a platform at the bottom of a plexiglas cylinder (height 35 cm, inner diameter 14.5 cm), where the number of jumps could be counted electromechanically for 20 min. The ED_{50} for inhibition of opioid-type withdrawal jumping was determined from a cubic spline curve and represents the dose that reduced the number of jumps by 50% compared to the control group.

Acknowledgment. On the occasion of his 60th birthday we thank Dr. Arnold Brossi for initiation and promotion of our research in the field of 6-ketomorphinan opioids. We further thank Dr. K.-H. Ongania for performing the mass spectra, Dr. D. Scholz, Mag. W. Schiestl (Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck), and the Analytical Department of Hoffmann-La Roche & Co. Inc., Basle, for elemental analyses. We are indebted to G. Kienel (Department of Pharmacology, University of Innsbruck) for technical assistance in the opioid receptor assay. The work was in part supported by the Austrian Science Research Fund, project P 5030.

Registry No. 1, 81165-08-4; 2, 92055-56-6; 3, 92055-57-7; 4, 92055-58-8; 5, 92055-59-9; 6, 92055-60-2; 7, 92055-61-3; 8, 38252-28-7; 9, 78072-08-9; 10, 92055-62-4; 11, 76-41-5; 12, 5868-03-1; 13, 92055-63-5; 14, 92055-64-6; 15, 92078-30-3; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4; benzyl bromide, 100-39-0.

[(Aminomethyl)aryloxy]acetic Acid Esters. A New Class of High-Ceiling Diuretics. 1. Effects of Nitrogen and Aromatic Nuclear Substitution[1]

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A series of Mannich bases and aminomethyl derivatives of ethyl [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetate were synthesized and tested for saluretic and diuretic activities. The effects of nitrogen and aromatic nuclear substitution, reorientation of the aminomethyl group relative to that of the phenolic hydroxyl group, and replacement of either the phenolic hydroxyl or the aminomethyl group by other functional groups are described. Ethyl [2,3-dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]acetate (**27**) was found to be a very potent, high-ceiling diuretic.

In the search for nonsulfonamide diuretics in our laboratories, we discovered that [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetic acid I is a low-ceiling, uricosuric agent.[2] In much earlier work, we found a series of bis-Mannich bases of alkyl-substituted phenol, exemplified by II, to display diuretic activity in animal tests.[3] Recently a series of papers reporting the diuretic activity of 2-(aminomethyl)phenols has appeared.[4-6] In an effort to enhance the potency and modify the pharmacological profile of I, we prepared the Mannich bases of I and observed that the ethyl ester of bis(dimethylamino)methyl derivative **17** is a potent, high-ceiling diuretic. This led

(1) Portions of this work were presented: (a) *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **1982**, *41*, 1724; (b) "Abstracts of Paper";, 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 1982; American Chemical Society: Washington, DC, 1982. (c) Martin, Y. C.; Kim, K. H. *Drug Inf. J.* **1984**, *18*, 113.

(2) Jones, P. H.; Bariana, D. S.; Fung, A. K. L.; Martin, Y. C.; Kyncl, J.; Lall, A. U.S. Patent 4 058 559, 1977.

(3) Unpublished results.

(4) Stokker, G. E.; Deanna, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Ludden, C. T.; Russo, H. F; Scriabine, A.; Sweet, C. S.; Watson, L. S. *J. Med. Chem.* **1980**, *23*, 1414.

(5) Stokker, G. E.; Deanna, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Russo, H. F.; Watson, L. S. *J. Med. Chem.* **1981**, *24*, 1063.

(6) Stokker, G. E.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Russo, H. F.; Watson, L. S.; Ludden, C. T.; Sweet, C. S. *J. Med. Chem.* **1983**, *26*, 585.

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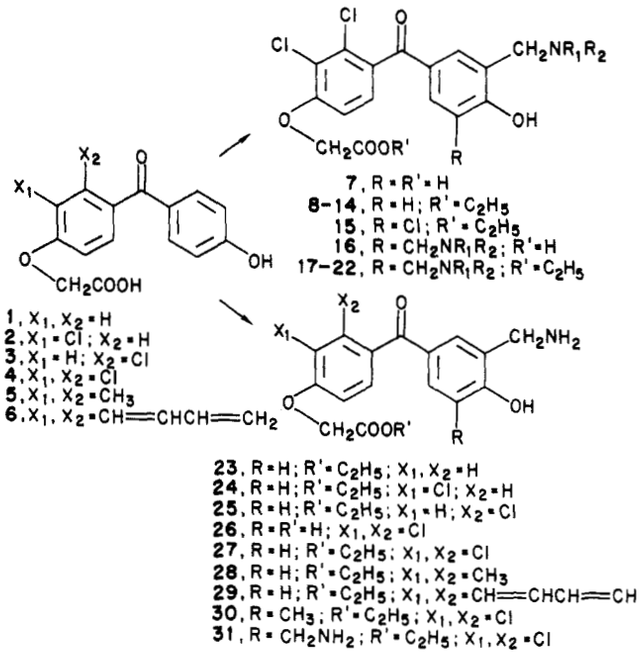
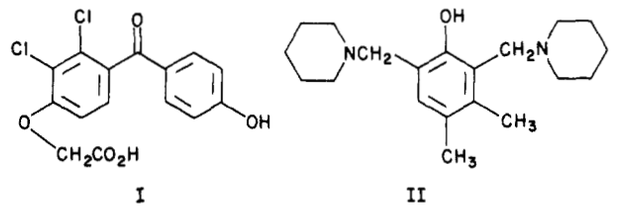
Scheme I



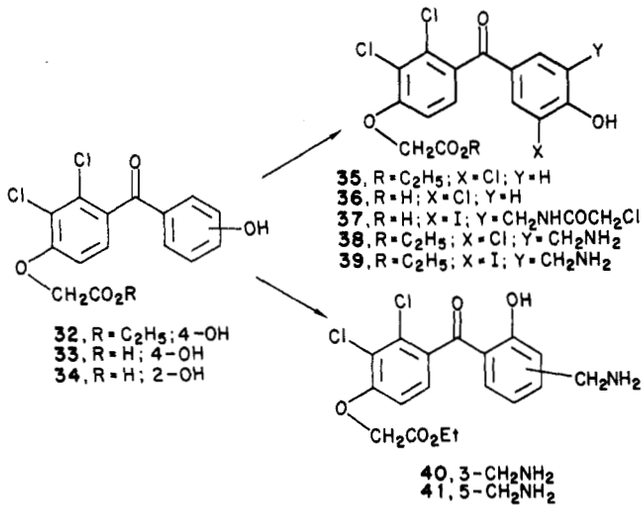
further to the synthesis of mono(aminomethyl) derivative **27**, which is a very potent, high-ceiling diuretic. In this paper, we report the synthesis and biological activity of



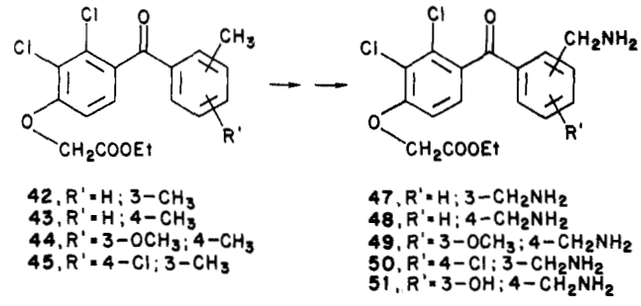
Mannich bases and aminomethyl derivatives of I and describe the effects of (1) variation of the aromatic nuclear substitution, (2) reorientation of the aminomethyl group relative to that of the phenolic hydroxyl group, and (3) replacement of either the phenolic hydroxyl or aminomethyl group by other functional groups.

Chemistry. The compounds prepared in this study are listed in Tables I and II and their syntheses are summarized in Schemes I–IV. The products from Friedel–Crafts acylation[7] of appropriately substituted anisoles with 4-nitrobenzoyl chloride and $AlCl_3$ in CH_2Cl_2 were dealkylated by heating with 48% aqueous HBr in AcOH or $AlCl_3$ in CH_2Cl_2. The substituted phenols, thus obtained, were alkylated with ethyl bromoacetate and powdered K_2CO_3 in 2-butanone to yield the nitro derivatives, which were converted to the corresponding [4-(4-hydroxybenzoyl)-phenoxy]acetic acids **1–6** with acetaldoxime and NaOH in DMF.[8] The mono- and bis-Mannich bases **7–22** were synthesized under standard Mannich reactions.[9] The aminomethyl compounds **23–31** were obtained by acid-catalyzed, nuclear amidoalkylation (Tscherniac–Einhorn reaction)[10] of **1–6** with 2-chloro-*N*-(hydroxymethyl)acetamide in CH_3SO_3H, H_2SO_4, or H_2SO_4–HOAc and subsequent EtOH–HCl hydrolysis (Scheme I).

