Table IV. Local Anesthetic Activity and Acute Toxicity of 2,3-Diaminopropionanilides

	duration of block,[a] min					LD_{50},[b] mg/kg	
no.	concn:[c] 0.125%	0.25%	0.5%	1.0%	2.0%	ip	iv
16		91 ± 11	66 ± 13	178 ± 54	184 ± 12[d]	70 (41-93)	
17	80 ± 13	116 ± 13	260 ± 52	days[e]	days[e]		11 (9-13)
18	77 ± 4	87 ± 6	100 ± 14	145 ± 19	265 ± 39		20 (16-23)
19	78 ± 3	105 ± 17	136 ± 18	189 ± 16	days[e]	94 (73-120)	
20	140 ± 19	138 ± 11	176 ± 14	days[e]	days[e]	81 (64-101)	
21	162 ± 5	151 ± 4	157 ± 10	150 ± 31	184 ± 24	102 (72-143)	
22	96 ± 1	107 ± 22	227 ± 49	days[e]	days[e]	66 (50-83)	
23	94 ± 9	125 ± 5	166 ± 15	273 ± 35	days[e]	81 (53-113)	
24	NB[f]	NB[f]	83 (2/10)	133 ± 22	147 ± 19		
25	72 ± 8	72 ± 8	102 ± 30	138 ± 25	193 ± 38		
1		102 ± 15	123 ± 10	162 ± 39		102 (73-142)	26 (23-33)
2			44 ± 8	79 ± 19			94 (81-106)
34		110 ± 5	146 ± 4	184 ± 10	days[e]		
35	156 ± 41	222 ± 54	279 ± 16			56 (47-65)	7 (6-8)

[a] Rat sciatic nerve block, mean plus or minus standard deviation. [b] Intraperitoneal or intravenous injection into female mice, LD_{50}, mg/kg (measured as base), with 95% confidence limits in parentheses. [c] Concentration as base. All solutions contained 1:100 000 epinephrine. [d] 5/10 legs, 5 legs "blocked" for days. [e] Required days for complete recovery of normal motor function. [f] No blocks (0/10).

groups of 10 mice. During a 20-min period the mice were observed for overt signs of toxicity (ataxia, convulsions, loss of righting reflex, or death). The mice were then placed individually in an atmosphere saturated with chloroform vapor until respiration ceased. Immediately thereafter, the thorax was opened and the presence or absence of tachycardia was determined visually. If coordinated ventricular contractions were observed, the mouse was considered to be "protected" from the arrhythmogenic effects of chloroform. At least three doses of drug were chosen to give low, intermediate, and high degrees of protection against fibrillation. From these data, the ED_{50} and the 95% Fieller limits for protection, ataxia, and convulsion were calculated according to the logit chi-square method of Berkson.[15]

Local anesthetic activity was evaluated in rats by means of the sciatic nerve block method described by Camougis and Takman.[16] Most compounds were tested at three to five concentrations with 1:100 000 epinephrine. Precisely 0.2 mL of test solution was injected into the mid-thigh region so as to deposit the solution around the sciatic nerve trunk. Each animal was examined at frequent intervals to ascertain onset of and recovery from motor block. Five animals were used at each concentration of test compound. Since both hind limbs were injected, there was a possible maximum of 10 blocks in each group of five rats.

LD_{50} values were determined[17] by administering the compounds intravenously or intraperitoneally to groups of female CRCD mice weighing between 20 and 25 g. Test compounds were dissolved in isotonic saline or distilled water and injected into a tail vein or intraperitoneally. LD_{50} values and 95% confidence limits were calculated by means of the minimum logit chi-square method.[15]

Acknowledgment. We thank B. Bosse, D. Charron, L. Dadah, R. Heideger, W. R. Millington, and Dr. S. Waraszkiewicz for skillful technical assistance and Dr. E. Byrnes for valuable discussions.

