from donor CDF_1 mice bearing 7-day growths. The suspension was centrifuged for 2 min (1600g), the supernatant peritoneal fluid was decanted, and a 10-fold dilution with isotonic saline was made. The cell number was determined with a Coulter particle counter, and the cell population was adjusted to 10^7 cells/mL. One-tenth milliliter of the resulting cell suspension (containing approximately 10^6 cells) was injected intraperitoneally into each animal. Drugs were administered by intraperitoneal injection, beginning 24 h after tumor implantation, once daily for 6 consecutive days. The test compounds were injected as fine suspensions following homogenization in 2–3 drops of 20% aqueous Tween 80 and then made up to volume with isotonic saline. All drugs were administered intraperitoneally in a volume of 0.5 mL. For any one experiment, animals were distributed into groups of five mice of comparable weight and maintained throughout the course of the experiment on Purina Laboratory Chow pellets and water "ad libitum". Controls given injections of a comparable volume of vehicle were included in each experiment. Mice were weighed during the course of the experiments, and the percentage change in body weight from onset to termination of therapy was used as an indication of drug toxicity. Determination of the sensitivity of ascitic neoplasms to these agents was based on the prolongation of survival time afforded by the drug treatments. Each experiment was repeated at least one time.

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2-(Aminomethyl)phenols, a New Class of Saluretic Agents. 4. Effects of Oxygen and/or Nitrogen Substitution[1]

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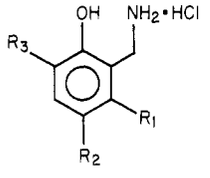
A series of oxygen and/or nitrogen substituted 2-(aminomethyl)phenols was synthesized and tested orally in rats for saluretic and diuretic effects. Intravenous dog data are included as supplementary material to demonstrate diuretic responses, or lack thereof, in a second species. In general, substitution on nitrogen with groups other than lower alkyl or substitution on nitrogen and/or oxygen with groups resistant to hydrolysis substantially diminished or ablated saluretic effects.

We reported previously on a series of 2-(aminomethyl)phenols[3] which were shown to possess a high order of diuretic activity in rats and dogs and discussed the effects of functional-group reorientation and modification.[4] The compounds reported herein were prepared in order to assess the biological consequences of oxygen and/or nitrogen substitution. From those 2-(aminomethyl)phenols described earlier,[3] compounds **1–3**, which exhibit good (1) to excellent (2 and 3) saluretic effects in rats and dogs, were chosen for demonstrating the effects of these substitutions.

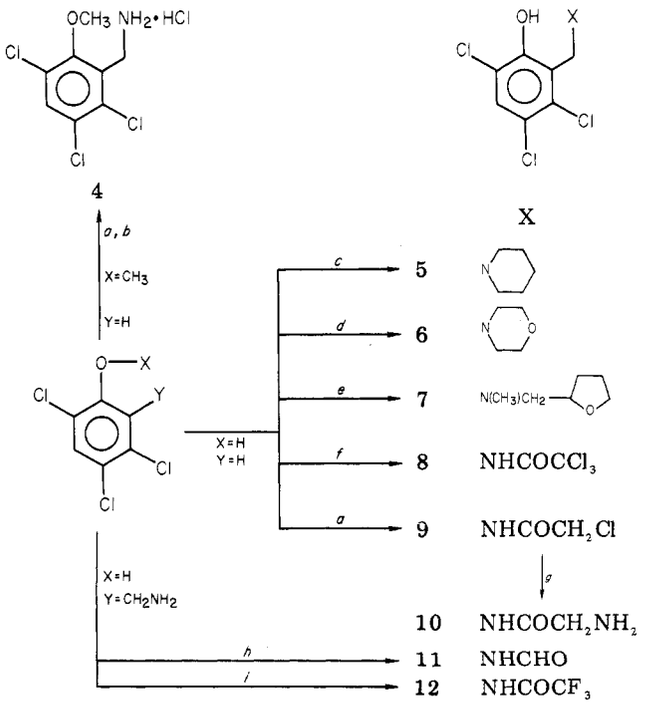


1, $R_1 = R_2 = R_3 = Cl$
2, $R_1 = H$; $R_2 = t\text{-}C_4H_9$; $R_3 = Cl$
3, $R_1 = H$; $R_2 = t\text{-}C_4H_9$; $R_3 = I$

Chemistry. The compounds prepared for this study are listed in Tables I–III, and their syntheses are outlined in Schemes I–IV. The compounds depicted in Schemes I–IV were prepared from the corresponding phenols, with the exception of **4** (methyl ether). Compounds **4**, **8**, and **9** were prepared by amidoalkylation (method A_2; without subsequent hydrolysis in the instances of **8** and **9**) as described in Part 1,[3] while **10** was obtained via subsequent amination of **9**.

Tertiary amines **5–7**, **13**, and **47** and secondary amine **44** (followed by iodination) were prepared under standard Mannich reaction conditions.[5] Diamine **45** was elaborated from dehalo **3a** via transamination with ethylenediamine

Scheme I



[a] $ClCH_2CONHCH_2OH$, H_2SO_4. [b] EtOH, HCl, Δ. [c] CH_2O, c-$NH(CH_2)_5$, Δ. [d] CH_2O, c-$NH(CH_2CH_2)_2O$, Δ. [e] CH_2O, 2-$NH(CH_3)CH_2$-c-C_4H_8O, Δ. [f] $Cl_3CCONHCH_2OH$, H_2SO_4. [g] NaI, NH_4OH. [h] $HCONH_2$, Δ. [i] $(F_3CCO)_2O$.

† Merck Sharp & Dohme Research Laboratories.
‡ Merck Institute for Therapeutic Research.

0022-2623/82/1825-0735$01.25/0

Table I. Effects of Oxygen Substitution

no.	X	method	yield, %	recrystn solvent	mp, °C	formula[b]	score[a] rat,[c] po	score[a] dog,[d] iv
1	H	*e*	51	EtOH/HCl	244.5-245 dec	$C_7H_6Cl_3NO \cdot HCl$	3	5[f]
3	H	*e*	81	EtOH/HCl	200-201 dec	$C_{11}H_{16}INO \cdot HCl$	6	6[g]
4	CH_3	*h, i*	22	EtOH/Et_2O	193-193.5 dec	$C_8H_8Cl_3NO \cdot HCl$	0	0[j]
23	CH_2CONH_2	*k*	23	EtOH/Et_2O	228.5-229 dec	$C_{13}H_{19}IN_2O_2 \cdot HCl$	0	1[j]
24	$CH_2CON(C_2H_5)_2$	*k*	46	EtOH/Et_2O	175.5-176.5	$C_{17}H_{27}IN_2O_2 \cdot HCl$	0	0
25	$SO_2N(CH_3)_2$	*k*	51	EtOH/Et_2O	239-240 dec	$C_{13}H_{21}IN_2O_3S \cdot HCl$	2	
26	$SO_2NHC_2H_5$	*k*	30	EtOH/Et_2O	168-169.5 dec	$C_{13}H_{21}IN_2O_3S \cdot HCl$	3	3
27	SO_2CH_3	*k*	69	EtOH/Et_2O	204-205 dec	$C_{12}H_{18}INO_3S \cdot HCl$	0	
28	$SO_2C_6H_5$	*k*	52	EtOH/Et_2O	222-223 dec	$C_{17}H_{20}INO_3S \cdot HCl$	2	
29	CH_3	*k*	72[l]	EtOH/Et_2O	187-188	$C_{12}H_{18}INO \cdot HCl$	0	0
30	SO_3H	*k*	60	EtOH/H_2O	231-232 dec	$C_{11}H_{16}INO_4S$	3	
49	$CH_2CO_2C_2H_5$	*k*	16	EtOH/Et_2O	200-202	$C_{15}H_{22}INO_3 \cdot HCl$	0	1

[a] For testing protocols and scoring system, see ref 3. [b] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [c] Score is for geometric mean of three animals per cage three cages per dose. [d] Score is average value of two dogs at 5 mg/kg stat (weight range 15-20 kg) unless otherwise designated. [e] Reference 3. [f] Score is average value of three dogs. [g] 1 mg/kg. [h] Amidoalkylation of corresponding methoxybenzene and subsequent hydrolysis, method A_2, ref 3. [i] See Harrison, W. S. W.; Peters, A. T.; Rowe, F. M. *J. Chem. Soc.* **1943**, 235, for preparation of 2,4,5-trichloromethoxybenzene. [j] Score is for single dog. [k] See Experimental Section. [l] Represents yield of last step only.

