[(3-Aryl-1,2-benzisoxazol-6-yl)oxy]acetic Acids. A New Diuretic Series

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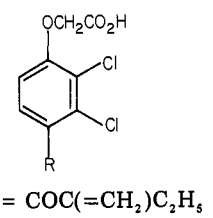
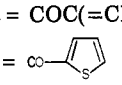
A series of [(3-aryl-1,2-benzisoxazol-6-yl)oxy]acetic acids was synthesized and tested for diuretic activity in saline-loaded mice and in conscious, water-loaded dogs. The structural requirements for good diuretic activity in both mice and dogs were found to be very specific. In summary, the compounds with the best diuretic activity (**13i**, **13q**, and **13ff**) were substituted with a 2-fluorophenyl group at the 3 position and chlorine or bromine at the 7 position. Compound **13ff**, [[7-bromo-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetic acid (HP 522), was found to be moderately uricosuric in chimpanzees and was selected for further development.

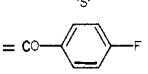
The family of phenoxyacetic acid diuretics has expanded greatly in recent years to include not only ethacrynic acid (**1a**) and the associated (acryloylphenoxy)acetic acids[1] but also the (indanyloxy)acetic acids[1,2] [exemplified by **2** (MK 196)] and the (4-acylphenoxy)acetic acids [**1b** (tienilic acid)[3] and **1c**].[4] Recent developments include the 5-acylbenzofuran-2-carboxylic acids[5] (**3**) and (4-arylsulfonyl)phenoxyacetic acids[6] (**4**).



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

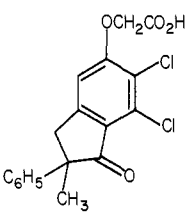


1b, R = CO-(2-thienyl)



1c, R = CO-(4-fluorophenyl)

4 R = SO_2Ar



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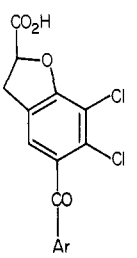

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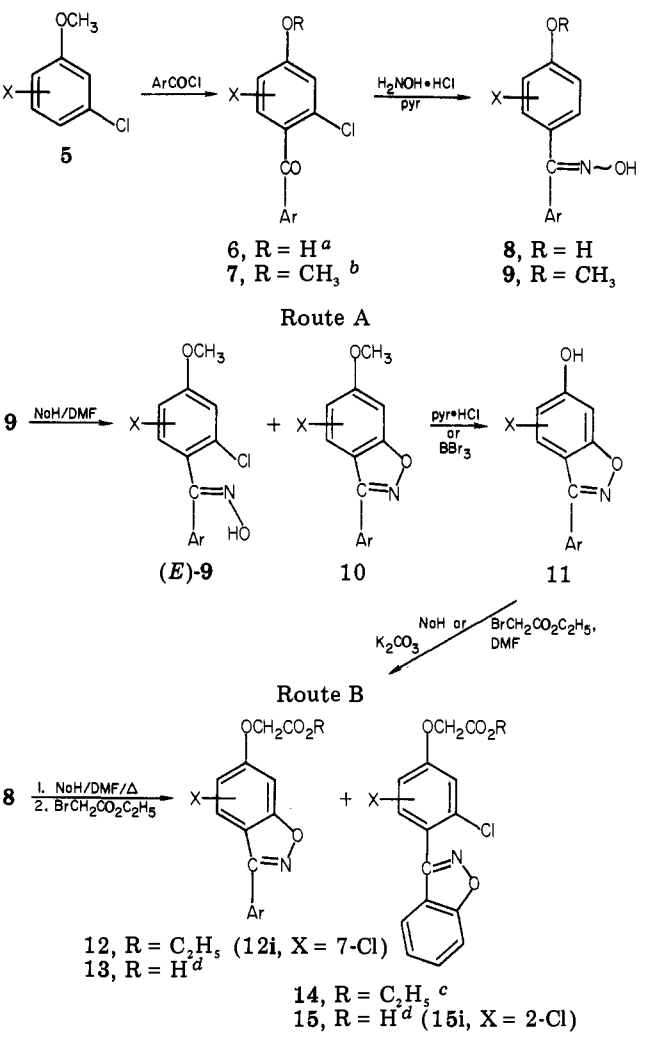
These compounds comprise a particularly interesting class of diuretics because they span the range from loop diuretics which cause uric acid retention (**1a**), to uricosuric loop diuretics (**2**), to uricosuric diuretics with a low-ceiling profile (**1b**). The salidiuretic and uricosuric activities of **3**[5] (Ar = 2-thienyl) have been found to reside separately in the (+) and (−) enantiomers, respectively. We report here a series of [(3-aryl-1,2-benzisoxazol-6-yl)oxy]acetic acids (**13**) which have their own unique place among the phenoxyacetic acid diuretics.[7]

Scheme I



[a] Excess $AlCl_3$. [b] 1 equiv of $AlCl_3$. [c] Obtained when Ar = 2-FC_6H_4 or 2-ClC_6H_4. [d] $NaOH/H_2O/EtOH$.

Chemistry. The synthesis of benzisoxazoles has been reviewed.[8] Most of the (1,2-benzisoxazol)oxyacetic acids (**13**, Table I) were synthesized from 2-chlorobenzophenones **6** and **7** (Scheme I), which were obtained from appropriately substituted 3-chloroanisoles and aroyl chlorides under typical Friedel–Crafts conditions. The hydroxybenzophenones **6** were obtained either in two steps through the intermediacy of the methoxybenzophenones **7** or in one

(1) O. W. Woltersdorf, Jr., S. J. deSolms, E. M. Schultz, and E. J. Cragoe, Jr., *J. Med. Chem.*, **20**, 1400 (1977), and references contained therein.
(2) O. W. Woltersdorf, Jr., S. J. deSolms, E. M. Schultz, E. J. Cragoe, Jr., L. S. Watson, and G. M. Fanelli, Jr., *J. Med. Chem.*, **21**, 437 (1978).
(3) G. Thuillier, J. Laforest, B. Cariou, P. Bessin, J. Bonnet, and J. Thuillier, *Eur. J. Med. Chem.*, **9**, 625 (1974).
(4) P. H. Jones, D. S. Bariana, A. K. L. Fung, Y. C. Martin, J. Kyncl, and A. Lall, U.S. Patent 4 058 559 (1977).
(5) W. F. Hoffman, O. W. Woltersdorf, Jr., F. C. Novello, E. J. Cragoe, Jr., J. P. Springer, L. S. Watson, and G. M. Fanelli, Jr., *J. Med. Chem.*, **24**, 865 (1981).
(6) E. J. Cragoe, Jr., and O. W. Woltersdorf, Jr., U.S. Patent 4 115 402 (1978).
(7) This work has been presented in part at the ASPET-FASEB meetings, Anaheim, CA, Apr 13–18, 1980. See also J. C. Wilker, J. Kitzen, W. J. Novick, S. Raite, L. Setescak, G. Shutske, and R. C. Allen, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **39**, 520 (1980).
(8) K.-H. Wünsch and A. J. Boulton, *Adv. Heterocycl. Chem.*, 8, 277 (1967).

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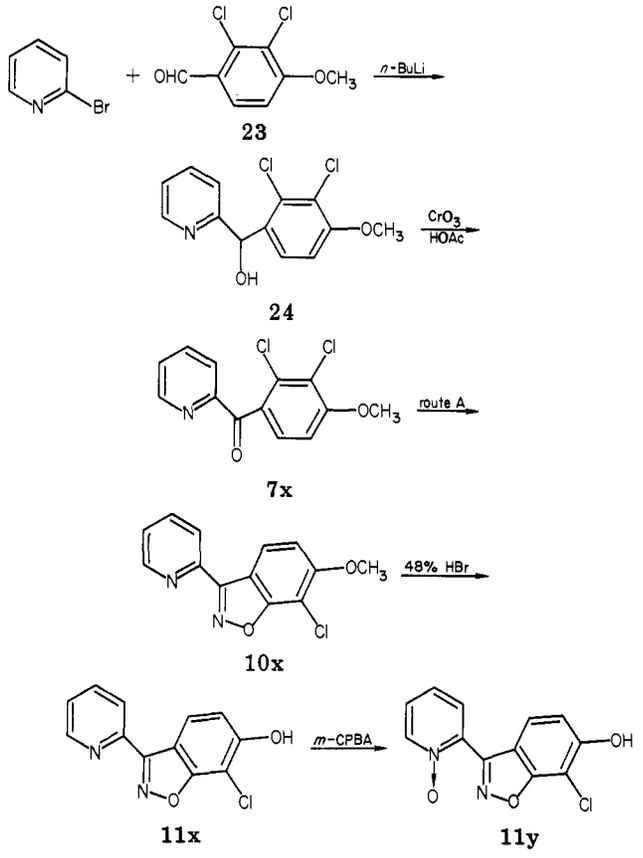
Scheme II



