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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 practolol¹ (Eraldin²), has led several groups of workers to examine analogous compounds which contain an amide function. Thus Cox and co-workers³ have examined a series of compounds of the general structure 1 where R and R₁ represent a variety of amidic



functions, and they have demonstrated a selectivity of action on cardiac vs. tracheal β -receptors. Similarly Shtacher and co-workers⁴ 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 1chloro-3-(substituted carbamoylphenoxy)-2-propanol (3) with the appropriate amine. The various hydroxy-N-



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



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



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 μ g/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 ED₅₀ 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

				RNHCO	0CH2 (CHOH CH ₂ NHR ₁					
					~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~				Method of	Dose, μg/kg, giving 50% inhibn of tachv-	Inhibn, $\%$ , of depres- sor re-
No.	R	R	$\mathbf{R}_2$	$R_f$	Mp,°C	Crystn solvent	Emp formula	Analyses	prepn	cardia	sponse
1	CH ₃	<i>i</i> -C ₃ H ₇	Н		146-148	Me ₂ CO	C ₁₄ H ₂₂ N ₂ O ₃ .	С, Н, N	C	1133	-2
63 63 43	C ₂ H ₅ C ₂ H ₅ C ₂ H ₅	<i>t</i> -C ₄ H, <i>i</i> -C ₄ H, <i>t</i> -C ₄ H,	H n-C ₃ H, n-C ₃ H,	0.8	132 116 116-118	Me ₂ CO EtOAc Me ₂ CO-	C1,H3,N,O3 C1,H3,N,O3 C1,H3,N,O3 C1,H3,N,O3	C, H, N C, H, N C, H, N	BAC	271 380 36	1 32 16
Q JI	C ₃ H ₅ C ₃ H ₅	i-C ₃ H, t-C ₄ H,	-CH ₂ CH=CH ₂ -CH ₂ CH=CH ₂	0.6	120-121 Oil	peur euner Me ₂ CO	C ₁₈ H ₂₈ N ₂ O ₃ C ₁₉ H ₃₀ N ₂ O ₃ .	C, H, N C, H, N	B	140 59	30 48
7 8 0	C ₂ H, C ₂ H, C ₂ H,	i-C ₃ H, i-C ₃ H, t-C ₄ H,	со со С	0.7	Oil 136-138 109	EtOAc Me ₂ CO-	U.5H2U C ₁ sH ₂₃ N ₃ O C ₁ sH ₂₃ CIN ₂ O C ₁ sH ₂₅ CIN ₂ O	C, H, N C, H, N C, H, N	000	N/A 106 32	26 - 5
10 11 12	C ₂ H, C ₂ H, C ₂ H,	<i>s</i> -С ₄ Н ₃ <i>n</i> -С ₄ Н ₃ с(СН ₃ ) ₂	555	0.5	90 106-108 129	peur etner EtOAc EtOAc Me ₂ CO-EtOH	Cı ₆ H ₃ ,CIN ₃ O ₃ Cı ₆ H ₃ ,CIN ₃ O ₃ Cı ₆ H ₁₅ CIN ₂ O ₄	C, H, N C, H, N C, H, N	A A U	$2417 \\ 787 \\ 176 \\ 176$	14 7 -2
13 14 15 16	C H C H C H	CH_OH n-C3H i-C3H i-C4H cC(H3)2	ت <b>a</b> a a	0.6 0.6	112 140 Oil 136-138	Me,CO EtÓAc Me,CO	C ₁₅ H ₂₅ ClN ₂ O ₃ C ₁₅ H ₂₅ BrN ₂ O ₃ C ₁₆ H ₂₅ BrN ₂ O ₃ C ₁₆ H ₂₅ BrN ₂ O ₃	NNN CCH,N CCCC	CODD	$2593 \\ 499 \\ 33 \\ 157$	8 21 - 25
17 18	$C_2 H_5 C_2 H_5$	ĊH2OH C2H3 ĊĦĊH2OC6H5	55		135 112-114	EtOAc EtOAc	C ₁₄ H ₂₁ CIN ₂ O ₃ C ₂₁ H ₂₇ CIN ₂ O ₃	С, Н, N С, Н, N	AA	$\begin{array}{c} 504 \\ 1003 \end{array}$	7 30
19	$C_2H_5$	$\dot{C}H_3$ $\dot{C}H(CH_2)_2C_6H_5$	CI		124	EtOAc	$C_{22}H_{29}CIN_2O_3$	С, Н, N	А	976	8
20	C ₂ H ₅	CH3 CHCH3 CH OH	G		116-118	EtOAc- Me2CO	C ₁₅ H ₂₃ ClN ₂ O ₄	С, Н, N	A	360	24
21	$C_2H_5$	c-C ₃ H ₅	CI		90-92	EtOAc	C ₁₅ H ₂₁ CIN ₂ O ₃ .	C, H, N	Α	862	47
22	$C_2H_5$	i-C ₃ H ₇	cocH ₃	0.5	117	EtOAc-	$C_{17}H_{26}N_{2}O_{4}$	C, H, N	В	725	- 28
23	$n$ -C $_{3}$ H $_{7}$	t-C4H9	Н		124-125	Me ₂ CO	$C_{1,7}H_{2,8}N_2O_3$ .	С, Н, N	C	462	41
24	n-C ₃ H ₇	CH(CH ₁ ) ₁ C,H ₅ CH ₃	Н		114-116	Me ₂ CO- petr ether ^b	$C_{23}H_{32}N_2O_3$	С, Н, N	C	1336	ъ 2

