All substances to be tested were dissolved in saline immediately before use. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose. Injection volumes were 5 or 10 mL/kg, and injection solutions had approximately neutral pH.

The biochemical experiments and the spectrophotometric determinations of Dopa were performed as previously described.[11] Separate dose–response curves based on four to six dose levels for each substance (subcutaneous administration) and brain area were constructed (cf. ref 11). From these curves, the dose of the drug yielding a half-maximal decrease of the Dopa level, the ED_{50} value (presented in Table I), was graphically estimated. In each point of the curves, the SEM was less than 15% of the mean value.

Motor Activity. The motor activity was measured by means of photocell recordings ("M/P 40 Fc Electronic Motility Meter", Motron Products, Stockholm) as previously described.[11]

The rats were treated with reserpine (10 mg/kg ip) and DL-α-methyl-p-tyrosine methyl ester hydrochloride (tyrosine hydroxylase inhibitor; 250 mg/kg ip) 6 and 1 h, respectively, prior to the motility testing (carried out between 1 and 6 p.m.). The different compounds under investigation were then administered subcutaneously in the neck region (n = 4), in a dose of 1 mg/kg (3000 nmol/kg: compounds **3** and **6**) or 10 mg/kg (30000 nmol/kg; compound **4**). Controls received isotonic saline.

Immediately after drug administration, the rats were placed in the test cages (one rat per cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 60 min. Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the experiments. The motor activity results are shown in Table I.

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Registry No. **3**, 90295-42-4; **3**·HBr, 90295-43-5; **4**, 90295-44-6; **4**·HBr, 90295-45-7; **5**·HBr, 90295-46-8; **7**, 33892-75-0; **8**, 90295-47-9; **9**, 90295-48-0; **9**·HCl, 90295-49-1; **9** N-propionyl deriv., 90295-50-4; **10**, 42263-75-2; **11**, 90295-51-5; **11**·HCl, 90295-52-6; **12**, 90365-41-6; **12**·HCl, 90365-42-7; **13**, 90295-53-7; **13**·HCl, 90295-54-8; **14**, 90365-43-8; **14**·HCl, 90365-44-9; **15**, 4003-87-6; **16**, 90295-55-9; **16**·HCl, 90295-56-0; **17**, 78950-90-0; **17**·HCl, 90295-57-1; 5-methoxy-1-methyl-2-tetralone oxime, 90295-58-2; propionyl chloride, 79-03-8; n-propylamine, 107-10-8.

[(Arylcarbonyl)oxy]propanolamines. 1. Novel β-Blockers with Ultrashort Duration of Action

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Novel [(arylcarbonyl)oxy]propanolamines were synthesized and investigated as potential ultrashort-acting β-adrenergic receptor blockers. Many of these analogues exhibited good potency and short duration. The N-ureidoalkyl analogue **85** (ACC-9089) has a potency equal to propranolol and a duration of action of about 21 min in the dog. It has been selected as a candidate for further clinical study. Structure–activity relationships and structure–duration relationships for these new β-blockers are also discussed.

In certain clinical situations, drugs with very short biological half-lives may be preferred over their longer acting counterparts. Intravenous infusion of an ultrashort-acting drug into a patient will allow rapid achievement of a steady-state therapeutic effect,[5] a rapid alteration of the desired effect in a dose–titration manner, and a rapid termination of undesirable responses should they occur. An ultrashort-acting drug is also useful for testing the patient response and tolerance to the therapy before using a long-acting compound.

The wide clinical indications of β-adrenergic blocking agents and the dangerous side effect of inducing cardiac failure during surgery[6] or after myocardial infarction[7] suggest a need for an ultrashort-acting β-blocker. A more detailed discussion of the pharmacological rationale for an ultrashort-acting β-blocker has recently been published.[8]

We felt that an ideal ultrashort-acting β-blocker should have the following profile: (1) Duration. The duration of β-blocking activity in patients should last from 10 to 30 min after termination of the infusion of the drug. A duration of action of about 15 min seems to be most desirable. A duration longer than 30 min or shorter than 10 min is less desirable since the former would prevent strict control of activity over an ever-changing situation and the latter would make precise minute to minute control too difficult to achieve. Our approach to try to achieve short duration of action was to incorporate into the skeleton of the β-blocker a "metabolically unstable" ester function that on breakdown in vivo by esterases would lead to products that are devoid of β-blocking activity. Esterases are widely distributed in body fluids and tissues.[9] (2) Toxicity. Due to the fast breakdown of the drug, the compound has to be replenished continuously to maintain a constant drug level in the blood. It is thus obvious that the cumulative

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Scheme I

$HOOCCH(OH)CH_2Cl$ (1) + $H_2NCH_2CH_2C_6H_3(OCH_3)_2$ (2) →

$HOOCCH(OH)CH_2NHCH_2CH_2C_6H_3(OCH_3)_2$ (3) —1. p-$CH_3OC_6H_4CH_2OCON_3$; 2. DHP, H^+; 3. H^+→

$HOOCCH(OTHP)CH_2N(COOCH_2C_6H_4OCH_3)CH_2CH_2C_6H_3(OCH_3)_2$ (4) —1. CDI; 2. ArOH→

$ArOC(=O)CH(OTHP)CH_2N(COOCH_2C_6H_4OCH_3)CH_2CH_2C_6H_3(OCH_3)_2$ (5) —H^+→

$ArOC(=O)CH(OH)CH_2NHCH_2CH_2C_6H_3(OCH_3)_2$ (6a–d)

Scheme II

$HOCH_2CH(-O-)CH_2$ (7) + H_2NR → $HOCH_2CH(OH)CH_2NHR$ (8) —ArCOCl→ $ArCOOCH_2CH(OH)CH_2NHR$

Scheme III

ArCOCl + $HOCH_2CH(-O-)CH_2$ → $ArCOOCH_2CH(-O-)CH_2$ (9) —H_2NR→ $ArCOOCH_2CH(OH)CH_2NHR$

Scheme IV

$ArC(=O)OCH_2CH(OH)CH_2NHR$ → $ArC(=O)-N(R)CH_2CH(OH)CH_2OH$ (10)

dose of a short-acting drug over a period of time will be much greater than that of a long-acting drug. Since the short-acting drug will exist in the body mainly in the metabolized form, it is extremely important that those metabolites should be inactive and innocuous, even at a high concentration. (3) Potency. A potent compound will help to reduce the amount of drug required and therefore the amount of metabolites produced. An ultrashort-acting β-blocker with an in vivo potency comparable to propranolol would be desirable. (4) Cardioselectivity. This is a desirable feature for patients with bronchial disease. However, β-blockers that are cardioselective (e.g., atenolol, metoprolol) usually are considerably less potent than the nonselective blockers (e.g., propranolol, nadolol, timolol). Since the amount of metabolites generated increases with a less potent compound, a potent nonselective short-acting β-blocker would also be acceptable. It should further be noted that since the β-blocker is very short acting, any undesirable β-blocking activity may be terminated very quickly merely by stopping the infusion of the drug. (5) Chemical stability. We anticipate that this ultrashort-acting β-blocker will be given to patients by continuous infusion for a period from a few hours to several days. Therefore, it should possess satisfactory chemical stability in an aqueous preparation throughout the infusion period.

Some of the synthetic work of incooperating an ester as part of the aromatic or nitrogen substituent of the β-blocker molecule has been previously reported.[10] The present report describes the incorporation of esters between the ring and the nitrogen.

Chemistry. The β-blockers with phenolic ester **6a–c** were prepared by the routes depicted in Scheme I. β-Chlorolactic acid (**1**) was heated with 3,4-dimethoxyphenethylamine (**2**) to produce the amino acid **3**. The amino group of **3** was then protected by p-methoxybenzyloxycarbonyl azide. Treatment of the intermediate with excess dihydropyran (DHP) followed by selective hydrolysis of the tetrahydropyranyl ester gave the acid **4**. Coupling of **4** with phenol or a substituted phenol was facilitated by carbonyldiimidazole (CDI) to give **5**. Deprotection of **5** with acid in nonaqueous medium gave the final products **6a–c** (Table I). Compound **6d** was obtained by direct esterification of **3** with 2-methoxybenzyl alcohol.

