= H; R_2 = F), 2648-00-2; III (R_1,$R_{2'}$ = H; R_2 = Cl), 1088-11-5; III (R_1,$R_{2'}$ = H; R^2 = CN), 17562-53-7; III (R_1,$R_{2'}$ = H; R_2 = NO_2), 146-22-5; III (R_1,$R_{2'}$ = H; R_2 = CF_3), 2285-16-7; III (R_1,$R_{2'}$ = H; R_2 = SCH_3), 2891-12-5; III (R_1 = CH_3; R_2 = Cl; $R_{2'}$ = H), 439-14-5; III (R_1 = CH_3; R_2 = NO_2; $R_{2'}$ = H), 2011-67-8; III (R_1 = CH_3; R_2 = CN; $R_{2'}$ = H), 3489-59-6; III (R_1 = CH_3; R_2 = $N(CH_3)_2$; $R_{2'}$ = H), 2891-09-0; III (R_1 = CH_3; R_2 = Cl; $R_{2'}$ = F), 3900-31-0; III (R_1 = CH_3; R_2,$R_{2'}$ = Cl), 2894-68-0; III (R_1 = CH_3; R_2 = NO_2; $R_{2'}$ = F), 1622-62-4; III (R_1 = CH_3; R_2 = NO_2; $R_{2'}$ = Cl), 5527-71-9; III (R_1 = CH_3; R_2 = NO_2; $R_{2'}$ = CF_3), 1959-37-1; III (R_1 = CH_3; R_2 = H; $R_{2'}$ = F), 844-11-1; III [R_1 = CH_3; R_2 = $N(CH_3)_2$; $R_{2'}$ =Cl], 30144-75-3; PNMT, 9037-68-7.

Ultra-Short-Acting β-Adrenergic Receptor Blocking Agents. 3. Ethylenediamine Derivatives of (Aryloxy)propanolamines Having Esters on the Aryl Function

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Various ethylenediamine derivatives have been incorporated into the nitrogen substituent of certain short-acting (aryloxy)propanolamine systems that contain esters on their aryl functions. Although several of these compounds showed durations of action comparable to their prototypes, most of the nitrogen substituents significantly prolonged the duration of β-adrenergic blockade. Similarly, while one of the compounds showed appreciable cardioselectivity in vitro, generally, little enhancement of cardioselectivity was obtained. A brief discussion of structure–activity relationships observed for the ethylenediamine derivatives is presented.

As part of a program intended to produce short-acting β-adrenergic receptor blocking agents,[1] we previously described the syntheses and pharmacology of several (aryloxy)propanolamines that contained ester moieties incorporated into their nitrogen substituent[2] and aryl functions.[3] These studies revealed that when certain ester and alkyl ester groups are placed on the aryl function, short-acting β-blockers can be obtained. Furthermore, when the aryl substitution pattern is para, compounds exhibit moderate β-blocking potency and tend to be cardioselective, whereas potent, nonselective compounds result from ortho substitution (e.g., compounds 1 and 2 in Table I). An attempt to obtain both high potency and cardioselectivity by combining an *o*-carboalkoxy system with the 3,4-dimethoxyphenethyl nitrogen substituent[4] (compound 3) caused the duration of action to increase considerably.

Our interest in obtaining cardioselective short-acting compounds was two-fold: first, potential problems associated with β_2-blockade in the airways should be less; and, second, β_1-selectivity would decrease the possibility that the balance between α- and β_2-adrenergic control could be disrupted in favor of α-induced vasoconstriction in the coronary vasculature. The latter possibility could result in coronary vasospasm[5] and exacerbate certain of the cardiovascular pathologies[6] envisioned for therapy with an ultra-short-acting β-blocker.[1]

In this report we describe several additional potent *o*-carboalkoxy derivatives where a variety of ethylenediamine moieties[7-9] have been employed in an attempt to enhance cardioselectivity. These compounds are listed in Table I.

