(95% EtOH) λ_{max} 232.2 nm (log ϵ 4.31), 280.0 (3.54). Anal. ($C_{22}H_{24}O_2$) C, H.

3,9-Dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[a,g]biphenylene (1a). To a stirred solution of 1.0 g (3.1 mmol) of diether 1b in 50 mL of CH_2Cl_2 was added dropwise a solution of 1.0 g (4.0 mmol) of BBr_3 in 5 mL of CH_2Cl_2.[22] The mixture was stirred for 12 h and then the solvent was removed under reduced pressure. The residue was treated with 50 mL of ether and 10 mL of H_2O and then extracted with 5% KOH. The aqueous phase was separated and acidified, and the precipitate was collected by filtration. Recrystallization from ether gave 0.60 g (55%) of diphenol 1a, mp 235-237 °C. An analytical sample was prepared by sublimation at 225 °C (0.2 mm): IR (KBr) 3300 (Ar OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 7.84 (s, 2, Ar OH), 6.94-6.56 (m, 6, Ar H), 3.26-3.06 (m, 2, Ar CH), 3.04-2.66 (m, 4, Ar CH_2), 2.60-2.30 (m, 2, Ar CHCH), 2.04-1.56 (m, 4, Ar CH_2CH_2); MS (70 eV) m/e $M^+/2$ (hemicleavage), 146 (100); UV (95% EtOH) λ_{max} 280 nm (log ϵ 3.64), with added base, 300 (3.78). Anal. ($C_{20}H_{20}O_2$) C, H.

Biological Testing. Oral Uterotropic (Estrogenic) Activity. Twenty-one-day old female rats, weighing 45-55 g, were treated for 3 consecutive days with a suspension of the diphenol 1a in 0.1 mL of sesame oil. Total doses of 1, 10, 100, and 1000 μg were administered to groups of 10 rats. A vehicle control group of 10 rats treated with sesame oil alone was also run. Autopsy was performed on the 4th day, and the uteri were excised, cleaned, and weighed to the nearest 0.2 mg. The average uterine weights for the four doses were 71.2 ± 3.6, 97.6 ± 5.3, 111.1 ± 5.3, and 117.7 ± 5.1 mg, respectively. The weight of the uteri of the control group was 38.2 ± 2.0 mg. The standard (DES) was tested for doses of 0.2, 0.4, and 0.8 μg and gave uterine weights of 57.7 ± 3.3, 72.5 ± 4.0, and 105.8 ± 5.3 mg, respectively. The potency is expressed as percent activity relative to DES.[19a]

Oral Postcoital Activity. Adult female rats were caged overnight with proven males and checked the next morning for the presence of sperm in vaginal washings (day of sperm = day 0). The diphenol 1a was suspended in 0.1 mL of sesame oil and administered orally to groups of 10 rats for 5 consecutive days starting on day 0. On day 10, autopsy was performed and the number of normal and resorbing fetuses was determined. ED_{100} is defined as the minimum dose [(μg/kg)/day] necessary to completely prevent implantation.[19a]

Antitumor Activity. Diphenol 1a, dissolved in cotton seed oil, was administered parenterally to three young adult Fisher male rats in the dose range of 10 μg, 100 μg, and 1 mg for 10 injections. These rats had previously received a transplanted squamous cell prostate carcinoma (11095). Autopsy on the 11th day showed tumor weight change/gram to be +15, +8, and 0, respectively. A second series using five young adult Fisher males with a dose range of 31.6 μg, 100 μg, 316 μg, 1 mg, and 3.16 mg showed a weight change/gram of +11, +7, +3, +1, and -3, respectively. The weight change/gram of controls for the two studies were +12 and +20, respectively.

A simultaneous comparison study using five adult Fisher males having received a dose range of 1 μg, 10 μg, 100 μg, 1 mg, and 10 mg/kg of DES showed a weight change/gram of +24.6, +13.3, -7, -10, and -18, respectively.[19b]

Acknowledgment. We thank the Contraceptive Development Branch, Center for Population Research, National Institutes of Child Health and Human Development, NIH, for support of this work through contract (NO1-HD-3-2846) and for permission to cite biological data. Support for the purchase of the Varian XL-100-15 is acknowledged (NSF Grant 17641 and HE 76-05571. We are grateful to Dr. A. Segaloff and his associates of the Alton Ochsner Medical Foundation for data from antitumor studies. We also thank Drs. H. K. Kim and M. Karten for helpful suggestions during the course of the work. The investigation at the University of Oklahoma was supported by Grant CA-17562, awarded by the National Cancer Institute, DHEW.

(22) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron Lett.*, 24, 2289 (1968).

2-(Aminomethyl)phenols, a New Class of Saluretic Agents. 1. Effects of Nuclear Substitution[1]

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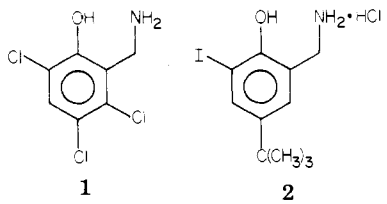
A series of 2-(aminomethyl)phenols was synthesized and tested in rats and dogs for saluretic and diuretic activity. A number of these compounds exhibit a high order of activity on iv or po administration. The most active compounds belong to a subseries of 4-alkyl-6-halo derivatives of which **2**, 2-(aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol, is the most active. Compound 2 also possesses significant antihypertensive activity, an adjunctive pharmacological parameter which distinguishes 2 from the other compounds prepared in this series. In addition, 2 displays both topical saluretic and antiinflammatory activities.

A continuing search for new renal agents in our laboratories by screening carefully selected compounds for diuretic and saluretic activity in rats and dogs led to the discovery of 2-(aminomethyl)-3,4,6-trichlorophenol (**1**). The unusual structural features, attractive electrolyte excretion profile and saluretic potency of **1**, relative to those of hydrochlorothiazide and furosemide provided impetus for an extensive synthetic program. The resulting data facilitated the delineation of the structure-activity relationships (SAR's) for a variety of 2-(aminomethyl)-phenols (**5**) and culminated in the development of 2-(aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol hydro-



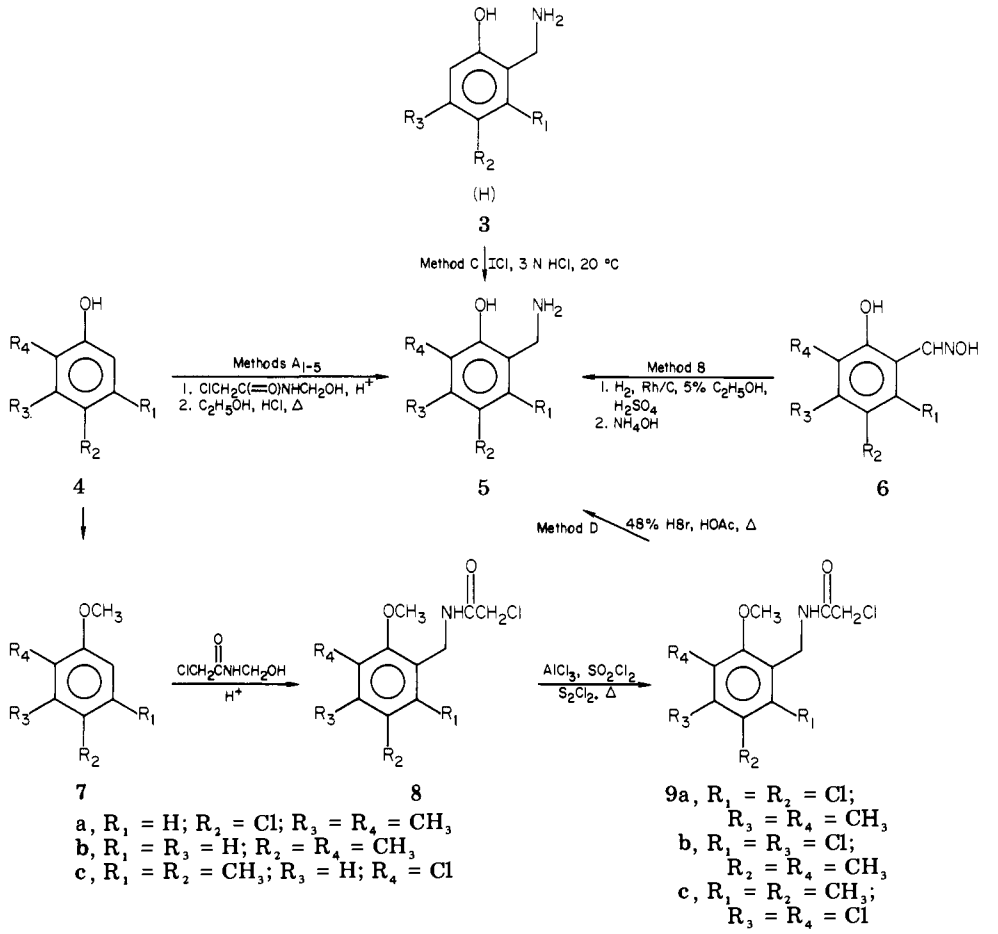
1 2

(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, Ill., 1977; American Chemical Society: Washington, D.C., 1977, and *ACS Symp. Ser.* **1978**, *83*, 93-124.

(2) Deceased, May 31, 1977.

0022-2623/80/1823-1414$01.00/0

Scheme I. Synthetic Methods for the Preparation of Substituted 2-(Aminomethyl)phenols



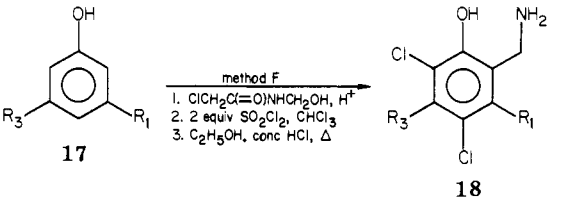
chloride **2** (MK-447). This compound was found to be a potent, high-ceiling salidiuretic agent with adjunctive antihypertensive and antiinflammatory properties; **2** is currently undergoing clinical evaluation. This report describes the effects of systematic variations of the aromatic nuclear substitutions as an approach to improving saluretic activity. The chemistry and biological activity resulting from reorientation and structural modification of the hydroxyl and aminomethyl groups in **5** will be the subject of subsequent reports.

Chemistry. The 2-(aminomethyl)phenols **5** prepared in this study are listed in Tables IV–VII; their syntheses are summariazed in Schemes I and II. The key step in the preparation of the majority of these compounds was accomplished readily via acid-catalyzed, nuclear amidoalkylation (Tscherniac–Einhorn reaction)[3] of an appropriately substituted phenol **4** which, after subsequent hydrolysis, afforded the target product **5** as indicated in Scheme I (methods A_{1-5}). The choice of the proper reaction sequence, as well as the optimum conditions for introducing the aminomethyl moiety, is governed primarily by the chemical nature and directing influences of the substituents R_1, R_2, R_3, and R_4. The importance of selecting the proper acid catalyst and reaction medium to control the amidoalkylation step is demonstrated in Scheme III.

The desired amine **11** was formed in good yield (50%) when HOAc–H_2SO_4 (v:v, 9:1) (method A_5) was used, whereas, the use of concentrated H_2SO_4 (method A_2) led to extensive diamidomethylation (**12**), even when equimolar quantities of the starting phenol and 2-chloro-*N*-(hydroxymethyl)acetamide were employed. The observed dependence on acid strength was further exemplified by

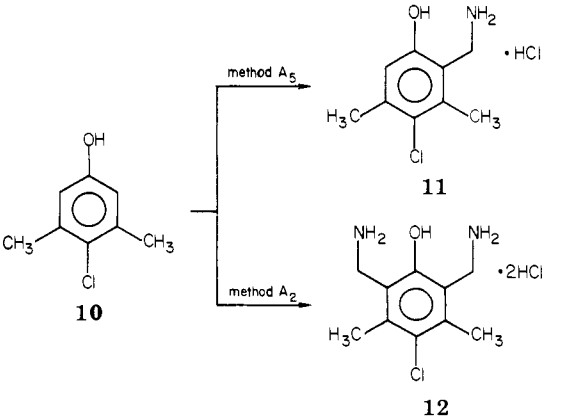
(3) For an extensive review of the Tscherniac–Einhorn reaction, see H. E. Zaugg and W. B. Martin *Org. React.* **1965**, *14*, 52–269.

