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Studies on Uricosuric Diuretics. II.[1] 6,7-Dichloro-4-nitro-, 6,7-Dichloro-4-sulfamoyl- and 6,7-Dichloro-4-acyl-2,3-dihydrobenzofuran-2-carboxylic Acids

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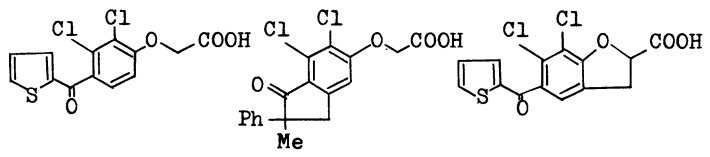
2,3-Dihydrobenzofuran-2-carboxylic acids substituted with electronegative nitro, acyl and sulfamoyl groups at the 4-position were synthesized and tested for oral diuretic and saluretic activities in rats and mice. The intraperitoneal uricosuric activity was also tested by a clearance method using oxonate-treated rats. The 4-nitro compounds (**11b**, **12b**, **13b** and **14b**) showed more potent saluretic activity than the corresponding 5-nitro compounds (**7b**, **18b**, **19b** and **20**). Although the 5-acyl compounds were reported to show potent saluretic activities, the 4-acyl compounds (**41a** and **b**) had much lower activities. On the other hand, the saluretic activities of the 4-sulfamoyl compounds (**22a**—**e**) were as potent as those of the 5-sulfamoyl compounds reported previously. Uricosuric activity was found in **14b** and **22a**.

Keywords——diuretic activity; saluretic activity; uricosuric activity; 4-nitro-2,3-dihydrobenzofuran-2-carboxylic acid; 4-sulfamoyl-2,3-dihydrobenzofuran-2-carboxylic acid; 4-acyl-2,3-dihydrobenzofuran-2-carboxylic acid; structure–activity relationship

Diuretics are widely used in hypertension therapy. Thiazide diuretics have been used safely and efficiently in long-term administration, but recently, various side effects, such as hypokalemia, glycohemia and hyperuricemia have been reported. Loop diuretics, which display potent but temporary action, are rarely used. However, their value as antihypertensive diuretics without the side effects caused by thiazides has been recognized following the development of sustained-release preparations.



