

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

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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 effects² 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 Jageneau¹⁰ 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 man¹² 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 Huygens¹¹ had used the mouse hot plate¹⁶ 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 Wendel¹⁷ 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 effect¹⁸⁻²⁰ 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 Juul²² 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 Pearl²³ 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 mid-night). A total of 24 rats per dose was used along with a concomitant control group. The ED₅₀ values were confirmed by repeating the test using doses that bracketed the original result. If an ED₅₀ 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

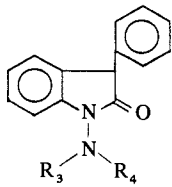
†Our thanks to Mr. H. D. Troutman who suggested the use of 4-ethylmorpholine as an acid acceptor as a means of conserving the 1,1-disubstituted hydrazines (triethylamine was inferior).

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

No.	<i>n</i>	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 ₃ O·HCl	C, H
2	3	CH ₃	CH ₃	CH ₃	CH ₃	16	21	206-207	65	A	C ₂₁ H ₂₇ N ₃ O·HCl	C, H, N
3	2	C ₂ H ₅	C ₂ H ₅	CH ₃	CH ₃	4	19	158-160 (0.3)	82	A	C ₂₂ H ₂₉ N ₃ O	C, H, N
4	1	CH ₃	CH ₃	CH ₃	CH ₃	8	47	163-165 (0.1)	84	A	C ₂₁ H ₂₇ N ₃ O	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 ₃ O·HCl	C, H
6	2	CH ₃	C ₆ H ₅ CH ₂	CH ₃	CH ₃	16	31	214.5-224	45	B	C ₂₆ H ₃₀ N ₃ O·HCl	C, H
7	2	H	(CH ₃) ₃ C	CH ₃	CH ₃	L/125	11.5	287-289	30	B	C ₂₂ H ₂₉ N ₃ O·HCl	C, H
8	2	H	H	CH ₃	CH ₃	L/125	0/50	70-72	67	B	C ₁₈ H ₂₁ N ₃ O	C, H, N
9	2		(CH ₂) ₂ O(CH ₂) ₂	CH ₃	CH ₃	4	0/50	108-109	59	B	C ₂₂ H ₂₇ N ₃ O ₂	C, H, N
10	2		(CH ₂) ₄	CH ₃	CH ₃	4	24	128-131	20	B	C ₂₂ H ₂₇ N ₃ O	C, H
11	2		(CH ₂) ₅	CH ₃	CH ₃	4	16	240.5-243	75	B	C ₂₃ H ₂₉ N ₃ O·HCl	C, H
12	2		(CH ₂) ₄ CH(CH ₃)	CH ₃	CH ₃	1	20	92.5-95	50	B	C ₂₄ H ₃₁ N ₃ O	C, H
13	2		(CH ₂) ₆	CH ₃	CH ₃	2	18	230-233	76	B	C ₂₄ H ₃₁ N ₃ O·HCl	C, H
14	4	C ₂ H ₅	C ₆ H ₅ CH ₂	CH ₃	CH ₃	0/250	0/50	205-207 (0.15)	40	A	C ₂₉ H ₃₅ N ₃ O	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 ₃ O	C, H
16	2	CH ₃	CH ₃	CH ₃	C ₆ H ₅ CH ₂	125	67	87-90	35	A	C ₂₆ H ₂₉ N ₃ O	C, H
17	3	CH ₃	CH ₃	CH ₃	C ₆ H ₅ CH ₂	0/250	52	187-189.5	68	A	C ₂₇ H ₃₁ N ₃ O·HCl	C, H
18	2	C ₂ H ₅	C ₂ H ₅	CH ₃	C ₆ H ₅ CH ₂	0/250	100	206-208 (0.46)	72.5	A	C ₂₈ H ₃₃ N ₃ O	C, H
19	3	C ₂ H ₅	C ₂ H ₅	CH ₃	C ₆ H ₅ CH ₂	L/125	54	192-196 (0.15)	82	A	C ₂₉ H ₃₅ N ₃ O	C, H
20	2	CH ₃	CH ₃	CH ₃	2-ClC ₆ H ₄ CH ₂	0/250	120	98.5-101.5	50	A	C ₂₆ H ₂₈ ClN ₃ O	C, H
21	3	CH ₃	CH ₃	CH ₃	2-ClC ₆ H ₄ CH ₂	L/250	112	209-211.5	52	A	C ₂₇ H ₃₀ ClN ₃ O·HCl	C, H, N
