1–2, 2–4, and 4–6 h time intervals. Urine volume was measured and an aliquot taken from each sample. Each aliquot was centrifuged to remove suspended materials, 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 mean Na excretion values, expressed in milliequivalents kilograms^{-1} (6 h)$^{-1}$ with at least two dogs/dose.

Diuretic Activity in Cynomolgus Monkeys. Male and female cynomolgus (*Macaca fascicularis*) monkeys were deprived of food for 16–18 h prior to dosing and allowed H_2O ad libitum until dosing, six monkeys/dose. Each monkey was captured, restained, and weighed. A pediatric nasogastric tube was inserted through either nostril into the stomach in order to administer the oral dose of compound or vehicle. Immediately after dosing, a water load of 50 mL/kg of body weight was administered through the nasogastric tube; then the tube was withdrawn. The monkey was placed into a clean stainless steel metabolism cage. No food or H_2O was given during the subsequent 6 h of the experiment. Urine samples were collected into plastic bottles from the metabolism pans at 0–1, 1–2, 2–4, and 4–6 h after dosing. Volumes were measured and aliquots taken for analyses of electrolytes, uric acid, and glucose by standard methodologies.

Antihypertensive Activity.[18] Male SH rats (age 9–12 weeks, Lab Supply, Indianapolis, IN) were trained for use in wire mesh restaining cylinders. The rats were warmed for 30 min at 36 °C prior to measurement of blood pressure (BP) and heart rate. An occluding cuff, attached to a programmed sphygmomanometer, was placed on the rat's tail near the base. Pressure in the cuff was programmed to increase and decrease automatically in cycles from 0 to 250 mmHg at the rate 10 mmHg/s. Cycle time was 50 s, with 10 s between cycles. A photocel placed on the tail distal to the cuff was used to detect the pulse from blood flow with each heart beat. Occlusion pressure measured at disappearance and reappearance of the pulse from five interference-free signals was used to estimate the systolic BP. Heart rate was determined from an expanded tracing with a Grass Model 7 polygraph. Oral dosings of compounds suspended in 0.2% methylcellulose in H_2O were administered by gavage. Only rats with a minimum control pressure of 170 mmHg or greater were used.

(18) Zaugg, H. E.; Kyncl, J. *J. Med. Chem.* **1983**, *26*, 214.

Acknowledgment. The microanalyses were done by J. Hood, IR spectra by W. Washburn and R. Anderson, NMR spectra by Dr. M. Nuss, R. Stanaszek, and M. Cirovic, hydrogenation by D. Dunnigan, and P. Morse assisted with the pharmacological tests.

Registry No. **1**, 82241-43-8; **1** (ethyl ester, 4′-nitro deriv.), 82241-42-7; **2**, 92270-34-3; **2** (ethyl ester, 4′-nitro deriv.), 92270-81-0; **3**, 92270-35-4; **3** (ethyl ester, 4′-nitro deriv.), 92270-84-3; **4**, 62967-00-4; **4** (ethyl ester, 4′-nitro deriv.), 75554-04-0; **5**, 82241-40-5; **5** (ethyl ester, 4′-nitro deriv.), 92270-80-9; **6**, 82241-54-1; **6** (ethyl ester, 4′-nitro deriv.), 82241-52-9; **7**, 78235-22-0; **8**, 78235-69-5; **8**·HCl, 78235-21-9; **9**, 78235-74-2; **9**·HCl, 78235-23-1; **10**, 92270-63-8; **10**·HCl, 78235-24-2; **11**, 92270-64-9; **11**·HCl, 78235-25-3; **12**, 92270-65-0; **12**·HCl, 78235-28-6; **13**, 78235-27-5; **14**, 92270-36-5; **15**, 78235-55-9; **15**·HCl, 78235-32-2; **16**, 78235-34-4; **16**·3HCl, 92270-37-6; **17**, 92270-66-1; **17**·2HCl, 78235-35-5; **18**, 92270-67-2; **18**·2HCl, 78235-59-3; **19**, 92270-68-3; **19**·2HCl, 78235-38-8; **20**, 92270-69-4; **20**·2HCl, 78235-40-2; **21**, 92270-83-2; **21**·2HCl, 78235-36-6; **22**, 78235-41-3; **23**, 82241-63-2; **23**·HCl, 82241-44-9; **24**, 82241-64-3; **24**·HCl, 92270-38-7; **25**, 82241-65-4; **25**·HCl, 92270-39-8; **26**, 78235-73-1; **26**·HCl, 78235-52-6; **27**, 78235-72-0; **27**·HCl, 78235-46-8; **28**, 78235-67-3; **28**·HCl, 78235-53-7; **29**, 82241-62-1; **29**·HCl, 82241-56-3; **30**, 78235-68-4; **30**·HCl, 78235-54-8; **31**, 82241-61-0; **31**·2HCl, 78235-47-9; **32**, 78235-15-1; **33**, 62967-00-4; **34**, 82241-55-2; **35**, 78235-16-2; **36**, 78235-17-3; **37**, 92270-40-1; **37** (x = H), 78235-49-1; **38**, 78235-70-8; **38**·HCl, 78235-48-0; **39**, 78235-71-9; **39**·HCl, 78235-50-4; **40**, 92270-70-7; **40**·HCl, 92270-41-2; **41**, 92270-71-8; **41**·HCl, 92270-42-3; **42**, 92270-43-4; **43**, 92284-30-5; **44**, 92270-44-5; **45**, 92270-45-6; **46**, 92270-46-7; **47**, 92270-72-9; **47**·HCl, 92270-47-8; **48**, 92270-73-0; **48**·HCl, 92270-48-9; **49**, 92270-74-1; **49**·HCl, 92270-49-0; **50**, 92270-75-2; **50**·HCl, 92270-50-3; **51**, 92270-76-3; **51**·HBr, 92270-51-4; **54**, 92270-52-5; **55**, 92270-53-6; **56**, 85297-76-3; **57**, 92270-54-7; **58**, 92270-55-8; **59**, 92270-77-4; **59**·HBr, 92270-56-9; **60**, 92270-57-0; **61**, 92270-58-1; **62**, 92270-78-5; **62**·HCl, 92270-59-2; **63**, 92270-60-5; **64**, 92270-61-6; **65**, 92270-79-6; **65**·HCl, 92270-62-7; $(CH_3)_2NH$, 124-40-3; *c*-C_4H_8NH, 123-75-1; *c*-$C_5H_{10}NH$, 110-89-4; *c*-$HN(CH_2CH_2)_2O$, 110-91-8; *c*-$HN(CH_2CH_2)_2SO_2$, 39093-93-1; *N*-(ethoxymethyl)diethylamine, 7352-03-6; 2-chloro-*N*-(hydroxymethyl)acetamide, 2832-19-1; *N*-[(benzyloxycarbonyl)oxy]succinimide, 13139-17-8; 2-methyl-2-thiopseudourea sulfate, 867-44-7; (β-methoxyethoxy)methyl chloride, 3970-21-6; [2,3-dichloro-4-(3-methyl-4-hydroxybenzoyl)phenoxy]acetic acid, 82241-41-6; ethyl [2,3-dichloro-4-(3-methyl-4-nitrobenzoyl)phenoxy]acetate, 92270-82-1; Na, 7440-23-5.

[(Aminomethyl)aryloxy]acetic Acid Esters. A New Class of High-Ceiling Diuretics. 2. Modifications of the Oxyacetic Side Chain[1]

Jacob J. Plattner,* Anthony K. L. Fung, Jill R. Smital, Cheuk-Man Lee, Steven R. Crowley, Andre G. Pernet, Paul R. Bunnell, Steven A. Buckner, and Lawrence T. Sennello

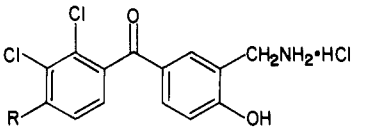
Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064. *Received November 10, 1983*

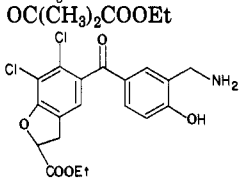
The discovery of high-ceiling natriuretic activity from a series of aminomethyl derivatives of ethyl [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetate prompted our continued investigation of this new class of (aryloxy)acetic acid diuretics. Systematic alteration of the oxyacetic side chain has shown that the carboxylic acid function is the active species in vivo and that the ethyl ester group serves as a prodrug to enhance oral absorption. Side-chain functional groups that are incapable of generating the carboxylic acid in vivo failed to impart diuretic activity to the target compounds. Additional side-chain modifications including homologation, methyl substitution, and heteroatom replacement are also described. Ring annelation of the oxyacetic side chain to a dihydrobenzofuran-2-carboxylic acid produced compound **32**, which displayed the highest level of saluretic activity for this series.

Recently, we reported[2] a new class of saluretic agents I that shows a high-ceiling profile in rats, dogs, and monkeys and that contains in one molecule elements of the phenoxyacetic acids[3] and the 2-(aminomethyl)phenols.[4]

0022-2623/84/1827-1587$01.50/0

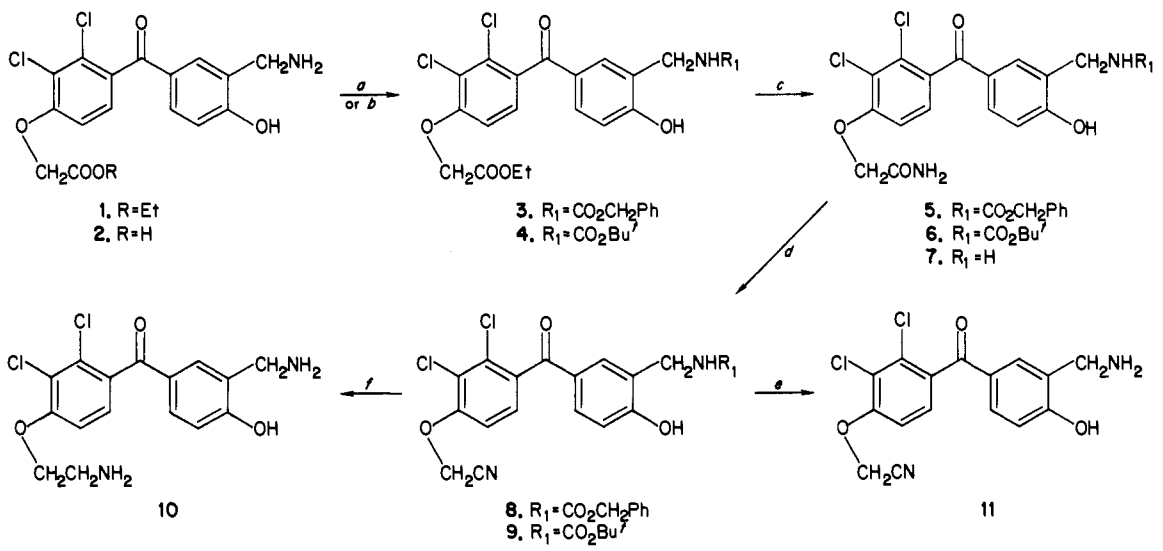
Table I. Variation of the Oxyacetate Side Chain in the Benzophenone Series