1 tienilic acid 2 indacrinone 3

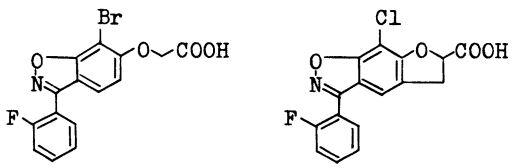


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Chart 1

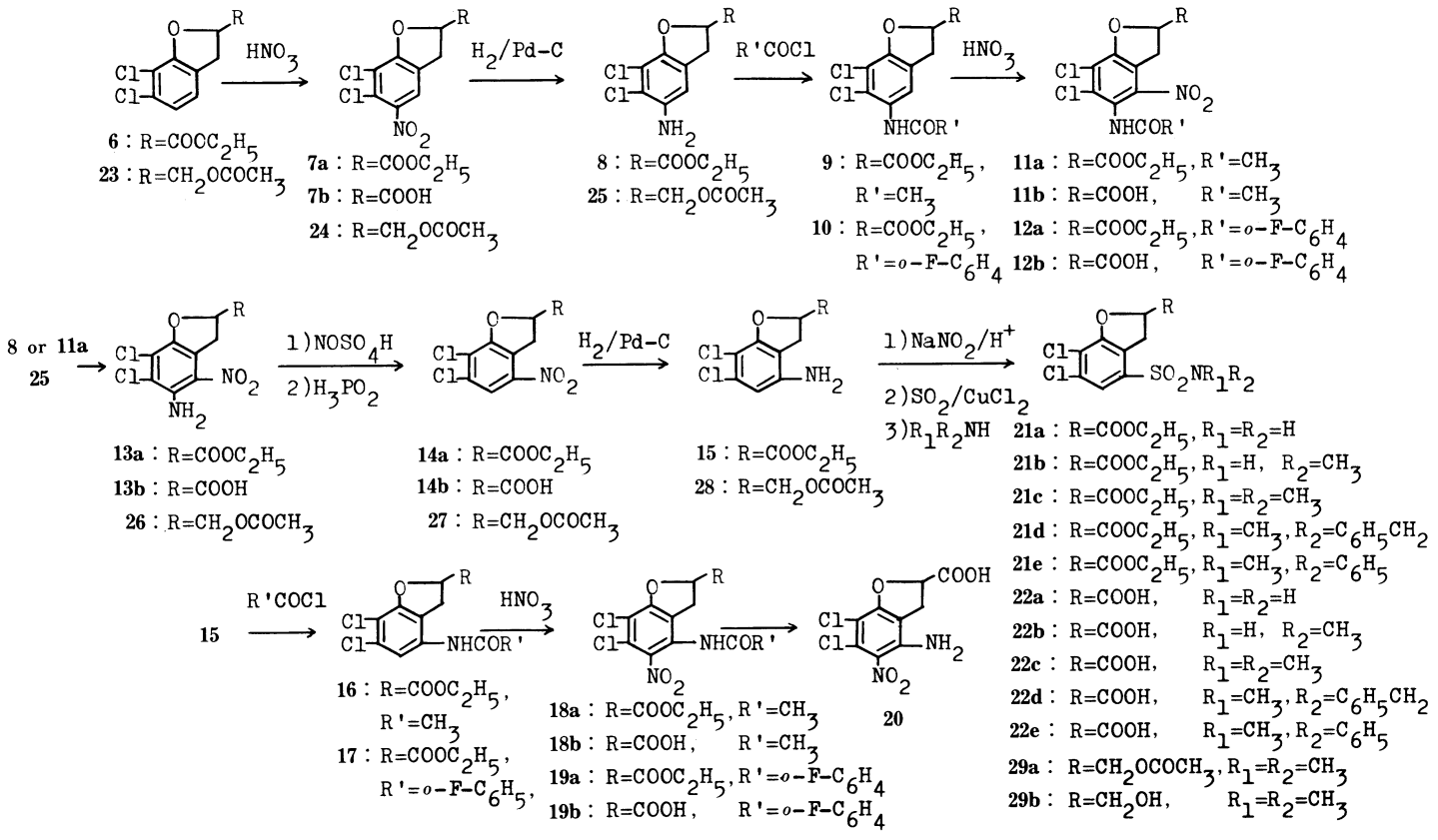

HNO3
H2/Pd-C
R'COCl
HNO3
6 : R=COOC2H5
23 : R=CH2OCOCH3
7a : R=COOC2H5
7b : R=COOH
24 : R=CH2OCOCH3
8 : R=COOC2H5
25 : R=CH2OCOCH3
9 : R=COOC2H5, R'=CH3
10 : R=COOC2H5, R'=o-F-C6H4
11a : R=COOC2H5, R'=CH3
11b : R=COOH, R'=CH3
12a : R=COOC2H5, R'=o-F-C6H4
12b : R=COOH, R'=o-F-C6H4
8 or 11a
25
1)NOSO4H
2)H3PO2
H2/Pd-C
1)NaNO2/H+
2)SO2/CuCl2
3)R1R2NH
13a : R=COOC2H5
13b : R=COOH
26 : R=CH2OCOCH3
14a : R=COOC2H5
14b : R=COOH
27 : R=CH2OCOCH3
15 : R=COOC2H5
28 : R=CH2OCOCH3
21a : R=COOC2H5, R1=R2=H
21b : R=COOC2H5, R1=H, R2=CH3
21c : R=COOC2H5, R1=R2=CH3
21d : R=COOC2H5, R1=CH3, R2=C6H5CH2
21e : R=COOC2H5, R1=CH3, R2=C6H5
22a : R=COOH, R1=R2=H
22b : R=COOH, R1=H, R2=CH3
22c : R=COOH, R1=R2=CH3
22d : R=COOH, R1=CH3, R2=C6H5CH2
22e : R=COOH, R1=CH3, R2=C6H5
29a : R=CH2OCOCH3, R1=R2=CH3
29b : R=CH2OH, R1=R2=CH3
15
R'COCl
HNO3
16 : R=COOC2H5, R'=CH3
17 : R=COOC2H5, R'=o-F-C6H5
18a : R=COOC2H5, R'=CH3
18b : R=COOH, R'=CH3
19a : R=COOC2H5, R'=o-F-C6H4
19b : R=COOH, R'=o-F-C6H4
20