Scheme II. Synthetic Route for the Preparation of Substituted 2-(Aminomethyl)phenols

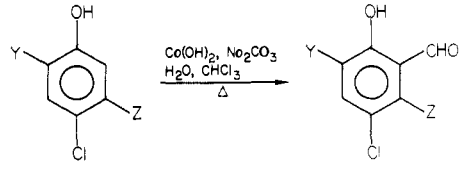


a, R_1 = H; R_3 = C_2H_5
b, R_1 = H; R_3 = *t*-C_4H_9
c, R_1 = CH_3; R_3 = *t*-C_4H_9

Scheme III



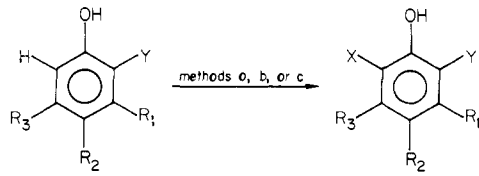
Scheme IV



13 14

	Y	Z
a	H	Cl
b	OCH_3	OCH_3

Scheme V



15 16

Table I. Preparation of Halophenols or Salicylaldehydes

	R_1	R_2	R_3	Y	X	method[a]
16a	H	*i*-C_3H_7	H	H	I	a
16b	H	*sec*-C_4H_9	H	H	Cl	b
16c	H	*t*-C_4H_9	H	H	I	a
16d	OC_2H_5	H	OC_2H_5	H	Cl	b
16e	CH_3	CH_3	CH_3	H	Cl	b
16f	OCH_3	Cl	OCH_3	H	H	b
16g	OCH_3	Cl	OCH_3	H	Br	c
16h	OCH_3	CH_3	OCH_3	H	Cl	b
16i	OC_2H_5	Cl	OC_2H_5	H	Cl	b
16j	OCH_3	Cl	OCH_3	CHO	Cl	b

[a] See Scheme V. a = ICl, HOAc, Δ; b = SO_2Cl_2, $CHCl_3$, Δ with salicylaldehydes and for 16d → 16i; c = Br_2, $CHCl_3$.

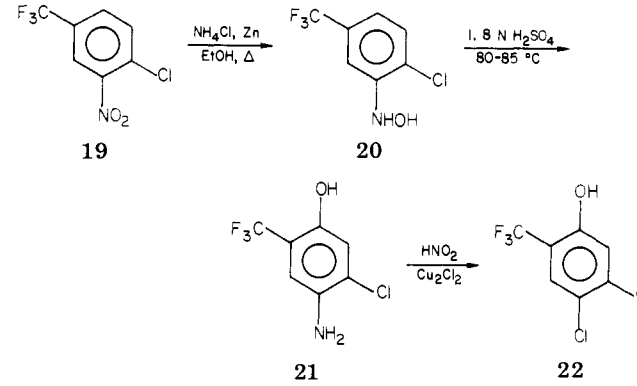
the synthesis of **69** from phenol **26b** via method A_3 using HOAc–H_2SO_4 (v:v, 1:1). When the synthesis of **69** was attempted via method A_2, extensive de-*tert*-butylation was observed.

The EtOH–HCl hydrolysis of the intermediate *N*-acylsalicylamines may produce functional group changes in existing nuclear substituents; for example, in the synthesis of **86** and **87** from **4** (R_2 = CO_2H; R_4 = Cl and I, respectively) the carboxyl group was esterified, whereas in the synthesis of **47** and **73** from **4** (R_2 = Cl and *t*-C_4H_9, respectively; R_4 = CO_2H) the carboxyl group remained unchanged.

The preparation of **30**, **36**, **40**, **104**, and **123** was accomplished via catalytic reduction of the corresponding salicyloximes (method B) as depicted in Scheme I. Those starting salicylaldehydes which were not commercially available were synthesized via a Reimer–Tiemann reaction as shown in Scheme IV. In the case of **123**, the commercially available 4,6-dimethoxysalicylaldehyde was dichlorinated as shown in Scheme V (see **16j**, Table I) and subsequently converted to its oxime **6**. The preparation of intermediate halophenols **16** is illustrated in Table I.

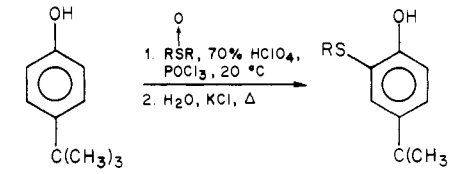
Iodination of **3** (obtainable via method A_5 when R_4 = H) to provide target **5** is shown in Scheme I. Method C (Scheme I) is the preferred synthetic pathway to these iodinated 2-(aminomethyl)phenols in view of the fact that the acidic conditions used for the Tscherniac–Einhorn amidoalkylation and subsequent acid hydrolysis are conducive to partial deiodination. Large quantities of **2** can

Scheme VI. Synthetic Route for the Preparation of 4,5-Dichloro-2-(trifluoromethyl)phenol



19 20 21 22

Scheme VII



23 24a, R = CH_3; b, R = C_2H_5

be prepared routinely in 50% overall yield using this method. Since the 6-iodo substituent is introduced under very mild conditions in the terminal step, this sequence is ideally suited for the synthesis of [^{131}I]**2**. Nevertheless, method A_5 (vide supra) is the method of choice for elaborating 2-(amino[^{14}C]methyl)-**2** from **16c** using *N*-(hydroxy[^{14}C]methyl)chloroacetamide which can be conveniently generated in situ from [^{14}C]paraformaldehyde and chloroacetamide.

The elaboration of **112**, **113**, and **115** (Scheme I, method D) required the introduction of a chlorine atom into the nucleus at an unactivated position (i.e., meta to the phenolic hydroxyl moiety). This was accomplished by the procedure of Silberrad;[4] the readily accessible *N*-acylsalicylamine methyl ethers **8** were chlorinated to afford **9**, which, after subsequent hydrolysis (48% HBr in HOAc at reflux), yielded fully substituted **5**.

Catalytic dehalogenation of the chloro-2-(aminomethyl)phenols **11**, **67**, and **105** in aqueous alkali (method E) provided **38** and intermediates **65a** and **106a**, respectively, which were subsequently iodinated (Scheme I, method C) to afford **65** and **106**.

Elaboration of **18a–c** was successfully negotiated by sequential amidoalkylation, dichlorination, and hydrolysis of the appropriate phenol as shown in Scheme II (method F). Obtention of the desired products was fortuitous in view of the fact that they were the only positional isomers to crystallize from their respective hydrolytic milieu when the original amidoalkylation afforded some of the other two isomers as shown by TLC and ^{1}H NMR.

Conversion of 4-chloro-3-nitro-1-(trifluoromethyl)-benzene (**19**) to the phenolic precursor of **92** was effected via the three step sequence **19** → **20** → **21** → **22** using the reagents indicated in Scheme VI.

2-(Alkylthio)-4-(1,1-dimethylethyl)phenols, **24**, were prepared by the simple expediency of reacting 4-(1,1-dimethylethyl)phenol with 1 equiv of dialkyl sulfoxide in acidic milieu using the general procedure of Hirose and Ukai[5] as shown in Scheme VII.

(4) Silberrad, O. *J. Chem. Soc.* **1922**, 1015.
(5) Hirose, K.; Ukai, S. *Yakugaku Zasshi* **1966**, *86*, 191.

Table II. Scoring System for Intravenous Dog Assay

score	μequiv of Na^+/min at 5 mg/kg iv stat
0	0-99
±	act. above 5 mg/kg
1	100-249
2	250-399
3	400-599
4	600-799
5	800-899
6	>900

Table III. Scoring System for Oral Rat Assay

	μequiv of Na^+ at given mg/kg dose				
score	1	5	16.5	50	81
0				<0.3	<0.3
±			0.4	0.7	0.9
1		0.3	0.5	1.2	1.5
2		0.4	0.6	1.8	2.4
3		0.5	1.4	2.4	2.9
4		1.4	2.7	3.3	
5	0.7	2.6	3.3	3.6	
6	2.1	3.6	4.2	3.9	

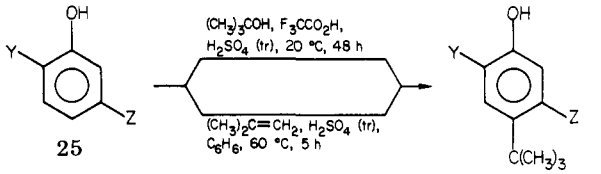
Introduction of the 1,1-dimethylethyl moiety into the 4 position of the appropriate phenol was accomplished by alkylation using concentrated H_2SO_4 as catalyst, either with isobutylene in benzene at 60 °C (**26a** and **26c**) or with *tert*-butyl alcohol in TFA at 20 °C (**26b**), as illustrated in Scheme VIII. Compound **26b** was also prepared in comparable yields using the isobutylene procedure.

The precursor to **75** was prepared by copper-catalyzed aryloxylation of 2-bromo-4-(1,1-dimethylethyl)anisole with sodium 4-chlorophenoxide at high temperature, which, after ether hydrolysis, provided the requisite phenol, **29** (Scheme IX).

Biological Activity. Structure–Activity Relationships. A. Saluresis–Diuresis. The target compounds were tested in dogs and/or rats for their salidiuretic properties and the results, shown for Na^+ excretion only and presented in a scored format (Tables II and III) for the sake of brevity, are reported in Tables IV–VII. Data for a series of monosubstituted salicylamines are shown in Table IV, along with that for furosemide, ethacrynic acid, and hydrochlorothiazide for comparative purposes. Although salicylamine per se is devoid of demonstrable salidiuretic activity, introduction of a chloro or alkyl (except *n*-butyl; cf. **33**) moiety in the 4 position imparts weak activity.

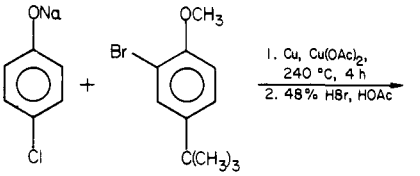
Appropriate nuclear disubstitution, particularly in positions 4 and 6, led to marked enhancement of saluretic activity as indicated in Table V. Consistently good activity was observed in the 6-halo-4-alkyl series, i.e., **2**, **48**, **51**, **55**,

Scheme VIII



	Y	Z
a	F	H
b	CF_3	H
c	Cl	OCH_3

Scheme IX



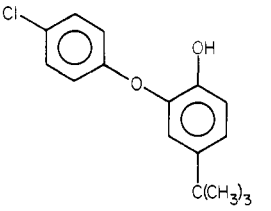
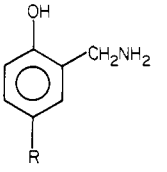


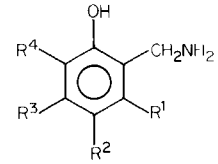
Table IV. Monosubstituted 2-(Aminomethyl)phenols **5**



compd[a]	R	yield, %	method	recrystn solvent[b]	mp, °C	formula[c]	score dog,[d] iv	score rat,[e] po
30[f]	Cl	38	B	EtOH	206-208 dec	C_7H_8ClNO	2	1
31	C_2H_5	21	A_5	conc HCl	186.5-187.5 dec	$C_9H_{13}NO{\cdot}HCl$	1[g]	1
32	C_3H_7	40	A_5	2	169-170 dec	$C_{10}H_{15}NO{\cdot}HCl$	2	
33	C_4H_9	42	A_5	2	194-195 dec	$C_{11}H_{17}NO{\cdot}HCl$	0	0
34	t-C_4H_9	57	A_5	2	226-228 dec	$C_{11}H_{17}NO{\cdot}HCl$	0	1
35	$C_6H_5C(CH_3)_2$	43	A_5	2	211-212 dec	$C_{16}H_{19}NO{\cdot}HCl$	2	
furosemide							6[h]	3
ethacrynic acid							6[h]	0
hydrochlorothiazide							2[h]	2

[a] The starting materials for compounds 31-35 were commercially available. [b] Solvents of recrystallization: 1, H_2O–EtOH; 2, EtOH–concentrated HCl; 3, H_2O–concentrated HCl; 4, EtOH–Et_2O. [c] Analytical results are within ±0.4% of the theoretical values. [d] Score is for a single dog unless otherwise designated; see Table II for scoring system. [e] Score is for geometric mean of three animals per cage, three cages per dose; see Table III for scoring system. [f] The starting oxime was prepared by the method of Biltz, H.; Stept, K. *Chem. Ber.* 1904, *37*, 4022. [g] Score is for average value of two dogs. [h] Score is for average value of 24 dogs.