22	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-ClC ₆ H ₄ CH ₂	0/250	67	214-215 (0.46)	72	A	C ₂₈ H ₃₂ ClN ₃ O	C, H
23	2	C ₃ H ₇	C ₃ H ₇	CH ₃	2-ClC ₆ H ₄ CH ₂	0/250	70	202.5-204	59	A	C ₃₀ H ₃₆ ClN ₃ O·HCl	C, H, N
24	3	C ₂ H ₅	C ₂ H ₅	CH ₃	2-ClC ₆ H ₄ CH ₂	L/125	47	199-200 (0.16)	66	A	C ₂₉ H ₃₄ ClN ₃ O	C, H
25	2		(CH ₂) ₅	CH ₃	2-ClC ₆ H ₄ CH ₂	0/250	61	118-120	62	B	C ₂₉ H ₃₂ ClN ₃ O	C, H, N
26	2		(CH ₂) ₆	CH ₃	2-ClC ₆ H ₄ CH ₂	0/250	14/35	109.5-111.5	70	B	C ₃₀ H ₃₄ ClN ₃ O	C, H, N
27	2	C ₂ H ₅	C ₂ H ₅	CH ₃	3-ClC ₆ H ₄ CH ₂	125	68	200-205 (0.165)	76	A	C ₂₈ H ₃₂ ClN ₃ O	C, H
28	3	CH ₃	CH ₃	CH ₃	3-ClC ₆ H ₄ CH ₂	L/250	44/100	195-203 (0.15)	69	A	C ₂₇ H ₃₀ ClN ₃ O	C, H
29	2	CH ₃	CH ₃	CH ₃	4-ClC ₆ H ₄ CH ₂	L/250	125	92-95	50	A	C ₂₆ H ₂₈ ClN ₃ O	C, H
30	3	CH ₃	CH ₃	CH ₃	4-ClC ₆ H ₄ CH ₂	L/250	94	221.5-224.5	62	A	C ₂₇ H ₃₀ ClN ₃ O·HCl	C, H
31	2	C ₂ H ₅	C ₂ H ₅	CH ₃	4-ClC ₆ H ₄ CH ₂	L/125	64	215-216 (0.475)	72	A	C ₂₈ H ₃₂ ClN ₃ O	C, H
32	3	CH ₃	CH ₃	CH ₃	2-BrC ₆ H ₄ CH ₂	0/250	21/50	<i>f</i>	75	A	C ₂₇ H ₃₀ BrN ₃ O	C, H
33	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-BrC ₆ H ₄ CH ₂	0/250	73	<i>f</i>	80	A	C ₂₈ H ₃₂ BrN ₃ O	C, H
34	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-CF ₃ C ₆ H ₄ CH ₂	L/250	52	185-187 (0.12)	70	A	C ₂₉ H ₃₂ F ₃ N ₃ O	C, H
35	3	CH ₃	CH ₃	CH ₃	2-CH ₃ C ₆ H ₄ CH ₂	L/250	40/125	195-197 (0.15)	65	A	C ₂₈ H ₃₃ N ₃ O	C, H
36	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-CH ₃ C ₆ H ₄ CH ₂	63	75	185-190 (0.15)	77	A	C ₂₈ H ₃₅ N ₃ O	C, H
37	3	CH ₃	CH ₃	CH ₃	2-CH ₃ SC ₆ H ₄ CH ₂	0/250	40	106.5-108.5	41	A	C ₂₈ H ₃₃ N ₃ OS	C, H, N
38	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-CH ₃ SC ₆ H ₄ CH ₂	125	24	218-222 (0.30)	53	A	C ₂₉ H ₃₅ N ₃ OS	C, H
39	3	C ₂ H ₅	C ₂ H ₅	CH ₃	2-CH ₃ SC ₆ H ₄ CH ₂	0/250	44	218-222 (0.20)	46	A	C ₃₀ H ₃₇ N ₃ OS	C, H
40	2		(CH ₂) ₅	CH ₃	2-CH ₃ SC ₆ H ₄ CH ₂	0/250	19	93.5-96	50	B	C ₃₀ H ₃₅ N ₃ OS	C, H
41	2	C ₂ H ₅	C ₂ H ₅	CH ₃	4-CH ₃ SC ₆ H ₄ CH ₂	L/250	62	212-221 (0.225)	62	A	C ₂₉ H ₃₅ N ₃ OS	C, H
42	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-C ₂ H ₅ SC ₆ H ₄ CH ₂	0/250	20	227-229 (0.35)	73	A	C ₃₀ H ₃₇ N ₃ OS	C, H, N
43	3	CH ₃	CH ₃	CH ₃	2-C ₂ H ₅ SC ₆ H ₄ CH ₂	0/250	100	221-226 (0.175)	25	A	C ₃₀ H ₃₇ N ₃ OS	C, H
44	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-C ₂ H ₅ SC ₆ H ₄ CH ₂	0/250	37	221-226 (0.25)	74	A	C ₃₁ H ₃₉ N ₃ OS	C, H
45	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2- <i>i</i> -C ₃ H ₇ SC ₆ H ₄ CH ₂	0/250	34	86.5-88	54	A	C ₃₁ F ₃₉ N ₃ OS	C, H, N
46	2	CH ₃	CH ₃	CH ₃	2-CH ₃ OC ₆ H ₄ CH ₂	L/250	81	215-217 (0.55)	63	A	C ₂₇ H ₃₁ N ₃ O ₂	C, H
47	3	CH ₃	CH ₃	CH ₃	2-CH ₃ OC ₆ H ₄ CH ₂	L/250	17/35	192-194 (0.25)	34	A	C ₂₈ H ₃₃ N ₃ O ₂	C, H
48	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-CH ₃ OC ₆ H ₄ CH ₂	0/250	47/70	149.5-153	50	A	C ₂₉ H ₃₅ N ₃ O ₂ ·2HBr	C, H
49	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-C ₂ H ₅ OC ₆ H ₄ CH ₂	0/250	64	195-205 (0.15)	55	A	C ₃₀ H ₃₇ N ₃ O ₂	C, H