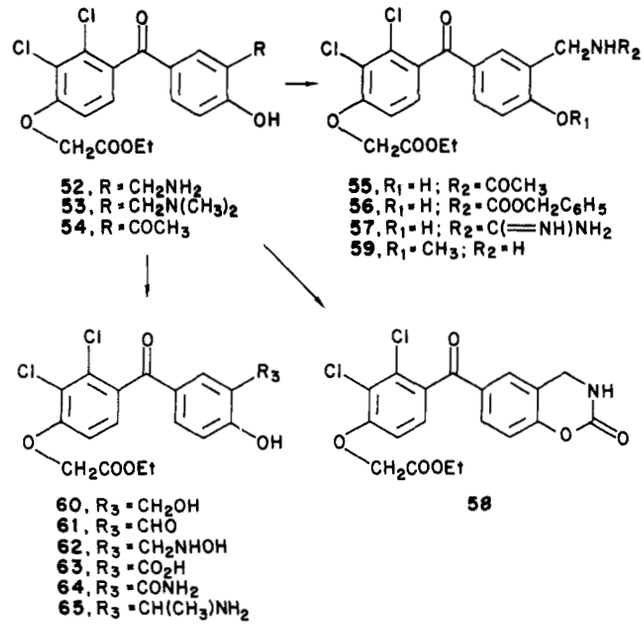
Scheme II



Scheme III



Scheme IV



The chloro derivative **38** was synthesized by chlorination of **32** with SO_2Cl_2 and subsequent amidoalkylation and hydrolysis. Attempts to introduce an iodine atom into the phenolic nucleus of **32** yielded a complex mixture. How-

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(8) Knudsen, R. D.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343.
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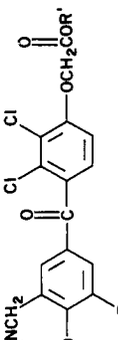
(10) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52–269.

Table I. Mono- and Bis-Mannich Bases



compd	R_1	R_2	R	R'	mp, °C	yield, %	recrystn solvent	emp formula[a]	rat ED_2,[b] mg/kg po
7	CH_3	CH_3	H	H	265–268	43	DMF	$C_{18}H_{17}Cl_2NO_5$	inactive
8	CH_3	CH_3	H	C_2H_5	186–188	41	EtOH	$C_{20}H_{21}Cl_2NO_5 \cdot HCl$	16
9	C_2H_5	C_2H_5	H	C_2H_5	115–120	82	MeCN–Et_2O	$C_{22}H_{25}Cl_2NO_5 \cdot HCl$[c]	inactive
10	$-(CH_2)_4-$		H	C_2H_5	149–152	31	EtOH–Et_2O	$C_{22}H_{23}Cl_2NO_5 \cdot HCl$	inactive
11	$-(CH_2)_5-$		H	C_2H_5	109–111	36	EtOH–Et_2O	$C_{23}H_{25}Cl_2NO_5 \cdot HCl \cdot C_2H_5OH$	inactive
12	$>(CH_2CH_2)_2O$		H	C_2H_5	glass	37		$C_{22}H_{23}Cl_2NO_6 \cdot HCl$	inactive
13	$>(CH_2CH_2)_2SO_2$		H	C_2H_5	184–185	39	Me_2CO–Et_2O	$C_{22}H_{23}Cl_2NO_7S$	inactive
14	$(CH_3)_3{}^+Cl^-$		H	C_2H_5	170–172	35	MeCN–Et_2O	$C_{21}H_{24}Cl_3NO_5{}^{-1}/_2H_2O$	inactive
15	CH_3	CH_3	Cl	C_2H_5	178–179	59	Me_2CO–Et_2O	$C_{20}H_{20}Cl_3NO_5 \cdot HCl$	5
16	CH_3	CH_3	$CH_2N(CH_3)_2$	H	221–223 dec	57	MeCN	$C_{21}H_{24}Cl_2N_2O_5 \cdot 3HCl$	inactive
17	CH_3	CH_3	$CH_2N(CH_3)_2$	C_2H_5	222–224 dec	33	EtOH	$C_{23}H_{28}Cl_2N_2O_5 \cdot 2HCl$	7
18	C_2H_5	C_2H_5	$CH_2N(C_2H_5)_2$	C_2H_5	glass	90		$C_{27}H_{36}Cl_2N_2O_5 \cdot 2HCl \cdot H_2O$	inactive
19	$-(CH_2)_4-$		CH_2-c-NC_4H_8	C_2H_5	171–173 dec	33	EtOH	$C_{27}H_{32}Cl_2N_2O_5 \cdot 2HCl^{-1}/_2H_2O$	inactive
20	$-(CH_2)_5-$		CH_2-c-NC_5H_{10}	C_2H_5	185–188	32	EtOH–Et_2O	$C_{29}H_{36}Cl_2N_2O_5 \cdot 2HCl^{-1}/_2H_2O$	inactive
21	$>(CH_2CH_2)_2O$		CH_2-c-$N(CH_2CH_2)_2O$	C_2H_5	glass	22		$C_{27}H_{32}Cl_2N_2O_7 \cdot 2HCl$	inactive
22	$>(CH_2CH_2)_2SO_2$		CH_2-c-$N(CH_2CH_2)_2SO_2$	C_2H_5	228–230	71	DMF–EtOH–Et_2O	$C_{27}H_{32}Cl_2N_2O_9S$	inactive

[a] Analytical results are within ±0.4% of the theoretical values in C, H, and N analyses. [b] Compounds reported as inactive showed a Na^+ excretion no different from the control value at the high dose of 100 mg/kg. [c] Anal. C: calcd, 53.84; found, 53.35.

ever, iodination of the amidoalkylated product using ICl afforded a clean product **37**, which was hydrolyzed and reesterified to give **39**. Amidoalkylation of 2-hydroxy derivative **34** and subsequent hydrolysis yielded a mixture of **40** and **41**, whose structures were determined by ^1H NMR (Scheme II).

The 3-hydroxy derivative **51** could not be prepared by the above amidoalkylation procedure because of the complexity of the reaction products. Thus, **51** was synthesized by bromination of **44** with *N*-bromosuccinimide, conversion of the bromo derivative to the azide, subsequent hydrogenation to **49**, and demethylation. Compounds **47**, **48**, and **50** were prepared similarly as illustrated in Scheme III.

Reaction of **52** with acetic anhydride and *N*-[(benzyloxycarbonyl)oxy]succinimide yielded the acetyl and benzyloxycarbonyl derivatives **55** and **56**, respectively. The methoxy derivative **59** was obtained by alkylation of **56** with CH_3I and subsequent removal of the Cbz moiety with 30% HBr and HOAc. Refluxing **52** with 2-methyl-2-thiopseudourea sulfate in EtOH yielded **57** and treatment of **52** with *N*,*N*′-carbonyldiimidazole afforded the cyclized product **58**. Scheme IV illustrates the transformation of the (dimethylamino)methyl moiety of **53** into other functional groups. Compound **60** was prepared by heating **53** with Ac_2O and NaOAc, followed by hydrolysis of the diacetyl derivative with KOH–EtOH. Oxidation of **60** with activated MnO_2 provided the aldehyde **61**, which was converted to **62** via reduction of the oxime with $NaBH_3CN$. Treatment of the methoxyethoxymethyl derivative of **61** with Jones reagent and subsequent removal of the protecting group afforded the carboxy derivative **63**. Conversion of **63** to **64** was accomplished by mixed anhydride procedure. Compound **65** was synthesized by reductive amination of **54** with $NaBH_3CN$ and NH_4OAc.

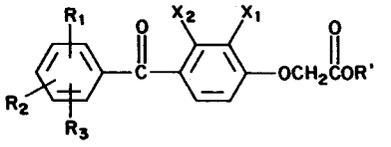
Biological Activity. A. Saluresis–Diuresis. The target compounds were tested orally in rats for their saliuretic properties; the results are limited to Na^+ excretion and are presented as ED_2 along with that of furosemide and MK-447 for comparative purposes (Tables I and II). ED_2 is the oral dose in milligram/kilogram necessary to produce an excretion of 2 mequiv of Na^+/kg (mequiv/kg) in the rat urine in the 4-h period after dosing. These values were obtained by plotting the linear regression of the response curve of Na^+ excretion vs. the log of the dose. A typical dose–response curve in the rat comparing furosemide, MK-447, and prototype structure **27** (A-49816) is shown in Figure 1.