Chart 2

Attempts to develop new types of uricosuric diuretics to avoid hyperuricemia led to the discovery of tienilic acid (**1**),[2] indacrinone (**2**)[2,3] and **3**,[2,4] HP-522 (**4**)[5] and **5**[6] in the 1970's (Chart 1).

We also tried to create a new type of uricosuric diuretic having temporary diuretic action and inhibiting reabsorption of uric acid by renal tubules. We found some dihydrobenzofuran-2-carboxylic acids with electronegative substituents that display both actions. In this paper, we discuss these 4-substituted-2,3-dihydrobenzofuran-2-carboxylic acids.

Chemistry

Compounds having 4-nitro or 4-sulfamoyl substituents were synthesized by the route shown in Chart 2. 6,7-Dichloro-2,3-dihydrobenzofuran-2-carboxylic acid ethyl ester (**6**)[4] or 6,7-dichloro-2,3-dihydrobenzofuran-2-ylmethyl acetate (**23**) was nitrated then reduced to **8** and **25**. The acetate (**9**) and *o*-fluorobenzoate (**10**) of **8** were nitrated to **11a** and **12a**. Hydrolysis of **11a** or direct nitration of **8** gave **13a**. Similar treatment of **25** gave **26**. Compounds **13a** and **26** were diazotized with nitrosylsulfuric acid then deaminated by reduction of the diazonium salts with hypophosphorus acid to obtain the 4-nitro compounds (**14** and **27**). After reduction of **14a** and **27**, the 4-amino substituents of the resultant compounds **15** and **28** were substituted with sulfamoyl groups *via* diazotization. Intermediates (**15**) were acetylated or *o*-fluorobenzoylated, then nitrated to obtain **18** and **19**. Compound **20** was obtained by hydrolysis of **18a**. The esters of the 2-substituents were hydrolyzed, then the free acids and alcohols obtained were tested for biological activities.

The synthetic pathway to the compounds with 4-acyl derivatives is shown in Chart 3. Nitration, methylation, then hydrogenation of 2,3-dichlorophenol (**30**) gave an anisidine derivative (**33**), which was acylated using boron trichloride–aluminum trichloride/benzonitrile or propionitrile, then hydrolyzed according to Sugasawa *et al.*[7] Deamination and demethylation of the aminoacyl compounds (**34**) gave phenols (**36**). Allylation of **36** and

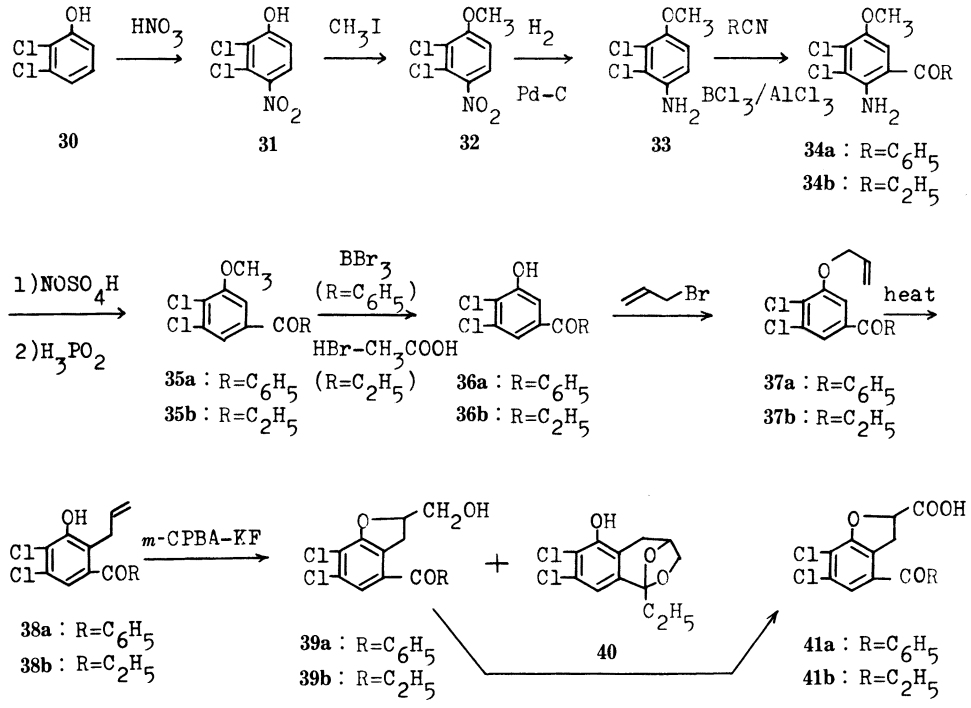
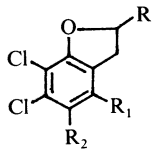


