately one-tenth as effective as morphine in causing the Straub tail effect and, as noted by Fraser and coworkers,[3] "although codeine accounts for at least 80% of the natural opiates sold on prescription. . ., the incidence of addiction to codeine is much less than that to morphine."

Our synthetic efforts have been directed toward maximizing the antidiarrheal action and eliminating or minimizing the Straub tail effect, the premise being that a compound which possesses a high degree of antidiarrheal activity with little or no Straub tail effect in mice will possess little or no addiction liability in man.

Since our work began, a study by Aceto, McKean, and Pearl[23] has shown the Straub tail test to be useful for studying structure-activity relations among opiates and opiate antagonists.

In Vivo **Biological Activity. Antidiarrheal.** The test compounds were evaluated for oral antidiarrheal activity in the rat using the method of Kennedy, Wiley, and Bass.[24] Briefly, the method involved dosing the animals po and collecting the fecal output over an 8-hr period (4 P.M.–12 midnight). A total of 24 rats per dose was used along with a concomitant control group. The ED_{50} values were confirmed by repeating the test using doses that bracketed the original result. If an ED_{50} was not obtained, the results were expressed as the per cent reduction of fecal output at the dose used.

Straub Tail and/or Provisional Acute Toxicity. The test compounds were injected intraperitoneally to groups of five mice at doses of 250, 125, 63, . . ., mg/kg until no drug effect was observed. The compounds were either dissolved in dilute HCl or propylene glycol. The animals were observed by highly trained personnel for 15–30 min. Surviving animals were held for 24 hr to establish a provisional acute toxicity. Compounds with a good separation of activity were tested in an anesthetized dog preparation against the effects of acetylcholine to check for anticholinergic activity.

Chemistry. A series of 1-(dialkylamino)-3-(dialkylaminoalkyl)-3-phenyloxindoles had demonstrated analgesic activity.[25] This early group of compounds showed a wide divergence between antidiarrheal activity, Straub tail effect, and analgesic potency, although the latter two were closely parallel. The preparation of these compounds followed the scheme outlined in Scheme I.

The first step is a modification of the original synthesis by Meyer.†,[26] When the unsymmetrical hydrazine was commercially available, it was used in excess. In general, an unsymmetrically substituted hydrazine was added to an

†Our thanks to Mr. H. D. Troutman who suggested the use of 4-ethylmorpholine as an acid acceptor as a means of conserving the 1,1-disubstituted hydrazines (triethylamine was inferior).

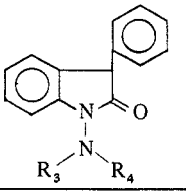
Table I. Compounds 1-97 (See Scheme I)

