Ultra-Short-Acting β-Adrenergic Receptor Blocking Agents. 2. (Aryloxy)propanolamines Containing Esters on the Aryl Function

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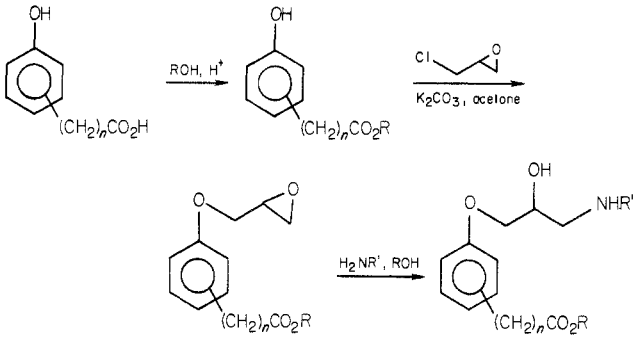
Several short-acting β-adrenergic receptor blocking agents have been prepared by incorporating ester functions into the aryl portion of certain (aryloxy)propanolamine systems. In particular, methyl 3-[4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl]propionate hydrochloride (ASL-8052) was found to be a moderately potent, cardioselective compound with a short duration of action when determined in in vivo canine models.

In the preceding paper in this issue,[1] several (aryloxy)propanolamines with an ester function incorporated into the nitrogen substituent were prepared and tested as part of a program to obtain an ultra-short-acting β-adrenergic receptor blocking agent.[2] Using a similar rationale, we describe in this paper the synthesis and structure–activity relationships for compounds where esters have been placed on the aryl portion of typical β-blocker nuclei. These structures are illustrated in Table I and resemble established β-blocking agents possessing amide functionalities in similar locations (e.g., **2**).[3,4] Because of the electronic similarities between these carboxy-containing groups, it was felt that reasonable potency could be expected from the aryl esters. However, hydrolysis of these esters produces compounds whose carboxylate anion (e.g., **14**) dramatically increases the polarity of the aryl system present in β blockers. As before,[1] it was suspected that such an alteration would render the hydrolyzed molecules unacceptable to the β-adrenergic receptor and that these compounds would, therefore, be inactive or only very weakly active as β-adrenergic blocking agents. It was also felt that by placing the esters close to the β-blocking pharmacophore the attenuation of blocking potency by the carboxylate anion would be maximized. Finally, the carboxylate anion containing metabolities have the potential to be secreted directly into the urine[5] or to undergo conjugation via the acid moiety,[6] either of which would tend to counteract any inherent β-blocking properties that they might possess. Certain aryl esters of this type have been reported in both the patent[7] and the scientific literature[8] to possess β-blocking activity. Furthermore, the acid **14** previously has been shown to be inactive as a β-blocking agent in whole animal studies.[8] With this rationale and literature precedent, initial compounds having esters attached directly to the aromatic ring were prepared to assess their duration of action and to evaluate the potential of the aryl ester approach.

Chemistry. The syntheses of **3–32** proceeded according to Scheme I. In many cases the substituted phenolic starting materials were available as their esters. For acid starting materials [e.g., 3-(4-hydroxyphenyl)propionic acid and the phenols required for compounds **15–19**], esterification was effected by refluxing in the desired alcohol while removing water with a Soxhlet extractor charged with 3A molecular sieves.[9] Phenolic esters were condensed with excess epichlorohydrin in a acetone–potassium carbonate solvent–base system.[1] The epoxides were then opened by reaction with either excess isopropylamine or by an equivalent amount of an alternate alkylamine employing an alcoholic solvent identical with the ester adduct. As expected,[10] attack at the secondary carbon atom was found to occur exclusively, as determined by TLC and

Scheme I



NMR studies of the crude reaction products. As examples of anticipated metabolic products, **11** and **16** were hydrolyzed to their corresponding acids **14** and **23**.