no.	rctn scheme	R	mp, °C	yield,[a] %	formula[b]	rat ED_2,[c] mg/kg
1	I	OCH_2COOEt	218–221	35[d]	$C_{18}H_{18}Cl_3NO_5$	2.5
2	I	OCH_2COOH	238–240 dec	95[e]	$C_{16}H_{14}Cl_3NO_5$	inactive
7	I	OCH_2CONH_2	258–260	62[f]	$C_{16}H_{15}BrCl_2N_2O_4$[g]	17.0
10	I	$OCH_2CH_2NH_2$	224–226	51[h]	$C_{16}H_{18}Cl_4N_2O_3$	16.2
11	I	OCH_2CN	225–230	58[i]	$C_{16}H_{12}Cl_2N_2O_3$[j]	inactive
19	II	OCH_2CH_2OH	127–130	25	$C_{16}H_{16}Cl_3NO_4 \cdot H_2O$	1.0
20	II	OCH_2COCH_3	217–220	41	$C_{17}H_{16}Cl_3NO_4$	28.5
22	III	$OCH(CH_3)COOEt$	122–124	12	$C_{19}H_{19}Cl_2NO_5$[j]	19.5
28	IV	OCH_3	138–140	54	$C_{15}H_{14}Cl_3NO_3$	inactive
29	IV	$OC(CH_3)_2COOEt$	180–185	22	$C_{20}H_{22}Cl_3NO_5$	inactive
32	V		224–227	25	$C_{19}H_{18}Cl_3NO_5$	0.11

[a] These yields are for the amidomethylation/hydrolysis except where otherwise noted. [b] All compounds gave satisfactory C, H, and N analyses. [c] The natriuretic potency of the compounds listed above is reported as an ED_2. This is the oral dose in mg/kg necessary to produce an excretion of 2 mequiv of Na^+/kg in the rat urine during the 4-h period after dosing. 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 2. [d] Reference 2. [e] Reference 2. Yield for hydrolysis of ethyl ester. [f] Yield for removal of Cbz group. [g] HBr salt. [h] Yield for hydrogenation/purification. [i] Yield for removal of *t*-Boc group. [j] Free base.

Scheme I



[a] $PhCH_2OCO_2NC(O)CH_2CH_2C(O)$. [b] Di-*tert*-butyl dicarbonate. [c] NH_3, EtOH. [d] $(CF_3CO_2)_2O$, pyridine. [e] CF_3COOH. [f] H_2, Pd-C.

Molecular features that were found to enhance diuretic activity for this series include (1) a phenolic hydroxylic function positioned para to the ketone, (2) an unsubstituted aminomethyl ortho to the phenol, and (3) the presence of chloro or methyl substituents at the 2- and/or 3-position of the oxyacetate aromatic ring. In this paper we have continued our systematic study of the structure–activity relationships within this series and describe the synthesis and biological activity of compounds in which the oxyacetic side chain of I has been modified.

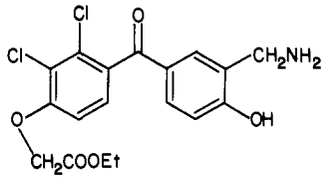
Chemistry. The compounds prepared for this study are listed in Table I and III and their syntheses are shown

(1) Portions of this work were presented at the 184th National Meeting of the American Chemical Society (see "Abstracts of Papers", 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 1982; American Chemical Society: Washington, DC, 1982) and the Drug Information Association Meeting, "Computer Assisted Chemistry in Drug Design", Philadelphia, PA, 1983.

(2) Lee, C-M.; Plattner, J. J.; Ours, C. W.; Horrom, B. W.; Smital, J. R.; Pernet A. G.; Bunnell, P. R.; ElMasry, S. E.; Dodge, P. W., preceding paper in this issue.

(3) Cragoe, E. J., Jr. "Diuretics. Chemistry, Pharmacology and Medicine"; Cragoe, E. J., Jr., Ed.; Wiley Interscience: New York, 1983; Chapter 4.

(4) Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Russo, H. F.; Watson, L. S. *J. Med. Chem.* **1982**, *25*, 735 and references cited therein.



I

in Schemes I–X. Several analogues in which the carboxylic ester group was altered were prepared from the parent ethyl ester 1 as depicted in Scheme I. Protection of the aminomethyl function in 1 as Cbz and *t*-Boc derivatives gave 3 and 4, respectively. These compounds underwent facile ammoniolysis at room temperature in EtOH to give the protected carboxamides 5 and 6. Deprotection of 5 using anhydrous HBr in acetic acid gave the phenoxyacetamide 7. The corresponding phenoxyacetonitrile 11 was prepared from 6 by dehydration of the amide to nitrile 9 followed by deprotection of the *t*-Boc group with trifluoroacetic acid in methylene chloride. Amine 10 was obtained by dehydration of amide 5 to 8 as described above, followed by catalytic hydrogenation with Pd/C catalyst.

The oxyacetone and oxyethanol side chain analogues were prepared as indicated in Scheme II. Friedel–Crafts reaction of *p*-methoxybenzoyl chloride and 2,3-dichloroanisole led to either 14 or 15 depending upon the reaction conditions. Selective alkylation[5] of 14 with 2-bromoethanol resulted in a reaction at the more acidic site and formation of adduct 17. Similar alkylation with bromoacetone produced 18. Introduction of the aminomethyl substituent on these intermediates was effected in a two-step process by employing a Tscherniac–Einhorn reaction[2,6] followed by hydrolysis of the chloroacetyl derivative.

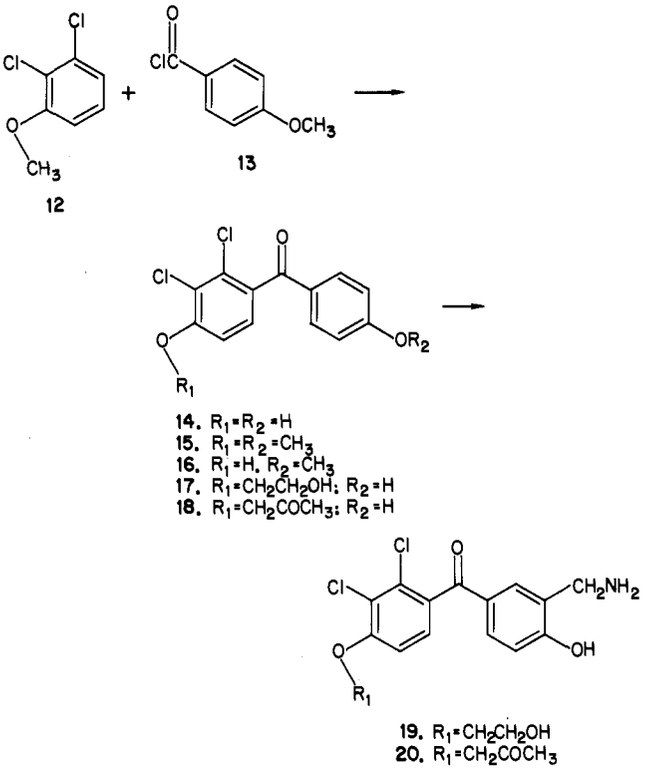
The α-methyl-α-phenoxyacetate analogue 22 was synthesized from phenol 16 in four steps as outlined in Scheme III. The requisite starting material 16 was obtained from 15 by selective dealkylation with $AlCl_3$ in refluxing methylene chloride.

Access to the methoxy and α,α-dimethylacetate analogues 28 and 29 began with Friedel–Crafts product 23 (Scheme IV). Direct replacement of the nitro function in 23 with a hydroxy group was accomplished by a nucleophilic aromatic displacement with the sodium salt of acetaldoxime[7] in DMF to give 24. Amidomethylation/hydrolysis of this compound then led to 28. To prepare 29, the anisole derivative 23 was demethylated to 25 with $AlCl_3$ and then converted to the α,α-dimethylacetate adduct 26 with 1,1,1-trichloro-2-methyl-2-propanol in the presence of powdered KOH.[8] Elaboration of 26 to 29 was achieved analogously to 28.

The ring annelated derivative 32 was synthesized as shown in Scheme V. Friedel–Crafts acylation of ethyl 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate[9] with *p*-nitrobenzoyl chloride gave 30. Nucleophilic displacement of the nitro group as above was followed by amidomethylation and hydrolysis to give 32.

Substituted phenylpropionate derivative 39 was obtained from 2,3-dichloro-4-hydroxybenzaldehyde 33[10]

Scheme II

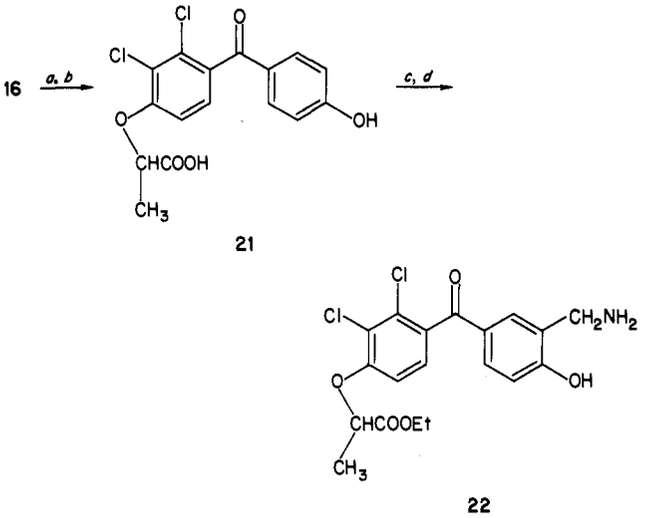


12 13

14. $R_1=R_2=H$
15. $R_1=R_2=CH_3$
16. $R_1=H$, $R_2=CH_3$
17. $R_1=CH_2CH_2OH$; $R_2=H$
18. $R_1=CH_2COCH_3$; $R_2=H$

19. $R_1=CH_2CH_2OH$
20. $R_1=CH_2COCH_3$

Scheme III



21

22

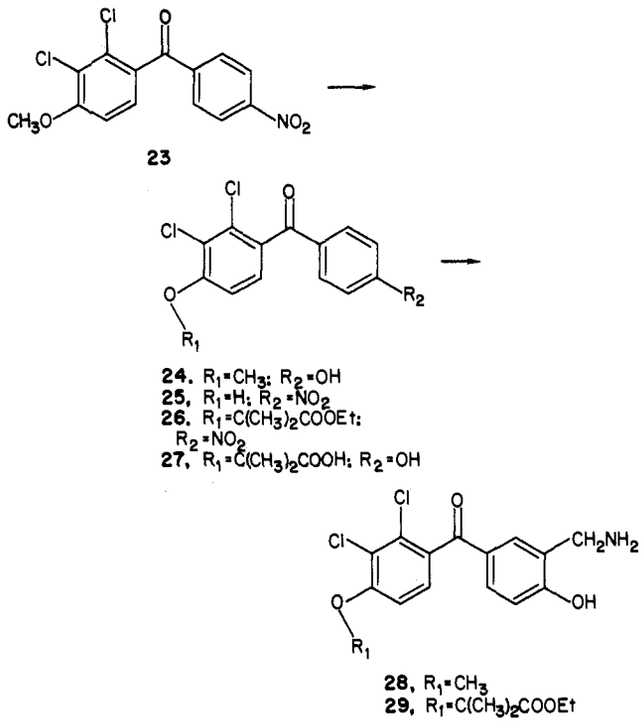
[a] $BrCH(CH_3)COOEt$, K_2CO_3. [b] HBr. [c] $ClCH_2CONHCH_2OH$, H_2SO_4, HOAc. [d] HCl, EtOH, Δ.