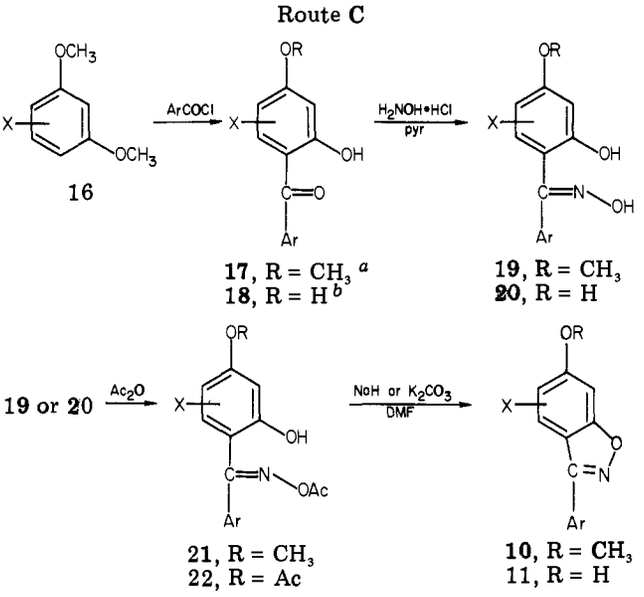
step using excess Lewis acid. Treatment of **6** or **7** with hydroxylamine hydrochloride in refluxing pyridine gave the hydroxy- or methoxybenzophenone oximes **8** or **9** as mixtures of *E* and *Z* isomers. The oxime isomer mixtures were then treated according to route A or route B, depending on the nature of the Ar group.

Compounds **9** were generally base sensitive and were treated with sodium hydride in DMF at room temperature (route A) to give methoxybenzisoxazoles (**10**) and unreacted (*E*)-oximes, (*E*)-**9**. Straightforward elaboration of the methoxy group of **10** via **11** gave the esters **12** and acids **13**. When the Ar group would withstand more vigorous conditions, the phenol oxime mixture (**8**) was treated with sodium hydride in hot DMF (route B), followed by alkylation of the resulting phenolate anion to give esters **12** directly. Hydrolysis then led to the corresponding acids **13**.

A slight variation on these procedures was used in the synthesis of the 2-pyridyl derivatives **11x** and **11y** (Scheme II). It was convenient to react aldehyde **23**[3] with 2-lithiopyridine and then oxidize carbinol **24** to the desired **7x**. Treatment according to route A gave phenol **11x** after cleavage of the methoxy group with 48% HBr. Oxidation with *m*-chloroperbenzoic acid gave the phenolic *N*-oxide **11y**. Phenols **11x** and **11y** then gave the oxyacetic acids **13x** and **13y** in a straightforward fashion.

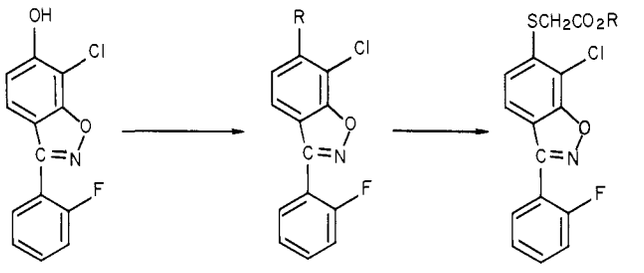
A complication arose when the Ar group was 2-chloro or 2-fluorophenyl (Scheme I). The two phenol oxime isomers gave rise, through route B, to a [(3-aryl-1,2-benzisoxazol-6-yl)oxy]acetic ester (**12i**, for example; see Experimental Section) and a 4-(1,2-benzisoxazol-3-yl)-phenoxyacetic ester (**14i**). Since maximal diuretic activity was found to reside in the 2-fluorophenyl derivatives of **13** (see structure–activity section), this was an undesirable complication. In one case (Scheme VI) it was convenient to separate the desired (*Z*)-oxime isomer (*Z*)-**9l** by its insolubility in diethyl ether and then regenerate the benzophenone from the residual (*E*)-oxime with sodium bisulfite in refluxing aqueous ethanol. In general, however, route C (Scheme III) was used to synthesize the 3-(2-fluorophenyl) derivatives.

Scheme III



[a] 1 equiv of $AlCl_3$. [b] Excess $AlCl_3$.

Scheme IV

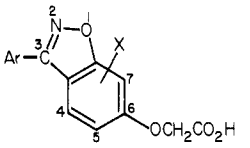


[a] $NaH/ClC(=S)N(CH_3)_2$/DMF. [b] 205 °C/45 min. [c] $NaOH/H_2O$/MeOH. [d] $BrCH_2CO_2C_2H_5/K_2CO_3$/DMF. [e] $NaOH/H_2O$/EtOH.

In route C, the appropriate resorcinol dimethyl ethers **16** were acylated with the required 2-fluorobenzoyl chloride. By controlling the Friedel–Crafts conditions, we obtained either the 2-hydroxy-4-methoxybenzophenone (**17**) or the dihydroxybenzophenone (**18**). Treatment of **17** or **18** with hydroxylamine hydrochloride in refluxing pyridine gave predominately the (*E*)-oximes **19** or **20**, respectively. Traces of (*Z*)-oxime were usually removed via recrystallization, although in one case (**19ee**, X = 3-CH_3, Ar = 2-FC_6H_4) the (*Z*)-oxime was isolated by chromatography for ^{13}C NMR comparison with the (*E*)-oxime.[9]

(9) Carbon-1 of the 2-fluorophenyl group was readily identified by combining a low-power noise-decoupling technique which identifies quaternary carbons (ref 10) with a consideration of ^{19}F coupling constants. This carbon absorbed at 125.5 ppm in the minor isomer (*Z*)-**19ee** and at 120.1 ppm in the major isomer (*E*)-**19ee**. These shifts are consistent with the shielding due to the syn oxygen (ref 11) and with published results for benzophenone-like oximes (ref 12). The ^{13}C NMR spectra of a number of compounds in this series will be the subject of a later paper.

Table I. [(3-Aryl-1,2-benzisoxazol-6-yl)oxy]acetic Acids [a]



no.	Ar	X	route	mp, °C	yield, [b] %	recrystn solvent [c]	formula [d]
13a	C_6H_5	7-Cl	B	219-221	55	E	$C_{15}H_{10}ClNO_4$
13b	4-ClC_6H_4	7-Cl	B	254-257	73	C-E	$C_{15}H_9Cl_2NO_4$
13c	4-$CH_3C_6H_4$	7-Cl	B	257-260	54	C	$C_{16}H_{12}ClNO_4$
13d	3,4-$Cl_2C_6H_3$	7-Cl	B	222-224	64	C-E	$C_{15}H_8Cl_3NO_4$
13e	2-$C_{10}H_7$	7-Cl	B	172-174	71	J	$C_{19}H_{12}ClNO_4$
13f	2,3-$(CH_3)_2C_6H_3$	7-Cl	B	170-172	96	J	$C_{17}H_{14}ClNO_4$
13g	2-$CH_3C_6H_4$	7-Cl	B	179-181	70	J	$C_{16}H_{12}ClNO_4$
13h	2-ClC_6H_4	7-Cl	B	165-168	64	J	$C_{15}H_9Cl_2NO_4$
13i	2-FC_6H_4	7-Cl	B	188-189	63	F-H	$C_{15}H_9ClFNO_4$
13j	3-FC_6H_4	7-Cl	A	205-209	84 [e]	F-H	$C_{15}H_9ClFNO_4$
13k	4-FC_6H_4	7-Cl	B	233-236	49 [e]	F-H	$C_{15}H_9ClFNO_4$
13l	2-F-4-OHC_6H_3	7-Cl	*f*	216-218	53 [e]	A-J	$C_{15}H_9ClFNO_5$
13m	2,4-$F_2C_6H_3$	7-Cl	A	200-203	54 [e]	B	$C_{15}H_8ClF_2NO_4$
13n	4-Cl-2-FC_6H_3	7-Cl	A	226-227	65 [e]	F	$C_{15}H_8Cl_2FNO_4$
13o	2,3-$F_2C_6H_3$	7-Cl	C	184-187	71 [e]	J	$C_{15}H_8ClF_2NO_4$
13p	2,5-$F_2C_6H_3$	7-Cl	C	193-196	76 [e]	J	$C_{15}H_8ClF_2NO_4$
13q	2,6-$F_2C_6H_3$	7-Cl	A	170-172	70 [e]	B-J	$C_{15}H_8ClF_2NO_4$
13r	2-furyl	7-Cl	B	230-233	71	I	$C_{13}H_8ClNO_5$
13s	3-furyl	7-Cl	B	225-227	72	C-G-H	$C_{13}H_8ClNO_5$
13t	5-CH_3-2-furyl	7-Cl	B	217-219	77	G	$C_{14}H_{10}ClNO_5$
13u	2-thienyl	7-Cl	B	217-220	91	F	$C_{13}H_8ClNO_4S$
13v	5-CH_3-2-thienyl	7-Cl	B	235-238	78	I	$C_{14}H_{10}ClNO_4S$
13w	3-CH_3-2-thienyl	7-Cl	A	180-182	75 [e]	E-K	$C_{14}H_{10}ClNO_4S$
13x	2-pyridyl	7-Cl	*g*	257-259	92 [e]	D-H	$C_{14}H_9ClN_2O_4$
13y	2-pyridyl *N*-oxide	7-Cl	*g*	214 dec	67 [e]	C-H	$C_{14}H_9ClN_2O_5$
13z	2-FC_6H_4	5-Cl	A	214-215	91	B-J	$C_{15}H_9ClFNO_4$
13aa	2-FC_6H_4	4-Cl	C	172-174	78	J	$C_{15}H_9ClFNO_5$ [h]
13bb	2-FC_6H_4	5,7-Cl_2	*i*	205-207	70	B-J	$C_{15}H_8Cl_2FNO_4$
13cc	2-FC_6H_4	4,5,7-Cl_3	*i*	222-224	85	J	$C_{15}H_7Cl_3FNO_4$
13dd	2-FC_6H_4	5-Br	C	223-224	73	B	$C_{15}H_9BrFNO_4$
13ee	2-FC_6H_4	7-CH_3	C	158-160	89 [e]	J	$C_{16}H_{12}FNO_4$
13ff	2-FC_6H_4	7-Br	*i*	180-182	84 [e]	B-J	$C_{15}H_9BrFNO_4$
13gg	2-FC_6H_4	7-I	*i*	178-180	76 [e]	J	$C_{15}H_9IFNO_4$
13hh	2-FC_6H_4	H	C	182-184	70 [e]	B-J	$C_{15}H_{10}FNO_4$