Biological Results and Discussion

The compounds were first studied in guinea pig right atria and tracheal preparations to determine their β_1- and β_2-blocking potencies. The duration of β blockade of active compounds was then assessed in an in vivo canine model after 40 min and/or 3 h infusion of the test compound.[1] In the first series of compounds, **3–7** where a carboalkoxy group was placed in an ortho relationship to the propoxy chain, excellent β-blocking potency was obtained. This result is in accord with structure–activity relationships for other ortho-substituted systems.[11] Similarly, the cardioselectivity observed for **7** reflects the influence of the 3,4-dimethoxyphenethyl nitrogen substituent.[12] Certain of these compounds, e.g., **3** and **4**, exhibited short durations of action after their 40-min infusion and were also sub-

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(6) H. G. Mandel, in ref 5.
(7) K. Nakagawa, S. Yoshizaki, N. Murakami, and T. Hiyama, Japan Kokai 7 375 539; *Chem. Abstr.*, **80**, 59728y (1974).
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(9) L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 705.
(10) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, 11, 1009 (1968).
(11) A. M. Barrett, *Drug Des.*, 3 (1972).
(12) M. L. Hoefle, S. G. Hastings, R. F. Meyer, R. M. Corey, A. Holmes, and C. D. Stratton, *J. Med. Chem.*, 18, 148 (1975).

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stantially shorter than propranolol after 3-h infusions. However, in general, their durations after 3-h infusions were longer than the desired range of ~10 min.

In the next series of compounds, **8–10**, an allyl group was utilized for the ester adduct so that the aryl substituent resembled that of alprenolol and oxprenolol. The decrease in potency and the increase in cardioselectivity observed when the allyl substituent is moved from the ortho to the para position are in accord with the literature.[13] Representatives from this series were found to have long durations of action after their 3-h infusion. The moderate cardioselectivity observed for **10** is comparable to practolol in our models and was regarded as a desirable property for our ultra-short-acting β-blocker target. Therefore, the para-substituted esters **11–13** were prepared where small alkyl groups replaced the allyl function in an attempt to decrease the duration of action. The acid analogue **14** was also prepared and found to be inactive. This is in accord with previous whole animal studies[8] and substantiated the hypothesis that hydrolysis of these aryl esters would result in compounds that lacked β-blocking activity. Although these esters still possessed unsatisfactory durations, an interesting trend was observed in that the ethyl ester **13** was longer acting that the methyl esters **11** and **12**. This was also true for compound **5** compared to **4** in the initial ortho-substituted series. If the shorter durations for **11** and **4** compared to **13** and **5** are attributed to a more rapid ester hydrolysis, one explanation for these results is that the enzyme system[14] interacting with these drugs may be very sensitive to steric factors associated with its substrates. Using this rationale, we suspected that there might be an inhibitory influence by the bulky aryl ring upon metabolic hydrolysis rates for esters attached directly to the ring. Therefore, the methylene-, ethylene-, and propylene-extended analogues **15–17** were prepared as steric probes to test this effect, since the bulky aryl group is pushed sequentially further from the ester linkage. The results of 40-min duration studies with **11** and **15–17** are depicted in Figure 1. The initial trend in this series indicates that this investigation was successful, since **16** possessed a duration of action within the desired range (12 min for 80% recovery). However, the longer duration observed for **17** is interesting and suggests that consideration of only a single steric variable is not adequate to fully explain the interaction of these drugs with the enzyme system. The potencies and cardioselectivities of compounds **15–17** are similar to the structurally related drug metoprolol.[15] When these analogues were subsequently studied in the 3-h infusion model, it was found that the duration obtained for **16** was unchanged, while the durations for **15** and **17** increased considerably. Similarly, the unsaturated extended ester **18** and the extended ortho-ester **19** exhibited long durations after their 3-h infusions.