50	2	CH ₃	CH ₃	CH ₃	3-CH ₃ OC ₆ H ₄ CH ₂	0/250	38/125	175-180 (0.125)	51	A	C ₂₇ H ₃₁ N ₃ O ₂	C, H
51	3	CH ₃	CH ₃	CH ₃	3-CH ₃ OC ₆ H ₄ CH ₂	L/250	33/125	195-199 (0.175)	50	A	C ₂₈ H ₃₃ N ₃ O ₂	C, H
52	2	C ₂ H ₅	C ₂ H ₅	CH ₃	3-CH ₃ OC ₆ H ₄ CH ₂	L/125	100	195-205 (0.20)	45	A	C ₂₉ H ₃₅ N ₃ O ₂	C, H, N
53	2	C ₂ H ₅	C ₂ H ₅	CH ₃	3-CH ₃ OC ₆ H ₄ CH ₂	L/125	48/100	208-215 (0.20)	50	A	C ₂₉ H ₃₅ N ₃ O ₂	C, H, N
54	2	CH ₃	CH ₃	CH ₃	4-CH ₃ OC ₆ H ₄ CH ₂	L/125	23/35	205-207 (0.26)	72	A	C ₂₇ H ₃₁ N ₃ O ₂	C, H
55	3	CH ₃	CH ₃	CH ₃	4-CH ₃ OC ₆ H ₄ CH ₂	L/250	94	218-224 (0.55)	68	A	C ₂₈ H ₃₃ N ₃ O ₂	C, H
56	2	C ₂ H ₅	C ₂ H ₅	CH ₃	4-CH ₃ OC ₆ H ₄ CH ₂	L/250	66	205-215 (0.30)	67	A	C ₂₉ H ₃₅ N ₃ O ₂	C, H
57	2	CH ₃	CH ₃	CH ₃	2-FC ₆ H ₄ CH ₂	63	22/35	200-203 (0.675)	67	A	C ₂₆ H ₂₈ FN ₃ O	C, H
58	3	CH ₃	CH ₃	CH ₃	2-FC ₆ H ₄ CH ₂	L/250	125	204.5-207 (0.70)	51	A	C ₂₇ H ₃₀ FN ₃ O	C, H
59	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-FC ₆ H ₄ CH ₂	63	48	180-190 (0.20)	75	A	C ₂₈ H ₃₂ FN ₃ O	C, H
60	2	C ₂ H ₅	C ₂ H ₅	CH ₃	4-FC ₆ H ₄ CH ₂	63	50	202-204 (0.40)	89	A	C ₂₈ H ₃₂ FN ₃ O	C, H
61	2	(CH ₂) ₄	(CH ₂) ₄	CH ₃	C ₆ H ₅ CH ₂	125	20	211.5-212.5	41	B	C ₂₈ H ₃₁ N ₃ O·HCl	C, ⁱ H, N
62	3	(CH ₂) ₄	(CH ₂) ₄	CH ₃	C ₆ H ₅ CH ₂	L/125	68	89.5-91	30	B	C ₂₉ H ₃₃ N ₃ O	C, H
63	2	(CH ₂) ₅	(CH ₂) ₅	CH ₃	C ₆ H ₅ CH ₂	0/250	57	215-225 (0.25)	53	B	C ₂₉ H ₃₃ N ₃ O	C, H
64	3	(CH ₂) ₅	(CH ₂) ₅	CH ₃	C ₆ H ₅ CH ₂	L/250	24/50	207-209	40	B	C ₃₀ H ₃₅ N ₃ O·HCl	C, H
65	3	CH ₂ CH(CH ₃)(CH ₂) ₃	CH ₂ CH(CH ₃)(CH ₂) ₃	CH ₃	C ₆ H ₅ CH ₂	L/250	18/50	204-207 (0.21)	39	B	C ₃₁ H ₃₇ N ₃ O	C, H
66	2	(CH ₂) ₆	(CH ₂) ₆	CH ₃	C ₆ H ₅ CH ₂	32	72	216-217 (0.21)	31	B	C ₃₀ H ₃₅ N ₃ O	C, H
