4-H_2C=$CHCH_2OC_6H_4COCl$, 36844-51-6; 4-$OHCC_6H_4COCl$, 16173-52-7; (2-Cl)(4-O_2N)C_6H_4COCl, 7073-36-1; (2-CH_3)(4-O_2N)C_6H_4COCl, 30459-70-2; (2-CH_3)(4-H_2N)C_6H_4COCl, 90531-76-3; 3-ClC_6H_4COCl, 618-46-2; $PhCH_2COCl$, 103-80-0; $Ph(CH_2)_2COCl$, 645-45-4; $Ph(CH_2)_3COCl$, 18496-54-3; $Ph_2CHCOCl$, 1871-76-7; c-C_5H_9COCl, 4524-93-0; 4-(C_5H_5N)COCl, 14254-57-0; 3-[[*N*-(3,4-dimethoxyphenethyl)-*N*-(4-methoxybenzyloxycarbonyl)]-amino]-2-hydroxypropionic acid, 83230-58-4; isopropylamine, 75-31-0; 3,4-(methylenedioxy)benzoyl chloride, 25054-53-9; methylbenzylamine, 103-67-3; 9-fluorenylcarbonyl chloride, 24168-51-2; 1,2-diamino-2-methylpropane, 811-93-8; urea, 57-13-6; 1,1-dimethyl-2-[(aminocarbonyl)amino]ethylamine, 87484-83-1.

Substituted 5,6-Dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic Acids: High-Ceiling Diuretics with Uricosuric Activity[1]

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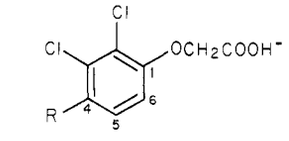
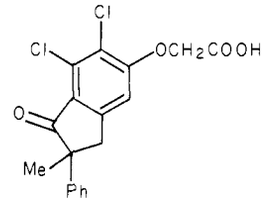
A series of substituted 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazoles was prepared and evaluated for their saluretic and uricosuric properties. Pharmacological evaluation of the title compounds was carried out in mice, rats, dogs, and monkeys. The diuretic/saluretic nature of these compounds was observed in all species, whereas the uricosuric activity was best seen in the Cebus monkey. Evaluation of the enantiomers of 8-chloro-3-(*o*-fluorophenyl)-5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (**15k**) revealed that only the (+) enantiomer (**29**) displayed diuretic and saluretic activity, whereas both enantiomers possessed uricosuric activity. X-ray analysis showed that the (−) enantiomer (**30**) possesses the 2*R* configuration.

Since the discovery of ethacrynic acid more than 20 years ago, many (aryloxy)acetic acid derivatives have been synthesized and evaluated for their diuretic properties.[2] The high level of interest in this class of compounds has been stimulated by the ability of medicinal chemists to dramatically alter the diuretic profile of these agents by structural manipulation of the phenoxyacetic acid pharmacophore. Thus, the uric acid retention caused by ethacrynic acid (**1a**) is sharply contrasted to the uricosuric nature of indacrinone (**2**)[3] and the dihydrobenzofuran derivative **3**.[4] Still further differences in profile are found with tienilic acid (**1b**), which elicits a low-ceiling uricosuric effect[5] and, more recently, **4** (HP-522), which has been described[6] as a high-ceiling moderate uricosuric. In our own laboratories we have discovered yet a new addition **5** to the class of (aryloxy)acetic acid diuretics that differs from all previous derivatives in that a basic nitrogen functionality is essential to their high-ceiling profile.[7] This broad range of renotrophic properties displayed within the class of (aryloxy)acetic acids reflects the high sensitivity of the renal tubular transport cells to small changes in the structure of these compounds.[8]



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

b, R = 



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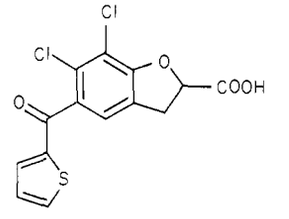

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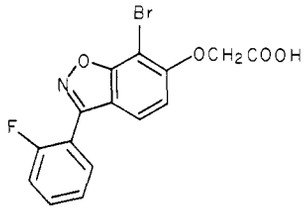

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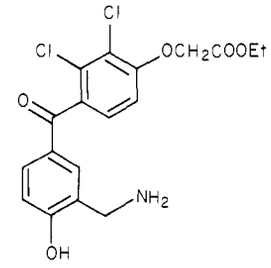

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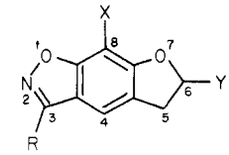

6

Our interest in obtaining a diuretic agent functionally equivalent to the clinically useful combination of furosemide and probenecid prompted a consideration of the structural requirements for high-ceiling uricosuric effects. Without exception, we observed that all phenoxyacetic acid diuretics with this profile possess structures that are for-

(1) Portions of this work were presented in September 1983, at the 186th National Meeting of the American Chemical Society. See "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Sept 1983; American Chemical Society: Washington, DC, 1983; MEDI 91.

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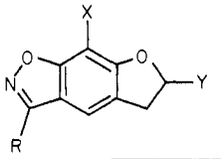
Table I. 5,6-Dihydrofuro[3,2-*f*]-2,3-benzisoxazoles



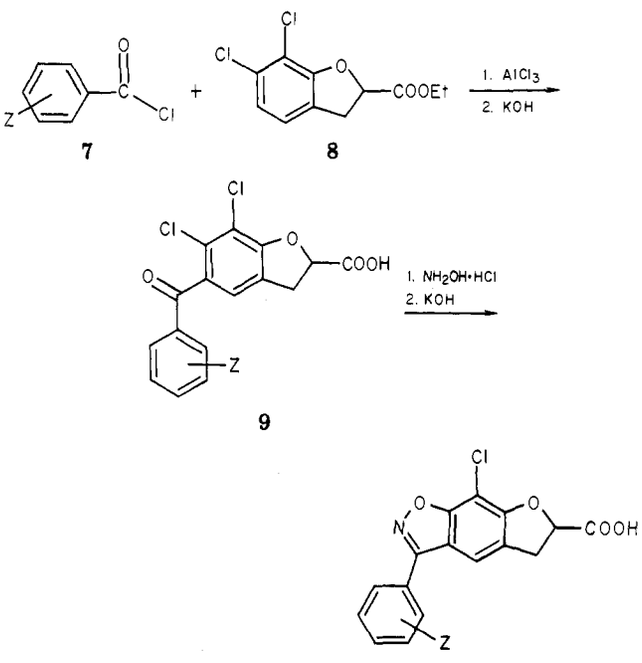
compd	R	X	Y	rctn scheme	mp, °C	recrystn solvent[a]	formula[b]
10a	C_6H_5	Cl	CO_2Y	I	214–215	A–B	$C_{16}H_{10}ClNO_4$
10b	2-$CH_3C_6H_4$	Cl	CO_2H	I	179–181	B[c]	$C_{17}H_{12}ClNO_4$
10c	2-ClC_6H_4	Cl	CO_2H	I	224–225	A–B	$C_{16}H_9Cl_2NO_4$
10d	4-OHC_6H_4	Cl	CO_2H	I	215–217	D[c]	$C_{16}H_9KClNO_5$[d]
10e	3-FC_6H_4	Cl	CO_2H	I	182.5–183.5	E–F	$C_{16}H_9ClFNO_4$
10f	4-FC_6H_4	Cl	CO_2H	I	225–226	E–F	$C_{16}H_9ClFNO_4$
15k	2-FC_6H_4	Cl	CO_2H	II	197.5–199	B[c]	$C_{16}H_9ClFNO_4$
15l	2-FC_6H_4	CH_3	CO_2H	II	188–189	B[c]	$C_{17}H_{12}FNO_4$
15m	2-FC_6H_4	H	CO_2H	II	194–196	B[c]	$C_{16}H_{10}FNO_4$
15n	2-FC_6H_4	OCH_3	CO_2H	II	127–129	G	$C_{17}H_{12}FNO_5$
15o	2-thienyl	Cl	CO_2H	II	272–274	D[c]	$C_{14}H_8ClNO_4S$
15p	CH_3	Cl	CO_2H	II	260–263	A–B	$C_{11}H_8ClNO_4$
15q	C_2H_5	Cl	CO_2H	II	213–215	C–B	$C_{12}H_{10}ClNO_4$
15r	$CH_2CH(CH_3)_2$	Cl	CO_2H	II	181–183	A–B	$C_{14}H_{14}ClNO_4$
15s	2-FC_6H_4	Br	COOH	II	189–191	D[c]	$C_{16}H_9BrFNO_4$
14k	2-FC_6H_4	Cl	$CO_2C_2H_5$	II	135–136	H	$C_{18}H_{13}ClFNO_4$
23	2-FC_6H_4	Cl	CH_2OH	II	147–149	B[c]	$C_{16}H_{11}ClFNO_3$
24	2-FC_6H_4	Cl	$CONH_2$	IV	203–204	A–H	$C_{16}H_{10}ClFN_2O_3$
25	2-FC_6H_4	Cl	CN	V	172–173	A	$C_{16}H_8ClFN_2O_2$
29	2-FC_6H_4	Cl	COOH	VI	169–171	B[c]	$C_{16}H_9ClFNO_4$
30	2-FC_6H_4	Cl	COOH	VI	168–170	B[c]	$C_{16}H_9ClFNO_4$

[a] A = ethyl acetate, B = hexane, C = tetrahydrofuran, D = water, E = chloroform, F = petroleum ether, G = benzene, H = ethanol. [b] All compounds gave satisfactory C, H, and N analyses. [c] The compound was triturated with the indicated solvent. [d] This compound was characterized as the monopotassium salt.

mally derived by a ring-annelation process. For example, annelation to position 5 of formula 1 affords the (indanyloxy)acetic acids,[9] as exemplified by indacrinone (**2**), while annelation to position 3 leads to the [1,2-benzisoxazol-6-yl)oxy]acetic acids,[10] of which HP-522 (**4**) is the prototype. The indeno[5,4-*b*]furan-2-carboxylic acids[11] are derived by annelation at both position 5 and position 6 and represent yet another class of high-ceiling diuretics that also display uricosuria. Interestingly, annelation to position 6 as in tienilic acid analogue **3** does not affect the uricosuric component of activity but substantially increases the saluretic potency and once again results in a high-ceiling uricosuric profile. We have extended this annelation concept to the preparation of new 5,6-dihydrofuro-[3,2-*f*]-1,2-benzisoxazoles **6** that are tricyclic structures derived formally by simultaneous annelations at positions 3 and 6 of formula 1. Herein we report the synthesis, optical resolution, and SARs for this new class of (aryloxy)acetic acids.