No.	n	R_1	R_2	R_3	R_4	Straub tail effect[a]	Antidiarrheal ED_{50}, mg/kg[b] po	Mp or bp (mm), °C[c]	Yield purified, %[d]	Procedure[e]	Empirical formula	Analyses
1	2	CH_3	CH_3	CH_3	CH_3	8	23	198-200	49	A	$C_{20}H_{25}N_3O\cdot HCl$	C, H
2	3	CH_3	CH_3	CH_3	CH_3	16	21	206-207	65	A	$C_{21}H_{27}N_3O\cdot HCl$	C, H, N
3	2	C_2H_5	C_2H_5	CH_3	CH_3	4	19	158-160 (0.3)	82	A	$C_{22}H_{29}N_3O$	C, H, N
4	*l*	CH_3	CH_3	CH_3	CH_3	8	47	163-165 (0.1)	84	A	$C_{21}H_{27}N_3O$	C, H, N
5	2	CH_3	CH_2=$CHCH_2$	CH_3	CH_3	2	21	182-184.5	57	B	$C_{22}H_{27}N_3O\cdot HCl$	C, H
6	2	CH_3	$C_6H_5CH_2$	CH_3	CH_3	16	31	214.5-224	45	B	$C_{26}H_{30}N_3O\cdot HCl$	C, H
7	2	H	$(CH_3)_3C$	CH_3	CH_3	L/125	11.5	287-289	30	B	$C_{22}H_{29}N_3O\cdot HCl$	C, H
8	2	H	H	CH_3	CH_3	L/125	0/50	70-72	67	B	$C_{18}H_{21}N_3O$	C, H, N
9	2		$(CH_2)_2O(CH_2)_2$	CH_3	CH_3	4	0/50	108-109	59	B	$C_{22}H_{27}N_3O_2$	C, H, N
10	2		$(CH_2)_4$	CH_3	CH_3	4	24	128-131	20	B	$C_{22}H_{27}N_3O$	C, H
11	2		$(CH_2)_5$	CH_3	CH_3	4	16	240.5-243	75	B	$C_{23}H_{29}N_3O\cdot HCl$	C, H
12	2		$(CH_2)_4CH(CH_3)$	CH_3	CH_3	1	20	92.5-95	50	B	$C_{24}H_{31}N_3O$	C, H
13	2		$(CH_2)_6$	CH_3	CH_3	2	18	230-233	76	B	$C_{24}H_{31}N_3O\cdot HCl$	C, H
14	4	C_2H_5	$C_6H_5CH_2$	CH_3	CH_3	0/250	0/50	205-207 (0.15)	40	A	$C_{29}H_{35}N_3O$	C, H
15	5	CH_3	CH_3	CH_3	CH_3	L/63	0/50	160-162 (0.15)	86	B	$C_{23}H_{31}N_3O$	C, H
16	2	CH_3	CH_3	CH_3	$C_6H_5CH_2$	125	67	87-90	35	A	$C_{26}H_{29}N_3O$	C,[g] H
17	3	CH_3	CH_3	CH_3	$C_6H_5CH_2$	0/250	52	187-189.5	68	A	$C_{27}H_{31}N_3O\cdot HCl$	C, H
18	2	C_2H_5	C_2H_5	CH_3	$C_6H_5CH_2$	0/250	100	206-208 (0.46)	72.5	A	$C_{28}H_{33}N_3O$	C, H
19	3	C_2H_5	C_2H_5	CH_3	$C_6H_5CH_2$	L/125	54	192-196 (0.15)	82	A	$C_{29}H_{35}N_3O$	C, H
20	2	CH_3	CH_3	CH_3	2-$ClC_6H_4CH_2$	0/250	120	98.5-101.5	50	A	$C_{26}H_{28}ClN_3O$	C, H
21	3	CH_3	CH_3	CH_3	2-$ClC_6H_4CH_2$	L/250	112	209-211.5	52	A	$C_{27}H_{30}ClN_3O\cdot HCl$	C, H, N
22	2	C_2H_5	C_2H_5	CH_3	2-$ClC_6H_4CH_2$	0/250	67	214-215 (0.46)	72	A	$C_{28}H_{32}ClN_3O$	C, H
23	2	C_3H_7	C_3H_7	CH_3	2-$ClC_6H_4CH_2$	0/250	70	202.5-204	59	A	$C_{30}H_{36}ClN_3O\cdot HCl$	C, H, N
24	3	C_2H_5	C_2H_5	CH_3	2-$ClC_6H_4CH_2$	L/125	47	199-200 (0.16)	66	A	$C_{29}H_{34}ClN_3O$	C, H
25	2		$(CH_2)_5$	CH_3	2-$ClC_6H_4CH_2$	0/250	61	118-120	62	B	$C_{29}H_{32}ClN_3O$	C, H, N
26	2		$(CH_2)_6$	CH_3	2-$ClC_6H_4CH_2$	0/250	14/35	109.5-111.5	70	B	$C_{30}H_{34}ClN_3O$	C,[h] H, N
27	2	C_2H_5	C_2H_5	CH_3	3-$ClC_6H_4CH_2$	125	68	200-205 (0.165)	76	A	$C_{28}H_{32}ClN_3O$	C, H
28	3	CH_3	CH_3	CH_3	3-$ClC_6H_4CH_2$	L/250	44/100	195-203 (0.15)	69	A	$C_{27}H_{30}ClN_3O$	C, H
29	2	CH_3	CH_3	CH_3	4-$ClC_6H_4CH_2$	L/250	125	92-95	50	A	$C_{26}H_{28}ClN_3O$	C, H
30	3	CH_3	CH_3	CH_3	4-$ClC_6H_4CH_2$	L/250	94	221.5-224.5	62	A	$C_{27}H_{30}ClN_3O\cdot HCl$	C, H
31	2	C_2H_5	C_2H_5	CH_3	4-$ClC_6H_4CH_2$	L/125	64	215-216 (0.475)	72	A	$C_{28}H_{32}ClN_3O$	C, H
32	3	CH_3	CH_3	CH_3	2-$BrC_6H_4CH_2$	0/250	21/50	*f*	75	A	$C_{27}H_{30}BrN_3O$	C, H
33	2	C_2H_5	C_2H_5	CH_3	2-$BrC_6H_4CH_2$	0/250	73	*f*	80	A	$C_{28}H_{32}BrN_3O$	C, H
34	2	C_2H_5	C_2H_5	CH_3	2-$CF_3C_6H_4CH_2$	L/250	52	185-187 (0.12)	70	A	$C_{29}H_{32}F_3N_3O$	C, H
35	3	CH_3	CH_3	CH_3	2-$CH_3C_6H_4CH_2$	L/250	40/125	195-197 (0.15)	65	A	$C_{28}H_{33}N_3O$	C, H
36	2	C_2H_5	C_2H_5	CH_3	2-$CH_3C_6H_4CH_2$	63	75	185-190 (0.15)	77	A	$C_{28}H_{35}N_3O$	C, H
37	3	CH_3	CH_3	CH_3	2-$CH_3SC_6H_4CH_2$	0/250	40	106.5-108.5	41	A	$C_{28}H_{33}N_3OS$	C, H, N
38	2	C_2H_5	C_2H_5	CH_3	2-$CH_3SC_6H_4CH_2$	125	24	218-222 (0.30)	53	A	$C_{29}H_{35}N_3OS$	C, H
39	3	C_2H_5	C_2H_5	CH_3	2-$CH_3SC_6H_4CH_2$	0/250	44	218-222 (0.20)	46	A	$C_{30}H_{37}N_3OS$	C, H
40	2		$(CH_2)_5$	CH_3	2-$CH_3SC_6H_4CH_2$	0/250	19	93.5-96	50	B	$C_{30}H_{35}N_3OS$	C, H
41	2	C_2H_5	C_2H_5	CH_3	4-$CH_3SC_6H_4CH_2$	L/250	62	212-221 (0.225)	62	A	$C_{29}H_{35}N_3OS$	C, H
42	2	C_2H_5	C_2H_5	CH_3	2-$C_2H_5SC_6H_4CH_2$	0/250	20	227-229 (0.35)	73	A	$C_{30}H_{37}N_3OS$	C, H, N
43	3	CH_3	CH_3	CH_3	2-$C_3H_7SC_6H_4CH_2$	0/250	100	221-226 (0.175)	25	A	$C_{30}H_{37}N_3OS$	C, H
44	2	C_2H_5	C_2H_5	CH_3	2-$C_3H_7SC_6H_4CH_2$	0/250	37	221-226 (0.25)	74	A	$C_{31}H_{39}N_3OS$	C, H
45	2	C_2H_5	C_2H_5	CH_3	2-*i*-$C_3H_7SC_6H_4CH_2$	0/250	34	86.5-88	54	A	$C_{31}H_{39}N_3OS$	C, H, N
46	2	CH_3	CH_3	CH_3	2-$CH_3OC_6H_4CH_2$	L/250	81	215-217 (0.55)	63	A	$C_{27}H_{31}N_3O_2$	C, H
47	3	CH_3	CH_3	CH_3	2-$CH_3OC_6H_4CH_2$	L/250	17/35	192-194 (0.25)	34	A	$C_{28}H_{33}N_3O_2$	C, H
48	2	C_2H_5	C_2H_5	CH_3	2-$CH_3OC_6H_4CH_2$	0/250	47/70	149.5-153	50	A	$C_{29}H_{35}N_3O_2\cdot 2HBr$	C, H
49	2	C_2H_5	C_2H_5	CH_3	2-$C_2H_5OC_6H_4CH_2$	0/250	64	195-205 (0.15)	55	A	$C_{30}H_{37}N_3O_2$	C, H