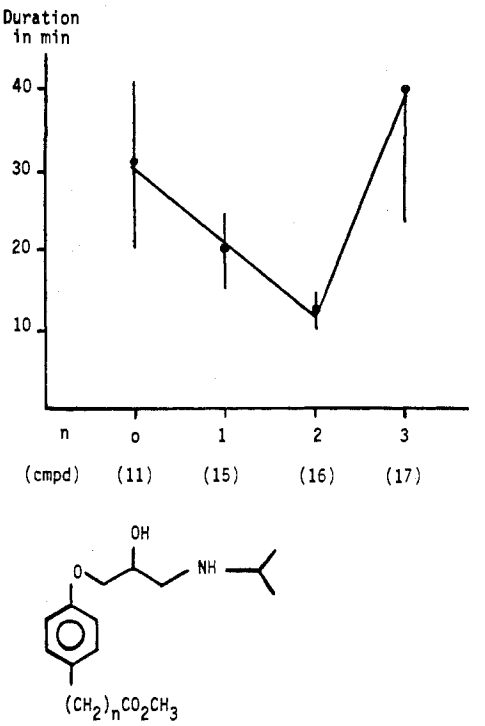


Figure 1. Duration relationship for compound **11** and the steric probes **15–17**. Ordinate: duration, in minutes, for 80% recovery from ~50% β blockade. Means ± SEM. Abscissa: number (*n*) of methylene units inserted into structure **11**.

Several analogues of **16** were prepared to further characterize this promising nucleus. The ethyl and *n*-propyl esters, **20** and **21**, were found to be somewhat less potent and, surprisingly, less cardioselective than **16**. The ethyl ester exhibited a longer duration of action, which is in accord with the substrate steric factor–enzyme system[14] considerations previously discussed. An amide analogue, **22**, was found to be nearly equipotent to **16**. The anticipated **16** hydrolytic metabolite **23** was shown to be essentially inactive (pA_2 in atria < 5). Interestingly, the observations that acid **23** exhibited at least a detectable blocking activity while the acid **14** did not, support our initial rationale where it was felt that the attenuation of blocking potency by the carboxylate anions would be maximized when the acid moieties are closest to the β-blocking molecular pharmacophore. The sequential decrease in cardioselectivity when going from the methyl ester **16** to the ethyl **20** and finally to the *n*-propyl ester **21** is also noteworthy. This trend is also apparent when comparing **11** to **13**.

Compounds **24–27** represent a series of modified nitrogen-substituent derivatives of **16**. Replacement of the isopropyl group with a *tert*-butyl group, **24**, resulted in a net decrease in cardioselectivity, which is in accord with published structure–activity relationships concerning the *tert*-butyl moiety.[16] Alternatively, replacements with the β_1-directing aralkyl functions **25**, **26**, and especially **27**[12] did not further increase cardioselectivity and, if anything, reduced selectivity compared to **16**. Only **24** and **27** seemed interesting enough to warrant study of their duration. They were found to be comparable to **16**.

In the final series, **28–32**, several multiple-ester compounds were synthesized. The very low potency obtained for **29** and **31** is similar to that observed previously when N-external esters are placed α to the pharmacophoric am-

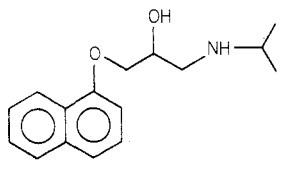
(13) B. Ablad, M. Brogard, E. Carlsson, and L. Ek, *Eur. J. Pharmacol.*, 13, 59 (1970).

(14) Although the decreased durations for the test compounds are presumably due to their ester hydrolysis, additional enzymatic and pharmacokinetic metabolism studies are required to substantiate this hypothesis. Nevertheless, our further molecular refinement continued to use esterase susceptibility as a useful working model. In this regard, even though it is likely that a variety of esterases (e.g., aryl esterases, aliphatic esterases) attack these substrates at varying rates and that each esterase possesses its own structure–activity relationships, it was more useful in our studies to regard them in an overall fashion. By treating them as a single esterase *system* it became possible to apply general structural modification–*system* duration relationships toward further molecular design.

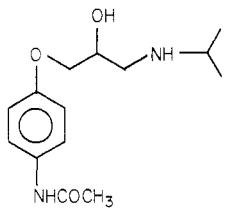
(15) B. Ablad, B. Carlsson, E. Carlsson, C. Dahlof, L. Ek, and E. Hultberg, *Adv. Cardiol.*, 12, 290 (1974).