2-(Aminomethyl)phenols, a New Class of Saluretic Agents. 3. Effects of Functional Group Reorientation and Modification[1]

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A series of modified 2-(aminomethyl)phenols was synthesized and tested orally in rats for saluretic and diuretic effects. Intravenous dog data are included as supplementary material to show that the diuretic responses, or lack thereof, may be obtained in a second species. Reorientation of the 2-(aminomethyl) group either meta or para to the hydroxyl substituent resulted in loss of diuretic effects. Similarly, replacement of either the phenolic hydroxyl or the aminomethyl group with other functional moieties substantially diminished saluretic effects.

Recently, we reported[3] on a series of 2-(aminomethyl)-phenols which were shown to possess a high order of diuretic activity in rats and dogs. This report describes the effects of (1) reorientation of the 2-(aminomethyl) group relative to that of the phenolic hydroxyl group and (2) replacement of either the phenolic hydroxyl or the 2-

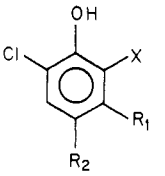
(1) Portions of this work were presented in August, 1977, at the 174th National Meeting of the American Chemical Society. See "Abstracts of Papers", 174th National Meeting of the American Chemical Society, Chicago, Il, 1977; American Chemical Society: Washington, DC, 1977, and *ACS Symp. Ser.* **1978**, *83*, 93–124.

(2) Deceased, May 31, 1977.

(3) For part 1, 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.

0022-2623/81/1824-1063$01.25/0

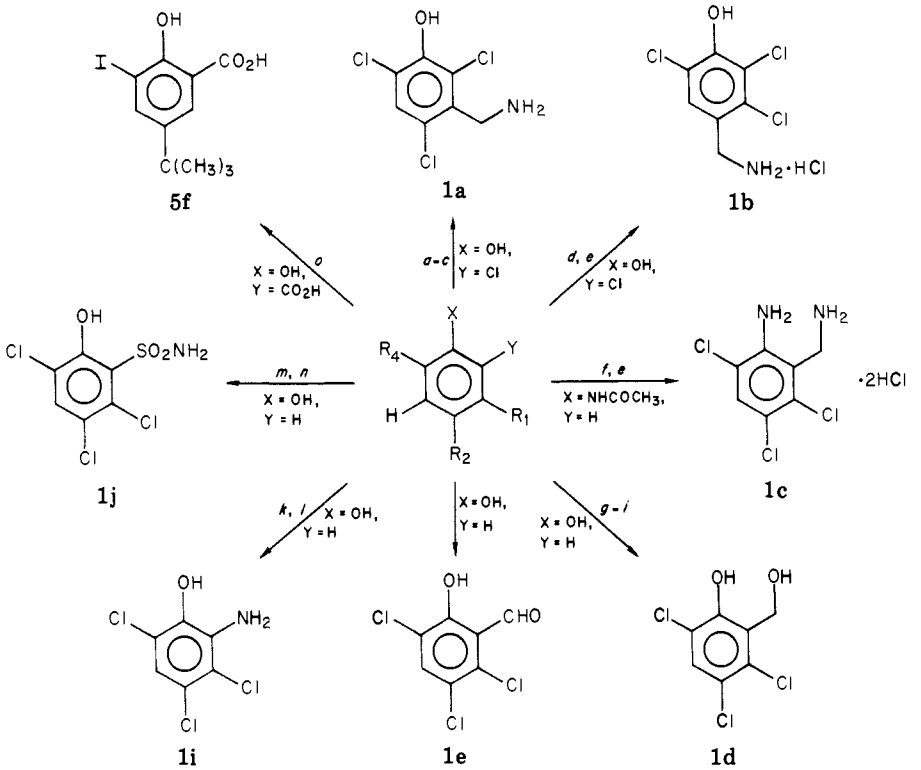
Table I. Orientation Effects



compd	X	R_1	R_2	method	yield, %	recrystn solvent	mp, °C dec	formula[b]	score[a] rat,[c] po	score[a] dog,[d] iv
1	CH_2NH_2	Cl	Cl	*e*	51	EtOH/HCl	244.5-245.0	$C_7H_6Cl_3NO \cdot HCl$	3	5[f]
1a	Cl	CH_2NH_2	Cl	*g, h*	30	DMF	240-241	$C_7H_6Cl_3NO$[i]	0	0[j]
1b	Cl	Cl	CH_2NH_2	*k, l*	45	EtOH/HCl	219-220	$C_7H_6Cl_3NO \cdot HCl$	0	0
furosemide									3	6[m,n]
hydrochlorothiazide									2	1[f]

