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(15) Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.
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β-Adrenergic Blocking Agents. 13. (3-Amino-2-hydroxypropoxy)benzamides

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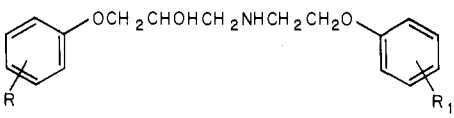
A series of (1-amino-2-hydroxypropoxy)benzamides has been tested in experimental animals. Several of the compounds are potent selective β-blockers; their structure–activity relationships and chemistry are discussed.

The search for cardioselective, β-adrenergic blocking agents, initiated by practolol[1] (Eraldin[2]), has led several groups of workers to examine analogous compounds which contain an amide function. Thus Cox and co-workers[3] have examined a series of compounds of the general structure 1 where R and R_1 represent a variety of amidic

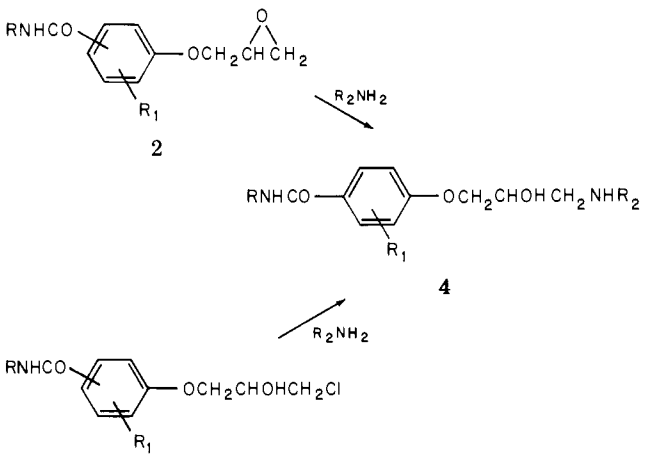


1

functions, and they have demonstrated a selectivity of action on cardiac vs. tracheal β-receptors. Similarly Shtacher and co-workers[4] found that compounds with a carbamoyl substituent show selectivity for cardiac vs. vascular β-receptors. In an extension of our work on selective β-blocking agents we have prepared a series of analogues in which the aryl residue has a para-substituted carbamoyl group together with an ortho substituent.[5]

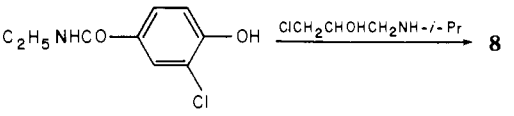
We report here the synthesis and biological activity of these compounds, some of which were more potent than practolol and exhibited similar selectivity for myocardial relative to vascular β-receptors. Some conclusions on structure–activity relationships in the series are also included.

Chemistry. The compounds were prepared in a manner analogous to that used for other 1-amino-3-(substituted phenoxy)-2-propanols using the reaction of 1,2-epoxy-3-(substituted carbamoylphenoxy)propane (**2**) or 1-chloro-3-(substituted carbamoylphenoxy)-2-propanol (**3**) with the appropriate amine. The various hydroxy-*N*-



2 4 3

substituted benzamides used as starting material were synthesized by well-known methods, those which are novel are listed in Table II. The epoxide **2** and chlorohydrin **3** intermediates were used without purification in most cases. A marked feature of the series was the difficulty experienced in isolating the final product, TLC separation being necessary for the isolation of one-third of the compounds quoted in Table I. As in previous work[1,6] we surmised that the chloropropanols (used in methods C and D) in the presence of base lost HCl to give the 1,2-epoxypropane. Confirmation that the epoxide ring of **2** opened up in the manner indicated was obtained when *N*-ethyl-3-chloro-4-hydroxybenzamide (**5**) was condensed with 1-chloro-3-isopropylamino-2-propanol in the presence of base to give the same compound (**8**, Table I) as that already obtained by method C. The oxazolidine **6** was formed when the



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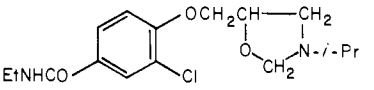
amino alcohol (**8**, Table I) as the free base was treated with formaldehyde in hot EtOH. Resolution of **8** to give the



6

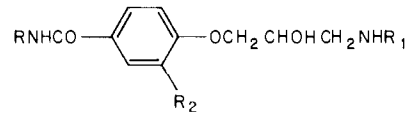
dextro and levo enantiomers was effected by the crystallization of the (+)- and (−)-*O,O*-di-*p*-toluoyl tartrate salts.[7]