Chemisty. The syntheses of the test compounds followed established procedures. Methyl or ethyl salicylate was treated with epichlorohydrin,[2,3] providing key intermediate epoxides, which were then opened with the appropriate diamines to produce **4–20**. The diamines required for **16–20** and **22–24** were commercially available, and those for **4–15** were prepared by literature methods.[8-10] Compounds **22–24** were prepared starting from methyl 4-hydroxybenzoate, compound **27** was prepared starting from 2-methylphenol, and compound **25** was prepared starting from *o*-hydroxycinnamic acid after esterification with methanol.[2] Compound **26** was obtained from **25** by catalytic hydrogenation. The preparations of **1–3**, **21**, and **28** have been described previously.[2,3]

Chemical data for the test compounds are listed in Table I. A representative synthesis is provided under Experimental Section.

Results and Discussion

Compounds were first screened in vitro in guinea pig right atrial and tracheal preparations.[2] Compounds showing pA_2 values equal to or greater than 7.0 were then tested for their duration of effect in a canine preparation following a 3-h intravenous infusion. Infusion rates were adjusted to produce approximately 50% inhibition of isoproterenol-induced tachycardia. Isoproterenol challenges were performed at 10-min intervals before, during, and after the infusion of test compounds.

In the first series, amides **4–7**, a very small increase in cardioselectivity compared to **1** was obtained based on in vitro data. These compounds possessed durations of action somewhat longer than our desired value of approximately 10 min.[2,3] Cardioselectivity was not observed for sulfon-

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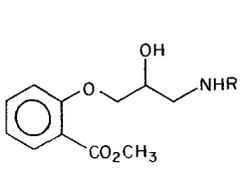
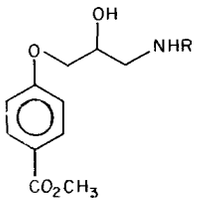
Table I. Structures, Chemistry Experimental, and Pharmacological Data for Test Compounds



1-20



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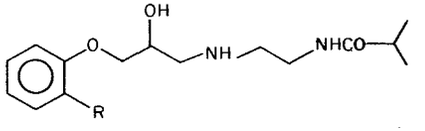
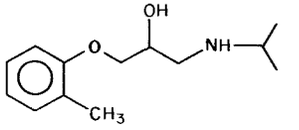


25-27



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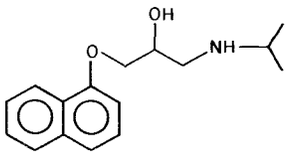