(Scheme VI). Attempted reaction of the sodium salt of 33 with *p*-fluoronitrobenzene did not proceed to any extent; however, the corresponding acetal 34 reacted smoothly in DMF solution to give ether 35 after acid-catalyzed deacetalization. Two-carbon homologation of 35 by the Wadsworth–Emmons procedure[11] gave cinnamate 36, which was reduced catalytically to 37. The phenol 38, obtained by a diazotization/hydrolysis sequence from 37, was converted to product 39 by using the standard Tscherniac–Einhorn procedure.[2,6]

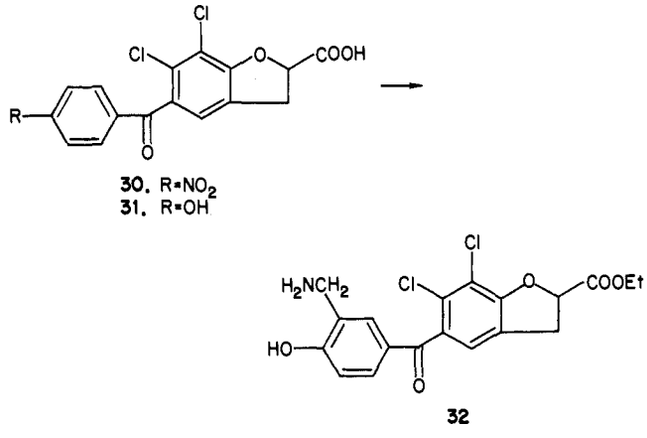
The preparation of the phenylacetate and benzoate analogues 44 and 47 is depicted in Schemes VII and VIII,

(5) Fung, A. K. L.; Morrison, D. E.; Pernet, A. G. U.S. Patent 4 268 691, 1981; *Chem. Abstr.* **1981**, *95*, 97357u.
(6) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.
(7) Knudsen, R. D.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343.
(8) Mieville, A. U.S. Patent 4 179 515, 1979; *Chem. Abstr.* **1978**, *88*, 22426n.
(9) 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.
(10) Bicking, J. B.; Holtz, W. J.; Watson, L. S.; Cragoe, E. J., Jr. *J. Med. Chem.* **1976**, *19*, 530.
(11) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

Scheme IV



Scheme V



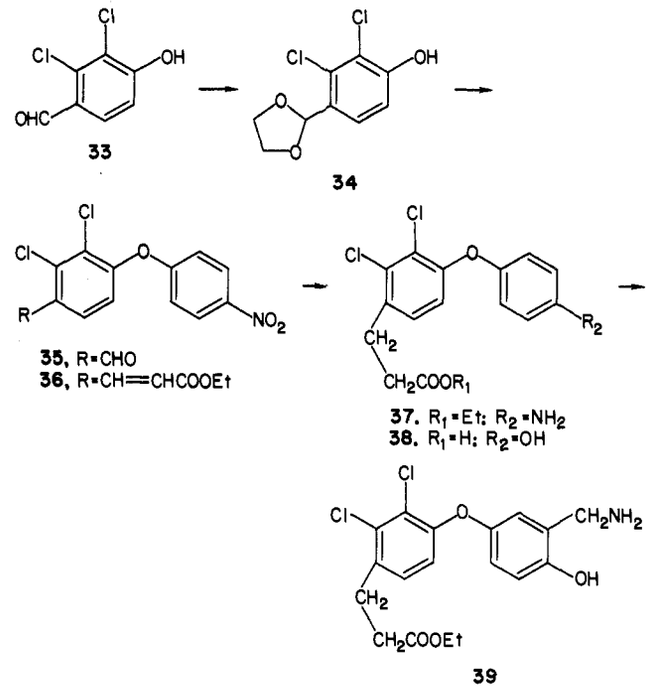
respectively. Starting with nitroaldehyde **35**, a one-carbon homologation was effected by $NaBH_4$ reduction, chlorination, and displacement with KCN to give **41**. Ethanolysis of **41** to ester **42** with EtOH–H_2SO_4 was followed by the standard amidomethylation procedure to give **44**. Analogue **47** was synthesized by first performing an oxidation directly on acetal **35a** with Jones reagent followed by esterification and then employing previously described transformations.

The thioacetate analogue **53** was elaborated as shown in Scheme IX. Alkylation of **48**[12] with ethyl bromoacetate was followed by demethylation and esterification to give **50**. Formation of diphenyl ether **51** was effected by a base-promoted displacement reaction of the sodium phenolate derivative with *p*-fluoronitrobenzene in DMF. Standard transformations as described above then gave analogue **53**.

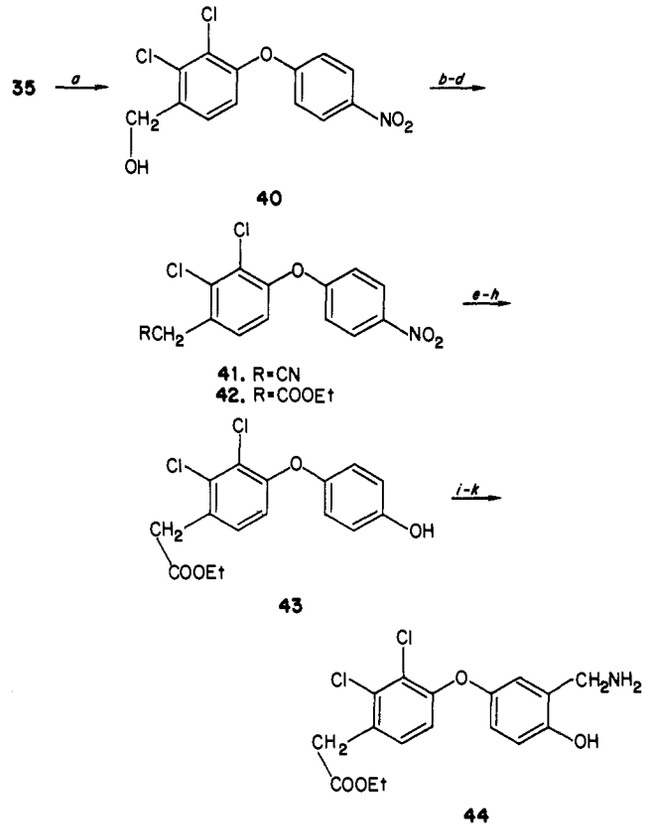
The phenoxybutyrate derivative **57** was synthesized as outline in Scheme X. Protection of the phenolic hydroxyl of **54**[12] as the benzyl ether was followed by reduction of the ester with diborane. The resulting substituted-phen-

(12) Plattner, J. J. U.S. Patent 4389416, 1983; *Chem. Abstr.* **1983**, *99*, 139494b.

Scheme VI



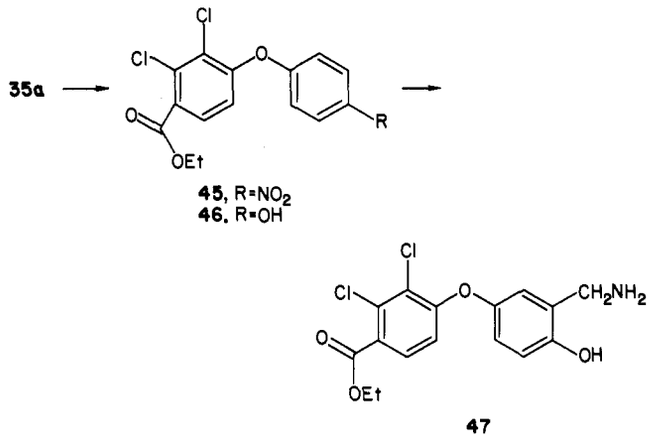
Scheme VII



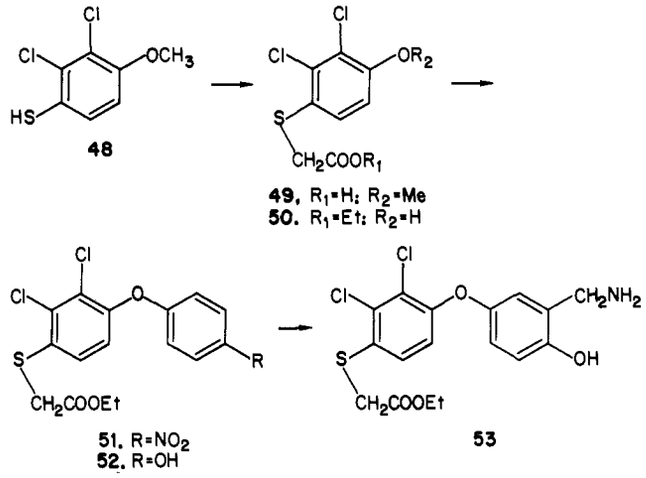
[a] $NaBH_4$. [b] $SOCl_2$, $CHCl_3$. [c] NaCN, EtOH. [d] EtOH, H_2SO_4, Δ. [e] H_2-Pd/C. [f] $NaNO_2$, HCl, H_2O. [g] H_2O, H_2SO_4, Δ. [h] EtOH, H_2SO_4. [i] $ClCH_2CONHCH_2OH$. [j] HCl, H_2O, EtOH, Δ. [k] EtOH, HCl.

oxyethanol derivative was dealkylated to **55** by a two-step sequence that involved mesylation with methanesulfonyl chloride followed by a reaction with excess sodium cyanide in DMF. The cyanide served a dual role in this reaction, first converting the mesylate to a phenoxypropionitrile derivative and then effecting a retro-Michael reaction to give **55**. Elaboration of **55** to **57** was achieved by alkylation