Pharmacology. β-Adrenoceptor blocking potency was estimated in vivo using the previously described cat preparation.[8] The results given in Table I are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg, dosed iv). The degree (%) of blockade of the vasodepressor response at that dose level is also given. The relative potencies of these two systems give some indication of selectivity for β_1 (cardiac) as opposed to β_2 (vascular) receptors. Statistical analysis of the results shows that the mean ED_{50} on the log scale for compounds with an average of two to three tests per compound was ±0.12 log units (i.e., a mean error of approximately 30%).

Discussion

The objective of this investigation was to determine whether the carbamoyl moiety, like the acylamino moiety, would confer β_1 cardiac selectivity. The data in Table I show that many of the compounds had a profile of activity similar to that of the practolol series,[1] in that they exhibit

Table I



No.	R	R_1	R_2	R_f	Mp, °C	Crystn solvent	Emp formula	Analyses	Method of prepn	Dose, μg/kg, giving 50% inhibn of tachycardia	Inhibn, %, of depressor response
1	CH_3	i-C_3H_7	H		146-148	Me_2CO	$C_{14}H_{22}N_2O_3 \cdot 0.25H_2O$	C, H, N	C	1133	−2
2	C_2H_5	t-C_4H_9	H		132	Me_2CO	$C_{16}H_{26}N_2O_3$	C, H, N	C	271	1
3	C_2H_5	i-C_3H_7	n-C_3H_7		116	EtOAc	$C_{18}H_{30}N_2O_3$	C, H, N	A	380	32
4	C_2H_5	t-C_4H_9	n-C_3H_7	0.8	116-118	Me_2CO-petr ether[b]	$C_{19}H_{32}N_2O_3$	C, H, N	B	36	16
5	C_2H_5	i-C_3H_7	$-CH_2CH=CH_2$		120-121	Me_2CO	$C_{18}H_{28}N_2O_3$	C, H, N	A	140	30
6	C_2H_5	t-C_4H_9	$-CH_2CH=CH_2$	0.6	Oil		$C_{19}H_{30}N_2O_3 \cdot 0.5H_2O$	C, H, N	B	59	48
7	C_2H_5	i-C_3H_7	NO_2	0.7	Oil		$C_{15}H_{23}N_3O_5$	C, H, N	D	N/A	
8	C_2H_5	i-C_3H_7	Cl		136-138	EtOAc	$C_{15}H_{23}ClN_2O_3$	C, H, N	C	106	26
9	C_2H_5	t-C_4H_9	Cl	0.5	109	Me_2CO-petr ether[b]	$C_{16}H_{25}ClN_2O_3$	C, H, N	D	32	−5
10	C_2H_5	s-C_4H_9	Cl		90	EtOAc	$C_{16}H_{25}ClN_2O_3$	C, H, N	A	2417	14
11	C_2H_5	n-C_4H_9	Cl		106-108	EtOAc	$C_{16}H_{25}ClN_2O_3$	C, H, N	A	787	−7
12	C_2H_5	$C(CH_3)_2$ | CH_2OH	Cl	0.5	129	Me_2CO-EtOH	$C_{16}H_{25}ClN_2O_4$	C, H, N	D	176	−2
13	C_2H_5	n-C_3H_7	Cl		112	Me_2CO	$C_{15}H_{23}ClN_2O_3$	C, H, N	C	2593	8
14	C_2H_5	i-C_3H_7	Br		140	EtOAc	$C_{15}H_{23}BrN_2O_3$	C, H, N	C	499	21
15	C_2H_5	t-C_4H_9	Br	0.6	Oil		$C_{16}H_{25}BrN_2O_3$	C, H, N	D	33	21
16	C_2H_5	$C(CH_3)_2$ | CH_2OH	Br	0.6	136-138	Me_2CO	$C_{16}H_{25}BrN_2O_4$	C, H, N	D	157	−25
17	C_2H_5	C_2H_5	Cl		135	EtOAc	$C_{14}H_{21}ClN_2O_3$	C, H, N	A	504	7
18	C_2H_5	$CHCH_2OC_6H_5$ | CH_3	Cl		112-114	EtOAc	$C_{21}H_{27}ClN_2O_4$	C, H, N	A	1003	30
19	C_2H_5	$CH(CH_2)_2C_6H_5$ | CH_3	Cl		124	EtOAc	$C_{22}H_{29}ClN_2O_3$	C, H, N	A	976	−8
20	C_2H_5	$CHCH_3$ | CH_2OH	Cl		116-118	EtOAc-Me_2CO	$C_{15}H_{23}ClN_2O_4$	C, H, N	A	360	24
21	C_2H_5	c-C_3H_5	Cl		90-92	EtOAc	$C_{15}H_{21}ClN_2O_3 \cdot 0.5H_2O$	C, H, N	A	862	47
22	C_2H_5	i-C_3H_7	$COCH_3$	0.5	117	EtOAc-petr ether[b]	$C_{17}H_{26}N_2O_4$	C, H, N	B	725	−28
23	n-C_3H_7	t-C_4H_9	H		124-125	Me_2CO	$C_{17}H_{28}N_2O_3 \cdot 0.5H_2O$	C, H, N	C	462	41
24	n-C_3H_7	$CH(CH_2)_2C_6H_5$ | CH_3	H		114-116	Me_2CO-petr ether[b]	$C_{23}H_{32}N_2O_3$	C, H, N	C	1336	5