50	2	CH_3	CH_3	CH_3	3-$CH_3OC_6H_4CH_2$	0/250	38/125	175–180 (0.125)	51	A	$C_{27}H_{31}N_3O_2$	C, H
51	3	CH_3	CH_3	CH_3	3-$CH_3OC_6H_4CH_2$	L/250	33/125	195–199 (0.175)	50	A	$C_{28}H_{33}N_3O_2$	C, H
52	2	C_2H_5	C_2H_5	CH_3	3-$CH_3OC_6H_4CH_2$	L/125	100	195–205 (0.20)	45	A	$C_{29}H_{35}N_3O_2$	C, H, N
53	2	C_2H_5	C_2H_5	CH_3	3-$CH_3OC_6H_4CH_2$	L/125	48/100	208–215 (0.20)	50	A	$C_{29}H_{35}N_3O_2$	C, H, N
54	2	CH_3	CH_3	CH_3	4-$CH_3OC_6H_4CH_2$	L/125	23/35	205–207 (0.26)	72	A	$C_{27}H_{31}N_3O_2$	C, H
55	3	CH_3	CH_3	CH_3	4-$CH_3OC_6H_4CH_2$	L/250	94	218–224 (0.55)	68	A	$C_{28}H_{33}N_3O_2$	C, H
56	2	C_2H_5	C_2H_5	CH_3	4-$CH_3OC_6H_4CH_2$	L/250	66	205–215 (0.30)	67	A	$C_{29}H_{35}N_3O_2$	C, H
57	2	CH_3	CH_3	CH_3	2-$FC_6H_4CH_2$	63	22/35	200–203 (0.675)	67	A	$C_{26}H_{28}FN_3O$	C, H
58	3	CH_3	CH_3	CH_3	2-$FC_6H_4CH_2$	L/250	125	204.5–207 (0.70)	51	A	$C_{27}H_{30}FN_3O$	C, H
59	2	C_2H_5	C_2H_5	CH_3	2-$FC_6H_4CH_2$	63	48	180–190 (0.20)	75	A	$C_{28}H_{32}FN_3O$	C, H
60	2	C_2H_5	C_2H_5	CH_3	4-$FC_6H_4CH_2$	63	50	202–204 (0.40)	89	A	$C_{28}H_{32}FN_3O$	C, H
61	2		$(CH_2)_4$	CH_3	$C_6H_5CH_2$	125	20	211.5–212.5	41	B	$C_{28}H_{31}N_3O \cdot HCl$	C,[i] H, N
62	3		$(CH_2)_4$	CH_3	$C_6H_5CH_2$	L/125	68	89.5–91	30	B	$C_{29}H_{33}N_3O$	C, H
63	2		$(CH_2)_5$	CH_3	$C_6H_5CH_2$	0/250	57	215–225 (0.25)	53	B	$C_{29}H_{33}N_3O$	C, H
64	3		$(CH_2)_5$	CH_3	$C_6H_5CH_2$	L/250	24/50	207–209	40	B	$C_{30}H_{35}N_3O \cdot HCl$	C, H
65	3		$CH_2CH(CH_3)(CH_2)_3$	CH_3	$C_6H_5CH_2$	L/250	18/50	204–207 (0.21)	39	B	$C_{31}H_{37}N_3O$	C, H
66	2		$(CH_2)_6$	CH_3	$C_6H_5CH_2$	32	72	216–217 (0.21)	31	B	$C_{30}H_{35}N_3O$	C, H
67	4		$(CH_2)_5$	CH_3	$C_6H_5CH_2$	L/250	15/50	148–153	30	B	$C_{31}H_{37}N_3O \cdot HCl$	C, H
68	2	C_2H_5	C_2H_5	CH_3	2-Cl, 3-$CH_3OC_6H_3CH_2$	L/250	18	100–102	65	A	$C_{29}H_{34}ClN_3O_2$	C, H
69	2	C_2H_5	C_2H_5	CH_3	2-Cl, 4-$CH_3OC_6H_3CH_2$	0/250	15	218–222 (0.40)	55	A	$C_{29}H_{34}ClN_3O_2$	C, H, N
70	2	C_2H_5	C_2H_5	CH_3	2-Cl, 5-$CH_3OC_6H_3CH_2$	0/250	28	*f*	35	A	$C_{29}H_{34}ClN_3O_2$	C, H,[j] N
71	2	C_2H_5	C_2H_5	CH_3	4-Cl, 2-$CH_3OC_6H_3CH_2$	L/125	37	188–190 (0.40)	63	A	$C_{29}H_{34}ClN_3O_2$	C, H
72	2	C_2H_5	C_2H_5	CH_3	5-Cl, 2-$CH_3OC_6H_3CH_2$	L/125	26	222–224 (0.40)	73	A	$C_{29}H_{34}ClN_3O_2$	C, H, N
73	3	CH_3	CH_3	CH_3	2,4-$Cl_2C_6H_3CH_2$	0/250	96	204–206 (0.15)	52	A	$C_{27}H_{39}Cl_2N_3O$	C,[k] H
74	2	C_2H_5	C_2H_5	CH_3	2,6-$Cl_2C_6H_3CH_2$	0/250	42/125	218–224 (0.20)	72	A	$C_{28}H_{31}Cl_2N_3O$	C, H
75	2	C_2H_5	C_2H_5	CH_3	2-Cl, 6-$FC_6H_3CH_2$	0/250	50	186–187 (0.01)	77	A	$C_{28}H_{31}ClFN_3O$	C, H, N
76	2	C_2H_5	C_2H_5	CH_3	2,3-$(CH_3O)_2C_6H_3CH_2$	L/250	36	222–223 (0.35)	70	A	$C_{30}H_{37}N_3O_3$	C, H
77	2	C_2H_5	C_2H_5	CH_3	2,5-$(CH_3O)_2C_6H_3CH_2$	L/250	35	213–216 (0.175)	63	A	$C_{30}H_{37}N_3O_3$	C, H, N
78	2	C_2H_5	C_2H_5	CH_3	3,4-$(CH_3O)_2C_6H_3CH_2$	0/250	32	225–228 (0.20)	69	A	$C_{30}H_{37}N_3O_3$	C, H, N
79	2	CH_3	CH_3	CH_3	2-$C_4H_3OCH_2$	16	34/100	178–179 (0.225)	72	A	$C_{24}H_{27}N_3O_2$	C, H
80	3	CH_3	CH_3	CH_3	2-$C_4H_3OCH_2$	L/125	44/100	180.5–181 (0.175)	55	A	$C_{25}H_{29}N_3O_2$	C, H
81	2	C_2H_5	C_2H_5	CH_3	2-C_4H_3O-CH_2	16	45	185–186 (0.30)	50	A	$C_{26}H_{31}N_3O_2$	C, H
82	3	CH_3	CH_3	CH_3	2-C_4H_3S-CH_2	L/125	125	80–83.5	57	A	$C_{25}H_{29}N_3OS$	C, H
83	2	C_2H_5	C_2H_5	CH_3	2-C_4H_3S-CH_2	16	64	96–99	79	A	$C_{26}H_{31}N_3OS$	C, H, N
84	2	CH_3	CH_3	C_2H_5	$C_6H_5CH_2$	32	120	92.5–95	64	A	$C_{27}H_{31}N_3O$	C, H
85	3	CH_3	CH_3	C_2H_5	$C_6H_5CH_2$	L/250	100	181–184	74	A	$C_{28}H_{33}N_3O \cdot HCl$	C, H
86	2	C_2H_5	C_2H_5	C_2H_5	$C_6H_5CH_2$	0/250	48	176–178.5	69	A	$C_{29}H_{35}N_3O \cdot 2HCl$	C, H
87	2	CH_3	CH_3	CH_3	$C_6H_5CH_2CH_2$	L/125	12/25	183–184.5	69	A	$C_{27}H_{31}N_3O \cdot HCl$	C, H
88	3	CH_3	CH_3	CH_3	$C_6H_5CH_2CH_2$	L/125	20/25	180.5–182.5	65	A	$C_{28}H_{33}N_3O \cdot HCl$	C, H
89	2	C_2H_5	C_2H_5	CH_3	$C_6H_5CH_2CH_2$	L/250	50	180–183 (0.31)	82	A	$C_{29}H_{35}N_3O$	C, H
90	2	CH_3	CH_3	CH_3	C_6H_5	32	11/35	222–226	50	A	$C_{25}H_{27}N_3O \cdot HCl$	C, H
91	2	C_2H_5	C_2H_5	CH_3	C_6H_5	63	33	*f*	30	A	$C_{27}H_{31}N_3O$	C, H
92	2	CH_3	CH_3		$(CH_2)_5$	0/250	0/50	206–209	68	A	$C_{23}H_{29}N_3O \cdot HCl$	C, H
93	3	CH_3	CH_3		$(CH_2)_5$	0/250	0/50	138–142	40	A	$C_{24}H_{31}N_3O$	C, H
94	2	C_2H_5	C_2H_5		$(CH_2)_5$	L/125	0/50	171–173.5	67	A	$C_{25}H_{33}N_3O \cdot HCl$	C, H
95	2	CH_3	CH_3		$(CH_2)_2O(CH_2)_2$	63	0/50	120–122	55	A	$C_{22}H_{27}N_3O_2$	C, H
96	3	CH_3	CH_3		$(CH_2)_2O(CH_2)_2$	125	0/50	173–177	60	A	$C_{23}H_{29}N_3O_2$	C, H
97	2	C_2H_5	C_2H_5		$(CH_2)_2O(CH_2)_2$	32	0/50	117–120	84	A	$C_{24}H_{31}N_3O_2$	C, H