Table V. Disubstituted 2-(Aminomethyl)phenols 5



no.	precursor[a]	R¹	R²	R³	R⁴	yield, %	method	recrystn solvent[b]	mp, °C	formula[c]	score: dog,[d] iv	score: rat,[e] po
36	36a	Cl	Cl			42	B	1	153–156 dec	$C_7H_7Cl_2NO$	2	1
37	CA	CH_3	Cl			13	A_5	2	>260 dec	$C_8H_{10}ClNO\cdot HCl$	2	
38	11	CH_3		CH_3		53	E	2	>300 dec	$C_9H_{13}NO\cdot HCl$	0	0
39	CA	t-C_4H_9		t-C_4H_9		59	A_5	2	200–200.5 dec	$C_{15}H_{25}NO\cdot HCl$	0	
40	*f*		Cl		Cl	94	B	1	196.5–197 dec	$C_7H_7Cl_2NO$	±	2
41	*g*		Cl		F	27	A_2	4	217.5–218 dec	$C_7H_7ClFNO\cdot HCl$	2	
42	30		Cl		I	78	C	2	215–216 dec	$C_7H_7ClINO\cdot HCl$	5[h]	2
43	*i*		F		Cl	55	A_2	2	228–229 dec	$C_7H_7ClFNO\cdot HCl$	0	
44	*j*		I		I	73	C	2	215–216 dec	$C_7H_7I_2NO\cdot HCl$	5[h]	3
45	CA		Cl		CH_3	50	A_5	2	258.5–259.5 dec	$C_8H_{10}ClNO\cdot HCl$	1[h]	
46	CA		Cl		C_6H_5	15	A_5	4	193–194 dec	$C_{13}H_{12}ClNO\cdot HCl$	2	
47	CA		Cl		COOH	53	A_2	2	260.5–261 dec	$C_8H_8ClNO_3\cdot HCl$	2	
48	*k*		CH_3		Cl	40	A_5	2	246–247 dec	$C_8H_{10}ClNO\cdot HCl$	1[h]	2
49	CA		CH_3		t-C_4H_9	26	A_5	2	222–225 dec	$C_{12}H_{19}NO\cdot HCl$	1[h]	
50	CA		CH_3		OCH_3	3	A_5	conc HCl	253–253.5 dec	$C_9H_{13}NO_2\cdot HCl$	1[h]	
51	*l*		C_2H_5		Cl	33	A_5	2	237–238 dec	$C_9H_{12}ClNO\cdot HCl$	6	4
52	CA		C_2H_5		CH_2NH_2	25	A_2	conc HCl	232–233 dec	$C_{10}H_{16}N_2O\cdot 2HCl$	0	
53	CA		$CH_2CH{=}CH_2$		OCH_3	13	A_5	EtOH	251–253 dec	$C_{11}H_{15}NO_2\cdot HCl$	4	3
54	*m*		C_3H_7		OCH_3	13	A_5	2	245–248 dec	$C_{11}H_{17}NO_2\cdot HCl$[n]	2	
55	*l*		C_3H_7		Cl	34	A_5	2	231–232 dec	$C_{10}H_{14}ClNO\cdot HCl$	6	4
56	32		C_3H_7		I	68	C	2	201–202 dec	$C_{10}H_{14}INO\cdot HCl$	4	2
57	*o*		C_3H_7		C_3H_7	30	A_5	2	158–160 dec	$C_{13}H_{21}NO\cdot HCl$	2	
58	*l*		i-C_3H_7		Cl	58	A_5	2	241–242 dec	$C_{10}H_{14}ClNO\cdot HCl$	6	5
59	16a		i-C_3H_7		I	46	A_5	2	211–212 dec	$C_{10}H_{14}INO\cdot HCl$	4[h]	5
60	*p*		C_4H_9		CH_3	72	A_5	2	240–243 dec	$C_{12}H_{19}NO\cdot HCl$	1[h]	
61	33		C_4H_9		I	85	C	2	200–201 dec	$C_{11}H_{16}INO\cdot HCl$	1	0
62	*q*		*sec*-C_4H_9		Cl	40	A_5	2	231.5–232 dec	$C_{11}H_{16}ClNO\cdot HCl$	5[h]	5
63	128		*sec*-C_4H_9		I	92	C	2	187–188 dec	$C_{11}H_{16}INO\cdot HCl$	6	3
64	16b		i-C_4H_9		Cl	46	A_5	2	230.5–231 dec	$C_{11}H_{16}ClNO\cdot HCl$	3[h]	3
65	131		i-C_4H_9		I	56	C	2	199–200 dec	$C_{11}H_{16}INO\cdot HCl$	1	1
66	26a		t-C_4H_9		F	27	A_5	conc HCl	227–228 dec	$C_{11}H_{16}FNO\cdot HCl$	6	4
67	CA		t-C_4H_9		Cl	44	A_5	2	251–251.5 dec	$C_{11}H_{16}ClNO\cdot HCl$	6	6
68	*r*		t-C_4H_9		Br	43	A_5	2	239–240 dec	$C_{11}H_{16}BrNO\cdot HCl$	6	6
2	16c		t-C_4H_9		I	40	A_5	2	200–201 dec	$C_{11}H_{16}INO\cdot HCl$	6[h]	6
	34					80	C					
69	26b		t-C_4H_9		CF_3	61	A_3	2	202–204 dec	$C_{12}H_{16}F_3NO\cdot HCl$	5[h]	4
70	CA		t-C_4H_9		CH_3	28	A_1	2	235–236 dec	$C_{12}H_{19}NO\cdot HCl$	4	
71	*s*		t-C_4H_9		C_3H_7	29	A_5	4	157–159 dec	$C_{14}H_{23}NO\cdot HCl$[t]	0	
72	CA		t-C_4H_9		t-C_4H_9	41	A_5	1	98.5–99 dec	$C_{15}H_{25}NO$	0	
73	*u*		t-C_4H_9		COOH	63	A_3	2	234–235 dec	$C_{12}H_{17}NO_3\cdot HCl$	5[h]	
74	*v*		t-C_4H_9		$COCH_3$	74	A_3	4	201–202 dec	$C_{13}H_{19}NO_2\cdot HCl$[w]	2	±
75	29		t-C_4H_9		pOC_6H_5Cl	70	A_5	4	205–207 dec	$C_{17}H_{20}ClNO_2\cdot HCl$	1[h]	2
76	24a		t-C_4H_9		SCH_3	50	A_5	4	179–181 dec	$C_{12}H_{19}NOS\cdot HCl$[x]	4	5

77	24b	t-C_4H_9	SC_2H_5	62	A_5	4	149–155 dec	$C_{13}H_{21}NOS\cdot HCl$[y]	3	1
78	*l*	t-C_5H_{11}	Cl	33	A_5	2	226–227 dec	$C_{12}H_{18}ClNO\cdot HCl$	4	3
79	129	t-C_5H_{11}	I	75	C	2	203–204 dec	$C_{12}H_{18}INO\cdot HCl$	5	3
80	130		I	89	C	2	184–185 dec	$C_{13}H_{18}INO\cdot HCl$	3	
81	*z*	c-C_6H_{11}	Cl	52	A_5	2	250–250.5 dec	$C_{13}H_{18}ClNO\cdot HCl$	3[h]	
82	CA	sec-C_7H_{15}	CH_3	11	A_5	4	194.5–195.5 dec	$C_{15}H_{25}NO\cdot HCl$	2	
83	*aa*	t-C_8H_{17}	Cl	52	A_5	2	194.5–195 dec	$C_{15}H_{24}ClNO\cdot HCl$[bb]	0	
84	CA	C_6H_5	Cl	28	A_5	2	241–242 dec	$C_{13}H_{12}ClNO\cdot HCl$	2	
85	*p*	$C(=O)C_3H_7$	CH_3	32	A_5	2	225–228 dec	$C_{12}H_{17}NO_2\cdot HCl$	1[h]	
86	CA	$CO_2C_2H_5$	Cl	26	A_2	4	220–221 dec	$C_{10}H_{12}ClNO_3\cdot HCl$	1[h]	
87	*cc*	$CO_2C_2H_5$	I	20	A_3	4	196–198 dec	$C_{10}H_{12}INO_3\cdot HCl$	2	0
88	*dd*	OC_2H_5	Cl	21	A_5	2	225.5–226 dec	$C_9H_{12}ClNO_2\cdot HCl$	2	

[a] The starting materials were commercially available (CA), prepared as described under Experimental Section (compound number), or prepared by known literature methods as indicated by designated footnote. [b–f] See corresponding footnotes to Table IV. [g] Finger, G. C.; Gortatowski, M. J.; Shiley, R. H.; White, R. H. *J. Am. Chem. Soc.* 1959, *81*, 94. [h] Footnote *g*, Table IV. [i] Kolomiets, A. F.; Kalatskii, L. A.; Bliznyuk, N. K. *Zh. Obshch. Khim.* 1967, *37*, 2486; *Chem. Abstr.* 1968, *68*, 114200z. [j] Holly, F. W.; Cope, A. C. *J. Am. Chem. Soc.* 1945, *66*, 1875. [k] Sah, P. P. T.; Anderson, H. H. *J. Am. Chem. Soc.* 1941, *63*, 3164. [l] Klarmann, E.; Shternov, V. A.; Gates, L. W. *J. Am. Chem. Soc.* 1933, *55*, 2576. [m] Levin, D. W.; Lowy, A. *J. Am. Chem. Soc.* 1933, *55*, 1995. [n] Anal. C: calcd, 57.02; found, 57.64. [o] Stoughton, R. W.; Baltzly, R.; Bass, A. *J. Am. Chem. Soc.* 1934, *56*, 2007. [p] Coulthard, C. E.; Marshall, J.; Pyman, F. L. *J. Chem. Soc.* 1930, 280. [q] Kryuchkova, V. G.; Zavgorodnii, S. V. *Zhur. Obshchii. Kim.* 1960, *30* 3872; *Chem. Abstr.* 1961, *55*, 22203*b*. Prepared, however, as described in ref *l*. [r] Jones, B. *J. Chem. Soc.* 1941, 358. [s] Sen, A. B.; Rastogi, R. P. *J. Indian Chem. Soc.* 1953, *30*, 355. [t] Anal. C: calcd, 65.22; found, 64.58. [u] Baine, O.; Adamson, G. F.; Barton, J. W.; Fitch, J. L.; Swayampati, D. R.; Jeskey, H. *J. Org. Chem.* 1954, *19*, 510. [v] Bui-Hoi, N. G. P. H.; Cogniant, E. T. P. *Recl. Trav. Chim. Pays-Bas.* 1945, *64*, 214. [w] Anal. C: calcd, 60.58; found, 58.76. [x] Anal. C: calcd, 55.05; found, 54.47. [y] Anal. C: calcd, 56.61; found, 56.10. [z] Simpson, H. N.; Hancock, C. K.; Meyers, E. A. *J. Org. Chem.* 1965, *30*, 2678; melting point only. [aa] Weiss, P.; Cordasco, M. G.; Carman, W.; Reiner, L. *J. Am. Pharm. Assoc.* 1951, *40*, 267. [bb] Anal. C: calcd, 58.82; found, 59.24. [cc] Auwers, K. v. *Chem. Ber.* 1879, *30*, 1473, as the acid. [dd] Nametkin, S. S.; Bokarev, K. S.; MeL'nikov, N. N. *Dokl. Akad. Nauk SSSR.* 1951, *77*, 293; *Chem. Abstr.* 1951, *45*, 10213*g*.

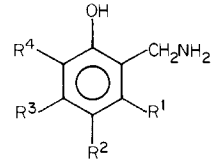
56, **58**, **59**, **61–68**, and **78–81**, particularly, where there is branching on the α-carbon atom. In the latter case, potency peaks with the introduction of a 4-(1,1-dimethylethyl) moiety, i.e., **2** and **66–68**. Alkyl groups larger than 4-(1,1-dimethylethyl) tend to decrease potency in a direct relationship to their size, i.e., **78–81** and **83**. The replacement of the 4-alkyl moiety with either strong electron-donating or electron-withdrawing groups markedly decreases the activity, e.g., compared **67** with **86–88** or **70** with **85**. Interestingly, the 6-chloro, 6-bromo, and 6-iodo derivatives, i.e., **67**, **68**, and **2**, respectively, elicit marked salidiuretic responses, whereas, the 6-fluoro analogue, **66**, is less active, at least in rats. As will be discussed subsequently, the pronounced antihypertensive properties of **2** served to distinguish it from a subseries of nearly equipotent saluretic agents which emerged during the course of this investigation.