Chemistry. The compounds prepared for this study are shown in Table I and their syntheses are outlined in Schemes I–VI. Prior to this work, only the fully aromatic furo[3,2-*f*]-1,2-benzisoxazole ring system has been described in the literature.[12] A selective reduction of the aromatic compounds was not viewed as a practical approach to 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazoles due to (1) the extreme sensitivity of 1,2-benzisoxazoles to reductive cleavage,[13] (2) the rather stringent conditions required to convert benzofuran-2-carboxylic acids to the corresponding 2,3-dihydro derivatives,[14] and (3) the presence of halogen substituents on many of the target compounds. We have therefore developed the chemistry

Scheme I



a, Z = H; b, Z = 2-Me; c, Z = 2-Cl; d, Z = 4-OH; e, Z = 3-F; f, Z = 4-F

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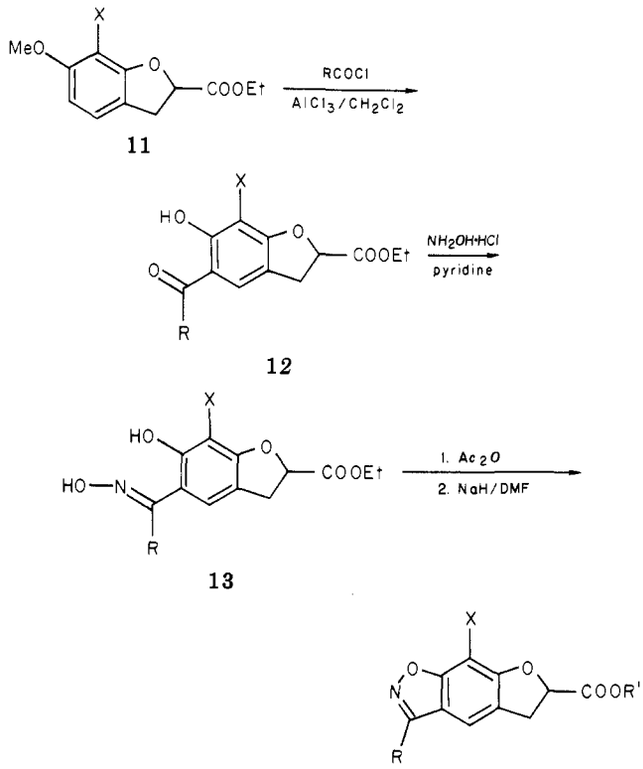
(14) Mustafa, A. In "The Chemistry of Heterocyclic Compounds"; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1974; Vol. 29, pp 56–59.

Scheme II



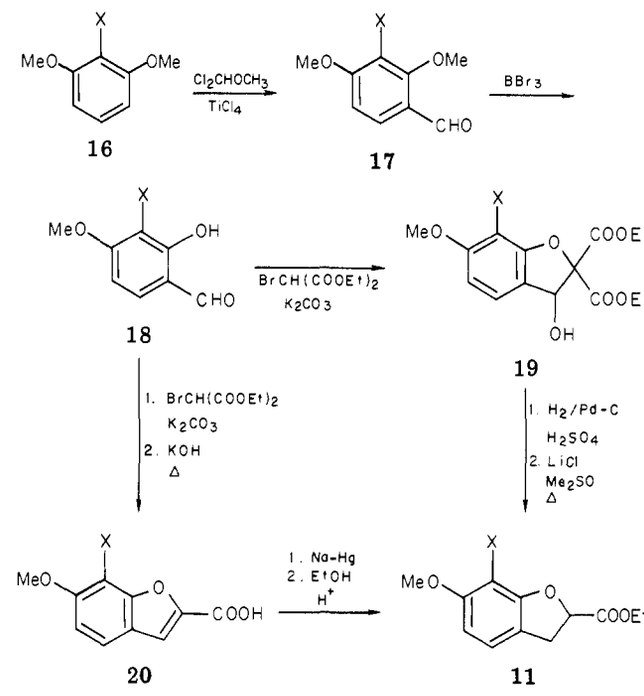
X = H, Me, OMe, halo; R = alkyl, aryl

to obtain the title compounds by two separate synthetic routes, the application of which depends upon the nature and position of the substituents.

Reaction Scheme I was particularly useful for preparing compounds containing a chloro substituent at position 8 and an aryl ring (without an ortho halogen) at position 3. In this process a suitably substituted benzoyl chloride derivative **7** was allowed to react with ethyl 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate (**8**)[9] in a Friedel–Crafts acylation. The resulting benzophenone derivative was hydrolyzed with aqueous base to give the intermediate **9**. Treatment of this compound with hydroxylamine hydrochloride in hot pyridine gave the corresponding oxime as a mixture of isomers, which was cyclized with ethanolic KOH to give the desired 8-chloro-3-aryl-5,6-dihydrofuro-[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (**10**).

Compounds containing an *o*-halo substituent on the pendant phenyl ring in **10** were not readily accessible by this route due to competing cyclization of the oxime anion at both ortho positions. For these derivatives as well as analogues containing variable substituents at position 8, the route shown in Scheme II was used. In this method, a dihydrobenzofuran intermediate **11** was subjected to a Friedel–Crafts reaction with an acid chloride or anhydride to give intermediate **12**. Use of mild reaction conditions in this acylation reaction gave the methyl ether of **12** whereas more vigorous conditions led directly to the demethylated product. Treatment of **12** with hydroxylamine hydrochloride in pyridine gave predominately[10] the *E* oxime **13**, which was converted to the oxime acetate with acetic anhydride. Cyclization to **14** was achieved by treatment of the oxime acetate intermediate with sodium hydride in *N*,*N*-dimethylformamide solution. The target carboxylic acid derivatives **15** were obtained by hydrolysis of the ethyl ester function with use of potassium hydroxide in aqueous ethanol.

Scheme III



g, X = Cl; h, X = Me; i, X = H; j, X = OMe

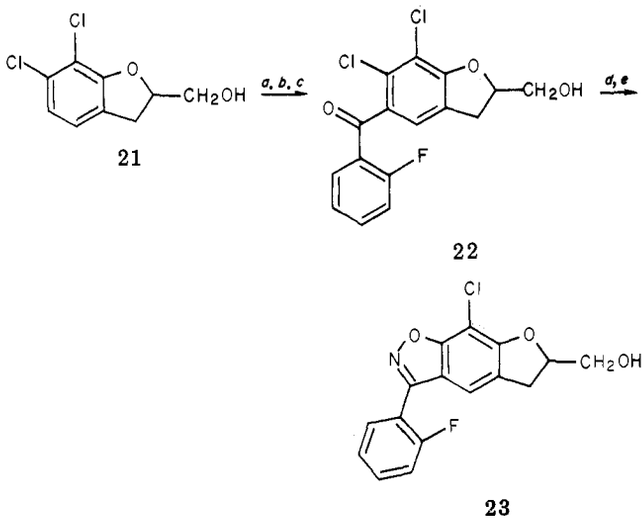
The 7-substituted 2,3-dihydrobenzofuran-2-carboxylate intermediates **11** required for use in Scheme II were prepared as indicated in Scheme III. In this sequence, a dimethoxybenzene derivative **16** was formylated to **17** with use of dichloromethyl methyl ether in the presence of titanium tetrachloride.[15] The methyl ether adjacent to the aldehyde group in **17** was selectively cleaved with boron tribromide, giving the salicylaldehyde intermediate **18**. From this point, two different pathways to **11** were employed, depending on the nature of the X substituent in intermediate **18**. In the case of X = Cl, the salicylaldehyde **18** was converted to the diester **19** by a reaction with diethyl bromomalonate in the presence of anhydrous potassium carbonate. This compound was then converted to **11** by catalytic hydrogenolysis of the hydroxy function followed by decarbethoxylation with lithium chloride in hot Me_2SO. The alternative pathway, which was used for non-halogen-containing compounds, involved a reaction with diethyl bromomalonate as above, followed by treatment with hot aqueous potassium hydroxide to give the benzofuran-2-carboxylic acid **20**. Sodium amalgam reduction of **20** followed by esterification then led to compound **11**.

An alternative procedure was required to prepare the analogue containing a bromo substituent at position 8 of the 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole nucleus, starting with the unsubstituted congener **14** (X = H, R = 2-FC_6H_4). Halogenation of this compound with *N*-bromosuccinimide in DMF solution at 60 °C led to the corresponding 8-Br derivative in high yield. Hydrolysis of the ester function as described above then gave the target bromo acid **15** (X = Br, R = 2-FC_6H_4).

Preparation of the analogue with a hydroxymethyl substituent at position 6 is depicted in Scheme IV. Dihydrobenzofuran alcohol **21**[9] was acetylated with acetic anhydride to give the corresponding acetoxy compound, which underwent a Friedel–Crafts acylation followed by deacetylation to give benzophenone **22**. Conversion of **22**

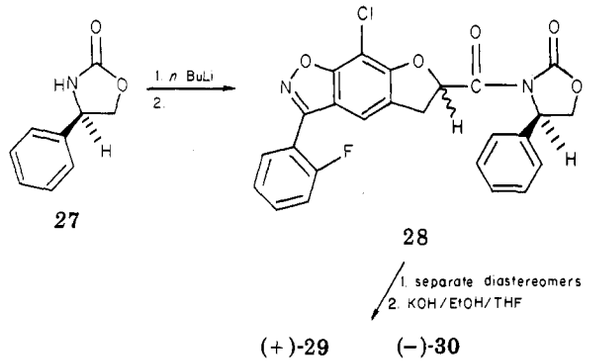
(15) Thuillier, G.; LaForest, J.; Cariou, B.; Bessin, P.; Bonnet, J.; Thuiller, J. *Eur. J. Med. Chem.* **1974**, *9*, 625.

Scheme IV



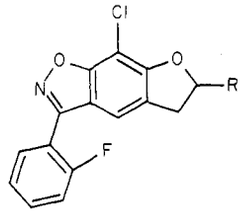
[a] Ac_2O/pyridine. [b] 2-F-$C_6H_4COCl/AlCl_3$. [c] NaOH. [d] $NH_2OH \cdot HCl$. [e] KOH.

Scheme V



to final product **23** followed the same course as described for Scheme I; however, in this case the ortho-F substituent on the phenyl ring resulted in a countercyclized impurity that required chromatographic purification for removal.

The carboxamide (**24**) and nitrile (**25**) analogues were synthesized from acid **15k** or ester **14k**. Reaction of **14k** with anhydrous ammonia in ethanol gave **24**, from which **25** was obtained by dehydration with phosphorus oxychloride. Alternatively, amide **24** was prepared by ammoniolysis of acid chloride **26**, which in turn was formed by a reaction of **15k** with thionyl chloride.