67	4	(CH ₂) ₅	(CH ₂) ₅	CH ₃	C ₆ H ₅ CH ₂	L/250	15/50	148-153	30	B	C ₃₁ H ₃₇ N ₃ O·HCl	C, H
68	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-Cl, 3-CH ₃ OC ₆ H ₃ CH ₂	L/250	18	100-102	65	A	C ₂₉ H ₃₄ ClN ₃ O ₂	C, H
69	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-Cl, 4-CH ₃ OC ₆ H ₃ CH ₂	0/250	15	218-222 (0.40)	55	A	C ₂₉ H ₃₄ ClN ₃ O ₂	C, H, N
70	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-Cl, 5-CH ₃ OC ₆ H ₃ CH ₂	0/250	28	<i>f</i>	35	A	C ₂₉ H ₃₄ ClN ₃ O ₂	C, H, ^f N
71	2	C ₂ H ₅	C ₂ H ₅	CH ₃	4-Cl, 2-CH ₃ OC ₆ H ₃ CH ₂	L/125	37	188-190 (0.40)	63	A	C ₂₉ H ₃₄ ClN ₃ O ₂	C, H
72	2	C ₂ H ₅	C ₂ H ₅	CH ₃	5-Cl, 2-CH ₃ OC ₆ H ₃ CH ₂	L/125	26	222-224 (0.40)	73	A	C ₂₉ H ₃₄ ClN ₃ O ₂	C, H, N
73	3	CH ₃	CH ₃	CH ₃	2,4-Cl ₂ C ₆ H ₃ CH ₂	0/250	96	204-206 (0.15)	52	A	C ₂₇ H ₂₉ Cl ₂ N ₃ O	C, ^k H
74	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2,6-Cl ₂ C ₆ H ₃ CH ₂	0/250	42/125	218-224 (0.20)	72	A	C ₂₈ H ₃₁ Cl ₂ N ₃ O	C, H
75	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-Cl, 6-FC ₆ H ₃ CH ₂	0/250	50	186-187 (0.01)	77	A	C ₂₈ H ₃₁ ClFN ₃ O	C, H, N
76	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2,3-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	L/250	36	222-223 (0.35)	70	A	C ₃₀ H ₃₇ N ₃ O ₃	C, H
77	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2,5-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	L/250	35	213-216 (0.175)	63	A	C ₃₀ H ₃₇ N ₃ O ₃	C, H, N
78	2	C ₂ H ₅	C ₂ H ₅	CH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	0/250	32	225-228 (0.20)	69	A	C ₃₀ H ₃₇ N ₃ O ₃	C, H, N
79	2	CH ₃	CH ₃	CH ₃	2-C ₄ H ₉ OCH ₂	16	34/100	178-179 (0.225)	72	A	C ₂₄ H ₂₇ N ₃ O ₂	C, H