The influences of nuclear trisubstitution on saluretic activity are presented in Table VI. Noteworthy is the fact that shifting the 3-chloro substituent in **1** to the 5 position, **108**, resulted in slightly improved activity; on the other hand, movement of the 6-chloro substituent in **1** to the 5 position, **89**, diminished activity in the dog, while marginally enhancing activity in the rat. Furthermore, introduction of electron-donating groups (i.e., methyl or methoxyl) in the 6 position, as in **93** or **95**, proved to be detrimental to activity as had been observed earlier in the disubstituted series. Interestingly, introduction of a 3-methoxy moiety into **67** and **2**, both of which are very active saluretics, to provide **105** and **106**, respectively, had a deleterious effect on activity.

Finally, the data recorded in Table VII illustrate the effects of nuclear tetrasubstitution on activity. These data reveal several interesting SAR trends. First, although replacement of all four chloro substituents of tetrachloro derivative **111** with methyl groups to provide **121** resulted in no change of activity in the dog and only slight diminution of activity in the rat, the replacement of the 3- and 5-chloro substituents in **111** with methyl groups, **114**, resulted in greatly enhanced activity in the dog, and, most suprisingly, the transposition of the chloro and methyl groups in **114**, i.e., to provide the isomeric derivative **113**, resulted in almost total loss of activity. These results indicate that electronic effects have a very subtle influence on the saluretic efficacy of these structures. Reinforcement of the subtleness of this influence is provided by an activity comparison of dichloro dimethyl derivatives **112** and **115** with each other and with the aforementioned dichloro dimethyl isomers **113** and **114**. Secondly, comparison of dichloro ethyl methyl derivative **118** with its methyl ethyl transpositional isomer, **122**, reflects the rather stringent steric requirements for substituents in the 3 position. Inherent steric limitations are also found in the 5 position, i.e., compare the 5-ethyl derivative **118** with the 5-(1,1-dimethylethyl) derivative **18c**. Thirdly, the results tabulated for **114**, **123**, and **127** suggest that, whereas the methyl groups in the 3 and 5 positions can be replaced with methoxy groups with maintenance of activity, their replacement with ethoxy groups substantially reduces activity. The latter result is in accord with the steric restraints discussed above for substituents in the 3 position. Finally, it should be noted that **118** and **123** display saluretic activities which are essentially of the same magnitude as those of the 4-(1,1-dimethylethyl)-6-halo derivatives **2**, **67**, and **68** cited above.

B. Pharmacology of 2. The diuretic and saluretic activity of **2** is compared with that of analogues **1**, **67**, **118**, and **123**, as well as with that of hydrochlorothiazide and

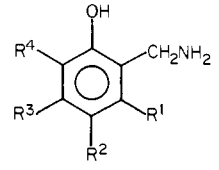
Table VI. Trisubstituted 2-(Aminomethyl)phenols 5



no.	precursor[a]	R¹	R²	R³	R⁴	yield, %	method	recrystn solvent[b]	mp, °C	formula[c]	score: dog,[d] iv	score: rat,[e] po
89	CA	Cl	Cl	Cl		22	A_5	2	270-271 dec	$C_7H_6Cl_3NO\cdot HCl$	3[f]	4
90	CA	CH_3	CH_3	CH_3		20	A_5	3	270-271 dec	$C_{10}H_{15}NO\cdot HCl$[g]	0	
11	CA	CH_3	Cl	CH_3		50	A_5	2	~280 dec	$C_9H_{12}ClNO\cdot HCl$	1[f]	
91	16f	OCH_3	Cl	OCH_3		30	A_5	1	220-222 dec	$C_9H_{12}ClNO_3\cdot HCl$	1[f]	
1	CA	Cl	Cl		Cl	51	A_2	2	244.5-245 dec	$C_7H_6Cl_3NO\cdot HCl$	5	3
92	22	Cl	Cl		CF_3	17	A_2	2	199-201 dec	$C_8H_6Cl_2F_3NO\cdot HCl$	3[f]	4
93	*h*	Cl	Cl		CH_3	30	A_2	2	242-243 dec	$C_8H_9Cl_2NO\cdot HCl$	2[f]	
94	*i*	Cl	CH_3		Cl	26	A_2	2	232.5-233 dec	$C_8H_9Cl_2NO\cdot HCl$	3	
95	*j*	Cl	Cl		OCH_3	31	A_3	4	231.5-232 dec	$C_8H_9Cl_2NO_2\cdot HCl$	1[f]	1
96	*k*	F	Cl		Cl	41	A_2	4	231-232 dec	$C_7H_6Cl_2FNO\cdot HCl$	5	4
97	CA	CH_3	Cl		Cl	33	A_2	2	260-261 dec	$C_8H_9Cl_2NO\cdot HCl$	6	
98	37	CH_3	Cl		I	72	C	2	225-227 dec	$C_8H_9ClINO\cdot HCl$	4	3
99	CA	CH_3	Cl		CH_3	14	A_2	3	256-257 dec	$C_9H_{12}ClNO\cdot HCl$	0	
100	CA	CH_3	CH_3		Cl	67	A_5	2	261-262 dec	$C_9H_{12}ClNO\cdot HCl$	3[f]	3
101	CA	CH_3	Cl		i-C_3H_7	20	A_5	4	213-214 dec	$C_{11}H_{16}ClNO\cdot HCl$	1[f]	
102	CA	CH_3	CH_3		CH_3	22	A_1	1	254-254.5 dec	$C_{10}H_{15}NO\cdot HCl$	2	2
103	*l*	CH_3	NH_2		CH_3	38	A_5	3	270 dec	$C_9H_{14}N_2O\cdot 2HCl$	0	
104	104a	OCH_3	Cl		OCH_3	24	B	4	196-197 dec	$C_9H_{12}ClNO_3\cdot HCl$	2	
105	26c	OCH_3	t-C_4H_9		Cl	26	A_5	2	212-213 dec	$C_{12}H_{18}ClNO_2\cdot HCl$	2	
106	132	OCH_3	t-C_4H_9		I	81	C	2	200-201 dec	$C_{12}H_{18}INO_2\cdot HCl$	5	3
107	CA	OH	Cl		Cl	35	A_2	3	250-251 dec	$C_7H_7Cl_2NO_2\cdot HCl$	0	1
108	*m*		Cl	Cl	Cl	38	A_2	2	228-229.5 dec	$C_7H_6Cl_2NO\cdot HCl$	6	4
109	CA		Cl	CH_3	CH_3	35	A_5	2	254-254.5 dec	$C_9H_{12}ClNO\cdot HCl$	0	
110	CA		CH_2NH_2	Cl	Cl	24	A_2	2	256-257 dec	$C_8H_{10}Cl_2N_2O\cdot 2HCl$	0	
18a	CA		Cl	C_2H_5	Cl	6	F	2	240-241 dec	$C_9H_{11}Cl_5NO\cdot HCl$	3	2
18b	CA		Cl	t-C_4H_9	Cl	18	F	2	215-216 dec	$C_{11}H_{15}Cl_2NO\cdot HCl$	6	3

[a-f] See corresponding footnotes to Table IV. [g] Anal. C: calcd, 59.55; found, 60.34. [h] Zincke, Th. *Justus Liebigs Ann. Chem.* 1918, *417*, 191. [i] Sprague, J. M.; Schultz, E. M. U.S. Patent 3 453 312 (1969). [j] Matell, M. *Acta Chem. Scand.* 1955, *9*, 1017. [k] Footnote *g*, Table V. [l] Jacobs, W. A.; Heidelberger, M. *J. Am. Chem. Soc.* 1917, *39*, 2204, as acetamide. [m] Groves, L. G.; Turner, E. E.; Sharp, G. I. *J. Chem. Soc.* 1929, 514.

Table VII. Tetrasubstituted 2-(Aminomethyl)phenols 5



no.	precursor[a]	R1	R2	R3	R4	yield, %	method	recrystn solvent[b]	mp, °C	formula[c]	score: dog,[d] iv	score: rat,[e] po
111	CA	Cl	Cl	Cl	Cl	37	A_2	2[f]	234 dec	$C_7H_5Cl_4NO\cdot HCl$	2	4
112	CA	Cl	Cl	CH_3	CH_3	11	D	2[f]	260.5–261 dec	$C_9H_{11}Cl_2NO\cdot HBr$	6	
113	CA	Cl	CH_3	Cl	CH_3	2	D	2[f]	305–305.5 dec	$C_9H_{11}Cl_2NO\cdot HBr$	1[g]	0
114	*h*	CH_3	Cl	CH_3	Cl	59	A_4	1	266–268 dec	$C_9H_{11}Cl_2NO\cdot HCl$	6	4
115	CA	CH_3	CH_3	Cl	Cl	7	D	2[f]	280–281 dec	$C_9H_{11}Cl_2NO\cdot HBr$	4	5
	i					10	A_4	4	225.5–226 dec	$C_9H_{11}Cl_2NO\cdot HCl$		
116	*j*	CH_3	Cl	CH_3	Br	33	A_4	2	255 dec	$C_9H_{11}BrClNO\cdot HCl$	6	
117	*k*	CH_3	Br	CH_3	Br	35	A_4	2	>310 dec	$C_9H_{11}Br_2NO\cdot HCl$	5[g]	4
118	CA	CH_3	Cl	C_2H_5	Cl	49	A_4	2	264–265 dec	$C_{10}H_{13}Cl_2NO\cdot HCl$	6	5
18c	CA	CH_3	Cl	t-C_4H_9	Cl	10	F	2	220–221 dec	$C_{12}H_{17}Cl_2NO\cdot HCl\cdot 0.5H_2O$		3
119	*l*	CH_3	Cl	CH_3	CH_3	68	A_5	2	263–263.5 dec	$C_{10}H_{14}ClNO\cdot HCl$	4	
12	CA	CH_3	Cl	CH_3	CH_2NH_2	24	A_2	H_2O/HCl	>300 dec	$C_{10}H_{15}ClN_2O\cdot 2HCl$[m]		0
120	16e	CH_3	CH_3	CH_3	Cl	79	A_5	2	258–259 dec	$C_{10}H_{14}ClNO\cdot HCl$	4	
121	*l*	CH_3	CH_3	CH_3	CH_3	70	A_5	2	249–250 dec	$C_{11}H_{17}NO\cdot HCl$	2	3
122	CA	C_2H_5	Cl	CH_3	Cl	83	A_4	2	233–234 dec	$C_{10}H_{13}Cl_2NO\cdot HCl$	1[g]	1
123	123a	OCH_3	Cl	OCH_3	Cl	75	B	4	174–175 dec	$C_9H_{11}Cl_2NO_3\cdot HCl$	6	5
124	16g	OCH_3	Cl	OCH_3	Br	19	A_5	2	155–156 dec	$C_9H_{11}BrClNO_3\cdot HCl$	4	5
125	91	OCH_3	Cl	OCH_3	I	12	C	4	159–160 dec	$C_9H_{11}ClINO_3\cdot HCl$	5	4
126	16h	OCH_3	CH_3	OCH_3	Cl	28	A_5	EtOH	135–136 dec	$C_{10}H_{14}ClNO_3$	2	
127	16i	OC_2H_5	Cl	OC_2H_5	Cl	29	A_5	2	195–196.5 dec	$C_{11}H_{15}Cl_2NO_3\cdot HCl$	0	3

[a-e] See corresponding footnotes to Table IV. [f] HBr used instead of concentrated HCl. [g] Footnote *g*, Table IV. [h] Lesser, R.; Gad, G. *Chem. Ber.* 1923, *56*, 963. [i] Hinkel, L. E. *J. Chem. Soc.* 1924, *125*, 1847. [j] Gleed, S. W.; Peters, A. T. *J. Chem. Soc.* 1948, 209. [k] Anwers, K. V.; Borsche, E. *Chem. Ber.* 1915, *48*, 1716. [l] Fitzgerald, J. S. *J. Appl. Chem.* (*London*) 1955, *5*, 289. [m] Anal. C: calcd, 41.76; found, 42.22.

furosemide, in both rats and dogs in Table VIII. Compound 2 displays marked saluretic and diuretic effects which are rapid in onset and relatively modest in duration, the major action occurring within the first 5 h. Compound 2 elicits slightly more chloruresis than naturiuresis. For those renal parameters measured, this comparison demonstrates that the ceiling effects of 2 are nearly equal to those of 67, and 123 in dogs, and exceed those of the remaining compounds shown therein. Interestingly, and unexpectedly, 2 elicits about the same diuretic and saluretic response in rats when administered iv, ip, or po and only slightly lower response when applied topically, a mode of administration not effective with hydrochlorothiazide or furosemide.[6]

When evaluated in spontaneously hypertensive (SH) rats, 2 (dose ≤0.312 mg/kg po) exhibits antihypertensive activity. At doses of 1.25 mg/kg po and above, the antihypertensive effects of 2 are rapid in onset (<1 h), pronounced in potency, and prolonged in duration (>24 h). Under conditions where 2 (0.312 mg/kg po) produces a pronounced antihypertensive response, none of the other compounds listed in Table VIII exhibit any hypotensive effect below 20 mg/kg po (hydrochlorothiazide) except hydralazine, a known antihypertensive agent. The latter agent is inactive at 0.5 mg/kg po but displays hypotensive activity equal to that of 2 at 1 mg/kg po. Hence, the pronounced antihypertensive properties of 2 serve to distinguish it from a subseries of potent salidiuretic agents which emerged from this study.