The β-blockers with benzoate esters **11–13** (Table I and Table II) have been reported by Tatsuno et al.[11] They synthesized these compounds through the reaction of 3,4-(methylenedioxy)benzoic acid salts with epichlorohydrin in the presence of a phase-transfer catalyst to obtain the intermediate glycidyl ester **9** (Scheme III), which was then treated with amines to obtain the blockers. We attempted to repeat these syntheses but failed to isolate any desired product **12** from the reaction of the glycidyl ester and isopropylamine. Two alternate routes were therefore developed. In the first synthesis (Scheme II), glycidol **7** was allowed to react with an amine to form the amino diol **8** which was then mixed with an acid chloride to give the products. For compound **11**, methylbenzylamine was used and the benzyl function was later removed by hydrogenolysis. When the amine employed in the reaction was unsubstituted on the α-carbon, the final [(arylcarbonyl)oxy]propanolamine could sometimes undergo intramolecular rearrangement to form the amide **10** (Scheme IV) during the workup process (e.g., **93**, **94**, Table I). To circumvent this problem, we protected the nitrogen of **8** by p-methoxybenzyloxycarbonyl azide prior to the condensation with the acid chloride. This protective group was removed later by anhydrous HCl under mild conditions to provide the desired products. The second synthesis (Scheme III) was similar to the reported[11] one except that the glycidyl ester intermediate **9** was prepared from the reaction of the acid chloride and glycidol.

Pharmacology. All the testing was performed as described in ref 8 and 10. The in vitro pA_2 values (Table I) of the blockers were obtained in guinea pig right atria (β_1)

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and trachea (β_2). Compounds that showed promising β-blocking activities were evaluated in vivo in a canine model. The β-blocker was infused into the animal for 3 h with a dose adjusted to give approximately 50% blockade of the isoproterenol-induced tachycardia. The infusion was then terminated and the time required for 80% recovery of blockage was recorded as duration of action of the compound. The amount of drug infused during the 3-h period was averaged and expressed as potency in microgram (kilogram minute) (Table I). Half-life ($t_{1/2}$, Table I) was measured in vitro in canine blood and liver and human blood.

Results and Discussion

β-Blockers with the phenolic ester linkage (**6a,b**) showed only moderate β-blocking activity with pA_2 values of 5.9 (Table I). It is possible, however, that the low potency could be due to the spontaneous decomposition of the compounds during the incubation period (1 h, pH 7.4). In fact, the hydrochloride salts of compounds **6a,b** are extremely unstable in water and no parent compounds could be detected by nuclear magnetic resonance after a period of 2 h at 25 °C. The 1-naphthyl derivative **6c** was even more labile and the free base of it decomposed completely within 5 min in a mixture of Me_2SO-d_6–D_2O (9:1). Such a high degree of instability is not totally unexpected in view of the possibility that intramolecular hydrogen bonding could exist between the carbonyl oxygen and the neighboring hydroxy or amino group and thus render the ester function very suceptible to nucleophilic attack or aqueous hydrolysis. Reduction of incubation time to 15 min for compound **6a** did not result in any increase in potency (pA_2 = 5.03, n = 2). Compound **6d**, which is more stable than **6a–c**, was totally inactive in atria. Problems in stability are anticipated with the formulation and storage of these "chemically unstable" compounds.

The benzoate esters **11–13** were reported[11] to have pA_2 values of 5.3, 6.9, and 6.9, respectively, in guinea pig atria. In addition, we found that compounds **12** and **13** showed no sign of decomposition in water for as long as 18 h. The in vivo duration of **12** was 50 min, which was not appreciably shorter than propranolol **98**. In dog liver homogenates, however, **12** had a half-life of 29 min compared to over 180 min for propranolol **98**. In light of these findings, a simple [(phenylcarbonyl)oxy]propranolamine (**14**) was synthesized. This compound is a moderately potent β-blocker with pA_2 values of 6.3 in atria and 7.1 in trachea and most important, a short duration of 26 min in the in vivo canine model (Table I). The half-life of this compound in canine and human plasma was 7.0 and 3.0 min,[12] respectively, and the metabolism was effected by the pseudocholinesterase in the plasma.[12] The hydrolysis of **14** by esterases should give benzoic acid and 3-(isopropylamino)-1,2-propanediol (**8**) as metabolites. Both of these compounds are highly hydrophilic and therefore should be excreted rapidly by the kidney. The isopropylamino diol 8 was reported[13] to have only insignificant β-blocking activity in guinea pig right atria (pA_2 = 4.0). Although **14** represents a useful lead that closely meets our criteria in chemical stability and duration of action, its β-blocking potency is low (pA_2 = 6.3) compared to that of propranolol (pA_2 = 8.7). Analogues of other [(arylcarbonyl)oxy]propanolamines were thus synthesized with the objective of identifying a more potent short-acting β-blocker.

Analogues **15–38** (*N*-isopropyl), **39–60** (*N-tert*-butyl), and **61–71** (*N*-3,4-dimethoxyphenethyl) were synthesized to examine the affect of the aromatic and nitrogen substitutions on the β-blocking potency and on the duration of action of **14**. All of these analogues are weaker β-blockers (pA_2 = 6–8) than propranolol (pA_2 = 8.7) in guinea pig atria (Table I). However, the in vivo potency in dog is generally greater than the in vitro potency in guinea pig. For example, although the 4-NH_2 derivative **33** is a weak blocker in vitro (~1/100 of propranolol), it is slightly more potent than propranolol in vivo. The following correlations also appears to exist between the potency of the analogues in the guinea pig atria and the physicochemical parameters of the aromatic substituents: (1) Compounds with the electron-donating and sterically small substituents (steric constant[14] $E_s < -1$, e.g., 4-OH **32, 53**; 4-NH_2 **33, 54**) at the para position of the ring are generally more potent than compounds with electronic-withdrawing (e.g., 4-NO_2 **35**, 4-CHO **56**) or bulky substituents (e.g., 4-CH_2OH **31**, 4-$OCH_2CH_2CH_2CH_3$ **50**) at the same locations. (2) For substituents at the ortho and meta positions, the only parameter that correlates well with β-blocking activity is the steric constant E_s. Groups with a smaller constant of less than -1.2[14] (e.g., 3-OH **46**; 3-CH_3 **21, 44**; 2-Cl **16, 41**; 2-OH **43**) give more potent compounds than the bulkier substituents (e.g., 2-$OCH_2CH_2CH_3$ **18**, 3-$NHCOCH_3$ **25**). Replacing the aromatic ring of **14** by aralkyl **72–75**, cyclopentyl **76**, 4-pyridinyl **77**, or 9-fluorenyl **78** results in a decrease in β-blocking potency (Table I).

According to the Easson-Stedman hypothesis[15] adrenergic drugs of the arylethanolamine series can attach to three different binding sites on the adrenergic receptor through the aromatic, the β-hydroxy, and the nitrogen functions of the molecule. With β-blockers of the (aryloxy)propanolamine series, it has been suggested[16] that these compounds can assume a bicyclic conformation that allows them to occupy the three sites on the adrenergic receptor. The short-acting [(arylcarbonyl)oxy]propanolamine (e.g., **14**) differs from the (aryloxy)propanolamines only in the distance between the aromatic ring and the ethanolamine side chain. The presence of an extra carbon in the central chain makes it impossible for **14** to acquire a spatial conformation that is similar to that of the (aryloxy)propanolamines. Consequently, the interaction between **14** and the β-receptor might involve only one or two but not all of the three binding sites. For maximum ligand–receptor interaction, the ethanolamine portion of **14** may attach to both the β-hydroxy and the nitrogen binding sites with the aromatic ring projecting away from the aromatic binding site. If this is true, the structure–activity relationships of the (aryloxy)propanolamines may only apply to the regions of the [(arylcarbonyl)oxy]pranolamines at the nitrogen or the ethanolamine side chain. The structure–activity relationships at the aromatic ring between these two series should be different. The following findings support this hypothesis.