(16) A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Wood, *J. Med. Chem.*, 12, 638 (1969).

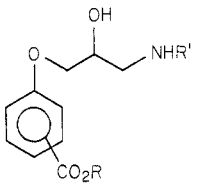
Table I. Structure and Pharmacological Data for Test Compounds



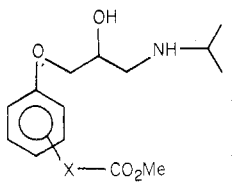
1 (propranolol)



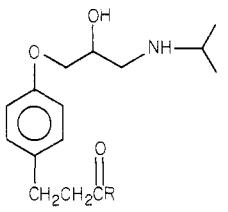
2 (practolol)



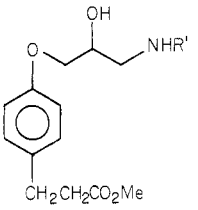
3–14



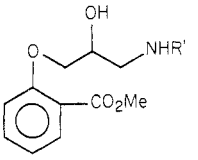
15–19



20–23



24–29



30–32

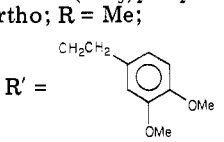
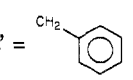
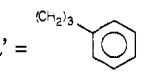
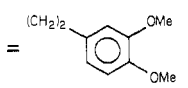
no.		in vitro pA_2[a] atria	trachea	cardio-selectivity[b]	in vivo duration[c] 40 min	3 h
1		8.7	8.9		46 ± 8	>60
2		6.6	5.8	6	61 ± 11	
3	ortho; R = Me; R′ = $CH(CH_3)_2$	8.3	7.9		15 ± 2	15 ± 2
4	ortho; R = Me; R′ = $C(CH_3)_3$	8.8	8.9		12 ± 1	22 ± 5
5	ortho; R = Et; R′ = $C(CH_3)_3$	8.5	8.8			38 ± 9
6	ortho; R = Me; R′ = $C(CH_3)_2CH_2OH$	7.3	7.4			55 ± 11
7	ortho; R = Me; R′ = 	8.3	7.1	15		30 ± 4
8	ortho; R = $CH=CH_2$; R′ = $CH(CH_3)_2$	7.9	7.9			36 ± 5
9	meta; R = $CH=CH_2$; R′ = $CH(CH_3)_2$	6.9	7.2			>60
10	para; R = $CH=CH_2$; R′ = $CH(CH_3)_2$	6.3	5.7	5		
11	para; R = Me; R′ = $CH(CH_3)_2$	6.8	5.5	20	31 ± 1	
12	para; R = Me; R′ = $C(CH_3)_3$	6.5	5.4	13	22 ± 8	
13	para; R = Et; R′ = $CH(CH_3)_2$	6.5	6.1		56 ± 6	
14	para; R = H; R′ = $CH(CH_3)_2$	inact[d]				
15	para; X = CH_2	6.4	5.4	10	20 ± 5	>60
16	(ASL-8052) para; X = CH_2CH_2	7.0	5.2	63	12 ± 2	12 ± 2
17	para; X = $(CH_2)_3$	6.6	5.5	13	40 ± 17	>60
18	para; X = CH=CH	7.3	6.1	18		>60
19	ortho; X = CH_2CH_2	8.6	8.9			29 ± 6
20	R = OEt	6.7	5.2	30		43 ± 14
21	R = $OCH_2CH_2CH_3$	5.4	5.2			
22	R = $NHCH(CH_3)_2$	6.8				
23	R = OH	4.7				>60
24	R′ = $C(CH_3)_3$	6.5	5.9	5	7 ± 2	15 ± 3
25	R′ = 	5.9	4.9	10		
26	R′ = 	6.1	4.8	20		
27	R′ = 	6.5	5.2	20		14 ± 3