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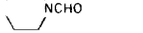
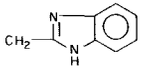
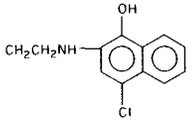
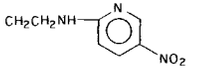
no.	R	formula[a]	salt	crystn solvents	yield,[b] %	mp, °C	in vitro pA_2[c] atria	trachea	cardio-selectivity[d]	in vivo duration[e]
1	$CH(CH_3)_2$	$C_{14}H_{21}NO_4$	free amine	Hex/EtOAc	52	78–79	8.3	7.9	2.5	15 ± 2
2	$C(CH_3)_3$	$C_{15}H_{24}NO_4Cl \cdot 0.5H_2O$	HCl	EtOAc	32	116–118	8.8	8.9		22 ± 5
3	$CH_2CH_2Ph[3,4\text{-}(OCH_3)_2]$	$C_{23}H_{29}NO_{10}$	oxalate	$MeOH/Et_2O$	15	125–126	8.3	7.1	15.8	30 ± 4
4	$CH_2CH_2NHCOCH_3$	$C_{15}H_{22}N_2O_5$	free amine	$EtOAc/Et_2O$	11	115–116	7.3	7.0	2.0	18 ± 1
5	$CH_2CH_2NHCOCH(CH_3)_2$	$C_{17}H_{26}N_2O_5$	free amine	$MeOH/Et_2O$	19	128–129	8.1	7.5	4.0	17 ± 1
6[f]	$CH_2CH_2NHCOCH(CH_3)_2$	$C_{18}H_{29}N_2O_5$	free amine	Hex/Et_2O	9	83–87	8.5	7.7	6.3	40 ± 5
7	$CH_2CH_2NHCOCH_2Ph$	$C_{21}H_{26}N_2O_5$	free amine	$EtOAc/Et_2O$	15	114–115	8.3	7.7	4.0	42 ± 2
8	$C(CH_3)_2CH_2NHSO_2Ph$	$C_{23}H_{30}N_2O_{10}S$	free amine	MeOH/acetone	22	117–118	8.6	8.8		>60[g]
9	$CH_2CH_2NHSO_2Ph(4\text{-}CH_3)$	$C_{21}H_{27}N_2O_8S$	hemioxalate	MeOH/acetone	30	168–169	6.8	7.1		
10	$CH_2CH_2NHSO_2N(CH_3)_2$	$C_{15}H_{26}N_3SO_6Cl$	HCl	$MeOH/Et_2O$	39	142–143	7.5	7.3		15 ± 9
11	$C(CH_3)_2CH_2NHCONH_2$	$C_{16}H_{25}N_3O_5 \cdot 0.5H_2O$	free amine	EtOAc/acetone	26	52–53	8.9	8.5	2.5	>60[g]
12[f]	$C(CH_3)_2CH_2NHCONH_2$	$C_{17}H_{27}N_3O_5$	free amine	acetone/Et_2O	26	162–163	9.9	9.3	4.0	>60[g]
13	$CH_2CH_2NHCONHPh$	$C_{20}H_{25}N_3O_5$	free amine	$MeOH/Et_2O$	8	133–134	8.1	6.7	25.1	>60[g]
14	$C(CH_3)_2CH_2NHCO\text{-}c\text{-}N(CH_2CH_2)_2O$	$C_{20}H_{31}N_3O_6$	free amine	acetone/Et_2O	56	113–114	9.7	9.0	5.0	>60[g]
15	$C(CH_3)_2CH_2NHCO_2CH_2CH_3$	$C_{20}H_{30}N_2O_{10}$	oxalate	$MeOH/Et_2O$	9	90–91	8.6	8.2	2.5	30 ± 6
16[h]		$C_{20}H_{28}N_2O_{10}$	oxalate	$MeOH/Et_2O$	11	128–129	<6.0[i]			
17[h]		$C_{20}H_{26}N_2O_{13}$	dioxalate	$MeOH/Et_2O$	5	187–188	<6.0[i]			
18		$C_{23}H_{25}N_3O_{12}$	dioxalate	MeOH/acetone	13	190–191	6.5			
19		$C_{25}H_{27}N_2O_9Cl$	oxalate	MeOH/acetone	12	101–102	6.2			
20		$C_{19}H_{23}N_4O_8$	oxalate	$MeOH/Et_2O$	33	212–213	7.5	7.1	2.5	15 ± 6
21	$CH(CH_3)_2$	$C_{14}H_{22}NO_4Cl$	HCl	$MeOH/Et_2O$	41	168–169	6.8	5.5	20	
22	$CH_2CH_2\text{-}c\text{-}NC_4H_8$	$C_{17}H_{28}N_2O_4Cl_2$	2HCl	MeOH/EtOAc	17	208–209	<6.0[i]			
23	$CH_2CH_2\text{-}c\text{-}NC_5H_{10}$	$C_{18}H_{30}N_2O_4Cl_2$	2HCl	MeOH/EtOAc	16	219–220	<6.0[i]			
24	$CH_2CH_2\text{-}c\text{-}N(CH_2CH_2)_2O$	$C_{17}H_{28}N_2O_4Cl_2$	2HCl	$MeOH/Et_2O$	12	226–227	<6.0[i]			
25	$CH{=}CHCO_2CH_3$	$C_{19}H_{28}N_2O_5$	free amine	acetone/Et_2O	37	141–142	9.4	9.1	2.0	>60[g]