80	3	CH ₃	CH ₃	CH ₃	2-C ₄ H ₉ OCH ₂	L/125	44/100	180.5-181 (0.175)	55	A	C ₂₅ H ₂₉ N ₃ O ₂	C, H
81	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-C ₄ H ₉ O-CH ₂	16	45	185-186 (0.30)	50	A	C ₂₆ H ₃₁ N ₃ O ₂	C, H
82	3	CH ₃	CH ₃	CH ₃	2-C ₄ H ₉ S-CH ₂	L/125	125	80-83.5	57	A	C ₂₅ H ₂₉ N ₃ OS	C, H
83	2	C ₂ H ₅	C ₂ H ₅	CH ₃	2-C ₄ H ₉ S-CH ₂	16	64	96-99	79	A	C ₂₆ H ₃₁ N ₃ OS	C, H, N
84	2	CH ₃	CH ₃	C ₂ H ₅	C ₆ H ₅ CH ₂	32	120	92.5-95	64	A	C ₂₇ H ₃₁ N ₃ O	C, H
85	3	CH ₃	CH ₃	C ₂ H ₅	C ₆ H ₅ CH ₂	L/250	100	181-184	74	A	C ₂₈ H ₃₃ N ₃ O·HCl	C, H
86	2	C ₂ H ₅	C ₂ H ₅	C ₂ H ₅	C ₆ H ₅ CH ₂	0/250	48	176-178.5	69	A	C ₂₉ H ₃₅ N ₃ O·2HCl	C, H
87	2	CH ₃	CH ₃	CH ₃	C ₆ H ₅ CH ₂ CH ₂	L/125	12/25	183-184.5	69	A	C ₂₇ H ₃₁ N ₃ O·HCl	C, H
88	3	CH ₃	CH ₃	CH ₃	C ₆ H ₅ CH ₂ CH ₂	L/125	20/25	180.5-182.5	65	A	C ₂₈ H ₃₃ N ₃ O·HCl	C, H
89	2	C ₂ H ₅	C ₂ H ₅	CH ₃	C ₆ H ₅ CH ₂ CH ₂	L/250	50	180-183 (0.31)	82	A	C ₂₉ H ₃₅ N ₃ O	C, H
90	2	CH ₃	CH ₃	CH ₃	C ₆ H ₅	32	11/35	222-226	50	A	C ₂₅ H ₂₇ N ₃ O·HCl	C, H
91	2	C ₂ H ₅	C ₂ H ₅	CH ₃	C ₆ H ₅	63	33	<i>f</i>	30	A	C ₂₇ H ₃₁ N ₃ O	C, H
92	2	CH ₃	CH ₃	(CH ₂) ₅	(CH ₂) ₅	0/250	0/50	206-209	68	A	C ₂₃ H ₂₉ N ₃ O·HCl	C, H
93	3	CH ₃	CH ₃	(CH ₂) ₅	(CH ₂) ₅	0/250	0/50	138-142	40	A	C ₂₄ H ₃₁ N ₃ O	C, H
94	2	C ₂ H ₅	C ₂ H ₅	(CH ₂) ₅	(CH ₂) ₅	L/125	0/50	171-173.5	67	A	C ₂₅ H ₃₃ N ₃ O·HCl	C, H
95	2	CH ₃	CH ₃	(CH ₂) ₂ O(CH ₂) ₂	(CH ₂) ₂ O(CH ₂) ₂	63	0/50	120-122	55	A	C ₂₂ H ₂₇ N ₃ O ₂	C, H
96	3	CH ₃	CH ₃	(CH ₂) ₂ O(CH ₂) ₂	(CH ₂) ₂ O(CH ₂) ₂	125	0/50	173-177	60	A	C ₂₃ H ₂₉ N ₃ O ₂	C, H
97	2	C ₂ H ₅	C ₂ H ₅	(CH ₂) ₂ O(CH ₂) ₂	(CH ₂) ₂ O(CH ₂) ₂	32	0/50	117-120	84	A	C ₂₄ H ₃₁ N ₃ O ₂	C, H