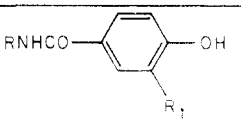
25	n-C_3H_7	i-C_3H_7	n-C_3H_7		128	EtOAc	$C_{19}H_{32}N_2O_3$	C, H, N	A	143	−42
26	n-C_3H_7	t-C_4H_9	n-C_3H_7	0.8	124	Me_2CO	$C_{20}H_{34}N_2O_3 \cdot H_2O$	C, H, N	B	44	50
27	n-C_3H_7	i-C_3H_7	OCH_3		134-136	Me_2CO	$C_{17}H_{28}N_2O_4$	C, H, N	C	783	59
28	n-C_3H_7	t-C_4H_9	OCH_3	0.46	Oil		$C_{18}H_{30}N_2O_4 \cdot 0.5H_2O$	C, H, N	B	275	77
29	n-C_3H_7	t-C_4H_9	NO_2		144-146	Me_2CO-petr ether[c]	$C_{17}H_{27}N_3O_5$	C, H, N	C	169	27
30	n-C_3H_7	i-C_3H_7	Cl		138	Me_2CO	$C_{16}H_{25}ClN_2O_3$	C, H, N	C	514	15
31	n-C_3H_7	t-C_4H_9	Cl		142	EtOH-H_2O	$C_{17}H_{27}ClN_2O_3 \cdot C_6H_3N_3O_7$	C, H, N	C	130	37
32	n-C_3H_7	i-C_3H_7	Br		146-148	Me_2CO-EtOH	$C_{16}H_{25}BrN_2O_3$	C, H, N	C	144	16
33	n-C_3H_7	t-C_4H_9	Br	0.8	140	Me_2CO	$C_{17}H_{27}BrN_2O_3 \cdot 0.5H_2O$	C, H, N	D	69	32
34	n-C_4H_9	i-C_3H_7	H		117	Me_2CO	$C_{17}H_{28}N_2O_3$	C, H, N	C	305	−17
35	n-C_4H_9	i-C_3H_7	Cl		128	Me_2CO	$C_{17}H_{27}ClN_2O_3$	C, H, N	C	219	5
36	n-C_4H_9	c-C_5H_9	Cl		117	Me_2CO	$C_{19}H_{28}ClN_2O_3$	C, H, N	C	984	−33
37	n-C_4H_9	$CH_2CH{=}CH_2$	Cl	0.8	Oil		$C_{17}H_{25}ClN_2O_3$	C, H, N	D	N/A	
38	i-C_4H_9	t-C_4H_9	Cl		110	EtOAc	$C_{18}H_{29}O_3N_2Cl$	C, H, N	A	30	−18
39	i-C_4H_9	i-C_3H_7	Cl		118-120	EtOAc	$C_{17}H_{27}O_3N_2Cl$	C, H, N	A	283	−43
40	n-C_5H_{11}	i-C_3H_7	H		124	Me_2CO	$C_{18}H_{30}N_2O_3$	C, H, N	C	1448	−4
41	n-C_5H_{11}	i-C_3H_7	Cl		130	Me_2CO	$C_{18}H_{29}ClN_2O_3$	C, H, N	C	61	−2
42	n-C_6H_{13}	t-C_4H_9	Cl	0.5	Oil		$C_{20}H_{33}ClN_2O_3$	C, H, N	D	23	15
43	n-C_6H_{13}	i-C_3H_7	Cl		124-125	Me_2CO	$C_{19}H_{31}ClN_2O_3$	C, H, N	C	217	50
44	n-C_6H_{13}	t-C_4H_9	$CH_2CH{=}CH_2$	0.6	Oil		$C_{23}H_{38}N_2O_3 \cdot H_2O$	C, N; H[a]	B	54	38
