(Acylaryloxy)acetic Acid Diuretics. 3. 2,3-Dihydro-5-acyl-2-benzofurancarboxylic Acids, a New Class of Uricosuric Diuretics

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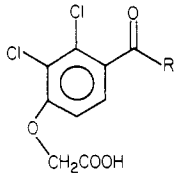
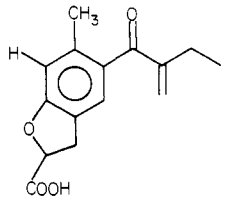
The discovery that dihydroethacrynic acid and other (4-acylphenoxy)acetic acids possessed modest but significant uricosuric and diuretic activity prompted our investigation of the related 2,3-dihydro-5-acyl-2-benzofurancarboxylic acids. Synthetic routes to a number of these compounds are presented along with the structure–activity relationships generated from studies in rats, dogs, and chimpanzee. Examination of the enantiomers of 6,7-dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxylic acid (**10c**) in the chimpanzee revealed that all diuretic and saluretic activity is due to the (+) enantiomer **10d**, while the (−) enantiomer **10e** is responsible for all of the uricosuric activity. X-ray analysis showed that the (−) enantiomer **10e** possesses the 2*R* configuration.

The mercurial phenoxyacetic acid diuretics, such as merbaphen and mersalyl, served as models which led to the discovery of the nonmercurial (4-acryloylphenoxy)-acetic acid diuretics,[2] such as ethacrynic acid (**1a**). Sat-



1a, R = $-C(=CH_2)C_2H_5$
b, R = $-CH(CH_3)C_2H_5$
c, R = 



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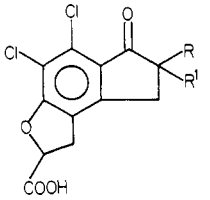

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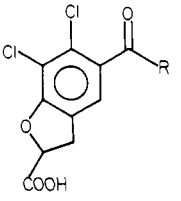

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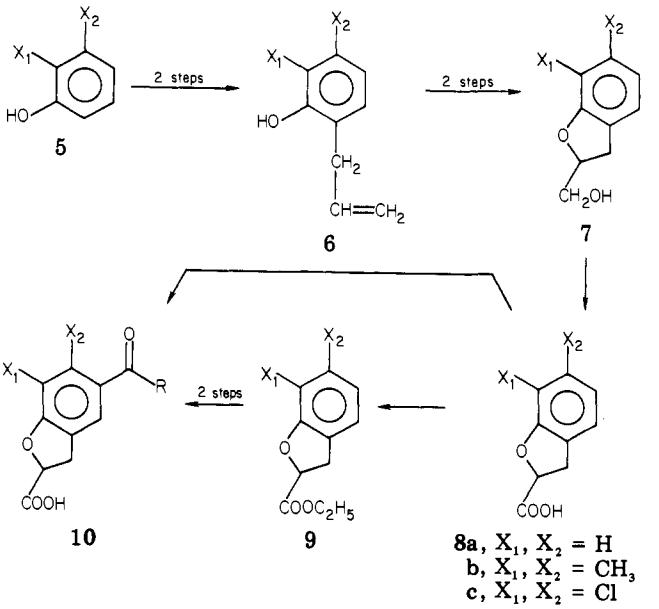
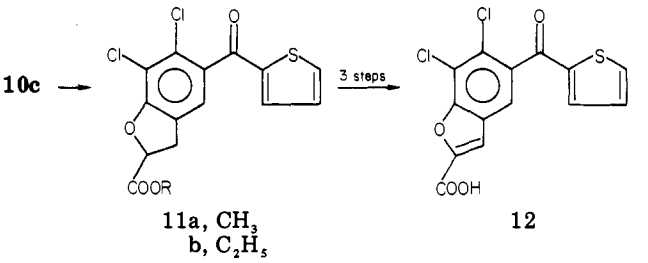
urated analogues of **1a**, such as "dihydroethacrynic acid"[3] (**1b**), were shown to possess both saluretic and uricosuric properties. Later, tienilic acid[4] (Ticrynafen, **1c**) was shown to possess similar renal properties. This discovery, coupled with the observation that annulation of (4-acryloylphenoxy)acetic acids and (indanyloxy)acetic acids to the corresponding dihydrobenzofurancarboxylic acids[5,6] **2** or dihydroindeno[5,4-*b*]furancarboxylic acids[7,8] **3** either maintained or improved diuretic activity, prompted us to annulate several (4-acylphenoxy)acetic acids to the corresponding acyldihydrobenzofurancarboxylic acids **4**. A preliminary disclosure of some of the medicinal chemistry[9] and pharmacology[10] of this series has been published. Herein we report a complete account of our research on this unique class of uricosuric diuretics.

Scheme I



Scheme II



11a, CH_3
b, C_2H_5

12

(1) Deceased May 31, 1977.
(2) Schultz, E. M.; Cragoe, E. J., Jr.; Bicking, J. B.; Bolhofer, W. A.; Sprague, J. M. *J. Med. Pharm. Chem.* **1962**, *5*, 660.
(3) Cragoe, E. J., Jr.; Schultz, E. M.; Schneeberg, J. D.; Stokker, G. E.; Woltersdorf, O. W., Jr.; Fanelli, G. M., Jr.; Watson, L. S. *J. Med. Chem.* **1975**, *18*, 225.
(4) Thuillier, G.; LaForest, J.; Cariou, B; Bessin, P.; Bonnet, J.; Thuillier, J. Eur. *J. Med. Chim. Ther.* **1974**, *9*, 625.
(5) Zergenyi, J.; Habicht, E. U.S. Patent 3676560 1972.
(6) Habicht, E.; Livis, B. U.S. Patent 3761494 1973.
(7) Cragoe, E. J., Jr.; Woltersdorf, O. W., Jr. U.S. Patent 3931239, 1976.
(8) Cragoe, E. J., Jr.; Woltersdorf, O. W., Jr. U.S. Patent 3984552, 1976.
(9) Cragoe, E. J., Jr.; Woltersdorf, O. W., Jr.; deSolms, S. J.; Hoffman, W. F.; Novello, F. C.; Watson, L. S.; Fanelli, G. M., Jr. "Abstracts of Papers"; ACS/CSJ Congress, Honolulu, HI, April 1979; American Chemical Society: Washington, DC, MEDI 66.
(10) Fanelli, G. M., Jr. *Pharmacology* **1979**, *21*, 275.

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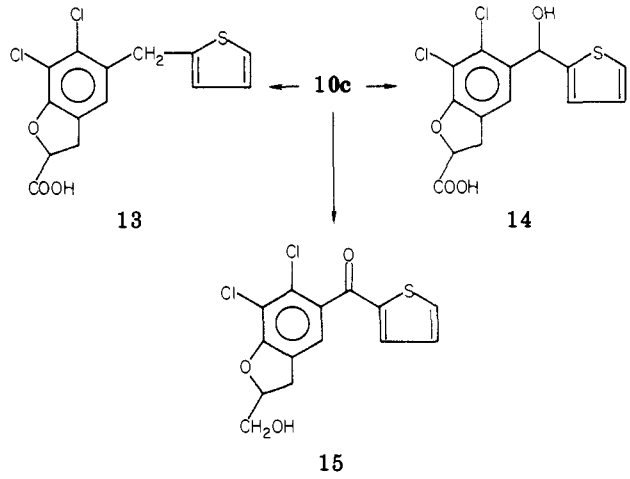
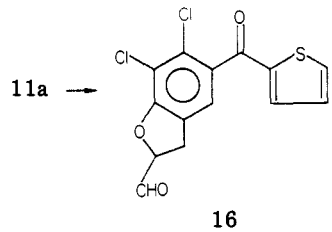
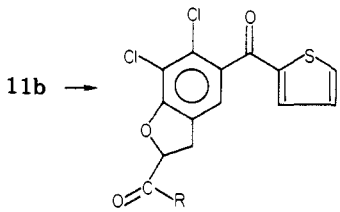
Scheme III