[a] All compound exhibited IR, ^1H NMR, and MS spectra consistent with the structures. [b] These yields are for the hydrolysis of the appropriate esters by method F except where otherwise indicated. [c] A = acetic acid, B = acetonitrile, C = dimethylformamide, D = dimethyl sulfoxide, E = ethyl acetate, F = ethanol, G = methanol, H = water, I = 2-propanol, J = toluene, K = hexane. [d] All compounds gave satisfactory C, H, and N analyses except where indicated. [e] This yield is from the appropriate phenol. See methods C or J in the Experimental Section. [f] Refer to Scheme VI. [g] Refer to Scheme II. [h] C: calcd, 56.00; found, 56.69. [i] Refer to Scheme V.

Treatment of **19** or **20** with acetic anhydride gave the oxime acetates **21** or **22**, which were cyclized with either sodium hydride/DMF at room temperature or potassium carbonate/DMF at 65 °C to give benzisoxazoles **10** or **11**. Typical synthetic transformations gave the desired acids **13**.

The thioacetic acid **29** (Scheme IV) was synthesized from phenol **11i** by the method of Newman.[13]

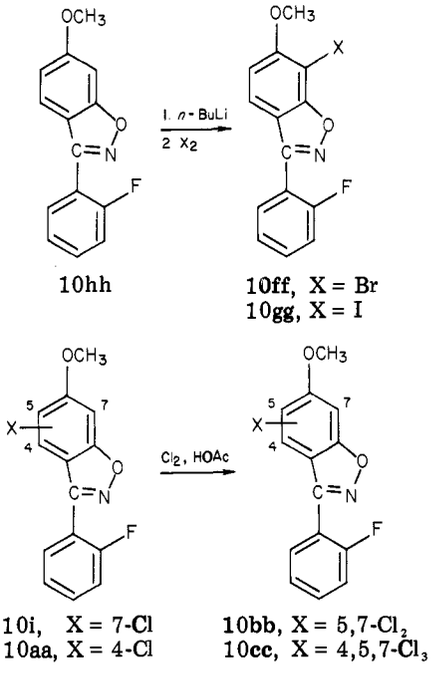
It was possible to metallate the 7 position of **10hh** (Scheme V) using *n*-butyllithium at low temperature and then treat it with either iodine in diethyl ether or liquid bromine to give the 7-bromo and 7-iodo derivatives **10ff** and **10gg**, respectively. The polychlorinated derivatives **10bb** and **10cc** were obtained from the chlorination of **10i** and **10aa**, respectively, in glacial acetic acid. The structures of halogenated derivatives **10bb,cc,ff,gg** were assigned unambiguously by ^{13}C NMR.[10]

Scheme VI deserves a final comment. The Friedel–Crafts acylation of 3-fluorophenetole[14] with the acid chloride **30**[3] gave approximately a 1:1 mixture of benzophenones **7l** and **7ii**, which were assigned unambiguously, again by ^{13}C NMR,[10] after separation by preparative HPLC. After generation and separation of the desired oximes as described above, the ring closure of (*Z*)-**9l** to **10l** proceeded in 89% yield. At this stage, pyridine hydrochloride differentiated sufficiently between the methoxy and ethoxy groups to give **11l** in 66% yield. Having selectively retained the ethoxy group, it was a simple matter to alkylate in typical fashion to give **12l** and cleave the ethyl ether and ethyl ester with boron tribromide, followed by sodium hydroxide, to give the desired 2-fluoro-4-hydroxy derivative **13l**.

Structure–Activity Relationships. Target compounds **13a–hh**, **29**, **15i**, and **12i** were evaluated for diuretic

(10) G. M. Shutske and M. N. Agnew, *J. Heterocycl. Chem.*, 18, 1025 (1981).
(11) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972, pp 129–131.
(12) J. H. Wikel, C. J. Paget, D. C. DeLong, J. D. Nelson, C. Y. E. Wu, J. W. Paschal, A. Dinner, R. J. Templeton, M. O. Chaney, N. D. Jones, and J. W. Chamberlin, *J. Med. Chem.*, **23**, 368 (1980).
(13) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, 31, 3980 (1966).
(14) F. Swarts, *Bull. Sci. Acad. R. Belg.*, 241 (1913).

Scheme V



10hh

10ff, X = Br
10gg, X = I

10i, X = 7-Cl
10aa, X = 4-Cl

10bb, X = 5,7-Cl_2
10cc, X = 4,5,7-Cl_3

activity per os in saline-loaded mice[15] at 4 and 64 mg/kg and in conscious water-loaded dogs at 20 mg/kg. Since urine, Na^+ and Cl^- excretion roughly paralleled each other, only Na^+ excretion is presented for brevity (Table II).

Saline-Loaded Mice. Several compounds in the 4-(1,2-benzisoxazol-3-yl)phenoxyacetic acid series, represented by **15i** (X = 2-Cl, Table II) were tested in mice and found to be less active in comparison to the [(3-aryl-1,2-benzisoxazol-6-yl)oxy]acetic acids (**13a–hh**). The latter compounds showed excellent diuretic activity within a well-defined pattern of structure–activity relationships.

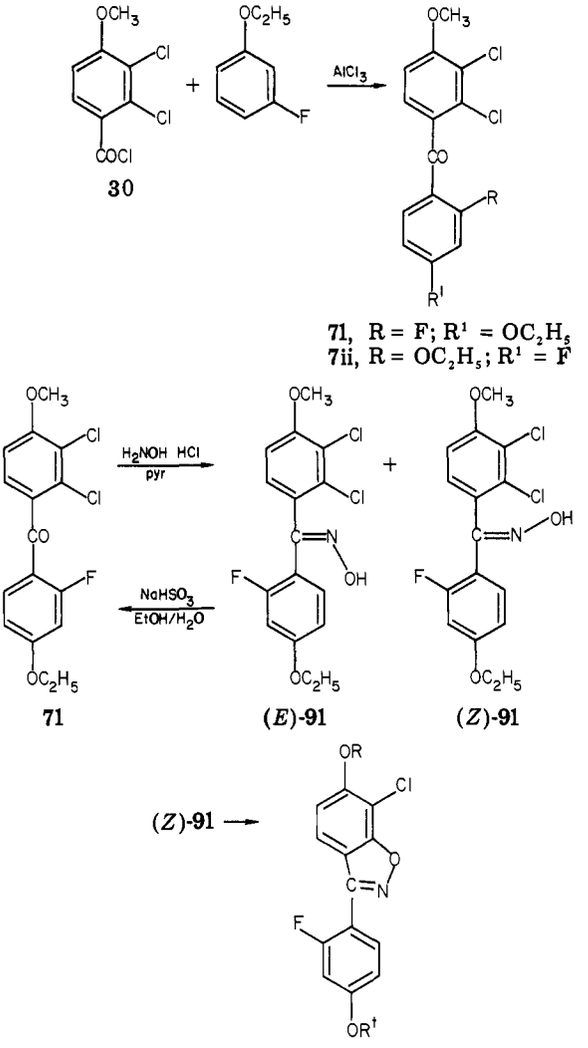
In considering the structural requirements for diuretic activity within this series, it is convenient to first group those compounds together in which the substituent on the benzisoxazole ring is constant at 7-chloro and the 3-aryl moiety is varied (**13a–y**, Table II). In addition, it is instructive to divide this group into two subgroups, the first comprising the substituted phenyl derivatives **13a–q** and the second including the heterocyclic derivatives **13r–y**.