Scheme VIII

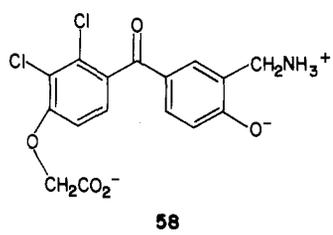


Scheme IX



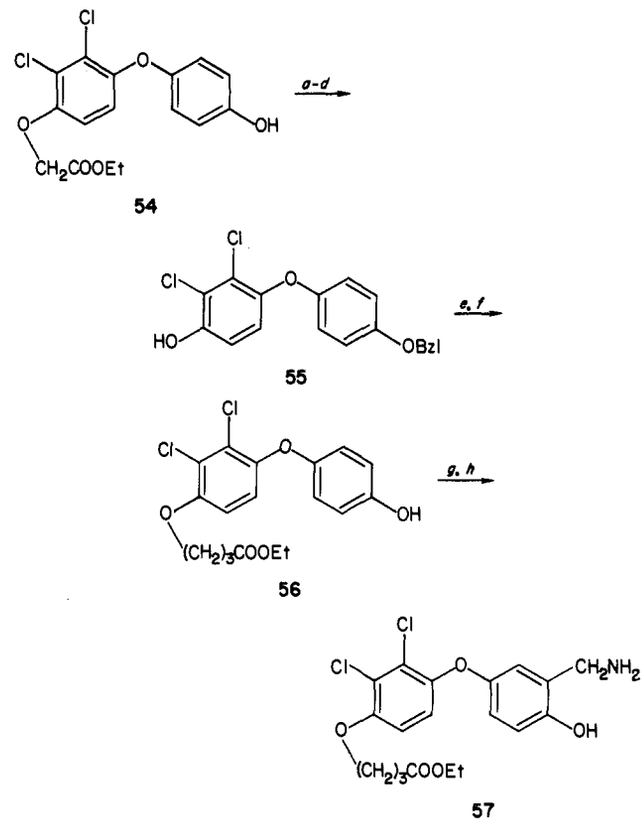
with ethyl 4-bromobutyrate, catalytic debenzylation, and application of the Tscherniac–Einhorn amidomethylation procedure.

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 or ED_5 as described in Tables I, II, and III. Previously we reported[2] that ethyl ester 1 displayed a high-ceiling diuretic profile in several species after oral administration, whereas the corresponding carboxylic acid 2 was essentially inactive by this route. Consideration of the pK_a values for 2[13] leads one to conclude that the ionic species 58 would predominate at physiological pH, and we expect that this highly charged form would be poorly absorbed from the gastrointestinal tract. Two lines of evidence indicate that the ethyl ester group serves as a prodrug in 58 to convert the negatively charged carboxyl group into a neutral form that enhances absorption but that the active species in vivo is the carboxylate ion. First, the deesterified compound 2 is a very potent diuretic intravenously but not orally. Second, we observed that rat and dog blood hydrolyze the ester in vitro in a few minutes. Additional support for the idea that the carboxylic function is essential for diuretic activity is found in the data of Table I. Methyl ether 28, which has no carboxylic acid function in the molecule, is devoid of saluretic activity. Nitrile 11 also lacks diuretic activity and would not be expected to readily form acid 2 in vivo. The carboxamide 7, amine 10, alcohol 19, and methyl ketone 20, on the other hand, all elicit some diuretic response.



(13) The pK_a values for compound 2 are 3, 6.4, and 10 for the carboxyl, phenol, and amine, respectively (Martin, Y. C., unpublished results).

Scheme X



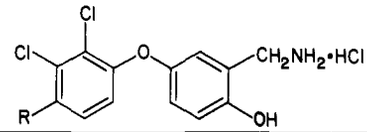
[a] $PhCH_2Br$, K_2CO_3. [b] B_2H_6. [c] CH_3SO_2Cl, Et_3N. [d] NaCN, DMF. [e] $Br(CH_2)_3COOEt$, K_2CO_3. [f] H_2, Pd–C. [g] $ClCH_2CONHCH_2OH$, HOAc, H_2SO_4. [h] HCl, EtOH, Δ.

Table II

compd	prodrug type	po dog ED_5,[a] mg/kg	Cl^- transport in frog cornea:[b] dose required for 50% inhibn, μM	rel amount of acid 2 appearing in dog plasma,[c] %
1	ester	1.0	14.6	100
7	amide	0.7	16.5	67
10	amine	8.0	no inhibn	25
19	alcohol	5.5	no inhibn	13
furosemide		6.2	64.0	
2		0.71[d]	8.4	

[a] The natriuretic potency of the compounds listed above is reported as an ED_5. This is the oral dose in mg/kg necessary to produce an excretion of 5 mequiv of Na^+/kg in the dog urine in the 6-h period after dosing. Details of the test protocol are described in ref 2. [b] Details for carrying out this procedure are described in ref 14. [c] The compounds were administered orally to dogs and blood samples were collected from 0–12-h postdosing. Ester 1, which is rapidly deesterified in plasma to acid 2, is assigned a value of 100%. Details of the test protocol are described in the text. [d] This is the bolus intravenous dose in mg/kg necessary to produce an excretion as described in footnote a.

Table III. Variation of the Oxyacetate Side Chain in the Diphenyl Ether Series



no.	rctn scheme	R	mp, °C	yield,[a] %	formula[b]	rat ED_2,[c] mg/kg
59		OCH_2COOEt	198–201	22[d]	$C_{17}H_{18}Cl_3NO_5$	0.80
39	VI	CH_2CH_2COOEt	197–198	31	$C_{18}H_{20}Cl_3NO_4$	10.70
44	VII	CH_2COOEt	218–219	26	$C_{17}H_{18}Cl_3NO_4$	21.50
47	VIII	$COOEt$	217–219	21	$C_{16}H_{16}Cl_3NO_4$	inactive
53	IX	SCH_2COOEt	185–186	33	$C_{17}H_{18}Cl_3NO_4S$	1.22
57	X	$O(CH_2)_3COOEt$	195–197	41	$C_{19}H_{22}Cl_3NO_5$	13.5

[a–c] See footnotes *a–c*, Table I. [d] Reference 12.

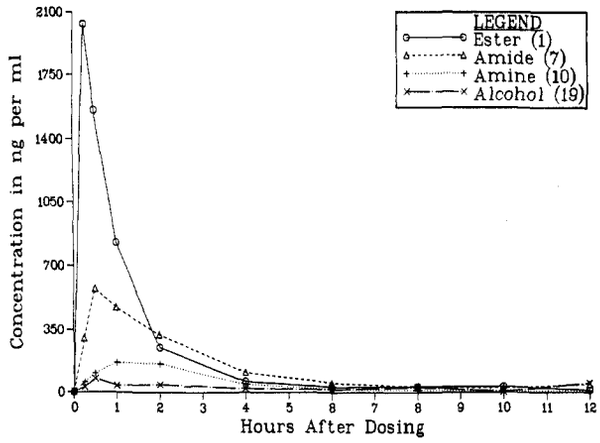


Figure 1. Mean dog plasma levels of acid **2** after oral administration of ester **1**, amide **7**, amine **10**, and alcohol **19**.

To confirm the possibility of a metabolic conversion to carboxylic acid **2**, several additional experiments were carried out on compounds **1**, **7**, **10**, and **19** (Table II). In one study, the effective oral diuretic dose of each compound was determined in dogs and is represented as an ED_5 as described in Table II. A second study was carried out in dogs to compare the circulating levels of acid **2**, following the oral administration of each compound at equimolar doses. Blood samples were collected from 0 to 12 h postdosing, and the experiment was conducted with use of a complete crossover design. The time–action curves for this study are shown in Figure 1. On the basis of the areas under the 0–12-h curves as determined by HPLC analysis, it was shown that the amide, amine, and alcohol delivered about 67%, 25%, and 13% of carboxylic acid **2**, respectively, to the circulation compared to ester **1** (100%). From this, it is concluded that at least some of the in vivo activities of **1**, **7**, **10**, and **19** are the result of metabolism to **2**, which is known to have intrinsic pharmacological activity. Analogue **20** was not evaluated in this study, and consequently, no definitive conclusion can be drawn regarding its metabolic conversion to acid **2**.

We have also examined several of these compounds for their ability to block chloride transport across the bullfrog cornea. The amphibian cornea is known to transport chloride actively[14] and has been used as a model of the ascending limb of Henle in the mammalian kidney, where loop diuretics are known[15] to act. As seen from the data in Table II, carboxylic acid **2** elicits a strong effect in blocking chloride transport, supporting the notion that the carboxyl function is the active species in vivo. The inhibition caused by ethyl ester **1** and carboxamide **7** would suggest that these prodrugs may also possess inherent diuretic activity; however, it is quite possible that an esterase and/or amidase enzyme may be present in the corneal preparation and may, in fact, be generating **2**. The inactivity of the amine **10** and alcohol **19** in this system is consistent with the expectation that an oxidative conversion of these compounds to **2** would be required and that the necessary oxidative enzymes are not present in the corneal preparation.

The effect of introducing alkyl substituents on the oxyacetate side chain is seen with compounds **22**, **29**, and **32** (Table I). Successive incorporation of methyl groups leads first to a reduction and then to a total elimination of saluretic activity. However, introduction of the alkyl substituent by ring annelation (compound **32**) resulted in a significant increase in natriuretic potency. These results parallel previous findings reported for tienilic acid[16] and the indeno[5,4-*b*]furan-2-carboxylic acids,[17] where ring annelation to a dihydrobenzofuran also caused a substantial increase in saliuretic potency. This large increase in potency upon ring annelation of the phenoxyacetic acids to the corresponding dihydrobenzofuran carboxylic acids most likely results from a highly favorable positioning of the essential carboxylic acid function. The absolute requirement of the carboxyl group in these compounds for diuretic activity has already been discussed, and it now appears that the conformation of the side chain also plays a critical role. The constraint imposed by the rigid dihydrobenzofuran ring apparently fixes the carboxyl group in an optimal spatial position.

Several additional modifications of the oxyacetic side chain were assessed in a subgroup of compounds in which an ether function linked the two aromatic rings. Table III reveals that the ether oxygen of the side chain may be replaced by sulfur with little change in activity whereas substitution by a methylene group causes a significant reduction in saluretic activity. Replacement of the oxygen by a direct linkage to give the corresponding phenylacetate was even less tolerated. Shortening the side chain to a benzoate ester eliminated activity altogether while lengthening the side chain to a phenoxybutyrate ester led to a reduction in saluretic activity.

Conclusion. The data presented above indicate that in the benzophenone series (1) the carboxylic acid function in these compounds is important for their diuretic activity, (2) prodrugs such as the corresponding ester, amide, or alcohol serve to facilitate oral absorption through the gut and then generate the carboxylic acid in vivo, and (3) alkyl

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substitution on the side chain diminishes diuretic activity unless accompanied by ring annelation, in which case a substantial potency enhancement is observed. In the diphenyl ether series, the data suggest that the oxygen atom in the side chain can be replaced by sulfur with maintenance of diuretic activity and that the distance between the aromatic ring and the carboxyl group of the side chain is an important factor.

