[(Aminomethyl)aryloxy]acetic Acid Esters. A New Class of High-Ceiling Diuretics. 4. Substituted 6,7-Dichloro-2,3-dihydrobenzofurans Derived by Ring Annelation[1]

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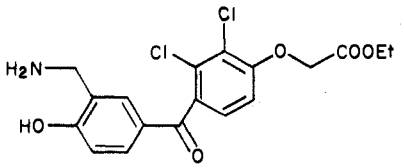
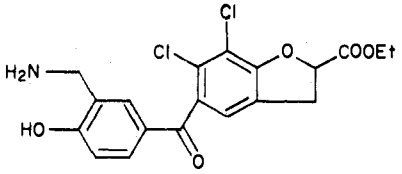
Ring annelation of the [(aminomethyl)aryloxy]acetic acids produced a series of substituted 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acids. Pharmacologic evaluation of these compounds in rats and dogs indicated that several congeners are extremely potent salidiuretics. Clearance and micropuncture experiments in rats for compound **5a** confirmed the high-ceiling diuretic profile and demonstrated that **5a** has a site of action at the thick ascending limb of Henle's loop.

Previous papers[2] from our laboratories have described a new class of [(aminoethyl)aryloxy]acetic acid derivatives **I** in which a basic nitrogen function was shown to play a pivotal role in modulating the salidiuretic potency. During the course of systematic structure–activity studies,[2b] we found that ring annelation of the oxyacetate side chain in **I** produced the dihydrobenzofuran **II** and led to a 20-fold increase in natriuretic potency. The ring annelated congener **II** represents the most potent diuretic agent that we have tested in our laboratories. In this paper we describe the synthesis and salidiuretic properties of ring annelated 6,7-dichloro-2,3-dihydrobenzofurans structurally related to **II**.



I



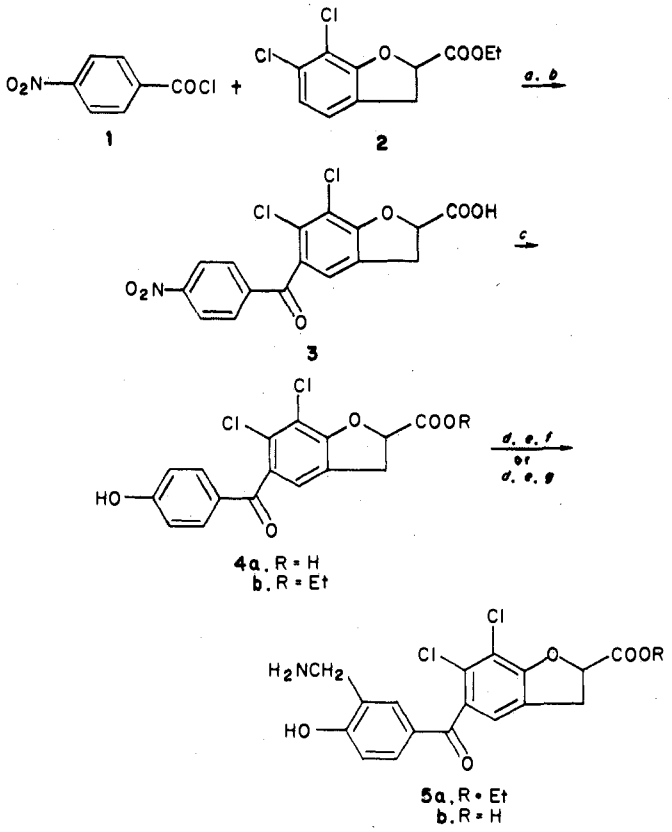
II

Chemistry. The compounds prepared for this study are shown in Table I and their syntheses are outlined in Schemes I–IV. Friedel–Crafts acylation of ethyl 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate[3] (**2**) with p-nitrobenzoyl chloride gave adduct **3** in 85% yield (Scheme I). Direct replacement of the nitro function in **3** with a hydroxyl group was accomplished by a nucleophilic aromatic displacement[4] with the sodium salt of acetaldoxime in DMF to give the key intermediate **4a**. Elaboration of **4a** to the target analogue **5a** was effected in a two-step process by employing a Tscherniac–Einhorn reaction[5] followed by hydrolysis of the chloroacetyl derivative. The corresponding carboxylic acid analogue **5b** was obtained by acid hydrolysis of ester **5a**.

The carboxamide derivative **7** was prepared as indicated in Scheme II. Protection of the aminomethyl function in **5a** as the carbobenzyloxy (Cbz) derivative gave **6**. This compound underwent facile ammoniolysis at room temperature in EtOH to give the protected carboxamide. Deprotection of this intermediate by catalytic hydrogenolysis then gave **7**.

Access to the hydroxymethyl analogue **9** began with the Cbz ester **6**. Reduction of this compound with $NaBH_4$ in EtOH at 0–5 °C gave a mixture of alcohol **8** and a diol resulting from reduction of both the ketone and ester

Scheme I



[a] $AlCl_3$, CH_2Cl_2. [b] NaOH, EtOH. [c] $CH_3CH{=}NOH$, NaOH, DMF. [d] $ClCH_2CONHCH_2OH$, H_2SO_4. [e] EtOH, H_2SO_4, 25 °C. [f] HCl, EtOH, Δ. [g] HCl, H_2O, Δ.

† Abbott Laboratories.
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(1) Portions of this work were presented in March 1984 at the first International Conference on Diuretics, Miami Beach, FL: Plattner, J. J.; Lee, C. M.; Horrom, B. W.; Fung, A. K. L.; Bunnell, P. R.; Bopp, B. A.; Field, M. J.; Giebisch, G. H. In "Diuretics: Chemistry, Pharmacology and Clinical Applications"; Puschett, J. B., Greenberg, A., Eds.; Elsevier: New York, 1984; pp 21–29.