The in vitro and in vivo β-blocking potencies of the N-substituted [(arylcarbonyl)oxy]propanolamines are roughly in the order of *N-tert*-butyl > *N*-isopropyl ≥ *N*-2,3-dimethoxyphenethyl (e.g., **40** > **15** ~ **62**). The

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Table I. Biological Activity of Potential Ultrashort-Acting β-Blockers

6a–d 11–13 14–38 39–60 61–71 72–78 79–94

no.	Ar or R	in vitro pA_2[a]: atria[b]	in vitro pA_2[a]: trachea[b]	in vitro pA_2[a]: cardiac selectivity[c]	$t_{1/2}$,[a,d] min: human blood	$t_{1/2}$,[a,d] min: canine blood	$t_{1/2}$,[a,d] min: canine liver	in vivo data[a,e]: dose μg/(kg min)[f]	in vivo data[a,e]: % inhib of isoproterenol induced tachycardia	in vivo data[a,e]: time for 80% recov
6a	Ph	5.9	5.9	1						
6b	2-MePh	5.9								
6c	1-$C_{10}H_7$									
6d	2-(MeO)$PhCH_2$	inactive	5.0							
11	CH_3	5.3	(lit.[11])							
12	$CH(CH_3)_2$	6.9	(lit.[11])				29	123		50
13	$C(CH_3)_3$	6.9	(lit.[11])					28		>60
14	H	6.3	7.2	−7	2.3	6.8	8.0	128 (85)	63	26 ± 8
15	2-F	6.6	7.1	−3	1.7	7	4	106	46	25 ± 9
16	2-Cl	6.8	7.4	−4	1.7	28	12	(44)		
17	2-CH_3	6.5	7.1	−4	>180	>180	147	50	83	>60
18	2-$OCH_2CH_2CH_3$	6.6	7.1	−3.5				172	69	>60
19	2-$OCH_2CH{=}CH_2$	6.4	6.2	−2						
20	3-F	6.5	7.0	−3	8.0	52	11			
21	3-CH_3	6.8	7.3	−3				(46)		
22	3-$OCH_2CH_2CH_3$	6.6								
23	3-$OCH_2CH{=}CH_2$	6.8	6.8	1						
24	3-NH_2	6.4	6.8	−2.5		>180	>180	7	80	>60
25	3-$NHCOCH_3$	6.1	6.4	−2						
26	3-NO_2	6.8	7.2	−2.5						
27	4-F	6.6	7.3	−5	3.5	4	3.0			
28	4-CH_3	6.8	6.8	1	6.0	67	10.4	(78)		
29	4-OCH_3	6.0	6.3	−2	55	150	37	209	67	>60
30	4-OCH_2Ph	<6.0								
31	4-CH_2OH	6.2	6.3	1						
32	4-OH	6.8	7.2	−2.5				25	79	>45
33	4-NH_2	6.7	6.6	1	60	>180	>180	0.59–1.26	80	>60
34	4-$NHCOCH_3$	5.8	5.2	4						
35	4-NO_2	6.1	6.2	1						
36	4-CN	5.7	5.7	1						
37	2′-CH=CHCH=CH-3′	6.6	7.0	−2.5						
38	3′-CH=CHCH=CH-4′	6.4	6.6	−2				182	54	>60
39	H	6.8	7.7	−8	5.3	7.3	20	70	65	>60
40	2-F	6.8	8.0	−16	1.6	30	10	20	60	17 ± 3
41	2-Cl	7.2	7.8	−4	6.0	31	72	18	67	>35
42	2-CH_3	7.3	7.9	−4	>180	>180	>180			
43	2-OH	7.1	8.0	−9		41	31	27	73	>60
44	3-CH_3	7.0	7.3	−2						
45	3-OCH_2Ph					>180	>180			
46	3-OH	7.4	7.6	−2		119	62	7	56	25 ± 5
47	3-NH_2	6.7	7.2	−3.5						
48	3-NO_2	6.8				74	>180			
49	4-F	7.3	8.0	−5	11.5	16	66			
50	4-$OCH_2CH_2CH_3$	5.4								
51	4-$OCH_2CH{=}CH_2$	6.0								
52	4-OCH_2Ph	6.2								
53	4-OH	7.4	6.5	9	56	>180	>180	4	71/74	>60
54	4-NH_2	7.0	7.0	1						
55	4-NO_2	6.1			5.5	>180	>180			

Table I (Continued)

		in vitro pA_2[a]			$t_{1/2}$,[a,d] min			in vivo data[a,e]		
				cardiac		canine			% inhib of	time for
no.	Ar or R	atria[b]	trachea[b]	selectivity[c]	human blood	blood	liver	dose μg/(kg min)[f]	isoproterenol induced tachycardia	80% recov
56	4-CHO	6.2	6.3	1		14	1.0			
57	2-Cl, 4-NO_2	6.6	6.5	1				23	85	>60
58	2-CH_3, 4-NO_2	6.6	7.3	−5						
59	2-CH_3, 4-NH_2	7.8	8.4	−4						
60	2′-CH=CHCH=CH-3′	6.8	7.4	−4		>180	>180			
61	H	7.0	6.3	5				121 (88)	45	29 ± 5
62	2-F	6.1	5.7	2.5				100	48	>60
63	2-Cl	7.8	7.5	2				(50)		
64	2-CH_3	7.0	6.8	2				226	85	>60
65	3-F	6.4	6.2	2						
66	3-Cl									
67	3-CH_3	6.9	6.6	2				(113)		
68	4-F	7.0	6.7	2				59	59	>60
69	4-CH_3	6.6	6.0	4				(430)		
70	4-CH_2OH	<5.5								
71	4-NH_2	6.5	5.7	6						
72	CH_2Ph	5.6			6.3	16				
73	$(CH_2)_2Ph$	<6.0			71	<2.5				
74	$(CH_2)_3Ph$	5.3								
75	$CHPh_2$	<5.5			120	>180				
76	c-C_5H_9	5.3								
77	4-py	5.3								
78	#a	<6.0								
79	$C(CH_3)_2C_2H_5$	6.7	7.7	−5		6	12			
80	$C(CH_3)_2C{\equiv}CH$	6.6	6.7	1		12	7			
81	$C(CH_3)_2CH_2NHCOCH_3$	7.5	8.0	−3		7.5		15	61	35
82	$C(CH_3)_2CH_2NHCOCH(CH_3)_2$	6.8	8.1	−18		20	3.5	3.3	62	22 ± 6
83	$C(CH_3)_2CH_2NHCOCH_2Ph$	7.4	8.1	−5		6	25	10	68	19
84	$C(CH_3)_2CH_2NHCOC_6H_{11}$	7.7	7.2	3				8	61	12 ± 3
85	$C(CH_3)_2CH_2NHCONH_2$	8.1	8.4	−2		15	2.5	1.0	49	21
86	$C(CH_3)_2CH_2NHCONHCH_3$	6.5	8.1	−39		12	5			
87	$C(CH_3)_2CH_2NHCON$ O #b	8.5	8.2	2				1.1	81/71	>60
88	$C(CH_3)_2CH_2NHCOOEt$	7.1	7.0	1		8	1	36	49	8 ± 3
89	$C(CH_3)_2CH_2NHCOOCH_2CH_2$-$OCH_3$	7.7	7.7	1						
90	$C(CH_3)_2CH_2NHSO_2Ph$	7.0	7.9	1		~15		57/122	43/55	6/36
91	$C(CH_3)_2CH_2NHSO_2N(CH_3)_2$	7.4	7.5	1						
92	$CH(CH_3)CH_2NHCOCH_3$	<6.3								
93	$CH_2CH_2NHCOCH_2Ph$	<6.0								
94	$CH_2CH_2NHCOCH(CH_3)_2$	6.1								
95	*N*-isopropyl-3-(phenyloxy)propan-2-olamine	8.0	7.4	4						
96	*N*-isopropyl-3-[(2-methylphenyl)oxy]propan-2-olamine	8.6	8.2	3						
97	practolol	6.6	5.8	6						
98	propranolol	8.7	8.9	−2		>180		1.3	68	>60
99	butoxamine	6.1	7.2	−13						

[a] Number of experiments is equal to or greater than two for each compound. [b] Guinea pig right atria and trachea, range ≤0.2. [c] $10[pA_2 \text{ (atria)} - pA_2 \text{ (trachea)}]$. Minus indicates β_2 selectivity. [d] Time in which $^1/_2$ of the initial amount of compound disappeared. [e] Tested drugs were infused for 3 h prior to the assessment of the 80% recovery time. [f] Average dose per minute over the 3-h infusion period. Doses in parentheses were obtained from a 40-min infusion model.

cardioselectivity, however, follows an inverted sequence of *N*-2,3-dimethoxyphenethyl > *N*-isopropyl > *N*-*tert*-butyl (e.g., **62** > **15** > **40**). Similar orders of potency[17,18] and cardioselectivity[19,20] have also been observed in the (aryloxy)propanolamine series with similar N-modifications. These similarities in potency and in selectivity profiles between the two series are consistent with the assumption that the ethanolamine side chains of the [(arylcarbonyl)oxy]propanolamines and the (aryloxy)propanolamines might be acting on common sites within the same receptor.