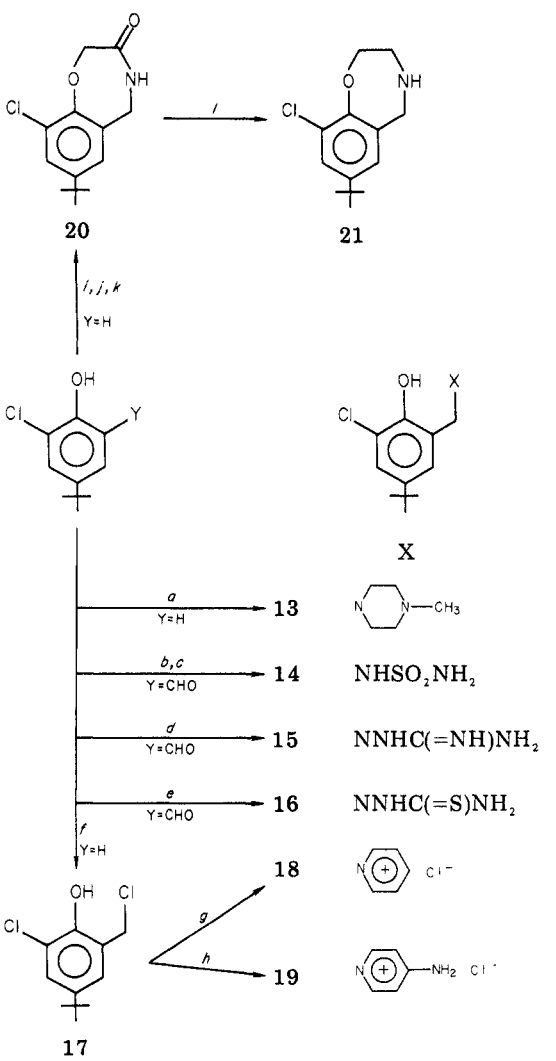
followed by iodination. Compounds **11**, **12**, **22**, and **43** were synthesized by acylation of the corresponding 2-(aminomethyl)phenols.

Hydrazones **15** and **16** were prepared from the corresponding hydroxybenzaldehydes as were compounds **14**, **39**, **40**, and **41** with subsequent reduction of the imine double bond in the latter cases. The formation of **46** was accomplished via condensation of dehalo **38** with ammonium sulfamide, followed by reduction using the general method of Yamaguchi[6] and then iodination.

Quaternary iodides **42** and **48** were synthesized from amines **3a** and **47**, respectively, while chlorides **18** and **19** were formed from chloromethylphenol **17**. Compounds **20** and **49** were prepared from the corresponding halophenols via amidoalkylation and subsequent ring closure, with the former being reduced to benzoxazepin **21** and the latter undergoing ring opening in acidic ethanol to phenoxyacetic ester **49**.

Compounds **23–28** were prepared from **22** by alkylation (**23–24**) or sulfonylation (**25–28**), followed by removal of the *t*-Boc moiety. On the other hand, **30** was synthesized directly from **3a** by reaction with either chlorosulfonic acid or pyridine–sulfur trioxide complex. However, unlike **4**, methyl ether **29** could not be prepared by direct amidoalkylation under conditions mild enough to prevent de-*tert*-butylation or deiodination (the acidic lability of these groups was alluded to earlier),[3] nor could deiodo **29** be iodinated under the conditions used so successfully for the phenolic compounds reported herein or earlier.[3,4] Thus, **29** was synthesized from **3a** via sequential amidation, alkylation, and hydrolysis.

Scheme II

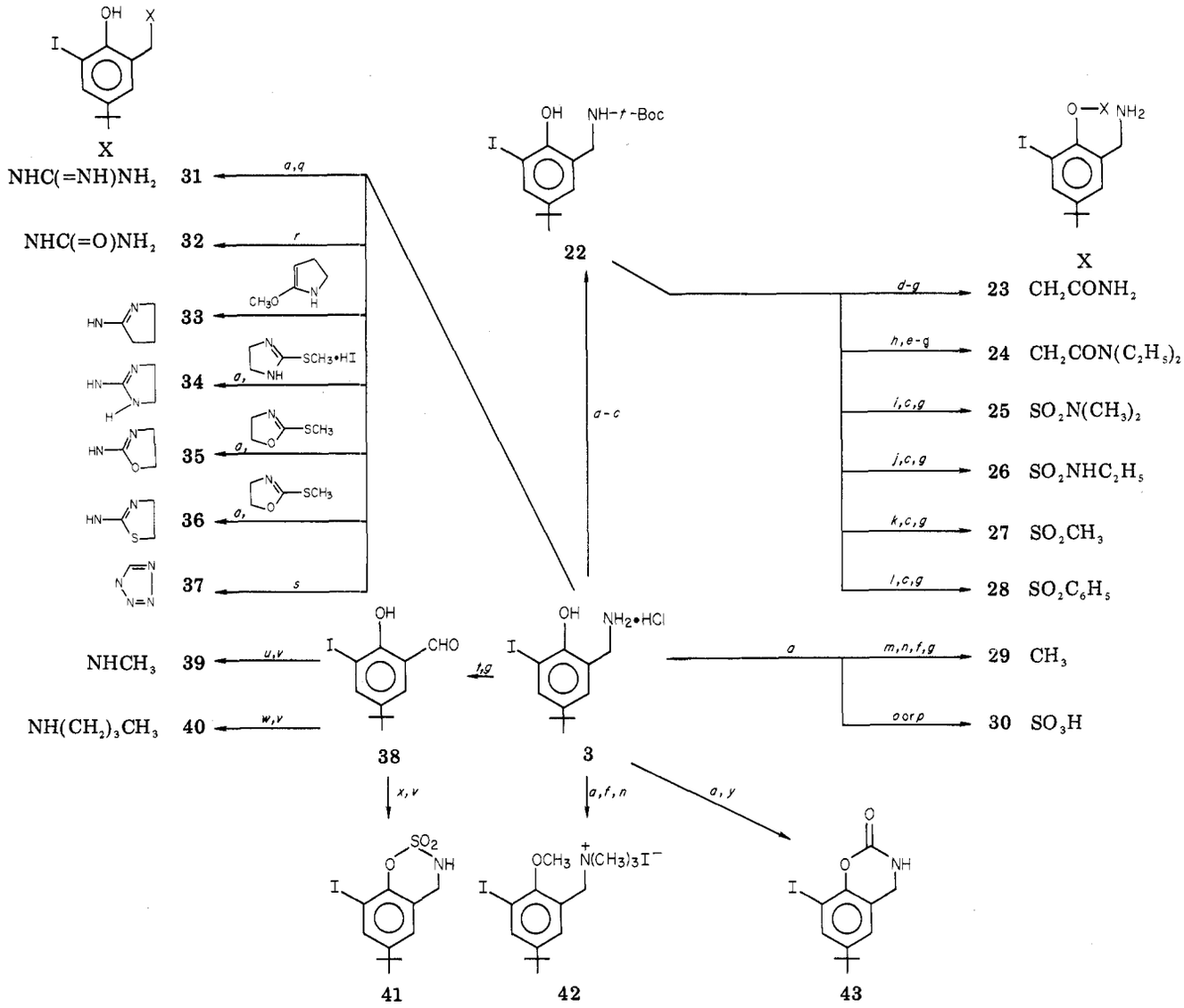


[a] CH_2O, c-$NH(CH_2CH_2)_2NCH_3$, Δ. [b] $H_2NSO_2NH_2$, Δ. [c] H_2, PtO_2. [d] $H_2NNHC(=NH)NH_2$. [e] $H_2NNHC(=S)NH_2$. [f] CH_2O, HCl. [g] c-NC_5H_5. [h] c-NC_5H_4-4-NH_2. [i] $ClCH_2CONHCH_2OH$, H_2SO_4. [j] NaI. [k] K_2CO_3. [l] Red Al.