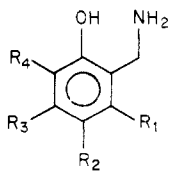
[a] For testing protocols and scoring system, see ref 3. [b] Analytical results are within ±0.4% of the theoretical values. [c] Score is for geometric mean of three animals per cage, three cages per dose. [d] Score is for a single dog at 5 mg/kg stat (weight range 15.2-21 kg) unless otherwise designated. [e] Reference 3. [f] Score is the average value of three dogs. [g] Catalytic reduction of corresponding oxime, method C, ref 3. [h] See Hodgson, H. H.; Beard, H. G. *J. Chem. Soc.* 1926, 147, for preparation of the oxime. [i] Anal. Calcd: C, 37.12; N, 6.18. Found: C, 36.59; N, 5.71. [j] 10 mg/kg. [k] Amidoalkylation of the corresponding phenol and subsequent hydrolysis, method A_2, ref 3. [l] For preparation of requisite phenol, see Experimental Section. [m] Score is the average value of two dogs. [n] 1 mg/kg.

Scheme I



[a] Cl_2, HOAc. [b] $HONH_2$, EtOH. [c] H_2, Rh/C. [d] $ClCH_2CONHCH_2OH$, H_2SO_4. [e] HCl, EtOH. [f] $ClCH_2CONHCH_2OH$, 30% oleum. [g] CH_2O, c-$NH(CH_2CH_2)_2O$, EtOH. [h] $(CH_3CO)_2O$, Δ. [i] CH_3OH, $C_6H_5SO_3H$, Δ. [j] $Ca(OH)_2$, Na_2CO_3, $CHCl_3$, H_2O. [k] HNO_3, HOAc. [l] Fe, CH_3OH, HCl. [m] $ClSO_3H$, $SOCl_2$. [n] NH_3 (liq). [o] ICl, HOAc, Δ.

(aminomethyl) group by other functional groups. Compounds 1-5, which exhibit modest (2) to excellent (4 and 5) saluretic effects in rats and dogs, were chosen from those 2-(aminomethyl)phenols described earlier[3] as models for demonstrating the effects of these structural modifications.

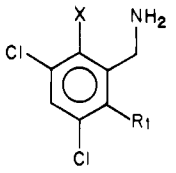


1, $R_1 = R_2 = R_4 = Cl$; $R_3 = H$
2, $R_1 = R_3 = H$; $R_2 = R_4 = Cl$
3, $R_1 = R_3 = OCH_3$; $R_2 = R_4 = Cl$
4, $R_1 = R_3 = H$; $R_2 = t\text{-}C_4H_9$; $R_4 = Cl$
5, $R_1 = R_3 = H$; $R_2 = t\text{-}C_4H_9$; $R_4 = I$

Chemistry. The compounds prepared in this study are listed in Tables I-III and their syntheses are summarized in Schemes I and II. Each compound depicted in Scheme I was prepared from the corresponding phenol, with exception of **1a** (hydroxybenzaldehyde), **1c** (trichloroacetanilide), and **5f** (*tert*-butylsalicylic acid). The synthesis of **1d**, **1i**, and **3e** are described in the literature and require no further comment.[4] Compounds **1a,b,e** and **5f** were

(4) Footnotes *e*, *i*, and *k* in Table III, respectively.