The third pharmacological attribute of 2, antiinflammatory activity, is demonstrated by its effect in reducing both carrageenan-induced foot edema in rats and croton oil-induced swelling in mouse ears.[7,8] These antiinflammatory properties, coupled with the antagonistic effects of indomethacin on the diuretic and antihypertensive actions of 2,[7,8] suggest that prostaglandins may play a role in mediating the pharmacological activities of 2.

The initial clinical study[9] in normal volunteers has shown that, in man, 2 elicits a marked dose-related saliuresis and diuresis with minimal kaliuresis.

Conclusion

The SAR studies cited above show that both the nuclear substitution pattern and the nature of the substituents of 2-(aminomethyl)phenols contribute significantly toward determining the level of salidiuretic activity. Nuclear substituents which induce optimal activity include a 3-position hydrogen, methyl or methoxy group, a 4-position halo or C_3–C_4 α-branched hydrocarbon, a 5-position hydrogen, lower alkyl or lower alkoxy moiety, and a 6-position iodo, bromo, or chloro group.

Experimental Section

Chemical. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Solutions were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (rotary evaporator). ^1H NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on either a Varian A-60 or T-60 NMR spectrometer. ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer. Chemical shifts for both ^1H and ^{13}C NMR are reported as δ values in parts per million relative to Me_4Si as internal standard Gas–liquid chromatography was performed on a Varian Model 1400 instrument equipped with a flame-ionization detector and a 6 ft × 2 mm i.d. glass column packed with 5% OV-210 on Chromosorb G (100–120 mesh). 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. The petroleum ether used has a boiling point range of 30–60 °C. All starting materials were commercially available unless otherwise noted.

Method A_1. 2-(Aminomethyl)-3,4,6-trimethylphenol Hydrochloride. (102). A clear solution of 2,4,5-trimethylphenol (40.8 g, 0.30 mol), 2-chloro-*N*-(hydroxymethyl)acetamide[10] (37.1 g, 0.30 mol), EtOH (200 mL), and concentrated HCl (10 mL) was heated at reflux for 30 min. Additional concentrated HCl (100 mL) was added and heating was continued for an additional 1.5 h. Crystallization of the crude hydrochloride, which separated on cooling, afforded 102 as fluffy colorless needles (13.4 g).

Method A_2. 2-(Aminomethyl)-4,6-dichloro-3-methylphenol Hydrochloride (97). A finely pulverized mixture of 2,4-dichloro-5-methylphenol (8.8 g, 0.05 mol) and 2-chloro-*N*-(hydroxymethyl)acetamide (6.2 g, 0.05 mol) was added portionwise with stirring to concentrated H_2SO_4 (50 mL) at 10 °C. After the mixture was stirred at 22 °C for 16 h, the resulting clear, dark red reaction solution was poured onto ice. The crude amide separated as a cream-colored powder, which was collected, air-dried, and hydrolyzed in EtOH–concentrated HCl (10:3, v:v; 130 mL) heated at reflux for 1.5 h. After cooling to −20 °C, the crude product was collected.

Method A_3. The amine hydrochlorides were prepared analogously to those in method A_2, except that the concentrated H_2SO_4 was replaced by an equal volume of a 1:1 mixture of concentrated H_2SO_4 and HOAc.

Method A_4. The amine hydrochlorides were prepared analogously to those in method A_2, except that the concentrated H_2SO_4 was replaced by an equal volume of a 1:2 mixture of concentrated H_2SO_4 and HOAc.

Method A_5. 2-(Aminomethyl)-4-chloro-3-methylphenol Hydrochloride (37). This compound was prepared analogously to 97 starting with 4-chloro-3-methylphenol (7.1 g, 0.05 mol), except that the concentrated H_2SO_4 was replaced by an equal volume of HOAc–concentrated H_2SO_4 (9:1; v:v): NMR (Me_2SO-d_6) δ 2.39 (3 H, s, CH_3), 4.00 (2 H, s, NCH_2), 6.96 (H-6, d, J_{5-6} = 9 Hz), 7.28 (H-5, d, J_{5-6} = 9 Hz).

Method B. 2-(Aminomethyl)-4,6-dichloro-3,5-dimethoxyphenol Hydrochloride (123). Oxime **123a** (39.8 g, 0.15 mol) was dissolved in a mixture of EtOH (500 mL) and concentrated H_2SO_4 (40 mL) and hydrogenated over 5% Rh/C (3 g) in a Parr apparatus (initial pressure = 40 psi) until no further drop in pressure was noted (ca. 2 h). The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure to afford the amine hydrosulfate as a pale yellow oil which solidified to a mass of tiny colorless needles. A solution of this solid in H_2O (600 mL) was filtered to remove traces of insoluble materials. The filtrate was made basic with 15 N NH_4OH to liberate the free base of 123 as a cream-colored powder (34 g), mp 161–162 °C. Crystallization from EtOH provided an analytical sample, mp 165–166 °C.

A suspension of the free base of 123 (34.4 g) in EtOH (150 mL) was stirred and heated on a steam bath until complete dissolution was effected by addition of saturated ethanolic HCl (ca. 30 mL). After the hot solution was filtered to remove tiny amounts of insoluble solids, the clear filtrate was cooled to ca. 5 °C and slowly diluted with ether (1.5 L). Cooling the resulting mixture to 0 °C afforded 123 (32 g).

Method C. 2-(Aminomethyl)-6-iodo-4-(1-methylpropyl)-phenol Hydrochloride (63). A solution of ICl (4.6 g, 0.027 mol) in 3 N HCl (25 mL) was added rapidly with vigorous stirring to a solution of 128 (5.8 g, 0.026 mol) in H_2O (75 mL) at 20 °C. The reaction mixture was stirred for an additional 2 h and then cooled to 0 °C. The precipitate was washed concentrated HCl and Et_2O

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Table VIII. Comparative Oral Diuretic Effects on Rats and Dogs and Effect on Arterial Pressure of Spontaneously Hypertensive Rats

	diuretic activity												
	rat					dog				activity in SH rat			
	dose, mg/kg	no. of cages	mequiv/0-5 h Na+	K+	Cl-	dose, mg/kg	no. of animals	mequiv/0-6 h Na+	K+	Cl-	dose, mg/kg po	no. of rats	max fall in MAP, mmHg (±SE)	duration of effect, h
1	3	3	0.41	0.25	0.46	1	4	5.25	2.25	6.50	20[a]	2	18	
	9	3	0.94	0.32	1.19	5	8	14.75	4.50	19.63				
	27	3	1.89	0.45	2.36	10	11	20.64	5.00	27.27				
	81	3	2.77	0.60	3.47	20	4	37.25	8.25	50.25				
2	3	9	1.46 ± 0.35	0.51 ± 0.09	2.11 ± 0.48	0.312	6	13.76 ± 2.7	4.34 ± 0.5	19.28 ± 3.5	0.078	24	16 ± 1.1	
	9	9	2.70 ± 0.19	0.77 ± 0.05	3.64 ± 0.28	0.625	6	22.3 ± 2.9	5.1 ± 0.5	30.3 ± 3.0	0.312	24	26 ± 2.1	12-18
	27	9	3.19 ± 0.16	0.88 ± 0.05	4.35 ± 0.24	2.0	3	44.9 ± 1.5	9.3 ± 0.7	57.0 ± 1.3	1.25	24	38 ± 1.6	>24
	81	9	3.51 ± 0.10	0.99 ± 0.05	4.89 ± 0.19	5.0	3	56.8 ± 5.7	9.9 ± 1.1	69.6 ± 7.7				
67	3	6	1.75	0.52	2.40	1	8	28.38	6.5	38.25	20	2	9	
	9	6	2.68	0.71	3.70	2	8	40.38	9.13	51.63	40	2	35	24
	27	6	3.16	0.94	4.31	5	8	43.13	10.38	54.25				
	81	6	3.40	0.90	4.87									
118	3	6	1.14	0.44	1.62	0.6	12	8.12	2.01	9.91	20[a]	2	10	
	9	6	2.02	0.56	2.84	1.8	12	19.43	3.62	22.93				
	27	6	2.17	0.55	3.14	5.4	4	33.15	5.90	37.20				
	81	6	2.29	0.44	3.20	16.2	4	33.33	6.25	38.78				
123	3	3	0.86	0.26	1.25						20[a]	2	35	8-12
	9	3	1.58	0.42	2.36	1	9	17.78	4.78	24.67	20	2	8	
	27	3	1.61	0.42	2.51	5	2	42.50	8.00	54.50	30	4	19 ± 4.4	
	81	3	2.17	0.39	3.26									
furosemide	9	6	0.07 ± 0.02	0.14 ± 0.02	0.22 ± 0.02	1	44	11.4 ± 1.2	4.1 ± 0.2	16.4 ± 1.5	3.75	5	12 ± 2.7	
	27	6	1.25 ± 0.14	0.55 ± 0.04	2.13 ± 0.19	5	24	28.2 ± 2.2	7.3 ± 0.4	37.0 ± 2.4	7.5	6	10 ± 1.4	
	81	6	2.44 ± 0.12	0.77 ± 0.06	3.70 ± 0.15	10	24	35.0 ± 2.4	8.4 ± 0.4	43.8 ± 3.1	30	5	12 ± 3.3	
hydrochloro-thiazide	3	6	1.23 ± 0.09	0.34 ± 0.03	1.54 ± 0.08	0.3	24	5.40 ± 0.64	1.98 ± 0.12	8.57 ± 0.72	10	9	14 ± 2.6	
	9	6	1.12 ± 0.12	0.38 ± 0.08	1.37 ± 0.21	1	24	16.4 ± 0.9	4.8 ± 0.3	22.0 ± 0.9	20	9	25 ± 2.9	<8
	27	6	1.31 ± 0.06	0.34 ± 0.05	1.56 ± 0.08	5	47	18.8 ± 1.2	7.4 ± 0.3	26.3 ± 1.2	40	10	26 ± 3.9	12
	81	6	1.28 ± 0.16	0.37 ± 0.07	1.43 ± 0.18	10	43	19.6 ± 0.9	7.1 ± 0.4	22.9 ± 0.9				
hydralazine	9	3	0.12	0.27	0.02	2	4	1.03	1.43	0.65	0.5	4	14 ± 4.7	
	27	5	0.04	0.07	0.02						1	8	37 ± 2.2	8
	81	2	0.17	0.11	0.01						2	8	57 ± 10.3	18
placebo		24	0.28 ± 0.02	0.16 ± 0.01	0.25 ± 0.01		24	0.8 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	saline	10	13 ± 1.4	

[a] ip administration.

to give **63** (8.2 g, 92%), mp 187–188 °C with dec.

Method D. 2-(Aminomethyl)-3,4-dichloro-5,6-dimethylphenol Hydrobromide (112). (a) 2-Chloro-*N*-[(5-chloro-2-methoxy-3,4-dimethylphenyl)methyl]acetamide (8a). To a solution of 4-chloro-2,3-dimethylanisole[11] (28.2 g, 0.116 mol) and 2-chloro-*N*-(hydroxymethyl)acetamide (20.4 g, 0.166 mol) in HOAc (150 mL) was added concentrated H_2SO_4 (30 mL) dropwise. The resulting reaction mixture was stirred for 16 h and then poured into H_2O (1 L). The crude amide was collected and recrystallized from EtOH–H_2O to yield acetamide **8a** (37.3 g, 81%), mp 138.5–139.5 °C. Anal. ($C_{12}H_{15}Cl_2NO_2$) C, H, N.