Ureidomethylphenol **32** and dihydropyrrolylaminomethylphenol **33** were prepared from **3** by condensation with potassium cyanate and 2,3-dihydro-5-methoxypyrrole,

(1) Portions of this work were presented in August, 1977, at the 174th National Meeting of the American Chemical Society. See "Abstracts of Papers", 174th National Meeting of the American Chemical Society, Chicago, IL, 1977; American Chemical Society: Washington, DC, 1977, and *ACS Symp. Ser.* **1978**, *83*, 93–124.
(2) Deceased, May 31, 1977.
(3) For Part I, see Stokker, G. E.; Deana, 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.
(4) Part III: Stokker, G. E.; Deana, 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.
(5) Mannich reaction: F. F. Blicke *Org. React.* **1942**, *1*, 303–341.
(6) Yamaguchi, S. *Nippon Kagaku Zasshi* **1968**, *89*, 1099.

Scheme III



[a] NH_4OH. [b] $C_6H_2Cl_3OCOO$-t-C_4H_9. [c] $(C_2H_5)_3N$. [d] $ClCH_2CONH_2$. [e] NaI. [f] K_2CO_3. [g] HCl. [h] $ClCH_2CON(C_2H_5)_2$. [i] $ClSO_2N(CH_3)_2$. [j] $ClSO_2NHC_2H_5$. [k] $ClSO_2CH_3$. [l] $ClSO_2C_6H_5$. [m] $(F_3CCO)_2O$. [n] CH_3I. [o] $ClSO_3H$. [p] $C_5H_5N{\cdot}SO_3$. [q] $NH{=}C(NH_2)SCH_3{\cdot}HI$. [r] KCNO. [s] NaN_3, $HC(OC_2H_5)_3$, HOAc. [t] $(CH_2)_6N_4$. [u] CH_3NH_2. [v] $NaBH_4$. [w] $C_4H_9NH_2$. [x] $ClSO_2NH_2$. [y] $(C_3H_3N_2)_2CO$.

respectively, while **37** was formed by condensation with sodium azide and ethyl orthoformate in acetic acid.[7] Compounds **31** and **34–36** were synthesized from **3a** by reaction with their corresponding *N*-methylthio derivatives.

Pharmacology. The target compounds were tested orally in rats for their saluretic properties. The results are limited to Na^+ excretion and are presented in a scored format[8] for the sake of brevity in Tables I–III. Intravenous dog data are included as supplementary material (see paragraph at the end of paper concerning supplementary material) to demonstrate diuretic responses, or lack thereof, in a second species. Data illustrating the saluretic effects resulting from substitution on the phenolic hydroxyl group are shown in Table I. In general, it appears that the saluretic effects engendered by these oxygen-substituted compounds are inversely proportional to their respective hydrolytic or enzymatic stability. Sulfate ester **30** is of particular interest in view of the fact that it is the major metabolite (90%) of MK-447 in rats and dogs and, to a lesser extent (17%), in man.[9] Accordingly, in addition to its role as an excretable entity, **30** may serve both as a reservoir and as a prodrug form of **3**.

The influence of nitrogen substitution on saluretic effects is illustrated by the data presented in Table II. As the data indicate, substitution on nitrogen by groups other than lower alkyl (C_1–C_4) or hydrolytically labile moieties substantially diminishes or ablates saluretic effects.

Finally, the data recorded in Table III illustrate the effects of nitrogen and oxygen substitution and provides further support for the detrimental consequences of N and O substitution described earlier.

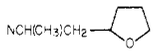
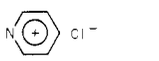
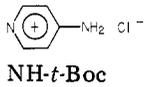
All of the above compounds were evaluated in spontaneously hypertensive (SH) rats, and only **40** displayed a modest antihypertensive response [maximum fall in MAP

(7) Kamitani, T.; Saito, Y.; Japanese Patent 7247031; *Chem. Abstr.* **1973**, *78*, 111331p for general procedure of tetrazole formation from amines.

(8) For testing protocols and scoring system, see ref 3.

(9) Tocco, D. J.; deLuna, F. A.; Duncan, A. E. W.; Walker, R. W.; Arison, B. H.; VandenHeuval, W. J. A. *Drug Metab. Dispos.* **1979**, *7*, 330.

Table II. Effects of Nitrogen Substitution

no.	X	method	yield, %	recrystn solvent	mp, °C	formula[b]	score[a] rat,[c] po	score[a] dog,[d] iv
2	NH_2	*e*	44	EtOH/HCl	251–251.5 dec	$C_{11}H_{16}ClNO \cdot HCl$	6	6
5	c-NC_5H_{10}	*f*	44	MeOH	111.5–112.5	$C_{12}H_{14}Cl_3NO$	0	0[g]
6	c-$N(CH_2CH_2)_2O$	*f*	63	MeOH	136–137	$C_{11}H_{12}Cl_3NO_2$	0	1
7		*f*	10	acetone	148–149	$C_{13}H_{16}Cl_3NO_2$	0	2
8	$NHCOCCl_3$	*h*	41	EtOH/H_2O	138.5–140	$C_9H_5Cl_6NO_2$[i]	0	3[g]
9	$NHCOCH_2Cl$	*j*	80	EtOH/H_2O	130–131	$C_9H_7Cl_4NO_2$	1	0[g]
10	$NHCOCH_2NH_2$	*k*	53	EtOH	191.5–192	$C_9H_9Cl_3N_2O_2$	0	1
11	NHCHO	*k*	76	EtOH/H_2O	132–133	$C_8H_6Cl_3NO_2$	0	0[l]
12	$NHCOCF_3$	*k*	81	HOAc/H_2O	110–111	$C_9H_5Cl_3F_3NO_2$	2	
13	c-$N(CH_2CH_2)_2N$-CH_3	*f*	71	EtOH/Et_2O	229–230	$C_{16}H_{25}ClN_2O \cdot 2HCl$	0	0
14	$NHSO_2NH_2$	*k*	27	EtOH/H_2O	141–143	$C_{11}H_{17}ClN_2O_3S$	0	0[l]
15	$NNHC(=NH)NH_2$	*k*	96	EtOH/H_2O	211–213 dec	$C_{12}H_{17}ClN_4O$	0	1[g]
16	$NNHC(=S)NH_2$	*k*	77	EtOH/H_2O	231–234 dec	$C_{12}H_{16}ClN_3OS$	0	1
18		*k*	86	EtOH/Et_2O	196–199	$C_{16}H_{19}Cl_2NO \cdot 0.5C_2H_5OH$	0	0
19		*k*	89	EtOH/Et_2O	221–223	$C_{16}H_{20}Cl_2N_2O$		0
22	NH-*t*-Boc	*k*	79	EtOAc	199–200 dec	$C_{16}H_{24}INO_3$	0	
31	$NHC(=NH)NH_2$	*k*	64	EtOH/H_2O	188–190 dec	$C_{12}H_{18}INO_3O$	0	
32	$NHC(=O)NH_2$	*k*	46	EtOAc	187–188 dec	$C_{12}H_{17}IN_2O_2$	0	0[g]
33		*k*	93	EtOH/Et_2O	210–211 dec	$C_{15}H_{21}IN_2O \cdot HCl$	0	
34		*k*	24	EtOH/H_2O	180–182 dec	$C_{14}H_{20}IN_3O$[m]	0	0[g]
35		*k*	43	EtOH	191–193 dec	$C_{14}H_{19}IN_2O_2$	0	
36		*k*	47	DMF	191–192	$C_{14}H_{19}IN_2OS$	0	
37		*k*	56	EtOH/H_2O	121–122.5 dec	$C_{12}H_{15}IN_4O$	0	1
39	$NHCH_3$	*k*	41[n]	pet. ether	86–88	$C_{12}H_{16}INO$	5	2
40	NHC_4H_9	*k*	45	EtOH/HCl	144.5–145	$C_{15}H_{24}INO \cdot HCl$	4	4[g]
44	NH-c-C_6H_{11}	*o, p*	70[n]	EtOH/HCl	204–205 dec	$C_{17}H_{26}INO \cdot HCl$	0	
45	$NH(CH_2)_2NH_2$	*k, p*	66[n]	H_2O/HCl	200–201 dec	$C_{13}H_{21}IN_2O \cdot 2HCl$	1	0
46	$NHSO_3H$	*k, p*	59	EtOH/H_2O	180–182 dec	$C_{11}H_{16}INO_4S$	1	
47	$N(CH_3)_2$	*f, q*	74	EtOH/H_2O	130–132	$C_{13}H_{20}INO$	4	0[g]
48	$^+N(CH_3)_3$ I^-	*k*	72	EtOH/H_2O	165–166 dec	$C_{14}H_{23}I_2NO$	0	0[g]