Scheme IV



Scheme V



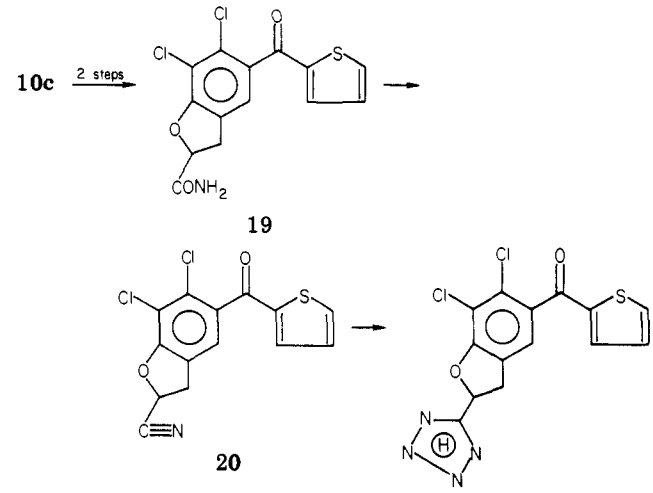
17, R = $NHNH_2$
18, R = $N{=}C(NH_2)_2$

Chemistry. The synthetic route used to prepare acyldihydrobenzofurancarboxylic acids **10** is illustrated in Scheme I. The disubstituted phenol **5** was alkylated with allyl bromide to give the intermediate allyl ether, which underwent Claisen rearrangement at 250 °C to afford **6**. Oxidation of **6** with peracetic acid gave the intermediate epoxide which, upon cyclization, afforded the benzofuran **7**. Jones oxidation of **7** yielded the carboxylic acid **8**. At the beginning of this study, **8** was acylated directly with the appropriate acyl chloride under Friedel–Crafts conditions to give **10** in low yield. Subsequently, the yield of **10** was doubled when ester **9**, readily prepared by esterification with EtOH–concentrated H_2SO_4, was acylated under Friedel–Crafts conditions and then saponified.

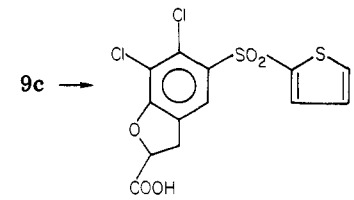
Scheme II shows the synthesis of the acylbenzofurancarboxylic acid **12**. Compound **10c** was esterified, and the resultant ester was brominated with NBS, dehydrobrominated with DBN in Me_2SO, and then hydrolyzed to give **12**.

Schemes III and IV show the chemical modification of the carbonyl and carboxy groups. In Scheme III the carbonyl bridge of **10c** was reduced to methylene **13** by zinc amalgam and HCl. The carbonyl group was reduced with KBH_4 in H_2O to give carbinol **14**. The carboxy group of **10c** was reduced to give the corresponding carbinol **15** using borane in THF. The carboxy group was further modified by reduction of its methyl ester **11a** with "Red-Al" at −78 °C to yield the carboxaldehyde **16** (Scheme IV).

Scheme VI



Scheme VII



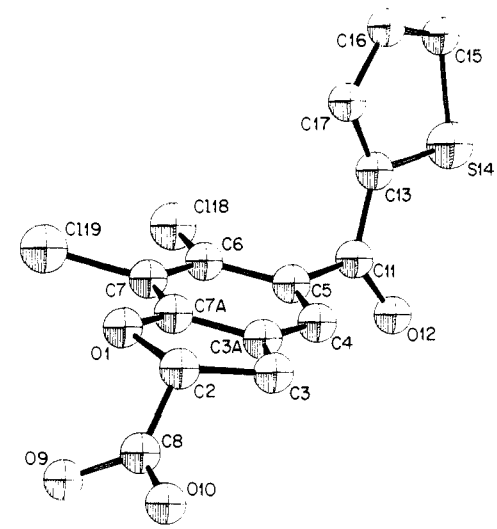


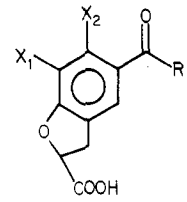
Figure 1. A computer-generated perspective drawing of **10e** showing the correct absolute configuration.

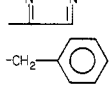
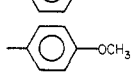
Other carboxyl derivatives include the hydrazide **17** and guanidide **18**, which were prepared by the reaction of the ester **11b** with hydrazine and guanidine, respectively (Scheme V). To study the effect of carboxy surrogates, the tetrazole **21** was prepared by the reaction sequence shown in Scheme VI. The carbonyl moiety was replaced with a sulfonyl group by treating **9** with 2-thiophenesulfonyl chloride under Friedel–Crafts conditions to give **22** as shown in Scheme VII.

Resolution of **10c** was accomplished by recrystallization of the (−)-cinchonidine salt to give the (+) enantiomer **10d** and the (+)-α-methylbenzylamine salt to give the (−) enantiomer **10e**.

X-ray Analysis of 10e. The absolute configuration of **10e** from the X-ray experiments is 2*R* (see Figure 1). The two independent molecules of **10e** in the crystals show different conformations for the dihydrofuran rings. In one

Table I. Title Compounds



no.[a]	X_1	X_2	R	% yield[b]	recrystn solvent	mp, °C	emp formula	anal.
10a	H	H		12	CH_3CN	195-197	$C_{14}H_{10}O_4S$	C, H
10b	CH_3	CH_3		67	EtOAc-cyclohexane	126-128	$C_{16}H_{14}O_4S$	C, H
10c	Cl	Cl		81	CH_3CN-BuCl	194-196	$C_{14}H_8Cl_2O_4S$	C, H, Cl
10d (*S*)	Cl	Cl		c	toluene	126-128	$C_{14}H_8Cl_2O_4S$	C, H
10e (*R*)	Cl	Cl		c	toluene	126-128	$C_{14}H_8Cl_2O_4S$	C, H
10f	Cl	Cl		22	CH_3CN-BuCl	164-166	$C_{14}H_8Cl_2O_5S$	C, H
10g	Cl	Cl		6	CH_3CN	186-188	$C_{12}H_6Cl_2N_2O_4S$	C, H, N
10h	Cl	Cl		28	CH_3CN-BuCl	140-145	$C_{17}H_{12}Cl_2O_4$	C, H
10i	Cl	Cl		21	ether-petr ether	168-171	$C_{16}H_{10}Cl_2O_4$	C, H
10j	Cl	Cl		8	*d*	180-187	$C_{17}H_{12}Cl_2O_5$	C, H, Cl
10k	Cl	Cl	$-CH_3$	29	$CHCl_3$	148-150	$C_{11}H_8Cl_2O_4$	C, H

[a] All compounds are racemic except **10d** and **10e** whose absolute stereochemistry is as indicated in parentheses. [b] Calculated yield is based on the last synthetic step. [c] See Experimental Section. [d] Purified by dissolution in 1% *N*-methylpiperazine and precipation with 6 N HCl.

molecule the ring is virtually planar with a largest deviation of 0.02 Å from the least-squares plane through the five-membered ring. However, the ring in the second molecule has a flattened envelope conformation with C2′ 0.30 Å from the best plane formed by the other four atoms. One significant intermolecular contact of 2.80 Å, which presumably is a hydrogen bond, is formed between O10 and O9′.