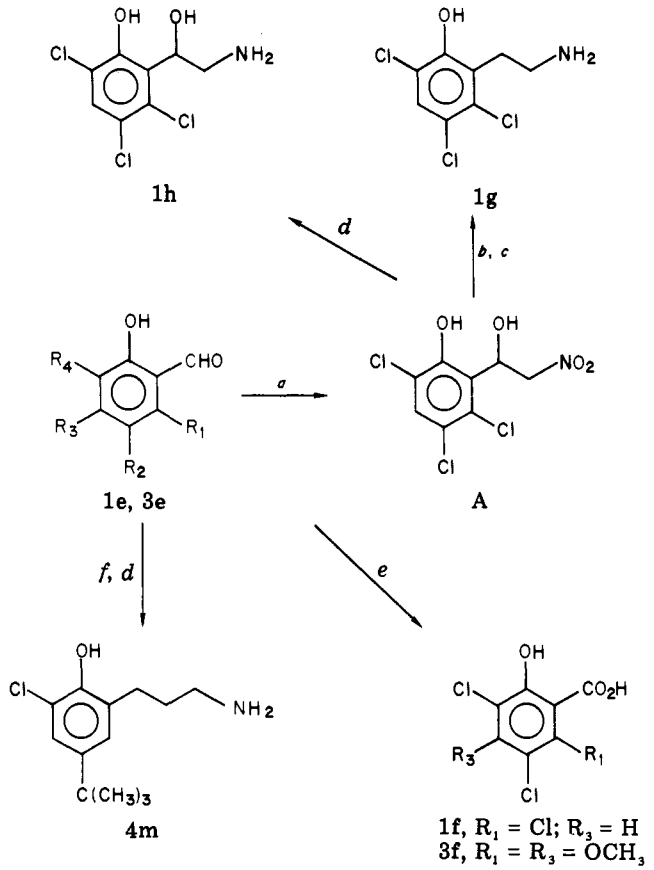
Table II. Effects of Phenolic Hydroxyl Replacement



compd	X	R_1	method	yield, %	recrystn solvent	mp, °C	formula[b]	score[a] rat,[c] po	score[a] dog,[d] iv
1c	NH_2	Cl	*e*	20[f]	EtOH/HCl	295-296	$C_7H_7Cl_3N_2 \cdot 2HCl$	±	0[g]
2	OH	H	*h*	94	EtOH/H_2O	196.5-197 dec	$C_7H_7Cl_2NO$	2	±
2k	H	H	*i*		MeOH/Et_2O	267-269	$C_7H_7Cl_2N \cdot HCl$	0	0[g]

[a-d] Footnotes *a-d*, Table I. [e] See Experimental Section. [f] Represents yield of last step only. [g] Score is the average value of two dogs. [h] Reference 3. [i] Commercially available as the free amine.

Scheme II



[a] CH_3NO_2, NaOH. [b] $SOCl_2$, NaOAc. [c] $LiAlH_4$, Et_2O. [d] H_2, Rh/C. [e] AgO. [f] $Ph_3P{=}CHCN$, PhH.

prepared by the general procedures described in part I[3] of this series or slight modification thereof; e.g., the synthesis of **1c** was catalyzed with 30% oleum instead of concentrated H_2SO_4. Chlorosulfonation of 2,4,5-trichlorophenol, followed by treatment with anhydrous ammonia, provided **1j** in low yield.

Scheme II illustrates the further modification of **1e** and **3e**. Oxidation with AgO proceeded smoothly to give **1f** and **3f** in moderate to low yields. Condensation of **1e** with nitromethane provided nitro alcohol A, which served as a common intermediate to **1g** (dehydration followed by $LiAlH_4$ reduction) and **1h** (catalytic reduction). Aminopropylphenol **4m** was prepared by condensation of the cyanomethylidene Wittig reagent with 3-chloro-5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde [prepared by formylation of 2-chloro-4-(1,1-dimethylethyl)phenol with $(CH_2)_6N_4$ in TFA[5]] and subsequent catalytic reduction.