(2) (a) Lee, C. M.; Plattner, J. J.; Ours, C. W.; Horrom, B. W.; Smital, J. R.; Pernet, A. G.; Bunnell, P. R.; El Masry, S. E.; Dodge, P. W. *J. Med. Chem.* **1984**, *27*, 1579. (b) Plattner, J. J.; Fung, A. K. L.; Smital, J. R.; Lee, C. M.; Crowley, S. R.; Pernet, A. G.; Bunnell, P. R.; Buckner, S. A.; Sennello, L. T. *J. Med. Chem.* **1984**, *27*, 1587. (c) Plattner, J. J.; Martin, Y. C.; Smital, J. R.; Lee, C. M.; Fung, A. K. L.; Horrom, B. W.; Crowley, S. R.; Pernet, A. G.; Bunnell, P. R.; Kim, K. H. *J. Med. Chem.* **1985**, *28*, 79.

(3) Hoffman, W. F.; Woltersdorf, O. W., Jr.; Novello, F. C.; Cragoe, E. J., Jr.; Springer, J. P.; Watson, L. S.; Fanelli, G. M., Jr. *J. Med. Chem.* **1981**, *24*, 865.

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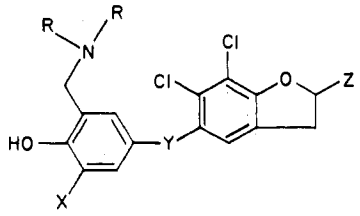
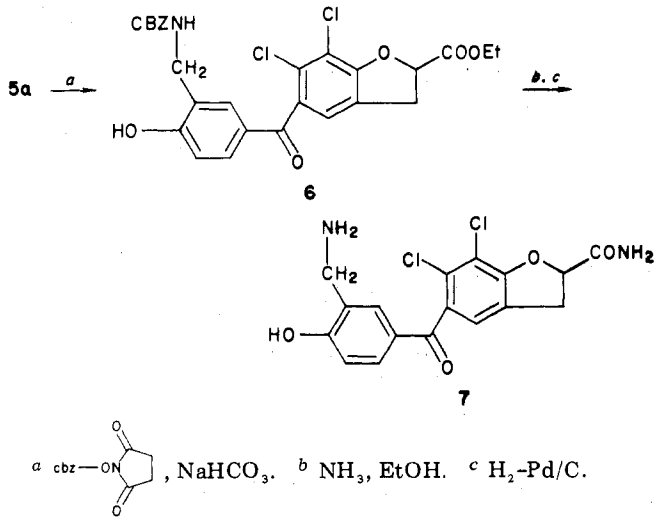
Table I. Substituted 6,7-Dichloro-2,3-dihydrobenzofurans



no.	R	X	Y	Z	mp, °C	recrystn solvent[a]	formula[b]	rat ED_2,[c] mg/kg
5a	H	H	CO	COOEt	224–227	A	$C_{19}H_{18}Cl_3NO_5$	0.12
5b	H	H	CO	COOH	222–225 dec	d	$C_{17}H_{14}Cl_3NO_5$	inactive
7	H	H	CO	$CONH_2$	>250	A	$C_{17}H_{15}Cl_3N_2O_4$	2.95
9	H	H	CO	CH_2OH	248–250	A	$C_{17}H_{16}Cl_3NO_4$	0.95
10	Me	CH_2NMe_2	CO	COOEt	173–176 dec	A	$C_{24}H_{30}Cl_4N_2O_5$	1.82
11	H	Cl	CO	COOEt	237–239	B	$C_{19}H_{17}Cl_4NO_5$	21.5
13a	H	H	CH_2	COOEt	227–230	d	$C_{19}H_{20}Cl_3NO_4$	8.0
13b	H	CH_2NH_2	CH_2	COOEt	215–219	d	$C_{20}H_{24}Cl_4N_2O_4$	49.0
14	H	H	CH_2	CH_2OH	227–230	d	$C_{17}H_{18}Cl_3NO_3$	10.2

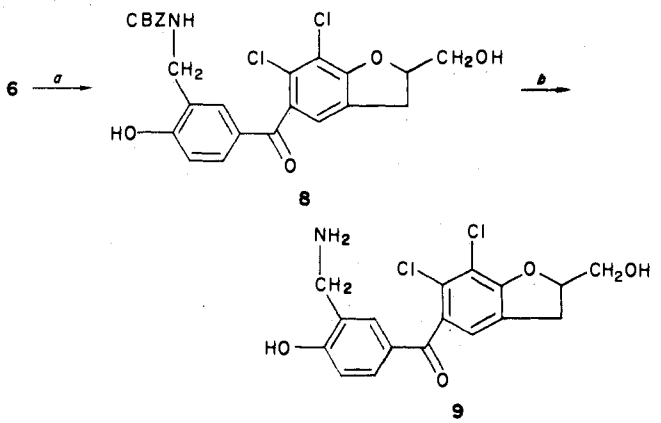
[a] A = ethanol/ether, B = ethanol. [b] All compounds gave satisfactory C, H, and N analyses. [c] The natriuretic potency of the compounds tested in this table is reported as an ED_2. An ED_2 is defined as the oral dose (milligrams/kilogram) required to produce an excretion of 2 mequiv of Na^+/kg of body weight during the 4-h collection period. These values were obtained by plotting the linear regression of the response curve of Na^+ excretion vs. the log of the dose. Compounds reported as inactive showed a Na^+ excretion no different from the control value at the high dose of 100 mg/kg. Details of the test protocol are described in ref 2a. [d] The compound was triturated with hexane.

Scheme II



[a] cbz—ON, $NaHCO_3$. [b] NH_3, EtOH. [c] H_2-Pd/C.

Scheme III



[a] $NaBH_4$, EtOH, 5 °C. [b] H_2-Pd/C.

functions. Chromatographic separation of the mixture was followed by catalytic removal of the Cbz group in **8** to give the desired analogue **9**.