In regard to the first subgroup, it is readily apparent from Table II that diuretic activity reaches a peak in the compounds containing a 2-chloro- or 2-fluorophenyl group, **13h,i,o,p,q**. The 2,3- and 2,5-difluorophenyl compounds **13o** and **13p** were only slightly less active over the 5-h testing period at 64 mg/kg than the 2-chloro-, 2-fluoro-, or 2,6-difluorophenyl derivatives **13h,i,q**. The 2,4-difluoro- and 2-fluoro-4-chlorophenyl derivatives **13m** and **13n**, however, were dramatically less active. This suggested the possibility of an active metabolite, perhaps hydroxylated at the 4 position of the phenyl ring. Such a compound **13l**, was considerably less active per os in the mouse, however.

Over the 5-h testing period, compounds **13h,i,p,q** caused a greater Na^+ excretion than **2**, ethacrynic acid, or tienilic acid at 64 mg/kg. This was also true for **13i,p,q** at 4 mg/kg.

With regard to the second subgroup of compounds, **13r–y**, no compound attained the level of activity in the mouse that was seen with **13h,i,o,p,q**. Even **13y**, the pyridyl *N*-oxide, which should have approximated the size and charge distribution of the 2-fluorophenyl group,[16] was only weakly active.

Scheme VI



30

71, R = F; R^1 = OC_2H_5
7ii, R = OC_2H_5; R^1 = F

71 (*E*)-91 (*Z*)-91

(*Z*)-91 →

101, R = CH_3; R^1 = C_2H_5 [a]
111, R = H; R^1 = C_2H_5 [b]
121, R = $CH_2CO_2C_2H_5$; R^1 = C_2H_5 [c]
121′, R = $CH_2CO_2C_2H_5$; R^1 = H [d]
131, R = CH_2CO_2H; R^1 = H [e]

[a] NaH/DMF. [b] Pyr·HCl. [c] $BrCH_2CO_2C_2H_5/K_2CO_3$/DMF. [d] BBr_3/CH_2Cl_2. [e] $NaOH/H_2O$/EtOH.

In the second group of compounds, **13z–hh**, the 3-aryl portion of the molecule was held constant at 2-fluorophenyl and the substituents in the benzisoxazole ring were varied. Here again the best diuretic activity in the mouse was tightly clustered around one substitution pattern, i.e., a single substituent at the 7 position (compounds **13ee** and **13ff**). The 7-methyl derivative (**13ee**) was slightly less active than the 7-chloro compound **13i** (the lead compound from the first group) at both 64 and 4 mg/kg per os. The 7-bromo compound **13ff** caused more Na^+ excretion at 64 mg/kg than **13i**. Most probably, either a steric or lipophilic limit was passed with the 7-iodo compound **13gg**, which was only slightly more active than the compound containing no additional substituents, **13hh**.

The conversion of the oxygen of the oxyacetic acid side chain to a sulfur was deliterious to diuretic activity in the mouse, even with the desirable 3-(2-fluorophenyl)-7-chloro substitution pattern (**29**). Also, the ethyl ester **12i** of po-

(15) M. F. Sim and R. H. Hopcroft, *J. Pharm. Pharmacol.*, 28, 609 (1976).

(16) H. Förster and F. Vögtle, *Angew. Chem., Int. Ed. Engl.*, 16, 429 (1977).

Table II. Oral Diuretic Activity in Mice and Dogs

compd	mouse,[a] (mequiv of Na^+/kg)/5 h			dog,[a] (μequiv of Na^+/kg)/h		
	4 mg/kg	64 mg/kg	vc[b]	n[c]	20 mg/kg[d]	vc[e]
13a	0.8	1.7	0.5	6	47.5 (1)	41.9
13b	0.5	0.5	0.2	3	41.2 (1)	51.7
13c	0.8	0.6	0.2	3	29.3 (4)	27.7
13d	0.6	0.1	0.4	6	101.6 (2)	125.1
13e	1.2	1.1	1.1	6	53.3 (2)	67.8
13f		0.02	0.5	4	219.9 (1)	79.3
13g	0.02	1.76	0.6	6	66.9 (2)	72.6
13h	0.6	9.1	0.6	3	48.2 (2)	65.4
13i	3.5	10.0	0.05	6	1267.5 (2)	54.4
13j	0.75	0.81	1.1	6	50.6 (3)	70.9
13k	0.4	0.4	1.1	6	178.7 (5)	44.9
13l	0.5	0.6	0.3	6	43.5 (1)	61.3
13m	0.7	0.9	0.8	5	41.7 (1)	66.8
13n	1.8	1.4	0.2	4	156.2 (1)	138.1
13o		5.8	1.4	6	80.0 (5)	58.1
13p	2.2	8.3	0.2	6	926.2 (5)	64.1
13q	5.3	10.4	0.6	5	1081.4 (4)	45.8
13r		0.6	0.5	6	199.2 (4)	63.7
13s	0.6	2.1	0.4	4	293.0 (2)	30.9
13t	0.3	1.5	0.2	6	37.4 (2)	30.8
13u	0.4	1.0	0.2	4	77.5 (1)	55.0
13v		0.5	0.8	6	122.4 (2)	101.0
13w		0.7	0.5	6	97.7 (4)	161.7
13x	0.5	1.0		5	61.2 (5)	41.9
13y	0.5	1.0	0.8	6	116.6 (1)	162.3
13z	0.6	0.2		5	49.8 (1)	85.2
13aa	1.59	1.16	0.22	3	82.1 (4)	86.8
13bb		0.41	0.32	4	85.7 (3)	88.2
13cc	0.53	1.65	0.10	4	109.0 (3)	67.0
13dd	0.47	0.28	0.55			
13ee	1.86[f]	7.24	0.16	6	478.9 (4)	132.4
13ff	1.02	11.53	0.71	5	1970.7 (2)	65.3
13gg	0.07	3.41	0.42	6	617.3 (3)	57.9
13hh	0.57[f]	2.89	0.07	3	33.6 (3)	96.9
29	1.37	4.67	0.42	6	328.4 (4)	100.9
15i	0.33	1.49	0.30	4	81.6 (1)	57.1
12i		1.48	1.47	3	39.1 (3)	52.7
furosemide	1.93	7.96	0.4	6	1311.5 (2)[g]	140.6
ethacrynic acid	1.09	4.14	0.3	6	703.6 (1)	17.8
2	2.1	7.6	0.2	4	1141.4 (2)[h]	122.7
tienilic acid	1.11	3.31	0.1	6	302.3 (2)	42.6

[a] See Experimental Section for testing methodology. [b] Vehicle control (saline). The mean vehicle control value for each group of mice or dogs is given as an indication of the reliability of the results. [c] Number of experimental animals contributing to the mean value. [d] The value in parentheses is the number of hours after dosing at which the observed peak effect occurred. [e] Each dog served as its own control. This value is from the hour immediately prior to dosing. [f] Dosed at 8 mg/kg. [g] Dosed at 5 mg/kg. [h] Dosed at 10 mg/kg.

Table III. Time Course of Diuretic Activity in Dogs

compd	n[b]	vc[c]	hourly μequiv of Na^+ following 5 mg/kg per os[a]						
			1	2	3	4	5	6	7
13i	6	62.6	48.6	499.4	727.0	503.7	458.2	241.7	146.2
13q	6	95.0	108.4	98.9	257.2	431.8	397.0	342.6	190.0
13ff	6	93.8	106.8	1083.0	1182.6	869.0	503.3		
furosemide	6	140.6	1207.0	1311.5	763.6	333.9	144.1	40.4	
tienilic acid[d]	6	42.6	127.5	302.3	207.3	77.4	36.5	22.1	21.2

[a] Refer to footnote *a* in Table II. [b] Refer to footnote *c* in Table II. [c] Refer to footnote *b* in Table II. [d] Dosed at 20 mg/kg.

tent **13i** was only weakly active.

Conscious Dog. In general, compounds in this series which did not show good activity in mice were similarly weakly active diuretics in conscious, water-loaded dogs at 20 mg/kg per os.

The 3-(2-chlorophenyl) compound (**13h**) and the 3-(2,3-difluorophenyl) compound (**13o**) showed minimal Na^+ excretion in the dog at this dose, while they had good activity in the mouse at 64 mg/kg. Also, the 3-(2,5-difluorophenyl) derivative (**13p**) had a delayed onset in dogs.

Compounds **13i,q,ee,ff** retained good activity in the dog, although their relative potencies (compared at the time of peak effect) were different than in the mouse. The 7-bromo derivative (**13ff**) caused the greatest hourly excretion of Na^+, surpassing the 5 mg/kg dose of furosemide per os. Compounds **13i** and **13q** were nearly equipotent, while **13ee**, the 7-methyl derivative, actually caused a lower peak effect than the 7-iodo compound (**13gg**).

Other Data. Table III shows the time course of the response in water-loaded dogs to 5 mg/kg per os of furosemide and **13i,q,ff** and 20 mg/kg of tienilic acid. It is apparent that the onset of action of the benzisoxazole diuretics is a little later than furosemide, but the duration of action is also longer. These compounds cause a much

more intense and more prolonged excretion of Na^+ than tienilic acid.