[a–d] Footnotes *a–d*, Table I. [e] Reference 3. [f] General method for Mannich reaction on corresponding phenols, ref 5. [g] Score is for single dog. [h] Amidoalkylation of corresponding phenol with 2,2,2-trichloro-*N*-(hydroxymethyl)acetamide, method A_2, ref 3. [i] Anal. Calcd: C, 29.07. Found: C, 29.61. [j] Amidoalkylation of corresponding phenol with 2-chloro-*N*-(hydroxymethyl)acetamide, method A_2, ref 3. [k] See Experimental Section. [l] Score is average value for three dogs. [m] Anal. Calcd: C, 45.05. Found: C, 44.61. [n] Represents yield of last step only. [o] See Burke, W. J. *J. Am. Chem. Soc.* **1949**, *71*, 609, for preparation of deiodoaminophenol. [p] Iodination of deiodophenol, method C, ref 3. [q] See Reference 3 for preparation of the corresponding iodophenol.

(mmHg) of 30–40 at 5 mg/kg po and <20 at 1.25 mg/kg po][10] when compared to **3** (38 ± 1.6 at 1.25 mg/kg po).[3]

Conclusion

The oral rat data presented above indicate that, in general, substitution on nitrogen with groups other than lower alkyl (C_1–C_4) or substitution on nitrogen and/or oxygen with groups that are not hydrolytically or enzymatically labile substantially diminished or ablated saluretic effects.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. ^1H NMR spectra were recorded in Me_2SO-d_6, unless otherwise noted, on either a Varian T-60 or EM-390 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were determined using a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise. All starting materials were commercially available unless so indicated.

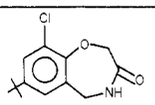
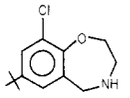
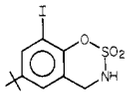
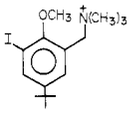
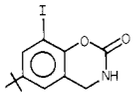
2-(Aminomethyl)-3,5,6-trichlorophenol (1a). A vigorously stirred solution of **1**[3] (20 g, 75 mmol) in warm H_2O (1.5 L) was treated with 15 N NH_4OH (100 mL) and then cooled to ~10 °C with continued stirring. The crude product was collected by filtration, thoroughly washed with H_2O, and dried in a vacuum oven: yield 16 g (96%); mp 190.5–191 °C. Anal. ($C_7H_6Cl_3NO$) C, H, N.

2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol (3a). This compound was prepared similarly to **1a** by neutralization of **3**[3] with 15 N NH_4OH: yield 97%; mp 146–146.5 °C dec (compound is light sensitive and should be kept in the dark). Anal. ($C_{11}H_{16}INO$) C, H, N.

2-Amino-*N*-[(2,3,5-trichloro-6-hydroxyphenyl)methyl]-acetamide (10). A solution of NaI (3.0 g, 20 mmol) in acetone (30 mL) was added to a solution of **9** (6.0 g, 20 mmol) in acetone

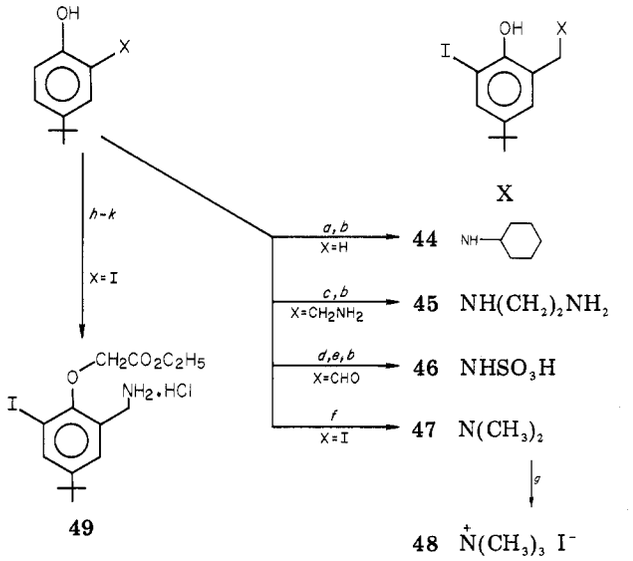
(10) Ludden, C. T., unpublished results.

Table III. Effects of Nitrogen and Oxygen Substitution

no.	compd	method	yield, %	recrystn solvent	mp, °C	formula[b]	score[a] rat,[c] po	score[a] dog,[d] iv
20		*e*	26	EtOH	214-215.5	$C_{13}H_{16}ClNO_2$	0	
21		*e*	61	EtOH/Et_2O	233-234	$C_{13}H_{18}ClNO \cdot HCl$	0	0
41		*e*	12	EtOH/HOAc	154-155	$C_{11}H_{14}INO_3S$	0	
42	 I^-	*e*	53	EtOH/Et_2O	216-218 dec	$C_{15}H_{25}I_2NO$		0[f]
43		*e*	71	C_6H_6	199-200	$C_{12}H_{14}INO$	±	

[a-e] Footnotes *a-d* and *k*, Table I. [f] Score is for single dog at 5 mg/kg po (<4 mequiv/0-6 h, compared with 56 mequiv/0-6 h for **3**; ref 3).

Scheme IV



[a] CH_2O, H_2N-c-C_6H_{11}, Δ. [b] ICl. [c] $H_2N(CH_2)_2NH_2$, Δ. [d] $H_2NSO_3NH_4$, Δ. [e] $NaBH_4$, then HCl. [f] CH_2O, $(CH_3)_2NH$, Δ. [g] MeI. [h] $ClCH_2CONHCH_2OH$, H_2SO_4. [i] NaI. [j] K_2CO_3. [k] EtOH, HCl, Δ.

(20 mL). After refluxing gently for 15 min, the mixture was filtered, and the clear filtrate was added dropwise to 15 N NH_4OH (500 mL) with vigorous stirring. After standing at 20 °C overnight, the reaction mixture was cooled to 0 °C, and the crude solid was collected as a tan powder (4.4 g), mp 187–190 °C. Crystallization gave an analytical sample of **10** (3 g) as tiny tan needles: ^1H NMR (F_3CCO_2H) δ 4.0–4.4 (2 H, m), 4.9 (2 H, d, J = 6 Hz), 7.5 (H-5, s).