Preparation of the remaining analogues in Table I was effected as indicated in Scheme IV. Mannich reaction[6] of **4a** with aqueous formaldehyde and dimethylamine led to a bis[(dimethylamino)methyl] intermediate, which was esterified with thionyl chloride in EtOH to give **10**. The chloro analogue **11** was prepared by a four-step process. Esterification of **4a** gave the corresponding ethyl ester, which underwent facile monochlorination with sulfuryl chloride in refluxing 1,2-dichloroethane to give an *o*-chlorophenol. Amidomethylation of this intermediate using the Tscherniac–Einhorn procedure was followed by acid hydrolysis in EtOH to give **11**. To prepare **13a** and **13b**, the ethyl ester of **4a** described above was reduced with $NaBH_4$ in trifluoroacetic acid.[7] This process resulted in hydrogenolysis of the diaryl ketone function and formation of the corresponding diarylmethane derivative. Amidomethylation as described above was followed by hydrolysis to give the mono- and bis(aminomethyl) analogues **13a** and **13b**. The intermediate monochloroacetyl derivative **12a**, formed during the amidomethylation procedure, was reduced with $NaBH_4$ and then hydrolyzed to give **14**.

Biological Activity. Structure–Activity Relationships. The target compounds prepared in this study were tested orally in rats and/or dogs for their natriuretic properties, with results represented as an ED_2 (rat) and ED_5 (dog) as described in earlier papers.[2] Initial structure–activity studies for these compounds centered on the side-chain carboxyl function. As seen from the data in Table I, the ethyl ester derivative **5a** shows potent, oral salidiuretic activity whereas the corresponding carboxylic acid **5b** is inactive. Both **5a** and **5b**, however, are potent diuretics when given intravenously. These results parallel our previous findings in the oxyacetate series,[2b] where we determined that the ethyl ester group serves as a prodrug for the carboxyl function by converting the ionizable group into a neutral form which has enhanced oral absorption.

Reasonably potent diuretic activity is also seen with carboxamide **7** and alcohol **9**. In our earlier work on compounds that were not ring annelated,[2b] we found that oral administration of the analagous carboxamide and alcohol congeners produced the corresponding carboxylic acid derivative in vivo. It is reasonable to speculate that

(4) Knudsen, R. D.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343.
(5) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.
(6) Blicke, F. F. *Org. React.* **1942**, *1*, 303–341.
(7) Gribble, G. W.; Leese, R. M. *Synthesis* **1977**, 172.

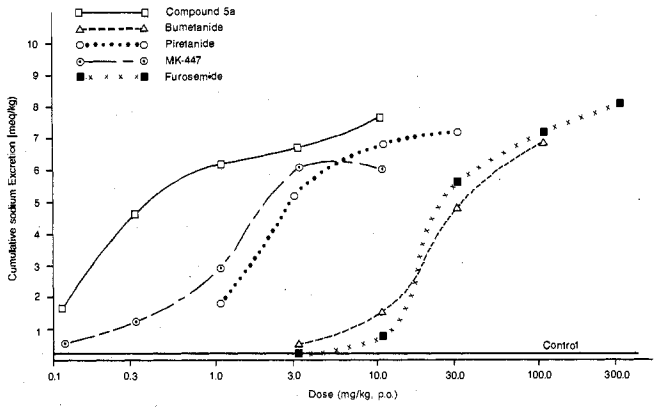


Figure 1. Sodium excretion during 4 h after po administration of **5a** and reference diuretics to female rats. Rats were fed glucose and water overnight, DOCA pretreatment, 5 mg, sc, 2 h prior to dosing, and loaded with isotonic NaCl–KCl (40:60) to 3% body weight immediately after dosing. Each point is the mean of four rat/dose.

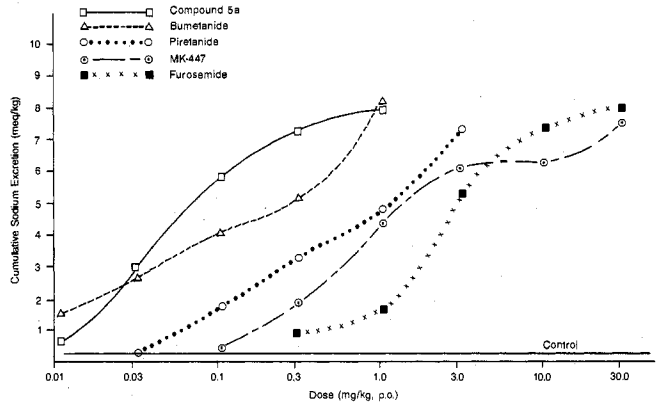


Figure 2. Sodium excretion during the 6-h period after po administration of **5a** and reference diuretics to conscious female dogs. Each point is the mean of four dogs/dose.

a similar metabolic transformation occurs with the dihydrobenzofuran series as well and that at least part of the diuretic activity of **7** and **9** results from their in vivo conversion to **5b**. Interestingly, the relative salidiuretic potency of ester > alcohol > amide in the ring annelated compounds differ from that in the oxyacetate series [2b] where alcohol > ester > amide. This difference may reflect divergent pharmacokinetic and/or metabolism rates between the two series of compounds.

The bis Mannich analogue **10** also displays potent natriuretic activity but less so than the parent compound **5a**. Introduction of a chloro substituent adjacent to the phenol in **5a** reduces diuretic activity (compound **11**). This result sharply contrasts the potency increase that is produced following the analogous chlorination in the oxyacetate series[2b] and in the 2-(aminomethyl)phenols.[8]

Diuretic activity for the 6,7-dichloro-2,3-dihydrobenzofurans is also affected by the nature of the functional group linking the two aryl rings. For example, reduction of the ketone function to a methylene group reduces diuretic potency (compare compounds **5a** and **9** vs. **13a** and **14**, respectively).