A comparison of the β-blocking potency of the aromatic modified [(arylcarbonyl)oxy]propanolamines **14**, **17**, **34**, and **37** with their similarly modified (aryloxy)propanolamine homologues **95**, **96**, **97**, and **98** (propranolol), respectively, in guinea pig atria and trachea indicates that compounds of the former series are generally less potent and more β_2-selective (Table I). It is also interesting to note that, although the [(arylcarbonyl)oxy]propanolamines with the phenyl **14** (pA_2 = 7.2), 2-methylphenyl **17** (pA_2 = 7.1), and 1-naphthyl **37** (pA_2 = 7.0) aromatic nuclei are essentially equipotent in guinea pig trachea, the corre-

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Table II. Physical Data of Potential Ultrashort-Acting β-Blockers

no.	synthetic scheme	mp,[a] °C	salt	crystn solv	yield,[b] %
6a		150.5–151	HCl	*i*-PrOH	24
6b		116–117	HCl	*i*-PrOH/Et_2O	66
6c		151	HCl	*i*-PrOH	17
6d		79.5–82.5	base	Oil	23
11	II	175–175	oxalate	EtOH	3
12	II	170–170.5	HCl	*i*-PrOH	8.6
13	II	165–165.5	HCl	*i*-PrOH	6
14	I	155.5–156.5	HCl	*i*-PrOH	22
15	II	144–145	HCl	$(CH_3)_2CO/Et_2O$	12
16	II	129	HCl	*i*-PrOH	54
17	II	120.5–121.5	HCl	*i*-PrOH	33
18	II	131.5–132.5	oxalate	*i*-PrOH	73
19	II	133.5–135	oxalate	*i*-PrOH	31
20	II	122.5-123	HCl	$(CH_3)_2CO/Et_2O$	33
21	I	137.5–138	HCl	$(CH_3)_2CO$	12
22	II	120–120.5	HCl	*i*-PrOH/Et_2O	94
23	II	111–112	HCl	*i*-PrOH/Et_2O	31
24	II	141–142	HCl	*i*-PrOH	61
25	II	130–132.5	oxalate	*i*-PrOH	30
26	II	160–160.5	HCl	*i*-PrOH	11
27	II	139–140	HCl	*i*-PrOH	35
28	I	151.5–152	HCl	*i*-PrOH	40
29	II	139–140	HCl	*i*-PrOH	36
30	II	137–137.5	HCl	MeOH	54
31	II	98–98.5	base	CH_2Cl_2/CCl_4	6
32	II	170–170.5	base	*i*-PrOH/MeOH	62
33	II	211–212	HCl	*i*-PrOH	55
34	II	195	HCl	$(CH_3)_2CO$	33
35	II	203–205	HCl	*i*-PrOH	63
36	II	167.5–168.5	HCl	*i*-PrOH	18
37	II	145–147	HCl	*i*-PrOH	>50
38	II	149.5–150	HCl	*i*-PrOH	33
39	II	105–106	base	CCl_4/*n*-C_6H_{14}	24
40	II	97.5–98	base	CCl_4	60
41	II	74.5–75.5	base	CCl_4	24
42	II	93–94	base	CCl_4/*n*-C_6H_{14}	38
43	II	208–208.5	$^1/_2$ oxalate	MeOH	2
44	II	72–73	base	CCl_4/*n*-C_6H_{14}	29
45	II	100–101	base	CCl_4/*n*-C_6H_{14}	41
46	II	220–221	$^1/_2$ oxalate	MeOH/Et_2O	37
47	II	159.5	oxalate	*i*-PrOH	80
48	II	91–92	base	CCl_4	46
49	II	109–110	base	CCl_4/*n*-C_6H_{14}	59
50	II	196–197	$^1/_2$ oxalate	*i*-PrOH	90
51	II	139–139.5	oxalate	*i*-PrOH	49
52	II	173–174	oxalate	MeOH	46
53	II	220–220.5	$^1/_2$ oxalate	*i*-PrOH/MeOH	74
54	II	168–170	oxalate	MeOH/*i*-PrOH	15
55	II	106–107	base	CCl_4/*n*-C_6H_{14}	19
56	II	170–171	oxalate	*i*-PrOH/Et_2O	59
57	II	197–200	$^1/_2$ oxalate	*i*-PrOH	33
58	II	170–171	HCl	*i*-PrOH	8
59	II	209–210	HCl	*i*-PrOH/*n*-C_6H_{14}	79
60	II	165–166	oxalate	*i*-PrOH	57
61	I	130	HCl	*i*-PrOH	40
62	II	109–110	HCl	*i*-PrOH/Et_2O	18
63	I	113.5–114	HCl	THF/Et_2O	11
64	II	169–170	oxalate	EtOH/*i*-PrOH	20
65	II	171–171.5	oxalate	*i*-PrOH	24
66	II	183–186	oxalate	*i*-PrOH	11
67	I	88.5	base	toluene	19
68	II	154–154.5	HCl	*i*-PrOH	12
69	I	153–153.5	HCl	*i*-PrOH	33
70	II	164–164.5	oxalate	EtOH	19
71	II	147–148	HCl	EtOH	78
72	II	150.5–151.5	oxalate	EtOH	2.5
73	II	151.5–152.5	$^1/_2$ oxalate	EtOH	0.9
74	II	148–149	$^1/_2$ oxalate	*i*-PrOH	9.8
75	II	152–153	HCl	EtOH	11
76	II	151–151.5	oxalate	EtOH	5
77	II	157.5–158	oxalate	EtOH	2
78	II	186–187	oxalate	*i*-PrOH	20
79	II	50–51	base	*n*-C_5H_{12}/Et_2O	28
80	I	124–125	base	*i*-PrOH/Et_2O	23
81	I	oil	base		10
82	I	134.5–137.5	oxalate·H_2O	*i*-PrOH	<10

Table II (Continued)

no.	synthetic scheme	mp,[a] °C	salt	crystn solv	yield,[b] %
83	I	145.5–146.5	HCl	*i*-PrOH	15
84	I	187–188	oxalate	*i*-PrOH/EtOAc	34
85	I	149–152	H_2SO_4	EtOH	43
86	I	149.5	$^1/_2$ oxalate	*i*-PrOH	26
87	I	58.5–59.5	HCl	*i*-PrOH	22
88	I	137	HCl	EtOAc	26
89	I	94–96	oxalate	EtOAc	21
90	I	152.4–153	oxalate	*i*-PrOH	10
91	I	124–125	oxalate	$(CH_3)_2CO$/EtOAc	8
92	I	30	base	EtOAc	31
93	II	140.5	HCl	*i*-PrOH	40
94	II	162.5–163	HCl	*i*-PrOH	56

[a] Melting points were uncorrected. [b] Yield of the last step.