Table I (*Continued*)

no.		in vitro pA_2 [a] atria	trachea	cardioselectivity [b]	in vivo duration [c] 40 min	3 h
28	R' = $(CH_2)_2CO_2Et$	5.9	<5.0			
29	R' = $CH(CO_2Et)_2$	<5.0				
30	R' = $(CH_2)_2CO_2Et$	6.6	6.6			10 ± 2
31	R' = $CH(CO_2Et)_2$	5.5				
32	R' = $C(Me_2)CO_2Et$	8.0	7.8			5

[a] Number of experiments is equal to or greater than two for each compound. Tabulated pA_2 values are mean values. The range for each value is equal to or less than ±0.2 unit. [b] Antilog [pA_2 (atria) − pA_2 (trachea)]. [c] Duration, in minutes, for 80% recovery from approximate 50% blockade of an isoproterenol-induced increase in heart rate. Test drugs were infused for 40 min and/or 3 h prior to stopping their infusion and assessing recovery from blockade. Number of experiments is equal to or greater than three for each compound. Tabulated data are mean values ± SEM. [d] At 10^{-5} M.

Table II. Experimental Data for Test Compounds[a]

no.	formula	salt form	cryst solvents	yield, %	mp, °C
3	$C_{14}H_{21}NO_4$	free amine	Hex/EtOAc	52	78–79
4	$C_{15}H_{24}NO_4Cl \cdot 0.5H_2O$	HCl	EtOAc	32	116–118
5	$C_{16}H_{26}NO_4Cl$	HCl	EtOH/Et_2O	25	117–119
6	$C_{15}H_{23}NO_5$	free amine	Hex/EtOAc	26	99–100
7	$C_{23}H_{29}NO_{10}$	oxalate	MeOH/Et_2O	15	125–126
8	$C_{18}H_{25}NO_8$	oxalate	MeOH/Et_2O	47	139–140
9	$C_{18}H_{25}NO_8$	oxalate	MeOH/Et_2O	43	125–126
10	$C_{16}H_{23}NO_4$	free amine	Hex/EtOAc	24	63–64
11	$C_{14}H_{22}NO_4Cl$	HCl	MeOH/Et_2O	41	168–169
12	$C_{15}H_{24}NO_4Cl$	HCl	EtOAc	12	182–184
13	$C_{15}H_{24}NO_4Cl$	HCl	MeOH/Et_2O	66	132–133
15	$C_{15}H_{24}NO_4Cl$	HCl	EtOAc, acetone	25	92–93
17	$C_{17}H_{28}NO_4Cl$	HCl	MeOH/Et_2O	40	93–94
18	$C_{16}H_{24}NO_4Cl$	HCl	MeOH/Et_2O	55	182–183
19	$C_{18}H_{27}NO_8 \cdot 0.25H_2O$	oxalate	MeOH/Et_2O	12	92–94
20	$C_{17}H_{28}NO_4Cl$	HCl	EtOH/Et_2O	35	90–92
21	$C_{18}H_{30}NO_4Cl$	HCl	1-propanol/Et_2O	27	97–98
24	$C_{17}H_{28}NO_4Cl$	HCl	MeOH/Et_2O	45	144–146
25	$C_{20}H_{26}NO_4Cl$	HCl	MeOH/Et_2O	40	180–181
26	$C_{23}H_{30}NO_4Cl$	HCl	MeOH/Et_2O	50	177–179
27	$C_{23}H_{32}NO_6Cl$	HCl	MeOH/Et_2O	40	138–140
28	$C_{18}H_{28}NO_6Cl$	HCl	EtOH/Et_2O	9	110–111
29	$C_{20}H_{30}NO_8Cl$	HCl	EtOH/Et_2O	20	144–145
30	$C_{18}H_{25}NO_{10} \cdot 0.5H_2O$	oxalate	acetone	32	90–91
31	$C_{20}H_{27}NO_{12}$	oxalate	EtOH/Et_2O	12	97–101
32	$C_{20}H_{29}NO_{10}$	oxalate	acetone/Et_2O	47	96–98

[a] The NMR spectra and C, H, and N elemental analyses data were correct for each assigned structure.

ino function.[1] Although the duration obtained for **30** is acceptable, its potency and especially its cardioselectivity are reduced from that of **16**. Similarly, the ultra-short-acting compound **32** did not exhibit a dramatic potency enhancement over **16** when determined in vivo and was essentially noncardioselective such that its overall profile seemed less attractive than that of **16**.