Pharmacology of 5a. On the basis of structure–activity studies described above, we selected compound **5a** for further testing. Comparative pharmacological evaluation of the salidiuretic activity of **5a** was done in rats and conscious nonloaded female dogs. Compound **5a** was shown to be an extremely potent high-ceiling diuretic when compared to furosemide, bumetanide, piretanide, and MK-447. The excretion patterns of the sodium dose response are shown for rats and dogs in Figures 1 and 2, respectively. The profile of volume and other electrolytes were not different, except for potency. Comparison of the ED_2 values in rats and the ED_5 values in dogs (Table II) indicates that **5a** represents a very potent salidiuretic agent. The onset of activity for **5a** and these reference compounds was rapid, within 0.5–1 h after oral dosing by gavage. The duration of action was dose dependent, with maximum duration of 4–6 h for all compounds. Despite the significant advantage in potency of **5a**, no other pharmacologic difference in the electrolyte excretion patterns was noted.

In order to further characterize the pharmacologic properties of this compound, we have carried out renal clearance and micropuncture studies. Male, adult Sprague–Dawley rats were used in all experiments and were prepared for standard free-flow micropuncture as previously described.[9] Animals were infused with Ringer's solution at a sustaining rate of 2 mL/100 g per h. They also received an infusion of [^{3}H]inulin, to deliver 100 μCi/h. Clearance studies involved first the collection of two 30-min urine samples ("control" period), together with blood samples at the midpoint of each.[9a] Compound **5a** was then injected as a single intravenous (iv) bolus of 0.1

Table II

compd	rat ED_2[a]	dog ED_5[b]
5a	0.12 (0.97)[c] (0.03–10.0 mg/kg, po)[d]	0.11 (0.98) (0.01–1.0 mg/kg, po)
furosemide	9.50 (0.94) (1.0–100.0 mg/kg, po)	3.50 (0.99) (0.3–30.0 mg/kg, po)
bumetanide	8.50 (0.98) (3.0–100.0 mg/kg, po)	0.15 (0.98) (0.01–1.0 mg/kg, po)
piretanide	0.89 (0.93) (1.0–30.0 mg/kg, po)	0.25 (0.99) (0.03–3.0 mg/kg, po)
MK-447	0.36 (0.96) (0.1–30.0 mg/kg, po)	2.90 (0.97) (0.1–30 mg/kg, po)

[a] ED_2 values based on N = four rats/dose. [b] ED_5 values based on N = two dogs/dose. Details of the test protocol are described in ref 2a. [c] Correlation coefficient of the linear regression of the dose–response curve. [d] Dose range tested.

Table III. Clearance Data for 5a

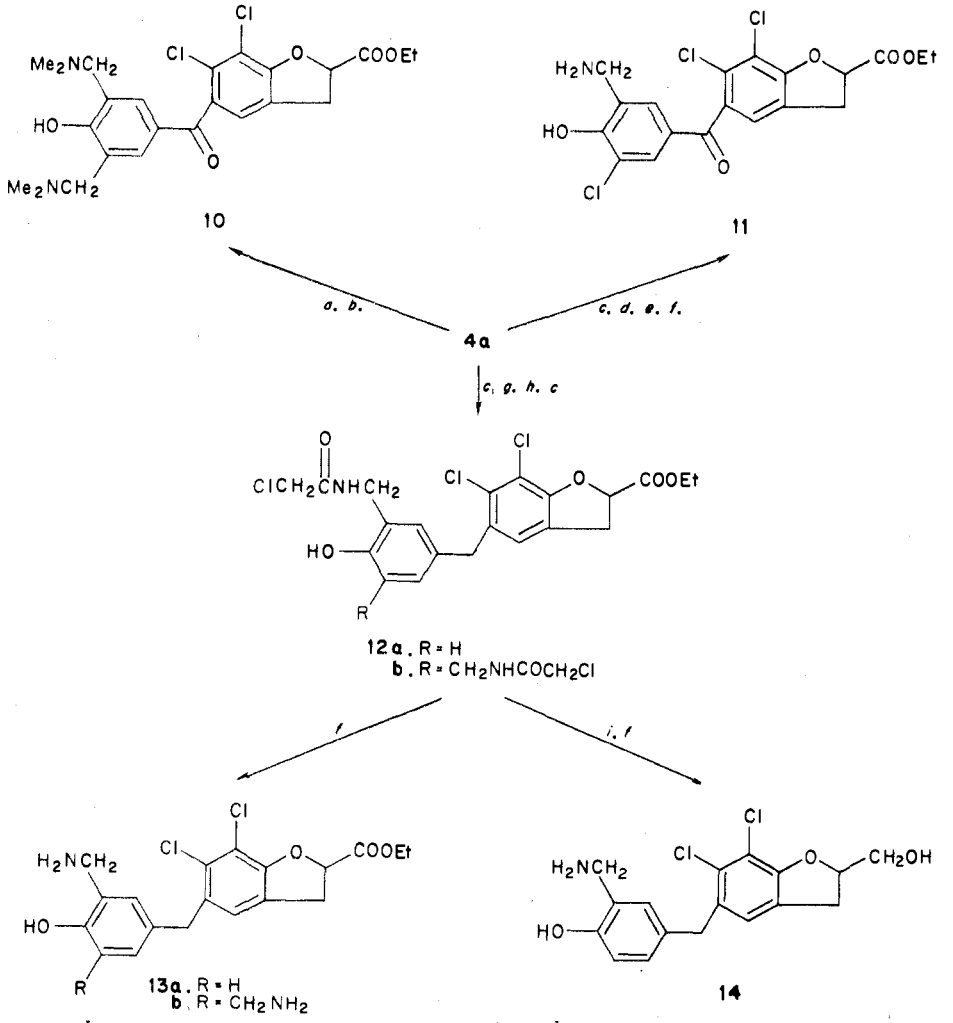
	control	5a	P (n = 8)[e]
urine flow rate, μL/min per kidney	6.0 ± 2.5	67.6 ± 7.9	<0.001
(U/P) inulin[a]	407.8 ± 85.0	19.7 ± 2.8	<0.01
GFR,[b] mL/min per 100 g of rat	0.56 ± 0.04	0.46 ± 0.03	<0.05
FE_{Na},[c] %	0.44 ± 0.23	6.30 ± 0.83	<0.001
FE_K,[d] %	23.3 ± 3.2	54.6 ± 3.8	<0.01
plasma Na, mM	144.0 ± 1.8	144.0 ± 1.5	NS
plasma K, mM	4.18 ± 0.06	3.57 ± 0.10	<0.01