26	$CH_2CH_2CO_2CH_3$	$C_{19}H_{30}N_2O_5$	free amine	MeOH/Et_2O	83	119–120	7.6	7.7	$>60^g$
27	CH_3	$C_{16}H_{26}N_2O_3$	free amine	MeOH/Et_2O	37	118–119	8.3	7.7	4.0	$>60^g$
28		$C_{13}H_{21}NO_2Cl$	HCl	EtOH/Et_2O	84	133–135	8.6	8.2	2.5	$>60^g$
29[j] (propranolol)							8.7	8.9		$>60^g$

[a] All NMR spectral and elemental analyses data were in accord with the assigned structures. [b] Final recrystallized product yields calculated for the last reaction step. [c] Negative log of the test drug concentration effecting 50% blockade of isoproterenol-induced rate responses. Number of experiments is equal to or greater than 2 for each compound. Tabulated pA_2 data are mean values. The range for each value is equal to or less than ±0.2 unit. [d] Antilog [pA_2 (atria) − pA_2 (trachea)]. Data are tabulated only for compounds where the ratio is equal to or greater than 2. [e] Time in minutes for 80% recovery from 50% blockade levels after 3-h infusions of drug. Number of experiments is equal to or greater than 3 for each compound. Tabulated data are mean values plus or minus SEM. In general, the in vivo potencies paralleled the relationships observed in vitro. [f] Ethyl ester instead of methyl ester. [g] Less than 80% recovery observed at 60 min after stopping drug infusion. [h] These cyclic tertiary-amine compounds do not contain a hydrogen on the nitrogen atom as suggested by the general structure. [i] No blockade was observed at 10^{-6} M. [j] Purchased from Sigma Chemical Co., St. Louis, MO.

amides **8** and **9** or for the sulfamide **10**. The primary ureas **11** and **12**, although extremely potent, showed minimal cardioselectivity and possessed long durations of action. Alternatively, the phenyl-substituted urea **13** was found to have considerable cardioselectivity, approximately 25-fold as determined in vitro. This finding is in accord with a recent independent report,[11] which also shows **13** to be cardioselective. However, this urea and the morpholinourea **14** possessed long durations of action when assessed in vivo. An ethyl carbamate, **15**, was found to have a small preference for β_1-blockade and was intermediate in its duration of effect. Despite some suggestion[12,13] that cyclic tertiary diamines can exhibit β-blocking effects, the related structures **16** and **17** were found to be essentially inactive in our models.

As part of this study, compounds **18–20** and **22–24** were synthesized to further explore the structure–activity relationships associated with the ethylenediamine system when incorporated into the β-blocker pharmacophore. Previous investigators[14-16] have shown that reasonable potency is obtained when the nitrogen substituent of various β-adrenergic agents contains a heteroatom, such as oxygen or sulfur, two carbons away from the amine moiety. In particular, amidic-type structures, as depicted by **30**, have been shown to possess excellent potencies and cardioselectivities.[7-9] Although little structural correlation, beyond this relationship, has been established,[8] it has been suggested that an "extra receptor site in some way associated with the cardiac β-receptor" may be responsible for the observed profile.[7] In the series **22–24**, a tertiary-amino function, rather than an amidic group, resides two carbons away from the amine analogous to *a* in **30**. All of these compounds were found to be essentially inactive relative to their standard **21**. These results are in accord with a previous report[17] where similar modifications performed on the nitrogen substituent of propranolol, **29**, resulted in greatly reduced potency. In compounds **18–20**, each analogous nitrogen *b* can be shown to be secondary and adjacent to a π electron system, which was intended to simulate the carbonyl moiety, *x*, present in the more active ethylenediamine derivatives. Although compounds **18** and **19** showed only weak activity, compound **20** was found to have reasonable potency, and it's duration of action was found to be comparable to **1**. Taken together, these studies suggest that nitrogen *b* is required to be secondary and/or α to a π-electron system, perhaps reflecting a preference for a combination of low Lewis basicity and low steric hindrance for interaction with the putative "extra receptor site". It follows that this interaction may be through hydrogen bonding to an unprotonated nitrogen *b*. Alternatively, the large size of the aminopyridine system relative to an amidic group suggests that rigorous steric requirements may not be present in the receptor area which would be closer to the carbonyl or *x* region of structures represented by **30**.