Compounds **13i,q,ff** were tested for diuretic and uricosuric activity iv in unconscious chimpanzees and for chronic uricosuric activity per os in normal chimps.[17,18] All three compounds produced a good acute diuretic response and a moderate to strong uricosuria. After chronic per os dosing, the 7-bromo derivative, **13ff**, produced a modest fall in blood uric acid levels that was maintained throughout the duration of the 10-day experiment and remained lower than control values for several days upon cessation of the drug. The need for a diuretic to be uricosuric at all has been adequately stated elsewhere.[19,20] We find this moderate uricosuria desirable because of the tendency of powerful uricosurics to precipitate acute crystalluria.[21]

The 7-bromo compound (**13ff**) has also been the subject of clearance experiments in the dog.[17] Results from this study suggest that **13ff** appears to be a potent diuretic with at least one site of action in the medullary ascending limb of Henle's loop.

It is tempting to assign a steric role to the key 2-fluoro substitution in the 3-aryl moiety of these diuretics. In 2-fluorobenzoic acid, for example, the carbonyl group is twisted about 10° out of the plane of the aromatic ring, at least in the crystalline state.[22] Benzoic acid, on the other hand, is estimated to be planar.[23,24] As Sharpe[25] points out, however, it is difficult to separate the electronic effect of the Ar–F bond from the steric effect. This was born out in our case by the lack of activity in the 2-pyridyl *N*-oxide (**13y**) in which steric effects should have been similar.[16]

In summary, [[7-bromo-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetic acid (HP 522) is a potent diuretic in mice and dogs with moderate uricosuric properties. Because of this desirable profile, it has been chosen for further study in man.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457), ^1H NMR (JEOL C60HL), and mass spectral (Finnigan Model 4000 GC–MS) data. In certain cases (see ref 9) structural assignments were supported by ^{13}C NMR (JEOL FX60). Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements (performed by Micro-Tech Laboratories, Skokie, IL) were within 0.4% of theoretical values.

Route A. (2,3-Dichloro-4-methoxyphenyl)(3-methyl-2-thienyl)methanone (7w). 3-Methyl-2-thiophenecarbonyl chloride (32.8 g, 0.20 mol) and 2,3-dichloroanisole (35.4 g, 0.20 mol) were dissolved in 200 mL of CS_2 and $AlCl_3$ (26.7 g, 0.20 mol) was added portionwise. The reaction was refluxed for 40 h and then poured into ice and 5% HCl. The crystalline **7w** was collected by filtration and washed with hexane to give 52 g (86%) of pure product. A small sample was recrystallized from toluene/hexane and had mp 136–138 °C. Anal. ($C_{13}H_{10}Cl_2O_2S$) C, H, S.

(2,3-Dichloro-4-methoxyphenyl)(3-methyl-2-thienyl)methanone Oxime (9w). Method A. A mixture of **7w** (36.0 g, 0.12 mol) and H_2NOH·HCl (42 g, 0.60 mol) was refluxed for 24 h in 350 mL of pyridine. The solvent was evaporated and the residue was partitioned between Et_2O and 5% HCl. From the organic phase was obtained 38 g (99%) of **9w** as a mixture of isomers that was not purified further.

7-Chloro-3-(3-methyl-2-thienyl)-6-methoxy-1,2-benzisoxazole (10w). The mixture **9w** was dissolved in 70 mL of DMF and added to a suspension of NaH (3.3 g, 0.14 mol) in 100 mL of DMF. After 1 h, the reaction mixture was poured into H_2O, and the precipitated products were collected by filtration after acidification with concentrated HCl. Recrystallization from Et_2O gave 11.9 g (35%) of pure **10w**, mp 155–156 °C. Anal. ($C_{13}H_{10}ClNO_2S$) C, H. N, S. Evaporation of the Et_2O mother liquors and recrystallization from $CHCl_3$/hexane gave 12.9 g of the unreacted (*E*)-oxime, (*E*)-**9w**, mp 141–143 °C. Anal. ($C_{13}H_{11}Cl_2NO_2S$) C, H, N.

7-Chloro-6-hydroxy-3-(3-methyl-2-thienyl)-1,2-benzisoxazole (11w). Method B. A mixture of **10w** (13.3 g, 0.048 mol) and BBr_3 (25 g, 0.10 mol) was refluxed overnight in 220 mL of CH_2Cl_2. Workup with H_2O/Et_2O gave 12.0 g (94%) of **11w** after trituration with hexane, mp 184–186 °C. The analytical sample was recrystallized from toluene and had mp 197–198 °C. Anal. ($C_{12}H_8ClNO_2S$) C, H, N.

[[7-Chloro-3-(3-methyl-2-thienyl)-1,2-benzisoxazol-6-yl]oxy]acetic Acid (13w). Method C. The phenol **11w** (10.3 g, 0.039 mol) was dissolved in 60 mL of DMF and added to a suspension of NaH (1.1 g, 0.046 mol) in 40 mL of DMF. Ethyl bromoacetate (6.7 g, 0.040 mol) was then added, after which the reaction was warmed to 50 °C for 30 min. Water (100 mL) and 25% NaOH (10 mL) were then added, and the reaction temperature increased to 90 °C. After an additional 3 h at this temperature, it was poured into H_2O and acidified with concentrated HCl. Extraction into Et_2O and then recrystallization from EtOAc/hexane gave 9.44 g of **13w** (75%), mp 180–182 °C. Anal. ($C_{14}H_{10}ClNO_4S$) C, H, N.

α-(2,3-Dichloro-4-methoxyphenyl)-2-pyridinemethanol (24). 2-Bromopyridine (Aldrich; 29.3 g, 0.185 mol) in 150 mL of dry THF was added to 75 mL of 2.6 M *n*-butyllithium (0.195 mol) that was chilled to −65 °C. 2,3-Dichloro-4-methoxybenzaldehyde[3] (**23**; 38.0 g, 0.185 mol) was then added in 300 mL of THF, and the reaction was allowed to come to room temperature. It was poured into H_2O, and the crystalline product was collected by filtration, washed with Et_2O, and dried to give 42.8 g (81%) of **24**, mp 174–176 °C. An analytical sample was recrystallized from $CHCl_3$, mp 175–178 °C. Anal. ($C_{13}H_{11}Cl_2NO_2$) C, H, N.

(2,3-Dichloro-4-methoxyphenyl)(2-pyridyl)methanone (7x). A solution of **24** (31.86 g, 0.107 mol) in 600 mL of HOAc and 100 mL of H_2O was treated portionwise with CrO_3 (11.0 g, 0.110 mol) over 5 min. After 3 h the reaction was poured into H_2O and extracted with Et_2O. The combined organic phase was washed well with 10% $NaHCO_3$. Evaporation of the organic phase gave 30.3 g of crystalline **7x** (96%), mp 104–107 °C. An analytical sample, recrystallized from MeOH, had mp 107–109 °C. Anal. ($C_{13}H_9Cl_2NO_2$) C, H, N.

7-Chloro-6-methoxy-3-(2-pyridyl)-1,2-benzisoxazole (10x) was obtained from **7x** in the same manner as **10w** in 69% yield, mp 182–184 °C. Anal. ($C_{13}H_{10}Cl_2N_2O_2$) C, H, N.

7-Chloro-6-hydroxy-3-(2-pyridyl)-1,2-benzisoxazole (11x). A solution of **10x** (24.4 g, 0.094 mol) in 450 mL of 48% HBr was refluxed for 1.5 h. The precipitated hydrobromide salt was filtered off, washed with Et_2O, and neutralized with 10% $NaHCO_3$. The free base was then filtered and dried to give 20.7 g (90%) of **11x**, mp 209–211 °C. Recrystallization from 1,2-dichloroethane gave an analytical sample, mp 211–213 °C. Anal. ($C_{12}H_9ClN_2O_2$) C, H, N.

7-Chloro-6-hydroxy-3-(2-pyridyl)-1,2-benzisoxazole 1'-Oxide (11y). Phenol **11x** (9.9 g, 0.040 mol) was dissolved in 600 mL of glacial HOAc at 60 °C and treated portionwise with *m*-

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chloroperbenzoic acid (8.3 g of 85%, 0.041 mol). After warming at 60 °C for a total of 14 h, the reaction was poured into 2 L of H_2O, and the precipitated **11y** was collected by filtration and washed with MeOH and then Et_2O. In this way, 7.3 g (60%) of **11y** was obtained, which analyzed correctly for the hemihydrate after recrystallization from DMF/H_2O, mp 214 °C dec. Anal. ($C_{17}H_7ClN_2O_3 \cdot 0.5H_2O$) C, H, N.

[[7-Chloro-3-(2-pyridyl)-1,2-benzisoxazol-6-yl]oxy]acetic acid (13x) was obtained from **11x** by method C in 92% yield, mp 257–259 °C after recrystallization from Me_2SO/H_2O. Anal. ($C_{14}H_9ClN_2O_4$) C, H, N.