[a] Urine-to-plasma concentration ratio for inulin. [b] Glomerular filtration rate (per one kidney). [c] Fractional excretion of Na^+ (percent of filtered load). [d] Fractional excretion of K^+ (percent of filtered load). [e] Significance levels based on paired t test. NS, not significant ($p > 0.05$).

(8) Smith, R. L. In "Diuretics. Chemistry, Pharmacology and Medicine"; E. J. Cragoe, Jr., Ed.; Wiley-Interscience: New York, 1983; Chapter 5.

(9) (a) Opava Stitzer, S.; Martinez-Maldonado, M. In "Methods in Pharmacology", M. Martinez-Maldonado, Ed.; Plenum Press: New York, 1978; Vol. 4B, Chapter 2. (b) Duarte, C. G.; Chomety, F.; Giebisch, G. *Am. J. Physiol.* 1971, *221*, 632.

Scheme IV



[a] HCHO, Me_2NH, H_2O. [b] $SOCl_2$, EtOH. [c] H_2SO_4, EtOH, 25 °C. [d] SO_2Cl_2, $ClCH_2CH_2Cl$, Δ. [e] $ClCH_2CONHCH_2OH$, CH_3SO_3H, 40 °C. [f] HCl, EtOH, Δ. [g] $NaBH_4$, CF_3COOH, CH_2Cl_2. [h] $ClCH_2CONHCH_2OH$, HOAc, H_2SO_4. [i] $NaBH_4$, EtOH.

Table IV. Micropuncture Data for 5a

	early distal			late distal		
	control	5a	P^e	control	5a	P^e
flow rate, nL/min	6.0 ± 0.5	8.2 ± 0.3	<0.01	2.9 ± 0.2	4.6 ± 0.7	<0.05
[TF/P] inulin[a]	4.59 ± 0.23	4.39 ± 0.20	NS	12.33 ± 1.07	8.48 ± 1.13	<0.05
$SNGFR_i$,[b] nL/min	28.4 ± 1.1	35.7 ± 1.9	<0.05	35.2 ± 3.2	33.9 ± 2.2	NS
FD_{Na},[c] %	5.6 ± 0.5	13.6 ± 0.7	<0.001	1.5 ± 0.2	8.1 ± 1.1	<0.001
FD_K,[d] %	10.8 ± 1.7	23.0 ± 2.2	<0.01	21.8 ± 3.2	23.6 ± 3.1	NS
N = tubules/rats	6/4	11/5		10/6	8/5	

[a] Tubular fluid-to-plasma concentration ratio for inulin. [b] Single nephron glomerular filtration rate. [c] Fractional delivery of Na^+ to puncture site (percent of filtered load). [d] Fractional delivery to K^+ to puncture site (percent of filtered load). [e] Significance levels based on unpaired t test. NS, not significant ($p > 0.05$).

mg/kg, given over 20–30 s. Thirty minutes later, two more 30-min clearance periods were observed ("diuretic" period), during which time supplementary iv fluid was administered to replace that lost by the diuretic. From the measurement of urine volumes, Na^+ and K^+ concentrations, and radioactive inulin counts in plasma and urine samples, glomerular filtration rate as well as absolute and fractional electrolyte excretion before and after diuretic treatment could be calculated, using standard formulae.[9a] Free-flow micropuncture samples were obtained from "early" and "late" distal tubular segments in the exposed kidney during the same "control" and "diuretic" periods described above. Results from these experiments are summarized in Tables III and IV and in Figure 3.

The data indicate the powerful diuretic action of **5a**, manifesting itself as an increase in urine flow rate, a fall in U/P inulin, a striking increase in fractional Na^+ and K^+ excretion and a modest fall in plasma [K^+]. Figure 3 provides a graphic demonstration of the diuretic effect as well as the natriuretic and kaliuretic effect; glomerular filtration rate shows only a modest decline.

Table IV summarizes the micropuncture data. A "loop" effect is apparent from the sharply augmented fractional delivery rates of both Na^+ and K^+ into the early distal tubule and by the increased flow rate of tubular fluid into and along the distal tubule. This pattern of transport changes resembles that previously reported with furosemide[9b] and is most likely due to drug-induced inhibition of solute reabsorption by the thick ascending limb of Henle's loop.

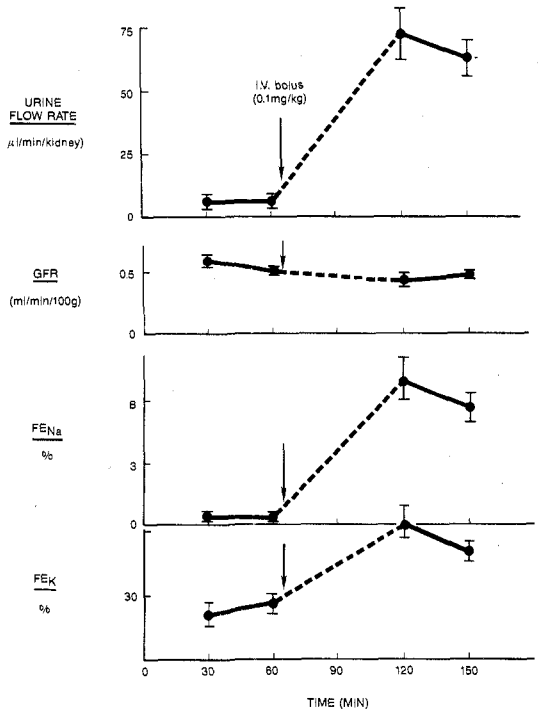


Figure 3. Principal results of clearance experiments conducted with **5a**. The compound was given as a single intravenous bolus of 0.1 mg/kg at the point indicated by the arrow. GFR, glomerular filtration rate (one kidney). FE_{Na}, FE_K, fractional excretion rates of Na^+ and K^+, respectively (percent of filtered load in each case).