In the last two test drugs, **25** and **26**, the *o*-carboalkoxy function was extended from the aryl moiety, and a simple

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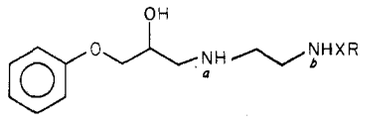

30, X = -CO-, -SO_2-; R = alkyl, aryl, substituted amino or oxygen

ethyleneamide was employed as the nitrogen substituent. Both compounds exhibited long durations of action. It should also be noted that the methyl ester **5** exhibited a shorter duration of action than its homologous ethyl ester **6**. This finding supports the previous suggestion that the enzymes responsible for degrading these β-blocker esters may be very sensitive to steric effects.[3] Finally, it is interesting that even modifications of the remote nitrogen substituents can significantly affect the rate of enzymatic hydrolysis of these esters.

In summary, with the exception of the phenylureido compound **13**, substitution with various ethylenediamine derivatives generally did not increase cardioselectivity within this series. That **13** was the most cardioselective compound is in accord with the recent report[11] that for the various amidic moieties, cardioselectivity is most evident in the ureido analogues. In the duration studies, only amides **4** and **5**, sulfamide **10**, and the pyridine compound **20** had durations of action comparable to the isopropyl standard **1**. In all other instances, the test compounds were found to have a significant increase in their duration of blocking activity.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Associates T-60A spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

The following experimental procedure leading to **13** is representative of the general procedures used to synthesize all of the compounds. Experimental data for **1–28** are provided in Table I.

Methyl 2-(2,3-Epoxypropoxy)benzoate (31). A mixture of 15.2 g (0.10 mol) of methyl 2-hydroxybenzoate, 27.6 g (0.20 mol) of potassium carbonate, and 31 mL (0.40 mol) of epichlorohydrin in 250 mL of acetone was heated to reflux for 24 h.[3] The reaction medium was then filtered and evaporated under reduced pressure. The resulting oil was dissolved in 100 mL of toluene and washed consecutively with 100 mL of water, 2 × 100 mL of 1.0 N sodium hydroxide, and 2 × 100 mL of water. The organic phase was then dried over magnesium sulfate and evaporated under reduced pressure to provide the crude product as an oil. Purification was effected by vacuum distillation to provide 5 g (25%) of an oil: bp 148 °C (75 μm); NMR ($CDCl_3$) δ 7.4 (m, 4, ArH), 4.2 (m, 2, OCH_2), 3.8 (s, 3, OCH_3), 3.3 (m, 1, OCH), 2.8 (m, 2, OCH_2). Anal. ($C_{11}H_{12}O_4$) C, H.

***N*-Acetylethylenediamine (32).** A mixture of 88 g (1.0 mol) of ethyl acetate and 180 g (3.0 mol) of ethylenediamine was heated in a Parr bomb at 100 °C for 36 h.[10] After cooling, the reaction medium was evaporated under reduced pressure to an oil, which was then taken up in 300 mL of ethyl acetate. Cooling this solution at 3 °C for 24 h caused undesired disubstituted byproduct to crystallize. This solid was removed by filtration, and the mother liquor was evaporated under reduced pressure to provide an oil. The oil was taken up in anhydrous ether, and the solution was cooled at 3 °C for 24 h to provide 72 g (81%) of white crystals: mp 51–52 °C (lit.[18] mp 50–51 °C); NMR spectrum identical with a commercial sample.[18]

2-[[(Phenylamino)carbonyl]amino]ethylamine Hydrochloride Hydrate (33). A 6.20 mL (0.057 mol) quantity of phenyl isocyanate was added dropwise to a stirred suspension of 5.82 g (0.057 mol) of **32** in 100 mL of methylene chloride at 10 °C. After the addition, a solid precipitated. Anhydrous ether (100 mL) was added, and the mixture was stirred for 30 min. The reaction medium was then filtered, and the solid was dissolved in 50 mL of 15% HCl. This solution was heated at 80 °C for 4 h and then evaporated under reduced pressure to a white solid, which was recrystallized from methanol–ether to provide 7.0 g (61%): mp 190–191 °C; NMR (CD_3OD) δ 7.3 (m, 5, ArH), 3.5 (t, J = 5 Hz, 2, CH_2), 3.1 (t, J = 5 Hz, 2, CH_2). Anal. ($C_9H_{14}N_3OCl·0.33H_2O$) C, H, N.