14k, R = COOEt
15k, R = COOH
24, R = $CONH_2$
25, R = CN
26, R = COCl

Resolution of **15k** was carried out by the sequence outlined in Scheme V. D-(−)-α-phenylglycinol was converted to oxazolidone **27** by treatment with dimethyl carbonate/K_2CO_3 in refluxing toluene. The lithio salt of **27**, generated with *n*-BuLi at −78 °C, was allowed to react with acid chloride **26** to give imide **28** as a mixture of diastereomers. Separation of this mixture was readily

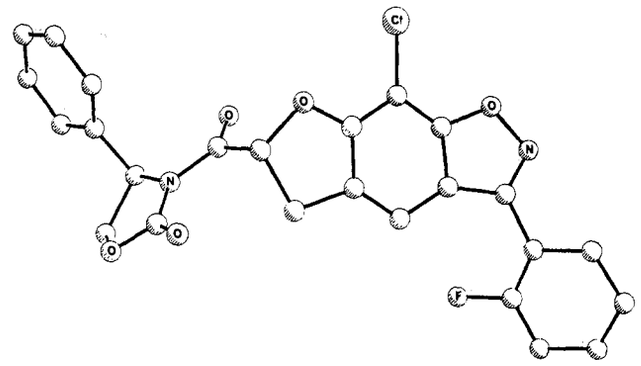


Figure 1. Computer-composed representation of the X-ray analysis of compound **28A**.

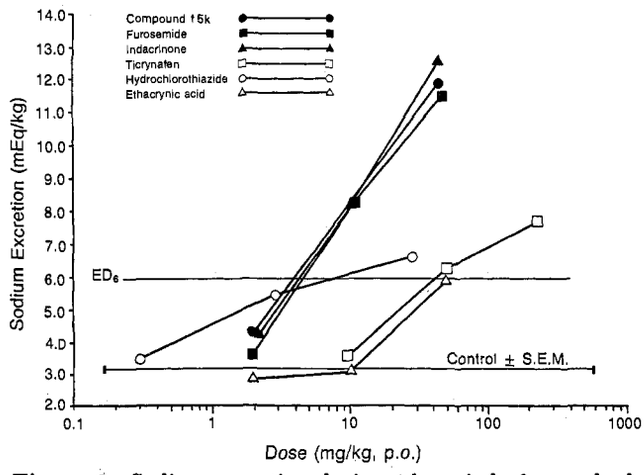


Figure 2. Sodium excretion during 4-h period after oral administration of **15k** and reference diuretics to male saline-loaded mice. Each point is the mean of four cages of five mice/cage. The area marked represents the excretion level used to calculate the ED_6 values.

effected and was followed by hydrolysis of each pure diastereomer to give (+)-**29** and (−)-**30**. To ascertain if partial racemization had occurred during the hydrolysis step, a sample of (+)-**29** was converted to the corresponding acid chloride and then to **28** as described above. Careful analysis of this product by NMR, TLC, and HPLC indicated that only one diastereomer had formed. Thus, the resolution procedure described above affords pure enantiomers. The absolute configuration of (−)-**30** as determined from X-ray analysis of the corresponding imide derivative is 2*R* (see Figure 1).

Biological Activity

Structure–Activity Relationships. A. Saluresis–Diuresis in Mice, Rats, and Dogs. The 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazoles described in this study were tested orally in mice, rats, and, in selected cases, dogs. Dose–response experiments measuring the urine volume and Na^+, K^+, and Cl^- concentrations were used to evaluate the saluretic properties of the target compounds. In order to compare the relative potencies of these derivatives, we have established the use of ED_x values as presented in Table II. An ED_x is defined as the oral dose (mg/kg) required to produce an excretion of x milliequivalents (mequiv) of Na^+ per kilogram of body weight during the relevant observation period. The specific ED_x values (e.g., ED_6 for mouse, ED_2 for rats, and ED_5 for dogs) were selected on the basis of two criteria: (1) the values represent doses that cause a significant natriuretic effect when compared statistically to control levels of excretion and (2) the values represent levels of excretion that are the

Table II. Oral Diuretic Activity[a] in Mice, Rats, and Dogs

compd	mouse ED_6,[b] mg/kg	rat ED_2,[c] mg/kg	dog ED_5,[d] mg/kg
10a	55	27.3	13.5
10b	8.4	14.3	
10c	inactive	22.5	
10d	inactive	190	
10e	inactive	63	
10f	66	7.3	
15k	4.2	40	0.60
15l	7.25	>100	0.79
15m	100	inactive	
15n	inactive	210	
15o	inactive	>100	
15p	inactive	40	
15q	6.8	3.8	inactive
15r	0.47	0.23	inactive
15s	9.9	117.5	
14k	inactive	inactive	
23	30	inactive	21.0
24	39	inactive	
25	inactive	inactive	
29	2.95		0.71
30	inactive		inactive
furosemide	5.0	9.5	3.5
indacrinone	4.40	5.2	7.64

[a] The natriuretic potency of the compounds tested in this table is reported as an ED_x. ED_x is the oral dose (mg/kg) required to produce an excretion of x milliequivalents of Na^+ per kilogram during the observation/collection period of the assay. ED_x values represent approximate midpoints of the linear regression of the response curve of Na^+ excretion vs. the log of the dose. See text for a discussion on the use of ED_x. [b] ED_6 in male mice; 0–4 h. Highest dose tested was 50 mg/kg. See Experimental Section for details for test protocol. [c] ED_2 in female rats; 0–4 h. Highest dose tested was 100 mg/kg. Details of test protocol are described in the Experimental Section. [d] ED_5 in female dogs; 0–6 h. Highest dose tested was 30 mg/kg. Details of test protocol are described in the Experimental Section.

approximate midpoints of the linear regression of the Na^+ response vs. the log of the doses for a family of curves representing the classes and/or relative activities of the compounds in question (see Figure 2 for representative dose–response curves in male mice). Although only the Na^+ excretion was used to determine the ED_x values, the urine volume and Cl^- excretion generally paralleled that of the Na^+, and thus either of these parameters could also be used for relative potency comparisons. The relative potencies of furosemide and indacrinone in these particular models are also listed in Table II for purposes of comparison.

Structural requirements for diuretic activity within this series were evaluated at three positions of the 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole ring system. Variants of the R group at position 3 include alkyl, aryl, and 2-thienyl. The 3-ethyl (**15q**) and 3-isobutyl (**15r**) derivatives displayed a high level of saluretic activity in both mice and rats; however, both compounds were essentially inactive in the dog model, which is probably a better indicator of activity in humans. No clear structure–activity patterns emerged for the series of 3-aryl-substituted compounds. The *o*-fluorophenyl analogue **15k** showed a high order of potency in mice and dogs and a moderate effect in rats. Resolution of **15k** into the optical isomers indicates that only the (+)-isomer **29** showed diuretic activity.

Variants at positions 6 and 8 of the tricyclic ring system were evaluated in a subgroup of compounds in which the *o*-fluorophenyl substituent was held constant at position 3. The relative effectiveness of substituents at position 8 in producing diuretic activity is Cl > Me = Br > H > OMe, while only the carboxyl function at position 6 resulted in high levels of diuretic activity. The carboxamido (**24**) and ester (**14k**) substituents at this position, which showed only moderate saluretic effects, are most likely serving as prodrugs and producing the carboxylic acid in vivo.[7]

Table III. Diuretic Activity of **15k**, **29**, **30**, and Reference Diuretics in Saline-Loaded Mice

compd	dose, mg/kg po	Na^+ excretion,[a] mequiv/kg, 0–4 h
control	10 ml/kg	3.2 ± 0.61
15k	2	4.2 ± 0.44
	10	8.2 ± 0.71[b]
	50	11.9 ± 0.24[b]
furosemide	2	3.7 ± 0.48
	10	7.9 ± 0.72[b]
	50	11.5 ± 0.43[b]
indacrinone	2	4.0 ± 0.50
	10	8.0 ± 0.60[b]
	50	12.6 ± 0.27[b]
hydrochlorothiazide	0.3	3.5 ± 0.51
	3.0	4.5 ± 0.46[b]
	30	6.7 ± 0.57[b]
ethacrynic acid	2	2.9 ± 0.45
	10	3.2 ± 0.40
	50	5.9 ± 0.72[b]
ticrynafen	10	3.7 ± 0.42
	50	6.3 ± 0.55[b]
	250	7.7 ± 0.60[b]
29	2	5.5 ± 0.32[c]
	10	8.1 ± 0.25[c]
	50	13.2 ± 0.28[c]
30	2	2.8 ± 0.25
	10	3.2 ± 0.31
	50	3.5 ± 0.24

[a] Mean values ± SEM. See Experimental Section for details of test protocol. [b] Significantly different from control ($p < 0.05$), based on analysis of variance and Duncan's multiple range test. [c] Significantly different from control ($p < 0.05$), using an unpaired t test.

B. Pharmacology of 15k. The diuretic, saluretic, and uricosuric activities of orally administered **15k** were evaluated in several species in comparison to various reference standards. Most compounds of this series, including **15k**, were not particularly active in rats. Furosemide and indacrinone were approximately 4 and 8 times more potent, respectively, than **15k** in our rat model (see Table II). This relatively weak potency in rats has been described for similar compounds.[6,10]

In saline-loaded male mice, the diuretic and natriuretic effects of **15k** were equipotent to furosemide and indacrinone (see Table II). Compound **15k** was also equipotent to hydrochlorothiazide and significantly more potent than ethacrynic acid and ticrynafen (Table III), although the thiazide displayed a different diuretic and natriuretic profile, typical of a low-ceiling diuretic.

In conscious female dogs, **15k** was approximately 6 times more potent than furosemide and greater than 10 times more potent than indacrinone (see Table II). Detailed studies showed no significant difference in the pattern of Cl^-, K^+, Ca^{2+}, or Mg^{2+} excretion. Urine volume was also increased in a dose-related manner. Onset of activity was dose related and the duration of activity was 4–6 h. Urate excretion was increased for **15k** and ticrynafen but not for furosemide or indacrinone during the 6-h collection period (Table IV).

Tests on water-loaded conscious Cebus monkeys demonstrated significant uricosuric activity that was equal to indacrinone but less than that of ticrynafen with single oral doses. Furosemide did not increase urate excretion in this assay (Table IV).