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.

6,7-Dichloro-2,3-dihydro-5-(4-hydroxybenzoyl)-2-benzofurancarboxylic Acid (4a). Compound 3[2b] (3.44 g, 9 mmol) was added to a stirred mixture of 1.77 g (30 mmol) of acetaldoxime and 1.6 g (40 mmol) of crushed NaOH pellets in 25 mL of dry DMF, cooled in an ice bath. The mixture was stirred at room temperature overnight and poured into 100 mL of H_2O. After acidification with HCl, the aqueous mixture was extracted with EtOAc. The EtOAc solution was washed with H_2O, dried over $MgSO_4$, and evaporated. The residue was recrystallized from aqueous HOAc to give 2.3 g (73%) of **4a**, mp 192–194 °C. Anal. ($C_{16}H_{10}Cl_2O_5$) C, H.

Ethyl 6,7-Dichloro-2,3-dihydro-5-(4-hydroxybenzoyl)-2-benzofurancarboxylate (4b). A mixture of **4a** (2.0 g, 5.7 mmol), EtOH (150 mL), and concentrated H_2SO_4 (0.5 mL) was stirred at room temperature for 24 h. After partial evaporation of the EtOH, the residue was diluted with EtOAc and the organic solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl. Drying over $MgSO_4$ was followed by evaporation of the solvent to give a residue which was chromatographed on silica gel, eluting with EtOAc/benzene mixtures. There was obtained 2.1 g (97%) of **4b** as an amorphous solid, mp 60–65 °C. Anal. ($C_{18}H_{14}Cl_2O_5$) C; H: calcd, 3.70; found, 4.16.

Ethyl 6,7-Dichloro-2,3-dihydro-5-[3-(aminomethyl)-4-hydroxybenzoyl]-2-benzofurancarboxylate Hydrochloride (5a). 2-Chloro-*N*-(hydroxymethyl)acetamide[10] (5.38 g, 40.4 mmol) was added, in small portions, to a stirred solution of **4a** (13.6 g, 38.5 mmol) in 200 mL of concentrated H_2SO_4 at 10–15 °C. The mixture was stirred at 10–15 °C for 6 h and poured into 650 mL of ice. The gum that formed was extracted into EtOAc and the resulting solution washed with aqueous NaCl and dried over $MgSO_4$. The residue obtained by evaporating the EtOAc was dissolved in 500 mL of absolute EtOH containing 1.0 mL of concentrated H_2SO_4. After the mixture stood overnight at room temperature, the EtOH was partially evaporated under reduced pressure and the residue distributed between CH_2Cl_2 and aqueous NaCl. The organic layer was washed several times with aqueous NaCl, dried over $MgSO_4$, and evaporated. The crude ethyl ester was chromatographed on a silica gel column eluting with benzene/EtOAc mixtures to give 9.20 g (54%) of the chloroacetyl derivative. This material was heated at reflux for 4 h in 100 mL of EtOH and 33 mL of concentrated HCl. Evaporation and azeotropic removal of the H_2O with absolute EtOH gave an oil, which was crystallized from EtOH/Et_2O to give 5.35 g (58%) of **5a**, mp 224–227 °C. Anal. ($C_{19}H_{18}Cl_3NO_5$) C, H, N.

6,7-Dichloro-2,3-dihydro-5-[3-(aminoethyl)-4-hydroxybenzoyl]-2-benzofurancarboxylic Acid Hydrochloride (5b). A 500-mg (1.12 mmol) portion of **5a** was suspended in 100 mL of 3 N HCl and heated at reflux for 2 h and then left to cool overnight. The resulting clear solution was partially evaporated and the white, crystalline precipitate was collected by filtration to give 410 mg (87.5%) of **5b**, mp 222–225 °C dec. Anal. ($C_{17}H_{14}Cl_3NO_5$) H, N; C: calcd, 48.77; found, 48.28.

Ethyl 6,7-Dichloro-2,3-dihydro-5-[3-[[(benzyloxycarbonyl)amino]methyl]-4-hydroxybenzoyl]-2-benzofurancarboxylate (6). To a stirred mixture of hydrochloride salt **5a** (4.02 g, 0.9 mmol) and *N*[(benzyloxycarbonyl)oxy]succinimide (2.37 g, 9.5 mmol) in 40 mL of CH_3CN was added 0.95 g (9.5 mmol) of $KHCO_3$ in 10 mL of H_2O at 0–5 °C. The ice bath was removed and the reaction mixture was stirred for 1.5 h. The clear solution was placed in a separatory funnel and the bottom water layer was drawn off. The remaining CH_3CN was evaporated and the residue distributed between CH_2Cl_2 and aqueous NaCl. The organic layer was dried over $MgSO_4$ and evaporated. Trituration of the residue with hexane gave 4.5 g (92%) of **6**, mp 150–154 °C. This material was used without purification in the next step. **6**: NMR (Me_2SO-d_6) δ 1.23 (3 H, t, J = 7 Hz, CH_3), 3.06–3.86 (4 H, m), 4.0–4.46 (4 H, m), 5.13 (2 H, s).