In the Mannich bases (Table I) the 3,5-bis[(dimethylamino)methyl] phenolic derivative **17** is more active than the monosubstituted derivative **8**. Increasing the N-substituted alkyl group from methyl to ethyl abolishes the activity, i.e., compare **8** with **9** or **17** with **18**. Heterocyclic derivatives **10**–**13** and **19**–**22** are totally inactive.

In the unsubstituted nitrogen derivatives (Table II), the monoaminomethyl compound **27** is much more active than the bis(aminomethyl) compound **31**. Additional molecular modifications were carried out with compound **27** to further delineate the structure–activity relationships. The saluretic effect is dependent to some extent on the substitution of the phenoxyacetic acid ring nucleus: the unsubstituted compound **23** is one-half as active as the monochloro derivatives **24** and **25**, which are slightly less active than the dichloro compound **27**; replacement of the chlorine atoms of **27** with methyl groups (**28**) or a fused benzene ring (**29**) reduces activity one-half to one-fifth, compared to that of **27**.

The relative position of the aminomethyl group compared to that of the hydroxyl group in the benzoyl ring nucleus is important for the activity. In the 2-hydroxy

Table II. Aminomethyl Derivatives and Analogues



compd	R_1	R_2	R_3	R'	X_1	X_2	mp, °C	yield,[c] %	recrystn solvent	emp formula[a]	rat ED_2,[b] mg/kg po
23	3-CH_2NH_2	4-OH	H	C_2H_5	H	H	114–115	22	IPA–Et_2O	$C_{18}H_{19}NO_5 \cdot HCl$	10
24	3-CH_2NH_2	4-OH	H	C_2H_5	Cl	H	109–113	25	IPA–Et_2O	$C_{18}H_{18}ClNO_5 \cdot HCl$	5
25	3-CH_2NH_2	4-OH	H	C_2H_5	H	Cl	127–128	20	EtOH–Et_2O	$C_{18}H_{18}ClNO_5 \cdot HCl$	5
26	3-CH_2NH_2	4-OH	H	H	Cl	Cl	237–240	36	2 N HCl	$C_{16}H_{13}Cl_2NO_5 \cdot HCl$	inactive
27	3-CH_2NH_2	4-OH	H	C_2H_5	Cl	Cl	218–221	47	EtOH–Et_2O	$C_{18}H_{17}Cl_2NO_5 \cdot HCl$	3
28	3-CH_2NH_2	4-OH	H	C_2H_5	CH_3	CH_3	204–207	23	EtOH–Et_2O	$C_{20}H_{23}NO_5 \cdot HCl$	6
29	3-CH_2NH_2	4-OH	H	C_2H_5	CH=CH–CH=CH		186–190	15	EtOH–Et_2O	$C_{22}H_{21}NO_5 \cdot HCl \cdot {}^1/_2H_2O$	15
30	3-CH_2NH_2	4-OH	5-CH_3	C_2H_5	Cl	Cl	231–233	34	EtOH	$C_{19}H_{19}Cl_2NO_5 \cdot HCl$	1
31	3-CH_2NH_2	4-OH	5-CH_2NH_2	C_2H_5	Cl	Cl	225–230	30	EtOH–Et_2O	$C_{19}H_{20}Cl_2N_2O_5 \cdot 2HCl$	11
38	3-CH_2NH_2	4-OH	5-Cl	C_2H_5	Cl	Cl	224–226	32	EtOH	$C_{18}H_{16}Cl_3NO_5 \cdot HCl$	1
39	3-CH_2NH_2	4-OH	5-I	C_2H_5	Cl	Cl	215–218	21	EtOH–Et_2O	$C_{18}H_{16}Cl_2INO_5 \cdot HCl$	1
40	3-CH_2NH_2	2-OH	H	C_2H_5	Cl	Cl	232–235	14	EtOH	$C_{18}H_{17}Cl_2NO_5 \cdot HCl$	inactive
41	5-CH_2NH_2	2-OH	H	C_2H_5	Cl	Cl	167–169	13	EtOH	$C_{18}H_{17}Cl_2NO_5 \cdot HCl \cdot {}^1/_2H_2O$	3
47	3-CH_2NH_2	H	H	C_2H_5	Cl	Cl	220–221	40[d]	EtOH	$C_{18}H_{17}Cl_2NO_4 \cdot HCl$	12
48	4-CH_2NH_2	H	H	C_2H_5	Cl	Cl	234–235	44[d]	EtOH	$C_{18}H_{17}Cl_2NO_4 \cdot HCl$	inactive
49	4-CH_2NH_2	3-OCH_3	H	C_2H_5	Cl	Cl	230–231	70[d]	EtOH	$C_{19}H_{19}Cl_2NO_5 \cdot HCl$	inactive
50	3-CH_2NH_2	4-Cl	H	C_2H_5	Cl	Cl	190–191	11[d]	EtOH	$C_{18}H_{16}Cl_3NO_4 \cdot HCl$	50
51	4-CH_2NH_2	3-OH	H	C_2H_5	Cl	Cl	215–217	46	EtOH–Et_2O	$C_{18}H_{17}Cl_2NO_5 \cdot HBr$	inactive
55	3-CH_2NHAc	4-OH	H	C_2H_5	Cl	Cl	164–166	42	EtOH	$C_{20}H_{19}Cl_2NO_6$[e]	inactive
57	3-$CH_2NHC(=NH)NH_2$	4-OH	H	C_2H_5	Cl	Cl	119–120	22	EtOH	$C_{19}H_{19}Cl_2N_3O_5$	34
58	(3)-$CH_2NHC(=O)O$–(4)		H	C_2H_5	Cl	Cl	213–214	47	MeOH–CH_2Cl_2[f]	$C_{19}H_{15}Cl_2NO_6$	inactive
59	3-CH_2NH_2	4-OCH_3	H	C_2H_5	Cl	Cl	149–151	61	EtOH–Et_2O	$C_{19}H_{19}Cl_2NO_5 \cdot HBr \cdot {}^1/_2H_2O$	inactive
60	3-CH_2OH	4-OH	H	C_2H_5	Cl	Cl	154–155	64	CH_2Cl_2–hexane	$C_{18}H_{16}Cl_2O_6$	inactive
61	3-CHO	4-OH	H	C_2H_5	Cl	Cl	157–158	60	CH_2Cl_2	$C_{18}H_{14}Cl_2O_6$	inactive
62	3-CH_2NHOH	4-OH	H	C_2H_5	Cl	Cl	62–63	57	CH_2Cl_2–Et_2O	$C_{18}H_{17}Cl_2NO_6 \cdot HCl \cdot {}^1/_4H_2O$	4
63	3-CO_2H	4-OH	H	C_2H_5	Cl	Cl	175–176	70	CH_2Cl_2	$C_{18}H_{14}Cl_2O_7$	inactive
64	3-$CONH_2$	4-OH	H	C_2H_5	Cl	Cl	188–189	40	EtOH	$C_{18}H_{15}Cl_2NO_6$	inactive
65	3-$CH(CH_3)NH_2$	4-OH	H	C_2H_5	Cl	Cl	127–128	90	CH_2Cl_2–Et_2O	$C_{19}H_{19}Cl_2NO_5 \cdot HCl$	1.2
furosemide								1			9.5
MK-447[g]											0.36

[a,b] See corresponding footnote, Table I. [c] These are overall yields for the amidomethylation/hydrolysis and ester formation except where otherwise noted. [d] Yields from methyl derivatives (42–45). [e] Anal. C: calcd, 54.56; found, 55.02. [f] Solvents for chromatography. [g] 2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol hydrochloride.