Structure–Activity Relationships

(A) Saluresis–Diuresis. General Discussion. The excretion of urine, Na^+, K^+, and Cl^- were measured in experiments conducted in rats, dogs, and chimpanzees. For brevity, only the Na^+ excretion is reported here. The excretion of Cl^- and urine generally paralleled that of Na^+; thus, any of these parameters could be used for relative potency comparisons. A detailed pharmacological study of **10c–e** by Fanelli et al has been published.[11]

Rat Data. The oral natriuretic activity of our 2,3-dihydro-5-acyl-2-benzofurancarboxylic acids and their derivatives at four dose levels is provided in Table II. Variants of the R group attached to the carbonyl include the 2-thienyl (**10c**), 2-furyl (**10f**), 3-thiadiazolyl (**10g**), benzyl (**10h**), phenyl (**10i**), 4-methoxyphenyl (**10j**), and methyl (**10k**). The heterocyclic analogues **10f,g** are slightly more active than their aromatic counterparts **10h–j**; maximal activity was observed with the 2-thienyl compound **10c**. When the substituent R was methyl, as in **10k**, the activity was very weak. The conversion of **10c** to the corresponding benzofuran **12** resulted in a marked decrease in activity. The nuclear substituents also greatly influence

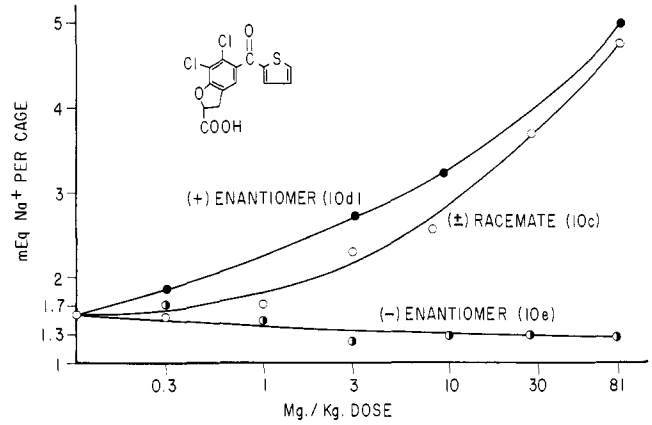


Figure 2. Oral 24-h rat Na^+ assay. (The assay is identical with that in Table II, footnote *a*, except that 0- to 24-h collections are taken and more doses are used.)

activity; as noted above, maximal activity is seen with the 6,7-dichloro compound **10c**. The 6,7-dimethyl analogue **10b** is much weaker than **10c**, and the dechloro compound **10a** has only marginal activity.

Reduction of the carbonyl function of **10c** to afford the carbinol **14** and then the methylene compound **13** greatly reduces natriuretic activity. The replacement of the carbonyl group with a sulfonyl group as in **22** also markedly reduces the activity in this species.

The conversion of carboxylic acid **10c** to the corresponding ethyl ester **11b**, carboxaldehyde **16**, hydrazide **17**, and acylguanidine **18** results in retention of considerable activity. However, the conversion to the carbinol **15**, nitrile **20**, or tetrazole **21** greatly reduces the natriuretic

(11) Fanelli, G. M., Jr.; Watson, L. S.; Bohn, D. L.; Russo, H. F. *J. Pharmacol. Exp. Ther.* **1980**, *212*, 190–197.

Table II. Oral Activity

compd	rat,[a-c] mequiv of $Na^+ \times 100$/cage				chimpanzee,[d] 5 mg/kg	
	3 mg/kg	9 mg/kg	27 mg/kg	81 mg/kg	Δ μequiv of Na^+/min	Δ C_{urate}/Δ C_{inulin}
10a	6	4	7	22		
10b	29	68	61	71		
10c	175	191	257	310	1360	0.340
10d	177	251	283	339	1451	0.132
10e	48	38	41	29	95	0.454
10f	69	150	218	322		
10g	38	82	230	284	88	0.096
10h	25	80	126	173	513	0.315
10i	59	85	117	119		
10j	40	96	129	194		
10k	13	26	76	161		
11b	76	87	128	167		
12	32	62	88	131	396	0.061
13	7	19	19	21	206	0.185
14	25	40	80	180	550[e]	0.150[e]
15	16	45	68	72		
16	74	84	107	144		
17	34	81	89	140		
18	72	98	143	159		
19	7	9	11	25		
20	6	9	10	8		
21	13	16	16	29		
22	10	19	44	65		
furosemide	6	7	125	234	1035	-0.02
hydrochlorothiazide	123	112	131	128	144	-0.02
thienilic acid	7	15	43	56	318	0.437

[a] Female rats (Charles River, 150-170 g) were maintained overnight on a sugar diet with water ad libitum. The test substance was dissolved in pure DMF and subsequently diluted with water (which contained 3 drops of ethanolamine per 100 mL) such that the final vehicle was 4% DMF. At the time of the test, animals were given the vehicle (as placebo) or test substance suspended in a final volume of 5.0 mL po. Rats were housed in groups of three in metabolism cages. Urine was collected for the 0- to 5-h interval in graduated cylinders and was analyzed for sodium, potassium, and chloride content. Animals that received placebo were run concurrently. Results are reported as milliequivalents per cage and are the geometric means of three cages per dose level. Standard methodology was used for determination of electrolyte levels. [b] Identical with the above rat test except Tween-80 was substituted for ethanolamine. This assay was used for 10c-f, furosemide, hydrochlorothiazide, tienilic acid and the placebo. [c] Milliequivalents of $Na^+ \times 100$ per cage for control rats (placebo) was 6. [d] Fasted, male chimpanzees weighing 21-77 kg were immobilized with phencyclidine (which was shown not to affect the results) (1.0-1.5 mg/kg im plus 0.25 mg/kg iv as needed) and were prepared by catheterization for standard renal clearance studies using routing clinical aseptic procedure. Pyrogen-free inulin (iv) was used to measure glomerular filtration rate (GFR). Clearance of inulin, urate, and the excretion rates of Na^+, K^+, and Cl^- were determined by standard Auto Analyzer techniques. (Inulin and urate in chimpanzee plasma are freely filterable.) Average control clearances were calculated from three 20-min consecutive periods. Drug-response values were derived as the average of eight 15-20 min clearance periods after oral administration of an aqueous solution of the compound through an indwelling nasal catheter. All data are reported as the difference between (average) treatment and control values obtained from single experiments. [e] 1 mg/kg iv.

activity. The enantiomers of **10c** exhibited a marked difference in activity; the (+) enantiomer **10d** possesses about twice the saluretic activity of the racemate. This is illustrated clearly by the data shown in Figure 2.

It can be seen from Table II that many of the subject compounds appear to have a higher natriuretic ceiling than tienilic acid and hydrochlorothiazide. A few of the compounds have a natriuretic ceiling as high or higher than that of furosemide. Figure 3 graphically illustrates that **10c**, in the oral rat assay (Table II), has a higher ceiling than hydrochlorothiazide, tienilic acid, and furosemide and possesses a smoother dose–response relationship than the latter two drugs.

Chimpanzee Data (Table II). Since these data are generally derived from single experiments, one cannot assign relative potency values from this information. However, it can be seen that the structure–activity relationships correlate well with those observed in the rats, except for **10g** which is relatively much less natriuretic in the chimpanzees than in the rats. Of special interest is the observation that the (+) enantiomer **10d** of the racemate **10c** possesses all of the natriuretic activity exhibited by the racemate, whereas the (-) enantiomer **10e** is devoid of natriuretic activity. Because of the efficacy exhibited by **10c** and **10d**, the presumed site of action of these agents

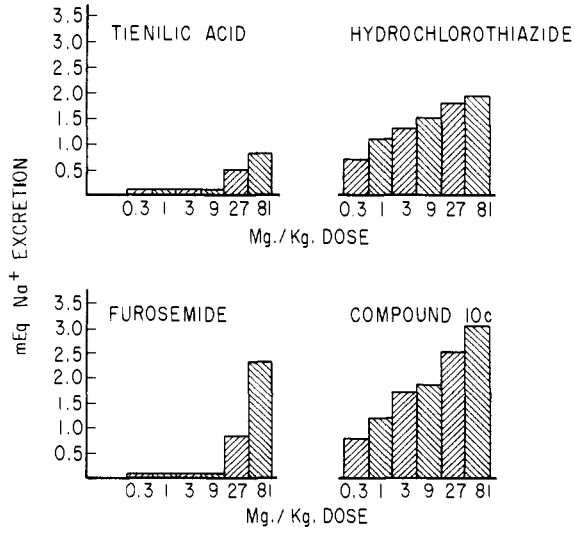


Figure 3. Oral 5-h rat assay. (The criteria are the same as for Table II, footnote *a*.)