6,7-Dichloro-2,3-dihydro-5-[3-(aminomethyl)-4-hydroxybenzoyl]-2-benzofurancarboxamide Hydrochloride (7). A 1.09-g (2.0 mmol) portion of **6** was dissolved in 150 mL of EtOH and anhydrous ammonia was passed into the solution for 4 h. After the mixture stood for 30 h at room temperature, the EtOH was evaporated and the residue was triturated with 1 N HCl (6 mL) and CH_2Cl_2 (3 mL). The solid product was filtered and the recrystallized from EtOH to give 0.95 g (92%) of the corresponding carboxamide derivative, mp 133–137 °C. A mixture of the above amide (0.87 g, 1.7 mmol), 5% Pd/C (90 mg), and concentrated HCl (0.6 mL) in methyl Cellosolve (100 mL) was hydrogenated under 3 atm of H_2 for 3 h. The catalyst was filtered and the filtrate was evaporated to a residue. Recrystallization from EtOH/Et_2O gave 0.33 g (46%) of **7**, mp >250 °C. Anal. ($C_{17}H_{15}Cl_3N_2O_4$) H, N; C: calcd, 48.88; found, 48.45.

6,7-Dichloro-2,3-dihydro-5-[3-[[(benzyloxycarbonyl)amino]methyl]-4-hydroxybenzoyl]-2-benzofuranmethanol (8). $NaBH_4$ (1.6 g, 42.3 mmol) was added to a solution of 3.0 g (5.5 mmol) of **6** in 150 mL of EtOH, cooled in an ice–water bath at 5–10 °C. The mixture was stirred at 5–10 °C for $2^1/_2$ h and evaporated under reduced pressure. The residue was triturated with H_2O, acidified with aqueous citric acid, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by high-pressure liquid chromatography using a silica gel column and eluting with 1,2-dichloroethane/EtOH (98.9:1.1) to give 1.5 g (54%) of **8**: NMR (Me_2SO-d_6) δ 3.05–3.43 (3 H, m), 3.5–3.8 (2 H, m), 4.2 (2 H, d, J = 6 Hz).

6,7-Dichloro-2,3-dihydro-5-[3-(aminomethyl)-4-hydroxybenzoyl]-2-benzofuranmethanol Hydrochloride (9). A solution of **8** (1.49 g, 2.96 mmol) and concentrated HCl (0.4 mL) in 100 mL of EtOH was hydrogenated over 5% Pd/C (150 mg) for 1 h. After removal of the catalyst, the solution was evaporated to dryness and the residue was recrystallized from EtOH/Et_2O to give 0.82 g (69%) of **9**, mp 248–250 °C. Anal. ($C_{17}H_{16}Cl_3NO_4$) C, H, N.

Ethyl 6,7-Dichloro-2,3-dihydro-5-[3,5-bis[(dimethylamino)methyl]-4-hydroxybenzoyl]-2-benzofurancarboxylate Dihydrochloride (10). To a stirred solution of 40% aqueous

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$(CH_3)_2NH$ (4.27 mL, 94 mmol) cooled in an ice bath was added 37% HCHO (2.14 mL, 28.5 mmol). After stirring at room temperature for 0.25 h, the mixture was treated with 1.77 g (5 mmol) of **4a** all at once. Stirring at reflux for 20 h was followed by evaporation of the solvents and recrystallization of the residue from DMF. There was obtained 1.3 g (56%) of bis Mannich product, mp 220 °C dec. A mixture of 0.78 g (1.7 mmol) of the above product, $SOCl_2$ (0.63 mL), and EtOH (16 mL) was heated at reflux for 4 h. After evaporation, the residue was recrystallized twice from $EtOH/Et_2O$ to give 0.47 g (47%) of **10**, mp 173–176 °C dec. Anal. ($C_{24}H_{30}Cl_4N_2O_5 \cdot H_2O$) C, H, N.

Ethyl 6,7-Dichloro-2,3-dihydro-5-[3-(aminomethyl)-5-chloro-4-hydroxybenzoyl]-2-benzofurancarboxylate Hydrochloride (11). A mixture of **4b** (1.57 g, 4.1 mmol) and SO_2Cl_2 (0.61 g, 4.5 mmol) in 20 mL of 1,2-dichloroethane was heated at reflux for 5 h. After evaporation of the solvent, the residue was triturated with Et_2O and the recrystallized from toluene to give 1.3 g (76%) of the corresponding *o*-chlorophenol, mp 168–171 °C. 2-Chloro-*N*-(hydroxymethyl)acetamide[10] (0.41 g, 3.3 mmol) was added to a stirred solution of the above phenol (1.25 g, 3 mmol) in 5 mL of CH_3SO_3H at 40 °C. After stirring at 95 °C for $3^3/_4$ h, the cooled mixture was poured into ice water. The resulting solid was filtered, dried, and then heated at reflux with concentrated HCl (7 mL) and EtOH (21 mL) for 8 h. After cooling, the solid product was filtered and recrystallized from EtOH to afford 0.68 g (46%) of **11**, mp 237–239 °C. Anal. ($C_{19}H_{17}Cl_4NO_5 \cdot {}^1/_2H_2O$) C, H, N.