[[7-Chloro-3-(2-pyridyl)-1,2-benzisoxazol-6-yl]oxy]acetic acid 1'-oxide (13y) was obtained similarly from **11y** in 67% yield, mp 214 °C dec. Anal. ($C_{14}H_9ClN_2O_5$) C, H, N.

2,3-Dichloro-4'-ethoxy-2'-fluoro-4-methoxybenzophenone (7l). The acid chloride **30**[3] (0.124 mol) was dissolved in 150 mL of $(ClCH_2)_2$, and *m*-fluorophenetole[14] (16.3 g, 0.116 mol) was added. This solution was chilled to 5 °C as $AlCl_3$ (16.5 g, 0.124 mol) was added slowly. After 2 h the reaction was distributed between H_2O and Et_2O to give product that was clearly two isomers by ^1H NMR and TLC (10% Et_2O/hexane). The mixture was separated by preparative HPLC (10% EtOAc/hexane; 250 mL/min) to give 12.0 g (30%) of pure **7l**, mp 94–96 °C. Anal. ($C_{16}H_{13}Cl_2FO_3$) C, H. Also obtained was 14.5 g (36%) of 2,3-dichloro-2'-ethoxy-4'-fluoro-4-methoxybenzophenone (**7ii**), mp 107–109 °C. Anal. ($C_{16}H_{13}Cl_2FO_3$) C, H.

(*Z*)-2,3-Dichloro-4'-ethoxy-2'-fluoro-4-methoxybenzophenone Oxime [(*Z*)-9l]. Under the conditions of method A, **7l** (26.59 g, 0.077 mol) gave 19.85 g of Et_2O-insoluble material that was primarily (*Z*)-**9l** by TLC. The Et_2O filtrate contained additional (*Z*)-**9l** plus (*E*)-**9l** (lower R_f). The Et_2O filtrate was evaporated and the residue was hydrolyzed overnight in 150 mL of 1:1 EtOH/H_2O containing 15 g of $NaHSO_3$. The reaction mixture was distributed between 5% HCl and Et_2O, and then the organic phase was separated and concentrated under reduced pressure. The residue was filtered through a silica gel column with toluene as the eluent to give 7.3 g of **7l** (27% recovery). Repetition of the foregoing conditions and washing with Et_2O gave an additional 4.6 g of (*Z*)-**9l** for a total yield of 24.45 g (88%). Recrystallization from toluene gave an analytical sample, mp 188–189 °C. Anal. ($C_{16}H_{14}Cl_2FNO_3$) C, H, N.

7-Chloro-3-(4-ethoxy-2-fluorophenyl)-6-methoxy-1,2-benzisoxazole (10l). The (*Z*)-oxime, (*Z*)-**9l** (23.26 g, 0.065 mol) in 175 mL of DMF was added to NaH (1.85 g, 0.077 mol) in 35 mL of DMF. After stirring for 30 min at room temperature, the reaction mixture was distributed between H_2O and 1:1 Et_2O/2-butanone. Concentration of the organic phase and trituration of the product with hexane gave 18.50 g (89%) of **10l**, mp 148–150 °C. Analytical sample was recrystallized from toluene/hexane and had mp 151–152 °C. Anal. ($C_{16}H_{13}ClFNO_3$) C, H, N.

7-Chloro-3-(2-fluoro-4-ethoxyphenyl)-6-hydroxy-1,2-benzisoxazole (11l). Method D. Compound **10l** (14.20 g, 0.044 mol) was heated for 2 h at 180 °C with 54 g of pyridine hydrochloride. The reaction mixture was shaken with 2-butanone and 5% HCl, and the product obtained from the organic phase was recrystallized from toluene to give 8.85 g (65.5%) of the monohydroxy compound **11l**, mp 170–172 °C. The ^1H NMR (Me_2SO-d_6) and MS (M^+ 307) were consistent with the structure.

Ethyl [[7-Chloro-3-(2-fluoro-4-ethoxyphenyl)-1,2-benzisoxazole-6-yl]oxy]acetate (12l). Method E. Alkylation of **11l** with ethyl bromoacetate (0.045 mol) and K_2CO_3 (0.045 mol) in 75 mL of DMF at 65 °C for 1 h gave **12l** in 57% from **10l**, mp 118–119 °C after recrystallization from CH_3CN. Anal. ($C_{19}H_{17}ClFNO_5$) C, H, N.

Ethyl [[(7-Chloro-3-(2-fluoro-4-hydroxyphenyl)-1,2-benzisoxazol-6-yl]oxy]acetate (12l') was obtained from **12l** by method B. It was contaminated with **13l** and was taken to the next step without further purification.

[[7-Chloro-3-(2-fluoro-4-hydroxyphenyl)-1,2-benzisoxazol-6-yl]oxy]acetic Acid (13l). Method F. The crude **12l'** from above was hydrolyzed for 30 min in 100 mL of EtOH and 150 mL of 5% NaOH at reflux. The precipitated salt was collected by filtration, and the acid was isolated by distribution between 2-butanone and 5% HCl and evaporation of the organic phase. Recrystallization from toluene/CH_3CN gave 4.20 g of **13l** (53% from **12l**), mp 216–218 °C. Anal. ($C_{15}H_9ClFNO_5$) C, H, N.

Route B. 2,3-Dichloro-4'-fluoro-4-hydroxybenzophenone oxime (8k) was obtained from 2,3-dichloro-4'-fluoro-4-hydroxybenzophenone (**6k**)[4] by method A in 58% yield as a mixture of isomers, which was used without further purification. A small sample was recrystallized from toluene, mp 150–156 °C. Anal. ($C_{13}H_8Cl_2FNO_2$) C, H, N.

[[7-Chloro-3-(4-fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetic Acid (13k). A solution of **8k** (20 g, 0.066 mol) in 100 mL of DMF was added dropwise to a suspension of NaH in 50 mL of DMF. The reaction mixture was heated to an internal temperature of 96 °C for 2 h and then cooled to 40 °C. Ethyl bromoacetate (12.3 g, 0.07 mol) was added dropwise and stirring was continued for 1 h. At the end of this time, 20 mL of 50% NaOH and 100 mL of H_2O were added, and the reaction was heated at 80–90 °C for an additional hour, then chilled, and acidified with concentrated HCl. The product crystallized upon the addition of more H_2O and was collected by filtration and recrystallized from 95% EtOH to give 10.54 g of **13k** (49%), mp 234–237 °C. Anal. ($C_{15}H_9ClFNO_4$) C, H, N.

2,3-Dichloro-2'-fluoro-4-methoxybenzophenone (7i). To a solution of 31.55 g of 2-fluorobenzoyl chloride (0.199 mol) in 100 mL of 1,2-dichloroethane was added 26.54 g (0.199 mol) of $AlCl_3$ over 30 min. A solution of 2,3-dichloroanisole (32 g, 0.181 mol) in 50 mL of 1,2-dichloroethane was then added dropwise. After 2 h the reaction mixture was shaken with Et_2O and 5% HCl. The product isolated from the concentrated organic phase was recrystallized from Et_2O/hexane to give 38.7 g of **7i** (70%), mp 75–77 °C. Anal. ($C_{14}H_9Cl_2NO_2$) C, H.

Friedel–Crafts reactions were generally run under these conditions rather than those described for **7w**.

2,3-Dichloro-2'-fluoro-4-hydroxybenzophenone (6i). $AlCl_3$ (34.7 g, 0.26 mol) was added to a solution of **7i** (38.5 g, 0.13 mol) in 250 mL of benzene. This mixture was refluxed for 5 h, then distributed between EtOAc and dilute HCl. The organic phase was then concentrated under reduced pressure. Trituration with hexane gave 32.8 g of **6i** (89%). The analytical sample was recrystallized from Et_2O/hexane, mp 128–131 °C. Anal. ($C_{13}H_7Cl_2FO_2$) C, H.

2,3-Dichloro-2'-fluoro-4-hydroxybenzophenone oxime (8i) was obtained as a mixture of isomers by method A, mp 168–175 °C. Anal. ($C_{13}H_8Cl_2FNO_2$) C, H, N.

Ethyl [[7-Chloro-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetate (12i) and Ethyl 4-(1,2-Benzisoxazol-3-yl)-2,3-dichlorophenoxyacetate (14i). The oxime mixture **8i** (18.4 g, 0.060 mol) was dissolved in 120 mL of DMF and 120 mL of benzene, and 3.6 g (0.15 mol) of NaH was added. The mixture was heated at 80–85 °C for 3 h and then cooled to room temperature, followed by the addition of ethyl bromoacetate (11 g, 0.066 mol). The reaction mixture was shaken with H_2O/EtOAc, after which the organic phase was separated and concentrated under reduced pressure. Successive recrystallizations of the residue from 95% EtOH gave 10 g (48%) of **12i**, mp 112–114 °C. Anal. ($C_{17}H_{13}ClFNO_4$) C, H, N. The ethanolic mother liquors were then evaporated and chromatographed over 500 g of silica gel with toluene. This gave 3.8 g (17%) of **14i**, mp 88–89 °C. Anal. ($C_{17}H_{13}Cl_2NO_4$) C, H, N.