25 26	n-C ₃ H ₇ n-C ₃ H ₇	<i>i</i> -C ₃ H, <i>t</i> -C ₄ H ₅	$n-\mathrm{C_3H}_{\eta}$ $n-\mathrm{C_3H}_{\eta}$	0.8	128 124	EtOAc Me,CO	C ₁₉ H ₃₂ N ₂ O ₃ C ₂₀ H ₃₄ N ₂ O ₃ .	C, H, N C, H, N	BB	143 44	42 50
27 28	$n-C_3H_n$ $n-C_3H_r$	<i>i</i> -C ₃ H, <i>t</i> -C ₄ H,	OCH ₃ OCH ₃	0.46	134-136 Oil	Me ₂ CO	H ₂ U C ₁ ,H ₂₈ N ₂ O C ₁₈ H ₃₀ N ₂ O ₄	C, H, N C, H, N	рс	783 275	59 77
29	n-C ₃ H ₇	<i>t</i> -C ₄ H ₉	NO2		144-146	Me ₂ CO-	0.2H2,0 C1,7H2,N3,O5	C, H, N	C	169	27
30 31	n-C ₃ H, n-C ₃ H ₇	<i>i</i> -C ₃ H ₇ <i>t</i> -C ₄ H ₅	55		138 142	peur euner Me,CO EtOH-H ₂ O	C ₁₆ H ₂₅ CIN ₂ O ₃ C ₁₇ H ₂₇ CIN ₂ O ₃	C, H, N C, H, N	CC	514 130	15 37
32 33	n-C ₃ H, n-C ₃ H,	<i>i</i> -C ₃ H ₇ <i>t</i> -C ₄ H ₅	Ŗ	0.8	146-148 140	Me ₂ CO-EtOH Me ₂ CO	C, H ₃ N ₃ O, C, H ₂ , BrN ₂ O, C, H ₂ , BrN ₂ O ₃ .	C, H, N C, H, N	DC	$\begin{array}{c} 144 \\ 69 \end{array}$	$\begin{array}{c} 16\\ 32 \end{array}$
34 35 36	n-C4H, n-C4H, n-C4H,	i-C ₃ H, i-C ₃ H, c-C ₅ H,	пGС		117 128 117	Me ₂ CO Me ₂ CO Me ₂ CO	C1,H1,N2O C1,H1,C1N2O C1,H1,C1N2O C1,H1,C1N2O	C, H, N C, H, N C, C, L, N	0000	305 219 984	-17 -33
37 38 39	$n-C_{4}H_{5}$ $i-C_{4}H_{5}$ $i-C_{4}H_{5}$	CH_CH=CH ₂ t-C ₄ H, i-C ₃ H,	555	0.8	Oil 110 118-120	EtOAc EtOAc	C1, H2, CIN2O3 C1, H2, O3N2C1 C1, H2, O3N2C1	ZZZ THH THH T	A A C	N/A 30 283	-18 -43
40 41 42	n-С,Н,, n-С,Н,,, n-С,Н,,,	i-C ₃ H, i-C ₃ H, i-C H,	HOD	0.5	124 130 Oil	Me ₂ CO Me ₂ CO	C1, H3, N2,O3 C1, H3, CIN2,O3 C2, H3, CIN2,O3	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	00C	$\begin{array}{c} 1448 \\ 61 \\ 23 \end{array}$	15 - 12
43 44	n-C ₆ H ₁₃ n-C ₆ H ₁₃	i-C ₃ H, t-C ₄ H,	CI CH ₂ CH=CH ₂	0.6	124-125 Oil	Me ₂ CO	C ₁ ,H ₃ ,CIN ₂ O ₃ C ₂₃ H ₃ ,N ₂ O ₃	C, H, N C, N; H ^a	BC	217 54	50 38
45 46 47	n-C ₆ H ₁₃ n-C ₆ H ₁₃ n-C ₉ H ₁₉	i-C ₃ H, i-C ₃ H, i-C ₃ H,	CH ₂ CH=CH ₂ Br CI		$\begin{array}{c} 100\\ 124-126\\ 108\end{array}$	Me ₂ CO EtOAc Me ₂ CO	$C_{22}^{113}H_{34}N_{3}O_{3}$ $C_{19}H_{31}BrN_{3}O_{3}$ $C_{22}H_{37}CIN_{2}O_{3}$	C, H, N C, H, N C, H, N	<b>A</b> A	89 80 360	36 27 71
48 49 50	<i>i</i> -C ₃ H ₇ <i>i</i> -C ₃ H ₇ -(CH ₂ ) ₂ OCH ₃ CH ₂ CH=CH ₂	i-C ₃ H, t-C ₄ H, i-C ₃ H, t-C ₄ H,	5555	0.45	150 124 94 118	Me,CO EtOAc EtOAc EtOAc	C, H1, CIN203 C, H1, CIN203 C, H1, CIN203 C, H1, CIN204 C1, H1, CIN204	С, Ӊ N С, Ӊ N С, Ҁ, N	A A A U	72 78 699 29	- 23 - 19 - 11 + 11
5 5 5 2 5 5 4 3 5 5 4 3	CH ₁ CH=CH ₂ CH ₁ CH=CH ₂ <i>i</i> -C ₅ H ₁₁ C(CH ₃ ) ₂	i-С ₃ Н, i-С ₃ Н, i-С ₃ Н, t-С ₄ Н,	5855	0.5	$120 \\ 136-138 \\ 122 \\ 72$	per eurer EtOAc EtOAc EtOAc EtOAc	C ₁₆ H ₂₃ ClN ₂ O ₃ C ₁₆ H ₂₃ BrN ₂ O ₃ C ₁₈ H ₂₉ ClN ₂ O ₃ C ₁₈ H ₂₉ ClN ₂ O ₃	C H N C H N C H N C C C C	BAAC	226 55 714 384	30 48 42
56	CH ₂ OH C(CH ₃ ) ₂	<i>i</i> -C ₃ H ₇	G	0.55	Oil		$C_{1,7}H_{2,7}CIN_2O_4$	С, Н, N	в	749	11
57	сн ₂ он снсн ₃	<i>i</i> -C ₃ H ₇	CI		134-136	Me ₂ CO	C1,6H25CIN2O4	С, Н, N	Α	1221	24
58	ĊH2OH c-C3H5	i-C ₃ H ₇	CI		166	Me2CO-EtOH	C ₁₆ H ₂₃ CIN ₂ O ₃ . 0.5H O	С, Н, N	C	212	- 23
59 60 62	c-C,H, c-C,H, CH2C,H, CH2C,H,	t-C,H, i-C,H, i-C,H, t-C,H,	5555	0.6 0.5	128 166-168 130 Oil	Me ₂ CO Me ₂ CO Me ₂ CO	C, H ₁ , CIN, O, C, H ₁ , CIN, O,	C C C C C C C C C C C C C C C C C C C	BAAB	42 146 181 114	$\begin{smallmatrix}10\\0\\1\\29\end{smallmatrix}$
63	C ₆ H ₅	<i>i</i> -C ₃ H ₇	CI		202	EtOH-Me ₂ CO	0.5H20 C1,H23CIN2O3	С, Н, N	C	526	- 19