***N*-[(3,5,6-Trichloro-2-hydroxyphenyl)methyl]formamide (11).** A solution of **1a** (1.4 g, 6.2 mmol) in formamide (2.8 g, ~60 mmol) was heated at 130 °C under N_2 for 3 h. The dark brown liquid was cooled, diluted with H_2O (200 mL), and stirred at 20 °C overnight. The crude solid was collected and crystallized to yield **11** (1.2 g).

2,2,2-Trifluoro-*N*-[(2,3,5-trichloro-6-hydroxyphenyl)methyl]acetamide (12). Compound **1a** (2.26 g, 10 mmol) was added portionwise to trifluoroacetic anhydride (5 mL) with stirring at 20 °C (vigorous reaction). The resulting clear pale yellow solution was stirred for an additional 15 min and then poured slowly into ice–water, whereupon, after stirring at 20 °C for ~30 min, crude amide (2.75 g), mp 110–111 °C, was deposited as a white powder. Crystallization gave an analytical sample of **12** (2.6 g) as colorless fluffy needles: NMR (F_3CCO_2H) δ 5.0 (2 H, d, J = 6 Hz), 7.5 (H-5, s).

***N*-[[3-Chloro-5-(1,1-dimethylethyl)-2-hydroxyphenyl]methyl]sulfamide (14).** A solution of 3-chloro-5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde[4] (4.25 g, 20 mmol) in MeOH (100 mL) was added dropwise to a gently refluxing solution of sulfamide (9.6 g, 100 mmol) in MeOH (50 mL). The resulting clear pale yellow solution was refluxed for 2 h and then evaporated to dryness.

The residue was dissolved in HOAc (200 mL) and hydrogenated over PtO_2 (200 mg) in a Parr apparatus (initial pressure = 50 psi) until no further drop in pressure was noted (~40 min). The reaction mixture was filtered, and the residue was triturated with H_2O and then crystallized to give **14** (1.6 g) as tiny colorless crystals: NMR δ 1.2 (9 H, s), 4.1 (2 H, d, J = 6 Hz), 7.13 (H, d, J_{3-5} = 2 Hz), 7.27 (H, d, J_{3-5} = 2 Hz).

3-Chloro-5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde 2-Amidinohydrazone (15). A mixture of 3-chloro-5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde[4] (6.3 g, 30 mmol) and aminoguanidine nitrate dihydrate (5.2 g, 30 mmol) in 40% aqueous EtOH (100 mL) was refluxed for 1 h and treated with 15 N NH_4OH (~50 mL). After the mixture was cooled to 0 °C, the crude solid was collected and crystallized to yield **15** (7.7 g): NMR δ 1.2 (9 H, s), 7.4 (2 H, m), 8.3 (H, s).

3-Chloro-5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde Thiosemicarbazone (16). A mixture of 3-chloro-5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde[4] (1.26 g, 5 mmol) and aminothiourea (550 mg, 6 mmol) in EtOH (60 mL) was refluxed for 1 h and then cooled to 0 °C. The crude solid was collected and crystallized to yield **16** (1.1 g).

***N*-[[3-Chloro-5-(1,1-dimethylethyl)-2-hydroxyphenyl]methyl]pyridinium Chloride Hemiethanolate (18).** Formaldehyde (37%, 20 mL) was added dropwise over 30 min to a stirred mixture of 2-chloro-4-(1,1-dimethylethyl)phenol (18.5 g, 100 mmol) and concentrated HCl (900 mL) at 65 °C. Hydrogen chloride was then bubbled rapidly through the warm mixture with vigorous stirring for 7 h. After the mixture stood at 20 °C for 16 h, the heavy oil was extracted into Et_2O. The ethereal solution was washed with saturated brine. Evaporation and subsequent distillation provided 2-chloro-6-(chloromethyl)-4-(1,1-dimethylethyl)phenol (**17**), 19 g (81%), as a colorless liquid: bp 90–92 °C (0.3 mm); NMR ($CDCl_3$) δ 1.4 (9 H, s), 4.8 (2 H, s), 7.4 (2 H, s). Anal. ($C_{11}H_{14}Cl_2O$) C, H.

A solution of pyridine (800 mg, 10 mmol) in DMF (5 mL) was added dropwise with stirring to a solution of **17** (2.3 g, 10 mmol) in DMF (5 mL). After stirring at 20 °C for 1 h, the solution was diluted with Et_2O (100 mL) to afford **18** (2.9 g). A small sample was crystallized for analysis (very hygroscopic!): NMR δ 1.2 (9 H, s), 6.1 (2 H, s), 7.37 (H, d, J_{3-5} = 2 Hz), 7.72 (H, d, J_{3-5} = 2 Hz), 8.0–8.8 (5 H, m). NMR confirms the presence of 0.5 mol of EtOH.

4-Amino-*N*-[[3-chloro-5-(1,1-dimethylethyl)-2-hydroxyphenyl]methyl]pyridinium Chloride (19). This compound was prepared analogously to **18**, starting with 4-aminopyridine (940 mg, 10 mmol). Crystallization gave **19** (2.9 g): NMR δ 1.2 (9 H, s), 5.5 (2 H, s), 7.0 (H, d, J_{3-5} = 6 Hz), 7.4 (H, d, J_{3-5} = 6 Hz), 8.1–8.8 (4 H, m).

9-Chloro-7-(1,1-dimethylethyl)-4,5-dihydro-1,4-benzoxazepin-3(2*H*)-one (20). Pulverized 2-chloro-*N*-(hydroxymethyl)acetamide[11] (6.15 g, 50 mmol) was added portionwise with stirring to a cold (5 °C) solution of 2-chloro-4-(1,1-dimethylethyl)phenol (9.25 g, 50 mmol) in HOAc–concentrated H_2SO_4 (9:1, v/v, 50 mL). After stirring at 22 °C for 4 h, the resulting clear colorless solution was poured into H_2O (500 mL). The crude amide separated as a white gum, which was extracted into Et_2O, washed successively with H_2O and saturated brine, and dried.

Evaporation of the dried solution gave the crude amide, which was dissolved in acetone (100 mL) and treated with a solution of NaI (7.5 g, 50 mmol) in acetone (100 mL). After refluxing gently for 15 min, the mixture was filtered and the clear filtrate was added dropwise to a vigorously stirred mixture of K_2CO_3 (7.6 g, 55 mmol) in DMF (400 mL) at 65 °C. After stirring for 1.5 h at 65 °C, the mixture was poured into H_2O (3 L). The crude solid was collected and crystallized to yield **20** (3.3 g): NMR δ 1.3 (9 H, s), 4.3 (2 H, d), 4.7 (2 H, s), 7.4–7.6 (2 H, m).

9-Chloro-7-(1,1-dimethylethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin Hydrochloride (21). A solution of Red Al (70% solution in benzene, 8.6 g, 30 mmol) in dry benzene (20 mL) was added slowly to a solution of **20** (3.3 g, 13 mmol) in dry benzene (200 mL) at 22 °C. The clear reaction mixture was stirred at reflux under N_2 for 2.5 h, cooled, and then treated dropwise with H_2O (10 mL), followed by 20% aqueous NaOH (30 mL). The organic layer was separated, washed successively with H_2O and saturated brine, and dried. Evaporation of the dried solution gave the crude free base of **21** (2.6 g) as a viscous oil, which slowly crystallized, mp 80–90 °C. A solution of the free base of **21** in EtOH (20 mL) was treated with concentrated HCl (1 mL) and then evaporated. Trituration of the residue with Et_2O provided crude **21** (2.5 g), mp 230–233 °C. Crystallization provided analytically pure **21** (2.2 g): NMR δ 1.3 (9 H, s), 3.4–3.7 (2 H, m), 4.2–4.6 (4 H, m), 7.5–7.7 (2 H, m).