Chart 3

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



No.	R	R_1	R_2	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	F or S
7b	COOH	H	NO_2	200—203	D	$C_9H_5Cl_2NO_5$	38.89 (38.79	1.81 2.09	25.50 25.21	5.04 5.02)	
11b	COOH	NO_2	$NHCOCH_3$	250—252 (dec.)	EA–E	$C_{11}H_8Cl_2N_2O_6$	39.43 (39.42	2.41 2.48	21.16 20.91	8.36 8.22)	
12b	COOH	NO_2	$NHCOC_6H_4$-*o*-F	227—230	EA–E	$C_{16}H_9Cl_2FN_2O_6$	46.29 (46.04	2.19 2.44	17.08 17.11	6.75 6.73	F=4.58 F=4.59)
13b	COOH	NO_2	NH_2	242—243 (dec.)	EA–H	$C_9H_6Cl_2N_2O_5$	36.89 (36.92	2.06 2.27	24.19 24.12	9.56 9.34)	
14b	COOH	NO_2	H	169—170	EA–H	$C_9H_5Cl_2NO_5$	38.88 (39.05	1.81 2.22	25.50 25.13	5.04 5.03)	
18b	COOH	$NHCOCH_3$	NO_2	248 (dec.)	EA–E	$C_{11}H_8Cl_2N_2O_6$	39.43 (39.22	2.41 2.49	21.16 21.25	8.36 8.30)	
19b	COOH	$NHCOC_6H_4$-*o*-F	NO_2	209—210	EA–E	$C_{16}H_9Cl_2FN_2O_6$	46.29 (46.20	2.19 2.54	17.08 16.92	6.75 6.51	F=4.58 F=4.66)
20	COOH	NH_2	NO_2	206—207 (dec.)	E–H	$C_9H_6Cl_2N_2O_5$	36.89 (37.26	2.06 2.44	24.19 24.01	9.56 8.95)	
22a	COOH	SO_2NH_2	H	237—238	EA–E	$C_9H_7Cl_2NO_5S \cdot 1/2\,H_2O$	33.66 (33.36	2.51 2.73	22.08 21.70	4.36 4.30	S=9.98 S=9.66)
22b	COOH	SO_2NHCH_3	H	225—226	EA–E	$C_{10}H_9Cl_2NO_5S$	36.83 (36.62	2.78 2.98	21.74 21.53	4.29 4.34	S=9.83 S=9.61)
22c	COOH	$SO_2N(CH_3)_2$	H	207—208	EA–E	$C_{11}H_{11}Cl_2NO_5S$	38.84 (38.60	3.26 3.35	20.84 20.85	4.12 4.14	S=9.43 S=9.30)
22d	COOH	$SO_2N(CH_3)CH_2Ph$	H	178—180	EA–E	$C_{17}H_{15}Cl_2NO_5S$	49.05 (49.00	3.63 3.70	17.03 17.02	3.36 3.38	S=7.70 S=7.58)
22e	COOH	$SO_2N(CH_3)Ph$	H	194—195	EA–E	$C_{16}H_{13}Cl_2NO_5S$	47.78 (47.62	3.26 3.39	17.63 17.37	3.48 3.51	S=7.97 S=7.77)
29b	CH_2OH	$SO_2N(CH_3)_2$	H	114	EA–E	$C_{11}H_{13}Cl_2NO_4S$	40.50 (40.77	4.02 4.06	21.74 21.40	4.29 4.28	S=9.83 S=9.85)
41a	COOH	COPh	H	152—154	D–H	$C_{16}H_{10}Cl_2O_4$	57.00 (56.70	2.99 3.14	21.03 21.36)		
41b	COOH	COC_2H_5	H	198—200	D	$C_{12}H_{10}Cl_2O_4$	49.85 (49.60	3.49 3.50	24.52 24.62)		