Table IV. Natriuretic and Uricosuric Activities of **15**, **29**, **30**, and Reference Diuretics

	conscious female dogs (3 mg/kg po)			conscious Cebus monkeys[a] (water-loaded, 20 mg/kg po)	
compd	N[c]	Na^+ excreted,[b] mequiv/kg, 0–6 h	urate excreted,[b] mg/kg, 0–6 h	N	urate excreted,[b] mg/kg, 0–6 h
15k	6	8.18 ± 0.62[e]	0.82 ± 0.09[e]	4	7.08 ± 1.14[e]
furosemide	6	5.23 ± 0.42[e]	0.70 ± 0.06	4	4.03 ± 1.35
indacrinone	4	1.44 ± 0.32[f]	0.71 ± 0.08	4	9.53 ± 2.31[e]
ticrynafen[d]	6	1.54 ± 0.10[f]	0.80 ± 0.15	4	11.81 ± 3.88[e]
29	2	7.60 ± 0.40[f]	1.32 ± 0.14[f]	6	8.34 ± 1.75[f]
30	2	0.62 ± 0.09[f]	1.25 ± 0.32[f]	6	8.32 ± 2.85[f]
vehicle control	6	0.24 ± 0.07	0.61 ± 0.07	4	3.40 ± 0.54

[a] Details of the test protocol are described in the Experimental Section. [b] Mean values ± SEM. [c] Number of animals. [d] Ticrynafen dose was 10 mg/kg po in dogs. [e] Significantly different from control ($p < 0.05$), based on analysis of variance and Duncan's multiple range test. [f] Significantly different from control ($p < 0.05$), using an unpaired t test.

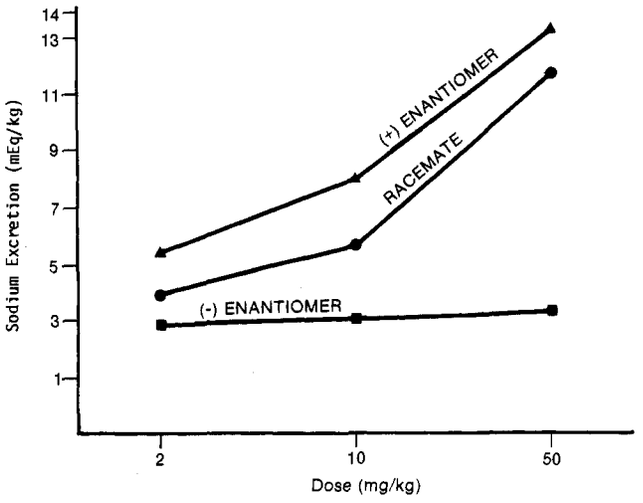


Figure 3. Sodium excretion during 4-h period after oral administration of **15k**, (+)-**29**, and (−)-**30** to male saline-loaded mice. Each point is the mean of four cages of five mice/cage.

Intraduodenal administration of equivalent natriuretic doses of **15k** and furosemide produced similar hemodynamic effects that were related to their potent diuretic activities. Both compounds lowered central venous pressure, maximum left ventricular dP/dt, and cardiac output. Pulmonary and systemic vascular resistances were increased by both compounds. In summary, studies to date indicate that **15k** is a potent, high-ceiling diuretic with moderate uricosuric activity and no adverse effects on the cardiovascular system.

The resolved enantiomers (+)-**29** and (−)-**30** were tested in mice, dogs, and monkeys in comparison to the racemate **15k**. Diuretic activity in male mice, as shown in Figure 3, indicated that the (+) enantiomer possesses all the diuretic activity and is approximately twice as potent as the racemate. This enantiomeric separation of diuretic activity was also confirmed in the dog assay (Table IV). In both the dog assay and in conscious Cebus monkeys, both enantiomers exhibited equivalent uricosuric activity as shown in Table IV.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. The NMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. Microanalyses were performed by the Abbott Analytical Department.

5-Benzoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic Acid (9a). To a solution of benzoyl chloride (14.71 g, 0.105 mol) and ethyl 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate[9] (13.66 g, 0.0523 mol) in 27 mL of CH_2Cl_2 was added with mechanical agitation anhydrous $AlCl_3$ (20.92 g, 0.157 mol). The resulting mixture was heated slowly to 90 °C on a hot water bath and held for 1.5 h during which time it became quite viscous. The mixture was diluted with 100 mL of 1,2-dichloroethane and decanted into a slurry of 500 mL of ice and 60 mL of concentrated HCl. After the mixture was stirred for 1 **h**, the slurry was extracted with Et_2O, and the ethereal extract was washed with brine solution and dried over $MgSO_4$. Evaporation yielded a gum, which was dissolved in 100 mL of absolute EtOH and treated with 500 mL of 2 M KOH overnight. The insoluble potassium salt was collected by filtration and partitioned in a separatory funnel between 4 M HCl and Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, decolorized with Darco, filtered, and evaporated to give 17.18 g of cream powder, mp 167–172 °C. Recrystallization from chloroform/*n*-hexane gave 11.90 g of **9a**, mp 188–190 °C. Anal. ($C_{16}H_{10}Cl_2O_4$) C, H.

6,7-Dichloro-2,3-dihydro-5-(*o*-methylbenzoyl)benzofuran-2-carboxylic acid (9b) was obtained from *o*-methylbenzoyl chloride and **8** in the same manner as **9a** in 79% yield, mp 159–160.5 °C. Anal. ($C_{17}H_{12}Cl_2O_4$) C, H.

5-(*o*-Chlorobenzoyl)-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid (9c) was obtained from *o*-chlorobenzoyl chloride and **8** as described for **9a** in 70% yield, mp 141–142 °C after recrystallization from EtOAc/*n*-hexane. Anal. ($C_{16}H_9Cl_3O_4$) C, H.

6,7-Dichloro-2,3-dihydro-5-(*p*-hydroxybenzoyl)benzofuran-2-carboxylic Acid (9d). Friedel–Crafts reaction of *p*-nitrobenzoyl chloride and **8** by the method described for **9a** gave 6,7-dichloro-2,3-dihydro-5-(*p*-nitrobenzoyl)benzofuran-2-carboxylic acid in 38% yield after recrystallization from acetonitrile/1-chlorobutane, mp 249–250 °C. Anal. ($C_{16}H_9Cl_2NO_6$) C, H, N. To a stirred suspension of sodium hydride (2.60 g, 0.045 mol, 50% in mineral oil) in DMF (40 mL) at 0 °C was added acetaldoxime (4.13 g, 0.07 mol) in portions over 10 min. After an additional 10 min, a solution of the above Friedel–Crafts product (6.95 g, 0.018 mol) in 30 mL of warm DMF was added dropwise, maintaining the temperature below 20 °C. The reaction mixture was stirred at room temperature for 6 h, filtered, and acidified with concentrated HCl. The resulting precipitate was collected by filtration and dissolved in EtOAc, and the solution was washed with water, then dried, and filtered. Evaporation afforded an oil, which was triturated with hexane, yielding 3.9 g (63.0%) of **9d**, mp 190–192 °C. Anal. ($C_{16}H_{10}Cl_2O_5$) C, H.

6,7-Dichloro-2,3-dihydro-5-(*m*-fluorobenzoyl)benzofuran-2-carboxylic acid (9e) was obtained from *m*-fluorobenzoyl chloride and **8** in the same manner as **9a** in 75% yield, mp 181.5–183 °C. Anal. ($C_{16}H_9Cl_2FO_4$) C, H.

6,7-Dichloro-2,3-dihydro-5-(*p*-fluorobenzoyl)benzofuran-2-carboxylic acid (9f) was prepared by the Friedel–Crafts reaction of *p*-fluorobenzoyl chloride and **8** as described for **9a**. There was obtained a 71% yield of product after recrystallization from Et_2O/hexane, mp 185–186 °C. Anal. ($C_{16}H_9Cl_2FO_4$) C, H.

8-Chloro-5,6-dihydro-3-phenylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic Acid (10a). Hydroxylamine hydrochloride (15.19 g, 0.2186 mol) and **9a** (10.84 g, 0.0322 mol) were heated at reflux in 75 mL of dry pyridine for 5 h and then evaporated to dryness on a rotary evaporator. The residue was taken up in EtOAc and the solution was washed with dilute HCl

and brine, then dried over $MgSO_4$, and evaporated to a gum containing both the *E* and *Z* isomers of the oxime. Without further purification, the gum was taken up in 20 mL of absolute EtOH and treated with 120 mL of 1 M alcoholic KOH at reflux on a steam bath for 3 h and then refrigerated at 5 °C for 48 h. The resulting precipitate was collected by filtration, washed with hexane, dried, and dissolved in 300 mL of warm H_2O. Acidification to pH 2.0 by addition of 4 M HCl gave a gelatinous precipitate, which was extracted with EtOAc. The organic solution was dried, decolorized with Darco, and evaporated. Recrystallization from EtOAc/hexane afforded 3.3 g (32%) of **10a**, mp 214–215 °C. Anal. ($C_{16}H_{10}ClNO_4$) C, H, N, Cl.

8-Chloro-5,6-dihydro-3-*o*-tolylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (10b) was prepared in a fashion analogous to **10a** from **9b** in 10% yield, mp 179–181 °C. Anal. ($C_{17}H_{12}ClNO_4$) C, H, N.

8-Chloro-3-(*o*-chlorophenyl)-5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (10c) was prepared from **9c** by using the procedure described for **10a**; however, the product contained a significant impurity, presumably the countercyclized 5-(1,2-benzisoxazol-3-yl)-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid. The mixture (12.0 g) was dissolved in 200 mL of absolute EtOH and treated with 0.5 mL of concentrated H_2SO_4 overnight. After partial evaporation, the residue was dissolved in EtOAc and the resulting solution was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Chromatography of the residue on silica gel eluting with $CHCl_3$/*n*-hexane in a 3:1 ratio gave a solid, mp 136 °C. Hydrolysis of this material at 60 °C in 25 mL of absolute EtOH and 200 mL of 1 M NaOH for 20 min furnished a white precipitate that was distributed between EtOAc and 4 M HCl. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Recrystallization from EtOAc/*n*-hexane gave 875 mg (8.1%) of **10c**, mp 224–225 °C. Anal. ($C_{16}H_9Cl_2NO_4$) C, H, N, Cl.

Potassium 8-chloro-5,6-dihydro-3-(*p*-hydroxyphenyl)-furo[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (10d) was prepared from **9d** by the same procedure as described for **10a**. Acidification of an aqueous solution of the dipotassium salt afforded the insoluble monopotassium salt as a precipitate, which was triturated in warm distilled water and dried to furnish **10d**, mp 215–217 °C, in 47.0% yield. Anal. ($C_{16}H_9ClKNO_5$) C, H, N.

8-Chloro-5,6-dihydro-3-(*m*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (10e) was obtained from **9e** as described for **10a** in 28% yield, mp 182.5–183.5 °C after recrystallization from $CHCl_3$/petroleum ether. Anal. ($C_{16}H_9ClFNO_4$) C, H, N.

8-Chloro-5,6-dihydro-3-(*p*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (10f) was prepared from **9f** as described for **10a** in 27% yield after recrystallization from $CHCl_3$/petroleum ether, mp 225–226 °C. Anal. ($C_{16}H_9ClFNO_4$) C, H, N.