(b) 2-Chloro-*N*-[(5,6-dichloro-2-methoxy-3,4-dimethylphenyl)methyl]acetamide (9a). To a stirred mixture of **8a** (2.76 g, 0.01 mol) and anhydrous aluminum chloride (1.45 g, 0.011 mol) was added a mixture of freshly distilled sulfuryl chloride (3.0 g) and sulfur monochloride (4 drops).[4] The frothy brown reaction mixture was stirred at 80–85 °C for 90 min. After cooling, the pasty mixture was added to a solution of concentrated HCl (20 mL) in H_2O (200 mL). A pale yellow powder (2.8 g) separated, which was collected and crystallized from H_2O–EtOH to afford **9a** (0.75 g, 24%), mp 189–190 °C. Anal. ($C_{12}H_{14}Cl_3NO_2$) C, H, N.

(c) 112. A mixture of **9a** (1.0 g, 0.032 mol), 48% HBr (10 mL), and acetic acid (10 mL) was refluxed for 30 min. The solid which separated upon cooling to 5 °C was collected and washed with Et_2O. Recrystallization from EtOH–48% HBr afforded **112** (0.53 g, 55%), as colorless needles.

2-(Aminomethyl)-3,5-dichloro-4,6-dimethylphenol Hydrobromide (113). (a) 2-Chloro-*N*-[(2-methoxy-3,5-dimethylphenyl)methyl]acetamide (8b). This compound was prepared analogously to **8a** beginning with 2,4-dimethylanisole[12] (42.2 g, 0.31 mol). Recrystallization from EtOH–H_2O gave **8b** (10.5 g, 14%), mp 124–124.5 °C. Anal. ($C_{12}H_{16}ClNO_2$) C, H, N.

(b) 2-Chloro-*N*-[(4,6-dichloro-2-methoxy-3,5-dimethylphenyl)methyl]acetamide (9b). This compound was prepared analogously to **9a**, starting with **8b** (8 g, 0.033 mol). Recrystallization from EtOH–H_2O gave **9b** (1.6 g, 16%), mp 205–206 °C. Anal. ($C_{12}H_{14}Cl_3NO_2$) C, H, N.

(c) 113. The methoxyacetamide **9b** (1.6 g, 5.2 mmol) was hydrolyzed as described for the preparation of phenol **112**. Recrystallization from EtOH–48% HBr gave **113** (1.06 g, 68%).

2-(Aminomethyl)-5,6-dichloro-3,4-dimethylphenol Hydrobromide (115). (a) 2-Chloro-4,5-dimethylanisole (7c). 2-Chloro-4,5-dimethylphenol (31.3 g, 0.20 mol) was reacted with dimethyl sulfate (75.6 g, 0.6 mol) in 20% NaOH (100 mL). Recrystallization from petroleum ether afforded **7c** (24.4 g, 72%), as colorless prisms, mp 46.5–47 °C.

(b) 2-Chloro-*N*-[(3-chloro-2-methoxy-5,6-dimethylphenyl)methyl]acetamide (8c). Anisole **7c** (3.4 g, 0.02 mol) was amidoalkylated using the procedure described for the preparation of **8a**. Recrystallization from H_2O–EtOH provided **8c** (2.05 g, 37%), mp 155–156 °C, as fluffy, colorless needles. Anal. ($C_{12}H_{15}Cl_2NO_2$) C, H, N.

(c) 2-Chloro-*N*-[(3,4-dichloro-2-methoxy-5,6-dimethylphenyl)methyl]acetamide (9c). This compound was prepared analogously to **9a** starting with **8c** (7.8 g, 0.028 mol). Recrystallization from H_2O–EtOH gave **9c** (2.8 g, 32%) mp 185–186 °C, as fluffy, colorless needles. Anal. ($C_{12}H_{14}Cl_3NO_2$) C, H, N.

(d) 115. The methoxy acetamide **9c** (2.8 g, 9 mmol) was hydrolyzed as described for the preparation of **112**. Recrystallization from EtOH–48% HBr gave **115** (2.15 g, 79%).

Method E. 2-(Aminomethyl)-3,5-dimethylphenol Hydrochloride (38). Chlorophenol **11** (4.4 g, 0.02 mol) was dissolved in H_2O (250 mL) containing NaOH (2.8 g, 0.07 mol) and hydrogenated over 5% Pd/C (1 g) in a Parr apparatus (initial pressure = 30 psi) until H_2 uptake ceased. The catalyst was removed by filtration, and the filtrate was acidified with concentrated HCl to pH 2, refiltered, and made basic with 15 N NH_4OH, whereupon crude aminomethylphenol (1.8 g), mp 141–143 °C, was deposited.

Method F. 6-(Aminomethyl)-2,4-dichloro-3-ethylphenol Hydrochloride (18a). Pulverized 2-chloro-*N*-(hydroxymethyl)acetamide (12.3 g, 0.10 mol) was added portionwise with stirring to a cold (5 °C) solution of 3-ethylphenol (12.2 g, 0.10 mol) in HOAc–concentrated H_2SO_4 (9:1, v:v; 100 mL). After the mixture was stirred at 22 °C for 16 h, the resulting clear solution was poured into H_2O (1 L). The crude amide separated as a brown oil, which was extracted into ether and washed successively with H_2O, saturated brine, and dried. Evaporation of the dried solution gave a brown oil (16.4 g), which was shown by TLC and ^1H NMR to be a mixture of at least three different amidoalkylation products.

The crude amide was dissolved in $CHCl_3$ (100 mL) and treated with SO_2Cl_2 (18 mL, 0.22 mol). After standing at ambient temperature for 3 h, the clear brown solution was evaporated and the residual oil was refluxed in EtOH–concentrated HCl (1:1; 140 mL) for 3 h. After cooling to −20 °C, the crude product was collected and washed well with ether: ^1H NMR (Me_2SO-d_6) δ 1.07 (3 H, t, CH_3, J = 7 Hz), 2.85 (2 H, q, CH_2, J = 7 Hz), 3.67 (2 H, s, NCH_2), 7.45 (H-3, s); ^{13}C NMR (Me_2SO-d_6) δ 12.3 (CH_3), 24.8 (CH_2), 37.2 (NCH_2), 122.4 (C-4, t), 122.8 (C-6, m), 123.4 (C-2, m), 129.2 (C-3, d, t), 139.7 (C-5, m), 150.4 (C-1, d, t). Both the ^1H and ^{13}C NMR spectra for compounds **18a**, **18c**, and **118** are consistent with the assigned structures.

6-(Aminomethyl)-2,4-dichloro-3-(1,1-dimethylethyl)phenol Hydrochloride (18b). This compound was prepared analogously to **18a**, starting with 3-(1,1-dimethylethyl)phenol (15 g, 0.10 mol).

2-(Aminomethyl)-4,6-dichloro-5-(1,1-dimethylethyl)-3-methylphenol Hydrochloride Hemihydrate (18c). This compound was prepared analogously to **18a**, starting with 5-(1,1-dimethylethyl)-3-methylphenol (8.2 g, 0.05 mol): ^1H NMR (Me_2SO-d_6) δ 1.67 (9 H, s, t-C_4H_9), 2.39 (3 H, s, CH_3), 4.08 (2 H, d, NCH_2). NMR confirms the presence of 0.5 mol of H_2O.

2-Iodo-4-(1-methylethyl)phenol (16a). This compound was prepared similarly to **16c**, starting with 4-(1-methylethyl)phenol (27.2 g, 0.20 mol). Distillation under reduced pressure yielded **16a** as a colorless oil (26.1 g, 50%): bp 137–140 °C (14 mm); 98.9% purity established by GLC analysis. Anal. ($C_9H_{11}IO$) H; C: calcd, 41.25; found, 41.79.

2-Chloro-4-(2-methylpropyl)phenol (16b). Freshly distilled sulfuryl chloride (5.34 mL, 8.94 g, 0.066 mol) was added dropwise to a solution of 4-(2-methylpropyl)phenol (9.2 g, 0.061 mol) in $CHCl_3$ (75 mL) with stirring at 20 °C. The clear, yellow reaction mixture was stirred at ambient temperature for an additional 16 h and then the $CHCl_3$ and excess sulfuryl chloride were removed. Distillation of the residual amber oil yielded **16b** as a pale yellow liquid (9 g, 80%): bp 85–90 °C (1–1.2 mm), lit.[13] bp 82 °C (3 mm); NMR (Me_2SO-d_6) δ 0.85 (6 H, d, $(CH_3)_2CH$), 2.39 (2 H, d, $CH_2C_6H_3$), 7.02–7.23 (3 H, m, C_6H_3), 9.88 (H, s, OH).

4-(1,1-Dimethylethyl)-2-iodophenol (16c). A mixture of 4-(1,1-dimethylethyl)phenol (75 g, 0.50 mol), ICl (82.6 g, 0.51 mol), and HOAc (375 mL) was refluxed for 8 h. The dark purple solution was cooled to ambient and poured into H_2O (2 L) containing $NaHSO_3$ (ca. 10 g) with vigorous stirring. After the reaction mixture was decanted, the insoluble crude solid was triturated with cold (−10 °C) petroleum ether (200 mL) to yield **16c** (124 g, 90%), mp 70–72 °C, as a pale beige powder. An analytical sample was prepared by distillation to give **16c** as a clear oil, bp 78–80 °C (0.3 mm), which crystallized as colorless feathery needles, mp 73–75 °C. Anal. ($C_{10}H_{13}IO$) C, H.

2-Chloro-3,4,5-trimethylphenol (16e).[14] This compound was prepared analogously to **16d**, starting with 3,4,5-trimethylphenol (27.2 g, 0.20 mol). After the steam distillate (3 L) cooled in an ice bath, the crude product separated as a faint yellow powder, which was collected and crystallized from petroleum ether to afford **16e** as tiny, faint yellow needles (8.5 g, 25%): mp 71–73 °C; NMR δ 2.15 (3H, s, CH_3), 2.22 (3 H, s, CH_3), 2.32 (3 H, s, CH_3), 5.41 (H, s, HO), 6.74 (H-6, s).

4-Chloro-3,5-dimethoxyphenol (16f).[15] This compound was prepared analogously to **16d**, starting with 3,5-dimethoxyphenol (11.2 g, 0.073 mol). After ca. 1.5 L of distillate was collected, the pot was cooled. The beige needles which separated were collected,

(11) Dahmi, K. S.; Stothers, J. B. *Can. J. Chem.* **1966**, *44*, 2855.
(12) Stohmann, F.; Rodatz, P.; Herzberg, W. *J. Prakt. Chem.* **1887**, *35*, 22.
(13) Footnote *m*, Table IV.
(14) Improved procedure over that of Kosower, E. M.; Wu, G. S. *J. Org. Chem.* **1963**, *28*, 633; mp 66.5–73 °C.
(15) Improved procedure over that of Grove, J. F.; Jeffs, P. W.; Rustidge, D. W. *J. Chem. Soc.* **1956**, 1956; mp 128–130 °C.

dried, and crystallized from benzene to give **16f** as pink crystals (3.34 g, 25%), mp 131–135 °C.

2-Bromo-4-chloro-3,5-dimethoxyphenol (16g). A solution of Br_2 (8 g, 0.05 mol) in $CHCl_3$ (25 mL) was added rapidly to a stirred solution of **16f** (9.4 g, 0.05 mol) in $CHCl_3$ (150 mL) at 20 °C. Stirring was continued for 30 min, and then the solvent was evaporated to provide a brown oil which was distilled at 132–135 °C (0.1 mm). The colorless, viscous distillate solidified upon standing at 20 °C to colorless needles, mp 57–59 °C. Recrystallization from benzene–hexane gave pure **16g** (2.58 g, 19%): mp 64–65 °C; NMR (Me_2SO-d_6) δ 3.75 (3 H, s, CH_3O), 3.78 (3 H, s, CH_3O), 6.53 (H-6, s), 10.37 (H, s, HO). Anal. ($C_8H_8BrClO_3$) C, H.