Table I ((	Continued)											
No.	Я	'n	Ŗ	$R_f$	Mp, °C	Crystn solvent	Emp formula	Analyses	Method of prepn	Dose, μg/kg, giving 50% inhibn of tachy- cardia	Inhibn, %, of depres- sor re- sponse	
64	CH3 CCH2C6H5	i-C ₃ H,	G	0.55	Oil		C ₂₃ H ₃₁ CIN ₂ O ₃ 0.5H ₂ O	С, Н, N	B	1705	- 25	
65	CH, CH, CCH,C,H, CCH,C,H,	<i>l</i> -C ₄ H,	ū	0.6	liO		C ₂₄ H ₃₃ ClN ₂ O ₃ . 0.5H ₂ O	С, Н, N	а	2400	19	
66 63 69	D-CH ₃ C ₆ H <i>p</i> -CH ₃ C ₆ H <i>p</i> -CIC ₆ H P-CIC ₆ H Practolc	i.C ₃ H, i.C ₃ H, i.C ₃ H, j	CCH		167-169 186 188	EtOH Me ₂ CO-EtOH Me ₂ CO-EtOH	C ₂₀ H ₂ ,N ₂ O ₃ C ₂₀ H ₂₅ CIN ₂ O ₃ C ₁₉ H ₂₂ CI ₂ N ₂ O ₃	C, H, N C, H, N C, H, N	AAC	80 257 378 167	- 10 - 30 67 8	
^a H: cal	lcd, 9.1; found, 9.8.	^b Bp 80-100°.	^c Bp 60-80°.									