Table III. Comparative Oral Diuretic Activity of **27** in Rats, Dogs, and Monkeys and Effects on Arterial Blood Pressure in Spontaneously Hypertensive Rats

diuretic activity														antihypertensive activity SH rats					
rat (saline-loaded, male)					dog					monkey									
dose, mg/kg po	N	mequiv kg^{-1} (0–6 h)$^{-1}$ Na$^+$	K$^+$	Cl$^-$	dose, mg/kg po	N	mequiv kg^{-1} (0–6 h)$^{-1}$ Na$^+$	K$^+$	Cl$^-$	dose, mg/kg po	N	mequiv kg^{-1} (0–6 h)$^{-1}$ Na$^+$	K$^+$	Cl$^-$	dose, mg/kg po	N	control BP, mmHg	% change at 2.5 h	6 h	24 h
vehicle	8	5.2	2.4	5.9	vehicle	12	0.1	0.1	0.3	vehicle	11	0.7	0.4	0.4	vehicle	8	218	−5	−1	1
27					**27**					**27**					**27**					
0.1	8	6.6[a]	2.6	8.1[a]	0.03	6	0.5	0.3	0.5	1	6	2.7[a]	0.7[a]	2.7[a]	1	8	215	−17[a]	−11	−6
0.3	8	9.6[a]	2.7	11.3[a]	0.1	6	0.7[a]	0.6[a]	1.0[a]	3	6	5.3[a]	1.1[a]	5.3[a]	3	8	221	−22[a]	−13[a]	−14[a]
1.0	8	12.8[a]	3.0	14.8[a]	0.3	6	2.7[a]	1.0[a]	3.0[a]	10	5	6.6[a]	1.3[a]	7.2[a]	10	8	219	−31[a]	−24[a]	−19[a]
3.0	8	13.9[a]	3.8[a]	16.3[a]	1.0	6	5.0[a]	1.6[a]	6.2[a]	30	5	6.4[a]	1.5[a]	6.9[a]						
10.0	8	14.0[a]	3.3[a]	16.4[a]	3.0	2	7.5[b]	1.8[b]	7.9[b]											
30.0	8	14.8[a]	3.8[a]	17.4[a]	10.0	2	6.3[b]	1.7[b]	7.0[b]											
100.0	8	13.8[a]	3.6[a]	16.6[a]																
furosemide					furosemide					furosemide					furosemide					
2.1	8	4.4	2.4	5.5	1	6	2.5[a]	0.9[a]	2.9[a]	3	6	3.4[a]	0.9[a]	3.4[a]	30	8	210	−10	−6	1
6.9	7	4.0	2.4	5.2	3	6	4.1[a]	1.3[a]	4.4[a]	10	5	4.9[a]	1.2[a]	5.2[a]	100	8	206	−11	−3	−12[a]
20.8	8	6.7[a]	2.5	8.4[a]	10	6	6.0[a]	1.7[a]	6.5[a]	30	6	5.7[a]	1.2[a]	5.9[a]	300	8	214	−21[a]	−31[a]	−37[a]
69.2	8	10.8[a]	3.9[a]	13.4[a]	30	6	7.5[a]	2.1[a]	7.5[a]	100	6	6.6[a]	1.6[a]	6.5[a]						
207.6	8	12.5[a]	3.8[a]	14.9[a]																
691.9	8	13.1[a]	4.8[a]	16.4[a]																

[a] Significantly different from control based on one-way analysis of variance and Duncan's multiple range test, $p < 0.05$. [b] Significantly different from control based on unpaired t test, $p < 0.05$.

derivatives, the 5-(aminomethyl) compound **41** is as active as **27**, but the 3-(aminomethyl) compound **40** is inactive. The 3-(aminomethyl)-4-hydroxy derivative **27** is very active, and the transposition of the hydroxyl and aminomethyl groups in **27** to provide **51** resulted in a total loss of saluretic effects.

Introduction of an electron-donating substituent (e.g., methyl) or electron-withdrawing substituents (e.g., chloro and iodo) in the 5-position of **27** produces the most active compounds (**30**, **38**, and **39**). However, introducing another aminomethyl substituent provides less active compounds (**31**). Replacement of the phenolic hydroxyl group by either a hydrogen (**47**) or a chlorine atom (**50**) decreases saluretic effects. Methylation of the hydroxyl group (**59**) completely eliminates activity.

Modification of the aminomethyl group (**55**, **57**, and **58**) essentially eliminates the activity. The (hydroxyamino)-methyl (**62**) and α-methyl (**65**) derivatives retain good activity. However, replacement of the aminomethyl substituent with hydroxymethyl (**60**), formyl (**61**), carboxyl (**63**), or carbamoyl (**64**) groups abolishes saluretic effects. It is interesting to note that the acids **7**, **16**, and **26** are inactive orally in rat. Further exploration of this observation forms the basis for the following paper in this series.[11]

B. Pharmacology of 27 (A-49816). The diuretic and saluretic activities of **27** were compared to that of furosemide in rats, dogs, and cynomolgus monkeys (Table III). The onset of activity for **27** and furosemide was less than 1 h in all species tested, and duration of action for both compounds was approximately 4 h in rats, 6 h or more in dogs, and 4 h in monkeys. Two hours after po administration of comparable natriuretic doses, **27** was approximately 200 times more potent than furosemide in saline-loaded male rats, though only 16 times more potent than furosemide in saline-loaded female rats, 4–5 times more potent than furosemide in conscious female dogs and water-loaded male and female cynomolgus monkeys. At doses of **27** and furosemide that produced equal natriuretic responses, both compounds had similar effects on the excretion of other ions (see Table III). Endogenous creatinine clearance[12] in conscious female dogs was used to determine glomerular filtration rate (GFR) for **27** and furosemide. These data indicate that both compounds caused

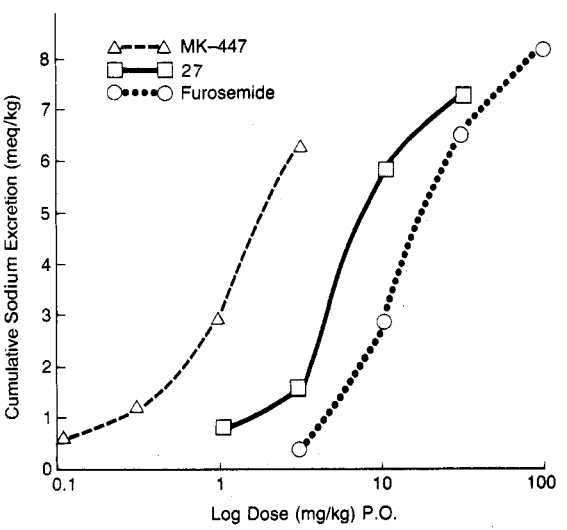


Figure 1. Sodium excretion during 4 h after po administration of MK-447, **27**, and furosemide to female rats. Rats were fed glucose and water overnight, DOCA pretreatment, 5 mg, sc, 2 h prior to dosing, and loaded with isotonic NaCl–KCl (40:60%) to 3% body weight immediately after dosing. Each point in the mean of four rats/dose.

(11) Plattner, J. J.; Fung, A. K. L.; Smital, J. R.; Lee, C-M., Crowley, S. R.; Pernet, A. G.; Bunnell, P. R.; Martin, Y. C.; Buckner, S. A.; Sennello, L. T., following paper in this issue.

(12) Pitts, R. F. "Physiology of the Kidney and Body Fluids"; Year Book Medical Publisher: Chicago, 1974; pp 66–67.

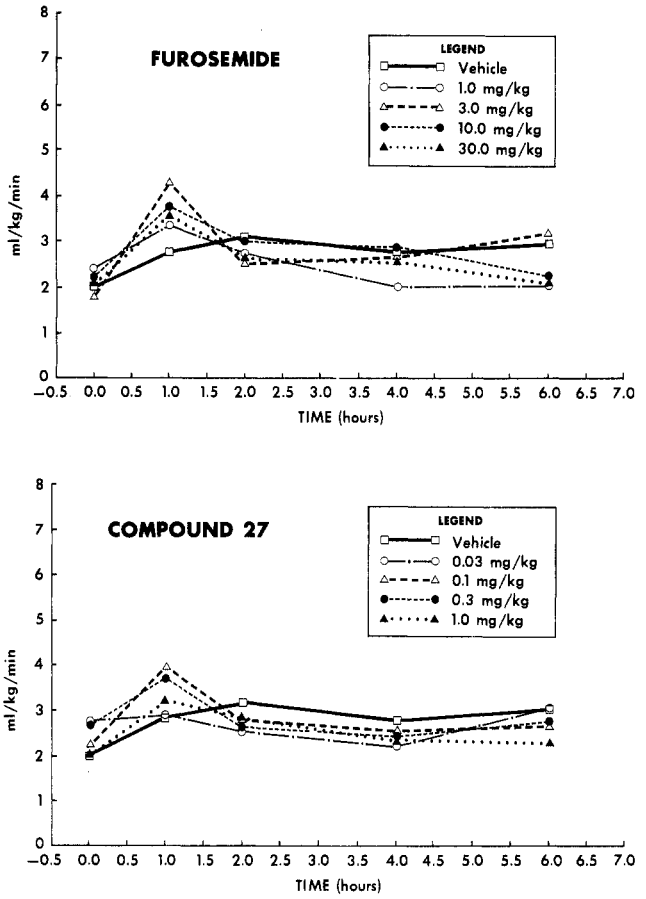


Figure 2. Creatinine clearance (endogenous) in conscious nonloaded female dogs for furosemide (upper panel) and **27** (lower panel). Each point is the mean of six dogs/dose.

a transient, nonsignificant increase in GFR during the period of maximal diuresis (1 h). No other changes in GFR were noted during the 6-h observation period (see Figure 2). Compound **27** was chosen for clinical evaluation in man and was found to be an active diuretic.[13]

When evaluated in male spontaneously hypertensive (SH) rats, **27** caused significant dose-related decreases in blood pressure after single po doses through 2.5, 6, and 24 h of observation. Furosemide also produced significant decreases on blood pressure during the same time periods at doses that were 30 times greater than those required for **27**. Both compounds demonstrated dose–related diuretic and saluretic effects in SH rats.