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[6] 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 show that the diuretic responses, or lack thereof, may be obtained in a second species. Data illustrating the saluretic effects resulting from reorientation of the 2-(aminomethyl) group are shown in Table I, along with that of furosemide and hydrochlorothiazide for comparative purposes. The reorientation of the 2-(aminomethyl) group to either a 3 (meta, **1a**) or 4 (para, **1b**) relationship with that of the phenolic hydroxyl group while simultaneously transposing the 3- or 4-chloro substitutent with the aminomethyl group resulted in a total loss of saluretic effects.

The influences of phenolic hydroxyl group replacement on saluretic effects are presented in Table II. As the data indicate, replacement of the hydroxyl group by either an amino (**1c**) or a hydrogen (**2k**) group essentially eliminates saluretic effects.

Finally, the data recorded in Table III illustrate the effects on saluresis caused by replacement of the 2-(aminomethyl) group with other functional moieties. These data show that modification of the aminomethyl group, e.g., by homologation (**1g**) or simultaneous α-substitution and homologation (**1h**), leads to substantial diminution of saluretic effects. Furthermore, replacement of the aminomethyl substituent with the hydroxymethyl (**1d**), formyl (**1e**, **3e**), carboxyl (**1f**, **3f**), amino (**1i**), sulfamoyl (**1j**), or 3-aminopropyl (bishomologation, **4m**) groups essentially eliminated saluretic effects, with the exception of hydroxy acid **5f**, which elicited a slight saluretic effect in dogs.

Conclusion

The oral rat data presented above, although not constituting a rigorous structure–activity relationship study, indicate that (1) reorientation of the 2-(aminomethyl) group to any relationship with the phenolic hydroxyl group other than a vicinal one and (2) replacement of either the phenolic hydroxyl or the aminomethyl groups with other functionalities lead to either a marked decrease or a total loss of saluretic effects.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. ^1H NMR spectra were recorded on a

(5) General formylation procedure of Smith, W. E. *J. Org. Chem.* **1972**, *37*, 3972.
(6) Footnote *a*, Table I.

Table III. Effects of Aminomethyl Replacement

compd	X	R_1	R_2	R_3	R_4	method	yield, %	recrystn solvent	mp, °C	formula[b]	score[a] rat,[c] po	score[a] dog,[d] iv
1d	CH_2OH	Cl	Cl		Cl	*e*	56[f]	C_6H_6/C_6H_{14}	120–121	$C_7H_5Cl_3O_2$	0	0[g]
1e	CHO	Cl	Cl		Cl	*h*	19	EtOH/H_2O	114–116	$C_7H_3Cl_3O_2$	0	0
1f	CO_2H	Cl	Cl		Cl	*i*	58	C_6H_6	205–207	$C_7H_3Cl_3O_3$	0	
1g	$(CH_2)_2NH_2$	Cl	Cl		Cl	*h*	36[f]	EtOH/HCl	299–303 dec	$C_8H_8Cl_3NO\cdot HCl$	1	1
1h	$CH(OH)CH_2NH_2$	Cl	Cl		Cl	*h*	39[f]	EtOH/HCl	204–206 dec	$C_8H_8Cl_3NO_2\cdot HCl$	0	1
1i	NH_2	Cl	Cl		Cl	*j*	70[f]	*k*	124–125	$C_6H_4Cl_3NO$	0	
1j	SO_2NH_2	Cl	Cl		Cl	*h*	10	EtOH/H_2O	190–192	$C_6H_4Cl_3NO_3S$	0	
3	CH_2NH_2	OCH_3	Cl	OCH_3	Cl	*l*	75	EtOH/Et_2O	174–175 dec	$C_9H_{11}Cl_2NO_3\cdot HCl$	5	6
3e	CHO	OCH_3	Cl	OCH_3	Cl	*l*	88	*k*	121–123	$C_9H_8Cl_2O_4$	0	0
3f	CO_2H	OCH_3	Cl	OCH_3	Cl	*m*, *i*	37	EtOH/H_2O	177–178 dec	$C_9H_8Cl_2O_5$	0	0
4	CH_2NH_2		*t*-C_4H_9		Cl	*l*	44	EtOH/HCl	251–251.5 dec	$C_{11}H_{16}ClNO\cdot HCl$	6	6[g]
4m	$(CH_2)_3NH_2$		*t*-C_4H_9		Cl	*h*	45[f]	EtOH/H_2O	156–160	$C_{13}H_{20}ClNO$[n]		0[g]
5	CH_2NH_2		*t*-C_4H_9		I	*l*	81	EtOH/HCl	200–201 dec	$C_{11}H_{16}INO\cdot HCl$	6	4[g,o]
5f	CO_2H		*t*-C_4H_9		I	*h*	72	HOAc/H_2O	226–228	$C_{11}H_{13}IO_3$	0	1[g]