is the thick ascending limb of the loop of Henle. This is further substantiated by the fact that **10c** inhibits short-circuit current, a measure of active Cl^- transport, across

Table III. Intravenous Dog Diuretic Assay (5 mg/kg Stat)[a]

compd	no. of expt (av)	control/drug treatment results: mequiv/min Na+	mequiv/min K+	mequiv/min Cl-	urine vol, mL/min
10a	1	4/193	4/55	7/198	1/6
10b	2	5/95	6/37	4/72	1/2
10c[b]	3	23/107	8/10	12/82	0.6/1.3
10d	3	29/1210	7/87	7/1385	0.8/10
10e	3	11/118	6/35	43/54	0.5/3
10f	2	30/671	6/28	10/722	1.3/6
10g	2	46/767	6/64	14/878	0.8/6
10h	2	20/108	6/36	5/102	0.8/2
10i	2	28/180	4/19	22/194	0.8/2
10j	2	33/124	10/18	6/70	0.7/2
10k	2	3/84	3/18	15/66	0.4/2
12	1	32/452	5/19	9/510	0.7/4
13	2	13/565	9/46	2/612	0.6/6
14	2	66/566	4/54	12/586	1/6
22	2	52/264	6/18	16/271	0.8/2
hydrochlorothiazide	3	12/166	15/33	5/156	1/3
furosemide[b]	2	29/960	18/141	1/1081	1/3
tienilic acid	2	22/144	3/8	9/132	0.6/2

[a] Conditioned female mongrel dogs, weighing approximately 20 kg in the postabsorptive state, were starved overnight and given 500 mL of water orally 1 h prior to induction of anesthesia with sodium pentobarbital (30 mg/kg, iv). After inducing anesthesia, each dog was catheterized and primed with creatinine (4 g as a 10% aqueous solution) injected sc in multiple sites. Prior to initiating clearance studies, 1.5 mL/kg of isoosmotic pH 7.4 phosphate buffer solution (20 mg of PO_4/kg) was given iv as a priming injection; 3 mL/min of isoosmotic pH 7.4 buffer containing 4% mannitol (6.9 mg of PO_4/min) was infused during the experiment. At the onset of timed clearances, the urinary bladder was emptied and replicate 15-min urine collections were made; venous blood samples were drawn at the midpoint of each period. Following this control phase, the test compound was given iv at 5 mg/kg over a 5-min period, and 15-min collections of urine were taken over a period of 2 h. Urinary electrolytes were assayed by standard methods. The data recorded were the average of the two highest consecutive 15-min collections. [b] 1 mg/kg.

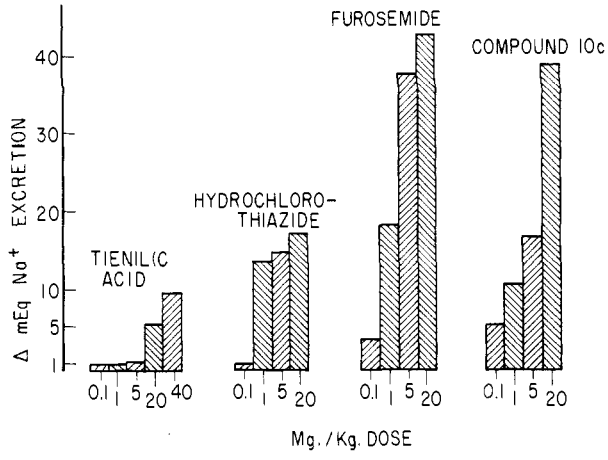


Figure 4. Oral 5-h dog assay. (The criteria are the same as for Table IV, footnote *a*.)

the isolated bullfrog cornea.[12]

Dog Data (Tables III and IV). In general, the compounds that exhibit good saluresis and diuresis in rats and chimpanzees give a comparable response when administered either intravenously or orally to dogs. The iv dog experiments were only designed to show that this species responds to these agents in a manner comparable to other loop diuretics. Time–action curves for selected members of this series will be published elsewhere. Of special interest are compounds **13** and **14**, which show a relatively improved saluretic effect in the dog vis-a-vis that shown in the rat. The high ceiling and smooth dose–response of **10c** is illustrated in Figure 4, where it is compared with tienilic acid, hydrochlorothiazide, and furosemide. That the diuretic activity resides in the (+) enantiomer **10d** is shown in Figure 5, where **10d** is shown to be about twice as natriuretic as the racemate **10c** and the (−) enantiomer **10e** has little or no activity. In this assay, tienilic acid has about one-fortieth the potency of **10c** and one-eightieth that of **10d**.

Table IV. Oral Dog[a] Diuretic Assay (5 mg/kg)

compd	no. of expt (av)	mequiv/min Na+	mequiv/min K+	mequiv/min Cl-	urine vol, mL
10c	6	18.7	4.2	24.6	432
10c[b]	3	37.7	5.2	48.5	541
10d[b]	5	46.0	8.3	53.7	501
10e[b]	6	4.8	2.5	4.3	233
10j	4	14.4	2.9	17.8	307
11b	4	7.7	1.6	8.7	166
12	4	6.9	1.6	9.8	270
13	3	30.1	7.4	40.6	433
16	4	16.3	3.1	21.6	337
18	4	4.9	1.2	4.8	212
19	4	2.1	1.7	3.0	229
20	2	1.0	1.1	2.2	190
22	8	7.6	1.4	9.1	246
tienilic acid	6	3.3	1.8	5.4	395
furosemide	23	30.7	7.6	35.6	700

[a] Oral tests were carried out on a colony of trained female mongrel dogs weighing 8–10 kg. All dogs received 100 mL of water the previous day and were fasted overnight. On the day of the test, 250 mL of water was administered orally, followed by 500 mL of water (orally) 1 h later. One hour after the last oral priming dose of water, bladders were emptied by catheterization and the study was commenced by administration of compound or placebo. Compounds were given in gelatin capsules and the animals were maintained in metabolism cages for collection of spontaneously voided urine. Spontaneously voided uring was combined with bladder uring collected by catheterization at the end of 5 h. Urine volumes were measured, and aliquots were analyzed for sodium, potassium, and chloride content by standard methodology. Values are reported as geometric means. [b] 20 mg/kg.

(12) Fanelli, G. M., Jr., personal communication.

Table V. Oral Chimpanzee Data for Mixtures of 10d and 10e[a]

% enantiomer		dose, mg/kg			no. of	Δ Na^+,	Δ C_{urate}/
10d	10e	total	10d	10e	expt (av)	mequiv	Δ C_{inulin}[c]
100	0	0.0312	0.0312	0	3	256	0.010
100	0	0.0625	0.0625	0	3	325	-0.003
50	50	0.0625	0.0312	0.0312	3	227	0.028
0	100	0.0625	0	0.0625	2	11	0.029
100	0	0.25	0.25	0	3	485	-0.006
50	50	0.25	0.125	0.125	3	340	0.037
5	95	0.25	0.0125	0.2375	3	89	0.061
0	100	0.25	0	0.25	3	20	0.087
100	0	1	1	0	2	540	-0.019
95	5	1	0.95	0.05	1	711	0.012
75	25	1	0.75	0.25	1	637	0.007
50	50	1	0.50	0.50	3	608	0.046
25	75	1	0.25	0.75	4	492	0.157
5	95	1	0.05	0.95	3	268	0.224
0	100	1	0	1	3	3	0.242
100	0	5	5	0	3	1451	0.029
75	25	5	3.75	1.25	1	844	0.045
50	50	5	2.5	2.5	2	1302	0.226
25	75	5	1.25	3.75	1	1333	0.327
12.5	87.5	5	0.625	4.375	2	425	0.323
5	95	5	0.25	4.75	2	474	0.290
0	100	5	0	5	3	67	0.344
12.5	87.5	10	1.25	8.75	2	622	0.376
5	95	10	0.5	9.5	2	482	0.358
0	0	0	0	0	4	26	0.013

[a] The criteria are the same as for Table II, footnote c.