The cardiopulmonary hemodynamic effects of intraduodenal administration of **27** and furosemide were evaluated in anesthetized female dogs. When compared to controls, both **27** and furosemide lowered mean arterial pressure and increased urine volume. No other significant effects were noted.

Conclusion. The oral rat data presented above indicate that (1) unsubstituted nitrogen derivatives are much more potent than the substituted nitrogen derivatives, (2) substitution at the 2- and/or 3-position of the phenoxyacetic acid ring nucleus with chloro or methyl groups increases activity, and (3) the presence of the phenolic hydroxyl group para to the keto group with a vicinal aminomethyl moiety contributes significantly to saluretic effects, which are further enhanced by substitution at the other vicinal position with either chloro, iodo, or methyl groups.

(13) Preliminary communication from Drs. K. G. Tolman and D. E. Rolling, Drug Research Center, University of Utah.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were conducted on a Perkin-Elmer model 240 instrument. IR spectra were recorded on a Perkin-Elmer 283B or 521 spectrophotometer. ^{1}H NMR spectra were recorded on either a Varian T-60 spectrometer or a Varian HA-100 instrument.

[2,3-Dimethyl-4-(4-hydroxybenzoyl)phenoxy]acetic Acid (5). To a stirred mixture of acetaldoxime (4.3 g, 0.072 mol), 5.8 g (0.14 mol) of crushed NaOH in DMF (90 mL), cooled in an ice bath, was added ethyl [2,3-dimethyl-4-(4-nitrobenzoyl)phenoxy]acetate (12.9 g, 0.036 mol) (mp 96–98 °C). The mixture was stirred at room temperature for 18 h, diluted with H_2O (300 mL), and acidified with 12 N HCl. The solid was collected and dried to afford 10 g (93%) of **5**: mp 190–193 °C; NMR (Me_2SO-d_6) δ 2.06 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 4.76 (s, 2 H, OCH_2), 6.78 (d, 1 H, Ar H, J = 8 Hz), 7.10 (d, 1 H, Ar H, J = 8 Hz), 6.90 (d, 2 H, Ar H, J = 8 Hz), 7.66 (d, 2 H, Ar H, J = 8 Hz), 10.10–12.33 (br, 2 H, OH and COOH).

Compounds **1** and **2** (mp 95–96 °C, MeOH–H_2O), **3** (mp 226–228 °C) **4**[2] (mp 225–227 °C, EtOH–H_2O), and **6** (mp 240–242 °C, AcOH) were prepared in a similar manner. [2,3-Dichloro-4-(3-methyl-4-hydroxybenzoyl)phenoxy]acetic acid was obtained by catalytical reduction of ethyl [2,3-dichloro-4-(3-methyl-4-nitrobenzoyl)phenoxy]acetate with Raney Ni in EtOH, followed by diazotization with $NaNO_2$ and concentrated H_2SO_4.

Ethyl [2,3-Dichloro-4-[3-[(dimethylamino)methyl]-4-hydroxybenzoyl]phenoxy]acetate Hydrochloride (8). A mixture of 40% aqueous $(CH_3)_2NH$ (20 mL, 0.2 mol) and 37% HCHO (10 mL, 0.1 mol) was added dropwise to a stirred solution of [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetic acid[2] (**4**) (34.0 g, 0.1 mol) in 40% aqueous $(CH_3)_2NH$ (20 mL, 0.2 mol). The mixture was refluxed for 16 h and concentrated in vacuo. The residue was triturated with H_2O and filtered, and the solid was triturated with hot DMF to afford 17 g of the acid **7**. The acid was converted to the ethyl ester by suspending in EtOH (300 mL), adding $SOCl_2$ (20 mL) dropwise, and refluxing for 16 h. The solution was evaporated in vacuo and the residue was recrystallized.

Compounds **16** and **17** were prepared in the same manner by using 4 mol of 37% HCHO and 8 mol of 40% $(CH_3)_2NH$; **19** and **20** were prepared by using 3 mol of 37% HCHO and 4 mol of the appropriate amines in EtOH.

Ethyl [2,3-Dichloro-4-[3-[(diethylamino)methyl]-4-hydroxybenzoyl]phenoxy]acetate Hydrochloride (9). A mixture of ethyl [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]-acetate (**32**)[14] (11.1 g, 0.03 mol) and *N*-(ethoxymethyl)diethylamine[15] (4.3 g, 0.033 mol) in 1,2-dimethoxyethane (40 mL) was refluxed for 4 h. The solution was concentrated and the resulting gum was taken up in Et_2O, which was filtered. To the filtrate was added ethereal HCl; the solid was filtered and recrystallized.

Compound **18** was similarly prepared by using 4 mol of *N*-(ethoxymethyl)diethylamine.

Ethyl [2,3-Dichloro-4-[4-hydroxy-3-(pyrrolidin-1-ylmethyl)benzoyl]phenoxy]acetate Hydrochloride (10). A solution of 37% HCHO (2.5 mL, 0.033 mol) and pyrrolidine (2.1 g, 0.03 mol) was added dropwise to a stirred solution of **32** (11.1 g, 0.03 mol) in EtOH (50 mL), cooled in an ice bath. The mixture was refluxed for 4 $^1/_2$ h and evaporated in vacuo. The residue was extracted with Et_2O and the solution was evaporated. The crude product was purified by chromatography on a Florisil column (100–200 mesh) using $CHCl_3$ and graded EtOH–$CHCl_3$

(14) Clinton, R. L.; Laskowski, S. C. *J. Am. Chem. Soc.* **1948**, *70*, 3135.

(15) Stewart, T. D.; Bradley, W. E. *J. Am. Chem. Soc.* **1932**, *54*, 4172.

mixtures for elution, and the product was isolated as hydrochloride.

Compounds **11** and **13** were prepared in a similar manner; **22** was obtained by using 3 mol of 37% HCHO and 4 mol of the amine without chromatography.

Ethyl [2,3-Dichloro-4-[3-chloro-5-[(dimethylamino)methyl]-4-hydroxybenzoyl]phenoxy]acetate Hydrochloride (15). A mixture of paraformaldehyde (1.5 g, 0.05 mol), 40% aqueous $(CH_3)_2NH$ (20 mL, 0.2 mol) in *t*-butyl alcohol (50 mL), and cyclohexane (50 mL) was refluxed for 2 h while water was removed with a Dean–Stark trap. To this solution were added [2,3-dichloro-4-(3-chloro-4-hydroxybenzoyl)phenoxy]acetic acid (8.0 g, 0.02 mol) and DMF (50 mL). The mixture was refluxed for 16 h and the solution was evaporated in vacuo. The residue was triturated with ethanol and the solid was filtered. The filtrate, on concentration, gave more solid which was dissolved in warm water and the solution was acidified with HOAc to obtain a white solid. The combined solids were converted to the ethyl ester following the procedure described for **8**.

Compound **12** was similarily prepared by using 1 mol of paraformaldehyde and 2 mol of morpholine and **21** by using 2 mol of paraformaldehyde and 4 mol of morpholine.

***N,N,N*-Trimethyl[2-hydroxy-5-[2,3-dichloro-4-(carbethoxymethoxy)benzoyl]phenyl]methanaminium Chloride (14).** A mixture of free base of **8** (10 g, 0.024 mol) and CH_3I (10 mL, 0.16 mol) in EtOAc (100 mL) was heated on a steam bath for $^1/_4$ h. After evaporation, the residue was dissolved in HOAc and the solution was saturated with HCl gas. Addition of Et_2O afforded an oil, which was separated and crystallized.

[2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]acetic Acid Hydrochloride (26). 2-Chloro-*N*-(hydroxymethyl)acetamide (32.1 g, 0.26 mol) was added portionwise to a stirred solution of [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetic acid[2] (**4**) (68.2 g, 0.20 mol) in CH_3SO_3H (300 mL). The mixture was stirred at room temperature for 3 h and poured into ice water. The solid was filtered and washed thoroughly with ice water. The solid was refluxed with 6 N HCl (200 mL) and EtOH (200 mL) for 1 h and the solution was distilled under atmospheric pressure to remove 100 mL of distillate; H_2O (100 mL) was added to the distilling flask and distillation was continued to remove another 100 mL of distillate. This process was repeated once more. On cooling, the solid was filtered and recrystallized; the filtrate yielded mostly the bis compound.