[a] A single number indicates the dose at which Straub tail was observed. L indicates that a minimum of 2/5 mice died at the dose indicated. 0/250 indicates that 0/5 mice died and Straub tail was not observed at 250 mg/kg. Morphine induced a Straub tail effect at a dose of 16 mg/kg; its antidiarrheal ED_{50} was 25 mg/kg. Diphenoxylate induced a Straub tail effect at doses of 16 mg/kg and mydriasis at doses as low as 2 mg/kg; its antidiarrheal ED_{50} was 1.9 mg/kg. [b] If an ED_{50} was not obtained, the result is indicated as % inhibition/dose mg/kg. [c] The recrystallization solvent for the solids was *i*-PrOH. [d] These yields were obtained in single experiments and are not optimum. [e] A is the alkylation procedure; B is the amination procedure. [f] These compounds were purified by chromatography over Woelm neutral alumina and dried at 140° (0.4 mm) for 6 hr. [g] C: calcd, 78.16; found, 77.62. [h] C: calcd, 73.82; found, 73.20. [i] C: calcd, 72.79; found, 72.03. [j] H: calcd, 6.97; found, 7.43. [k] C: calcd, 67.22; found, 67.92. [l] This compound was a mixture of $CH(CH_3)CH_2$ and $CH_2CH(CH_3)$ isomers by nmr.