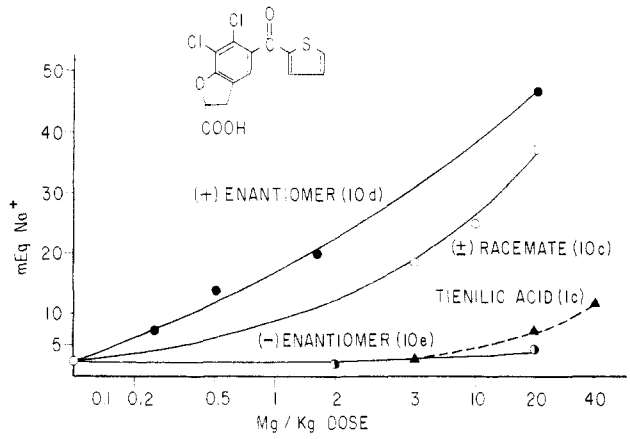


Figure 5. Oral 5-h dog assay. (The criteria are the same as for Table IV, footnote a.)

Uricosuria (Table II). Like the (4-acylaryloxy)acetic acid and indanylacetic acid diuretics, the acylbenzofuran-2-carboxylic acid diuretics are uricosuric in the chimpanzee. Although one cannot make quantitative structure–activity relationships from single oral experiments, some general trends can be noted. The ratio of saluretic to uricosuric activity is lower in **10h** than in **10c**. Compounds **10g** and **12**, which were saluretic in the rat and dog, are not uricosuric in the chimpanzee. The (-) enantiomer **10e** is unique in that it possesses all of the uricosuric activity and very little of the saluretic activity of the racemate **10c**.

Since (+) enantiomer **10d** contributes the diuretic activity while (-) enantiomer **10e** provides the uricosuric activity, various ratios of diuretic to uricosuric activity can be obtained by using the appropriate ratios of the two enantiomers. Table V provides the results of studying various *enantiomeric ratios* at various *total doses* in chimpanzees. In general, as the dose of **10d** is increased, either alone or in combination with **10e**, there is a corresponding increase in the saluretic response. Likewise, the greater the dose of **10e**, either alone or in combination with **10d**, the greater the uricosuric response.

This is the first time, to the best of our knowledge, in which a virtually complete separation of saluretic and uricosuric activities in the enantiomers of a saluretic–uricosuric compound has been achieved. This is especially interesting since one enantiomer, **10e**, presumably acts in the proximal tubule, the site of uricosuric action, whereas the other one, **10d**, appears to exert its saluretic effects in the loop of Henle.

Thus, it has been possible to design and synthesize a class of potent saluretic–uricosuric agents in which any desired ratio of the two pharmacodynamic activities can be obtained by adjusting the enantiomeric ratio of the agent.

Experimental Section

^1H NMR spectra were recorded on either a Varian T-60 or T-60-A spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported as δ values with respect to Me_4Si used as the internal standard. Specific rotations were determined with a Perkin-Elmer Model 141 polarimeter. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses are within ±0.4% of theoretical values when indicated by the symbols of the elements. Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. Organic extracts were dried over $MgSO_4$ and concentrated using a Buchi rotary evaporator under reduced pressure (ca. 20 mm).

2,3-Dichloro-6-propenylphenol (6c). A mixture of **5c** (163 g, 1.0 mol), K_2CO_3 (152 g, 1.1 mol), and DMF (500 mL) was heated at 60 °C with stirring for 30 min. The allyl bromide (127 g, 1.05 mol) was added dropwise over 20 min, and the reaction mixture was stirred for an additional hour at 60 °C and then poured into ice–H_2O (2 L). The aqueous mixture was extracted with Et_2O (4 × 200 mL). The organic extracts were combined, washed with brine (2 × 200 mL), dried, filtered, and evaporated to give the intermediate 2,3-dichloro-1-(propenyloxy)benzene as a red oil. This oily product was subjected to Clasien rearrangement by heating at 250 °C for 20 min. The resultant oil was distilled to yield 186.9 g (92%) of **6c**: bp 132–134 °C (13 mm); NMR δ 3.40 (d, 2, J = 5 Hz, $ArCH_2$), 4.87–5.30 (m, 2, CH_2=CH), 5.67–6.53 (m, 1, CH_2=C*H*), 7.0 (s, 2, ArH). Anal. ($C_9H_8Cl_2O$) H; C: calcd, 53.23; found, 52.37.

6,7-Dichloro-2,3-dihydro-2-(hydroxymethyl)furan (7c). A solution of **6c** (186.9 g, 0.92 mol) in AcOH (100 mL) was added dropwise over 30 min to a cooled (15 °C) solution of 40% peracetic

acid (171 g, 0.92 mol) and NaOAc (2.9 g, 0.035 mol). The resultant solution was stirred for 2 h at 15 °C and for 70 h at 25 °C and then poured slowly into 1.75 L of H_2O containing Na_2CO_3 (500 g). The resultant mixture was extracted with Et_2O. The organic extracts were combined, washed with saturated Na_2CO_3 solution (2 × 100 mL), H_2O (100 mL), aqueous $FeSO_4$ solution (2 × 100 mL), and brine (2 × 100 mL), dried, and evaporated to give the intermediate 2,3-dichloro-6-(2,3-epoxypropyl)phenol as a brown viscous oil. This oil was heated at 110 °C for 10 min and then distilled to give 142.5 g (71%) of **7c**: bp 168–170 °C (0.2 mm); NMR δ 3.18 (dd, 2, J = 8 and 2 Hz, C_3 H), 3.67–3.90 (m, 2, CH_2OH), 4.73–5.20 (m, 1, C_2H), 6.87 (s, 2, Ar H). Anal. ($C_9H_8Cl_2O$) C, H.

6,7-Dichloro-2,3-dihydro-2-benzofurancarboxylic Acid (8c). Jones reagent[13] (300 mL) was added dropwise to a stirred, cooled solution of **7c** (98.4 g, 0.449 mol) in acetone (1.8 L) at such a rate that the internal temperature did not exceed 20 ± 5 °C. The resultant mixture was stirred for 18 h at 25 °C. Then the insoluble chromium salts were collected by filtration and washed with acetone (2 × 200 mL). The washings were combined with the filtrate, and the resultant solution was concentrated to 500 mL and poured into H_2O (2 L). This mixture was extracted with Et_2O (4 × 300 mL). The organic extracts were combined, washed with brine (2 × 200 mL), and then extracted with 2 N NaOH (3 × 100 mL). The NaOH extracts were combined and acidified with 12 N HCl to give a solid, which was recrystallized from $CHCl_3$ (1 L) to provide 52.3 g (50%) of **8c**: mp 175–178 °C; NMR (Me_2SO-d_6) δ 3.03–3.97 (m, 2, C_3 H), 5.17–5.53 (m, 1, C_2 H), 7.07 (s, 2, Ar H). Anal. ($C_9H_6Cl_2O_3$) C, H.