Table III. Stability Study of Certain Ortho-Substituted [(Arylcarbonyl)oxy]propanolamines in pH 7.4 Phosphate Buffer at 37 °C

compd no.	R	Substituent on nitrogen	% remaining after 18 h
39	H	*tert*-butyl	99
40	2-F	*tert*-butyl	98
15	2-F	isopropyl	83
62	2-F	3,4-dimethoxyphenethyl	35
41	2-Cl	*tert*-butyl	98
16	2-Cl	isopropyl	92
63	2-Cl	3,4-dimethoxyphenethyl	59
42	2-CH_3	*tert*-butyl	100
17	2-CH_3	isopropyl	100
64	2-CH_3	3,4-dimethoxyphenethyl	94

sponding analogues of the (aryloxy)propanolamine series showed a definite and substantial increase in potency in the order of phenyl **95** (pA_2 = 7.4) < 2-methylphenyl **96** (pA_2 = 8.2) < 1-napthyl *98* (pA_2 = 8.9, propranolol). Similar activity profiles with the [(arylcarbonyl)oxy]-propanolamines and the (aryloxy)propanolamines are also observed in guinea pig atria although the contrast is less dramatic. Since we have shown that the ethanolamine side chains of the [(arylcarbonyl)oxy]propanolamines and the (aryloxy)propanolamines might be acting on similar functional groups on the β-receptors, the discrepancy in potency trends that we observed here with the two series of identically modified blockers suggests that their aromatic functions might be interacting with different regions on the β-receptors.

Selected compounds that possessed good β-blocking potency were also examined for their half-lives in blood and liver in vitro and their durations in vivo (Table I). From these results, it appears that the biological stability of an [(arylcarbonyl)oxy]propanolamine is greatly influenced by the electronic and the steric characteristics of the aromatic substituents, especially when they are located at the position ortho to the ester. In this regard, compounds with a bulky 2-CH_3 (**17**, **42**) group exhibit much longer half-lives and durations than the unsubstituted (**14**, **39**) or the 2-halogenated analogues (**15**, **16**, **40**, **41**). These observations suggest that ester hydrolysis is the major pathway for the inactivation of these [(arylcarbonyl)-oxy]propanolamines. The longer half-lives of compounds **17** and **42** suggest that a bulky 2-CH_3 group prevents the hydrolysis of the ester, probably by sterically hindering the approach of the esterases to the ester and/or by its electron-donating effect that stabilizes the ester toward nucleophilic attack. When the ortho substituent is a halogen, the electronic effect becomes withdrawing due to the strong electronegativity of the atom and the resulting destabilizing effect on the ester probably account for the short duration of the 2-halogenated compounds. The 2-fluorine, which offers minimum steric hinderance but maximum electronic-withdrawing effect, was the most promising aromatic substituent for short action. In fact, compounds **15** and **40** have extremely short half-lives of less than 2 min in human blood. In addition, compound **40** also exhibited a promising duration of 17 ± 3 min in dogs.

The chemical stability of some ortho-substituted esters was studied in pH 7.4 buffer, and the results are shown in Table III. A bulky, electron-donating ortho aromatic substituent appears to enhance the chemical stability of a blocker in the same way as it enhanced the biological stability (2-CH_3 **64** > 2-Cl **63** > 2-F **62**, Table III). On the other hand, branching on the α-carbon of the nitrogen substituent also increased chemical stability in the order of *N*-*tert*-butyl **40** > *N*-isopropyl **15** > *N*-3,4-dimethoxyphenethyl **62** (Table III). The sterically hindered groups on the ring and/or on the nitrogen prevent the intramolecular rearrangement of an [(arylcarbonyl)oxy]-propanolamine to the amide **10** (Scheme IV) and thus increase the chemical stability. The 2-fluoro blocker **40**, which has been shown to posses very short action (17 ± 3 min) and a moderate β-blocking potency (Table I), was quite stable at pH 7.4 (Table III) and retained a satisfactory 98% of the parent compound after 18 h of incubation at 37 °C (Table III). Thus, we concluded that the ideal ultrashort-acting β-blocker of the [(arylcarbonyl)-oxy]propanolamine series should have the 2-fluorine on the ring and the *N*-α,α-dimethylalkyl on the nitrogen since the former helps to reduce the duration of action while the latter enhances potency and chemical stability.

Further modification of **40** for better potency focused on the N-substituents. It has been reported[21] that the *N*-amidoethyl and the *N*-ureylenethyl derivatives of (aryloxy)propanolamines are generally more potent β-agonists or β-antagonists than their *N*-alkyl analogues. Since our earlier findings suggested that the ethanolamine side chains of the (aryloxy)propanolamines and the [(arylcarbonyl)oxy]propanolamines are probably acting on common sites within the same β-receptor, the structure–activity relationships of the N-substituents of the former should apply to the nitrogen of the latter. By retaining the ortho fluorine and the *N*-α,α-dimethylethyl function as the common features, analogues of **40** with amide, urea, carbamate, and sulfonamide functions on the *N*-α,α-dimethylethyl function were prepared (**79–94**, Table I). These analogues indeed show considerable improvement in β-blocking potency over the previous blockers. One of the compounds that has a *N*-α,α-dimethyl-β-[(morpholinocarbonyl)amino]ethyl group (**87**) is, in fact, slightly more potent than propranolol in vivo. The duration of action, however, varies substantially from compound to compound, with the shortest being 8 min (**88**) and the longest

(21) Barlon, J. J.; Main, B. G.; Snow, H. M. *J. Med. Chem.* **1981**, *24*, 315. Large, M. S.; Smith, L. H. *Ibid.* **1983**, *26*, 352; **1982**, *25*, 1417; **1980**, *23*, 112.

(87) showing no breakdown within an hour. Four compounds (82–85) were found to exhibit both good potency and short duration. The most promising one is the *N*-ureido derivative **85** (ACC-9089), which has a potency equal to that of propranolol and a duration of 21 min in dogs. Also, this compound has less β_2-antagonist activity (nonselective) compared to the other compounds of the same series. It has an extremely low calculated partition coefficient, which is about 7000 times[22] less than that of propranolol. The strong hydrophilic character of **85** is particularly important since it not only will limit the access of the blocker to the central nervous system and thus avoid unwanted CNS effect but also may enhance kidney excretion. Hydrolysis of **85** by esterases presumably would give two metabolites: the simple *o*-fluorobenzoic acid and the highly hydrophilic amino diol $HOCH_2CHOHCH_2NHC(CH_3)_2CH_2NHCONH_2$. The former metabolite has no reported toxicity and the latter metabolite is inactive as a β-blocker in guinea pig atria (unpublished result). Compound **85** has been selected for toxicological evaluation and clinical study.

F, O, COCH2CHCH2NH—C—CH2NHCNH2 H2SO4, OH, O

85 (ACC-9089)

Our results with the [(arylcarbonyl)oxy]propanolamines demonstrate that it is possible to insert an extra "planar" function (e.g., C=O) between the ring and the ether oxygen of an (aryloxy)propanolamine molecule and preserve reasonable β-blocking potency.

Experimental Section

Chemistry. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or by the Analytical Section of American Critical Care and were within the ±0.4% limit. Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrometer. NMR was determined on a Varian T-60A instrument. Spectral data (IR, NMR) were consistent with the assigned structures in all cases.

3-[(3,4-Dimethoxyphenethyl)amino]-2-hydroxypropionic Acid (3). A mixture of 20 g (0.16 mol) of β-chlorolactic acid and 86 g (0.48 mol) of 3,4-dimethoxyphenethylamine was heated at 110 °C for 15 h. The resulting product was dissolved in about 200 mL of water and the pH was adjusted to about 8 with Na_2CO_3. The aqueous solution was extracted twice with 500 mL of chloroform and neutralized to pH 7 with diluted HCl. The solution was evaporated to dryness and the residue was recrystallized in EtOH to give 24.6 g (61.6%) of crystals: mp 187.5–188.5 °C. Anal. ($C_{13}H_{19}NO$) C, H, N.

3-[(3,4-Dimethoxyphenethyl)(4-methoxybenzyloxycarbonyl)amino]-2-[(tetrahydro-2-pyranyl)oxy]propionic Acid (4). To a solution of 0.245 g (0.91 mmol) of the amino acid from the previous experiment in 10 mL of dioxane–H_2O (1:1) was added 0.23 g (2.73 mmol) of $NaHCO_3$ and 0.19 g (0.92 mmol) of *p*-methoxybenzyloxycarbonyl azide. The reaction mixture was stirred at room temperature for 16 h and extracted between 20 mL of water and 2 × 20 mL of ether. Evaporation of the ether gave 0.08 g (36%) of the product 3-[(3,4-dimethoxyphenethyl)(4-methoxybenzyloxycarbonyl)amino]-2-hydroxypropionic acid. To 3.6 g (8.9 mmol) of this acid in 20 mL of methylene chloride was added 3.74 g (44.5 mmol) of dihydropyran and a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 3 h and neutralized by concentrated NH_4OH. The reaction mixture was filtered and the solvent was evaporated. The residue was then stirred with 70 mL of ether and 0.3 mL of HCl at room temperature for 1 h, neutralized with NH_4OH, and filtered, and the ether was removed in vacuo to afford 3.92 g (90.1%) of product.