Ethyl 6,7-Dichloro-2,3-dihydro-5-[3-[(chloroacetamido)methyl]-4-hydroxybenzyl]-2-benzofurancarboxylate (12a). To trifluoroacetic acid (120 mL) under a nitrogen atmosphere was added 5.39 g (140 mmol) of $NaBH_4$ pellets over a period of 30 min at 5 °C. A solution of **4b** (7.35 g, 190 mmol) in 50 mL of CH_2Cl_2 was added dropwise at 15–20 °C over a period of 30 min. The reaction mixture was stirred overnight at room temperature while the $NaBH_4$ pellets slowly dissolved. At this time the reaction mixture was poured into water and the resulting solution extracted with CH_2Cl_2. The organic extract was washed with aqueous NaCl and dried over $MgSO_4$. Evaporation of the CH_2Cl_2 furnished a residue which was crystallized from $CHCl_3$/hexane to give 4.67 g (66%) of ethyl 6,7-dichloro-2,3-dihydro-5-(4-hydroxybenzyl)-2-benzofurancarboxylate, mp 104–105 °C. Anal. ($C_{18}H_{16}Cl_2O_4$) C, H, O. 2-Chloro-*N*-(hydroxymethyl)acetamide (1.41 g, 11 mmol) was added, in small portions, to a stirred solution of the above ester (4.1 g, 11 mmol) in 36 mL of acetic acid and 4 mL of concentrated H_2SO_4 at 10–15 °C. The mixture was stirred at room temperature overnight and poured into ice water. The solid that formed was extracted into EtOAc and the resulting solution washed with aqueous NaCl and dried over $MgSO_4$. The residue obtained by evaporating the EtOAc was dissolved in 150 mL of absolute EtOH containing 0.75 mL of concentrated H_2SO_4. After the mixture stood overnight at room temperature, the EtOH was partially evaporated under reduced pressure and the residue distributed between CH_2Cl_2 and aqueous NaCl. The organic layer was washed several times with aqueous NaCl, dried over $MgSO_4$, and evaporated. The crude ethyl ester was chromatographed on a silica gel column eluting with benzene/EtOAc (3:1) to give 2.41 g (45%) of **12a**, mp 185–187 °C. Anal. ($C_{21}H_{20}Cl_3NO_5$) C, H, N.

Ethyl 6,7-dichloro-2,3-dihydro-5-[3,5-bis[(chloroacetamido)methyl]-4-hydroxybenzyl]-2-benzofurancarboxylate (12b) was also isolated from the chromatographic separation described above for **12a**. The product obtained after evaporating the chromatographic fractions was recrystallized from $CHCl_3$/hexane to give 480 mg (7.4%) of **12b**, mp 156–160 °C. Anal. ($C_{24}H_{24}Cl_4NO_6$) C, H, N.

Ethyl 6,7-Dichloro-2,3-dihydro-5-[3-(aminomethyl)-4-hydroxybenzyl]-2-benzofurancarboxylate Hydrochloride (13a). A solution of **12a** (1.71 g, 3.6 mmol) in 80 mL of EtOH and 20 mL of concentrated HCl was heated at reflux for 4 h. The mixture was evaporated to dryness and the residue was chased several times with EtOH. Trituration with Et_2O gave 1.4 g (89%) of **13a**, mp 227–230 °C. Anal. ($C_{19}H_{20}Cl_3NO_4 \cdot {}^1/_4H_2O$) C, H, N.

Ethyl 6,7-dichloro-2,3-dihydro-5-[3,5-bis(aminomethyl)-4-hydroxybenzyl]-2-benzofurancarboxylate dihydrochloride (13b) was prepared in 89% yield from **12b** by using the procedure described for **13a**, mp 215–219 °C dec. Anal. ($C_{20}H_{24}Cl_4N_2O_4$) C, H, N.

6,7-Dichloro-2,3-dihydro-5-[3-(aminomethyl)-4-hydroxybenzyl]-2-benzofuranmethanol Hydrochloride (14). To a solution of **12a** (0.7 g, 1.48 mmol) in 50 mL of EtOH was added 0.67 g (1.78 mmol) of $NaBH_4$ portionwise over a 1-h period. After stirring for 21 h, the reaction mixture was distributed between EtOAc and aqueous NaCl. The organic layer was dried and evaporated to a residue. Chromatography on silica gel eluting with EtOAc/benzene mixtures gave 510 mg (80%) of the dihydrobenzofuran-2-methanol derivative as a glass. A solution of this material (500 mg) in 20 mL of EtOH and 100 mL of 3 N HCl was heated at reflux for 4 h. Partial evaporation followed by cooling caused the product to crystallize. Filtration gave 400 mg (88%) of **14**, mp 227–230 °C. Anal. ($C_{17}H_{18}Cl_3NO_3 \cdot {}^1/_3H_2O$) C, H, N.

Registry No. **3**, 90246-58-5; **4a**, 90246-55-2; **4b**, 95249-99-3; **5a**, 92285-33-1; **5b**, 95250-00-3; **6**, 95250-01-4; **7**, 95250-02-5; **8**, 95250-03-6; **9**, 95250-04-7; **10**, 95250-05-8; **11**, 95250-06-9; **12a**, 95250-07-0; **12b**, 95250-08-1; **13a**, 95250-09-2; **13b**, 95250-10-5; **14**, 95250-11-6; $ClCH_2C(O)NHCH_2OH$, 2832-19-1; acetaldoxime, 107-29-9; ethyl 6,7-dichloro-2,3-dihydro-5-[3-[(chloroacetamido)methyl]-4-hydroxybenzoyl]-2-benzofurancarboxylate, 95250-12-7; *N*-[(benzyloxycarbonyl)oxy]succinimide, 13139-17-8; 6,7-dichloro-2,3-dihydro-5-[3-[[(benzyloxycarbonyl)amino]methyl]-4-hydroxybenzoyl]-2-benzofurancarboxamide, 95250-13-8; 6,7-dichloro-2,3-dihydro-5-[3,5-[bis(dimethylamino)methyl]-4-hydroxybenzoyl]-2-benzofurancarboxylic acid, 95250-14-9; ethyl 6,7-dichloro-2,3-dihydro-5-(3-chloro-4-hydroxybenzoyl)-2-benzofurancarboxylate, 95250-15-0; ethyl 6,7-dichloro-2,3-dihydro-5-(4-hydroxybenzyl)-2-benzofurancarboxylate, 95250-16-1; 6,7-dichloro-2,3-dihydro-5-[3-[(chloroacetamido)methyl]-4-hydroxybenzyl]-2-benzofuranmethanol, 95250-17-2.