Ethyl 6,7-Dichloro-2,3-dihydro-2-benzofurancarboxylate (9c). A solution of **8c** (70 g, 0.3 mol) and 96.6% H_2SO_4 (2 mL) in EtOH (250 mL) was refluxed for 2 h and then evaporated. The resulting residue was suspended in aqueous $NaHCO_3$ (300 mL) and extracted with Et_2O (4 × 250 mL). The ethereal extracts were combined, washed with brine 2 × 100 mL), dried, and evaporated. The deposited solid recrystallized from hexane to give 72 g (92%) of **9c**: mp 73–75 °C; NMR δ 1.3 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 3.47 (dd, 2, J = 8 and 2 Hz, C_3 H), 4.26 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.26 (dd, 1, J = 9 and 8 Hz, C_2 H), 6.93 (s, 2, Ar H). Anal. ($C_{11}H_{10}Cl_2O_3$) C, H.

(±)-6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxylic Acid (10c). Anhydrous $AlCl_3$ (121 g, 0.9 mol) was added over 30 min to a well-stirred solution of **9c** (72 g, 0.275 mol) and 2-thiophenecarbonyl chloride (80.8 g, 0.55 mol) in CH_2Cl_2 (150 mL) which was protected from the atmosphere with a $CaCl_2$ tube. The resultant reaction mixture was warmed to 95 °C to remove the CH_2Cl_2 and then maintained at 95 °C for an additional 2.5 h. The resulting residue was cooled and partially dissolved in CH_2Cl_2. This mixture was added to ice (2 kg) and 12 N HCl (125 mL). The resulting mixture was extracted with Et_2O (4 × 300 mL). The ethereal extracts were combined, washed with brine (3 × 100 mL), dried, and evaporated to give the ethyl ester of **10c** as a brown oil. The crude ethyl ester was added to cold 40% NaOH solution (500 mL). The resulting mixture was stirred for 30 min and filtered to collect the sodium salt of **10c**. The wet sodium salt was suspended with stirring in 6 N HCl (200 mL) to afford a heterogeneous mixture, which was extracted with Et_2O (3 × 200 mL). The ethereal extracts were combined, washed with brine (3 × 100 mL), dried, and evaporated to give a yellow solid, which was recrystallized from CH_3CN–BuCl to afford 76.2 g (81%) of **10c**: mp 194–196 °C; NMR (Me_2SO-d_6) δ 3.3–4.03 (m, 2, C_3 H), 5.57 (dd, 1, J = 10 and 8 Hz, C_2 H), 7.27 (dd, 1, J = 4 and 4 Hz thiophene C_4 H), 7.43–7.67 (m, 3, Ar H and thiophene C_5 H), 8.16 (d, 1, J = 5 Hz, thiophene C_3 H). Anal. ($C_{14}H_8Cl_2O_4S$) C, H, Cl.

Compounds **10f–k** were prepared in an analogous manner to **10c** by substituting the appropriate acid chloride for 2-thiophenecarbonyl chloride.

10a was prepared by reacting **9a** (prepared by dechlorination of **9c** by catalytic hydrogenation with 5% Pd/C as the catalyst) with 2-thiophenecarbonyl chloride under the reaction conditions reported for the synthesis of **10c**. **10b** was prepared by reacting **9b** (prepared by esterification of **8b**)[14] with 2-thiophenecarbonyl chloride according to the conditions reported for the synthesis of **10c**.

(+)-6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxylic Acid (10d). A solution of **10c** (73.7 g, 0.214 mol) in CH_3CN (1000 mL) was mixed with a solution of (–)-cinchonidine (63.2 g, 0.214 mol) in 600 mL of boiling EtOH. The resultant solution was concentrated to 1600 mL, diluted with H_2O (200 mL), and stored at 25 °C for 18 h. The insoluble salt (69.4 g) was collected by filtration and recrystallized (4 times) by dissolving the salt in EtOH (1000 mL) and then adding H_2O (50 mL) to yield 51.7 g of the salt of the pure (+) enantiomer. The salt was converted to carboxylic acid **10d** by treatment with a mixture of ether (1 L) and 6 N HCl (500 mL). The ether layer was separated, washed with brine (3 × 100 mL), dried, and evaporated to give a tan semisolid. This material was stirred with cold 6 N HCl to give a solid, which was collected by filtration and washed with H_2O to yield 26.7 g (36%) of **10d**: $[\alpha]^{25}_{436}$ +11.5° (c 1, acetone).

(–)-6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxylic Acid (10e). *d*-(+)-α-Methylbenzylamine (13.6 g, 0.112 mol) was added to partially resolved 6,7-dichloro-2,3-dihydro-5-(2-thienylcarbonyl)benzofuran-2-carboxylic acid (38.7 g, 0.112 mol) [obtained from the mother liquor of the resolution of the (+) enantiomer described above], dissolved in CH_3CN (2 L). The resulting salt (46.2 g) was recrystallized (2 times) from EtOH–CH_3CN (1:2; v/v;) (1 L) to provide the salt (21.2 g) of the pure (–) enantiomer. The salt was converted to the carboxylic acid in the same manner as described above to give 15.1 g (41%) of **10e**: $[\alpha]^{25}_{436}$ –11.5° (c 1, acetone).

Methyl 6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxylate (11a). **10c** (3.4 g, 0.01 mol) was dissolved in MeOH (50 mL) containing concentrated H_2SO_4 (0.5 mL). The resulting solution was heated at reflux for 1 h. The CH_3OH was evaporated to leave a residue, which was suspended in aqueous $NaHCO_3$ (50 mL) and extracted into Et_2O (3 × 100 mL). The ethereal extracts were combined, washed with brine (2 × 50 mL), dried, and evaporated to yield a yellow oil which solidified upon trituration with ether to give 3.0 g (84%) of **11a**: mp 110–112 °C; NMR (Me_2SO-d_6) δ 3.3–3.67 (m, 2, C_3 H), 3.75 (s, 3, CO_2CH_3), 5.7 (dd, 1, J = 10 and 7 Hz, C_2 H), 7.27 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.43 (m, 2, Ar H and thiophene C_5 H), 8.17 (dd, 1, J = 5 and 1 Hz, thiophene C_3 H). Anal. ($C_{15}H_{10}Cl_2O_4S$) C, H.

6,7-Dichloro-5-(2-thienylcarbonyl)-2-benzofurancarboxylic Acid (12). NBS (1.8 g, 0.01 mol) was added to a solution of **11a** (3.6 g, 0.01 mol) and benzoyl peroxide (50 mg) in CCl_4 (100 mL). The mixture was refluxed for 1 h and then cooled to 25 °C. The deposited succinimide was removed by filtration and the filtrate was evaporated to give the intermediate brominated compound as a yellow oil (3.8 g). This oil was dissolved in Me_2SO (25 mL) containing DBN (1.3 g, 0.01 mol). The resulting solution was stirred under an N_2 atmosphere for 2 h and then diluted with H_2O (100 mL) and acidified with 6 N HCl to give 2.7 g (77%) of the methyl ester of **12**, which was recrystallized from CH_3CN: mp 184–187 °C. Anal. ($C_{15}H_8Cl_2O_4S$) C, H.

The methyl ester of **12** (2.7 g, 0.0076 mol) was dissolved in dioxane (50 mL) containing 1 N NaOH (10 mL). The resulting solution was refluxed for 2 h and evaporated to afford a residue, which was suspended in 6 N HCl (50 mL). This mixture was extracted with Et_2O (3 × 100 mL). The ethereal extracts were combined, washed with brine (3 × 50 mL), dried, and evaporated to give a solid, which was recrystallized from CH_3CN. Thereby was obtained 2.2 g (85%) of **12**: mp 244–245 °C; NMR (Me_2SO-d_6) δ 7.23 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.53 (dd, 1, J = 4 and 1 Hz thiophene C_5 H), 7.77 (s, 1, Ar H), 8.0 (s, 1 C_2 H), 8.17 (dd, 1, J = 4 and 1 Hz, thiophene C_3 H). Anal. ($C_{14}H_6Cl_2O_4S$) C, H.