a) D=dichloromethane, E=ether, EA=ethyl acetate, H=hexane.

subsequent Claisen rearrangement gave **38**. Epoxidation of **38a** with *m*-chloroperbenzoic acid resulted in recovery of the starting materials, but the use of potassium fluoride/*m*-chloroperbenzoic acid according to Camps *et al.*,[8] followed by alkaline treatment successfully gave 2,3-dihydrobenzofurans. In the case of **38b**, the intramolecular ketal (**40**) was obtained as a by-product. Jones oxidation of **39a** and **b** gave the 2-carboxylic acids (**41a** and **b**).

The products used in this study are listed in Table I.

Biological Activities

Saluresis and Diuresis——Diuretic and saluretic activities on rats and mice of the compounds listed in Table I are shown in Table II. Tienilic acid and indacrinone were used as reference compounds. Indacrinone showed more potent activity than tienilic acid in mice. Diuretic and kaliuretic activities paralleled the natriuretic activity. The diuretic–saluretic activities of 5-nitro substituted 2,3-dihydrobenzofuran-2-carboxylic acid derivatives (**7b**, **18b**, **19b**, **20**) were negative or weak, while those of 4-nitro compounds (**11b**, **12b**, **13b**, **14b**) were equivalent to or more potent than those of the reference compounds in rats and were similar to those of tienilic acid in mice. 4-Sulfamoyl compounds were more potent than the reference compounds. In these compounds, the activities of **22b** and **c** were equivalent even in mice. On the other hand, the activities of compounds with 4-acyl derivatives were weak, although the 5-propionyl derivative was reported to show very potent activities.[2] Thus, the diuretic–saluretic activities varied markedly according to the substituents and their positions. For compounds with the nitro, sulfamoyl and acyl groups, the potencies of diuretic-saluretic activities in relation to the position of substitution were $4 \gg 5$, $4 \geqq 5$, and $4 \ll 5$, respectively.

Uricosuric Activity——Uricosuric activity was evaluated in terms of the fractional excretion of uric acid (FEua) and urine-excreted amounts of uric acid (UuaV) values using potassium oxonate-treated rats.[9] The results are shown in Table III.

TABLE II. Diuretic and Saluretic Activities[a,b] in Rats and Mice (Oral Administration)