1,1-Dimethylethyl *N*-[[5-(1,1-dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]carbamate (22). To a solution of **3a** (12 g, 40 mmol) in THF–H_2O (10:3, v/v, 130 mL) was added 1,1-dimethylethyl-2,4,5-trichlorophenyl carbonate (13 g, 44 mmol) and triethylamine (4.4 g, 44 mmol). The resulting pale yellow solution was stirred and heated at 60–65 °C for 24 h, cooled to 20 °C, and diluted with H_2O (700 mL). The solid which precipated was collected, air-dried, triturated with petroleum ether, and dried to give crude **22** (14.3 g), mp 196–197 °C dec. Crystallization afforded analytically pure **22** (12.8 g) as colorless crystals: NMR δ 1.2 (9 H, s), 1.4 (9 H, s), 4.1 (2 H, d, J = 6 Hz), 7.2 (H-3, d, J_{3-5} = 2 Hz), 7.6 (H-5, d, J_{3-5} = 2 Hz).

2-[2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenoxy]acetamide (23). 2-Chloroacetamide (1.02 g, 11 mmol) was dissolved in acetone (10 mL) and treated with a solution of NaI (1.65 g, 11 mmol) in acetone (15 mL). After refluxing gently for 15 min, the mixture was filtered, and the clear filtrate was added dropwise to a vigorously stirred mixture of **22** (4.0 g, 10 mmol), K_2CO_3 (1.52 g, 11 mmol), and DMF (25 mL) at 65 °C. After stirring for 2 h at 65 °C, the mixture was poured into H_2O (500 mL). The crude *t*-Boc intermediate was collected and crystallized from EtOH–H_2O to yield 4 g, mp 168–170 °C.

A solution of the *t*-Boc intermediate in EtOH (100 mL) was treated similarly to *t*-Boc **25**, providing **23** (1.0 g): NMR δ 1.3 (9 H, s), 4.2 (2 H, s), 4.5 (2 H, s), 7.5–8.0 (2 H, unresolved multiplet).

***N*,*N*-Diethyl-2-[2-(aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenoxy]acetamide (24).** This compound was prepared similarly to **23**, starting with 2-chloro-*N*,*N*-diethylacetamide (1.65 g, 11 mmol). Crystallization gave **24** (2.3 g).

2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenyl *N*,*N*-Dimethylsulfamate Hydrochloride (25). To a solution of *N*,*N*-dimethylsulfamoyl chloride (8.7 g, 60 mmol) in dry CH_2Cl_2 (25 mL) maintained under a N_2 atmosphere was added slowly, and with good stirring, a solution of **22** (4 g, 10 mmol) and Et_3N (6 g, 60 mmol) in dry CH_2Cl_2 (100 mL) at 20–25 °C. The resulting reaction mixture was kept under a N_2 atmosphere with stirring for 72 h. Evaporation of the solvent left a residual solid, which was washed with H_2O and extracted into Et_2O. The organic extract was washed with H_2O and saturated brine and dried. Evaporation of the dried solution provided a pale yellow oil, which slowly solidified upon storage at 60–80 °C under high vacuum (0.1 mm) for 2 h to give a colorless solid (6.9 g), mp 114–118 °C. A slurry of the latter in hexane (50 mL) was stirred at 20–25 °C for 0.5 h, cooled to 5 °C, and filtered to yield 3.3 g (63%) of the intermediate 2-[[[[(1,1-dimethylethyl)oxy]carbonyl]amino]methyl]-4-(1,1-dimethylethyl)-6-iodophenyl *N*,*N*-dimethylsulfamate, mp 118–120 °C.

A solution of the *t*-Boc intermediate (3.3 g, 6.4 mmol) in EtOH (150 mL) was treated with concentrated HCl (20 mL) and stirred at 20–25 °C for 3 h. After evaporation of the solution, the residual solid was triturated with Et_2O, collected, washed with Et_2O, and air-dried to give **25** as a colorless solid (2.5 g, 80%), mp 238–239 °C dec. Crystallization of the latter afforded analytically pure **25** (2.3 g) as colorless crystals: NMR δ 1.2 (9 H, s), 3.1 (6 H, s), 4.1 (2 H, br s), 7.75–7.95 (2 H, m).

2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenyl *N*-Ethylsulfamate Hydrochloride (26). This compound was prepared analogously to **25**, starting with *N*-ethylsulfamoyl chloride[12] (8.7 g, 60 mmol). Recrystallization gave **26** (1.35 g): NMR δ 1.2 (3 H, t, J = 8 Hz), 1.3 (9 H, s), 3.4 (2 H, q, J = 8 Hz), 4.2 (2 H, br s), 7.8–7.9 (2 H, m).

2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenyl Methanesulfonate (27). This compound was prepared analogously to **25** starting with methanesulfonyl chloride (4.6 g, 40 mmol) and Et_3N (4 g, 40 mmol). Crystallization gave **27** (2.9 g): NMR δ 1.3 (9 H, s), 3.7 (3 H, s), 4.1 (2 H, s), 7.7–7.9 (2 H, m).

2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenyl Benzenesulfonate (28). This compound was prepared analogously to **25**, starting with benzenesulfonyl chloride (3.5 g, 20 mmol) and Et_3N (2 g, 20 mmol). Crystallization gave **28** (2.5 g): NMR δ 1.3 (9 H, s), 3.9–4.2 (2 H, m), 7.7–8.1 (7 H, m).

1-[5-(1,1-Dimethylethyl)-3-iodo-2-methoxyphenyl]-methylamine Hydrochloride (29). 2,2,2-Trifluoro-*N*-[[5-(1,1-dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]acetamide was prepared by the procedure used for **12**, starting with **3a** (4.5 g, 15 mmol). Crystallization from HOAc–H_2O provided the pure amide as colorless crystals (5 g, 85%), mp 117.5–118.5 °C.

Potassium carbonate (1.9 g, 14 mmol) was added to a solution of the amide in DMF (50 mL), followed immediately by an excess of methyl iodide (3.9 mL, 60 mmol). The mixture was stirred at 50 °C for 4 h, cooled, and poured into H_2O (300 mL). The crude amide separated as a heavy oil, which was extracted into Et_2O and washed successively with H_2O, saturated brine, and dried. Evaporation of the solvent left a residual oil, which was hydrolyzed by refluxing in EtOH–concentrated HCl (3:1, v/v, 20 mL) for 2 h. The residue obtained after evaporation of the solvent was triturated with Et_2O and crystallized to afford **29** (3.2 g): NMR δ 1.3 (9 H, s), 3.8 (3 H, s), 4.1 (2 H, br s), 7.8 (2 H, br s).

2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenyl Hydrogen Sulfate (30). Chlorosulfonic acid (2.3 g, 20 mmol) was added dropwise to a solution of **3a** (3 g, 10 mmol) in CH_2Cl_2 (100 mL) and pyridine (1.6 g, 20 mmol). The colorless solution was stirred at 22 °C for 16 h and then evaporated. The residual solid was washed with H_2O and air-dried to provide 2.9 g of crude **30**, mp 230–232 °C dec. Crystallization afforded analytically pure **30** (2.3 g) as a colorless solid: NMR δ 1.26 (9 H, s), 4.16 (2 H,

(11) Einhorn, A.; Mauermayer, T. *Justus Liebigs Ann. Chem.* **1905**, *343*, 282.

(12) Hansen, N. C. *Acta Chem. Scand.* **1963**, *17*, 2141.

br s), 7.44 (H-3, d, J_{3-5} = 2 Hz), 7.72 (H-5, d, J_{3-5} = 2 Hz).

Alternatively, **30** may be prepared by adding pyridine–sulfur trioxide complex (1.6 g, 10 mmol) to a solution of the amine (3 g, 10 mmol) in THF (75 mL) and stirring at 20 °C for 72 h after first forming a clear solution by heating initially to reflux. The white powder was filtered off and crystallized to provide **30** (1.2 g, 30%), mp 231–232 °C dec.