6,7-Dichloro-2,3-dihydro-5-(2-thienylmethyl)-2-benzofurancarboxylic Acid (13). Zinc amalgam (60 g) was added to a well-stirred mixture of **10c** (9.2 g, 0.027 mol), toluene (50 mL), and 12 N HCl (35 mL). After 6 h at reflux, additional 12 N HCl (10 mL) was added and refluxing was continued for 24 h. The

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(14) Livis, B.; Habicht, E. German Offen. 1 927 393 1969.

organic layer was separated, diluted with Et_2O (100 mL), washed with brine (3 × 50 mL), dried, and evaporated to give 5.3 g of a yellow solid. The solid was chromatographed on silica gel (250 g). Elution with benzene–dioxane–acetic acid (25:5:1, v/v) gave 1.8 g (20%) of **13**: mp 170–171 °C; NMR (Me_2SO-d_6) δ 3.07–4.00 (m, 2, C_3 H), 4.23 (s, 2, Ar CH_2), 5.43 (dd, 1, J = 10 and 7 Hz, C_2 H), 6.87–7.10 (m, 2, Ar H and thiophene C_4 H), 7.23–7.43 (m, 2, thiophene C_3 and C_5 H). Anal. ($C_{14}H_{10}Cl_2O_3S$) C, H.

6,7-Dichloro-2,3-dihydro-5-(hydroxy-2-thienylmethyl)-2-benzofurancarboxylic Acid (14). KBH_4 (0.8 g, 0.015 mol) was added slowly to a stirred mixture of **10c** (3.4 g, 0.01 mol) and H_2O (20 mL) cooled in an ice bath. After the addition was completed, the solution was stirred for 2 h at 25 °C and then acidified with 6 N HCl to give a yellow gum. The gum was triturated with 6 N HCl to provide a solid, which was washed with H_2O to yield 1.8 g (52%) of **14**: mp 175 °C dec; NMR (Me_2SO-d_6) δ 3.27–3.70 (m, 2, C_3 H), 5.33 (dd, 1, J = 10 and 7 Hz, C_2 H), 6.13 (s, 1, Ar CH), 6.70–7.00 (m, 2, Ar H, thiophene C_4 H), 7.17–7.60 (m, 2, thiophene C_3 and C_5 H). Anal. ($C_{14}H_{10}Cl_2O_4S$) C, H.

6,7-Dichloro-2,3-dihydro-2-(hydroxymethyl)-5-(2-thienylcarbonyl)benzofuran (15). Borane–tetrahydrofuran complex (25 mL, 0.00625 mol) was added dropwise to a stirred solution of **10c** (3.4 g, 0.01 mol) in THF (50 mL) cooled to 0 °C. The reaction solution was stirred for 1 h at 0 °C and for 18 h at 25 °C and then diluted with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with Et_2O (2 × 25 mL). The organic extracts were combined, washed with brine, dried, and evaporated to give a yellow oil. The oil was chromatographed on silica gel (150 g). Elution with benzene–MeOH (19:1, v/v) gave 0.7 g (21%) of **15**: mp 65–68 °C; NMR (Me_2SO-d_6) δ 3.17–3.50 (m, 2, C_3 H), 3.70–3.90 (m, 2, CH_2OH), 4.90–5.43 (m, 1, C_2 H), 7.17–7.47 (m, 2, Ar H, thiophene C_4 H), 7.55 (dd, 1, J = 4 and 1 Hz, thiophene C_5 H), 8.10 (dd, 1, J = 4 and 1 Hz, thiophene C_3 H). Anal. ($C_{14}H_{10}Cl_2O_3S$) C, H.

6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxaldehyde (16). A solution of Red-Al (1.5 g, 10.7 mmol) in THF (10 mL) was added dropwise over 15 min to a stirred solution of the ester (3.57 g, 10 mmol) **11a** in THF (50 mL) cooled to −70 °C. After the solution stirred for 1 h at −70 °C, 24% H_2SO_4 (10 mL) was added dropwise and the mixture was allowed to warm to 25 °C. The organic layer was separated and the aqueous layer was extracted with THF (2 × 10 mL). The organic layers were combined, diluted with Et_2O (50 mL), washed with brine (3 × 25 mL), dried, and evaporated to give a yellow oil. A solution of the oil in *n*-BuCl (50 mL) was added to a solution of $NaHSO_3$ (6 g, 57.5 mmol) in H_2O (10 mL), and the resultant mixture was stirred for 18 h. The bisulfite addition product was removed by filtration and converted to the aldehyde by treatment with a mixture of Et_2O (50 mL) and aqueous $NaHCO_3$ (25 mL). The organic layer was separated, washed with brine (2 × 10 mL), dried, and evaporated to give a mixture of **13** and hydrated **13**. The water was removed by refluxing the mixture for 2 h in benzene and collecting the azeotrope in a Dean–Stark apparatus. The dried solution was evaporated to give a residue, which was triturated with petroleum ether to afford 1.0 g (31%) of **16**: mp 162–164 °C; NMR (Me_2SO-d_6) δ 3.23–3.73 (m, 2, C_3 H), 5.57 (dd, 1, J = 10 and 7 Hz, C_2 H), 7.13 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.3–7.53 (m, 2, Ar H, thiophene C_5 H), 8.07 (dd, 1, J = 4 and 1 Hz), 9.75 (s, 1, CHO). Anal. ($C_{14}H_6Cl_2O_3S$) C, H.

Ethyl 6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxylate (11b). A solution of acid **10c** (1.0 g, 2.9 mmol) in EtOH (10 mL) containing concentrated H_2SO_4 (0.1 mL) was refluxed for 1 h. Removal of solvent afforded a residue, which was suspended in aqueous $NaHCO_3$ solution (50 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with brine (2 × 25 mL), dried, and evaporated. The resulting solid was recrystallized from EtOH–H_2O to give 0.7 g (65%) of **11b**: mp 64–66 °C; NMR δ 1.3 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 3.37–3.83 (m, 2, C_3 H), 4.27 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 5.33 (dd, 1, J = 9 and 7 Hz, C_2 H), 6.77–7.20 (m, 2, Ar H and thiophene C_4 H), 7.33 (dd, 1, J = 4 and 1 Hz, thiophene C_5 H), 7.67 (dd, 1, J = 4 and 1 Hz, thiophene C_3 H). Anal. ($C_{16}H_{12}Cl_2O_4S$) C, H.

6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxylic Acid Hydrazide (17). Hydrazine (0.35 g, 11 mmol) was added to a stirred solution of the ester **11b** (3.7 g, 10 mmol) in EtOH (50 mL). After 2 h, the solid which separated from the reaction was collected and recrystallized from DMF–H_2O to give 1.9 g (53%) of **17**: mp 220–222 °C eff; NMR (Me_2SO-d_6) δ 3.30–3.67 (m, 2, C_3 H), 4.45 (br s, 2, $CNHNH_2$), 5.37 (dd, 1, J = 9 and 7 Hz, C_2 H), 7.23 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.33–7.60 (m, 2, Ar H, thiophene C_5 H), 8.13 (dd, 1, J = 4 and 1 Hz, thiophene C_3 H), 9.57 (br, s, 1, $CNHNH_2$). Anal. ($C_{14}H_{10}Cl_2N_2O_3S$) C, H, N.