Ethyl [2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]acetate Hydrochloride (27). Hydrogen chloride was passed into a stirred mixture of **26** (48.7 g, 0.12 mol) in EtOH (550 mL) for 20 min. The mixture was refluxed for 6 h and the solution was concentrated by distillation to 200 mL. The solid was filtered and recrystallized.

Compounds **23–25**, **28–30** were similarly prepared.

Ethyl [2,3-Dichloro-4-[3,5-bis(aminomethyl)-4-hydroxybenzoyl]phenoxy]acetate Dihydrochloride (31). 2-Chloro-*N*-(hydroxymethyl)acetamide (5.4 g, 0.044 mol) was added, in small portions, to a stirred solution of **4** (6.8 g, 0.02 mol) in HOAc (135 mL) and concentrated H_2SO_4 (15 mL) at 57 °C. After stirring at 57 °C for $^1/_2$ h and then at room temperature for 3 h, the mixture was poured into ice water. The gummy solid was collected and refluxed with EtOH (100 mL) and 12 N HCl (20 mL) for 10 h. After evaporation, the residue was recrystallized.

Ethyl [2,3-Dichloro-4-(3-chloro-4-hydroxybenzoyl)phenoxy]acetate (35). Sulfuryl chloride (14.8 g, 0.11 mol) was added, within a period of 1 h, to a warm solution of **32** (36.9 g, 0.1 mol) in $ClCH_2CH_2Cl$ (200 mL). After the addition, the mixture was refluxed for 2 h and evaporated to dryness. The residue was triturated with Et_2O, filtered, and recrystallized with $C_6H_5CH_3$ to yield 35.8 g (89%) of **35**: mp 152–154 °C.

[2,3-Dichloro-4-(3-chloro-4-hydroxybenzoyl)phenoxy]acetic Acid (36). A solution of **35** (10.1 g, 0.025 mol) in 2 N NaOH (37.5 mL) was stirred and heated at 95 °C for 1 h. The solution was cooled to 50 °C and acidified with 6 N HCl. The white solid was filtered, washed with H_2O, and recrystallized from aqueous HOAc to yield 8.7 g (93%) of **36**: mp 190–191 °C; NMR (Me_2SO-d_6) δ 5.03 (s, 2 H, OCH_2), 7.05–7.75 (m, 5 H, Ar H), 10.66–13.66 (br, 2 H, OH and COOH).

Ethyl [2,3-Dichloro-4-[3-(aminomethyl)-5-chloro-4-hydroxybenzoyl]phenoxy]acetate (38). 2-Chloro-*N*-(hydroxymethyl)acetamide (2.6 g, 0.021 mol) was added portionwise to a stirred solution of **36** (7.5 g, 0.02 mol) in CH_3SO_3H (35 mL) at 50 °C. After the addition, the mixture was heated at 95 °C for 4 h and poured into water. The solid was filtered and washed thoroughly with water. The amidoalkylated product was stirred and refluxed with 12 N HCl (15 mL) and EtOH (75 mL) for 5 h. On cooling, the solid was filtered and recrystallized.

Ethyl [2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxy-5-iodobenzoyl]phenoxy]acetate Hydrochloride (39). A solution of ICl (3.6 g, 0.02 mol) in HOAc (10 mL) was added dropwise to a stirred solution of [2,3-dichloro-4-[3-[(2-chloroacetamido)methyl]-4-hydroxybenzoyl]phenoxy]acetic acid (8.9 g, 0.02 mol) in HOAc (100 mL) at 75–80 °C. The mixture was stirred at 75 °C for 20 h and evaporated in vacuo. The residue was triturated with H_2O; the solid was filtered and refluxed with a mixture of EtOH (100 mL) and 12 N HCl (20 mL) for 7 h. After cooling, the product was filtered and recrystallized.

Ethyl [2,3-Dichloro-4-[3-(aminomethyl)-2-hydroxybenzoyl]phenoxy]acetate Hydrochloride (40) and Ethyl [2,3-Dichloro-4-[5-(aminomethyl)-2-hydroxybenzoyl]phenoxy]acetate Hydrochloride (41). The experiment was carried out by the same procedure as **27** with use of **34** (obtained by hydrolysis of the ethyl ester with KOH in EtOH at room temperature). The crude ester hydrochlorides were recrystallized from EtOH to yield **40**: NMR (Me_2SO-d_6) δ 1.16 (t, 3 H, CH_3, J = 7 Hz), 4.08 (s, 2 H, NCH_2), 4.28 (q, 2 H, CH_2, J = 7 Hz), 5.08 (s, 2 H, OCH_2), 6.98 (t, 1 H, Ar H, J = 8 Hz), 7.24 (d, 1 H, Ar H, J = 8 Hz), 7.48 (d, 1 H, Ar H, J = 8 Hz), 7.26 (dd, 1 H, Ar H, J = 8, 2 Hz), 7.82 (dd, 1 H, Ar H, J = 8, 2 Hz), 9.40 (br, 2 H, NH_2). The triplet at 6.98 ppm has ortho coupling to the resonances at 7.82 and 7.26 ppm. The meta coupling is between resonances at 7.82 and 7.26 ppm. To the mother liquor was added Et_2O; the solid was filtered and recrystallized from EtOH to give **41**: NMR (Me_2SO-d_6) δ 1.26 (t, 3 H, CH_3, J = 7 Hz), 3.94 (s, 2 H, NCH_2), 4.28 (q, 2 H, CH_2, J = 7 Hz), 5.06 (s, 2 H, OCH_2), 7.08 (d, 1 H, Ar H, J = 8 Hz), 7.20 (d, 1 H, Ar H, J = 8 Hz), 7.42 (d, 1 H, Ar H, J = 8 Hz), 7.62 (d, 1 H, Ar H, J = 2 Hz), 7.68 (dd, 1 H, Ar H, J = 8, 2 Hz), 9.05 (br, 2 H, NH_2). Spin decoupling shows ortho coupling of the doublet at 7.68 ppm to the doublet at 7.08 ppm and meta to the doublet at 7.62 ppm.

Ethyl [2,3-Dichloro-4-[4-(bromomethyl)-3-methoxybenzoyl]phenoxy]acetate (46). A mixture of **44** (19.9 g, 0.05 mol), *N*-bromosuccinimide (8.9 g, 0.05 mol) and dibenzoyl peroxide (0.5 g) in CCl_4 (200 mL) was stirred and refluxed for 18 h. After cooling, the solid was removed by filtration and the filtrate was evaporated. The solid residue was triturated with pentane and filtered: mp 132–134 °C (quantitative yield); IR ($CHCl_3$) 1670, 1759 cm^{-1}.

Ethyl [2,3-Dichloro-4-[4-(aminomethyl)-3-methoxybenzoyl]phenoxy]acetate Hydrochloride (49). A mixture of **46** (16.0 g, 0.03 mol), NaN_3 (3.3 g, 0.05 mol), and a crystal of KI in EtOH (175 mL) was stirred and refluxed for 16 h. After evaporation, the residue was treated with EtOAc–Et_2O which was washed with H_2O, dried, and concentrated in vacuo. The residue was reduced by catalytical hydrogenation with 1.5 g of 5% Pd–C in EtOH (240 mL) and 12 N HCl (11 mL) under 3 atm for 13 h to yield **49**.

Compounds **47–49** were prepared in a similar manner.

Ethyl [2,3-Dichloro-4-[4-(aminomethyl)-3-hydroxybenzoyl]phenoxy]acetate Hydrobromide (51). A mixture of **49** (3.0 g, 0.007 mol) in HOAc (30 mL) and 48% HBr (30 mL) was refluxed for 21 h. After evaporation, the residue was triturated with Et_2O; the solid was filtered and recrystallized from aqueous HBr to afford the acid, mp 237–239 °C. The acid (2.1 g) was converted to **51** by heating in EtOH and HBr for 3 h.

Ethyl [2,3-Dichloro-4-[3-[(benzyloxycarbonyl)aminomethyl]-4-hydroxybenzoyl]phenoxy]acetate (56). To a stirred mixture of **27** (22.8 g, 0.052 mol) and *N*-[(benzyloxycarbonyl)oxy]succinimide (13.5 g, 0.054 mol) in MeCN (225 mL) was added a solution of $KHCO_3$ (5.4 g, 0.054 mol) in water (60 mL) at 0–5 °C. The reaction mixture was allowed to warm to room temperature and stirred for an addtional $1^1/_2$ h. The organic layer was separated and evaporated. The residue was taken up in CH_2Cl_2 which was washed with aqueous $NaHCO_3$, dried, and evaporated to give 22 g (80%) of **56**; mp 117–119 °C after recrystallization from EtOAc–hexane.