[a–d] Footnotes *a–d*, Table I. [e] Arct, J.; Eckstein, Z.; Gwiazdecka, I.; Krzywicka, H. *Przemysl. Chem.* **1962**, *41*, 582; *Chem. Abstr.* **1963**, *59*, 608e. [f–g] Footnotes *f–g*, Table II. [h] Footnote *e*, Table II. [i] General method for oxidation of corresponding aldehydes via AgO by Pearl, I. A. *Org. Synth.* **1963**, *4*, 1972. [j] Katz, L.; Cohen, M. S. *J. Org. Chem.* **1954**, *19*, 758; mp 125–127 °C. [k] Sublimed. [l] Reference 3. [m] Grove, J. F.; MacMillan, J.; Mulholland, T. P. C.; Zealley, J. *J. Chem. Soc.* **1952**, 3967; mp 181–182 °C. [n] Anal. Calcd: C, 64.58. Found: C, 63.84. [o] 1 mg/kg.

Varian A-60 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analysis 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. Petroleum ether with a boiling point range of 30–60 °C was used. All starting materials were commercially available unless noted otherwise.

2-(Aminomethyl)-3,4,6-trichloroaniline Dihydrochloride (1c). 2,4,5-Trichloroaniline (9.8 g, 0.05 mol) was stirred on a steam bath in acetic anhydride (50 mL) for 1 h and then cooled to −20 °C. The crude acetamide which separated was collected, dried, and crystallized from HOAc–H_2O to provide the amide as pale purple needles (10.4 g, 87%), mp 187–187.5 °C (lit.[7] mp 190 °C).

A finely pulverized mixture of the acetamide (4.8 g, 0.02 mol) and 2-chloro-*N*-(hydroxymethyl)acetamide[8] (2.5 g, 0.02 mol) was added portionwise with stirring to 30% fuming H_2SO_4 (30 mL) at 5 °C. After stirring at 22 °C for 70 h, the resulting clear, purple reaction solution was poured onto ice. The crude amide separated as a white powder, which was collected, air-dried, and hydrolyzed in EtOH–concentrated HCl (3:1; v:v; 400 mL) heated at reflux for 1.5 h. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was crystallized to give 1c (1.2 g): ^1H NMR (D_2O) δ 4.4 (2 H, s, CH_2), 7.3 (H-5, s).

2,3,5-Trichloro-6-hydroxybenzaldehyde (1e). To a mixture of $Ca(OH)_2$ (105 g), Na_2CO_3 (115 g), and 2,4,5-trichlorophenol (63 g, 0.32 mol) in H_2O (800 mL) was added dropwise $CHCl_3$ (120 g, 1.0 mol) with stirring over 1 h at 65 °C. Heating and stirring were continued for an additional 16 h. The mixture was acidified with concentrated HCl (pH 2) and steam distilled. When the distillate cooled, the yellow solid that separated was collected and crystallized to afford 1e (13.4 g): ^1H NMR ($CDCl_3$) δ 7.7 (H-4, s), 10.4 (H, s, CHO).