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.

Ethyl [2,3-Dichloro-4-[3-[(benzyloxycarboxamido)methyl]-4-hydroxybenzoyl]phenoxy]acetate (3). To a stirred mixture of hydrochloride salt 1[2] (22.8 g, 0.052 mol) and *N*-[(benzyloxycarbonyl)oxy]succinimide (13.5 g, 0.054 mol) in 225 mL of CH_3CN was added 5.4 g (0.054 mol) of $KHCO_3$ in 60 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 22 g (79%) of **3**, mp 117–119 °C. Anal. ($C_{26}H_{23}Cl_2NO_7$) C, H, N.

Ethyl [2,3-Dichloro-4-[3-[(*tert*-butoxycarboxamido)methyl]-4-hydroxybenzoyl]phenoxy]acetate (4). This compound was prepared analogously to **3**, using di-*tert*-butyl dicarbonate in place of *N*-[(benzyloxycarbonyl)oxy]succinimide. The crude product was triturated with hexane to afford a 75% yield of pure **4**, mp 132–133 °C. Anal. ($C_{23}H_{25}Cl_2NO_7$) C, H. N.

[2,3-Dichloro-4-[3-[(*tert*-butoxycarboxamido)methyl]-4-hydroxybenzoyl]phenoxy]acetamide (6). A 20-g (0.04 mol) portion of **4** was dissolved in 300 mL of EtOH and anhydrous ammonia was passed into the solution for 4 h. After standing for 30 h at room temperature, the EtOH was evaporated and the residue was dissolved in 100 mL of cold MeOH. This solution was acidified by dropwise addition of cold, aqueous citric acid. The mixture was then diluted with H_2O and extracted with EtOAc. The organic extract was washed, dried, and evaporated to a solid product. Trituration with hexane gave 15.5 g (82%) of **6**, mp 131–133 °C. Anal. ($C_{21}H_{22}Cl_2N_2O_6$) C, H; N: calcd, 5.97; found, 5.14.

[2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]acetamide Hydrobromide (7). A 5-g (9.39 mmol) portion of **3** was dissolved in 100 mL of absolute EtOH and anhydrous ammonia was passed into the solution for 2 h. After standing overnight at room temperature, the EtOH was evaporated. The solid residue was dissolved in methyl Cellosolve (100 mL) and the solution acidified with concentrated HCl. The acidic solution was poured into 350 mL of cold H_2O and the resulting solid filtered and dried. Recrystallization from EtOH gave 3.5 g (72%) of **5**, mp 187–189 °C. A sample of **5** (2.0 g, 3.97 mmol) was added all at once to a 33% solution of HBr in anhydrous HOAc (10 mL). After 35 min, the reaction mixture was poured into 100 mL of ether and the resulting solid product filtered. Trituration with ether furnished 1.1 g (62%) of **7**, mp 258–260 °C. Anal. ($C_{16}H_{15}BrCl_2N_2O_4$) C, H, N.

[2,3-Dichloro-4-[3-[(benzyloxycarboxamido)methyl]-4-hydroxybenzoyl]phenoxy]acetonitrile (8). To a solution of 2.75 g (5.46 mmol) of **5** dissolved in 15 mL of THF and 5 mL of CH_2Cl_2 was added 1.8 mL of pyridine. To the resulting mixture cooled in an ice bath was added 1.69 mL (12 mmol) of trifluoroacetic anhydride dropwise over a period of 40 min. The reaction was then stirred for 2.5 h at room temperature and poured into brine solution. Extraction with CH_2Cl_2 was followed by washing the organic phase with aqueous citric acid and aqueous $NaHCO_3$. Evaporation of the CH_2Cl_2 gave a viscous liquid which was crystallized from hexane/EtOAc to give 2 g (75%) of **8**, mp 157–158 °C. Anal. ($C_{24}H_{18}Cl_2N_2O_5$) H, N; C: calcd, 59.40; found 58.49.

[2,3-Dichloro-4-[3-[(*tert*-butoxycarboxamido)methyl]-4-hydroxybenzoyl]phenoxy]acetonitrile (9). This compound was prepared analogously to **8** in 70% yield, mp 154–156 °C. Anal. ($C_{21}H_{20}Cl_2N_2O_5$) C, H, N.

[4-(2-Aminoethoxy)-2,3-dichlorophenyl][3-(aminomethyl)-4-hydroxyphenyl]methanone Dihydrochloride (10). A 10-g (0.021 mol) sample of **8** was dissolved in 200 mL of methyl Cellosolve and hydrogenated in a Parr apparatus over 1 g of 5% Pd–C in the presence of 8 mL of 6 N hydrochloric acid. The catalyst was filtered and the solvent was evaporated to give 8.8 g of crude dihydrochloride salt after trituration with ether. This material was purified by conversion to the bis-*t*-Boc derivative followed by high-pressure liquid chromatography (HPLC). The bis-*t*-Boc derivative was obtained by treating the above salt with 10.0 g (0.046 mol) of di-tert-butyl dicarbonate in 50 mL of DMF containing 6.4 mL of triethylamine. After 1 h at room temperature, the reaction was poured into brine solution and extracted with CH_2Cl_2. The organic extract was washed with brine solution and dried over $MgSO_4$. Evaporation of the CH_2Cl_2 furnished the bis-*t*-Boc compound which was purified on a Waters PrepPAK-500 silica gel cartridge (57 mm i.d. × 30 cm) eluting with 20/80 hexane–Et_2O to give 5.9 g of pure material as an oil. The *t*-Boc groups were removed by stirring 5.5 g of this material in 50 mL of saturated ethanolic HCl. After 5 h the precipitated salt was filtered and washed with ether to give 3.26 g of pure product, mp 224–226 °C. Anal. ($C_{16}H_{18}Cl_4N_2O_3$) C, H, N.

[2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]acetonitrile (11). A 3.5-g (7.75 mmol) portion of **9** was dissolved in 50 mL of 10% trifluoroacetic acid in CH_2Cl_2 at 0–5 °C. The reaction mixture was stirred at 0–5 °C for 6 h and then poured into 200 mL of hexane. The trifluoroacetate salt separated as a gum and was separated from the solvent by decantation. After drying in vacuo, the salt was dissolved in cold water and treated with 25 mL of saturated aqueous $NaHCO_3$. The solid free base that precipitated was filtered, dried, and triturated with ether to give 1.58 g (58%) of **11**, mp 225–230 °C. Anal. ($C_{16}H_{12}Cl_2N_2O_3$) C, H, N.

(2,3-Dichloro-4-methoxyphenyl)(4-methoxyphenyl)methanone (15). 2,3-Dichloroanisole (17.7 g, 0.1 mol) and *p*-methoxybenzoyl chloride (17.1 g, 0.1 mol) were dissolved in 150 mL of CH_2Cl_2 and $AlCl_3$ (13.3 g, 0.1 mol) was added portionwise at 0–5 °C. The reaction was stirred at room temperature for 15 h and then poured into ice and 6 N HCl. The resulting precipitate was filtered and dried to give the crude product. Trituration with MeOH afforded 25 g (80%) of **15**, mp 158–159 °C. Anal. ($C_{15}H_{12}Cl_2O_3$) C, H.

[2,3-Dichloro-4-(2-hydroxyethoxy)phenoxy](4-hydroxyphenyl)methanone (17). A solution of **14**[5] (28.3 g, 0.1 mol) in 200 mL of absolute EtOH was treated with sodium metal (2.3 g, 0.1 mol) and heated at reflux for 2 h. The solid sodium salt that precipitated was filtered and washed successively with EtOH and Et_2O. To a solution of this salt in DMF (200 mL) was added 2-bromoethanol (13.7 g, 0.11 mol) and the resulting mixture heated at 110–120 °C. After 8 h, the cooled reaction mixture was poured into H_2O, which caused the product to separate as an oil. The aqueous solution was decanted from the oil and the residue was taken into EtOAc and dried over $MgSO_4$. Evaporation of the solvent was followed by chromatography of the residue on silica gel eluting with Et_2O to give 13 g (40%) of **17**: mp 174–176 °C; NMR (Me_2SO-d_6) δ 3.8 (2 H, m, CH_2OH), 4.3 (2 H, t, J = 4 Hz, $ArOCH_2$), 7.0–7.6 (6 H, aromatic).

[2,3-Dichloro-4-(2-oxopropoxy)phenyl](4-hydroxyphenyl)methanone (18). A mixture of **14**[5] (6.7 g, 0.0237 mol) and anhydrous K_2CO_3 (1.7 g, 0.0123 mol) in 50 mL of DMF was heated at 60 °C for 20 min. At this time, bromoacetone (3.25 g, 0.0237 mol) was added and heating was continued at 120 °C for 3 h. The cooled reaction was poured into H_2O and the resulting mixture extracted with Et_2O. The organic extract was washed several times with aqueous NaCl, dried, and evaporated. Chromatography of the residue on silica gel eluting with EtOAc/hexane mixtures gave 4 g (50%) of **18**, mp 145–148 °C. Anal. ($C_{16}H_{12}Cl_2O_4$) C, H.

[3-(Aminomethyl)-4-hydroxyphenyl][2,3-dichloro-4-(2-hydroxyethoxy)phenyl]methanone (19). Compound **17** (6 g, 0.0184 mol) was added portionwise to stirred, concentrated H_2SO_4 (30 mL) at room temperature in the course of 20 min. With

cooling to 10–15 °C, 2-chloro-*N*-(hydroxymethyl)acetamide[18] (2.3 g, 0.0186 mol) was added in one portion and the reaction mixture then stirred at 10–15 °C. After 2.5 h, the reaction was poured onto 150 g of ice and the resulting mixture extracted with EtOAc. The organic portion was washed, dried, and evaporated to give an amorphous solid. Trituration with ether was followed by recrystallization from EtOH to give 2.4 g of the (chloroacetamido)methyl derivative, mp 178–180 °C. A 2.3-g (5.3 mmol) portion of this compound dissolved in 15 mL of concentrated HCl and 20 mL of EtOH was heated at reflux for 5.5 h and then evaporated to dryness. Trituration of the residue with cold EtOH gave 1.8 g (25% from **17**) of **19**, mp 127–130 °C. Anal. ($C_{16}H_{16}Cl_3NO_4 \cdot H_2O$) H, N; C: calcd, 46.76; found, 46.26.