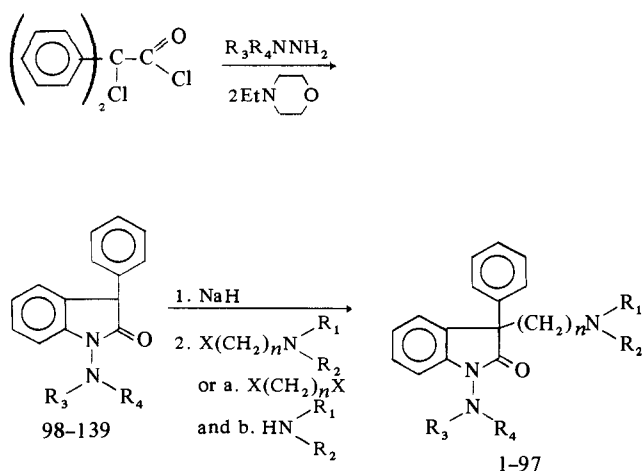
^aA single number indicates the dose at which Straub tail was observed. L indicates that a minimum of 2/5 mice died at the dose indicated. 0/250 indicates that 0/5 mice died and Straub tail was not observed at 250 mg/kg. Morphine induced a Straub tail effect at a dose of 16 mg/kg; its antidiarrheal ED₅₀ 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 ED₅₀ was 1.9 mg/kg. ^bIf an ED₅₀ was not obtained, the result is indicated as % inhibition/dose mg/kg. ^cThe recrystallization solvent for the solids was *i*-PrOH. ^dThese yields were obtained in single experiments and are not optimum. ^eA is the alkylation procedure; B is the amination procedure. ^fThese compounds were purified by chromatography over Woelm neutral alumina and dried at 140° (0.4 mm) for 6 hr. ^gC: calcd, 78.16; found, 77.62. ^hC: calcd, 73.82; found, 73.20. ⁱC: calcd, 72.79; found, 72.03. ^jH: calcd, 6.97; found, 7.43. ^kC: calcd, 67.22; found, 67.92. ^lThis compound was a mixture of CH(CH₃)CH₂ and CH₂CH(CH₃) 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 ₂ O	C, H, N
99		(CH ₂) ₅	120.5-122.5	A	72	C ₁₉ H ₂₀ N ₂ O	C, H
100		(CH ₂) ₂ O(CH ₂) ₂	134-136.5	A	67	C ₁₈ H ₁₈ N ₂ O ₂	C, H
101	CH ₃	C ₆ H ₅	114-116	A	32	C ₂₁ H ₁₈ N ₂ O	C, H
102	CH ₃	2-C ₄ H ₉ OCH ₂	91-93	B	75	C ₂₀ H ₁₈ N ₂ O ₂	C, H
103	CH ₃	2-C ₄ H ₉ SCH ₂	126.5-129	B	47	C ₂₀ H ₁₈ N ₂ OS	C, H
104	C ₂ H ₅	C ₆ H ₅ CH ₂	69-71	A	61	C ₂₃ H ₂₂ N ₂ O	C, H
105	CH ₃	C ₆ H ₅ CH ₂ CH ₂	85-87	A	68	C ₂₃ H ₂₂ N ₂ O	C, H
106	CH ₃	C ₆ H ₅ CH ₂	83-85	A	71	C ₂₂ H ₂₀ N ₂ O	C, H
107	CH ₃	2-FC ₆ H ₄ CH ₂	88-90	B	68	C ₂₂ H ₁₉ FN ₂ O	C, H
108	CH ₃	4-FC ₆ H ₄ CH ₂	86-88	B	47	C ₂₂ H ₁₉ FN ₂ O	C, H
109	CH ₃	2-ClC ₆ H ₄ CH ₂	100-102	A	70	C ₂₂ H ₁₉ ClN ₂ O	C, H
110	CH ₃	3-ClC ₆ H ₄ CH ₂	87-91	B	71	C ₂₂ H ₁₉ ClN ₂ O	C, H
111	CH ₃	4-ClC ₆ H ₄ CH ₂	121-122	D	52	C ₂₂ H ₁₉ ClN ₂ O	C, H
112	CH ₃	2-BrC ₆ H ₄ CH ₂	80-82	B	69	C ₂₂ H ₁₉ BrN ₂ O	C, H
113	CH ₃	2-CF ₃ C ₆ H ₄ CH ₂	84-86	B	52	C ₂₃ H ₁₉ F ₃ N ₂ O	C, H