3-Chloro-2,4-dimethoxybenzaldehyde (17g). To a solution of 10.0 g (0.058 mol) of 2-chlororesorcinol dimethyl ether[10] in 75 mL of CH_2Cl_2 at −40 °C under N_2 was added by dropwise addition 12.7 mL (0.116 mol) of $TiCl_4$. This was followed by dropwise addition of 6.7 g (0.58 mol) of dichloromethyl methyl ether at −20 °C. The mixture was stirred for 1 h at 0 °C and then was allowed to warm to room temperature. The reaction mixture was poured into 100 mL of 1:1 HCl/ice water and was then extracted with CH_2Cl_2. The organic solution was washed with dilute $NaHCO_3$ and then with aqueous NaCl. After drying over Na_2SO_4, the CH_2Cl_2 was evaporated to provide 9.2 g (79%) of **17g**, mp 109–111 °C. Anal. ($C_9H_9ClO_3$) C, H.

3-Methyl-2,4-dimethoxybenzaldehyde (17h). By use of the procedure described above for **17g**, 2,6-dimethoxytoluene was converted to **17h** in 73% yield, mp 51–52 °C. Anal. ($C_{10}H_{12}O_3$) C, H.

3-Chloro-2-hydroxy-4-methoxybenzaldehyde (18g). To a solution of 72.0 g (0.359 mol) of **17g** in 450 mL of CH_2Cl_2 at −50 °C under N_2 was added dropwise 90.0 g (0.359 mol) of BBr_3. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was then poured into 500 mL of ice water and extracted with EtOAc. The organic solution was washed with aqueous NaCl and dried over Na_2SO_4. Evaporation of the EtOAc gave a residue that was rapidly passed through a silica gel column eluting with EtOAc/CH_2Cl_2 to give 49.5 g (74%) of **18g**, mp 114–117 °C. Anal. ($C_8H_7ClO_3$) C, H.

2-Hydroxy-4-methoxy-3-methylbenzaldehyde (18h) was obtained from **17h** in the same manner as **18g** in 75% yield, mp 61–62 °C.

Diethyl 7-Chloro-2,3-dihydro-3-hydroxy-6-methoxybenzofuran-2,2-dicarboxylate (19g). To a solution of **18g** (69.91 g, 0.375 mol) and diethyl bromomalonate (79.9 mL, 0.468 mol) in 2-butanone (400 mL) was added freshly powdered anhydrous K_2CO_3 (51.78 g). The suspension was stirred vigorously and heated at reflux for 4.5 h and then filtered and evaporated to dryness. The oil obtained was redissolved in carbon tetrachloride and filtered and then evaporated and recrystallized from chloroform/hexane to yield 103 g (79.6%) of **19g**, mp 115.5–117 °C. Anal. ($C_{15}H_{17}ClO_7$) C, H.

6-Methoxy-7-methylbenzofuran-2-carboxylic Acid (20h). A mixture of **18h** (68 g, 0.41 mol), diethyl bromomalonate (102.8 g, 0.43 mol), and anhydrous K_2CO_3 (55 g, 0.4 mol) in 250 mL of methyl ethyl ketone was heated at reflux for 4 h. After filtering, the filtrate was partly evaporated and the residue distributed between CH_2Cl_2 and aqueous NaCl solution. The organic layer was dried and evaporated to a residue. This material was dissolved in 85 mL of absolute EtOH and treated all at once with a hot solution of 47.5 g of KOH in 500 mL of EtOH. The potassium carboxylate that precipitated was filtered and then dissolved in a minimum amount of water. Acidification with 6 N HCl gave, after cooling and filtration, 46.5 g (55%) of **20h**, mp 237–239 °C. Anal. ($C_{11}H_{10}O_4$) C, H.

6,7-Dimethoxybenzofuran-2-carboxylic acid (20j) was obtained from **18j**[16] in the same manner as **20h** in 64% yield, mp 198–200 °C. Anal. ($C_{11}H_{10}O_5$) C, H.

Ethyl 7-Chloro-2,3-dihydro-6-methoxybenzofuran-2-carboxylate (11g). A solution of **19g** (2.67 g, 0.008 mol) and 3 drops of concentrated H_2SO_4 in 100 mL of glacial HOAc was shaken with 0.3 g of 20% Pd–C in a Parr apparatus under 3 atm of hydrogen for 2 h. The solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$. This organic solution was washed with aqueous $NaHCO_3$ and brine solutions, dried over anhydrous Na_2SO_4, and evaporated, affording 2.11 g (82.9 %) of diethyl 7-chloro-2,3-dihydro-6-methoxybenzofuran-2,2-dicarboxylate, mp 97–99 °C. Anal. ($C_{15}H_{17}ClO_6$) C, H.

The above intermediate (16.79 g, 0.0509 mol), distilled water (1.0 mL, 0.0555 mol), dry LiCl (4.36 g, 0.1018 mol), and Me_2SO (150 mL, previously dried over 5-Å molecular sieves) were combined and heated at reflux for 2 h and then allowed to cool to 90 °C. Most of the Me_2SO was removed by vacuum distillation, and the residue was decanted into excess brine solution. The brine was acidified with concentrated HCl and extracted several times with EtOAc. The combined washes were in turn washed with fresh brine and then evaporated. The residue obtained was dissolved in 300 mL of dry EtOH containing 1 mL of H_2SO_4 and stirred overnight at room temperature. The EtOH was evaporated and replaced with EtOAc and this solution was washed with aqueous $NaHCO_3$ and brine solution. Drying over $MgSO_4$, decolorization with Darco, and evaporation was followed by recrystallization from EtOH/H_2O to afford 9.1 g (69%) of **11g**, mp 108.5–110 °C. Anal. ($C_{12}H_{13}ClO_4$) C, H.

Ethyl 2,3-Dihydro-6-methoxy-7-methylbenzofuran-2-carboxylate (11h). To a solution of **20h** (29 g, 0.14 mol) dissolved in aqueous NaOH (15 g of NaOH in 750 mL of H_2O) was added 550 g of 5% sodium amalgam portionwise over a period of 30 min. The mixture was stirred for 5 h and then decanted from the mercury and filtered through Celite. The filtrate was acidified with concentrated HCl and cooled in an ice bath. There was obtained 26 g of crude acid after filtering. Recrystallization from CH_2Cl_2/hexane gave pure 2,3-dihydro-6-methoxy-7-methylbenzofuran-2-carboxylic acid, mp 142–143 °C. Esterification of this material by the procedure described for **11g** gave 16.5 g of **11h** as an oil in 50% yield. Anal. ($C_{13}H_{16}O_4$) C, H.

Ethyl 2,3-dihydro-6-methoxybenzofuran-2-carboxylate (11i) was obtained as an oil from **20i**[17] in the same manner as **11h** in 53% overall yield. Anal. ($C_{12}H_{14}O_4$) C, H.

(16) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *J. Am. Chem. Soc.* **1982**, *104*, 536.
(17) Tanaka, S. *J. Am. Chem. Soc.* **1951**, *73*, 872.

Ethyl 6,7-dimethoxy-2,3-dihydrobenzofuran-2-carboxylate (11j) was prepared from **20j** in the same manner as **11h** in 80% yield, mp 69.5–70.5 °C. Anal. ($C_{13}H_{16}O_5$) C, H.

Ethyl 7-Chloro-2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxybenzofuran-2-carboxylate (12k). A solution of **11g** (7.79 g, 0.0304 mol) and *o*-fluorobenzoyl chloride (7.25 mL, 0.0607 mol) in 80 mL of 1,2-dichloroethane was stirred in an ice brine bath and treated with anhydrous $AlCl_3$ (16.17 g, 0.1215 mol) in small portions, keeping the temperature below 5 °C. After 45 min, the cooling bath was removed and the reaction mixture was allowed to stir at room temperature for 3 h. Decantation into 400 mL of iced dilute HCl was followed by gentle warming to produce a pale yellow oil, which was extracted into EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, decolorized with Darco, and evaporated to give 7.7 g (69.2%) of **12k**, mp 119–119.5 °C, after recrystallization from EtOAc/*n*-hexane. Anal. ($C_{18}H_{14}ClFO_5$) C, H.

Ethyl 2,3-Dihydro-5-(*o*-fluorobenzoyl)-6-hydroxy-7-methylbenzofuran-2-carboxylate (12l). A solution of **11h** (2.7 g, 0.011 mol) and *o*-fluorobenzoyl chloride (2.73 mL, 0.022 mol) in 30 mL of 1,2-dichloroethane was stirred at 0–5 °C and treated with $AlCl_3$ (4.57 g, 0.05 mol) in small portions. After 10 min, the reaction mixture was poured onto ice and then extracted with CH_2Cl_2. The organic layer was washed with brine solution, dried over $MgSO_4$, and evaporated to give 2.7 g (68%) of ethyl 2,3-dihydro-5-(*o*-fluorobenzoyl)-6-methoxy-7-methylbenzofuran-2-carboxylate, mp 101.5–102.5 °C. A solution of this compound (2.0 g, 0.0056 mol) in 20 mL of CH_2Cl_2 was cooled to 0 °C and treated by dropwise addition with 6.14 mL (0.006 mL) of 1 M BBr_3 in CH_2Cl_2. After 15 min, the reaction was poured into ice water and the resulting mixture extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give 1.8 g (93%) of **12l** after recrystallization from EtOH, mp 103.5–105.5 °C. Anal. ($C_{19}H_{17}FO_5$) C, H.

Ethyl 2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxybenzofuran-2-carboxylate (12m) was obtained from **11i** in 62% yield by using the procedure described for **12l**, mp 120–121 °C. Anal. ($C_{18}H_{15}FO_5$) C, H.

Ethyl 2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxy-7-methoxybenzofuran-2-carboxylate (12n) was obtained from **11j** in 32% yield by using the procedure described for **12k** except the Friedel–Crafts reaction required 5 equiv of $AlCl_3$ and the reaction product was purified by chromatography on silica gel, eluting with CH_2Cl_2. The product had mp 95–96 °C. Anal. ($C_{19}H_{17}FO_6$) C, H.

Ethyl 7-chloro-2,3-dihydro-6-hydroxy-5-(α-thienylcarbonyl)benzofuran-2-carboxylate (12o) was obtained from **11q** and 2-thiophenecarbonyl chloride in the same manner as **12k** in 90% yield, mp 133.5–134 °C. Anal. ($C_{16}H_{13}ClO_5S$) C, H, Cl.