No.	Rats				Mice			
	Dose mg/kg	Urine volume ml/kg B.W.	Na meq/kg B.W.	K meq/kg B.W.	Dose mg/kg	Urine volume ml/kg B.W.	Na meq/kg B.W.	K meq/kg B.W.
7b	100	33 (N)	1.3 (1.8)	0.36 (N)	30	25 (N)	0.49 (N)	0.55 (N)
11b	100	40 (1.3)	2.3 (3.8)	0.64 (3.5)	30	45 (1.7)	3.7 (5.2)	1.2 (1.5)
12b	100	48 (1.6)	3.4 (3.9)	0.93 (4.9)	30	42 (1.4)	2.8 (4.5)	1.3 (2.1)
13b	100	47 (1.5)	3.0 (5.0)	0.93 (5.1)	30	35 (1.3)	3.0 (4.1)	1.3 (1.6)
14b	50	38 (1.4)	2.6 (3.8)	0.96 (N)	30	36 (1.4)	2.4 (3.2)	0.78 (1.3)
18b	50	33 (N)	0.87 (N)	0.25 (N)	30	30 (N)	1.5 (1.8)	0.67 (N)
19b	50	33 (N)	0.86 (N)	0.29 (N)	30	26 (N)	1.2 (2.4)	0.64 (N)
20	50	30 (N)	1.6 (N)	0.49 (N)	30	37 (N)	2.4 (4.6)	0.91 (1.7)
22a	50	35 (1.5)	2.3 (4.4)	0.68 (3.2)	30	44 (1.5)	4.1 (3.7)	1.3 (2.0)
22b	50	42 (1.8)	3.3 (6.3)	1.0 (4.8)	30	61 (2.2)	6.4 (5.8)	1.8 (2.6)
22c	50	48 (1.7)	4.2 (6.5)	1.4 (5.6)	30	60 (2.6)	6.8 (7.7)	2.0 (2.5)
22d	50	34 (1.4)	1.9 (3.7)	0.51 (2.4)	30	39 (N)	3.6 (5.2)	1.2 (1.8)
22e	50	27 (1.1)	1.2 (2.3)	0.26 (N)	30	34 (1.4)	2.7 (3.9)	1.1 (1.6)
29b	50	28 (1.2)	2.0 (2.7)	0.52 (2.2)	30	47 (2.0)	4.6 (7.7)	1.1 (3.2)
41a	50	26 (N)	0.63 (N)	0.23 (N)	30	28 (1.3)	1.2 (1.8)	0.78 (1.6)
41b	50	31 (1.4)	1.8 (3.2)	0.57 (2.7)	30	37 (N)	2.2 (2.5)	0.89 (N)
Tienilic acid	100	39 (1.8)	2.2 (1.7)	1.3 (5.7)	30	36 (2.4)	3.9 (5.4)	1.2 (1.9)
Indacrinone	50	34 (1.2)	1.3 (2.3)	0.5 (2.0)	30	72 (2.5)	6.4 (8.4)	1.9 (2.8)

a) The experimental details are discribed in the experimental section. *b*) Ratio to the control (treated/control value) is shown in parenthesis; N indicates that the difference from the control is not statistically significant.

TABLE III. Uricosuric Effect of 5-Sulfamoyl-6,7-dichloro-2,3-dihydrobenzofurans in Intraperitoneally Oxonate-Treated Rats

No.	Dose mg/kg	Increase of UuaV mg/kg min	Increase of FEua
11b	50	−0.006	−0.188
12b	50	=	−0.128
14b	50	0.126	0.259
22a	50	0.029	0.097
22c	50	0.048	−0.106
22d	50	0.032	=
41b	50	0.030	=
Probenecid	50	0.124	0.070
Tienilic acid	100	0.123	0.055
Indacrinone	50	0.063	=
Furosemide	50	0.028	−0.124

Increases of UuaV and FEua were calculated as the average values for 80 min after dosing. The symbol = represents no change compared with the control.

Probenecid and tienilic acid, used as positive reference compounds, showed hyperuricosuric activities with increases in both FEua and UuaV values. Indacrinone, however, showed only an increase of UuaV. Furosemide showed a decrease in FEua, suggesting the possibility of hypouricosuric action. Among the 4-nitro compounds, **11b** and **12b** showed marked decrease of both FEua and UuaV, and thus have a hypouricosuric character. Compound **14b** was hyperuricosuric because both values increased, but its diuretic character is not potent enough to allow its use as a diuretic agent. Among the 4-sulfamoyl compounds, only **22a** showed hyperuricosuric activity, and **22c** and **d** increased the UuaV values but not the FEua values. The observed increase of FEua in **22a** was only temporary.

As reported in the previous paper, some 5-sulfamoyl-2,3-dihydrobenzofuran derivatives showed both diuretic and uricosuric characteristics. However, among the 4-substituted-2,3-dihydrobenzofurans used in this study, none showed a good balance of diuretic and uricosuric actions, although compounds **14b** and **22a** showed both activities.

Experimental

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a Varian EM-390 spectrometer with tetramethylsilane (TMS) as an internal standard. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet). Chemical shifts are expressed in δ values and coupling constants are given in Hertz. Abbreviations are as follows: Ph, phenyl; arom. H, aromatic proton(s). For column chromatography, Silica gel 60 (E. Merck, 0.063—0.200 mm) was used.