2-(2-Aminoethyl)-3,4,6-trichlorophenol Hydrochloride (1g). A 10% aqueous NaOH solution (10 mL) was added dropwise to a stirred solution of 1e (2.3 g, 10 mmol) and nitromethane (2.5 mL) in DMF (20 mL) at 0 °C. The ice bath was removed and the reaction mixture was stirred at room temperature for 2 h before quenching with ice-cold 1 N HCl (200 mL). The resulting mixture was stirred vigorously for 4 h at room temperature, cooled to 0 °C, and filtered. The collected crude solid was dried and crystallized from Et_2O–petroleum ether to provide 2-(1-hydroxy-2-nitroethyl)-3,4,6-trichlorophenol (A) as pale yellow crystals (2.1 g, 73%), mp 133–136 °C. Anal. ($C_8H_6Cl_3NO_4$) C, H, N.

A mixture of A (0.43 g, 1.5 mmol) and thionyl chloride (0.5 mL) was stirred at room temperature for 16 h and then on a steam bath for an additional 0.5 h before evaporation to dryness. The residual yellow oil was refluxed in EtOH (5 mL) containing NaOAc (0.5 g) for 0.5 h. The red-brown solution was then evaporated and the residue was dissolved in H_2O. The yellow powder obtained on acidification of the aqueous solution was crystallized from Et_2O–petroleum ether to provide 2-(2-nitroethenyl)-3,4,6-trichlorophenol (0.1 g, 37%), mp 125–127 °C. Anal. ($C_8H_4Cl_3NO_3$) C, H, N.

A solution of the nitroethenylphenol (1.35 g, 5 mmol) in Et_2O (100 mL) was added to a suspension of $LiAlH_4$ (0.95 g, 25 mmol) in Et_2O (150 mL), and the mixture was stirred at reflux for 10 h. After cooling to 0 °C, the reaction mixture was quenched by the dropwise addition of 1 N H_2SO_4 (100 mL). The aqueous layer was separated and neutralized with LiOH to pH 6. After filtration, a solution of picric acid (1.5 g) in EtOH (25 mL) was added to the clear filtrate. The picrate (1.1 g), mp 185–190 °C dec, was dissolved in hot H_2O (~100 mL), treated with concentrated HCl (10 mL), and cooled. The crude hydrochloride was collected and crystallized to provide 1g as tiny colorless crystals (0.5 g).

2-(2-Amino-1-hydroxyethyl)-3,4,6-trichlorophenol Hydrochloride (1h). A solution of A (2.86 g, 10 mmol) in EtOH (100 mL) containing 6 N HCl (5 mL) was hydrogenated over 5% Rh/C (0.5 g) in a Parr apparatus (initial pressure = 32 psi) until no further drop in pressure was noted (ca 48 h). The reaction

(7) Chattaway, F. D.; Orton, K. J. P.; Hurtley, W. H. *J. Chem. Soc.* **1900**, *77*, 800.
(8) Einhorn, A.; Mauermayer, T. *Justus Liebigs Ann. Chem.* **1905**, *343*, 282.

mixture was filtered and the filtrate evaporated. Crystallization of the residue provided **1h** as tiny colorless crystals (1.15 g).

2,3,5-Trichloro-6-hydroxybenzenesulfonamide (1j). 2,4,5-Trichlorophenol (5.9 g, 30 mmol) was added portionwise to chlorosulfonic acid (25 mL) with stirring and cooling (ice bath). The reaction mixture was heated on a steam bath for 1 h and then cooled to room temperature. Thionyl chloride (10 mL) was added dropwise, and then the mixture was refluxed for 0.5 h, cooled, and added dropwise with stirring to ice and water. The crude sulfonyl chloride was collected, washed with H_2O, partially air-dried, and added to NH_3 (liq) (300 mL). After evaporation in a fume hood, the solid residue was suspended in H_2O (200 mL) and filtered; acidification with concentrated HCl gave crude **1j**. Crystallization first from C_6H_6–cyclohexane and then from EtOH–H_2O provided **1j** as small colorless crystals (0.9 g): ^1H NMR (CD_3COCD_3) δ 7.9 (H 4, s).