Methyl 2-[2-Hydroxy-3-[[2-[[(phenylamino)carbonyl]amino]ethyl]amino]propoxy]benzoate (13). A 4.8 g (0.024 mol) quantity of **33** was dissolved in 100 mL of methanol, and 2.5 g (0.024 mol) of triethylamine was added. While stirring, a solution of 5 g (0.024 mol) of **31** in 25 mL of methanol was added slowly. The solution was heated to reflux for 4 h. After the reaction, the methanol was removed under reduced pressure, and the resulting gel-like solid was dissolved in 100 mL of methylene chloride. The organic layer was washed twice with 100 mL of water and dried over anhydrous magnesium sulfate. Evaporation of the methylene chloride left an oil, which was dissolved in 50 mL of methanol/ether (1:1) from which the product crystallized slowly at 3 °C to provide 0.7 g (8%): mp 133–134 °C; NMR ($CDCl_3$) δ 7.3 (m, 9, ArH), 3.8 (s, 3, OCH_3). Anal. ($C_{20}H_{25}N_3O_5$) C, H, N.

Biological Studies. The biological experiments were performed in identical fashion with those described previously.[2,3]

Registry No. **1**, 33947-95-4; **2**, 51698-60-3; **2**·HCl, 33948-14-0; **3** oxalate, 83356-56-3; **4**, 85850-21-1; **5**, 85850-22-2; **6**, 85850-23-3; **7**, 85850-24-4; **8**, 85850-25-5; **9** 0.5-oxalate, 85850-27-7; **10**, 85850-49-3; **10**·HCl, 85850-28-8; **11**, 85864-51-3; **12**, 85850-29-9; **13**, 83019-57-2; **14**, 85850-30-2; **15** oxalate, 85850-32-4; **16** oxalate, 85850-34-6; **17** 2-oxalate, 85850-36-8; **18** 2-oxalate, 85850-38-0; **19** oxalate, 85850-40-4; **20** oxalate, 85850-42-6; **21**, 33947-97-6; **21**·HCl, 33947-96-5; **22**, 85850-50-6; **22**·2HCl, 85850-43-7; **23**, 85850-51-7; **23**·2HCl, 85850-44-8; **24**, 85850-52-8; **24**·2HCl, 85850-45-9; **25**, 85850-46-0; **26**, 85850-47-1; **27**, 53671-23-1; **28**, 29044-59-5; **28**·HCl, 16799-82-9; **31**, 22589-46-4; **32**, 1001-53-2; **33**·HCl, 85850-48-2; methyl 4-hydroxybenzoate, 99-76-3; 2-methylphenol, 95-48-7; methyl *o*-hydroxycinnamate, 20883-98-1; methyl 2-hydroxybenzoate, 119-36-8; ethyl acetate, 141-78-6; ethylenediamine, 107-15-3; phenyl isocyanate, 103-71-9.

Resolution and Absolute Configuration of an Ergoline-Related Dopamine Agonist, *trans*-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1*H*(or 2*H*)-pyrazolo[3,4-*g*]quinoline

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The title compound (±)-**5** (R = Pro) (LY141865) has been resolved into a (−) isomer and a (+) isomer as the D- and L-tartrate salts, respectively. Biological studies have shown that dopamine agonist activity is a property of only the (−) isomer. Crystallographic analysis has proven that the absolute configuration of the active (−) isomer is the same as that of the natural ergolines.

In a previous paper[1] we reported the synthesis of rigid bicyclic and tricyclic ergoline partial structures **1–3** and their pyrazole isosteres **4–6**. The pyrroles, especially the tricyclic members **2** and **3**, were shown to have very sig-

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