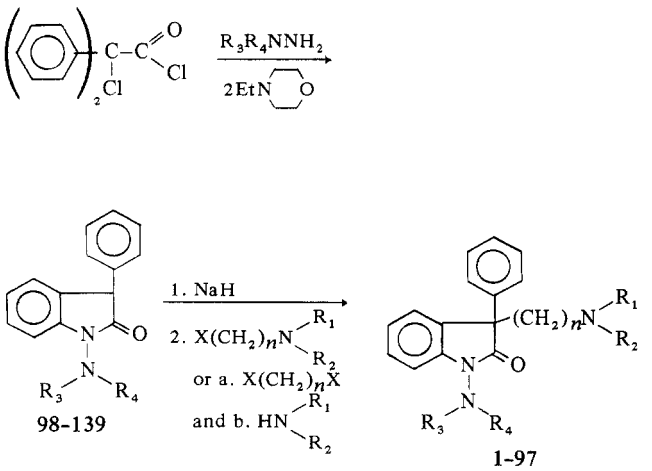
Table II[a]



No.	R_3	R_4	Mp or bp (mm), °C	Purification solvent[c]	Yield, %	Formula	Analyses
98[b]	CH_3	CH_3	90–91	C	75	$C_{16}H_{16}N_2O$	C, H, N
99		$(CH_2)_5$	120.5–122.5	A	72	$C_{19}H_{20}N_2O$	C, H
100		$(CH_2)_2O(CH_2)_2$	134–136.5	A	67	$C_{18}H_{18}N_2O_2$	C, H
101	CH_3	C_6H_5	114–116	A	32	$C_{21}H_{18}N_2O$	C, H
102	CH_3	2-$C_4H_3OCH_2$	91–93	B	75	$C_{20}H_{18}N_2O_2$	C, H
103	CH_3	2-$C_4H_3SCH_2$	126.5–129	B	47	$C_{20}H_{18}N_2OS$	C, H
104	C_2H_5	$C_6H_5CH_2$	69–71	A	61	$C_{23}H_{22}N_2O$	C, H
105	CH_3	$C_6H_5CH_2CH_2$	85–87	A	68	$C_{23}H_{22}N_2O$	C, H
106	CH_3	$C_6H_5CH_2$	83–85	A	71	$C_{22}H_{20}N_2O$	C, H
107	CH_3	2-$FC_6H_4CH_2$	88–90	B	68	$C_{22}H_{19}FN_2O$	C, H
108	CH_3	4-$FC_6H_4CH_2$	86–88	B	47	$C_{22}H_{19}FN_2O$	C, H
109	CH_3	2-$ClC_6H_4CH_2$	100–102	A	70	$C_{22}H_{19}ClN_2O$	C, H
110	CH_3	3-$ClC_6H_4CH_2$	87–91	B	71	$C_{22}H_{19}ClN_2O$	C, H
111	CH_3	4-$ClC_6H_4CH_2$	121–122	D	52	$C_{22}H_{19}ClN_2O$	C, H
112	CH_3	2-$BrC_6H_4CH_2$	80–82	B	69	$C_{22}H_{19}BrN_2O$	C, H
113	CH_3	2-$CF_3C_6H_4CH_2$	84–86	B	52	$C_{23}H_{19}F_3N_2O$	C, H
114	CH_3	2-$CH_3OC_6H_4CH_2$	213–215 (1.3)		66	$C_{23}H_{22}N_2O_2$	C, H
115	CH_3	3-$CH_3OC_6H_4CH_2$	180–185 (0.15)		60	$C_{23}H_{22}N_2O_2$	C, H, N[d]
116	CH_3	4-$CH_3OC_6H_4CH_2$	102–103.5	B	68	$C_{23}H_{22}N_2O_2$	C, H
117	CH_3	2-$C_2H_5OC_6H_4CH_2$	185–195 (0.30)		50	$C_{24}H_{24}N_2O_2$	C, H
118	CH_3	2-$CH_3SC_6H_4CH_2$	118–120	B	74	$C_{23}H_{22}N_2OS$	C, H
119	CH_3	4-$CH_3SC_6H_4CH_2$	114–115.5	E	31	$C_{23}H_{22}N_2OS$	C, H
120	CH_3	2-$C_2H_5SC_6H_4CH_2$	105–108	E	61	$C_{24}H_{24}N_2OS$	C, H, N
121	CH_3	2-$C_3H_7SC_6H_4CH_2$	122–126	B	48	$C_{25}H_{26}N_2OS$	C, H
122	CH_3	2-$(CH_3)_2CH$-$SC_6H_4CH_2$	108–110	F	79	$C_{25}H_{26}N_2OS$	C, H, N
123	CH_3	2-$CH_3C_6H_4CH_2$	78–80	B	67	$C_{23}H_{22}N_2O$	C, H
124	CH_3	2-Cl, 3-$CH_3OC_6H_3CH_2$	112–113	B	71	$C_{23}H_{21}ClN_2O_2$	C, H
125	CH_3	2-Cl, 4-$CH_3OC_6H_3CH_2$	97–99	F	48	$C_{23}H_{21}ClN_2O_2$	C, H
126	CH_3	2-Cl, 5-$CH_3OC_6H_3CH_2$	117–120	E	54	$C_{23}H_{21}ClN_2O_2$	C, H
127	CH_3	2-Cl, 6-$CH_3OC_6H_3CH_2$	118–120	B	63	$C_{23}H_{21}ClN_2O_2$	C, H, N
128	CH_3	3-Cl, 2-$CH_3OC_6H_3CH_2$	96–99	F	56	$C_{23}H_{21}ClN_2O_2$	C, H, N
129	CH_3	4-Cl, 2-$CH_3OC_6H_3CH_2$	124–127	F	65	$C_{23}H_{21}ClN_2O_2$	C, H, N
130	CH_3	5-Cl, 2-$CH_3OC_6H_3CH_2$	90–93	E	52	$C_{23}H_{21}ClN_2O_2$	C, H, N
131	CH_3	2,3-$Cl_2C_6H_3CH_2$	110–112	A	52	$C_{22}H_{18}Cl_2N_2O$	C, H, N
132	CH_3	2,4-$Cl_2C_6H_3CH_2$	97–99	A	66	$C_{22}H_{18}Cl_2N_2O$	C, H
133	CH_3	2,5-$Cl_2C_6H_3CH_2$	110–112	A	70	$C_{22}H_{18}Cl_2N_2O$	C, H, N
134	CH_3	2,6-$Cl_2C_6H_3CH_2$	123–125	A	65	$C_{22}H_{18}Cl_2N_2O$	C, H, N
135	CH_3	2,3-$(CH_3O)_2C_6H_3CH_2$	87–92	A	47	$C_{24}H_{24}N_2O_3$	C, H
136	CH_3	2,5-$(CH_3O)_2C_6H_3CH_2$	81.5–83.5	F	77	$C_{24}H_{24}N_2O_3$	C, H, N
137	CH_3	3,4-$(CH_3O)_2C_6H_3CH_2$	97–100	B	57	$C_{24}H_{24}N_2O_3$	C, H
138	CH_3	2-Cl, 6-$FC_6H_3CH_2$	99–101	A	50	$C_{22}H_{18}ClFN_2O$	C, H, N
139	CH_3	2-Cl, 5-$FC_6H_3CH_2$	116.5–117.5	A	50	$C_{22}H_{18}ClFN_2O$	C, H, N