***N*-[[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]guanidine (31).** A solution of **3a** (2.45 g, 8 mmol) and *S*-methylthiourea hydroiodide (2.0 g, 9 mmol) in EtOH (15 mL) was refluxed for 16 h and then poured into H_2O (200 mL) containing concentrated NH_4OH (5 mL). The crude guanidine was triturated with Et_2O (50 mL) and then with acetone–Et_2O (1:1, v/v, 30 mL) to afford **31** (1.8 g), mp 186–190 °C dec, as a pale yellow powder. A sample was crystallized for analysis: NMR δ 1.2 (9 H, s), 4.1 (2 H, br s), 7.1 (H, d, J_{3-5} = 3 Hz), 7.5 (H, d, J_{3-5} = 3 Hz).

***N*-[[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]urea (32).** A solution of KCNO (1.0 g, 12 mmol) in H_2O (10 mL) was added slowly with agitation to a warm mixture of **3** (3.4 g, 10 mmol), H_2O (20 mL), and EtOAc (40 mL). After the solution was cooled to ambient temperature, the layers were separated. The EtOAc layer was dried over Na_2SO_4, evaporated to ~20 mL, and cooled to 5 °C. The crude urea was crystallized to yield **32** (1.6 g) as a pale yellow solid.

5-[[[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]amino]-3,4-dihydro-2*H*-pyrrole Hydrochloride (33). A solution of **3** (3.4 g, 10 mmol) and 3,4-dihydro-5-methoxy-2*H*-pyrrole[13] (1.5 g, 15 mmol) in anhydrous MeOH (10 mL) was refluxed for 1 h, then evaporated to one-half volume, and diluted with concentrated HCl (2 mL). After the mixture was cooled to −20 °C, **33** (3.8 g) was obtained, mp 210–211 °C dec. A sample was crystallized for elemental analysis: NMR δ 1.2 (9 H, s), 1.7–2.4 (2 H, m), 2.83 (2 H, t, J = 5 Hz), 3.57 (2 H, t, J = 5 Hz), 4.6 (2 H, s), 7.53 (H, d, J = 2 Hz), 7.73 (H, d, J = 2 Hz).

2-[[[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]amino]-4,5-dihydro-1*H*-imidazole (34). This compound was prepared analogously to **31**, starting with 4,5-dihydro-2-(methylthio)-1*H*-imidazole hydriodide[14] (2.2 g, 9 mmol). Crystallization gave **34** (0.9 g) as a light yellow solid: NMR δ 1.2 (9 H, s), 3.5 (4 H, s), 4.1 (2 H, s), 7.1 (H, d, J = 3 Hz), 7.5 (H, d, J = 3 Hz).

2-[[[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]amino]-4,5-dihydrooxazole (35). A mixture of **3a** (2.0 g, 6.5 mmol) and 4,5-dihydro-2-(methylthio)oxazole[15] (0.85 g, 7 mmol) in EtOH (25 mL) was stirred at reflux for 16 h and then cooled to 0 °C. The crude solid was collected and crystallized to give **35** (1.05 g): NMR δ 1.2 (9 H, s), 3.6 (2 H, t), 4.2 (4 H, m), 7.2 (H, d, J = 2 Hz), 7.6 (H, d, J = 2 Hz).

2-[[[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]amino]-4,5-dihydrothiazole (36). This compound was prepared identically to **35**, starting with 4,5-dihydro-2-(methylthio)thiazole[16] (1.1 g, 8 mmol). Crystallization gave **36** (1.2 g).

1-[[[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]methyl]amino]tetrazole (37). A mixture of **3** (1.7 g, 5 mmol), NaN_3 (0.9 g), ethyl orthoformate (4 mL), and HOAc (6 mL) was heated on a steam bath for 3 h and then evaporated to dryness. The residue was triturated with H_2O and then crystallized to yield **37** (1 g): NMR δ 1.2 (9 H, s), 5.8 (2 H, s), 7.4 (H, d, J = 2 Hz), 7.8 (H, d, J = 2 Hz), 9.4 (H, s).

4-(1,1-Dimethylethyl)-2-[(methylamino)methyl]-6-iodophenol (39). To a solution of **3** (51.3 g, 150 mmol) in HOAc–H_2O (11:3, v/v, 1.4 L) was added a solution of hexamethylenetetramine (22.0 g, 158 mmol) in H_2O (75 mL) to provide a clear solution, which was stirred at reflux for 4 h. The reaction mixture was treated with 4.5 N HCl (225 mL) and then stirred at reflux for an additional 15 min. Upon slow cooling to −10 °C, 5-(1,1-dimethylethyl)-2-hydroxy-3-iodobenzaldehyde (**38**) was deposited as pale yellow crystals (20.4 g, 45%), mp 76–78 °C. Sublimation provided an analytical sample of **38**, mp 77 °C. Anal. ($C_{11}H_{13}IO_2$) C, H.

A solution of **38** (6.1 g, 20 mmol) in warm EtOH (35 mL) was treated with 40% aqueous methylamine (2.0 g, ~25 mmol) and stirred at 20 °C before being poured into H_2O (300 mL). The crude imine (**39a**) was collected (4.6 g), mp 102–108 °C, and a sample was crystallized from MeOH–H_2O for analysis, mp 109–111 °C. Anal. ($C_{12}H_{16}INO$) C, H, N.

The crude imine (3.2 g, 10 mmol) was dissolved in MeOH (150 mL) and treated with $NaBH_4$ (450 mg, 12 mmol). After a few hours, the solution was evaporated, and the residue was distributed between $CHCl_3$ and H_2O. The organic layer was washed with H_2O and brine and dried ($MgSO_4$). Evaporation and subsequent crystallization of the residue afforded **39** (1.3 g): NMR ($CDCl_3$) δ 1.3 (9 H, s), 2.4 (3 H, s), 3.9 (2 H, s), 6.95 (H, d, J_{3-5} = 2 Hz), 7.6 (H, d, J_{3-5} = 2 Hz).

4-(1,1-Dimethylethyl)-2-[(butylamino)methyl]-6-iodophenol Hydrochloride (40). This compound was prepared analogously to **39**, starting with *n*-butylamine (1.55 g, 21 mmol). Crystallization gave **40** (3.6 g) as colorless needles.

6-(1,1-Dimethylethyl)-3,4-dihydro-8-iodo-2,2-dioxo-1,2,3-benzoxathiazine (41). To a solution of sulfamoyl chloride [13.8 g, 120 mmol; prepared by adding 2.9 mL of 12 N HCl dropwise to 10.5 mL of chlorosulfonyl isocyanate, keeping the internal temperature between −10 and −30 °C (violent reaction), removing the cooling bath, and after 20 min heating at 40 °C for 1 h, all under an atmosphere of N_2] in dry CH_2Cl_2 (75 mL) was added a solution of **38** (6 g, 20 mmol) and Et_3N (12.1 g, 120 mmol) in dry CH_2Cl_2 (100 mL) dropwise with stirring at 20 °C. After the addition was complete, the resulting reaction mixture was stirred at 20 °C for 3 days. The solvent was evaporated, and the sticky residue was partitioned between Et_2O and 2 N HCl. The organic layer was washed with H_2O and saturated brine, dried (Na_2SO_4), and filtered. Evaporation of the filtrate provided an oily residue (6 g), which was chromatographed on silica gel (300 g). Elution with C_6H_6 (840 mL) gave recovered **38** (2.2 g, 37% recovery). Continued elution with C_6H_6 (500 mL) provided an impure solid, which was triturated with hexane (20 mL) to afford 6-(1,1-dimethylethyl)-8-iodo-2,2-dioxo-1,2,3-benzoxathiazine (**41a**) as a pale yellow solid (1.0 g, 14%), mp 130–134 °C. Crystallization from hexane–benzene (9:1, v/v) gave an analytical sample of **41a**, mp 135–136 °C. Anal. ($C_{11}H_{12}INO_3S$) C, H, N.