45	n-C_6H_{13}	i-C_3H_7	$CH_2CH{=}CH_2$		100	Me_2CO	$C_{22}H_{36}N_2O_3$	C, H, N	A	89	36
46	n-C_6H_{13}	i-C_3H_7	Br		124-126	EtOAc	$C_{19}H_{31}BrN_2O_3$	C, H, N	A	80	27
47	n-C_9H_{19}	i-C_3H_7	Cl		108	Me_2CO	$C_{22}H_{37}ClN_2O_3 \cdot 0.5H_2O$	C, H, N	A	360	71
48	i-C_3H_7	i-C_3H_7	Cl		150	Me_2CO	$C_{16}H_{25}ClN_2O_3$	C, H, N	A	72	−23
49	i-C_3H_7	t-C_4H_9	Cl		124	EtOAc	$C_{17}H_{27}ClN_2O_3$	C, H, N	A	78	−19
50	$-(CH_2)_2OCH_3$	i-C_3H_7	Cl		94	EtOAc	$C_{16}H_{25}ClN_2O_4$	C, H, N	A	699	17
51	$CH_2CH{=}CH_2$	t-C_4H_9	Cl	0.45	118	EtOAc-petr ether[b]	$C_{17}H_{25}ClN_2O_3$	C, H, N	D	29	−11
52	$CH_2CH{=}CH_2$	i-C_3H_7	Cl		120	EtOAc	$C_{16}H_{23}ClN_2O_3$	C, H, N	C	226	−3
53	$CH_2CH{=}CH_2$	i-C_3H_7	Br		136-138	EtOAc	$C_{16}H_{23}BrN_2O_3$	C, H, N	A	55	−30
54	i-C_5H_{11}	i-C_3H_7	Cl		122	EtOAc	$C_{18}H_{29}ClN_2O_3$	C, H, N	A	714	48
55	$C(CH_3)_2$ | CH_2OH	t-C_4H_9	Cl	0.5	72	EtOAc	$C_{18}H_{29}ClN_2O_4$	C, H, N	B	384	42
56	$C(CH_3)_2$ | CH_2OH	i-C_3H_7	Cl	0.55	Oil		$C_{17}H_{27}ClN_2O_4$	C, H, N	B	749	11
57	$CHCH_3$ | CH_2OH	i-C_3H_7	Cl		134-136	Me_2CO	$C_{16}H_{25}ClN_2O_4$	C, H, N	A	1221	24
58	c-C_3H_5	i-C_3H_7	Cl		166	Me_2CO-EtOH	$C_{16}H_{23}ClN_2O_3 \cdot 0.5H_2O$	C, H, N	C	212	−23
59	c-C_5H_9	t-C_4H_9	Cl	0.6	128	Me_2CO	$C_{19}H_{29}ClN_2O_3$	C, H, N	B	42	10
60	c-C_5H_9	i-C_3H_7	Cl		166-168	Me_2CO	$C_{18}H_{27}ClN_2O_3$	C, H, N	A	146	0
61	$CH_2C_6H_5$	i-C_3H_7	Cl		130	Me_2CO	$C_{20}H_{25}ClN_2O_3$	C, H, N	A	181	1
62	$CH_2C_6H_5$	t-C_4H_9	Cl	0.5	Oil		$C_{21}H_{27}ClN_2O_3 \cdot 0.5H_2O$	C, H, N	B	114	29
63	C_6H_5	i-C_3H_7	Cl		202	EtOH-Me_2CO	$C_{19}H_{23}ClN_2O_3$	C, H, N	C	526	−19