114	CH ₃	2-CH ₃ OC ₆ H ₄ CH ₂	213-215 (1.3)		66	C ₂₃ H ₂₂ N ₂ O ₂	C, H
115	CH ₃	3-CH ₃ OC ₆ H ₄ CH ₂	180-185 (0.15)		60	C ₂₃ H ₂₂ N ₂ O ₂	C, H, N ^d
116	CH ₃	4-CH ₃ OC ₆ H ₄ CH ₂	102-103.5	B	68	C ₂₃ H ₂₂ N ₂ O ₂	C, H
117	CH ₃	2-C ₂ H ₅ OC ₆ H ₄ CH ₂	185-195 (0.30)		50	C ₂₄ H ₂₄ N ₂ O ₂	C, H
118	CH ₃	2-CH ₃ SC ₆ H ₄ CH ₂	118-120	B	74	C ₂₃ H ₂₂ N ₂ OS	C, H
119	CH ₃	4-CH ₃ SC ₆ H ₄ CH ₂	114-115.5	E	31	C ₂₃ H ₂₂ N ₂ OS	C, H
120	CH ₃	2-C ₂ H ₅ SC ₆ H ₄ CH ₂	105-108	E	61	C ₂₄ H ₂₄ N ₂ OS	C, H, N
121	CH ₃	2-C ₂ H ₅ SC ₆ H ₄ CH ₂	122-126	B	48	C ₂₅ H ₂₆ N ₂ OS	C, H
122	CH ₃	2-(CH ₃) ₂ CH-SC ₆ H ₄ CH ₂	108-110	F	79	C ₂₅ H ₂₆ N ₂ OS	C, H, N
123	CH ₃	2-CH ₃ C ₆ H ₄ CH ₂	78-80	B	67	C ₂₃ H ₂₂ N ₂ O	C, H
124	CH ₃	2-Cl, 3-CH ₃ OC ₆ H ₃ CH ₂	112-113	B	71	C ₂₃ H ₂₁ ClN ₂ O ₂	C, H
125	CH ₃	2-Cl, 4-CH ₃ OC ₆ H ₃ CH ₂	97-99	F	48	C ₂₃ H ₂₁ ClN ₂ O ₂	C, H
126	CH ₃	2-Cl, 5-CH ₃ OC ₆ H ₃ CH ₂	117-120	E	54	C ₂₃ H ₂₁ ClN ₂ O ₂	C, H
127	CH ₃	2-Cl, 6-CH ₃ OC ₆ H ₃ CH ₂	118-120	B	63	C ₂₃ H ₂₁ ClN ₂ O ₂	C, H, N
128	CH ₃	3-Cl, 2-CH ₃ OC ₆ H ₃ CH ₂	96-99	F	56	C ₂₃ H ₂₁ ClN ₂ O ₂	C, H, N
129	CH ₃	4-Cl, 2-CH ₃ OC ₆ H ₃ CH ₂	124-127	F	65	C ₂₃ H ₂₁ ClN ₂ O ₂	C, H, N
130	CH ₃	5-Cl, 2-CH ₃ OC ₆ H ₃ CH ₂	90-93	E	52	C ₂₃ H ₂₁ ClN ₂ O ₂	C, H, N
131	CH ₃	2,3-Cl ₂ C ₆ H ₃ CH ₂	110-112	A	52	C ₂₂ H ₁₈ Cl ₂ N ₂ O	C, H, N
132	CH ₃	2,4-Cl ₂ C ₆ H ₃ CH ₂	97-99	A	66	C ₂₂ H ₁₈ Cl ₂ N ₂ O	C, H
133	CH ₃	2,5-Cl ₂ C ₆ H ₃ CH ₂	110-112	A	70	C ₂₂ H ₁₈ Cl ₂ N ₂ O	C, H, N
134	CH ₃	2,6-Cl ₂ C ₆ H ₃ CH ₂	123-125	A	65	C ₂₂ H ₁₈ Cl ₂ N ₂ O	C, H, N
135	CH ₃	2,3-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	87-92	A	47	C ₂₄ H ₂₄ N ₂ O ₃	C, H
136	CH ₃	2,5-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	81.5-83.5	F	77	C ₂₄ H ₂₄ N ₂ O ₃	C, H, N
137	CH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	97-100	B	57	C ₂₄ H ₂₄ N ₂ O ₃	C, H
138	CH ₃	2-Cl, 6-FC ₆ H ₃ CH ₂	99-101	A	50	C ₂₂ H ₁₈ ClFN ₂ O	C, H, N
139	CH ₃	2-Cl, 5-FC ₆ H ₃ CH ₂	116.5-117.5	A	50	C ₂₂ H ₁₈ ClFN ₂ O	C, H, N