[a] These compounds possessed no Straub tail or antidiarrheal activity. [b] See ref 26. [c] A, 2-propanol; B, ethanol; C, cyclohexane; D, 2-propanol–methanol; E, methanol; F, benzene–petroleum ether. [d] C: calcd, 77.07; found, 77.82. N: calcd, 7.82; found, 6.70.

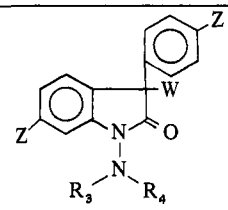
Scheme I



Et_2O (THF) solution of 1 equiv of α-chlorodiphenylacetyl chloride[27] followed by the addition of 2 equiv of 4-ethylmorpholine to yield the 1-dialkylamino-3-phenyloxindoles. Physical data of these new compounds are in Table II. Treatment of the oxindoles with 1 equiv of NaH in THF–$PhCH_3$ followed by the addition of a dialkylaminoalkyl halide resulted in the final products. In some cases, an α,ω-dihaloalkane was used and the resulting 1-(dialkylamino)-3-(ω-haloalkyl)-3-phenyloxindole was allowed to react with the appropriate amine. The title compounds along with their biological activities are in Table I. Table III contains 3-(ω-haloalkyl)oxindoles, oxindoles that are substituted on the aromatic rings, and some miscellaneous derivatives. The active compounds have been disclosed in a U. S. Patent.[28]

Structure–Activity Relationship. A significant separation of antidiarrheal activity from the Straub tail effect was obtained when the 1 substituent was an alkylaralkylamino

Table III[a]



No.	R_3	R_4	W	Z	Mp or bp (mm), °C	Purification solvent[b]	Yield, %	Empirical formula	Analyses
140[c]	CH_3	CH_3	H	Cl	173–175	A	65	$C_{16}H_{14}Cl_2N_2O$	C, H
141[d]	CH_3	CH_3	H	CH_3O	120–121	A	50	$C_{18}H_{20}N_2O_3$	C, H, N
142	CH_3	CH_3	$(CH_2)_2Br$	H	88–90	A	71	$C_{18}H_{19}BrN_2O$	C, H, N
143	CH_3	CH_3	$(CH_2)_5Br$	H	101–103	A	70	$C_{21}H_{25}BrN_2O$	C, H
144	CH_3	$C_6H_5CH_2$	$(CH_2)_2Br$	H	Oil[e]			$C_{24}H_{23}BrN_2O$	
145	CH_3	$C_6H_5CH_2$	$(CH_2)_3Br$	H	Oil[e]			$C_{25}H_{25}BrN_2O$	
146	CH_3	$C_6H_5CH_2$	$(CH_2)_4Br$	H	Oil[e]			$C_{26}H_{27}BrN_2O$	
147	CH_3	2-$ClC_6H_4CH_2$	$(CH_2)_2Br$	H	116.5–120	B	50	$C_{24}H_{22}BrClN_2O$	C, H
148	CH_3	2-$CH_3SC_6H_4CH_2$	$(CH_2)_2Br$	H	104–106	A	63	$C_{25}H_{26}BrN_2OS$	C, H, N
149	CH_3	CH_3	$(CH_2)_2N(C_2H_5)_2$	Cl	190–193	A	55	$C_{22}H_{27}Cl_2N_3O\cdot HCl$	C, H
150	CH_3	CH_3	$(CH_2)_2N(CH_3)_2$	Cl	129.5–131	A	60	$C_{20}H_{23}Cl_2N_3O$	C, H
151	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	Cl	101–104	G	50	$C_{21}H_{25}Cl_2N_3O$	C, H
152[f]	CH_3	H	$(CH_2)_2N(CH_3)_2$	H	193–196	A	50	$C_{19}H_{23}N_3O\cdot HCl$	C, H
153[g]	CH_3	H	$(CH_2)_3N(CH_3)_2$	H	232–237	E	54	$C_{20}H_{24}N_3O\cdot HCl$	C, H
154	CH_3	CH_3	$(CH_2)_2N(C_2H_5)_2$	CH_3O	185–195 (0.15)		75	$C_{24}H_{33}N_3O_3$	C, H, N

[a] These compounds possessed no Straub tail or antidiarrheal activity. [b] See footnote *b*, Table II, G, heptane. [c] Bis(4-chlorophenyl)acetic acid was converted to the acid chloride using $SOCl_2$ and treated with Br_2 and *hν*, and the resulting α-bromobis(4-chlorophenyl)acetyl chloride was treated with an excess of 1,1-dimethylhydrazine. [d] *p*-Anisilic acid was treated with 1 equiv of PCl_5 in the manner of Stevens and French[27] and the crude product was allowed to react with an excess of 1,1-dimethylhydrazine. [e] These oils were used crude in the amination reaction. [f] This compound was prepared by catalytic (20% Pd/C) hydrogenation of compound no. **16** in MeOH. [g] This was prepared as in footnote *f* on compound no. **17**.