[3-(Aminomethyl)-4-hydroxyphenyl][2,3-dichloro-4-(2-oxopropoxy)phenyl]methanone Hydrochloride (20). 2-Chloro-*N*-(hydroxymethyl)acetamide (0.48 g, 3.9 mmol) was added, in small portions, to a stirred solution of **18** (1.26 g, 3.72 mmol) in 15 mL of HOAc and 4.5 mL of concentrated H_2SO_4 at 10–15 °C. The mixture was stirred at room temperature overnight and poured into ice water. The resulting mixture was extracted with EtOAc and the organic phase was washed with aqueous NaCl and dried over $MgSO_4$. The residue obtained by evaporating the EtOAc was chromatographed on silica gel eluting with EtOAc/hexane mixtures to give 0.78 g (47%) of the chloroacetamido derivative, mp 173–175 °C. A 0.65-g (1.46 mmol) sample of this compound was heated at reflux in 4 mL of concentrated HCl and 9 mL of EtOH. After 4 h, the solvent was evaporated and the residue triturated with Et_2O to give 0.52 g (88%) of **20**, mp 217–220 °C. Anal. ($C_{17}H_{16}Cl_3NO_4$) C, H, N.

2-[2,3-Dichloro-4-(4-hydroxybenzoyl)phenoxy]propionic Acid (21). A mixture of **15** (16 g, 0.052 mol) and $AlCl_3$ (13.8 g, 0.104 mol) was refluxed for 5 h in 250 mL of CH_2Cl_2. After cooling, the reaction was poured onto ice and the resulting mixture extracted with CH_2Cl_2. The organic layer was extracted with 2 N NaOH, the aqueous portion was acidified with concentrated HCl, and the resulting mixture was extracted with CH_2Cl_2. Evaporation of the CH_2Cl_2 gave a crude product which was triturated with hexane to give 7 g (42%) of **16**, mp 172–174 °C. Ethyl 2-bromopropionate (11.8 g, 0.065 mol) was added within a period of 2 h to a stirred, refluxing mixture of **16** (14.9 g, 0.05 mol) and powdered K_2CO_3 (9.7 g, 0.07 mol) in acetone (250 mL). After refluxing 48 h, the hot mixture was filtered and the filtrate was evaporated. The residue was heated at reflux with 48% HBr (350 mL) for 24 h, diluted with H_2O, filtered, and dried to yield 17.2 g (83%) of **21**: mp 208–212 °C; NMR (Me_2SO-d_6) δ 1.58 (3 H, d, J = 7 Hz, CH_3), 5.13 (1 H, q, J = 7 Hz, ArOCH), 6.86–7.73 (6 H, m, aromatic).

Ethyl 2-[2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]propionate (22). Amidomethylation of **21** was carried out in methanesulfonic acid by the procedure described for **20** to give the corresponding (chloroacetamido)methyl derivative in which the ester group had been hydrolyzed. The compound was esterified by stirring a 4-mmol sample overnight in 50 mL of EtOH containing 5 drops of concentrated H_2SO_4. Partial evaporation of the EtOH and aqueous workup of the residue gave the esterified product, which was purified on silica gel eluting with EtOAc/benzene mixtures. Hydrolysis of the chloroacetyl group by the procedure described for **20** gave the hydrochloride salt of **22**. The corresponding free base was prepared by dissolution of the salt in H_2O, neutralization with aqueous $KHCO_3$, and extraction of the mixture with CH_2Cl_2. The organic extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from EtOH to give a 12% yield (from **21**) of **22**, mp 122–124 °C. Anal. ($C_{19}H_{19}Cl_2NO_5$) C, H, N.

(2,3-Dichloro-4-methoxyphenyl)(4-nitrophenyl)methanone (23) was prepared from 2,3-dichloroanisole and *p*-nitrobenzoyl chloride in the same manner as **15** in 83% yield, mp 197–200 °C. Anal. ($C_{14}H_9Cl_2NO_4$) C, H, N.

(2,3-Dichloro-4-methoxyphenyl)(4-hydroxyphenyl)-methanone (24). Compound **23** (2.93 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 solid product that precipitated was filtered, washed well with H_2O, and dried. Trituration with Et_2O gave 2 g (75%) of **24**, mp 215–217 °C. Anal. ($C_{14}H_{10}Cl_2O_3$) C, H.

(2,3-Dichloro-4-hydroxyphenyl)(4-nitrophenyl)methanone (25). A mixture of **23** (8.6 g, 26.4 mmol) and $AlCl_3$ (8.8 g, 66 mmol) in 53 mL of 1,2-dichloroethane was heated at reflux for 1.5 h. After cooling, the reaction mixture was poured onto ice and concentrated HCl. The solid product was filtered, washed well with H_2O, and dried to give 7.85 g (95%) of **25**, mp 201–204 °C. Anal. ($C_{13}H_7Cl_2NO_4$) C, H, N.

Ethyl 2-[2,3-Dichloro-4-(4-nitrobenzoyl)phenoxy]-2-methylpropionate (26). A solution of 1,1,1-trichloro-2-methyl-2-propanol (19.5 g, 0.1 mol) in acetone (400 mL) was added within a period of 20 min to a stirred mixture of **25** (19.4 g, 0.062 mol) and crushed KOH (22.4 g, 0.4 mol) in acetone (500 mL). The mixture was refluxed for 15 h, cooled, and filtered. The filtrate was evaporated, the residue was dissolved in H_2O, acidified with concentrated HCl, and extracted with Et_2O. The ether solution was washed with 10% of $NaHCO_3$, and the bicarbonate solution was acidified with concentrated HCl and extracted with Et_2O. After evaporation, the residue was converted to the ethyl ester by heating with EtOH and HCl gas and purified by chromatography on silica gel eluting with CH_2Cl_2 to give 8.9 g (36%) of **26**, mp 118–120 °C. Anal. ($C_{19}H_{17}Cl_2NO_6$) C, H, N.

2-[2,3-Dichloro-4-(4-hydroxybenzoyl)phenoxy]-2-methylpropionic acid (27) was obtained from **26** in the same manner as **24**. The crude product was purified by chromatography on silica gel eluting with 20% EtOH in CH_2Cl_2 to give the desired product in 61% yield, mp 169–171 °C. Anal. ($C_{17}H_{14}Cl_2O_5$) C, H.

[3-(Aminomethyl)-4-hydroxyphenyl][2,3-dichloro-4-methoxyphenyl]methanone hydrochloride (28) was obtained from **24** in the same manner as **20** in 54% yield, mp 138–140 °C. Anal. ($C_{15}H_{14}Cl_2NO_3$) H, N; C: calcd, 49.68; found, 49.27.

Ethyl 2-[2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]-2-methylpropionate Hydrochloride (29). 2-Chloro-*N*-(hydroxymethyl)acetamide (0.8 g, 0.0065 mol) was added portionwise to a stirred solution of **27** (1.8 g, 0.005 mol) in CH_3SO_3H (15 mL). The mixture was stirred at room temperature for 16 h and poured into ice H_2O. The solid was filtered and dissolved in EtOAc. The EtOAc solution was washed with H_2O, dried, and evaporated. The crude amidoalkylated product (2.4 g) was converted to the ethyl ester with EtOH and few drops of concentrated H_2SO_4 at room temperature and purified by chromatography on silica gel eluting with EtOAc/CH_3Cl_2 mixtures. The purified (chloroacetamido)methyl ethyl ester (0.78 g) was heated at reflux with EtOH (20 mL) and concentrated HCl (5 mL) for 3 h. The solution was evaporated and the residue recrystallized from EtOH–Et_2O to give 0.5 g (22%) of **29**, mp 180–185 °C. Anal. ($C_{20}H_{22}Cl_3NO_5$) H, N; C: calcd, 51.91; found, 51.43.

6,7-Dichloro-2,3-dihydro-5-(4-nitrobenzoyl)-2-benzofurancarboxylic Acid (30). A solution of 10 g (0.038 mol) of ethyl 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate[8] and 14.2 g (0.077 mol) of 4-nitrobenzoyl chloride in CH_2Cl_2 (40 mL) was placed on a cold bath with mechanical agitation and treated with $AlCl_3$ (15.3 g, 0.115 mol) portionwise over 5 min. The reaction mixture was heated at 80–90 °C for 1 h, diluted with 100 mL of CH_2Cl_2, and decomposed with 500 mL of ice and 60 mL of concentrated HCl. The resulting mixture was extracted with CH_2Cl_2 and the organic portion was washed with aqueous saturated NaCl and evaporated to dryness. The residue was dissolved in 200 mL of EtOH, treated with 200 mL of 1 N aqueous NaOH, and stirred at 60 °C overnight. The sodium salt was collected by filtration and distributed between ethyl acetate and dilute aqueous HCl. The organic layer was dried and evaporated to a residue which was recrystallized from acetonitrile/*n*-butyl chloride to give 7.26 g (50%) of **30**, mp 249–250 °C. Anal. ($C_{16}H_9Cl_2NO_6$) C, H, N.

6,7-Dichloro-2,3-dichloro-5-(4-hydroxybenzoyl)-2-benzofurancarboxylic acid (31) was obtained from **30** in the same manner as **24** in 73% yield, mp 192–194 °C. Anal. ($C_{16}H_{10}Cl_2O_5$) C, H.

(18) Einhorn, A.; Mauermayer, T. *Justus Liebigs Ann. Chem.* **1905**, *343*, 282.

Ethyl 6,7-dichloro-2,3-dihydro-5-[3-(aminomethyl)-4-hydroxybenzoyl]-2-benzofurancarboxylate hydrochloride (32) was prepared from **31** in 25% yield in an analogous procedure as described for **29**. The product was recrystallized from EtOH/Et_2O, mp 224–227 °C. Anal. ($C_{19}H_{18}Cl_3NO_5$) C, H, N.

2,3-Dichloro-4-hydroxybenzaldehyde Ethylene Acetal (34). A mixture of 31.7 g (0.166 mol) of 2,3-dichloro-4-hydroxybenzaldehyde,[10] ethylene glycol (14.5 g, 0.23 mol), and *p*-TsOH (0.5 g) in 300 mL of benzene was heated at reflux with a Dean–Stark trap for 1 h. The cooled solution was washed with H_2O, dried, and evaporated to give 33 g (84%) of **34**, mp 101–103 °C. This material was used without purification for the next step. **34**: NMR (Me_2SO-d_6) δ 4.03 (4 H, s, OCH_2CH_2O), 5.97 (1 H, s, ArCH), 6.95 (1 H, d, J = 9 Hz, aromatic), 7.35 (1 H, d, J = 9 Hz, aromatic).