Phenyl 3-[(3,4-Dimethoxyphenethyl)(4-methoxybenzyloxycarbonyl)amino]-2-[(tetrahydro-2-pyranyl)oxy]propionate (5). A solution that consisted of 3.92 g (7.5 mmol) of the acid 4, 30 mL of THF, and 1.48 g (9 mmol) of carbonyldiimidazole was stirred at room temperature for 0.5 h. To the reaction mixture were added 0.855 g (10.5 mmol) of phenol and a catalytic amount of sodium imidazole. The reaction mixture was stirred for 10 h and partitioned between 2 × 100 mL of ether and 100 mL of water. Evaporation of the ether gave an oil, which was purified by column chromatography (silica gel/EtOAc–hexane = 1:1) to give 1.1 g (24%) of oily product. Anal. ($C_{33}H_{39}NO_9$) C, H, N.

Phenyl 3-[(3,4-Dimethoxyphenethyl)amino]-2-hydroxypropionate Hydrochloride (6a). A mixture of 1 g of the propionate 5 and 50 mL of 2% HCl in ether was stirred at room temperature for 2 h. The precipitate was collected by filtration and recrystallized in 2-propanol to give 0.3 g (46.6%) of white crystals: mp 150.5–151 °C; NMR (Me_2SO-d_6) δ 2.7–3.6 (br m, 6 H, CH_2, CH_2CH_2), 3.62 (d, 6 H, 2, OCH_3), 4.6–4.85 (br m, 1 H, CH), 6.4–7.3 (br m, 8 H, aromatic); IR (KBr) cm^{-1} 1754 (C=O). Anal. ($C_{19}H_{34}NO_5Cl$) C, H, N.

2-Methoxybenzyl 3-[(3,4-Dimethoxyphenethyl)amino]-2-hydroxypropionate (6d). To 3 g of 3-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropionic acid (3) was added 200 mL of benzene and 20 mL of 2-methoxybenzyl alcohol. About 0.5 mL of concentrated HCl was added to catalyze the reaction. The reaction mixture was heated to reflux for 6 h and the water was collected by a moisture trap. The reaction mixture was extracted with 200 mL of 0.5% HCl in water. The aqueous layer was basified with $NaHCO_3$ and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave an oily residue, which after chromatography on a column (silica gel/Et_2O–EtOH = 5:1) gave 1 g (23%) of a white solid: mp 79.5–82.5 °C. Anal. ($C_{21}H_{27}NO_6$) C, H, N.

3-(Isopropylamino)-1,2-propanediol[23] (8). A mixture of 37 g (0.5 mol) of glycidol and 35.4 g (0.6 mol) of isopropylamine was stirred at 25 °C overnight. Excess isopropylamine was evaporated in vacuo and the mixture was distilled to give 53 g of product 8: bp 80 °C (0.1 mmHg). Anal. ($C_6H_{15}NO_2$) C, H, N.

3-(Isopropylamino)-2-hydroxypropyl 3,4-(Methylenedioxy)benzoate Hydrochloride (12). A solution of 10 g (75 mmol) of the diol 8 was mixed with 13.8 g (75 mmol) of 3,4-(methylenedioxy)benzoyl chloride in 20 mL of a pyridine–toluene (1:1) mixture. The reaction mixture was stirred at room temperature for 2 h and the pyridine was removed by azeotroping with toluene. The residue was partitioned between 100 mL of H_2O and 200 mL of ether. The aqueous layer was then adjusted to basic with K_2CO_3 and extracted with CH_2Cl_2. The methylene chloride layer was acidified with ether–HCl and evaporated to dryness. The residue was crystallized in *i*-PrOH to give 0.2 g (8.6%) of product: mp 170–170.5 (lit.[11] mp 170–171 °C). Anal. ($C_{14}H_{20}NO_5Cl$) C, H, N.

3-(Isopropylamino)-2-hydroxypropyl 2-Chlorobenzoate Hydrochloride (16). A solution of 10 g (75 mmol) of 3-(isopropylamino)-1,2-propandiol (8) and 5.9 g (75 mmol) of pyridine hydrochloride in 20 mL of pyridine was treated with 13.1 g (75 mmol) of 2-chlorobenzoyl chloride. The mixture was stirred at room temperature for 2 h and 100 mL of water was added. The pyridine was evaporated in vacuo at 55–60 °C and the aqueous solution was washed with 100 mL of ether. The aqueous layer was then basified with K_2CO_3 and extracted with methylene chloride. The methylene chloride layer was acidified with ether–HCl and evaporated to dryness. The residue was crystallized in 2-propanol to give 12.5 g (54%) of product: mp 129 °C; NMR (D_2O) δ 1.3 (d, 6 H, $C(CH_3)_2$), 3.0–3.9 (m, 3 H, CH_2NCH), 4.2–4.4 (m, 3 H, $COOCH_2CH$), 7.2–7.9 (m, 4 H, aromatic); IR (KBr) cm^{-1} 1732 (COO). Anal. ($C_{13}H_{19}NO_3Cl_2$) C, H, N.

2,3-Epoxypropyl Benzoate 9. A mixture containing 14.8 g (0.2 mol) of glycidol, 150 mL of anhydrous ether, 16 g (0.4 mol) of pyridine, and 28 g (0.2 mol) of benzoyl chloride was stirred at room temperature for 2 h. The mixture was filtered and the ether was evaporated to leave an oil. This oil was distilled to give 21 g (60%) of colorless oil: bp 92 °C (0.5 mmHg); NMR ($CDCl_3$)

(22) Calculated according to the method of Hellenbrecht et al.: Hellenbrecht, D.; Lemmer, B.; Wiethold, G.; Grobecker, H. *Arch. Pharmacol.* **1973**, *277*, 211. Substituted π-values estimated from ref 14.

(23) Weinstock, L. M.; Mulvey, D. M.; Tull, R. *J. Org. Chem.* **1976**, *41*, 3121.

δ 2.55–2.85 (m, 2 H, OCH_2), 3.1–3.45 (m, 1 H, OCH), 3.9–4.8 (m, 2 H, $COOCH_2$), 7.1–7.6 (m, 3 H, aromatic), 7.8–8.1 (m, 2 H aromatic); IR (neat) cm^{-1} 1720 (C=O).

3-(Isopropylamino)-2-hydroxypropyl Benzoate Hydrochloride (14). To 1 g of the epoxide **9** was added 10 g of isopropylamine and the resultant solution was refluxed for 16 h and evaporated to dryness. The oily residue was chromatographed on a column (silica gel/EtOH–CH_2Cl_2 = 1.5:3.5) to afford 0.35 g (22%) of the product, which was converted to its HCl salt by addition of ethereal HCl. The amine salt was collected by filtration and recrystallized in 2-propanol to give white crystals: mp 155.5–156.5 °C; NMR (D_2O) δ 1.3 (d, 6 H, 2 CH_3), 3.0–3.8 (m, 3 H, CH_2NCH), 4.0–4.4 (br m, 3 H, OCH_2CH), 7.2–8.1 (br m 5 H, aromatic); IR (KBr) cm^{-1} 1697 (C=O). Anal. ($C_{13}H_{26}NO_3Cl$) C, H, N.