To a solution of **41a** (2 g, 5.5 mmol) in CH_3OH (75 mL) was added $NaBH_4$ (210 mg, 5.5 mmol) portionwise with stirring at 20 °C. The resulting solution was stirred at 20 °C for 16 h and then concentrated in vacuo, leaving a solid residue which was triturated with H_2O (50 mL). The solid was collected and crystallized to give **41** (1.7 g, 85%) as colorless crystals: NMR δ 1.2 (9 H, s), 4.5 (2 H, s), 7.28 (H, d, J = 2 Hz), 7.72 (H, d, J = 2 Hz).

***N*,*N*,*N*-Trimethyl-1-[5-(1,1-dimethylethyl)-3-iodo-2-methoxyphenyl]methanaminium Iodide (42).** Potassium carbonate (2.8 g, 20 mmol) was added to a solution of **3a** (3 g, 10 mmol) in DMF (40 mL), followed immediately by a large excess of methyl iodide (20 mL). The mixture was stirred at 20 °C for 16 h, diluted with Et_2O (150 mL), and filtered, and the crystals were washed with Et_2O and then H_2O. Crystallization gave **42** (2.6 g): NMR δ 1.3 (9 H, s), 3.1 (9 H, s), 3.8 (2 H, s), 7.7 (H, d, J_{3-5} = 2 Hz), 7.9 (H, d, J_{3-5} = 2 Hz).

6-(1,1-Dimethylethyl)-8-iodo-2-oxo-2*H*-3,4-dihydro-1,3-benzoxazine (43). *N*,*N*′-Carbonyldiimidazole (0.8 g, 5 mmol) was added to a cold (0 °C) solution of **3a** (1.5 g, 5 mmol) in THF (25 mL). After stirring at 20 °C for 16 h, the solution was evaporated, and the residue was distributed between $CHCl_3$ and 5% HCl. The organic layer was washed with H_2O and brine and dried ($MgSO_4$). Evaporation and subsequent crystallization of the residue provided **43** (1.2 g) as colorless, sparkling platelets: NMR δ 1.2 (9 H, s), 4.4 (2 H, s), 7.30 (H, d, J = 2 Hz), 7.67 (H, d, J = 2 Hz).

2-[[(2-Aminoethyl)amino]methyl]-4-(1,1-dimethylethyl)-6-iodophenol Dihydrochloride (45). A solution of 2-(aminomethyl)-4-(1,1-dimethylethyl)phenol[3] (4.5 g, 25 mmol) in ethylenediamine (150 mL) was refluxed under N_2 for 24 h. The residue, after evaporation of excess ethylenediamine, was crystallized from EtOH–concentrated HCl (1:1, v/v, 40 mL) to provide 2-[[(2-aminoethyl)amino]methyl]-4-(1,1-dimethylethyl)phenol

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dihydrochloride (**45a**; 5.2 g, 70%), mp 233–233.5 °C dec. Anal. ($C_{13}H_{22}N_2O\cdot 2HCl$) C, H, N. Iodination with ICl in dilute HCl provided **45** (4.9 g): NMR δ 1.2 (9 H, s), 3.3 (4 H, br s), 4.5 (2 H, br s), 7.6 (2 H, br s).

1-[5-(1,1-Dimethylethyl)-2-hydroxy-3-iodophenyl]-methanesulfamic Acid (46). A solution of 5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde[17] (3.56 g, 20 mmol) and ammonium sulfamate (2.28 g, 20 mmol) in anhydrous MeOH (100 mL) was stirred and heated at reflux for 1.5 h. The resulting clear, yellow solution was cooled to 5 °C, treated with $NaBH_4$ (0.76 g, 20 mmol) added portionwise over 5 min, and stirred at 20 °C for 20 h. Evaporation of the solvent left a residue, which was triturated with H_2O (150 mL). The resulting mixture was cooled to 0 °C, cautiously acidified with concentrated HCl, and filtered to give 2.3 g (44.3%) of 1-[5-(1,1-dimethylethyl)-2-hydroxyphenyl]-methanesulfamic acid (**46a**), mp 260–262 °C dec. Crystallization from Et_2O–THF afforded an analytical sample as colorless crystals, mp 264–265 °C dec. Anal. ($C_{11}H_{17}NO_4S$) C, H, N.

Iodination with ICl in H_2O–THF (5:1, v/v, 90 mL) provided **46** (1.9 g): NMR δ 1.2 (9 H, s), 4.3 (2 H, s), 4.10 (H, d, J = 2 Hz), 4.33 (H, d, J = 2 Hz).

***N,N,N*-Trimethyl-1-[5-(1,1-dimethylethyl)-2-hydroxy-3-iodophenyl]methanaminium Iodide (48).** Methyl iodide (5 mL) was added to a solution of **46** (3.3 g, 10 mmol) in DMF (5 mL). After standing at 20 °C for 16 h, the cloudy solution was evaporated, and the gummy residue was crystallized to give **48** (3.4 g): NMR δ 1.2 (9 H, s), 3.1 (9 H, s), 4.8 (2 H, s), 4.25 (H, d, J = 2 Hz), 4.50 (H, d, J = 2 Hz).

Ethyl [2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenoxy]acetate Hydrochloride (49). This compound was prepared similarly to **20**, starting with 4-(1,1-dimethylethyl)-2-iodophenol[3] (13.8 g, 50 mmol). The crude amide was collected, air-dried, and hydrolyzed in EtOH–concentrated HCl (4:1, v/v, 250 mL) heated at reflux for 3 h. The residue obtained by evaporation was triturated with Et_2O and crystallized to provide **49** as colorless needles (3.5 g).

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Supplementary Material Available: Intravenous dog diuretic data providing the milliequivalent per minute values for Na^+, K^+ and Cl^-, along with urine volume and creatinine clearance vs. controls and time of maximum effect (2 pages). Ordering information is given on any current masthead page.

Notes

Alkaline Phosphatase Inhibition by a Series of Pyrido[2,1-*b*]quinazolines: A Possible Relationship with Cromolyn-like Antiallergy Activity

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Several known antiallergic agents, including cromolyn sodium and a series of pyrido[2,1-*b*]quinazolines, inhibit human alkaline phosphatase (ALP), a membranal enzyme associated with calcium uptake in certain tissues. A comparison of ALP and rat passive cutaneous anaphylaxis (PCA) inhibition indicates that PCA inhibition may be associated with drug–ALP interaction, since ALP inhibition potency parallels PCA inhibitory activity. The unpredictability of the PCA test toward clinical efficacy could in part be related to the uncompetitive nature of these inhibitors. The results also suggest that alkaline phosphatase may be a component of membranal calcium channels.

During the past several years, many potential antiallergy series have been reported in the literature. Except for cromolyn sodium, none have been proven efficacious enough in clinical trials to warrant introduction onto the market.[1] A major problem with the discovery of better antiallergy agents has been the apparent lack of a pharmacological model which can predict efficacy in humans. Also, a poor understanding as to the mechanism of cromolyn sodium action has contributed to this problem.

Calcium ions appear to play a major role in allergic mediator release. Several mediator release inhibitors, including bufrolin, cromolyn sodium, doxantrazole, and lodoxamide, were reported to block antigen-induced calcium ion uptake and subsequent histamine release.[2-4]

Recently, a series of structurally diverse mediator release inhibitors were reported to inhibit human leukocyte alkaline phosphatase (ALP), a membranal enzyme associated with calcium ion uptake in certain tissues.[5] We wish to report that this same series has also been evaluated against human placental alkaline phosphatase. In addition, a series of pyrido[2,1-*b*]quinazolines possessing antiallergy activity was also evaluated against human placental alkaline phosphatase. Activities as inhibitors of the enzyme and rat PCA, an allergy model, were compared for a possible relationship.

Chemistry. The synthesis of the 11-oxo-11*H*-pyrido[2,1-*b*]quinazolinecarboxylic acids in Table II has previously been reported.[6] The synthesis of the tetrazole analogues was accomplished in the following manner. Equal quantities of the substituted 2-aminobenzoic acid and 6-chloronicotinamide were reacted in refluxing ethanol

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