Ethyl 6,7-Dichloro-5-nitro-2,3-dihydrobenzofuran-2-carboxylate (7a)——Fuming nitric acid (d=1.50, 25 ml) was added dropwise to a solution of ethyl 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate (10 g, 0.038 mol) in dichloromethane (150 ml) at 4 °C with stirring. After 1.5 h, the reactant was poured into ice water, then extracted with dichloromethane, and the extract was dried and evaporated *in vacuo*. Chromatography of the residue using dichloromethane as the eluant gave **7a** (9.4 g, 80%), mp 111—113 °C (hexane–ether). *Anal.* Calcd for $C_{11}H_9Cl_2NO_5$: C, 43.16; H, 2.96; Cl, 23.16; N, 4.58. Found: C, 42.96; H, 2.99; Cl, 23.07; N, 4.62. ^{1}H-NMR (in $CDCl_3$) δ: 1.33 (3H, t, J=7.2, C$\underline{H}_3$), 3.48 (1H, 3×d, J=17.3, 7.2, 1.1, Ph–C$\underline{H}_2$–CH), 3.73 (1H, 3×d, J=17.3, 7.2, 1.1, Ph–C$\underline{H}_2$–CH), 4.30 (2H, q, J=7.2, O–C$\underline{H}_2$–CH$_3$), 5.42 (1H, 2×d, J=10.2, 7.2, O–C$\underline{H}$), 7.72 (1H, t, J=1.1, 4-H).

Compound **24** was obtained in a similar manner starting from **23**, which was obtained by acetylation of 6,7-dichloro-2,3-dihydrobenzofuran-2-ylmethanol.[4] ^{1}H-NMR (in $CDCl_3$) δ: 2.08 (3H, s, COC$\underline{H}_3$), 3.16 (1H, 3×d, J=16.5, 7.5, 1.2, Ph–C$\underline{H}_2$–CH), 3.50 (3H, 3×d, J=16.5, 9.3, 1.2, Ph–C$\underline{H}_2$–CH), 4.16—4.54 (2H, m, C$\underline{H}_2$–OCOCH$_3$), 5.10—5.45 (1H, m, O–C$\underline{H}$), 7.72 (1H, t, J=1.2, 4-H).

6,7-Dichloro-5-nitro-2,3-dihydrobenzofuran-2-carboxylic Acid (7b)——A mixture of **7a** (0.500 g, 0.0016 mol) and

5% aqueous sodium hydroxide (20 ml) in tetrahydrofuran (THF) (10 ml) was stirred for 1 h, then concentrated *in vacuo*. The alkaline solution was acidified, then extracted with ethyl acetate and the organic layer was dried and evaporated. The residue was treated with dichloromethane and gave **7b** (0.440 g, 97%). ^{1}H-NMR (in acetone-d_6) δ: 3.57 (1H, 3×d, J=17.3, 6.5, 1.2, Ph–CH$_2$–CH), 3.88 (1H, 3×d, J=17.3, 10.5, 1.2, Ph–CH$_2$–CH), 5.58 (1H, 2×d, J=10.5, 6.5, O–CH), 7.07 (1H, br, COOH), 7.90 (1H, t, J=1.2, 4-H).

Ethyl 5-Amino-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate (8)——A solution of **7a** (1.44 g, 0.0047 mol) in ethyl acetate (50 ml) was hydrogenated over 10% palladium carbon catalyst (0.1 g). The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*, giving **8** (1.3 g, 100%), which was used for the next reaction without further purification.

Compound **25** was prepared in a similar manner. Yield 95%, mp 126—127 °C (ethyl acetate–ether).