Figure 2 depicts the β-blocking profile of **16** relative to propranolol. After a 3-h infusion of propranolol, there was essentially no decay of β-blocking effect for 60 min, while 80% recovery from the blockade by **16** occurred in 12 ± 3 min, and complete recovery was observed within 20 min after stopping its infusion. In addition, steady-state blockade with **16** was attained relatively quickly (10–15 min), whereas the degree of blockade observed for propranolol continued to increase for 2 h during the course of the infusion. Additional pharmacological, toxicological, and metabolic studies with **16** have proven equally promising, and the drug is currently undergoing preliminary clinical examination.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 283 spectrophotometer either as thin films or as KBr disks. NMR spectra were recorded on a Varian Associates T-60A spectrometer. Thin-layer chromatography was performed on Analtech 250 silica gel GF plates, and visualization was effected by fluorescence quenching while under 254-nm UV lamp irradiation. Column chromatography was performed on a Waters Associates Prep-500 system at a flow rate of 250 mL/min. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Mass spectra were obtained from the Analytical Services Laboratory at Northwestern University, with a Hewlett-Packard 5985 quadrapole instrument.

The Synthesis of Methyl 3-[4-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl]proprionate Hydrochloride (16) Is Representative of the General Route Employed to Prepare All of the Compounds. Experimental data are provided in Table II.

Methyl 3-(4-Hydroxyphenyl)propionate (33). A solution of 300 g (1.81 mol) of 3-(4-hydroxyphenyl)propionic acid in 1 L of anhydrous methanol containing 10 drops of concentrated H_2SO_4 was heated to reflux for 72 h in a Soxhlet extractor charged with 200 g of 3A molecular sieves.[9] The reaction medium was then evaporated under reduced pressure, and the resulting oil was taken up in 750 mL of toluene and washed with three 500-mL portions of water. The toluene phase was then dried with $MgSO_4$ and evaporated under reduced pressure to provide 228.4 g (70%) of a clear oil, which was utilized directly in the next step without additional purification: TLC (toluene/methanol, 9:1) $R_f \sim 0.5$; NMR ($CDCl_3$) δ 7.2 (s, 1, Ar OH), 6.8 (m, 4, Ar H), 3.6 (s, 3, CO_2CH_3), 2.7 (m, 4, CH_2CH_2). An analytical sample was obtained by Kugelrohr distillation [90 °C (3 mm)]. Its NMR spectrum and TLC were identical with the parent material. Anal. ($C_{10}H_{12}O_3$) C,H.

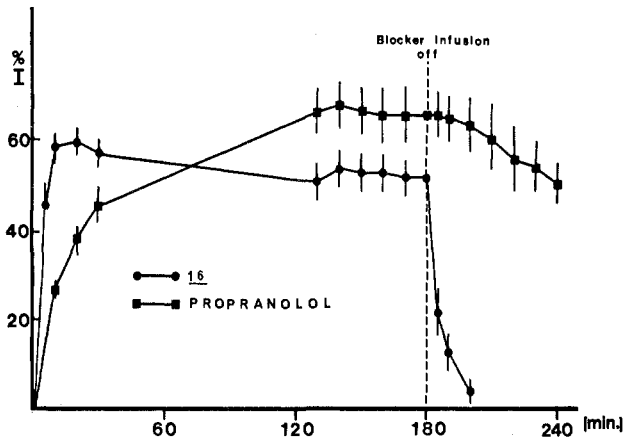


Figure 2. Time course of β blockade during and following constant intravenous infusion of **16** and propranolol. Ordinate: percent inhibition (% *I*) of HR response to isoproterenol (0.5 μg/kg, iv). Abscissa: time after initiation of infusion of blockers. Infusions terminated at 180 min. Dose rates employed: **16**, 50.0 (μg/kg)/min; propranolol, 1.125 (μg/kg)/min (0.2 mg/kg, cumulative). Means ± SEM.