Synthesis of 85. 2,3-Epoxypropyl *o*-Fluorobenzoate (9). To a three-neck round-bottom flask were added 280.3 g (3.78 mol) of glycidol and 2.5 L of ether. The solution was cooled to −10 °C and 385 g (3.8 mol) of Et_3N was added. A solution of 600 g (3.78 mol) of *o*-fluorobenzoyl chloride in 0.5 L of ether was then added rapidly dropwise over a period of 1 h while the reaction flask was maintained at −5 to 5 °C. Stirring and cooling was continued for another 2 h at room temperature. The slurry mixture was filtered and washed with 0.5 L of water. The ether was evaporated and the oil was dissolved in 1 L of toluene, filtered, and evaporated to dryness. The product was distilled through a 15-cm Vigreux column and the first fraction (~20 g; bp 25–70 °C) was discarded. The second fraction (713 g, 96.2%) was the desired product: bp 145–153 °C (0.5–1.1 mmHg); NMR ($CDCl_3$) δ 2.6–3.0 (m, 2 H, OCH_2), 3.2–3.5 (m, 1 H, OCH), 4.0–4.85 (m, 2 H, $COOCH_2$), 6.9–8.1 (m, 4 H, aromatic); IR (neat) cm^{-1} 1730 (COO). Anal. ($C_{10}H_9O_3F$) C, H.

1,1-Dimethyl-2-[(aminocarbonyl)amino]ethylamine. A mixture of 88.16 g (1 mol) of 1,2-diamino-2-methylpropane, 60.06 g (1 mol) of urea, and 176 mL of water was gently refluxed for 10 h and stirred at room temperature for another 8 h. The resulting solution was evaporated and azeotroped to dryness with dioxane. The solid was dissolved in methanol and evaporated to form an oil. This oil was dissolved in 350 mL of hot EtOAc and filtered, and the filtrate was allowed to crystalize at 25 °C. The product was recrystallized in EtOAc to give 75 g (57%) of solid: mp 88–90 °C; NMR (D_2O) δ 1.0 (s, 6 H, $C(CH_3)_2$), 3.0 (s, 2 H, CH_2), 4.65 (s, 5 H, protons on nitrogen); IR (KBr) cm^{-1} 1635 (CONH). Anal. ($C_5H_{13}N_3O$) C, H, N.

3-[[1,1-Dimethyl-2-[(aminocarbonyl)amino]ethyl]amino]-2-hydroxypropyl 2-Fluorobenzoate Monosulfate (85). A mixture of 15 g (0.0765 mol) of 2,3-epoxypropyl *o*-fluorobenzoate (**9**), 10.03 g (0.0765 mol) of 1,1-dimethyl-2-[(aminocarbonyl)amino]ethylamine and 45 mL of DMF was heated at 65 °C for 6 h and then stirred at room temperature for 12 h. The DMF was evaporated at 75 °C under reduced pressure and the residue oil was dissolved in a cold solution (−10 °C) of 8 g of concentrated sulfuric acid in 45 mL of absolute ethanol. The solution was filtered and stored at 5 °C to give 21.2 g (65%) of crystals, mp 145–147 °C. Two recrystallizations from 95% ethanol gave 14 g (43%) of product: mp 149–152 °C; NMR (D_2O) δ 1.4 (s, 6 H, $C(CH_3)_2$), 3.2–3.6 (m, 4 H, CH_2N, CH_2NCO), 4.2–4.6 (m, 3 H, $COOCH_2CH$), 7.0–8.1 (m, 4 H, aromatic); IR (KBr) cm^{-1} 1730. Anal. ($C_{15}H_{24}N_3O_8FS$) C, H, N.

Pharmacological Testings. The in vitro potency and the in vivo potency and duration were determined in the same way as described previously.[8,10] The half-life ($t_{1/2}$) of the compound in human whole blood, dog whole blood, and dog liver homogenate is defined as the time period in which one-half of the initial amount of compound disappears. In each experiment, 1 mL of solution containing 50 μg of the test compound was added to 1 mL of whole blood or 1 mL of a 33% (w/v) liver homogenate. The samples were incubated in a Dubnoff shaking metabolic incubator for 2.5, 5.0, 10.0, 20.0, 30.0, and 60.0 min at 37 °C. At the designated time periods, the test mixtures were removed from the incubator and transferred to a 0 °C ice bath. Acetonitrile (2 mL) was immediately added, and the mixtures were mixed to stop enzymatic hydrolysis. Zero-time samples were prepared by adding 2 mL of acetonitrile to denature the proteins prior to addition of the test compounds. After centrifugation to sediment denatured proteins, 2 mL of the supernatant was removed and analyzed by high-pressure liquid chromatography, using a mobile phase of 60% acetonitrile/40% 0.05 M sodium phosphate buffer (pH 6.6), a UV detector, and Waters μ Bondapak phenyl column. The half-life of each test compound was determined graphically by plotting the decrease in concentration as a function of time.