group. The separation was enhanced when the aralkyl moiety was a benzyl group with an *o*-chloro, bromo, methoxy, alkylthio, or trifluoromethyl substituent (see compounds no. **22, 25, 33, 34, 40, 42, 44, 45**). This was also true of a number of disubstituted analogs (see compounds no. **68–70, 78**). A dialkylaminoalkyl substituent on the three position was essential for any biological activity. Separation of the amino from the three position by two carbons gave the most potent compounds. Most other changes resulted in the reduction or elimination of either or both biological actions. These are represented in Table I with a minimum of examples. Some inactive derivatives with substituents on the 3-aryl group and aryl portion of the oxindole are included in Table III. The active compounds did not antagonize the blood pressure effects of acetylcholine in an anesthetized dog preparation.

Experimental Section‡

General Procedure for the Preparation of the Oxindoles. To a stirred solution of 265.15 g (1.0 mol) of α-chlorodiphenylacetyl chloride[27] in 1 l. of THF was added a solution of 1 equiv of a 1,1-disubstituted hydrazine in 100 ml of THF. The mixture was refluxed 1 hr and cooled under N_2 to 15°. With stirring, 230.4 g (2.0 mol) of 4-ethylmorpholine was added and the mixture was refluxed 90 min. The mixture was cooled to 0° under N_2 and the 4-ethylmorpholine hydrochloride was removed by filtration. The filtrate was concentrated on a rotary evaporator and diluted with an equal volume of *i*-PrOH. In the majority of cases, the oxindole crystallized and could be alkylated without further purification. If the product failed to crystallize, the *i*-PrOH was stripped from the oil. The oil was dissolved in Et_2O or $PhCH_3$ and washed with dilute NaOH. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and redissolved in *i*-PrOH. A few of the oxindoles were distilled and used as oils. The amide ir band was found between 1680 and 1720 cm^{-1}. The nmr spectra of the 1-(benzylmethylamino)-3-phenyloxindole type is complex because of restricted rotation around the N–N bond. The benzylic protons and the 3-H appear as a multiplet between 3.9 and 4.8 ppm depending upon the substituent on the aromatic ring. The *N*-methyl protons appear as an unequal doublet between 2.7 and 3.1 ppm.

General Procedure for the Alkylation of the Oxindoles (Procedure A). This is a variation of the procedure of Zaugg and DeNet.§,[29] To a heated (60–70°) stirred solution of 0.1 mol of NaH in 150 ml of $PhCH_3$ and 25 ml of THF under a gentle stream of N_2 § was added 0.1 mol of oxindole (portionwise through a powder funnel). Then a solution of 0.1 mol of a dialkylaminoalkyl halide in 100 ml of $PhCH_3$ was added over a 15-min period. The mixture was refluxed 3–18 hr depending upon the reactivity of the halide. The mixture was cooled to 25° and 10 ml of H_2O added. The product was extracted into dilute HCl. The acidic extracts were made strongly basic with NaOH and extracted with Et_2O. The extracts were dried over anhydrous $MgSO_4$, filtered, concentrated, and distilled or recrystallized. The C=O ir absorption was in the same range as in the unalkylated oxindoles. The alkylations with α,ω-dihaloalkanes were carried out in the same manner or by addition of a twofold excess of the α,ω-dihaloalkane before the addition of the NaH. All of the 1-(dialkylamino)-3-(ω-haloalkyl)-3-phenyloxindoles were contaminated with the product from the reaction of the anion with both halogens. This type of impurity was separated by the acid extraction step following amination.

General Procedure for the Reaction of the 1-(Dialkylamino)-3-(ω-haloalkyl)-3-phenyloxindoles with Amines (Procedure B). The halides were refluxed for 18 hr with an excess of a secondary amine. If the amine was low boiling, the two components were heated at 100° for 18 hr in a sealed pressure vessel. The isolation procedure was the same as that used for the alkylation reaction.

The 1,1-disubstituted hydrazines were prepared by methods summarized elsewhere.[30] As reported by others,[31] many of these

‡ The melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. A Beckman IR-9 spectrophotometer was used to determine the infrared spectra. The nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer. Where analyses are indicated by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

§ DMF, THF, and DMSO have all been used successfully; however, up to 30% of the alkylated product has been found in the water–polar solvent mixture by concentration on the rotary evaporator and reextraction. The procedure described makes this unnecessary. The alkylation has also been carried out using $NaOCH_3$ in MeOH. The N_2 atmosphere is necessary because of the ease of oxidation at the 3 position of the oxindole in the presence of base and air.

were difficult to analyze as bases. They were used successfully in the oxindole synthesis after distillation and without further purification.

Acknowledgments. The authors wish to express their appreciation to Dr. L. M. Long, Dr. A. C. Bratton, Jr., and the late Dr. D. H. Kaump for encouragement in this investigation. We also thank Mr. C. E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and associates for the spectral data, and Mr. W. M. Pearlman for the performance of many hydrogenations involved in the preparation of starting materials. We also thank Dr. D. A. McCarthy and associates for the Straub tail and anesthetized dog data.