2-(3-Aminopropyl)-6-chloro-4-(1,1-dimethylethyl)phenol (4m). A mixture of 2-chloro-4-(1,1-dimethylethyl)phenol (18.5 g, 0.10 mol), hexamethylenetetramine (14.0 g, 0.10 mol), and trifluoroacetic acid (150 mL) was heated at reflux (83–90 °C) for 8 h.[5] The reaction mixture was cooled slightly, diluted with 3 N HCl (200 mL), and refluxed for an additional 30 min. After cooling to −20 °C, the supernatant liquid was decanted and the residual yellow oil was dissolved in Et_2O. The ethereal solution was washed well with H_2O and saturated brine and dried ($MgSO_4$). Evaporation and subsequent crystallization of the residue from EtOH–H_2O afforded 3-chloro-5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde (6.2 g, 29%): mp 76.5–77 °C (lit.[9] mp 72 °C); ^1H NMR (Me_2SO-d_6) δ 1.3 (9 H, s, t-C_4H_9), 7.7 (2 H, s), 10.2 (H, s).

A mixture of the aldehyde (2.12 g, 10 mmol) and cyanomethylenetriphenylphosphorane[10] (3.1 g, 10 mmol) was dissolved in benzene (80 mL) and refluxed for 4 h under N_2. The reaction mixture was cooled and extracted with 20% $NaHSO_3$ and then with 20% Na_2CO_3 (3 × 100 mL). A yellow solid at the interface was isolated by filtration, digested in hot H_2O (~100 mL), and after decantation from a small amount of insoluble yellow sludge, was added to the carbonate extracts. Acidification and crystallization of the resultant precipitate from EtOH–H_2O gave 3-[3-chloro-5-(1,1-dimethylethyl)-2-hydroxyphenyl]propenenitrile as colorless crystals (1.2 g, 51%), mp 186–189 °C. Anal. ($C_{13}H_{14}ClNO$) C, H, N.

A solution of the nitrile (2.8 g, 12 mmol) in EtOH (120 mL) containing concentrated H_2SO_4 (1 mL) was hydrogenated over 5% Rh/Cd (0.6 g) in a Parr apparatus (initial pressure = 28 psi) until no further drop in pressure was noted (ca. 20 h). The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure to afford the amine hydrosulfate as a pale yellow semisolid. A solution of this residue in H_2O (150 mL) was filtered to remove traces of insoluble materials. The filtrate was made basic with 15 N NH_4OH to liberate the free base, which was subsequently crystallized to yield **4m** as a tan powder (1.3 g): ^1H NMR ($CDCl_3$) δ 1.2 (9 H, s, t-C_4H_9), 1.5 (2 H, m), 2.7 (4 H, m), 6.9 (H-3, d), 7.1 (H-5, d).

5-(1,1-Dimethylethyl)-2-hydroxy-3-iodobenzoic Acid (5f). A mixture of 5-(1,1-dimethylethyl)-2-hydroxybenzoic acid[11] (3.9 g, 0.02 mol), ICl (3.6 g, 0.022 mol), and HOAc (50 mL) was refluxed for 12 h. The dark purple solution was cooled to ambient temperature and poured into H_2O (300 mL) containing $NaHSO_3$ (~3 g) with vigorous stirring. The crude product was collected and washed well with H_2O. Crystallization gave **5f** (4.6 g): ^1H NMR (Me_2SO-d_6) δ 1.28 (9 H, s, t-C_4H_9), 7.85 (H-4, d), 8.05 (H-6, d).

2,3,6-Trichlorophenol. A mixture of 1,2,3,4-tetrachlorobenzene (21.6 g, 0.10 mol), NaOH (8 g, 0.20 mol), and ethylene glycol (50 mL) was stirred at reflux for 16 h, cooled, poured into H_2O (~300 mL), and filtered to remove some insoluble material. The clear filtrate was acidified, whereupon the crude product separated as an off-white powder. Crystallization from petroleum ether provided the phenol as tiny needles (5.8 g, 15%), mp 53–55 °C (lit.[12] mp 55 °C).

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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 (1 page). Ordering information is given on any current masthead page.

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