Methyl 5-Acetyl-7-chloro-2,3-dihydro-6-hydroxybenzofuran-2-carboxylate (12p). To 1,2-dichloroethane (50 mL) were added sequentially methyl 7-chloro-2,3-dihydro-6-methoxybenzofuran-2-carboxylate[18] (4.53 g, 0.0187 mol) and acetic anhydride (3.5 mL, 0.0373 mol). The solution was stirred in an ice–brine bath at 0–5 °C and treated with anhydrous $AlCl_3$ (9.95 g, 0.0747 mol) portionwise over 20 min. Cooling was removed after 1.5 h and the mixture was left to stir at room temperature overnight. The reaction mixture was decanted into cold dilute HCl, producing a precipitate which was extracted into EtOAc, and the resulting solution was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The crystalline product was triturated with $CHCl_3$/hexane and recrystallized from CH_3CN/H_2O to yield 4.14 g (81.9%) of light pink crystals, mp 175–177 °C. Anal. ($C_{12}H_{11}ClO_5$) C, H.

Ethyl 7-Chloro-2,3-dihydro-6-hydroxy-5-propionylbenzofuran-2-carboxylate (12q). To 1,2-dichloroethane (50 mL) were added **11q** (4.25 g, 0.016 56 mol) and propionyl chloride (2.58 mL, 0.033 11 mol). The solution was stirred in an ice bath and treated with anhydrous $AlCl_3$ (6.62 g, 0.049 67 mol) at 0–5 °C for 45 min. At this time, an additional portion of $AlCl_3$ (2.21 g, 0.016 56 mol) was added and the mixture left to stir overnight. The reaction was worked up as described for **12p** to yield 4.0 g (80.9%) of white crystals, mp 109–111 °C after recrystallization from EtOAc/hexane. Anal. ($C_{14}H_{15}ClO_5$) C, H.

Ethyl 7-chloro-2,3-dihydro-6-hydroxy-5-isovaleroylbenzofuran-2-carboxylate (12r) was prepared in a fashion analogous to **12q** in 33% yield, mp 84–85 °C. Anal. ($C_{16}H_{19}ClO_5$) C, H.

Ethyl (*E*)-7-Chloro-2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxybenzofuran-2-carboxylate Oxime (13k). A mixture of **12k** (1.7 g, 4.65 mmol) and hydroxylamine hydrochloride (1.55 g, 22.3 mmol) was heated at reflux in 17 mL of pyridine for 4 h. The solvent was evaporated and the residue was partitioned between EtOAc and 5% HCl. From the organic phase was obtained 0.350 g (20%) of **13k** after chromatography on silica gel, mp 171–172 °C. Anal. ($C_{18}H_{15}ClFNO_5$) C, H, N.

Ethyl (*E*)-2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxy-7-methylbenzofuran-2-carboxylate oxime (13l) was obtained from **12l** in the same manner as **13k** in 21% yield, mp 70–71 °C. Anal. ($C_{19}H_{18}FNO_5$) C, H, N.

Ethyl (*E*)-2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxybenzofuran-2-carboxylate oxime (13m) was prepared from **12m** in the same manner as **13k** in 24% yield, mp 179–181 °C. Anal. ($C_{18}H_{16}FNO_5$) C, H, N.

Ethyl (*E*)-2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxy-7-methoxybenzofuran-2-carboxylate oxime (13n) was prepared in a fashion analogous to **13k** in 18% yield.

Ethyl (*E*)-7-chloro-2,3-dihydro-6-hydroxy-5-(α-thienylcarbonyl)benzofuran-2-carboxylate oxime (13o) was obtained from **12o** in the same manner as **13k** in 24% yield after chromatography on silica gel, mp 138–140 °C. Anal. ($C_{16}H_{14}ClNO_5S$) C, H, N.

Ethyl (*E*)-5-Acetyl-7-chloro-2,3-dihydro-6-hydroxybenzofuran-2-carboxylate Oxime (13p). A suspension of **12p** (3.96 g, 0.0015 mol) in 50 mL of H_2O was treated with 2 M aqueous NaOH (9.2 mL, 1.25 equiv) at room temperature for 2 h. Acidification with concentrated HCl produced a fine white crystalline precipitate, which was collected by filtration and dried in vacuo, giving 94.0% of the corresponding acid, mp 227–231 °C. Anal. ($C_{11}H_9ClO_5$) C, H. A mixture of this acid (2.95 g, 0.0115 mol) and hydroxylamine hydrochloride (5.55 g, 0.0804 mol) was added to pyridine (100 mL) and the mixture was heated at reflux for 7 h. The pyridine was then removed on a rotary evaporator and chased with EtOH. The residue was dissolved in EtOAc and the organic solution was washed with dilute aqueous HCl and brine solution, dried over anhydrous $MgSO_4$, and evaporated to dryness, giving 3.72 g (99.5%) of oxime, mp 234–235 °C. Anal. ($C_{11}H_{10}ClNO_5$) C, H, N. The oxime was esterified by stirring the crude product in 100 mL of THF/EtOH/concentrated H_2SO_4 (39:60:1) for 16 h at room temperature. The resulting solution was evaporated and the residue dissolved in EtOAc. The organic solution was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. Recrystallization from EtOAc/hexane furnished 3.15 g (76.1%) of **13p**, mp 154–155 °C. Anal. ($C_{13}H_{14}ClNO_5$) C, H, N.

Ethyl (*E*)-7-chloro-2,3-dihydro-6-hydroxy-5-propionylbenzofuran-2-carboxylate oxime (13q) was prepared from **12q** in a fashion analogous to **13p** in 87% yield, mp 145.5–147 °C. Anal. ($C_{14}H_{16}ClNO_5$) C, H, N.

Ethyl (*E*)-7-chloro-2,3-dihydro-6-hydroxy-5-isovaleroylbenzofuran-2-carboxylate oxime (13r) was obtained from **12r** in the same manner as **13p** in 75% yield, mp 159–162 °C. Anal. ($C_{16}H_{20}ClNO_5$) C, H, N.

Ethyl 8-Chloro-5,6-dihydro-3-(*o*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14k). A solution of **13k** (400 mg, 1.06 mmol) in 8 mL of Ac_2O was stirred at 90 °C for 1 h and then kept at room temperature for 18 h. The reaction mixture was evaporated in vacuo and the residue triturated with EtOH to give a 58% yield of the *O*-acetyl oxime, mp 111–112 °C. Anal. ($C_{20}H_{17}ClFNO_6$) C, H, N. To a solution of this intermediate (400 mg, 1.0 mmol) in 5 mL of DMF at 0–5 °C was added NaH (45 mg of a 50% mineral oil dispersion). The reaction mixture was stirred at room temperature for 4 h and then poured into cold H_2O. The product that precipitated was dissolved in EtOAc and the resulting solution was washed with brine solution and aqueous $NaHCO_3$. After the solution was dried over $MgSO_4$, the EtOAc was evaporated and the residue recrystallized from EtOH/H_2O

(18) This compound was prepared analogously to the corresponding ethyl ester derivative[9] by using MeOH for the esterification step.

to give 0.140 g (38%) of **14k**, mp 134–136 °C. Anal. ($C_{18}H_{13}ClFNO_4$) C, H, N.

Ethyl 5,6-dihydro-3-(*o*-fluorophenyl)-8-methylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14l) was obtained from **13l** in the same manner as **14k** in 25% yield, mp 124–125 °C. Anal. ($C_{19}H_{16}FNO_4$) C, H, N.

Ethyl 5,6-dihydro-3-(*o*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14m) was obtained from **13m** as described for **14k** in 29% yield, mp 115–116 °C. Anal. ($C_{18}H_{14}FNO_4$) C, H, N.

Ethyl 5,6-dihydro-3-(*o*-fluorophenyl)-8-methoxyfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14n) was obtained as an oil from **13n** in the same manner as **14k** in 22% yield. The product was purified by chromatography on silica gel, eluting with CH_2Cl_2. Anal. ($C_{19}H_{16}FNO_5$) C, H, N.

Ethyl 8-chloro-5,6-dihydro-3-α-thienylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14o) was prepared in a fashion analogous to **14k** in 33% yield, mp 124–125 °C. Anal. ($C_{16}H_{12}ClNO_4S$) C, H, N.

Ethyl 8-chloro-5,6-dihydro-3-methylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14p) was prepared from **13p** in the same manner as **14k** in 49% yield after recrystallization from EtOAc/hexane, mp 123–124 °C. Anal. ($C_{13}H_{12}ClNO_4$) C, H, N.

Ethyl 8-chloro-5,6-dihydro-3-ethylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14q) was obtained from **13q** analogously to **14k** in 69% yield after recrystallization from $CHCl_3$/hexane, mp 95–96 °C. Anal. ($C_{14}H_{14}ClNO_4$) C, H, N.

Ethyl 8-chloro-5,6-dihydro-3-isobutylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14r) was obtained from **13r** in the same manner as **14k** in 47% yield after recrystallization from hexane at low temperature, mp 74–75 °C. Anal. ($C_{16}H_{18}ClNO_4$) C, H, N.

Ethyl 8-Bromo-5,6-dihydro-3-(*o*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-carboxylate (14s). A stirred mixture of **14m** (942 mg, 2.84 mmol) and NBS (2.53 g, 14.2 mmol) in DMF (10 mL) was heated at 60 °C for 30 min. After cooling, the reaction mixture was poured into ice water and the resulting mixture was extracted with EtOAc. The organic layer was washed with H_2O, dried, and evaporated to a residue. Recrystallization from EtOH gave 500 mg 43% of **14s**, mp 125–126 °C. Anal. ($C_{18}H_{13}BrFNO_4$) C, H, N.

8-Chloro-3-(*o*-fluorophenyl)-5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic Acid (15k). To a solution of **14k** (1 g, 2.76 mmol) in 10 mL of warm MeOH was added a solution of KOH (0.36 g, 5.52 mmol) in 1 mL of H_2O. After 1 h, the reaction mixture was partially evaporated, diluted with H_2O, and warmed to dissolve the resulting potassium salt. Acidification with 2 N HCl gave a white precipitate, which was filtered and dried. There was obtained 0.85 g (92%) of **15k**, mp 197.5–199 °C. Anal. ($C_{16}H_9ClFNO_4$) C, H, N.

3-(*o*-Fluorophenyl)-5,6-dihydro-8-methylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic Acid (15l). By use of the procedure described for **15k**, **15l** was prepared in 89% yield from **14l**, mp 188–189 °C. Anal. ($C_{17}H_{12}FNO_4$) C, H, N.

3-(*o*-Fluorophenyl)-5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (15m) was obtained from **14m** in the same manner as **15k** in 90% yield, mp 194–196 °C. Anal. ($C_{16}H_{10}FNO_4$) C, H, N.

3-(*o*-Fluorophenyl)-5,6-dihydro-8-methoxyfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (15n) was prepared from **14h** analogously to **15k** in 63% yield, mp 127–129 °C. Anal. ($C_{17}H_{12}FNO_5$) C, H, N.