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Registry No. **1**, 1713-85-5; **2**, 120-20-7; **3**, 83230-57-3; **4**, 83230-59-5; **5** (Ar = Ph), 83230-60-8; **6a**, 90531-34-3; **6a**·HCl, 83230-56-2; **6b**, 90531-35-4; **6b**·HCl, 83230-61-9; **6c**·HCl, 83230-63-1; **6d**, 83230-64-2; **7**, 556-52-5; **8** (R = *i*-Pr), 6452-57-9; **9** (Ar = Ph), 13443-29-3; **9** (Ar = *O*-FC_6H_4), 85515-51-1; **11**, 61555-29-1; **11**·oxalate, 61555-30-4; **12**, 90531-36-5; **12**·HCl, 41908-82-1; **13**, 90531-37-6; **13**·HCl, 61555-31-5; **14**, 83231-44-1; **14**·HCl, 83230-65-3; **15**, 90531-38-7; **15**·HCl, 83230-78-8; **16**, 85515-32-8; **16**·HCl, 83230-71-1; **17**, 90531-39-8; **17**·HCl, 83230-77-7; **18**, 83230-87-9; **18**·oxalate, 83230-88-0; **19**, 83230-84-6; **19**·oxalate, 83230-85-7; **20**, 90531-40-1; **20**·HCl, 83230-79-9; **21**, 90531-41-2; **21**·HCl, 83230-67-5; **22**, 90531-42-3; **22**·HCl, 83230-89-1; **23**, 90531-43-4; **23**·HCl, 83230-86-8; **24**, 90531-44-5; **24**·HCl, 83231-20-3; **25**, 83231-33-8; **25**·oxalate, 83231-34-9; **26**, 90531-45-6; **26**·HCl, 83230-81-3; **27**, 90531-46-7; **27**·HCl, 83230-80-2; **28**, 90531-47-8; **28**·HCl, 83230-69-7; **29**, 90531-48-9; **29**·HCl, 83230-83-5; **30**, 90531-49-0; **30**·HCl, 83230-92-6; **31**, 83231-35-0; **32**, 83231-21-4; **33**, 90531-50-3; **33**·HCl, 83231-19-0; **34**, 83231-45-2; **34**·HCl, 83231-31-6; **35**, 90531-51-4; **35**·HCl, 83230-82-4; **36**, 90531-52-5; **36**·HCl, 83233-89-0; **37**, 90531-53-6; **37**·HCl, 83230-75-5; **38**, 90531-54-7; **38**·HCl, 83230-76-6; **39**, 83231-02-1; **40**, 83231-04-3; **41**, 83231-03-2; **42**, 83231-06-5; **43**, 83231-25-8; **43**·$^1/_2$ oxalate, 83231-26-9; **44**, 83231-07-6; **45**, 83231-11-2; **46**, 83231-27-0; **46**·$^1/_2$ oxalate, 83231-28-1; **47**, 83231-22-5; **47**·oxalate, 83231-23-6; **48**, 83231-08-7; **49**, 83231-05-4; **50**, 90531-55-8; **50**·$^1/_2$ oxalate, 90531-77-4; **51**, 83231-12-3; **51**·oxalate, 83231-13-4; **52**, 83250-88-8; **52**·oxalate, 83250-89-9; **53**, 83231-29-2; **53**·$^1/_2$ oxalate, 83231-30-5; **54**, 90531-56-9; **54**·oxalate, 90531-78-5; **55**, 83231-09-8; **56**, 83231-16-7; **56**·oxalate, 83231-17-8; **57**, 90531-57-0; **57**·$^1/_2$ oxalate, 90531-79-6; **58**, 90531-58-1; **58**·HCl, 83231-10-1; **59**, 90531-59-2; **59**·HCl, 83231-24-7; **60**, 83231-14-5; **60**·oxalate, 83231-15-6; **61**, 90531-60-5; **61**·HCl, 83230-66-4; **62**, 90531-61-6; **62**·HCl, 83230-97-1; **63**, 90531-62-7; **63**·HCl, 83230-72-2; **64**, 83230-93-7; **64**·oxalate, 83230-94-8; **65**, 83230-98-2; **65**·oxalate, 83230-99-3; **66**·oxalate, 83230-96-0; **67**, 83230-68-6; **68**, 90531-63-8; **68**·HCl, 83231-00-9; **69**, 90531-64-9; **69**·HCl, 83230-70-0; **70**, 83231-40-7; **70**·oxalate, 83231-41-8; **71**, 90531-65-0; **71**·HCl, 90531-80-9; **72**, 90531-66-1; **72**·oxalate, 90531-81-0; **73**, 90531-67-2; **73**·$^1/_2$ oxalate, 90531-82-1; **74**, 90531-68-3; **74**·$^1/_2$ oxalate, 90531-83-2; **75**, 90531-69-4; **75**·HCl, 90531-84-3; **76**, 90531-70-7; **76**·oxalate, 90531-85-4; **77**, 90531-71-8; **77**·oxalate, 90531-86-5; **78**, 90531-72-9; **78**·oxalate, 90531-87-6; **79**, 83231-18-9; **80**, 85515-35-1; **81**, 87721-53-7; **82**, 87721-54-8; **82**·oxalate, 87721-55-9; **83**, 87721-59-3; **83**·HCl, 87721-58-2; **84**, 87721-56-0; **84**·oxalate, 87721-57-1; **85**, 87721-62-8; **85**·H_2SO_4, 88844-73-9; **86**, 87721-63-9; **86**·$^1/_2$ oxalate, 87721-64-0; **87**, 87721-51-5; **87**·HCl, 87721-50-4; **88**, 87721-61-7; **88**·HCl, 87721-60-6; **89**, 87721-68-4; **89**·oxalate, 87721-69-5; **90**, 90531-73-0; **90**·oxalate, 90531-88-7; **91**, 87721-70-8; **91**·oxalate, 87721-71-9; **92**, 87721-52-6; **93**, 87721-67-3; **93**·HCl, 87721-66-2; **94**, 87721-49-1; **94**·HCl, 87721-48-0; **95**, 7695-63-8; **96**, 29044-59-5; **97**, 6673-35-4; **98**, 525-66-6; **99**, 2922-20-5; DHP, 110-87-2; 4-$MeOC_6H_4CH_2OCON_3$, 25474-85-5; PhOH, 108-95-2; 2-MeC_6H_4OH, 95-48-7; 1-$C_{10}H_7OH$, 90-15-3; 2-$(MeO)C_6H_4CH_2OH$, 612-16-8; H_2NBu-*t*, 75-64-9; PhCOCl, 98-88-4; 2-FC_6H_4COCl, 393-52-2; 2-ClC_6H_4COCl, 609-65-4; 2-$CH_3C_6H_4COCl$, 933-88-0; 2-$CH_3CH_2CH_2OC_6H_4COCl$, 54090-36-7; 2-H_2C=$CHCH_2OC_6H_4COCl$, 52542-42-4; 3-FC_6H_4COCl, 1711-07-5; 3-$CH_3C_6H_4COCl$, 1711-06-4; 3-$CH_3CH_2CH_2OC_6H_4COCl$, 83230-74-4; 3-H_2C=$CHCH_2OC_6H_4COCl$, 83230-73-3; 3-$H_2NC_6H_4COCl$, 21563-72-4; 3-$(CH_3CONH)C_6H_4COCl$, 90531-74-1; 3-$O_2NC_6H_4COCl$, 121-90-4; 4-FC_6H_4COCl, 403-43-0; 4-$CH_3C_6H_4COCl$, 874-60-2; 4-$CH_3OC_6H_4COCl$, 100-07-2; 4-$PhCH_2OC_6H_4COCl$, 1486-50-6; 4-$HOCH_2C_6H_4COCl$, 90531-75-2; 4-HOC_6H_4COCl, 28141-24-4; 4-$H_2NC_6H_4COCl$, 16106-38-0; 4-$(CH_3CONH)C_6H_4COCl$, 16331-48-9; 4-$O_2NC_6H_4COCl$, 122-04-3; 4-NCC_6H_4COCl, 6068-72-0; (2′-CH=CH-CH=CH-3′)C_6H_3COCl, 879-18-5; (3′-CH=CH-CH=CH-4′)C_6H_3COCl, 2243-83-6; 2-HOC_6H_4COCl, 1441-87-8; 3-$PhCH_2OC_6H_4COCl$, 61535-46-4; 3-HOC_6H_4COCl, 40812-76-8; 4-$CH_3CH_2CH_2OC_6H_4COCl$, 40782-58-9;

4-H_2C=$CHCH_2OC_6H_4COCl$, 36844-51-6; 4-$OHCC_6H_4COCl$, 16173-52-7; (2-Cl)(4-O_2N)C_6H_4COCl, 7073-36-1; (2-CH_3)(4-O_2N)C_6H_4COCl, 30459-70-2; (2-CH_3)(4-H_2N)C_6H_4COCl, 90531-76-3; 3-ClC_6H_4COCl, 618-46-2; $PhCH_2COCl$, 103-80-0; $Ph(CH_2)_2COCl$, 645-45-4; $Ph(CH_2)_3COCl$, 18496-54-3; $Ph_2CHCOCl$, 1871-76-7; c-C_5H_9COCl, 4524-93-0; 4-(C_5H_5N)COCl, 14254-57-0; 3-[[N-(3,4-dimethoxyphenethyl)-N-(4-methoxybenzyloxycarbonyl)]amino]-2-hydroxypropionic acid, 83230-58-4; isopropylamine, 75-31-0; 3,4-(methylenedioxy)benzoyl chloride, 25054-53-9; methylbenzylamine, 103-67-3; 9-fluorenylcarbonyl chloride, 24168-51-2; 1,2-diamino-2-methylpropane, 811-93-8; urea, 57-13-6; 1,1-dimethyl-2-[(aminocarbonyl)amino]ethylamine, 87484-83-1.

Substituted 5,6-Dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic Acids: High-Ceiling Diuretics with Uricosuric Activity[1]

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A series of substituted 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazoles was prepared and evaluated for their saluretic and uricosuric properties. Pharmacological evaluation of the title compounds was carried out in mice, rats, dogs, and monkeys. The diuretic/saluretic nature of these compounds was observed in all species, whereas the uricosuric activity was best seen in the Cebus monkey. Evaluation of the enantiomers of 8-chloro-3-(*o*-fluorophenyl)-5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (**15k**) revealed that only the (+) enantiomer (**29**) displayed diuretic and saluretic activity, whereas both enantiomers possessed uricosuric activity. X-ray analysis showed that the (−) enantiomer (**30**) possesses the 2*R* configuration.

Since the discovery of ethacrynic acid more than 20 years ago, many (aryloxy)acetic acid derivatives have been synthesized and evaluated for their diuretic properties.[2] The high level of interest in this class of compounds has been stimulated by the ability of medicinal chemists to dramatically alter the diuretic profile of these agents by structural manipulation of the phenoxyacetic acid pharmacophore. Thus, the uric acid retention caused by ethacrynic acid (**1a**) is sharply contrasted to the uricosuric nature of indacrinone (**2**)[3] and the dihydrobenzofuran derivative **3**.[4] Still further differences in profile are found with tienilic acid (**1b**), which elicits a low-ceiling uricosuric effect[5] and, more recently, **4** (HP-522), which has been described[6] as a high-ceiling moderate uricosuric. In our own laboratories we have discovered yet a new addition **5** to the class of (aryloxy)acetic acid diuretics that differs from all previous derivatives in that a basic nitrogen functionality is essential to their high-ceiling profile.[7] This broad range of renotrophic properties displayed within the class of (aryloxy)acetic acids reflects the high sensitivity of the renal tubular transport cells to small changes in the structure of these compounds.[8]

1a, R = $COC(=CH_2)C_2H_5$

b, R = CO-(2-thienyl)

2

3

4

5

6

Our interest in obtaining a diuretic agent functionally equivalent to the clinically useful combination of furosemide and probenecid prompted a consideration of the structural requirements for high-ceiling uricosuric effects. Without exception, we observed that all phenoxyacetic acid diuretics with this profile possess structures that are for-

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