2-Chloro-3,5-dimethoxy-4-methylphenol (16h). This compound was prepared analogously to **16b**, starting with 3,5-dimethoxy-4-methylphenol[16] (10.7 g, 0.064 mol). Distillation of the brown oil afforded **16h** as a pale yellow, viscous oil (7.0 g, 54%), bp 106–108 °C (0.5 mm). Anal. ($C_9H_{11}ClO_3$) C, H.

2,4-Dichloro-3,5-diethoxyphenol (16i). (a) **4-Chloro-3,5-diethoxyphenol (16d).** 3,5-Diethoxyphenol[17] (20.6 g, 0.113 mol) was chlorinated with freshly distilled sulfuryl chloride (9.14 mL, 0.113 mol) as described in the preparation of **16b**. The residual brown oil was steam distilled to remove traces of the 2-chloro isomer (ca. 5 L of distillate was collected). The white solid which separated upon cooling the pot residue was collected, dried, and crystallized from benzene–hexane (2:1) to give **16d** (8.5 g 35%), mp 107.5–109 °C. Anal. ($C_{10}H_{13}ClO_3$) C, H.

(b) **16i.** A solution of freshly distilled sulfuryl chloride (3.23 mL, 0.04 mol) in $CHCl_3$ (10 mL) was added dropwise to a solution of **16d** (8.4 g, 0.04 mol) in $CHCl_3$ (100 mL) maintained at reflux. The reaction mixture was heated at reflux for an additional 10 min and then cooled to and stored at 20 °C for 40 h. Evaporation of the solvent left a residue, which crystallized from petroleum ether to provide **16i** (5 g, 50%), mp 61–62 °C. Anal. ($C_{10}H_{12}Cl_2O_3$) C, H.

4,5-Dichloro-2-(trifluoromethyl)phenol (22). (a) ***N*-[2-Chloro-5-(trifluoromethyl)phenyl]hydroxylamine (20).** A solution of NH_4Cl (4.2 g) in H_2O (50 mL) was added to a refluxing solution of 4-chloro-3-nitro-1-(trifluoromethyl)benzene (**19**; 45.12 g, 0.20 mol) in EtOH (210 mL). The heat was removed and Zn dust (ca. 38 g) was added portionwise to the stirred mixture over a 30-min period at such a rate as to maintain a gentle reflux. After heating for an additional 30 min, the mixture was filtered, cooled, and diluted with H_2O (500 mL). The oil that subsequently separated was extracted into Et_2O. The ethereal extract was dried and evaporated to afford **20** (38 g, 90%) as a red-brown oil. A small portion was crystallized from petroleum ether to afford beige prisms, mp 59–64 °C.

(b) **4-Amino-3-chloro-6-(trifluoromethyl)phenol (21).** The hydroxylamine **20** (38 g, 0.18 mol) was dissolved in 1.8 N H_2SO_4 (350 mL). The resulting mixture was heated at 80–85 °C under CO_2 for 45 min, cooled, and extracted with Et_2O. The aqueous phase was adjusted to pH 6.5 with 10% NaOH and, finally, to neutrality with $NaHCO_3$. The precipitated solid was extracted into Et_2O. After drying, the organic extract was evaporated. The residue was crystallized from benzene to give **21** (8.36 g, 22%): mp 181–183 °C dec; NMR (CF_3CO_2H) δ 6.87 (H-4, s), 7.37 (H-2, s).

(c) **22.** A solution of **21** (10.6 g, 0.05 mol) in 3.2 N HCl (300 mL) was treated with a solution of $NaNO_2$ (3.5 g) in H_2O (10 mL) added dropwise at 0–5 °C. The cold reaction solution was then added with stirring to a solution of freshly prepared Cu_2Cl_2 (from 15.6 g of $CuSO_4 \cdot 10H_2O$) in concentrated HCl (30 mL) cooled in an ice bath. The mixture was allowed to warm to 20 °C and then heated at 80–85 °C for 1 h. The mixture was steam distilled to give **22** (6.28 g, 54%), which crystallized from petroleum ether as colorless needles: mp 60–61 °C; NMR δ 5.58 (H, s, OH), 7.15 (H-6, s), 7.63 (H-3, s). Anal. ($C_7H_3Cl_2F_3O$) H; C: calcd, 36.39; found, 35.25.

4-(1,1-Dimethylethyl)-2-(methylthio)phenol (24a).[5] Me_2SO (3.6 mL, 0.05 mol) was added dropwise with vigorous stirring to a mixture of 4-(1,1-dimethylethyl)phenol (7.5 g, 0.05 mol), 70% $HClO_4$ (10 mL), and $POCl_3$ (8 mL) at 0 °C. The ice bath was removed after an additional 1 h, and the reaction mixture was stirred at 20 °C for 16 h. The resulting clear solution was poured onto ice, whereupon the crude salt separated as a gum which gradually changed to a white powder on warming to 20 °C. The heterogeneous mixture was cooled to 0 °C and filtered. The collected precipitate was washed with ice–H_2O (20 mL), air-dried, washed with Et_2O, and added to a hot saturated solution of KCl (100 mL). The resulting mixture was refluxed for 4 h, cooled to 20 °C, and extracted with Et_2O. After the phases were separated, the orgamic layer was washed with H_2O and saturated brine and dried. Evaporation of the dried extract provided **24a** as a colorless liquid (5.7 g, 58%): NMR δ 1.25 (9 H, s, *t*-C_4H_9), 2.28 (3 H, s, CH_3S), 6.42 (H, s, HO), 6.75–7.43 (3 H, m, C_6H_3). Anal. ($C_{11}H_{16}OS$) C, H.

4-(1,1-Dimethylethyl)-2-(ethylthio)phenol (24b). This compound was prepared similarly to **24a**, starting with 4-(1,1-dimethylethyl)phenol (5.4 g, 0.036 mol) and diethylsulfoxide (5 g, 0.036 mol). Distillation of the residue afforded **24b** as a colorless oil (2 g, 26%), bp 67–72 °C (0.4 mm). Anal. ($C_{12}H_{18}OS$) H, S; C: calcd, 68.50; found, 68.04.

4-(1,1-Dimethylethyl)-2-fluorophenol (26a). This compound was prepared analogously to **26c** starting with 2-fluorophenol (**25a**; 11.2 g, 0.10 mol). Concentration of the reaction mixture by distillation (≤110 °C at 30 mm) left **26a** in the distillation pot as an oily residue (3.5 g, 21%): NMR δ 1.27 (9 H, s, *t*-C_4H_9), 5.30 (H, s, HO), 6.83–7.40 (3 H, m, C_6H_3).

4-(1,1-Dimethylethyl)-2-(trifluoromethyl)phenol (26b). A mixture of 2-(trifluoromethyl)phenol (**25b**; 25 g, 0.15 mol), *tert*-butyl alcohol (12 g, 0.16 mol), CF_3COOH (100 mL), and concentrated H_2SO_4 (2 mL) was stirred at 20 °C for 48 h.[18] The reaction mixture was concentrated in vacuo at ≤40 °C to a residual liquid, which was dissolved in benzene (500 mL) and washed successively with H_2O, saturated $NaHCO_3$, and saturated brine and dried. Evaporation of the dried solution gave a deep purple residual oil, which was distilled to provide **26b** as a pale pink oil (13.6 g, 41%), bp 120–132 °C (65 mm), of 98% purity (GLC analysis) which crystallized on standing at 20 °C. Recrystallization from petroleum ether afforded pure **26b**: mp 83–85 °C; NMR δ 1.30 (9 H, s, *t*-C_4H_9), 5.50 (H, s, HO), 6.78–7.72 (3 H, m, C_6H_3).

2-Chloro-4-(1,1-dimethylethyl)-5-methoxyphenol (26c). A mixture of 2-chloro-5-methoxyphenol (**25c**; 15.8 g, 0.10 mol), benzene (30 mL), and concentrated H_2SO_4 (0.5 mL) was stirred vigorously at 60 °C while isobutylene (excess) was introduced via a gas-dispersion tube over a 5-h period. Then the mixture was cooled and extracted with 5% NaOH (100 mL). The aqueous layer was acidified with concentrated HCl and the oily product was extracted into benzene. The organic extract was dried, concentrated, and distilled to provide **26c** as a light yellow oil (12.5 g, 58%), bp 102–103 °C (1 mm), which crystallized on standing at 20 °C: NMR δ 1.32 (9 H, s, *t*-C_4H_9), 3.78 (3 H, s, CH_3O), 5.40 (H, s, HO), 6.57 (H-6, s), 7.15 (H-3, s).

Compound **26c** was prepared also in 49–52% yield by the method used in the preparation of **26b**.

2-(4-Chlorophenoxy)-4-(1,1-dimethylethyl)phenol (29). (a) **4′-Chloro-5-(1,1-dimethylethyl)-2-methoxydiphenyl Ether (29a).** An intimate mixture of pulverized sodium 4-chlorophenoxide (**27**; 48 g, 0.32 mol), Cu powder (4 g), anhydrous copper acetate (3 g), and 2-bromo-4-(1,1-dimethylethyl)anisole (**28**;[19] 77.5 g, 0.32 mol) was heated at 240 °C for 4 h. The reaction mixture was cooled and distributed between H_2O and Et_2O. The organic layer was washed with 2 N NaOH (2 times) and H_2O and dried. Evaporation of the solvent left a residual oil, which was distilled to yield **29a** as a colorless liquid (30.3 g, 33%): bp 125–132 °C (0.2 mm); NMR δ 1.27 (9 H, s, *t*-C_4H_9), 3.77 (3 H, s, CH_3O), 6.75–7.32 (7 H, m, aromatic H's).

(b) **29.** A mixture of HOAc (75 mL), 48% HBr (20 mL), and **29a** (20 g, 0.07 mol) was heated at reflux for 6 h. Upon cooling and pouring into H_2O, the crude phenol was deposited as a white powder. Crystallization from petroleum ether (200 mL) afforded **29** (14 g, 74%): mp 86–88 °C; NMR δ 1.22 (9 H, s, *t*-C_4H_9), 5.37

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(H, s, OH), 6.90–7.43 (7 H, m, aromatic H's).

2,3-Dichloro-6-hydroxybenzaldehyde Oxime (36a). (a) **2,3-Dichloro-6-hydroxybenzaldehyde (14a).** To a mixture of $Ca(OH)_2$ (200 g), Na_2CO_3 (225 g), and 3,4-dichlorophenol (**13a**; 82 g, 0.50 mol) in H_2O (1 L) was added dropwise $CHCl_3$ (108 g, 1.50 mol) with stirring over 1.75 h at 65 °C. Heating and stirring were continued for an additional 6 h. The mixture was acidified with concentrated HCl (60 mL) and steam distilled. When the distillate (2.5 L) cooled, the solid that separated was collected and crystallized from EtOH to afford **14a** (16.4 g, 17%): mp 95–97 °C; NMR δ 6.88 (H-5, d, $J_{4,5}$ = 9 Hz), 7.56 (H-4, d, $J_{4,5}$ = 9 Hz). Anal. ($C_7H_4Cl_2O_2$) C, H, Cl.

(b) **36a.** To a warm solution of **14a** (5.7 g, 30 mmol) in EtOH (30 mL) was added a solution of hydroxylamine hydrochloride (6.7 g, 100 mmol) and Na_2CO_3 (5.5 g, 50 mmol) in H_2O (15 mL). The resulting clear solution was heated at reflux for 1 h and evaporated to one-half its original volume. The solid that separated upon cooling was crystallized from 90% EtOH to afford **36a** (5.5 g, 89%), mp 179–182 °C. Anal. ($C_7H_5Cl_2NO_2$) C, H, N.

5-Chloro-2-hydroxy-3,6-dimethoxybenzaldehyde Oxime. (104a). (a) **5-Chloro-2-hydroxy-3,5-dimethoxybenzaldehyde** (14b). This compound was prepared analogously to **14a**, starting with 4-chloro-2,5-dimethoxyphenol (13b;[20] 19.2 g, 0.102 mol). Crude 14b (2.3 g), mp 76–84 °C, was obtained as light yellow crystals from the steam distillate.

(b) **104a.** This compound was prepared similarly to **36a**, starting with 14b (2.3 g, 0.011 mol). The reaction mixture was diluted with hot H_2O (15 mL) and cooled to give the crude oxime which, after crystallization from H_2O–EtOH, provided **104a** (1.2 g), mp 125–145 °C.