2,3-Dichloro-4-(4-nitrophenoxy)benzaldehyde (35). To a suspension of NaH (7.19 g, 0.15 mol of a 50% mineral oil dispersion) in 160 mL of DMF was added **34** (32 g, 0.136 mol) portionwise in 15 min. The reaction mixture was stirred at room temperature under N_2 for 15 min and then 4-fluoronitrobenzene (21.1 g, 0.15 mol) was rapidly added. The resulting mixture was heated at 100 °C for 2.5 h, cooled, and poured into ice water. The gum that formed was separated from the H_2O and dissolved in CH_2Cl_2. The organic solution was washed with aqueous NaCl, dried, and evaporated. The residue was triturated with hexane to give 15.1 g (83%) of 2,3-dichloro-4-(4-nitrophenoxy)benzaldehyde ethylene acetal (**35a**), mp 94–95 °C. Anal. ($C_{15}H_{11}Cl_2NO_5$) C, H, N. The acetal group in **35a** was removed by stirring an 81.8-g (0.23 mol) portion in 2 L of acetone, 400 mL of H_2O, and 80 mL of H_2SO_4 for 48 h. The acetone was partly evaporated and the residue diluted with H_2O to precipitate the product. Trituration with EtOH gave 47 g (65%) of **35**, mp 143–145 °C. Anal. ($C_{13}H_7Cl_2NO_4$) C, H, N.

Ethyl 2,3-Dichloro-4-(4-nitrophenoxy)cinnamate (36). To a slurry of NaH (4.8 g, 0.1 mol of a 50% mineral oil dispersion) in 370 mL of THF was added under N_2 triethyl phosphonoacetate (22.4 g, 0.1 mol) dropwise over a period of 15 min. This mixture was stirred for 15 min at room temperature and then 30 g (0.096 mol) of **35** was added in small portions over a period of 10 min. After stirring for 1 h, the reaction mixture was poured into H_2O and the solid product was filtered and washed with EtOH to give 29.8 g (81%) of **36**: mp 145–145.5 °C; NMR ($CDCl_3$) δ 1.4 (3 H, t, J = 7 Hz, CH_3), 4.3 (2 H, q, J = 7 Hz, OCH_2), 6.3–8.3 (8 H, complex pattern, aromatic and olefinic).

Ethyl 3-[2,3-Dichloro-4-(4-aminophenoxy)phenyl]propionate Hydrochloride (37). A solution of **36** (30 g, 0.078 mol) in 1 L of EtOH was hydrogenated on the Parr apparatus over prewashed Raney nickel catalyst (12 g). After the hydrogen uptake was complete, the catalyst was removed by filtration through Celite and the filtrate mixed with ethanolic HCl. Evaporation of the EtOH gave 28.6 g (94%) of **37**: mp 181–183 °C; NMR (Me_2SO-d_6) δ 1.18 (3 H, t, J = 7 Hz, CH_3), 2.7 (2 H, multiplet, CH_2COO), 2.98 (2 H, multiplet, $ArCH_2$), 6.9–7.5 (6 H, multiplet, aromatic).

3-[2,3-Dichloro-4-(4-hydroxyphenoxy)phenyl]propionic Acid (38). To a stirred suspension of **37** (28.6 g, 0.073 mol) in 100 mL of concentrated H_2SO_4 and 400 mL of H_2O was added 5.3 g (0.077 mol) of $NaNO_2$ in 20 mL of H_2O while the internal temperature was kept below 5 °C. After stirring for 3 h at 0–5 °C, excess urea was added and the slurry of the diazonium salt was slowly poured into a boiling mixture of H_2O (1 L) and concentrated H_2SO_4 (500 mL). The clear solution was heated at reflux for 1 h and then cooled and the solid product filtered. Drying and trituration with hexane gave 23.9 g (99%) of **38**: mp 135–136 °C; NMR (Me_2SO-d_6) δ 2.63 and 2.95 (4 H total, set of multiplets, $ArCH_2CH_2COOH$), 6.65–7.3 (6 H, complex pattern, aromatic).

Ethyl 3-[2,3-dichloro-4-[3-(aminomethyl)-4-hydroxyphenoxy]phenyl]propionate hydrochloride (39) was prepared from **38** by using the procedure described for **29** except that HOAc–concentrated H_2SO_4 (9/1) was used as the reaction medium. The product was obtained in 31% yield after precipitation with EtOH/Et_2O, mp 197–199 °C. Anal. ($C_{18}H_{20}Cl_3NO_4$) C, H, N.

2,3-Dichloro-4-(4-nitrophenoxy)benzyl Alcohol (40). To a suspension of **35** (20.9 g, 0.067 mol) in 125 mL of EtOH was added 0.79 g (0.021 mol) of $NaBH_4$. After stirring for 20 min at room temperature, the mixture was poured into ice water. Careful acidification with dilute HCl was followed by partial evaporation under reduced pressure. The residue was extracted with CH_2Cl_2 and the organic portion was washed with aqueous NaCl, dried, and evaporated to a residue. Trituration with hexane gave 20 g (95%) of **40**, mp 133–135 °C. Anal. ($C_{13}H_9Cl_2NO_4$) C, H, N.

[2,3-Dichloro-4-(4-nitrophenoxy)phenyl]acetonitrile (41). To a solution of alcohol **40** (19.5 g, 0.062 mol) dissolved in 150 mL of $CHCl_3$ was added 18.5 mL of $SOCl_2$ all at once. The mixture was stirred at room temperature for 5 h and then evaporated to dryness. Trituration of the residue with hexane gave 19.6 g (95%) of the corresponding benzyl chloride derivative, mp 121.5–123 °C. Anal. ($C_{13}H_8Cl_3NO_3$) C, H, N. To a solution of this compound (19 g, 0.057 mol) in 150 mL of 95% EtOH was added NaCN (3.74 g, 0.076 mol) dissolved in 25 mL of H_2O. The mixture was heated at reflux for 8 h and then partly evaporated under reduced pressure. The aqueous residue was distributed between CH_2Cl_2 and saturated NaCl solution. The organic layer was dried and evaporated to a residue, which was chromatographed on silica gel eluting with CH_2Cl_2. There was obtained 13.6 g (74%) of **41**, mp 117–120 °C. Anal. ($C_{14}H_8Cl_2N_2O_3$) C, H, N.

Ethyl [2,3-Dichloro-4-(4-nitrophenoxy)phenyl]acetate (42). To a solution of **41** (6.5 g, 0.02 mol) in 15 mL of 95% EtOH was added 5 mL of concentrated H_2SO_4. The solution was heated at reflux for 24 h and then partly evaporated under reduced pressure. The residue was diluted with water and the aqueous mixture extracted with $CHCl_3$. The organic solution was washed with aqueous NaCl, dried over Na_2SO_4, and evaporated to provide 6.9 g (91%) of **42**: NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 6 Hz, CH_3), 3.80 (2 H, s, $ArCH_2$), 4.20 (2 H, t, J = 6 Hz, OCH_2), 6.8–7.4 (4 H, m, aromatic), 8.2 (2 H, d, J = 9 Hz, aromatic); IR ($CHCl_3$) 1730 cm^{-1}.

Ethyl [2,3-Dichloro-4-(4-hydroxyphenoxy)phenyl]acetate (43). A 25.5-g sample of **42** was hydrogenated over 5 g of Raney nickel catalyst as described for **37** to give 26.5 g of ethyl [2,3-dichloro-4-(4-aminophenoxy)phenyl]acetate hydrochloride. This material was diaotized as described for **38** to give **43** in 59% yield: NMR ($CDCl_3$) δ 1.23 (3 H, t, J = 8 Hz, CH_3), 3.70 (2 H, s, $ArCH_2$), 4.14 (2 H, q, J = 8 Hz, OCH_2), 6.4–7.4 (6 H, m, aromatic).

Ethyl [2,3-Dichloro-4-[3-(aminomethyl)-4-hydroxyphenoxy]phenyl]acetate hydrochloride (44) was obtained from **43** in the same manner as **39** in 26% yield, mp 218–219 °C. Anal. ($C_{17}H_{18}Cl_3NO_4$) H, N; C: calcd, 50.20; found, 49.66.

Ethyl 2,3-Dichloro-4-(4-nitrophenoxy)benzoate (45). To a stirred solution of 36.7 g (0.103 mol) of **35a** (see experimental details for **35**) dissolved in 2 L of acetone was added 240 mL of Jones reagent over a period of 90 min. After stirring for 16 h at room temperature, the reaction mixture was quenched with 1.2 L of EtOH and then partly evaporated under reduced pressure. The residue was diluted with 2 L of H_2O and the solid that formed was filtered and dried to give 32 g of crude acid. This material was dissolved in 250 mL of EtOH containing 1 mL of concentrated H_2SO_4 and heated at reflux for 15 h. Partial evaporation of the EtOH was followed by distribution of the residue between aqueous $NaHCO_3$ and CH_2Cl_2. Evaporation of the CH_2Cl_2 gave 13.4 g (37%) of **45** after trituration with hexane, mp 81–82 °C. Anal. ($C_{15}H_{11}Cl_2NO_5$) C, H, N.

Ethyl 2,3-Dichloro-4-(4-hydroxyphenoxy)benzoate (46). A 13.4-g (0.038 mol) sample of **45** was reduced with 3 g of Raney nickel as described for **37** to give 13.2 g (96%) of the amine hydrochloride, mp 188–195 °C. To this salt suspended in 200 mL of H_2O was added 100 mL of concentrated H_2SO_4 with cooling. The resulting mixture was treated with a solution of $NaNO_2$ (2.63 g, 0.038 mol) in 10 mL of H_2O over a period of 0.5 h while the internal temperature was kept at 0–5 °C. After stirring at 0–5 °C for 3.5 h, excess urea was added to destroy excess nitronium ion. The reaction mixture was then added in 15 min to a boiling mixture of H_2O (500 mL) and concentrated H_2SO_4 (250 mL). Heating at reflux was continued for 1 h followed by stirring at room temperature overnight. The solid product was filtered and dried to give 8.6 g (79%) of 2,3-dichloro-4-(4-hydroxyphenoxy)-benzoic acid. The acid was heated at reflux in EtOH/H_2SO_4 as described for **45** to give 8.77 g of ester **46** as a glass. This material was used without purification for the next step. **46**: NMR (Me_2SO-d_6) δ 1.40 (3 H, t, J = 7 Hz, CH_3), 4.42 (2 H, q, J = 7 Hz), 6.92 (4 H, s, aromatic), 6.73 (1 H, d, J = 9 Hz, aromatic), 7.75 (1 H, d, J = 9 Hz, aromatic).

Ethyl 2,3-dichloro-4-[3-(aminomethyl)-4-hydroxyphenoxy]benzoate hydrochloride (47) was obtained from **46** in the same manner as **29** except that HOAc/concentrated H_2SO_4 (10/1) was used as the reaction medium. The product was obtained in 21% yield after trituration with Et_2O, mp 217–219 °C. Anal. ($C_{16}H_{16}Cl_3NO_4$) C, H. N.