Methyl 3-[4-(2,3-Epoxypropoxy)phenyl]propionate (34). A mixture of 228 g (1.27 mol) of **33**, 263 g (1.90 mol) of K_2CO_3, and 298 mL (3.80 mol) of epichlorohydrin in 2 L of acetone was stirred and heated to reflux for 20 h. The reaction medium was then filtered and evaporated under reduced pressure. The resulting oil was taken up in 1 L of toluene and washed consecutively with 500 mL of water, 2 × 500 mL of 1 N NaOH, and 2 × 500 mL of water. The toluene phase was then dried over $MgSO_4$ and evaporated under reduced pressure to provide a clear oil, which was further purified by vacuum distillation. The final yield of purified oil was 131.2 g (44%): bp 156 °C (0.4 mm); IR (thin film) no significant absorptions above 3100 cm^{-1} (no OH), 1740 cm^{-1} (ester carbonyl); NMR ($CDCl_3$) δ 6.8 (m, 4, Ar H), 3.9 (m, 2, OCH_2), 3.6 (s, 3, CO_2CH_3), 3.2 (m, 1, ring CHO), 2.6 (m, 6, ring CH_2O and CH_2CH_2); EIMS, *m/e* 236.1 (M^+, 25), 107.1 (100); CIMS, *m/e* 237.1 (M + 1^+, 20) 236.1 (96), 163 (100). Anal. ($C_{13}H_{16}O_4$) C, H.

Methyl 3-[4-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl]propionate Hydrochloride (16). A solution of 50 g (0.21 mol) of **34** in 100 mL of methanol and 100 mL of isopropylamine was heated to reflux for 4 h. The reaction medium was then evaporated under reduced pressure to provide the crude product free amine as an oil.[17] The oil was taken up in methanol and treated with ethereal HCl until acidic (pH ~3) and provided crystals upon standing in the refrigerator. A recrystallization was similarly effected from methanol–ether to finally provide 28 g (47%) of white crystals: mp 85–86 °C; HPLC single peak; NMR[18] ($CDCl_3$) δ 9.3 and 8.5 [2 br s, 2, NH_2^+ (disappear upon addition of CD_3OD)] 6.9 (m, 4, para-substituted Ar), 5.0 [broad s, 1, OH (disappears upon addition of CD_3OD)], 4.6 [m, 1, CH(OH)], 4.0 (d, 2, OCH_2), 3.3 (m, 3, CH_2N^+CH) 2.7 (m, 4, CH_2CH_2), 1.5 [d, *J* = 6 Hz, 6, $C(CH_3)_2$]; CIMS, *m/e* 297.3 (M + 1^+ – HCl, 17), 296.3 (100). Anal. ($C_{16}H_{26}ClNO_4$) C, H, N.

4-[2-Hydroxy-3-(isopropylamino)propoxy]benzoic Acid Hydrochloride (14). A solution of 3.0 g (0.01 mol) of **11** in 50 mL of 15% aqueous HCl was heated to reflux for 6 h. The reaction medium was then concentrated while crystallization occurred slowly at room temperature to provide 1.5 g (52%) of **14**: mp 210–211 °C; NMR (CD_3OD) δ 7.3 (m, 4, Ar H), 4.1 [m, 3, OCH_2 and *CH*(OH)], 3.2 (m, 3, CH_2N and NCH), 1.3 [d, *J* = 6 Hz, 6, $CH(CH_3)_2$]. Anal. ($C_{13}H_{20}NO_4Cl$) C, H, N.

***N*-Isopropyl-3-[4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl]propionamide (22).**[19] A solution of 6 g (0.018 mol) of **16** in 50 mL of isopropylamine was heated to reflux for 7 days. The reaction medium was then evaporated under reduced pressure. The resulting oil was taken up in aqueous dilute NaOH/chloroform. The organic phase was separated, washed once with water, dried over $MgSO_4$, and then evaporated to a solid residue. Crystallization was effected from ether/ethyl acetate/acetone (5:1:1) to provide 3.6 g (62%) of **22**: mp 119 °C; NMR (CD_3OD) δ 7.0 (m, 4, para-substituted Ar), 4.0 [m, 4, OCH_2CH(OH) and *NHCO*], 2.6 (m, 8, CH_2NCH, NCH, and CH_2CH_2), 1.1 [m, 12, 2 $C(CH_3)_2$]. Anal. ($C_{18}H_{30}N_2O_3$) C, H, N.