Ethyl [2,3-Dichloro-4-[3-(guanidinomethyl)-4-hydroxybenzoyl]phenoxy]acetate Hydrochloride (57). A solution of 2-methyl-2-thiopseudourea sulfate (0.7 g, 0.0025 mol) in H_2O (13 mL) was added dropwise to a stirred, warm solution of **52** (2.0 g, 0.005 mol) (obtained by neutralizing **27** with aqueous $NaHCO_3$) in EtOH (300 mL). After refluxing for 18 h, the solution was concentrated to 50 mL and refrigerated. The gummy solid was separated and dissolved in ethanolic HCl. After removal of the solvent, the residue was neutralized with 5% aqueous $NaHCO_3$. The solid was filtered and treated again with ethanolic HCl to yield **57**.

Ethyl [2,3-Dichloro-4-[(2-oxo-2*H*-3,4-dihydro-1,3-benzoxazin-6-yl)carbonyl]phenoxy]acetate (58). A solution of *N,N'*-carbonyldiimidazole (0.9 g, 0.005 mol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of **52** (2.0 g, 0.005 mol) and Et_3N (0.5 g, 0.005 mol) in CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 16 h. After evaporation, the residue was taken up in CH_2Cl_2 which was washed with aqueous $NaHCO_3$, 2 N HCl, and brine and concentrated. The residue was purified by chromatography on a silica gel 60 column (70–230 mesh) and eluting with a graded mixture of MeOH–CH_2Cl_2.

Ethyl [2,3-Dichloro-4-[3-(aminomethyl)-4-methoxybenzoyl]phenoxy]acetate Hydrobromide (59). A mixture mixture of **55** (10 g, 0.019 mol), MeI (25 mL, 0.39 mol), K_2CO_3 (10 g, 0.072 mol), and acetone (100 mL) was stirred and refluxed for 24 h. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was taken up in hot MeCN which was filtered to remove inorganic salt. After evaporation, the residue was recrystallized from EtOH to furnish the methylated derivative (8.8 g, mp 137–139 °C), which was treated with 30% HBr in HOAc (24 mL) at room temperature for $^3/_4$ h. The solution was diluted with Et_2O; the solid was collected and recrystallized.

Ethyl [2,3-Dichloro-4-[4-hydroxy-3-(hydroxymethyl)benzoyl]phenoxy]acetate (60). A mixture of **53** (12.5 g, 0.027 mol), anhydrous NaOAc (3.7 g, 0.045 mol), and Ac_2O (140 mL) was stirred and refluxed for 16 h. The mixture was evaporated, and the residue was dissolved in H_2O which was extracted with EtOAc. The extract was washed with brine, dried, and evaporated to provide an oil which solidified: mp 90–91 °C. The solid (12 g) was stirred with KOH (6.9 g) in EtOH (120 mL) for $1^1/_2$ h at room temperature. The mixture was diluted with H_2O (360 mL), acidified with 12 N HCl to pH 3, and extracted with EtOAc. After evaporation, the residue was treated with EtOH and a catalytical amount of concentrated H_2SO_4 at room temperature to afford **60**.

Ethyl [2,3-Dichloro-4-(3-formyl-4-hydroxybenzoyl)phenoxy]acetate (61). To a stirred solution of **60** (7.5 g, 0.019 mol) in CH_2Cl_2 (200 mL) was added activated MnO_2[16] (16.3 g, 0.19 mol) and the mixture was stirred for 24 h at room temperature. After filtering through Celite, the filtrate was evaporated to yield a crystalline solid.

Ethyl [2,3-Dichloro-4-[4-hydroxy-3-[(hydroxyamino)methyl]benzoyl]phenoxy]acetate Hydrochloride (62). To a solution of **61** (2.0 g, 0.005 mol) and NH_2OH·HCl (2.0 g, 0.029 mol) in EtOH (16 mL) was added pyridine (5.5 mL). After stirring for 1 h at room temperature, the solution was poured into ice–H_2O which was extracted with CH_2Cl_2. The extracts were washed with 15% aqueous citric acid and H_2O, dried, and evaporated to yield 1.9 g of oxime. The oxime was dissolved in EtOH (80 mL) and was treated with $NaCNBH_3$ (0.9 g, 0.014 mol). The mixture was stirred for 2 h while the pH was maintained at 3–4 with ethanolic HCl and then evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and precipitated with Et_2O. This process was repeated to afford pure **62**.

Ethyl [2,3-Dichloro-4-(3-carboxy-4-hydroxybenzoyl)phenoxy]acetate (63). To a stirred solution of **61** (4.0 g, 0.01 mol) in CH_2Cl_2 (20 mL) was added *N,N*-diisopropylethylamine (1.9 g, 0.015 mol) and (β-methoxyethoxy)methyl chloride (1.9 g, 0.015 mol). After stirring at room temperature for 3 h, the solution was diluted with CH_2Cl_2 (150 mL), washed with H_2O, dried, and evaporated to provide 4.6 g of the MEM derivative. Jones reagent[17] (28 mL) was added, over a period of $^1/_2$ h, to a stirred solution of the MEM derivative in acetone (420 mL), cooled in an ice bath. The mixture was stirred at room temperature for 3 h, diluted with EtOH (165 mL), and filtered. The filtrate was evaporated to dryness and the residue was taken up in CH_2Cl_2. The solution was washed with H_2O, dried, and evaporated to yield **63**.

Ethyl [2,3-Dichloro-4-(3-carbamoyl-4-hydroxybenzoyl)phenoxy]acetate (64). To a solution of **63** (1.0 g, 0.0024 mol) and Et_3N (0.3 g, 0.005 mol) in CH_2Cl_2 (200 mL) was added dropwise ethyl chloroformate (0.6 g, 0.0054 mol). After the mixture was stirred at room temperature for 1 h, a solution of NH_3 in EtOH (20 mL) was added and the mixture was stirred for $1^1/_2$ h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was taken up in CH_2Cl_2 which was washed with H_2O, dried, and evaporated. The residue was recrystallized to afford **64**.

Ethyl [2,3-Dichloro-4-[3-(1-aminoethyl)-4-hydroxybenzoyl]phenoxy]acetate Hydrochloride (65). A mixture of ethyl [2,3-dichloro-4-(3-acetyl-4-hydroxybenzoyl)phenoxy]acetate (4.0 g, 0.0097 mol) (mp 127–128 °C), $NaCNBH_3$ (0.6 g, 0.0097 mol), NH_4OAc (6.8 g, 0.088 mol), and EtOH (45 mL) was stirred at room temperature for 20 h. The mixture was acidified with 12 N HCl and was filtered. The filtrate was evaporated and the residue was purified by repeated precipitation of a CH_2Cl_2 solution with Et_2O to yield **65**.

Acute Diuretic Activity in Rats. Acute diuretic experiments were performed in female Sprague–Dawley rats weighing 175–225 g, which were provided a diet of sucrose and water for 18 h prior to treatment. Each rat was pretreated 2 h before dosing with 5.0 mg of DOCA (desoxycorticosterone acetate) subcutaneously. All compounds were dissolved or suspended in 0.2% methylcellulose in water and administered orally by gavage. Oral dosage volume was 2 mL/kg, which was immediately followed by a volume/saline load. The load consisted of 30 mL/kg of an isotonic solution of NaCl (0.34%) and KCl (0.69%) in water. The animals were housed in individual stainless steel metabolism cages and urine collections were made into graduated collection tubes for a single 4-h sampling period. The volume of each sample was measured and an aliquot was taken for determination of Na^+, K^+, and Cl^- concentrations by standard methods. Each compound was screened at two doses (30 and 100 mg/kg) using two rats/dose, and all active compounds were further evaluated at a minimum of four doses with four rats/dose. Sodium excretion values were expressed as the mean milliequivalents kilogram^{-1} (4 h)$^{-1}$. These values were used to calculate the ED_2.

Diuretic Activity in Normotensive Saline-Loaded Rats. Male normotensive rats (Sprague–Dawley), weighing 275–375 g, were used. The test compound or the control was treated in eight animals. The test compound was dissolved or suspended in the vehicle (0.2% methylcellulose in water) and the dosage volume for all compounds was 2 mL/kg. The test compound or vehicle was administered orally to each animal and immediately followed by a saline load (0.9% normal saline) equivalent to 5% of the animal's body weight. The animals were placed into individual stainless steel metabolism cages immediately after the dosing regimen to begin the urine collections. Food and water were allowed ad libitum prior to testing, but no food or water was given to the rats during the test period. Urine volume was measured and recorded and an aliquot taken for analysis at 2, 6, and 24 h after dosing. The samples were analyzed for Na^+, K^+, Cl^-, uric acid, and osmolality by standard methods.