3,5-Dichloro-2-hydroxy-4,6-dimethoxybenzaldehyde Oxime (123a). (a) **3,5-Dichloro-2-hydroxy-4,6-dimethoxybenzaldehyde (16j).** A solution of sulfuryl chloride (42 mL, 0.53 mol) in $CHCl_3$ (50 mL) was added dropwise over a 1-h period to a refluxing solution of freshly distilled 2-hydroxy-3,5-dimethoxybenzaldehyde (43.7 g, 0.24 mol) in $CHCl_3$ (100 mL). Halfway through the sulfuryl chloride solution addition, a solid precipitated which redissolved on further addition of the sulfuryl chloride solution. The reaction mixture was refluxed for 3 h. Additional sulfuryl chloride (4.6 mL) was added and the mixture was refluxed for an additional 16 h. Removal of the solvent left a peach-colored powder, which was triturated with petroleum ether to yield **16j** (53 g, 88%), mp 112–118 °C. A sample was purified for analysis by recrystallization first from a mixture of HOAc–H_2O (3:1, v:v) and then from EtOH–H_2O (3:2) and, finally, sublimation at 100 °C (0.1 mm). Thereby was obtained pure **16j**, mp 121–123 °C. Anal. ($C_9H_8Cl_2O_4$) C, H.

(b) **123a.** This compound was prepared similarly to **36a**, starting with **16j** (45.5 g, 0.18 mol). The reaction mixture, after being reduced in volume, was poured into H_2O (400 mL) whereupon the crude oxime separated. Crystallization from 50% EtOH yielded **123a** (39.8 g, 82.9%) as essentially colorless needles, mp 173–175 °C. Anal. ($C_9H_9Cl_2NO_4$) C, H, N.

2-(Aminomethyl)-4-(1-methylpropyl)phenol Hydrochloride (128). This compound was prepared by method A_5, starting with 4-(1-methylpropyl)phenol (15 g, 0.10 mol). The hot EtOH–concentrated HCl hydrolysis solution was diluted with 2 volumes of concentrated HCl and cooled to −20 °C. Thereby was obtained **128** as fluffy colorless needles (5.8 g, 26%), mp 187–188 °C. Anal. ($C_{11}H_{17}NO$·HCl) H, N; C: calcd, 61.25; found 61.73.

2-(Aminomethyl)-4-(1,1-dimethylpropyl)phenol (129). This compound was prepared by method A_5, starting with 4-(1,1-dimethylpropyl)phenol (32.8 g, 0.20 mol). The residue obtained by evaporation of the EtOH–concentrated HCl solution (after hydrolysis) was triturated with Et_2O and crystallized from EtOH–Et_2O and EtOH–concentrated HCl to provide **129** as colorless needles (17.1 g, 37%): mp 192–193.5 °C; NMR (Me_2SO-d_6/D_2O) δ 0.60 (3 H, t, CH_3CH_2), 1.17 [6 H, s, $(CH_3)_2C$], 1.57 (2 H, q, CH_2CH_3), 3.97 (2 H, d, CH_2N), 6.73–7.33 (3 H, m, C_6H_3). Anal. ($C_{12}H_{19}NO$·HCl) C, H, N.

2-(Aminomethyl)-4-(1-methylcyclopentyl)phenol (130). This compound was prepared by method A_5, starting with 4-(1-methylcyclopentyl)phenol[21] (5.28 g, 0.03 mol). Crystallization from EtOH–concentrated HCl provided **130** (4.3 g, 59%), mp 224–225 °C. Anal. ($C_{13}H_{19}NO$·HCl) C, H, N.

2-(Aminomethyl)-4-(2-methylpropyl)phenol (131). This compound was prepared by method E, starting with **64** (2.1 g, 8.4 mmol) and using 33% EtOH (300 mL) as solvent. Treatment with 15 N NH_4OH gave **131** (1.3 g, 86%): mp 145–146 °C; NMR (Me_2SO-d_6) δ 0.85 [6 H, d, $(CH_3)_2CH$], 1.43–2.00 [H, m, $HC(CH_3)_2$], 2.35 (2 H, d, CH_2CH), 3.87 (2 H, s, CH_2N), 5.15 (3 H, s, HO + H_2N), 6.60–7.00 (3 H, m, C_6H_3).

2-(Aminomethyl)-4-(1,1-dimethylethyl)-3-methoxyphenol Hydrochloride (132). This compound was prepared by method E, starting with **105** (3.2 g, 0.0114 mol). Crystallization from EtOH–Et_2O (1:50) gave **132** (1.8 g, 64%), mp 207–208 °C.

Pharmacology. Intravenous Dog Diuretic Assay. Conditioned female mongrel dogs in the postabsorptive state were given 500 mL of water orally 1 h before induction of anesthesia with sodium pentobarbital (30 mg/kg iv). After induction of anesthesia, each dog was prepared with an indwelling bladder catheter, and also at that time exogenous creatinine (4 g as a 10% solution) was administered subcutaneously in multiple injection sites. To ensure uniform hydration and urine production, a phosphate–mannitol buffer, pH 7.4, was administered throughout the study. Administration of phosphate–mannitol buffer, pH 7.4, was carried out in the following manner. Two solutions were prepared: solution A, phosphate stock (devoid of mannitol) for *stat* presentation of phosphate, pH 7.4, Na_2HPO_4 (15.62 mg/mL) and KH_2PO_4 (4.08 mg/mL); and solution B, phosphate infusion (containing mannitol) for venoclysis (3.0 mL/min) of phosphate and mannitol, pH 7.4, Na_2HPO_4 (2.60 mg/mL), KH_2PO_4 (0.68 mg/mL), and mannitol (40.00 (mg/mL). Multiliter quantities of the above solutions were prepared in advance as sterile, pyrogen-free reagents. Before clearance studies were commenced, 1.5 mL/kg of phosphate stock solution A (20 mg of phosphate/kg) was administered intravenously, *stat*, followed by 3.0 mL/min of phosphate infusion solution B (6.9 mg of phosphate/min). At the start of timed clearances, the urinary bladder was emptied and replicate 15-min urine collections were made, with venous blood samples being drawn at the midpoint of each period. Following this control phase, the compound in question was administered intravenously as a *stat* injection, and replicate 15-min clearances were obtained for a period of 2 h. In occasional experiments, direct mean arterial blood pressures were obtained by needle puncture of a femoral artery. For effective renal plasma flow studies, 150 mg/kg po of *p*-aminohippurate (PAH) was administered by gavage with the 500-mL water load. The diuretic response was scored from 0 to 6 according to the criterion shown in Table II.

Oral Rat Diuretic Activity.[22] Female rats (Charles-River, 150–170 g) were maintained overnight on a sugar diet with water ad libitum. The test substance was dissolved in pure DMF and subsequently diluted with water (which contained 3 drops of Tween 80 per 100 mL) such that the final vehicle was 4% DMF. At the time of the test, animals were given the vehicle (as placebo) or test substance suspended in a final volume of 5.0 mL po. Rats were housed in groups of three in metabolism cages. Urine was collected for the 0–5 h interval in graduated cylinders and was analyzed for sodium, potassium, and chloride content. Animals that received placebo were run concurrently. Results are reported as milliequivalents × 100 per cage and are the geometric means of three cages per dose level. Standard methodology was used for determination of electrolyte levels. The diuretic response was scored from 0 to 6 according to the Na^+ criterion shown in Table III.

Oral Dog Diuretic Activity.[22] Oral tests were carried out on a colony of trained female mongrel dogs weighing 8–10 kg. All dogs received 100 mL of water the previous day and were fasted overnight. On the day of the test, 250 mL of water was administered orally, followed by 500 mL of water (orally) 1 h later. One hour after the last oral priming dose of water, bladders were

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emptied by catheterization and the study was commenced by administration of compound or placebo. Compounds were given in gelatin capsules and the animals were maintained in metabolism cages for collection of spontaneously voided urine. Spontaneous urine was combined with bladder urine collected by catheterization at the end of 6 h. Urine volumes were measured, and aliquots were analyzed for sodium, potassium, and chloride content by standard methodology. Values are reported as geometric means.

Oral Activity in SH Rat. Antihypertensive activity was estimated in vivo in spontaneously hypertensive (SH) rats as described by Watson and Ludden.[23]

Topical Rat Activity. Female rats (Charles-River, 150–170 g) were maintained overnight on a sugar diet with water ad libitum. The substance was dissolved in a mixture of 70% ether, 25% pyridine, and 5% H_2O such that each 0.2-mL aliquot contains the doese to be evaluated. At the time of the test, each animal was given 5 mL of H_2O po and 0.2 mL of drug mixture in the vehicle topically to the shaved back. Warm air (using a hair dryer) was blown across the back for 1 min to evaporate moisture. Rats were housed in groups of three in metabolism cages. Urine was collected for 0 to 5 h and 5 to 24 h in graduated cylinders and was analyzed for sodium, potassium, and chloride content. Animals receiving placebo (vehicle) were run concurrently. Results were tabulated as milliequivalents (or milliliters) per cage and were the geometric means (±SE) of the number of cages for each dose level.

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Analgesic Narcotic Antagonists. 4.[1] 7-Methyl-*N*-(cycloalkylmethyl)-3-hydroxymorphinan-6-ones and -isomorphinan-6-ones

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3,6-Dimethoxy-7β,17-dimethyl-4-hydroxy-5,6,8,14-tetradehydromorphinan (**2**) was converted to the 4-deoxy compound **4** and hydrolyzed to a mixture of the B/C-cis (C series) and B/C-trans (T series) isomers of 7,8-didehydromorphinan-6-one, **5**. Hydrogenation of the separated isomers gave 7-methyl-6-oxo derivatives **6a**. 7,8-Dimethyl- (**6b**) or 7-methyl-8-ethylmorphinan-6-one (**6c**) was prepared by reaction of **5** with lithium organocuprates. The analgesic *N*-methyl compounds **6** were converted to 17-(cyclopropylmethyl) or 17-(cyclobutylmethyl) derivatives **10–13**. Some of these compounds had mixed profiles of narcotic agonist–antagonist effects. Studies with drug-dependent monkeys indicated that several of these compounds with an analgesic–antagonist ratio of less than 0.4 substitute for morphine.

The modification of opiate compounds continues to be an actively investigated area of medicinal chemistry. The goal of these studies is to prepare analgesic compounds, based on naturally occurring structures, which do not possess addiction liability and do not have other undesirable side effects. As part of our program directed toward this goal, we have studied the influence of alkyl groups in the 8 position of various *N*-(cycloalkylmethyl)morphinans.[2,3] During work to extend these studies, we unexpectedly found that thebaine (**1**) reacts with lithium dimethylcuprate to yield 7β-methyldihydrothebaine-φ (**2**).[4] This unique starting material offered entry into a series of 7-methyl- and 7-methyl-8-alkylmorphinan- and -isomorphinan-6-ones. These derivatives could be converted to potential mixed analgesic narcotic antagonists. This report concerns the results of our studies in this area.

Chemistry. It is recognized that 4-hydroxymorphinans are less potent analgesic agents than the corresponding 4-deoxy derivatives. Removal of this group from **2** was carried out in a manner analogous to that reported by Sawa and co-workers for dihydrothebaine-φ.[5] Compound **2** was converted to the 4-phenyl ether **3** by reaction with bromobenzene and cleaved to yield **4** by use of sodium in a liquid ammonia–toluene mixture (Scheme I).

Various acidic conditions were investigated for hydrolysis of enol ether **4**. Treatment of **4** with hot 25% HCl gave an equimolar mixture of the B/C-cis and -trans isomers, **5C** and **5T**. On a preparative scale, 90% aqueous acetic acid produced an approximately 2:1 mixture of **5C** and **5T**. The separated isomers **5** were hydrogenated to give saturated compounds **6**. The assignment of stereochemistry to the B/C juncture in **6Ta** and **6Ca**, and thus in **5**, is based on the characteristic *m/e* 59 ion found in the mass spectral fragmentation pattern of ring C saturated B/C-cis isomers and by the relative abundance of the molecular ions (trans > cis).[6] In the spectrum of **6Ca**, *m/e* 59 was the base peak with a low observable M^+ peak; for **6Ta**, the molecular ion was usually the base peak. The 7-methyl group is assigned the more stable equatorial configuration[4] in each case.

Reaction of **5** with Me_2CuLi proceeded smoothly to give good yields of the 7,8-dimethyl compounds, **6b**. In contrast, the reaction of **5** with Et_2CuLi did not proceed in

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