3-[4-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl]propionic Acid (23). A solution of 25 g (0.075 mol) of **16** was hydrolyzed in 100 mL of 1 N NaOH solution at 100 °C for 16 h. The basic solution was then acidified to pH 5–6 with dilute HCl at 0–5 °C. Acetone was added to the aqueous solution until it became turbid. It was then refrigerated to precipitate the sodium chloride generated as a side product from the acidification. The precipitate was removed by filtration, and the solution was evaporated to dryness under reduced pressure, leaving a semisolid representing a mixture of the desired product and residual sodium chloride. About 50 mL of methanol was employed to dissolve the semisolid, and then acetone was again added until the solution became turbid. The turbid solution was again refrigerated to precipitate the remaining inorganic salt. The precipitate was removed, and the solution was again refrigerated until no additional precipitate was observed. The solution was then treated with ether until it became turbid. Upon cooling and scratching, **23** began to crystallize. The solution was refrigerated for an additional 24 h. The product was collected as a white crystalline solid in 15 g (63%) yield: mp 128–129 °C; NMR (CD_3OD) δ 7.1 (m, 4, para-substituted Ar), 4.2 [m, 1, *CH*(OH)], 4.1 (d, *J* = 5 Hz, 2, OCH_2), 3.3 (m, 3, CH_2N^+CH), 2.7 (m, 4, CH_2CH_2), 1.4 [d, *J* = 6 Hz, 6, $C(CH_3)_2$]; HPLC, single peak chromatogram. Anal. ($C_{15}H_{24}NO_4Cl$) C, H, N.

Biological Studies. The biological experiments were performed in identical fashion with those described previously.[1]

Acknowledgment. The technical contributions of Lee Preusser and Alain Levanho during the biological testing and of Martine Bunting during the typing of this manuscript are greatly appreciated.

(17) A small sample of the free amine oil was set aside and it gradually formed crystalline rosettes at room temperature: mp ~48–50 °C; NMR ($CDCl_3$) δ 7.9 (m, 4, para-substituted Ar), 4.0 [m, 3, OCH_2CH(OH)], 3.6 (s, 3, CO_2CH_3), 3.2 (br s, 2, OH and NH), 2.8 (m, 7, CH_2CH_2 and CH_2NCH), 1.05 [d, *J* = 6 Hz, 6, $C(CH_3)_2$]. Anal. ($C_{16}H_{25}NO_4$) C, H, N. A small amount of this oil was distilled [118 °C (0.2 mm)] in Kugelrohr fashion and was accompanied by ~50% decomposition.

(18) A C^{13} NMR spectra has also been recorded (IBM NR-80 Instrument; D_2O DSS): δ 20 (-CH(CH_3)$_2$), 32 (-CH_2CO-), 37 (Ar-CH_2-), 49 (CH_2N), 53 (OCH_3), 55 [NH$CH(CH_3)_2$], 68 [CH(OH)], 72 (ArOCH_2), 117 (Ar ortho to alkyl subst) 132 (Ar ortho to ether subst) 136 (Ar at alkyl subst), 160 (Ar at ether subst), 179 (ester carbonyl).

(19) Procedure adapted from that described by B. K. Wasson, W. K. Gibson, R. S. Stuart, H. W. R. Williams, C. H. Yates, *J. Med. Chem.*, **15**, 651 (1972).

(20) Preliminary results from reverese-phase HPLC studies of structural representatives of the various aryl and aralkyl esters, including compound **16**, suggest that significant spontaneous hydrolysis does not occur at pH 7.4 in aqueous media within 1 h. Detailed results will be published elsewhere.