Diuretic Activity in Dogs. Female beagle dogs weighing 8–12 kg were allowed water ad libitum during an overnight 18-h fasting period prior to testing. The dogs were placed into supportive body slings and no further fluids were given. Each dog was prepared by shaving the areas of the jugular and cephalic veins for taking blood samples. The vulvar area was washed and cleaned with an antiseptic solution and was rinsed clean with distilled water. An appropriate size Foley catheter (10 or 12 French) was inserted into the bladder and remained in situ throughout the experiment. The urine from the bladders was drained by free flow. Thirty-minute base-line urine samples were collected just prior to dosing. Urine samples were collected for the $-^1/_2$–0, 0–$^1/_2$, $^1/_2$–1,

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1–2, 2–4, and 4–6 h time intervals. Urine volume was measured and an aliquot taken from each sample. Each aliquot was centrifuged to remove suspended materials, then decanted, and chilled on ice in a glass test tube. Four-milliliter venous blood samples were drawn into heparinized syringes at the urine collection times. Blood samples were centrifuged to separate the plasma within 30 min of withdrawing blood samples. Each sample of urine and plasma was analyzed for concentrations of Na^+, K^+, Cl^-, urate, and glucose by standard methods. Each dog was administered only one dose of the test compound in a given experiment. Calculations were made for mean excretion values for each variable, for each time interval and each dog tested. Data presented were the mean Na excretion values, expressed in milliequivalents kilograms^{-1} (6 h)$^{-1}$ with at least two dogs/dose.

Diuretic Activity in Cynomolgus Monkeys. Male and female cynomolgus (*Macaca fascicularis*) monkeys were deprived of food for 16–18 h prior to dosing and allowed H_2O ad libitum until dosing, six monkeys/dose. Each monkey was captured, restained, and weighed. A pediatric nasogastric tube was inserted through either nostril into the stomach in order to administer the oral dose of compound or vehicle. Immediately after dosing, a water load of 50 mL/kg of body weight was administered through the nasogastric tube; then the tube was withdrawn. The monkey was placed into a clean stainless steel metabolism cage. No food or H_2O was given during the subsequent 6 h of the experiment. Urine samples were collected into plastic bottles from the metabolism pans at 0–1, 1–2, 2–4, and 4–6 h after dosing. Volumes were measured and aliquots taken for analyses of electrolytes, uric acid, and glucose by standard methodologies.

Antihypertensive Activity.[18] Male SH rats (age 9–12 weeks, Lab Supply, Indianapolis, IN) were trained for use in wire mesh restaining cylinders. The rats were warmed for 30 min at 36 °C prior to measurement of blood pressure (BP) and heart rate. An occluding cuff, attached to a programmed sphygmomanometer, was placed on the rat's tail near the base. Pressure in the cuff was programmed to increase and decrease automatically in cycles from 0 to 250 mmHg at the rate 10 mmHg/s. Cycle time was 50 s, with 10 s between cycles. A photocel placed on the tail distal to the cuff was used to detect the pulse from blood flow with each heart beat. Occlusion pressure measured at disappearance and reappearance of the pulse from five interference-free signals was used to estimate the systolic BP. Heart rate was determined from an expanded tracing with a Grass Model 7 polygraph. Oral dosings of compounds suspended in 0.2% methylcellulose in H_2O were administered by gavage. Only rats with a minimum control pressure of 170 mmHg or greater were used.

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Registry No. 1, 82241-43-8; 1 (ethyl ester, 4′-nitro deriv.), 82241-42-7; 2, 92270-34-3; 2 (ethyl ester, 4′-nitro deriv.), 92270-81-0; 3, 92270-35-4; 3 (ethyl ester, 4′-nitro deriv.), 92270-84-3; 4, 62967-00-4; 4 (ethyl ester, 4′-nitro deriv.), 75554-04-0; 5, 82241-40-5; 5 (ethyl ester, 4′-nitro deriv.), 92270-80-9; 6, 82241-54-1; 6 (ethyl ester, 4′-nitro deriv.), 82241-52-9; 7, 78235-22-0; 8, 78235-69-5; 8·HCl, 78235-21-9; 9, 78235-74-2; 9·HCl, 78235-23-1; 10, 92270-63-8; 10·HCl, 78235-24-2; 11, 92270-64-9; 11·HCl, 78235-25-3; 12, 92270-65-0; 12·HCl, 78235-28-6; 13, 78235-27-5; 14, 92270-36-5; 15, 78235-55-9; 15·HCl, 78235-32-2; 16, 78235-34-4; 16·3HCl, 92270-37-6; 17, 92270-66-1; 17·2HCl, 78235-35-5; 18, 92270-67-2; 18·2HCl, 78235-59-3; 19, 92270-68-3; 19·2HCl, 78235-38-8; 20, 92270-69-4; 20·2HCl, 78235-40-2; 21, 92270-83-2; 21·2HCl, 78235-36-6; 22, 78235-41-3; 23, 82241-63-2; 23·HCl, 82241-44-9; 24, 82241-64-3; 24·HCl, 92270-38-7; 25, 82241-65-4; 25·HCl, 92270-39-8; 26, 78235-73-1; 26·HCl, 78235-52-6; 27, 78235-72-0; 27·HCl, 78235-46-8; 28, 78235-67-3; 28·HCl, 78235-53-7; 29, 82241-62-1; 29·HCl, 82241-56-3; 30, 78235-68-4; 30·HCl, 78235-54-8; 31, 82241-61-0; 31·2HCl, 78235-47-9; 32, 78235-15-1; 33, 62967-00-4; 34, 82241-55-2; 35, 78235-16-2; 36, 78235-17-3; 37, 92270-40-1; 37 (x = H), 78235-49-1; 38, 78235-70-8; 38·HCl, 78235-48-0; 39, 78235-71-9; 39·HCl, 78235-50-4; 40, 92270-70-7; 40·HCl, 92270-41-2; 41, 92270-71-8; 41·HCl, 92270-42-3; 42, 92270-43-4; 43, 92284-30-5; 44, 92270-44-5; 45, 92270-45-6; 46, 92270-46-7; 47, 92270-72-9; 47·HCl, 92270-47-8; 48, 92270-73-0; 48·HCl, 92270-48-9; 49, 92270-74-1; 49·HCl, 92270-49-0; 50, 92270-75-2; 50·HCl, 92270-50-3; 51, 92270-76-3; 51·HBr, 92270-51-4; 54, 92270-52-5; 55, 92270-53-6; 56, 85297-76-3; 57, 92270-54-7; 58, 92270-55-8; 59, 92270-77-4; 59·HBr, 92270-56-9; 60, 92270-57-0; 61, 92270-58-1; 62, 92270-78-5; 62·HCl, 92270-59-2; 63, 92270-60-5; 64, 92270-61-6; 65, 92270-79-6; 65·HCl, 92270-62-7; $(CH_3)_2NH$, 124-40-3; c-C_4H_8NH, 123-75-1; c-$C_5H_{10}NH$, 110-89-4; c-$HN(CH_2CH_2)_2O$, 110-91-8; c-$HN(CH_2CH_2)_2SO_2$, 39093-93-1; *N*-(ethoxymethyl)diethylamine, 7352-03-6; 2-chloro-*N*-(hydroxymethyl)acetamide, 2832-19-1; *N*-[(benzyloxycarbonyl)oxy]succinimide, 13139-17-8; 2-methyl-2-thiopseudourea sulfate, 867-44-7; (β-methoxyethoxy)methyl chloride, 3970-21-6; [2,3-dichloro-4-(3-methyl-4-hydroxybenzoyl)phenoxy]acetic acid, 82241-41-6; ethyl [2,3-dichloro-4-(3-methyl-4-nitrobenzoyl)phenoxy]acetate, 92270-82-1; Na, 7440-23-5.

[(Aminomethyl)aryloxy]acetic Acid Esters. A New Class of High-Ceiling Diuretics. 2. Modifications of the Oxyacetic Side Chain[1]

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The discovery of high-ceiling natriuretic activity from a series of aminomethyl derivatives of ethyl [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetate prompted our continued investigation of this new class of (aryloxy)acetic acid diuretics. Systematic alteration of the oxyacetic side chain has shown that the carboxylic acid function is the active species in vivo and that the ethyl ester group serves as a prodrug to enhance oral absorption. Side-chain functional groups that are incapable of generating the carboxylic acid in vivo failed to impart diuretic activity to the target compounds. Additional side-chain modifications including homologation, methyl substitution, and heteroatom replacement are also described. Ring annelation of the oxyacetic side chain to a dihydrobenzofuran-2-carboxylic acid produced compound **32**, which displayed the highest level of saluretic activity for this series.

Recently, we reported[2] a new class of saluretic agents I that shows a high-ceiling profile in rats, dogs, and monkeys and that contains in one molecule elements of the phenoxyacetic acids[3] and the 2-(aminomethyl)phenols.[4]

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