Table I (Continued)

No.	R	R_1	R_2	R_f	Mp, °C	Crystn solvent	Emp formula	Analyses	Method of prepn	Dose, μg/kg, giving 50% inhibn of tachycardia	Inhibn, %, of depressor response
64	CH_3 $-CCH_2C_6H_5$ CH_3	*i*-C_3H_7	Cl	0.55	Oil		$C_{23}H_{31}ClN_2O_3 \cdot 0.5H_2O$	C, H, N	B	1705	−25
65	CH_3 $-CCH_2C_6H_5$ CH_3	*t*-C_4H_9	Cl	0.6	Oil		$C_{24}H_{33}ClN_2O_3 \cdot 0.5H_2O$	C, H, N	B	2400	−19
66	*p*-$CH_3C_6H_5$	*i*-C_3H_7	H		167–169	EtOH	$C_{20}H_{26}N_2O_3$	C, H, N	C	80	−10
67	*p*-$CH_3C_6H_5$	*i*-C_3H_7	Cl		186	Me_2CO-EtOH	$C_{20}H_{25}ClN_2O_3$	C, H, N	A	257	−30
68	*p*-ClC_6H_5	*i*-C_3H_7	Cl		188	Me_2CO-EtOH	$C_{19}H_{22}Cl_2N_2O_3$	C, H, N	A	378	67
69	Practolol									167	8

[a] H: calcd, 9.1; found, 9.8. [b] Bp 80–100°. [c] Bp 60–80°.

Table II[a]

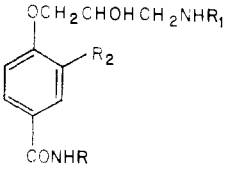


R	R_1	Mp, °C	Crude yield, %
C_2H_5	Cl	92	80
i-C_3H_7	Cl	88	75
$-C(CH_3)_2$ CH_2OH	Cl	166–168	76
$C_6H_5CH_2$	Cl	114	46
c-C_5H_9	Cl	96–98	80
$CH_2=CHCH_2$	Cl	86–88	77
p-$CH_3C_6H_5$	Cl	210	66
p-ClC_6H_5	Cl	184	52
$CH_2=CHCH_2$	Br	280–290	86
C_2H_5	*n*-C_3H_7	106	54
n-C_3H_7	*n*-C_3H_7	122–124	47
C_2H_5	CH_3CO-	80	60
n-C_3H_7	NO_2	124–126	54

[a] The above phenols are novel and were characterized only by ir and melting point.

marked inhibition of an isoproterenol-induced tachycardia with only small effects on the vascular response.

The compounds synthesized are represented by structure **7** and consist primarily of compounds substituted



7

at R_1 by *i*-Pr and *t*-Bu groups and at R by alkyl chains ranging from C_2 to C_6.

The ortho substituent, R_2, was noted at an early stage in the work to be playing an important part in the potency (ED_{50}) of the compounds. We, therefore, submitted the data to a multiple parameter analysis using the Hansch approach. The methods used in this analysis have been applied to several series of β-adrenergic blocking agents and are shortly to be published.[9] The *conclusions* of this analysis that relate to this series are as follows.

(1) The replacement of an acylamino group (–NHCO–) in the para position of an aryloxypropanolamine by a carbamoyl group (–CONH–) results in a reduction of the total β-blocking activity of the series, this being attributed to the weaker hydrogen bond donor properties of the –NH– moiety in the carbonyl group (cf. compounds **1** and **69**). (2) The electron contribution of the group R_2 can be correlated and is independent of the steric bulk of the substituent. This would indicate steric freedom in the ortho position of the molecule. Electron-withdrawing groups in this position were found to increase potency, the effect being less than that observed in the acylamino series. (3) The lipophilic contribution from the groups R, R_1, and R_2 was observed to be additive and produced a marked effect on potency. (4) Throughout the series the *t*-Bu group at R_1 is intrinsically more potent than the *i*-Pr group (cf. compounds **9** and **8**, **38** and **39**, **42** and **43**, **59** and **60**).

Experimental Section

Chemistry. All melting points are uncorrected and were obtained using an Electrothermal capillary melting point apparatus. Ir spectra were recorded in KBr disks on a Perkin-Elmer 457 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those

elements were within ±0.4% of the theoretical values.