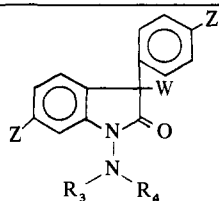
^aThese compounds possessed no Straub tail or antidiarrheal activity. ^bSee ref 26. ^cA, 2-propanol; B, ethanol; C, cyclohexane; D, 2-propanol-methanol; E, methanol; F, benzene-petroleum ether. ^dC: calcd, 77.07; found, 77.82. N: calcd, 7.82; found, 6.70.

Scheme I



Et₂O (THF) solution of 1 equiv of α -chlorodiphenylacetyl chloride²⁷ 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-PhCH₃ 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^d

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 ₂ N ₂ O	C, H
141 ^d	CH ₃	CH ₃	H	CH ₃ O	120-121	A	50	C ₁₈ H ₂₀ N ₂ O ₃	C, H, N
142	CH ₃	CH ₃	(CH ₂) ₂ Br	H	88-90	A	71	C ₁₈ H ₁₉ BrN ₂ O	C, H, N
143	CH ₃	CH ₃	(CH ₂) ₅ Br	H	101-103	A	70	C ₂₁ H ₂₃ BrN ₂ O	C, H
144	CH ₃	C ₆ H ₅ CH ₂	(CH ₂) ₂ Br	H	Oil ^e			C ₂₄ H ₂₃ BrN ₂ O	
145	CH ₃	C ₆ H ₅ CH ₂	(CH ₂) ₃ Br	H	Oil ^e			C ₂₅ H ₂₅ BrN ₂ O	
146	CH ₃	C ₆ H ₅ CH ₂	(CH ₂) ₄ Br	H	Oil ^e			C ₂₆ H ₂₇ BrN ₂ O	
147	CH ₃	2-ClC ₆ H ₄ CH ₂	(CH ₂) ₂ Br	H	116.5-120	B	50	C ₂₄ H ₂₂ BrClN ₂ O	C, H
148	CH ₃	2-CH ₃ SC ₆ H ₄ CH ₂	(CH ₂) ₂ Br	H	104-106	A	63	C ₂₅ H ₂₆ BrN ₂ OS	C, H, N
149	CH ₃	CH ₃	(CH ₂) ₂ N(C ₂ H ₅) ₂	Cl	190-193	A	55	C ₂₂ H ₂₇ Cl ₂ N ₃ O·HCl	C, H
150	CH ₃	CH ₃	(CH ₂) ₂ N(CH ₃) ₂	Cl	129.5-131	A	60	C ₂₀ H ₂₃ Cl ₂ N ₃ O	C, H
151	CH ₃	CH ₃	(CH ₂) ₃ N(CH ₃) ₂	Cl	101-104	G	50	C ₂₁ H ₂₅ Cl ₂ N ₃ O	C, H
152 ^f	CH ₃	H	(CH ₂) ₂ N(CH ₃) ₂	H	193-196	A	50	C ₁₉ H ₂₃ N ₃ O·HCl	C, H
153 ^g	CH ₃	H	(CH ₂) ₃ N(CH ₃) ₂	H	232-237	E	54	C ₂₀ H ₂₄ N ₃ O·HCl	C, H
154	CH ₃	CH ₃	(CH ₂) ₂ N(C ₂ H ₅) ₂	CH ₃ O	185-195 (0.15)		75	C ₂₄ H ₃₃ N ₃ O ₃	C, H, N

^aThese compounds possessed no Straub tail or antidiarrheal activity. ^bSee footnote b, Table II, G, heptane. ^cBis(4-chlorophenyl)acetic acid was converted to the acid chloride using SOCl₂ and treated with Br₂ and *hν*, and the resulting α-bromobis(4-chlorophenyl)acetyl chloride was treated with an excess of 1,1-dimethylhydrazine. ^d*p*-Anisic acid was treated with 1 equiv of PCl₅ in the manner of Stevens and French²⁷ and the crude product was allowed to react with an excess of 1,1-dimethylhydrazine. ^eThese oils were used crude in the amination reaction. ^fThis compound was prepared by catalytic (20% Pd/C) hydrogenation of compound no. 16 in MeOH. ^gThis 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 chloride²⁷ 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 N₂ 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 N₂ 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 Et₂O or PhCH₃ and washed with dilute NaOH. The organic layer was dried over anhydrous MgSO₄, filtered, concen-

trated, 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.^{8,29} To a heated (60-70°) stirred solution of 0.1 mol of NaH in 150 ml of PhCH₃ and 25 ml of THF under a gentle stream of N₂⁸ 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 PhCH₃ 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 H₂O added. The product was extracted into dilute HCl. The acidic extracts were made strongly basic with NaOH and extracted with Et₂O. The extracts were dried over anhydrous MgSO₄, 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 NaOCH₃ in MeOH. The N₂ 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.

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

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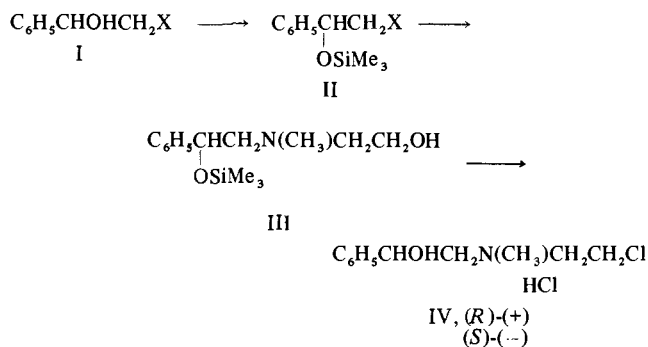
The synthesis of the title compounds is described from the corresponding mandelic acids. The compounds were significantly less effective than phenoxybenzamine as irreversible α -adrenergic receptor antagonists. The *S* isomer was more effective than the *R* isomer by a factor of 6. Interpretation of 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 receptor³ 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