References

(1) H. L. Dupont and R. B. Hornik, "Diarrheal diseases. Disease-a-Month," Yearbook Medical Publishers, Chicago, Ill., 1969.
(2) L. S. Goodman and A. Gilman in "The Pharmacological Basis of Therapeutics," 3rd ed, Macmillan, New York, N. Y., 1965, p 271.
(3) H. F. Fraser, G. D. Van Horn, W. R. Martin, A. B. Wolbach, and H. Isbell, *J. Pharmacol. Exp. Ther.*, **133**, 371 (1961).
(4) A. M. Connell, *Gut*, **3**, 342 (1962).
(5) H. Kruger, *Physiol. Rev.*, **17**, 618 (1937).
(6) J. Neely, *Brit. J. Surg.*, **56**, 925 (1969).
(7) P. Bass and J. N. Wiley, *Amer. J. Physiol.*, **208**, 908 (1965).
(8) P. Bass and J. N. Wiley, *Amer. J. Dig. Dis.*, **10**, 183 (1965).
(9) J. A. Rinaldo, Jr., E. A. Orinion, R. V. Simpelo, F. E. Check, and W. Beauregard, *Gastroenterology*, **60**, 438 (1971).
(10) P. A. J. Janssen and A. H. Jageneau, *J. Pharm. Pharmacol.*, **9**, 381 (1957).
(11) P. A. J. Janssen, A. H. Jageneau, and J. Huygens, *J. Med. Pharm. Chem.*, **1**, 299 (1959).
(12) H. F. Fraser and H. Isbell, *Bull. Narcotics*, **13**, 29 (1961); *Chem. Abstr.*, **61**, 3592 (1964).
(13) D. A. McCarthy, R. H. Burns, G. A. Deneau, and M. H. Seevers in "Committee on Drug Addiction and Narcotics," Minutes of Nineteenth Meeting, Addendum 2, National Academy of Sciences, National Research Council, Washington, D. C., 1958, p 10.
(14) J. T. Harries and M. Rossiter, *Lancet*, **1**, 150 (1969).
(15) W. Henderson and A. Psaila, *ibid.*, **1**, 307 (1969).
(16) F. Haffner, *Deut. Med. Wochenschr.*, **55**, 731 (1929).
(17) I. Shemano and H. Wendel, *Toxicol. Appl. Pharmacol.*, **6**, 334 (1964).
(18) W. Straub, *Deut. Med. Wochenschr.*, **37**, 1462 (1911).
(19) W. J. R. Heinekamp, *J. Pharmacol. Exp. Ther.*, **2**, 107 (1922).
(20) D. L. J. Bilbey, H. Salem, and M. H. Grossman, *Brit. J. Pharmacol.*, **15**, 540 (1960).
(21) H. Collumbine and T. S. Konop, *Can. J. Biochem. Physiol.*, **37**, 1075 (1959).
(22) A. Juul, *Arch. Int. Pharmacodyn. Ther.*, **62**, 69 (1939).
(23) M. D. Aceto, D. B. McKean, and J. Pearl, *Brit. J. Pharmacol.*, **36**, 225 (1969).
(24) J. A. Kennedy, J. N. Wiley, and P. Bass, *Amer. J. Dig. Dis.*, **17**, 925 (1972).
(25) R. F. Meyer to Parke, Davis and Co., U. S. Patent 3,314,954 (1967).
(26) R. F. Meyer, *J. Org. Chem.*, **30**, 3451 (1965).
(27) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **75**, 657 (1953).
(28) D. E. Butler to Parke, Davis and Co., U. S. Patent 3,595,866 (1971).
(29) H. E. Zaugg and R. W. DeNet, *J. Amer. Chem. Soc.*, **84**, 4576 (1962).
(30) D. E. Butler and S. M. Alexander, *J. Med. Chem.*, **14**, 1052 (1971).
(31) H. Zimmer, L. F. Audrieth, M. Zimmer, and R. A. Rowe, *J. Amer. Chem. Soc.*, **77**, 790 (1955).

Irreversible Adrenergic α-Receptor Antagonism by (*R*)- and (*S*)-*N*-(2-Chloroethyl)-*N*-methyl-2-phenyl-2-hydroxyethylamine and Related Agents

S. McLean, V. C. Swamy, D. Tomei, and D. J. Triggle*

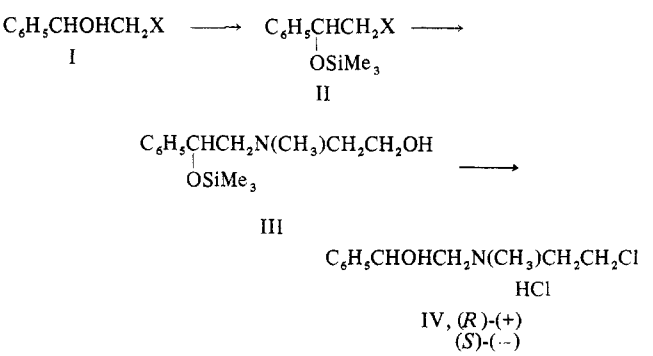
Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214.
Received June 26, 1972

The synthesis of the title compounds is described from the corresponding mandelic acids. The compounds were significantly less effective than phenoxybenzamine as irreversible α-adrenergic receptor antagonists. The *S* isomer was more effective than the *R* isomer by a factor of 6. Interpretation of these differences is complicated by the finding that these agents, in common with many other 2-halogenoethylamines, appear to produce their actions through at least two different sites of reaction.

The 2-halogenoethylamines have been extensively employed as irreversible adrenergic α-receptor antagonists,[1,2] although their activity is not confined to this receptor system.[2] Attempts to analyze the structure-activity relationships of these agents in terms of postulated models of norepinephrine binding at the α receptor[3] suffer from a number of disadvantages.[2] In particular, the structural relationship of many of these agents, with the possible exception of the *N,N*-dimethyl-2-aryl-2-halogenoethylamines,[2,4,5] to norepinephrine seems rather obscure. Furthermore, we have recently shown that a major site of interaction of irreversible adrenergic α-receptor antagonists is at a Ca^{2+} binding/mobilization site rather than the norepinephrine recognition site.[6,7]

It thus appeared of interest to investigate compounds that are structurally more closely related to norepinephrine. Our initial investigations centered on *N*-(2-chloroethyl)-*N*-methyl-2-hydroxy-2-phenylethylamine (IV) in its enantiomeric forms. These were synthesized from optically active mandelic acids, agents of impeccable stereochemical pedigree,[8] according to the sequence shown in Scheme I.

Scheme I



Experimental Section

Melting points were determined on a Thomas-Kofler hot stage and are corrected. Analyses were performed by Dr. A. E. Bernhardt