General Methods. Method A. 1-(4-Ethylcarbamoyl-2-*n*-propylphenoxy)-3-isopropylamino-2-propanol (3). 1,2-Epoxy-3-(4-ethylcarbamoyl-2-propylphenoxy)propane (1.5 g, 0.0057 mol) and *i*-$PrNH_2$ (20 ml, 0.234 mol) were left at room temperature for 24 h. The mixture was evaporated to dryness and the residue was stirred with 1 N HCl (25 ml) and Et_2O (25 ml). The acidic phase was basified with 11 N NaOH and extracted with EtOAc (25 ml). The EtOAc extract was dried ($MgSO_4$) and evaporated to dryness and the residue was crystallized from EtOAc: yield 0.8 g (33%); mp 116°.

Method B. 1-(4-Ethylcarbamoyl-2-*n*-propylphenoxy)-3-*tert*-butylamino-2-propanol (4). 1,2-Epoxy-3-(4-ethylcarbamoyl-2-*n*-propylphenoxy)propane (1.5 g, 0.0057 mol) and *t*-$BuNH_2$ (20 ml, 0.19 mol) were left at room temperature for 24 h. The mixture was evaporated to dryness and the residue was stirred with 1 N HCl (25 ml) and Et_2O (25 ml). The acidic phase was basified with 11 N NaOH and extracted twice with Et_2O (50 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was subjected to thick-layer chromatography on a 2-mm thick plate of silica gel (Merck, Kieselgel PF_{254} gipshaltig), area 20 × 40 cm, using a mixture of 1 part by volume of NH_4OH (sp gr 0.89) and 99 parts by volume of MeOH as eluting solvent. The material with an R_f value of 0.8 was extracted with methanol, the methanol extract was evaporated to dryness, and the residue was crystallized from acetone–petroleum ether (bp 80–100°): yield 0.1 g (4%); mp 116–118°.

Method C. 1-(2-Chloro-4-ethylcarbamoylphenoxy)-3-isopropylamino-2-propanol (8). 1-Chloro-3-(2-chloro-4-ethylcarbamoylphenoxy)-2-propanol (2.9 g, 0.01 mol), *i*-$PrNH_2$ (10 ml, 0.12 mol), and *n*-PrOH (40 ml) were heated together under reflux for 24 h. The mixture was evaporated to dryness and the residue was stirred with 2 N HCl (20 ml) and Et_2O (25 ml). The acidic phase was basified with 11 N NaOH and extracted twice with EtOAc (25 ml). The combined EtOAc extracts were dried ($MgSO_4$) and evaporated to dryness and the residue was crystallized from EtOAc: yield 1.4 g (45%); mp 136–138°.

Method D. 1-*tert*-Butylamino-3-(2-chloro-4-*n*-hexylcarbamoylphenoxy)-2-propanol (42). 1-Chloro-3-(2-chloro-4-*n*-hexylcarbamoylphenoxy)-2-propanol (3.25 g, 0.0093 mol), *t*-$BuNH_2$ (10 ml, 0.096 mol), and *n*-PrOH (30 ml) were heated together under reflux for 18 h. The mixture was evaporated to dryness and the residue was stirred with 2 N HCl (25 ml) and ether (50 ml). The acidic phase was basified with 11 N NaOH and extracted twice with EtOAc (25 ml). The combined EtOAc extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was subjected to thick-layer chromatography on a 2-mm thick plate of silica gel (Merck, Kieselgel PF_{254} gipshaltig), area 20 × 40 cm, using a mixture of 1 part by volume of NH_4OH (sp gr 0.89) and 99 parts by volume of MeOH as eluting solvent. The material with an R_f value of 0.5 was extracted with methanol and the methanol extract was evaporated to dryness to leave an oil.

1-(2-Chloro-4-ethylcarbamoylphenoxy)-3-isopropylamino-2-propanol (8). A mixture of *N*-ethyl-3-chloro-4-hydroxybenzamide (1 g, 0.005 mol), NaOH (0.4 g, 0.01 mol), 1-chloro-3-isopropylamino-2-propanol hydrochloride (0.67 g, 0.0035 mol), H_2O (2 ml), and EtOH (12.5 ml) was heated under reflux for 3 h. The mixture was evaporated to dryness and the residue was stirred with a mixture of EtOAc (25 ml) and H_2O (25 ml). The EtOAc phase was dried ($MgSO_4$) and evaporated under reduced pressure and the residue was crystallized from EtOAc: mp 136–138°.