[[7-Chloro-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetic acid (13i) was obtained by method F from **12i** in 63% yield,mp 190–191 °C after recrystallization from EtOH/H_2O. Anal. ($C_{15}H_9ClFNO_4$) C, H, N.

4-(1,2-Benzisoxazol-3-yl)-2,3-dichlorophenoxyacetic Acid (15i). Ester **14i** was hydrolyzed as for **12i** above to give 4.1 g (65%) of **15i**, mp 166–167 °C after recrystallization from EtOH/H_2O. Anal. ($C_{15}H_9Cl_2NO_4$) C, H, N.

Route C. 2'-Fluoro-2-hydroxy-4-methoxy-3-methylbenzophenone (17ee). Method G. 2,6-Dimethoxytoluene (**16ee**; 20.0 g, 0.131 mol) and 2-fluorobenzoyl chloride (19.8 g, 0.125 mol) were dissolved in 250 mL of 1,2-dichloroethane and chilled to 5 °C. $AlCl_3$ (17.3 g, 0.13 mol) was added portionwise, and the reaction was allowed to warm to room temperature over 30 min and then refluxed for 30 min. It was distributed between 5% HCl and Et_2O to give 30.2 g (93%) of **17ee**, mp 118–120 °C, after washing well with hexane. An analytical sample was recrystallized from Et_2O, mp 119–120 °C. Anal. ($C_{15}H_{13}FO_3$) C, H, F.

2-Chlororesorcinol Dimethyl Ether (16i). Resorcinol dimethyl ether (**16hh**; 69.10 g, 0.50 mol) was dissolved in 250 mL

of anhydrous Et_2O, and *n*-butyllithium (240 mL of 2.2 M, 0.53 mol) was added at room temperature. This mixture was refluxed for 2.5 h and then chilled to −65 °C as hexachloroethane (137.8 g, 0.575 mol) in 250 mL of THF was added. After the addition was complete, the reaction was allowed to come to room temperature and was poured into H_2O. The organic layer was separated and yielded an oil upon evaporation. Crystallization from hexane gave 61.2 g of **16i** (71%), mp 69–71 °C. Anal. ($C_8H_9ClO_2$) C, H, Cl.

3-Chloro-2′-fluoro-2-hydroxy-4-methoxybenzophenone (17i) was obtained in 67% from **16i** by method G, mp 132–133 °C. Anal. ($C_{14}H_{10}ClFO_3$) C, H, Cl.

2′-Fluoro-2-hydroxy-4-methoxybenzophenone (17hh) was obtained in 78% yield from resorcinol dimethyl ether by method G, mp 53–54 °C (lit.[26] mp 49–50 °C).

2-Chloro-2′-fluoro-6-hydroxy-4-methoxybenzophenone (17aa) was obtained in 96% yield from 5-chlororesorcinol dimethyl ether (**16aa**) by method G, mp 108–110 °C after recrystallization from Et_2O/hexane. Anal. ($C_{14}H_{10}ClFO_3$) C, H, F.

(*E*)-2′-Fluoro-2-hydroxy-4-methoxy-3-methylbenzophenone oxime [(*E*)-19ee] was obtained from **17ee** by method A in 71% yield as the pure *E* isomer, mp 167–169 °C after recrystallization from toluene. Anal. ($C_{15}H_{14}FNO_3$) C, H, N. Chromatography of the mother liquors over silica (30% Et_2O/hexane) yielded a small amount of the *Z* isomer, mp 148–151 °C (see text).

(*E*)-3-Chloro-2′-hydroxy-4-methoxybenzophenone oxime (19i) was obtained in 76% yield from **17i** by method A after recrystallization from toluene, mp 185–186 °C. Anal. ($C_{14}H_{11}ClFNO_3$) C, H, N.

(*E*)-2′-Fluoro-2-hydroxy-4-methoxybenzophenone oxime (19hh) was obtained in 95% yield as an oil from **17hh** by method A and was used without further purification.

(*E*)-2-Chloro-2′-fluoro-6-hydroxy-4-methoxybenzophenone oxime (19aa) was obtained from **17aa** as an oil. An initial 1:1 mixture of *E* and *Z* isomers was obtained, out of which the *Z* isomer crystallized. By heating this above its melting point, it was converted to a 1:1 mixture of *E* and *Z* isomers. By repeating this process, an eventual yield of 75% of **19aa** was obtained as an oil, which was not purified further.

(*E*)-2′-Fluoro-2-hydroxy-4-methoxy-3-methylbenzophenone *O*-Acetyl Oxime (21ee). Method H. The (*E*)-oxime (**19ee**; 20.0 g, 0.073 mol) was warmed on a steam bath for 1 h with 12 mL of Ac_2O (0.127 mol). The Ac_2O was evaporated, the residue was distributed between Et_2O and H_2O, and then the Et_2O was washed with 10% $NaHCO_3$. The crystalline product obtained in this manner was triturated with hexane to give 22.1 g (96%) of **21ee**, mp 82–86 °C. The analytical sample, recrystallized from hexane, had mp 89–91 °C. Anal. ($C_{12}H_{16}FNO_4$) C, H, N.

(*E*)-3-Chloro-2′-fluoro-2-hydroxy-4-methoxybenzophenone *O*-acetyl oxime (21i) was obtained from **19i** in 98% by method H after recrystallization from Et_2O/hexane, mp 127–129 °C. Anal. ($C_{16}H_{13}ClFNO_4$) C, H, N.

(*E*)-2′-Fluoro-2-hydroxy-4-methoxybenzophenone *O*-acetyl oxime (21hh) was obtained from **19hh** in 85% yield by method H after recrystallization from cyclohexane, mp 111–112 °C. Anal. ($C_{16}H_{14}FNO_4$) C, H, N.

(*E*)-2-Chloro-2′-fluoro-6-hydroxy-4-methoxybenzophenone *O*-acetyl oxime (21aa) was obtained from **19aa** in 95% yield by method H as an oil, which was not purified further.

3-(2-Fluorophenyl)-6-methoxy-7-methyl-1,2-benzisoxazole (10ee). Method I. The oxime acetate **21ee** (22.0 g, 0.069 mol) was dissolved in 100 mL of DMF and added to a suspension of 2.5 g of NaH (0.10 mol) in 100 mL of DMF. An ice bath was applied to keep the reaction temperature less than 30 °C. After 40 min the reaction was poured into H_2O and extracted with Et_2O. After the extract was washed well with H_2O, the Et_2O was dried and evaporated to give crystalline product, which was washed with cold hexane to give 16.2 g (91%) of fluffy, colorless needles of **10ee**, mp 105–108 °C. The analytical sample was recrystallized from hexane, mp 108–109 °C. Anal. ($C_{15}H_{12}FNO_2$) C, H, N.

7-Chloro-3-(2-fluorophenyl)-6-methoxy-1,2-benzisoxazole (10i) was obtained by method I from **21i** in 84% yield after recrystallization from toluene, mp 155–158 °C. Anal. ($C_{14}H_9ClFNO_2$) C, H, N.

3-(2-Fluorophenyl)-6-methoxy-1,2-benzisoxazole (10hh) was obtained from **21hh** by method I in 90% yield after trituration with hexane, mp 105–106 °C. Anal. ($C_{14}H_{10}FNO_2$) C, H, N.

4-Chloro-3-(2-fluorophenyl)-6-methoxy-1,2-benzisoxazole (10aa) was obtained from **21aa** by method I in 51% yield after recrystallization from ether/hexane, mp 116–117 °C. Anal. ($C_{14}H_9ClFNO_2$) C, H, N.

3-(2-Fluorophenyl)-6-hydroxy-7-methyl-1,2-benzisoxazole (11ee) was obtained from **10ee** by method D in 93% yield, mp 220–222 °C after recrystallization from toluene/CH_3CN. Anal. ($C_{14}H_{10}FNO_2$) C, H, N.

7-Chloro-3-(2-fluorophenyl)-6-hydroxy-1,2-benzisoxazole (11i) was obtained similarly from **10i** in 91% yield, mp 240–241 °C after recrystallization from toluene. Anal. ($C_{13}H_7ClFNO_2$) C, H, N.

[[3-(2-Fluorophenyl)-7-methyl-1,2-benzisoxazol-6-yl]oxy]acetic Acid (13ee). Method J. The phenol **11ee** (10.6 g, 0.044 mol) was dissolved in 90 mL of DMF and treated with 8.0 g of ethyl bromoacetate (0.048 mol) and 6.7 g of K_2CO_3 (0.048 mol). The reaction was warmed at 60 °C for 2 h and then allowed to return to room temperature overnight. Water (200 mL) and 50% NaOH (15 mL) were added, and the solution was heated at 90 °C for 90 min. It was poured into H_2O and acidified; then the product was extracted into 1:1 Et_2O/2-butanone. Evaporation gave crystalline **13ee**, which was recrystallized from toluene to give 11.6 g (89%), mp 158–160 °C. Anal. ($C_{16}H_{12}FNO_4$) C, H, N.