8-Chloro-5,6-dihydro-3-α-thienylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (15o) was obtained from **14o** as described for **15k** in 74% yield, mp 272–274 °C. Anal. ($C_{14}H_8ClNO_4S$) C, H, N.

8-Chloro-5,6-dihydro-3-methylfuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic Acid (15p). Ethyl ester **14p** (2 g, 7.1 mmol) was dissolved in 50 mL of absolute EtOH and hydrolyzed with 10 mL of 2 M NaOH. The insoluble sodium salt was collected by filtration and shaken with EtOAc/dilute HCl. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Recrystallization of the residue from EtOAc/hexane gave a quantitative yield of the **15p**, mp 260–263 °C. Anal. ($C_{11}H_8ClNO_4$) C, H, N.

8-Chloro-5,6-dihydro-3-ethyl[3,2-*f*]-1,2-benzisoxazole-6-carboxylic Acid (15q). Ester **14q** (2.2 g, 7.4 mmol) was dissolved in 80 mL of absolute EtOH and treated with 40 mL of alcoholic KOH at room temperature for 20 min and then diluted with H_2O. Workup as in **15p** and recrystallization from tetrahydrofuran/hexane gave 1.5 g (75%) of **15q**, mp 213–215 °C. Anal. ($C_{12}H_{10}ClNO_4$) C, H, N, Cl.

8-Chloro-5,6-dihydro-3-isobutylfuro[3,2-*f*]-1,2-benzoisoxazole-6-carboxylic acid (15r) was obtained from **14r** by the procedure described for **15q** in 72% yield, mp 181–183 °C. Anal. ($C_{14}H_{14}ClNO_4$) C, H, N, Cl.

8-Bromo-3-(*o*-fluorophenyl)-5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acid (15s) was prepared from **14s** in the same manner as **15k** in 89% yield, mp 189–191 °C. Anal. ($C_{16}H_9BrFNO_4$) C, H, N.

6,7-Dichloro-2,3-dihydro-5-(*o*-fluorobenzoyl)benzofuran-2-methanol (22). To a solution of **21**[9] (14.62 g, 66.7 mmol) in 75 mL of CH_2Cl_2 were added Ac_2O (15 g, 0.147 mol) and pyridine (0.5 mL). After stirring overnight at room temperature, the mixture was evaporated to approximately 10% of the original volume and the residue was mixed with 200 mL of hexane. The resulting solution was decanted from some gummy material that did not dissolve, and the hexane was evaporated to give 16.2 g (93%) of pure 2-(acetoxymethyl)-6,7-dichloro-2,3-dihydrobenzofuran. A stirred mixture of this compound (13.0 g, 49.8 mmol) and *o*-fluorobenzoyl chloride (11.9 mL, 99.6 mmol) in 25 mL of CH_2Cl_2 was cooled to 15 °C and treated with $AlCl_3$ (19.9 g, 149.4 mmol) portionwise over a period of 15 min. The reaction mixture was heated at 90 °C for 2 h and then poured into 550 mL of cold 4% HCl. After extraction with Et_2O, the organic layer was dried and evaporated. Chromatography of the residue on silica gel eluting with benzene/EtOAc (6:1) gave 5.6 g (56%) of 2-(acetoxymethyl)-6,7-dichloro-2,3-dihydro-5-(*o*-fluorobenzoyl)benzofuran, mp 92–93 °C. Anal. ($C_{18}H_{13}Cl_2FO_4$) C, H. A 5.8-g (0.015 mol) sample of the above compound was dissolved in 150 mL of EtOH and treated with 25 mL of 2 M NaOH for 5 min. Addition of excess H_2O caused the product to precipitate. The solid was filtered and then distributed between CH_2Cl_2 and aqueous NaCl. Evaporation of the solvent gave 4.4 g (85%) of **22**, mp 146–147 °C. Anal. ($C_{16}H_{11}Cl_2FO_3$) C, H.

8-Chloro-5,6-dihydro-3-(*o*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-methanol (23) was prepared from **22** by the same procedure as described for **10c** in 19% yield, mp 147–149 °C. Anal. ($C_{16}H_{11}ClFNO_3$) C, H, N, Cl.

8-Chloro-5,6-dihydro-3-(*o*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-carboxamide (24). Anhydrous ammonia was passed through a suspension of **14k** (5 g, 0.0138 mol) in 200 mL of EtOH for 5 h at room temperature. After standing overnight, the solid product was filtered and recrystallized from EtOAc/EtOH to give 3.2 g (70%) of **24**, mp 203–204 °C. Anal. ($C_{16}H_{10}ClFN_2O_3$) C, H, N.

8-Chloro-6-cyano-5,6-dihydro-3-(*o*-fluorophenyl)furo-[3,2-*f*]-1,2-benzisoxazole (25). To a suspension of **24** (1.5 g, 4.5 mmol) in 12.3 mL of $POCl_3$ was added 0.9 g (9 mmol) of triethylamine at 5–10 °C. After heating at 95 °C for 1 h, the mixture was evaporated on the rotary evaporator and the residue was dissolved in CH_2Cl_2. The organic solution was washed with aqueous NaCl, dried, and evaporated. Recrystallization of the residue from EtOAc gave 900 mg (63%) of **25**, mp 172–173 °C. Anal. ($C_{16}H_8ClFN_2O_2$) C, H, N.

8-Chloro-5,6-dihydro-3-(*o*-fluorophenyl)furo[3,2-*f*]-1,2-benzisoxazole-6-carbonyl Chloride (26). A mixture of **15k** (4.5 g, 0.0135 mol) and $SOCl_2$ (2.8 mL, 0.038 mol) in 40 mL of benzene was heated at reflux for 2 h. Evaporation of the solvent was followed by the addition of benzene (25 mL) and evaporation to a residue. Trituration with hexane gave a solid product, which was used without additional purification, mp 52–55 °C.

(4*R*)-4-Phenyl-2-oxazolidone (27). A mixture of D-(−)-α-phenylglycinol (1.37 g, 0.01 mol), dimethyl carbonate (10 mL), anhydrous K_2CO_3 (3.45 g, 0.025 mol), and toluene (1.5 mL) was heated at reflux for 2 h. After cooling, the reaction mixture was distributed between EtOAc and H_2O. The organic phase was washed with aqueous NaCl, dried, and evaporated to a residue. Recrystallization from MeOH–H_2O gave 1.2 g (75%) of **27**: mp 135–136 °C; $[\alpha]^{24}_D$ −69.7° (*c* 0.86, EtOAc). Anal. ($C_9H_9NO_2$) C, H, N.

Resolution of the Optical Isomers of 15k. A solution of **27** (2.05 g, 0.013 mol) in 40 mL of THF was cooled to −78 °C under N_2 and treated by dropwise addition with *n*-BuLi in hexane (7.9 mL of a 1.6 M solution). After stirring for 1.5 h at −78 °C, a solution of **26** (4.5 g, 0.013 mol) in 20 mL of THF was rapidly added. Stirring was continued at −78 °C for 1.5 h and at −30 °C for 5 min. At this time, the reaction mixture was distributed between cold H_2O containing 802 mg (0.015 mol) of dissolved NH_4Cl and Et_2O. A solid material, which was insoluble in both the aqueous and ethereal layers, was filtered and washed with a small amount of cold EtOH. There was obtained 2.2 g of the more polar diastereomer (**28A**), mp 250–252 °C. Anal. ($C_{25}H_{16}ClFN_2O_5$) C, H, N. The EtOH wash from above was combined with the ethereal layer and the resulting solution was washed with aqueous NaCl. After drying and evaporation, there was obtained 3.7 g of a gummy solid. Chromatography on silica gel eluting with EtOAc/hexane (4:6) gave 2.3 g of the less polar diastereomer (**28B**), mp 93–95 °C. Anal. ($C_{25}H_{16}ClFN_2O_5$) C, H, N. A solution of **28A** (1.25 g, 2.6 mmol) in 40 mL of THF and 5 mL of EtOH was cooled to 5 °C and treated by dropwise addition with a solution of KOH (168 mg, 2.55 mmol) in 7 mL of EtOH. After 10 min, 25 mL of Et_2O was added and the precipitated potassium carboxylate salt was filtered. The salt (800 mg) was dissolved in 5 mL of EtOH and 30 mL of H_2O and mixed with 4 mL of 2 N HCl. After the mixture was stirred for 2 h at room temperature, the solvent was partially evaporated in vacuo at 28 °C and the residue diluted with H_2O. The resulting solid was filtered, dried, and triturated with hexane to give 676 mg (78%) of **30**: mp 168–170 °C; $[\alpha]^{25}_D$ −28° (*c* 1.5, EtOAc). Hydrolysis of **28B** as described for **28A** gave **29** in 79% yield: mp 169–171 °C; $[\alpha]^{25}_D$ +25° (*c* 1.5, EtOAc).

Conscious Cebus Monkey Uricosuric Assay. Male and female Cebus monkeys were randomly assigned, four to six per treatment group. No food was allowed during the first 6 h after dosing. Water was available ad libitum. Test compounds were suspended in 0.2% hydroxypropylmethylcellulose in water and administered at the volume of 1.0 mL/kg po, using a nasogastric feeding tube. Treatments were followed immediately by a water load equivalent to 5% of the body weight of each monkey. Urine was collected at 2, 6, and 24 h after dosing with use of stainless steel metabolism pans. Urinary volume was measured, and samples were analyzed for concentrations of sodium, potassium, chloride, and uric acid.

Diuretic Model in Saline-Loaded Mice. Male mice, weighing 16–30 g, were used in a model that was a modification of the methods of Hill[19] and Sim.[20] Food and water was available ad libitum until the start of the experiment. Test compounds were suspended in 0.2% hydroxypropylmethylcellulose in water and the appropriate concentrations administered in a dose volume of 10 mL/kg po. Control mice received 10 mL/kg of the vehicle. Treatments were followed immediately by a volume load of 0.9% isotonic saline (3% of the animal's body weight), po. Four cages of five mice were assigned to each treatment group. After treatment, the five mice for each test group were placed into a stainless steel metabolism cage, and their combined urine output was collected over a 4-h period. Urine volume was measured and an aliquot of the sample was analyzed for sodium, potassium, chloride, and uric acid. Data presented are the means of four cages/dose, and the excretions calculated were in milliequivalents per kilogram of body weight per cage. These data were used to calculate the ED_6 values.