^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



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 (ED₅₀) 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  $\beta$ -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  $\beta$ -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  $\mathbf{R}_2$  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  $\mathbf{R}_2$  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

#### (3-Amino-2-hydroxypropoxy)benzamides

elements were within  $\pm 0.4\%$  of the theoretical values.

General Methods. Method A. 1-(4-Ethylcarbamoyl-2n-propylphenoxy)-3-isopropylamino-2-propanol (3). 1,2-Epoxy-3-(4-ethylcarbamoyl-2-propylphenoxy)propane (1.5 g, 0.0057 mol) and *i*-PrNH₂ (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 Et₂O (25 ml). The acidic phase was basified with 11 N NaOH and extracted with EtOAc (25 ml). The EtOAc extract was dried (MgSO₄) 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)-3tert-butylamino-2-propanol (4). 1,2-Epoxy-3-(4-ethylcarbamoyl-2-n-propylphenoxy)propane (1.5 g, 0.0057 mol) and t-BuNH₂ (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 Et₂O (25 ml). The acidic phase was basified with 11 N NaOH and extracted twice with Et₂O (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 NH₄OH (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  $80-100^\circ$ ): yield 0.1 g (4%); mp 116-118°.

Method C. 1-(2-Chloro-4-ethylcarbamoylphenoxy)-3isopropylamino-2-propanol (8). 1-Chloro-3-(2-chloro-4ethylcarbamoylphenoxy)-2-propanol (2.9 g, 0.01 mol), *i*-PrNH₂ (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 Et₂O (25 ml). The acidic phase was basified with 11 N NaOH and extracted twice with EtOAc (25 ml). The combined EtOAc extracts were dried (MgSO₄) 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-BuNH₂ (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 (MgSO₄) and evaporated to dryness. The residue was subjected to thick-layer chromatography on a 2-mm thick plate of silica gel (Merck, Kieselgel PF₂₅₄ gipshaltig), area  $20 \times 40$  cm, using a mixture of 1 part by volume of NH₄OH (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-4hydroxybenzamide (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), H₂O (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 H₂O (25 ml). The EtOAc phase was dried (MgSO₄) and evaporated under reduced pressure and the residue was crystallized from EtOAc: mp 136-138°.

1-Amino-3-(4-ethylcarbamoyl-2-chlorophenoxy)-2propanol. A solution of 1,2-epoxy-3-(4-ethylcarbamoyl-2chlorophenoxy)propane (2.55 g, 0.01 mol) in MeOH (20 ml) was added to a 12% w/v solution of NH₃ 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 (MgSO₄) 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. (C₁₂H₁₇N₂O₃·HCl) C, H, N.

5-(2-Chloro-4-ethylcarbamoylphenoxymethyl)-3-isopropyloxazolidine Dipicrate. A mixture of 1-(2-chloro-4ethylcarbamoylphenoxy)-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-H₂O): yield 0.55 g (43%); mp 86°. Anal. (C₁₆H₂₃ClN₂O₃·2C₆H₃N₃O₇·0.5H₂O) 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-ptoluoyltartaric acid (1.9 g) in EtOH (10 ml) and the mixture was maintained at  $-20^{\circ}$  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°; [ $\alpha$ ]²¹D +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. (C10H12ClNO2) 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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### **References and Notes**

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