1-Amino-3-(4-ethylcarbamoyl-2-chlorophenoxy)-2-propanol. A solution of 1,2-epoxy-3-(4-ethylcarbamoyl-2-chlorophenoxy)propane (2.55 g, 0.01 mol) in MeOH (20 ml) was added to a 12% w/v solution of NH_3 in MeOH (100 ml) and left at room temperature for 72 h. The mixture was evaporated to dryness and the residue was stirred with 1 N HCl (25 ml) and EtOAc (25 ml). The acidic phase was basified with 11 N NaOH and extracted with EtOAc (50 ml). The EtOAc extract was dried ($MgSO_4$) and acidified with ethereal HCl. The mixture was filtered and the solid residue was crystallized from *i*-PrOH: yield 0.12 g (4%); mp 198–200°. Anal. ($C_{12}H_{17}N_2O_3$·HCl) C, H, N.

5-(2-Chloro-4-ethylcarbamoylphenoxymethyl)-3-isopropyloxazolidine Dipicrate. A mixture of 1-(2-chloro-4-ethylcarbamoylphenoxy)-3-isopropylamino-2-propanol (0.5 g, 0.0016 mol), 36% w/v formalin (4 ml), and EtOH (25 ml) was heated under reflux for 6 h. The mixture was evaporated under reduced pressure and the residue was dissolved in EtOH (10 ml) and acidified with ethanolic picric acid. The mixture was filtered and the solid residue was crystallized (EtOH–H_2O): yield 0.55 g (43%); mp 86°. Anal. ($C_{16}H_{23}ClN_2O_3$·$2C_6H_3N_3O_7$·$0.5H_2O$) C, H, N.

(−)-1-(2-Chloro-4-ethylcarbamoylphenoxy)-3-isopropylamino-2-propanol. A solution of 1-(2-chloro-4-ethylcarbamoylphenoxy)-3-isopropylamino-2-propanol (1.5 g, 0.0048 mol) in EtOH (10 ml) was added to a solution of (+)-*O,O*-di-*p*-toluoyltartaric acid (1.9 g) in EtOH (10 ml) and the mixture was maintained at −20° for 48 h. The mixture was filtered and the solid residue was crystallized from EtOH: mp 172–170° dec. The crystallized solid was then stirred with 1 N NaOH (10 ml) and EtOAc (10 ml); the EtOAc phase was separated, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The solid residue was stirred with a mixture of allylamine (6 ml) and petroleum ether (bp 60–80°) (12 ml) for 15 min. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure, this procedure was repeated, and the product was stirred with Et_2O (5 ml) and filtered, leaving the pure optical isomer: yield 0.17 g (22%); mp 122–124°; $[\alpha]^{21}D$ −13.0° (*c* 1.9, 1 N HCl).

(+)-1-(2-Chloro-4-ethylcarbamoylphenoxy)-3-isopropylamino-2-propanol. The above procedure was repeated using (−)-*O,O*-di-*p*-toluoyltartaric acid. The product was isolated in a 14% yield: mp 122–124°; $[\alpha]^{21}D$ +13.2° (*c* 2.1, 1 N HCl).

The phenols used as starting material in this series were synthesized by the following general method.

3-Chloro-4-hydroxy-*N*-(*n*-propyl)benzamide. A mixture of 3-chloro-4-hydroxybenzoic acid (8.6 g, 0.05 ml) and acetyl chloride (30 ml, 0.42 mol) was heated under reflux for 30 min and then evaporated to dryness. The residue was then heated under reflux with thionyl chloride (30 ml, 0.42 ml) for 3 h. The mixture was then evaporated to dryness to give 4-acetoxy-3-chlorobenzoyl chloride which was used without further purification. A solution of 4-acetoxy-3-chlorobenzoyl chloride (11.5 g, 0.05 mol) in benzene (50 ml) was added to a stirred solution of *n*-propylamine (8.2 ml, 0.1 mol) in benzene (50 ml) at ambient temperature. The mixture was stirred for 1 h, evaporated to dryness, and then heated under reflux for 5 min with 1 N NaOH (150 ml). The mixture was cooled and filtered, the filtrate was acidified with 11 N HCl and filtered, and the solid residue was washed with H_2O, dried, and crystallized from a mixture of EtOH (25 ml) and H_2O (50 ml): yield 7.4 g (75%); mp 76–78°. Anal. ($C_{10}H_{12}ClNO_2$) C, H, N. In general, the phenols thus prepared were used without further purification; several were oils. Table II lists those phenols that were characterized by ir analysis and melting point.

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