Diuretic Activity in Dogs. Female beagle dogs weighing 8–12 kg were allowed water ad libitum during an overnight 18-h fasting period prior to testing. The dogs were placed into supportive body slings and no further fluids were given. Each dog was prepared by shaving the areas of the jugular and cephalic veins for taking blood samples. The vulvar area was washed and cleaned with an antiseptic solution and was rinsed clean with distilled water. An appropriate size Foley catheter (10 or 12 French) was inserted into the bladder and remained in situ throughout the experiment. The urine from the bladders was drained by free flow. Thirty-minute base-line urine samples were collected just prior to dosing. Urine samples were collected for the $-^1/_2$–0, 0–$^1/_2$, $^1/_2$–1, 1–2, 2–4, and 4–6 h time intervals. Urine volume was measured and an aliquot taken from each sample. Each aliquot as centrifuged to remove suspended materials and then decanted and chilled on ice in a glass test tube. Four-milliliter venous blood samples were drawn into heparinized syringes at the urine collection times. Blood samples were centrifuged to separate the plasma within 30 min of withdrawing blood samples. Each sample of urine and plasma was analyzed for concentrations of Na^+, K^+, Cl^-, urate, and glucose by standard methods. Each dog was administered only one dose of the test compound in a given experiment. Calculations were made for mean excretion values for each variable, for each time interval and each dog tested. Data presented were the cumulative Na excretion values, expressed in milliequivalents/(kilograms 6 h) with at least two dogs/dose. Data of this type were used to calculate the ED_5 values.

Acute Diuretic Activity in Rats. Acute diuretic experiments were performed in female Sprague-Dawley rats weighing 175–225 g, which were provided a diet of sucrose and water for 18 h prior to treatment. Each rat was pretreated 2 h before dosing with 5 mg of DOCA (desoxycorticosterone acetate) subcutaneously. All compounds were dissolved or suspended in 0.2% methylcellulose in water and administered orally by gavage. Oral dosage volume was 2 mL/kg, which was immediately followed by a volume/saline load. The load consisted of 30 mL/kg of an isotonic solution of NaCl (0.34%) and KCl (0.69%) in water. The animals were housed in individual stainless steel metabolism cages and urine collections were made into graduated collection tubes for a single 4-h sampling period. The volume of each sample was measured and an aliquot was taken for determination of Na^+, K^+, and Cl^- concentrations by standard methods. Each compound was tested in a statistically designed two-stage, two-dose screening procedure using two rats/dose. All active compounds were further evaluated at a minimum of four doses with four rats/dose. Sodium excretion values were expressed as the mean milliequivalents/(kilogram 4 h). These values were used to calculate the ED_2.

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Registry No. Ethyl (*E*)-7-chloro-2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxybenzofuran-2-carboxylate *O*-acetyloxime, 122-04-3; **7** (Z = 2-F), 393-52-2; **7a**, 98-88-4; **7b**, 933-88-0; **7c**, 609-65-4; **7e**, 1711-07-5; **7f**, 403-43-0; **8**, 62717-20-8; **9** (Z = 4-NO_2), 90246-58-5; **9a**, 90246-52-9; **9a** (*E* oxime), 90246-65-4; **9a** (*Z* oxime), 90246-66-5; **9b**, 90246-53-0; **9c**, 90246-54-1; **9c** (oxime), 90246-68-7; **9d**, 90246-55-2; **9e**, 90246-56-3; **9f**, 90246-57-4; **10a**, 90246-59-6; **10b**, 90246-60-9; **10c**, 90246-61-0; **10d**, 90246-62-1; **10d** (dipotassium salt), 90246-69-8; **10d** (monopotassium salt), 90246-70-1; **10e**, 90246-63-2; **10f**, 90246-64-3; **11g**, 90246-72-3; **11h**, 90246-74-5; **11i**, 90246-76-7; **11j**, 90246-77-8; **12k**, 90246-78-9; **12l**, 90246-79-0; **12m**, 90246-81-4; **12n**, 90246-82-5; **12o**, 90246-83-6; **12p** (methyl ester), 90246-84-7; **12p** (acid), 90246-94-9; **12p** (acid oxime), 90246-95-0; **12q**, 90246-86-9; **12r**, 90246-87-0; **13k**, 90246-88-1; **13l**, 90246-89-2; **13m**, 90246-90-5; **13n**, 90246-91-6; **13o**, 90246-92-7; **13p**, 90246-93-8; **13q**, 90246-96-1; **13r**, 90246-97-2; **14k**, 90246-98-3; **14l**, 90247-00-0; **14m**, 90247-01-1; **14n**, 90247-02-2; **14o**, 90247-03-3; **14p**, 90247-04-4; **14q**, 90247-05-5; **14r**, 90247-06-6; **14s**, 90247-07-7; **15k**, 90247-08-8; **15k** (potassium salt), 90247-09-9; **15l**, 90247-10-2; **15m**, 90247-11-3; **15n**, 90247-12-4; **15o**, 90247-13-5; **15p**, 90247-14-6; **15p** (sodium salt), 90247-15-7; **15q**, 90247-16-8; **15r**, 90247-17-9; **15s**, 90247-18-0; **16g**, 7051-15-2; **16h**, 5673-07-4; **17g**, 72482-14-5; **17h**, 7149-92-0; **18g**, 72482-15-6; **18h**, 54700-36-6; **19g**, 90246-71-2; **20h**, 55364-64-2; **20j**, 76313-60-5; **21**, 62717-16-2; **22**, 90247-19-1; **23**, 90247-22-6; **24**, 90247-23-7; **25**, 90247-24-8; **26**, 90247-25-9; **27**, 90319-52-1; **28a**, 90247-26-0; **28b**, 90247-27-1; **29**, 90247-30-6; **30**, 90247-29-3; **30** (potassium carboxylate salt), 90247-28-2; hydroxylamine hydrochloride, 5470-11-1; 5-(1,2-benzisoxazol-3-

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yl)-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid, 90246-67-6; dichloromethyl methyl ether, 4885-02-3; diethyl bromomalonate, 685-87-0; diethyl 7-chloro-2,3-dihydro-6-methoxybenzofuran-2,2-dicarboxylate, 90246-73-4; 2,3-dihydro-6-methoxy-7-methylbenzofuran-2-carboxylic acid, 90246-75-6; ethyl 2,3-dihydro-5-(*o*-fluorobenzoyl)-6-methoxy-7-methylbenzofuran-2-carboxylate, 90246-80-3; 2-thiophenecarbonyl chloride, 5271-67-0; methyl 7-chloro-2,3-dihydro-6-methoxybenzofuran-2-carboxylate, 90246-85-8; propionyl chloride, 79-03-8; isovaleroyl chloride, 108-12-3; ethyl (*E*)-7-chloro-2,3-dihydro-5-(*o*-fluorobenzoyl)-6-hydroxybenzofuran-2-carboxylate *O*-acetyl oxime, 90246-99-4; 2-(acetoxymethyl)-6,7-dichloro-2,3-dihydrobenzofuran, 90247-20-4; 2-(acetoxymethyl)-6,7-dichloro-2,3-dihydro-5-(*o*-fluorobenzoyl)-benzofuran, 90247-21-5; D-(−)-α-phenylglycinol, 56613-80-0.

Synthesis and Antiviral/Antitumor Activities of Certain Pyrazolo[3,4-*d*]pyrimidine-4(5*H*)-selone Nucleosides and Related Compounds

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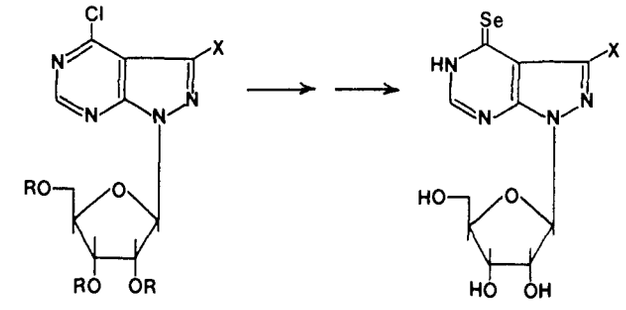
Several pyrazolo[3,4-*d*]pyrimidine-4(5*H*)-selone ribonucleosides were prepared as potential antiparasitic agents. Treatment of 4-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**5a**) with selenourea and subsequent deacetylation gave 1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine-4(5*H*)-selone (**6a**). A similar treatment of 3-bromo-4-chloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**5b**) with selenourea, followed by debenzoylation, gave the 3-bromo derivative of **6a** (**6b**). Glycosylation of persilylated 4-chloro-6-methylpyrazolo[3,4-*d*]pyrimidine (**7**) with tetra-*O*-acetylribofuranose (**8**) provided the key intermediate 4-chloro-6-methyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**9**). Ammonolysis of **9** gave 4-amino-6-methyl-1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine (**10**), whereas treatment with sodium hydroxide gave 6-methylallopurinol ribonucleoside (**11a**). Reaction of **9** with either thiourea or selenourea, followed by deacetylation, provided 6-methylpyrazolo[3,4-*d*]pyrimidine-4(5*H*)-thione ribonucleoside (**11c**) and the corresponding seleno derivative (**11d**), respectively. The structural assignment of these nucleosides was made on the basis of spectral studies. These compounds were tested in vitro against certain viruses and tumor cells. All the compounds except **11c** exhibited significant activity against HSV-2 in vitro, whereas **11c** exhibited the most potent activity against measles and has a very low toxicity. Compounds **6a**, **6b**, and **11d** were found to be potent inhibitors of growth of L1210 and P388 leukemia in vitro.

3-β-D-Ribofuranosylpyrazol[4,3-d]pyrimidine-7-(6*H*)-thione[1] (thioformycin B, **2**) has shown significant activity (ED_{50} = 3.6 μM) against *Leishmania tropica* in human monocyte-derived macrophages in vitro[2] and is less toxic than formycin B (**1**). Recently Santi and co-workers[3] have found that 3-β-D-ribofuranosylpyrazolo[4,3-*d*]pyrimidine-7(6*H*)-selone[4] (selenoformycin B, **3**) is more active than thioformycin B but less active than formycin B against *L. tropica* promastigotes in vitro with an ED_{50} of 0.2 μM. Both allopurinol (pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one) and its ribonucleoside (**4**) exhibited significant activity against several species of *Leishmania*[5,6] and *Trypanosoma*.[7] Allopurinol ribonucleoside (**4**) is a structural analogue of formycin B and, as in the case of formycin B, the glycosidic linkage in **4** appears to be remarkably stable toward enzymatic hydrolysis, especially in various parasitic systems.[8,9] In view of these observations, it was decided to synthesize hitherto unreported sulfur and selenium derivatives of certain pyrazolo[3,4-*d*]pyrimidine nucleosides containing the exocyclic thiono and seleno function at position 4.

Scheme I



5a, X = H; R = Ac

b, X = Br; R = Bz

6a, X = H

b, X = Br

Chemistry. The selenopurine nucleosides are generally synthesized from the corresponding halonucleosides with either sodium hydrogen selenide[10–13] or selenourea.[4] Re-

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