The treatment of **11i** under the conditions of method J gave **13i**, which was identical in all respects with **13i** isolated through route B above.

2,4-Dihydroxy-2′-fluorobenzophenone (18hh). Resorcinol dimethyl ether (27.6 g, 0.20 mol) and 2-fluorobenzoyl chloride (31.7 g, 0.20 mol) were dissolved in 200 mL of dichloroethane, and $AlCl_3$ (28.0 g, 0.21 mol) was added portionwise. After 2 h, an additional 56 g (0.42 mol) of $AlCl_3$ was added, and the reaction warmed at 60 °C for 1.5 h. It was then poured into H_2O and extracted with EtOAc. Drying and evaporation gave crystalline compound. Trituration with toluene gave 27.5 g (59%) of product, mp 109–111 °C. The analytical sample was recrystallized from $CHCl_3$, mp 112–114 °C. Anal. ($C_{13}H_9FO_3$) C, H, F.

(*E*)-2,4-Dihydroxy-2′-fluorobenzophenone oxime (20hh) was obtained in 78% yield from **18hh** by method A after recrystallization from toluene, mp 170–172 °C. Anal. ($C_{13}H_{10}FNO_3$) C, H, N.

(*E*)-4-Acetoxy-2-hydroxy-2′-fluorobenzophenone *O*-Acetyl Oxime (22hh). The (*E*)-oxime **20hh** (18.6 g, 0.075 mol) was warmed at 50 °C in 18.0 mL of acetic anhydride (0.190 mol) for 5 h and then at 60 °C for 6 h. An additional 3.0 mL of acetic anhydride was added, and the reaction was allowed to remain undisturbed at room temperature for 3 days. The crystalline product that separated from the reaction mixture was washed with cold Et_2O to give 18.5 g (75%) of pure **22hh**, mp 132–134 °C. The analytical sample was recrystallized from Et_2O/hexane and had mp 130–131 °C. Anal. ($C_{17}H_{14}FNO_5$) C, H, N.

3-(2-Fluorophenyl)-6-hydroxy-1,2-benzisoxazole (11hh) was synthesized from **22hh** by method I. Recrystallization from toluene/CH_3CN gave a 77% yield, mp 210–212 °C. Anal. ($C_{13}H_8FNO_2$) C, H, N.

[[3-(2-Fluorophenyl)-1,2-benzisoxazol-6-yl]oxy]acetic acid (13hh) was synthesized from **11hh** by method J in 70% yield, mp 182–184 °C (toluene/CH_3CN). Anal. ($C_{15}H_{10}FNO_4$) C, H, N.

7-Chloro-6-*O*-(*N*,*N*-dimethylthiocarbamyl)-3-(2-fluorophenyl)-1,2-benzisoxazole (25). To a suspension of NaH (1.0 g of a 50% suspension in oil, 10% excess) in 50 mL of DMF was added a solution of 5.0 g (0.019 mol) of **11i** in 50 mL of DMF. The solution was stirred for 1 h at room temperature, then cooled to 5 °C, and 3.5 g (0.028 mol) of *N*,*N*-dimethylthiocarbamoyl chloride was added all at once. The reaction was brought gradually to 60 °C and stirred for 2.5 h. The solution was then poured into water and extracted with methylene chloride until the extracts were colorless. The combined organic extracts were washed with 10% K_2CO_3 and then with saturated NaCl. The solvent was removed in vacuo and the crude compound was recrystallized from

(26) D. N. Gray and R. D. Knight, U.S. Patent 3387035 (1968).

ethyl acetate/ethyl ether to afford 5.0 g (75%) of white needles, mp 153–154 °C, which darkened on long exposure to air. Anal. ($C_{16}H_{12}ClFN_2O_2S$) C, H, N, S.

7-Chloro-6-*S*-(*N*,*N*-dimethylthiocarbamyl)-3-(2-fluorophenyl)-1,2-benzisoxazole (26). Compound **25** (4.5 g, 0.013 mol) was placed in a round-bottomed flask and heated under nitrogen at 205 °C for 45 min. The cooled solid was recrystallized from ethyl acetate to afford 3.6 g (80%) of colorless prisms, mp 140–142 °C. Anal. ($C_{16}H_{12}ClFN_2O_2S$) C, H, N, S.

7-Chloro-3-(2-fluorophenyl)-6-mercapto-1,2-benzisoxazole (27). Two grams (5 mmol) of **26** was dissolved in methanol and 25 mL of 15% aqueous NaOH was added. The solution was refluxed for 3 h. The reaction mixture was poured into a large quantity of water and acidified with HCl to precipitate the product as a flocculant white solid. It was recrystallized from toluene/petroleum ether to afford colorless needles, mp 125–127 °C (1.2 g, 75%), which darkened on exposure to air or heat. Anal. ($C_{13}H_7ClFNOS$) C, H, N, S.

Ethyl [[7-chloro-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]thio]acetate (28) was obtained in 77% yield from **27** by method E, mp 79–81 °C after recrystallization from Et_2O. Anal. ($C_{17}H_{13}ClFNO_3$) C, H, N, S.

[[7-Chloro-3-(2-fluorophenyl)-1,2-benzisoxazol-6-yl]thio]acetic acid (29) was obtained in 95% yield from **28** by method F, mp 170 °C after recrystallization from toluene/acetonitrile–petroleum ether. Anal. ($C_{15}H_9ClFNO_3S$) C, H, N, S.

7-Bromo-3-(2-fluorophenyl)-6-methoxy-1,2-benzisoxazole (10ff). Method K. Ten grams of **10hh** (0.041 mol) was dissolved in 400 mL of dry THF and treated at −40 °C (CH_3CN slush) with 21 mL of 2.2 M *n*-butyllithium (0.046 mol). After the mixture was stirred for 1 h, bromine (2.5 mL, 0.046 mol) was added dropwise. The reaction was poured into H_2O, extracted into Et_2O, and washed with $Na_2S_2O_3$ solution. Drying and evaporation gave a yellow material that contained 80% of the desired brominated product by ^1H NMR. Recrystallization from toluene/cyclohexane gave 8.1 g of pure product (61%), mp 150–153 °C. The analytical sample was recrystallized again, mp 154–155 °C. Anal. ($C_{14}H_9BrFNO_2$) C, H, N, Br.

3-(2-Fluorophenyl)-7-iodo-6-methoxy-1,2-benzisoxazole (10qq) was obtained from **10hh** by method K in 89% yield, mp 140–142 °C (cyclohexane). Anal. ($C_{14}H_9FINO_2$) C, H, N, I; C: calcd, 45.55; found, 44.94.

5,7-Dichloro-3-(2′-fluorophenyl)-6-methoxy-1,2-benzisoxazole (10bb). A solution of **10i** (10.0 g, 0.036 mol) in 800 mL of glacial HOAc was treated with gaseous Cl_2 for 0.5 h and then stirred at room temperature overnight. The reaction was then poured into H_2O, and the precipitated product was collected by filtration and recrystallized from 95% ethanol to give 10.6 g of **10bb** (95%), mp 129–130 °C. Anal. ($C_{14}H_8Cl_2FNO_2$) C, H, N.

4,5,7-Trichloro-3-(2-fluorophenyl)-6-methoxy-1,2-benzisoxazole (10cc) was obtained in analogous fashion from **10aa** in 95% yield, mp 148–150 °C after recrystallization from ether/hexane. Anal. ($C_{14}H_7Cl_3FNO_2$) C, H, N.

Acute Diuretic Evaluation in Sodium-Loaded Mice. The acute sodium-loaded mouse experiments were performed with groups of male CD-1 mice weighing 18–24 g. Drugs were prepared in 1% saline and orally administered in a dosage volume of 10 mL/kg. The animals were housed in metabolic cages, each treatment group consisting of 10 animals, 5 per cage. Tests consisted of a vehicle control and the potential diuretic agent given at 4 and 64 mg/kg. The pooled urine samples were analyzed for sodium using a flame photometer (IL Model 343). Sodium values were expressed as the mean milliequivalents (mequiv)/kilogram/5 h.

Unanesthetized Dogs. Male mongrel dogs weighing 20–25 kg were given 20 mL/kg tap water by gavage approximately 15 h prior to drug. Water was available ad libitum overnight between this dose and the first urine collection on the morning of the test. On the morning of the test, each dog was placed in an individual metabolism cage. The bladder was emptied by catheterization and then rinsed with 20 mL of sterile distilled water. Each dog was then given 20 mL/kg tap water by gavage. One hour later, the bladder was catheterized and drained. The volume was recorded and a small sample was retained for analysis. Each animal received 4 mL/kg tap water at this point and once each hour for the ensuing 7 h. At these time intervals, the bladder was emptied, the volume was recorded, and a sample was retained for analysis. After the third urine sample was drawn, drug was administered by gavage in the 4 mL/kg water load. Tween 80 was added to aid suspension if the compound was not readily soluble in water. Urine samples were analyzed by flame photometry for Na^+ concentrations. Calculations were made for the mean excretory rates (microequivalents/kilogram) for each interval and for each animal.

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