[(2,3-Dichloro-4-methoxyphenyl)thio]acetic Acid (49). A mixture of **48**[12] (59 g, 0.28 mol), ethyl bromoacetate (50 g, 0.3 mol), and pulverized K_2CO_3 (41 g, 0.3 mol) in 450 mL of 2-butanone was heated at reflux for 22 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue was triturated with hexane to give 60 g (73%) of ethyl [(2,3-dichloro-4-methoxyphenyl)thio]acetate, mp 53–55 °C. The corresponding acid was obtained by heating the ester (60 g, 0.2 mol) with KOH (26.4 g, 0.4 mol) in 500 mL of MeOH and 200 mL of H_2O at reflux for 3.5 h. After cooling, the solid potassium salt was filtered and dissolved in warm H_2O. Acidification with concentrated HCl was followed by filtration of the precipitate to give 40 g (75%) of **49**: mp 150–151 °C; NMR (Me_2SO-d_6) δ 3.8 (2 H, s, $ArSCH_2$), 3.9 (3 H, s, OCH_3), 7.1 (1 H, d, J = 8 Hz, aromatic), 7.3 (1 H, d, J = 8 Hz, aromatic).

Ethyl [(2,3-Dichloro-4-hydroxyphenyl)thio]acetate (50). A solution of **49** (35 g, 0.131 mol) in 500 mL of HOAc and 300 mL of 48% HBr was heated at reflux for 24 h. The reaction mixture was partially evaporated and the residue poured into cold H_2O. The solid product was filtered and dried to give 30 g (90%) of [(2,3-dichloro-4-hydroxyphenyl)thio]acetic acid after trituration with hexane, mp 177–180 °C. A 25-g (0.099 mol) portion of acid was esterified by stirring overnight in 350 mL of EtOH containing 1 mL of H_2SO_4. The EtOH was partially evaporated and the residue distributed between EtOAc and aqueous $NaHCO_3$. The organic layer was dried and evaporated to give 20 g (72%) of **50** after trituration with hexane: mp 125–126 °C; NMR (Me_2SO-d_6) δ 1.1 (3 H, t, J = 7 Hz, CH_3), 3.75 (2 H, s, $ArSCH_2$), 4.05 (2 H, q, J = 7 Hz, OCH_2), 6.9 (1 H, d, J = 8 Hz, aromatic), 7.3 (1 H, d, J = 8 Hz, aromatic).

Ethyl [[2,3-dichloro-4-(4-nitrophenoxy)phenyl]thio]acetate (51) was prepared from **50** by using the procedure described for **35** except that the reaction was run at 70 °C and the deacetalization step was omitted. The crude product was recrystallized from EtOH to give a 61% yield of **51**, mp 78–79 °C. Anal. ($C_{16}H_{13}Cl_2NO_5S$) C, H, N.

Ethyl [[2,3-dichloro-4-(4-hydroxyphenoxy)phenyl]thio]acetate (52) was obtained from **51** in the same manner as **46** in 29% yield, mp 100–102 °C. Anal. ($C_{16}H_{14}Cl_2O_4S$) H; C: calcd, 47.76; found, 47.28.

Ethyl [[2,3-dichloro-4-[3-(aminomethyl)-4-hydroxyphenoxy]phenyl]thio]acetate (53) was obtained from **52** in the same manner as **44** in 33% yield, mp 185–186 °C. Anal. ($C_{17}H_{17}Cl_2NO_4S$) C, H, N.

2,3-Dichloro-4-[4-(benzyloxy)phenoxy]phenol (55). A mixture of **54**[12] (15.8 g, 0.044 mol), benzyl bromide (9.4 g, 0.055 mol), and pulverized K_2CO_3 (12.6 g, 0.091 mol) in 150 mL of 2-butanone was heated at reflux for 2 h. The reaction mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was triturated with hexane to afford 17.5 g (89%) of ethyl [2,3-dichloro-4-[4-(benzyloxy)phenoxy]phenoxy]acetate, mp 74–75 °C. Anal. ($C_{23}H_{20}Cl_2O_5$) C, H. To a solution of 17.0 g (0.038) of the above ester in 100 mL of dry THF was added by dropwise addition 60 mL (0.06 mol) of diborane in THF. The reaction mixture was stirred at reflux under N_2 for 3 h and then left at room temperature overnight. After quenching with MeOH, the mixture was evaporated to dryness and the residue triturated with hexane to give 13.8 g (89%) of the corresponding phenoxyethanol derivative, mp 109–110 °C. To a solution of this compound (8.1 g, 0.02 mol) in 80 mL of CH_2Cl_2 containing 4.2 mL of Et_3N was added at 0 °C by dropwise addition 1.7 mL (0.022 mol) of mesyl chloride. After stirring for $^1/_2$ h at 0–5 °C, the organic solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl. The dried organic layer was evaporated, and the residue was triturated with hexane and recrystallized from EtOH to give 8.6 g (89%) of the mesylate. A 2-g (4.14 mmol) sample of the mesylate was mixed with NaCN (400 mg, 8.16 mmol) in 10 mL of DMF and stirred at room temperature for 48 h. The reaction mixture was poured into aqueous NaCl and extracted with CH_2Cl_2. The organic layer was washed with aqueous NaCl, dried over $MgSO_4$, and evaporated to a residue. Chromatography on silica gel eluting with 50% hexane/CH_2Cl_2 gave 0.67 g (45%) of **55**, mp 83–84 °C. Anal. ($C_{19}H_{14}Cl_2O_3$) C, H.

Ethyl 4-[2,3-Dichloro-4-(4-hydroxyphenoxy)phenoxy]butyrate (56). A mixture of **55** (2.8 g, 7.75 mmol), ethyl 4-bromobutyrate (2.73 g, 0.014 mol), and pulverized K_2CO_3 (1.38 g, 0.01 mol) in 20 mL of DMF was heated at 60 °C for 2 h. The reaction mixture was poured into 125 mL of H_2O and stirred until the product solidified. The solid was filtered, dried, and triturated with hexane to give 3.5 g (95%) of phenoxybutyrate derivative, mp 65–67 °C. Anal. ($C_{25}H_{24}Cl_2O_5$) C, H. A solution of the above butyrate ester (2.65 g, 5.58 mmol) in 100 mL of EtOH containing 1.43 mL of concentrated HCl was hydrogenated on the Parr apparatus over 0.52 g of 10% Pd–C. After the hydrogen uptake was complete, the catalyst was filtered and the filtrate evaporated to a residue, which solidified. There was obtained 1.8 g (84%) of **56**, mp 70–72 °C. Anal. ($C_{18}H_{18}Cl_2O_5$) C, H.

Ethyl 4-[2,3-dichloro-4-[3-(aminomethyl)-4-hydroxyphenoxy]phenoxy]butyrate hydrochloride (57) was prepared from **56** by using the procedure described for **29** except that HOAc–concentrated H_2SO_4 (9/1) was used as the reaction medium. The product was obtained in 56% yield after trituration with Et_2O/EtOH (25/1), mp 195–197 °C. Anal. ($C_{19}H_{22}Cl_3NO_5$) C, H, N.

Acknowledgment. We are grateful to D. Dunnigan for performing catalytic hydrogenations, to J. Hood for microanalyses, and to P. Morse for expert technical assistance.

Registry No. 1·HCl, 78235-46-8; 2·HCl, 78235-52-6; 3, 85297-76-3; 4, 92285-19-3; 5, 85297-75-2; 6, 92285-20-6; 7, 82241-66-5; 7·HBr, 82241-45-0; 8, 85297-77-4; 9, 92285-21-7; 10, 92285-56-8; 10·2HCl, 85297-78-5; 10 (bis-BOC deriv.), 92285-61-5; 11, 92285-22-8; 11·CF_3CO_2H, 92314-29-9; 12, 1984-59-4; 13, 100-07-2; 14, 78697-41-3; 15, 92285-23-9; 16, 78235-18-4; 17, 85297-69-4; 18, 92285-24-0; 19, 92285-68-2; 19·HCl, 85297-71-8; 19 (chloroacetamide), 85297-70-7; 20, 92285-69-3; 20·HCl, 92285-25-1; 21, 78235-20-8; 22, 78235-51-5; 22·HCl, 92285-63-7; 23, 92285-26-2; 24, 92285-27-3; 25, 92285-28-4; 26, 92285-29-5; 27, 92285-30-8; 28, 92285-64-8; 28·HCl, 92285-31-9; 29, 92285-65-9; 29·HCl, 92285-32-0; 30, 90246-58-5; 31, 90246-55-2; 32, 92285-66-0; 32·HCl, 92285-33-1; 33, 16861-22-6; 34, 92285-34-2; 35, 87181-38-2; 35a, 92285-62-6; 36, 87181-40-6; 37·HCl, 92285-35-3; 38, 92285-36-4; 39, 92285-57-9; 39·HCl, 87181-44-0; 40, 92285-37-5; 40 (chloride), 92285-48-8; 41, 87181-47-3; 42, 87181-48-4; 42 (amine·HCl), 87181-49-5; 43, 87181-50-8; 44, 87181-52-0; 44·HCl, 92285-38-6; 45, 92285-39-7; 45 (R = NH_2·HCl), 92285-49-9; 46, 92285-40-0; 46 (acid), 92285-50-2; 47, 92285-58-0; 47·HCl, 92285-41-1; 48, 83119-51-1; 49, 83119-48-6; 49 (R = Et), 92285-67-1; 50, 92285-42-2; 50 (R = H), 92285-51-3; 51, 92285-43-3; 52, 92314-28-8; 53, 92285-59-1; 53·HCl, 92285-44-4; 54, 87181-15-5; 55, 92285-45-5; 56, 92285-46-6; 56 (*O*-benzyl deriv.), 92285-55-7; 57, 92285-60-4; 57·HCl, 92285-47-7; $(BOC)_2O$, 24424-99-5; $Br(CH_2)_2OH$, 540-51-2; $BrCH_2COCH_3$, 598-31-2; $ClCH_2CONHCH_2OH$, 2832-19-1; $BrCH(CH_3)COOEt$, 535-11-5; *p*-$O_2NC_6H_4COCl$, 122-04-3; $Cl_3CC(CH_3)_2OH$, 57-15-8; *p*-$FC_6H_4NO_2$, 350-46-9; $(EtO)_2P(O)CH_2COOEt$, 867-13-0; $BrCH_2COOEt$, 105-36-2; $PhCH_2Br$, 100-39-0; $Br(CH_2)_3COOEt$, 2969-81-5; Na, 7440-23-5; *N*-[(benzyloxycarbonyl)oxy]succinimide, 13139-17-8; ethyl 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate, 62717-20-8; ethyl [2,3-dichloro-4-[4-(benzyloxy)phenoxy]phenoxy]acetate, 92285-52-4; [2,3-dichloro-4-[4-(benzyloxy)phenoxy]phenoxy]ethanol, 92285-53-5; 2-[2,3-dichloro-4-[4-(benzyloxy)phenoxy]phenoxy]ethyl mesylate, 92285-54-6.