***N*-(Aminoiminomethyl)-6,7-dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxamide (18).** A solution of ester **11b** (3.7 g, 10 mmol) in EtOH (50 mL) was added to a stirred mixture of guanidine hydrochloride (0.95 g, 10 mmol) and NaOMe (0.54 g, 10 mmol) in EtOH (25 mL). The resulting mixture was stirred for 2 h at 25 °C and then evaporated to give a beige foam, which was chromatographed on silica gel (250 g). Elution with THF–3 N NH_4OH 95:5, v/v, 180 mL) provided an impure material which was discarded. Continued elution with the same eluant (350 mL) gave a slightly impure solid, which was converted to its HCl salt by treatment with 6 N HCl (20 mL). The insoluble solid was collected and washed with H_2O to give 0.8 g (20%) of **18**: mp 240–241 °C; NMR (Me_2SO-d_6) δ 3.33–3.93 (m, 2, C_3 H), 5.70 (dd, 1, J = 9 and 7 Hz, C_2 H), 7.23 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.33–7.60 (m, 2, Ar H and thiophene C_5 H), 8.13 (d, 1, J = 4 Hz, thiophene C_4 H), 8.57 [br s, 4, $CONH{=}{-}(NH_2)_2^+$], 12.20 [br s, 1, $CONH{=}{-}(NH_2)_2^+$]. Anal. ($C_{15}H_{11}Cl_2N_3O_3S$·HCl) C, H; N: calcd, 9.99; found, 9.43.

6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarboxamide (19). A solution of **10c** (3.4 g, 10 mmol) and $SOCl_2$ (2 mL) in benzene (25 mL) was refluxed for 2 h. The solvent and excess $SOCl_2$ were removed by evaporation to give the intermediate carbonyl chloride (3.6 g) as an oil. Addition of this oil to concentrated NH_4OH (50 mL) gave a mixture, which was heated at 95 °C for 30 min. The deposited solid was collected and recrystallized from CH_3CN to provide 2.45 g (72%) of **19**: mp 248–250 °C; NMR (Me_2SO-d_6) δ 3.07–3.67 (m, 2, C_3 H), 5.33 (dd, 1, J = 10 and 7 Hz, C_2 H), 7.16 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.27–7.67 (m, 2, Ar H, thiophene C_5 H), 8.07 (dd, 1, J = 4 and 1 Hz, thiophene C_3 H). Anal. ($C_{14}H_9Cl_2NO_3S$) C, H, N.

6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofurancarbonitrile (20). A mixture of **19** (2.5 g, 7.3 mmol) and $POCl_3$ (20 mL) at 0 °C was treated with Et_3N (1.5 g, 14.6 mmol). The resulting mixture was heated at 95 °C for 1 h, after which the excess $POCl_3$ was removed at reduced pressure. The residue was treated with ice and H_2O and extracted with $CHCl_3$ (3 × 100 mL). The organic extracts were combined, washed with $NaHCO_3$ solution (2 × 50 mL) and brine (50 mL), dried, and evaporated to give a yellow solid. The yellow solid was recrystallized from *i*-PrOH–H_2O and then from MeOH–H_2O to give 1.4 g (59%) of **20**: mp 188–190 °C; NMR (Me_2SO-d_6) δ 3.62–3.88 (m, 2, C_3 H), 6.05 (dd, 1, J = 9 and 7 Hz, C_2 H), 7.18 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.41–7.58 (m, 2, Ar H, thiophene C_5 H), 8.11 (dd, 1, J = 4 and 1 Hz, thiophene C_3 H). Anal. ($C_{14}H_7Cl_2NO_2S$) C, H, N.

5-[6,7-Dichloro-2,3-dihydro-5-(2-thienylcarbonyl)-2-benzofuranyl]-1*H*-tetrazole (21). A solution of nitrile **20** (0.46 g, 1.4 mmol), NaN_3 (0.10 g, 1.6 mmol), and NH_4Cl (0.086 g, 1.6 mmol) in DMF (30 mL) was stirred at 100 °C for 70 h. The DMF was evaporated to afford a residue, which was dissolved in aqueous $NaHCO_3$ (20 mL) and extracted with ether (2 × 10 mL). The aqueous layer was acidified with 6 N HCl and extracted with Et_2O (3 × 20 mL). The extracts were combined, washed with brine (3 × 20 mL), dried, and evaporated to give a yellow solid. The solid was purified by dissolution in aqueous $NaHCO_3$ and acidification of the alkaline solution with 6 N HCl to give, after filtration, 0.25 g (48%) of **21**: mp 108–115 °C; NMR δ 3.80 (br d, 2, J = 9 Hz, C_3 H), 6.32 (br t, 1, J = 9 Hz, C_2 H), 6.90–7.20 (m, 2, Ar H, thiophene C_4 H), 7.37 (dd, 1, J = 4 and 1 Hz, thiophene C_5 H), 7.68 (dd, 1, J = 4 and 1 Hz, thiophene C_3 H). Anal. ($C_{14}H_8Cl_2N_4O_2S$) C, H; N: calcd, 15.26; found, 15.79.

6,7-Dichloro-2,3-dihydro-5-(2-thienylsulfonyl)-2-benzofurancarboxylic Acid (22). Anhydrous $AlCl_3$ (2.6 g, 20 mmol) was added over 5 min to a well-stirred mixture of ester **9** (5.2 g, 20 mmol) and 2-thiophenesulfonyl chloride (3.6 g, 20 mmol) protected from the atmosphere with a $CaCl_2$ drying tube. The reaction mixture was stirred at 25 °C for 18 h and at 90 °C for

1 h and then poured into ice–water (150 mL) and 12 N HCl (15 mL). The resulting mixture was extracted with Et_2O (3 × 250 mL). The ethereal extracts were combined, washed with brine (3 × 100 mL), dried, and evaporated to give the crude esterified product (7.8 g) as a tan oil. The tan oil was hydrolyzed by dissolution in 10% NaOH (100 mL). The solution was acidified with 12 N HCl to give a tan oil (5.8 g), which was chromatographed on silica gel (700 g). Elution with benzene–dioxane–AcOH (25:5:1, v/v, 1350 mL) provided a forerun which was discarded. Continued elution with the same eluant (1785 mL) gave a slightly impure product which was purified by precipitation from 2 N NaOH with 6 N HCl to give 1.2 g (15%) of **22**: mp 189–193 °C; NMR (Me_2SO-d_6) δ 3.30–3.83 (m, 2, C_3 H), 5.57 (dd, 1, J = 10 and 7 Hz, C_2 H), 7.20 (dd, 1, J = 4 and 4 Hz, thiophene C_4 H), 7.87 (dd, 1, J = 4 and 1 Hz, thiophene C_5 H), 8.00–8.20 (m, 2, Ar H and thiophene C_4 H). Anal. ($C_{13}H_8Cl_2O_5S$·0.5H_2O) C, H.

X-ray of Crystal Structure. Crystals of **10e** ($C_{14}H_8Cl_2O_4S$) suitable for X-ray analysis crystallized with space group symmetry $P2_12_12_1$ from toluene. Cell constants determined through initial experiments were a = 6.994 (1) Å, b = 17.237 (2) Å, and c = 23.400 (3) Å with Z = 8 for a calculated density of 1.62 g/cm^3. Of the 2214 unique reflections measured with graphite monochromated Cu Kα radiation (λ = 1.5418 Å), 1677 (76%) were observed ($I \geq 3\sigma I$). The crystal structure was solved using a standard multisolution method[15] and Fourier difference calculations.[16] The structure was refined using full matrix least-squares techniques by minimizing $\sum w(|F_o| - |F_c|)^2$ with $w = (1/\sigma F_o)^2$. At the end of anisotropic refinement for the nonhydrogen atoms and utilizing anomalous scattering factors for S and Cl, the R factor was 0.085 for one enantiomer and 0.090 for the other. This difference, which is significant at the 99.5% level,[17] was confirmed by careful remeasurement of 15 enantiomorphic sensitive reflections. The final residual index obtained after adding hydrogens with fixed isotropic temperature parameters was 0.075. The correct absolute configuration for **10e** is shown in the computer-generated drawing in Figure 1.[18] Tables VI, VII, and VIII (containing fractional coordinates and temperature parameters, bond distances, and bond angles) are located in the supplementary material.

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Supplementary Material Available: Fractional coordinates and temperature parameters, bond distances, and bond angles for **10e** (5 pages). Ordering information is given on any current masthead page.

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