Ethyl 5-Acetamido-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate (9)——Acetyl chloride (1.53 g, 0.019 mol) was added to a solution of **8** (3.59 g, 0.013 mol) and 4-*N*,*N*-dimethylaminopyridine (1.90 g, 0.016 mol) in dichloromethane (40 ml) at 3 °C with stirring, and the mixture was allowed to react at room temperature for 0.5 h, then washed, dried and evaporated. Treatment of the residue with ether gave **9** (3.95 g, 96%), mp 169—172 °C (ethyl acetate–ether). *Anal.* Calcd for $C_{13}H_{13}Cl_2NO_4$: C, 49.08; H, 4.12; Cl, 22.29; N, 4.40. Found: C, 48.77; H, 4.19; Cl, 22.52; N, 4.53. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.1, CH$_3$), 2.22 (3H, s, COCH$_3$), 3.37 (1H, 3×d, J=15.8, 8.7, 1.2, Ph–CH$_2$–CH), 3.63 (1H, 3×d, J=15.8, 10.2, 1.2, Ph–CH$_2$–CH), 4.24 (2H, q, J=7.1, O–CH$_2$), 5.25 (1H, 2×d, J=10.2, 8.7, O–CH), 7.47 (1H, br s, NH), 8.00 (1H, t, J=1.2, 4-H).

Compound **10** was obtained in a similar manner. Yield 91%, mp 141—143 °C (ether). *Anal.* Calcd for $C_{18}H_{14}Cl_2FNO_4$: C, 54.19; H, 3.54; Cl, 17.81; F, 4.77; N, 3.52. Found: C, 54.10; H, 3.82; Cl, 17.83; F, 4.75; N, 3.54. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.0, CH$_3$), 3.41 (1H, 3×d, J=16.2, 6.9, 1.2, Ph–CH$_2$–CH), 3.67 (1H, 3×d, J=16.2, 10.0, 1.2, Ph–CH$_2$–CH), 4.24 (2H, q, J=7.0, O–CH$_2$), 5.27 (1H, 2×d, J=10.0, 6.9, O–CH), 6.93—7.66 (3H, m, arom. H), 8.14 (1H, d, t, J=2.3, 7.8, arom. H), 8.29 (1H, t, J=1.2, 4-H), 8.95 (1H, d, J=16.5, NH).

Ethyl 5-Acetamido-6,7-dichloro-4-nitro-2,3-dihydrobenzofuran-2-carboxylate (11a)——Fuming nitric acid (d=1.50, 20 ml) was added to a solution of **9** (3.85 g, 0.012 mol) in dichloromethane (100 ml), and the mixture was allowed to react for 1.5 h at 4 °C with stirring. The reactant was then poured into ice water, and the dichloromethane layer was separated. The aqueous layer and the precipitated materials were extracted with ethyl acetate. The dichloromethane and ethyl acetate extracts were combined, dried, and evaporated. Treatment of the residue with ether gave **11a** (4.00 g, 91%), mp 169—172 °C (ethyl acetate–hexane). *Anal.* Calcd for $C_{13}H_{12}Cl_2N_2O_6$: C, 43.00; H, 3.33; Cl, 19.52; N, 7.71. Found: C, 42.85; H, 3.52; Cl, 19.68; N, 7.84. ^{1}H-NMR (in $CDCl_3$) δ: 1.32 (3H, t, J=7.1, CH$_3$), 2.19 (3H, s, COCH$_3$), 3.65 (1H, 2×d, J=18.0, 7.2, Ph–CH$_2$–CH), 3.94 (1H, 2×d, J=18.0, 10.2, Ph–CH$_2$–CH), 5.35 (1H, 2×d, J=10.2, 7.2, O–CH), 7.47 (1H, br s, NH).

Compound **12a** was obtained in a similar manner. Yield 92%, mp 154—155 °C (ethyl acetate–ether). *Anal.* Calcd for $C_{18}H_{13}Cl_2FN_2O_6$: C, 48.78; H, 2.96; Cl, 16.00; F, 4.29; N, 6.32. Found: C, 48.83; H, 3.00; Cl, 15.83; F, 4.47; N, 6.42. ^{1}H-NMR (in $CDCl_3$) δ: 1.32 (3H, t, J=7.0, CH$_3$), 3.69 (1H, 2×d, J=18.0, 7.0, Ph–CH$_2$–CH), 3.99 (1H, 2×d, J=18.0, 9.8, Ph–CH$_2$–CH), 4.28 (2H, q, J=7.0, O–CH$_2$), 5.40 (1H, 2×d, J=9.8, 7.0, O–CH), 6.80—7.75 (3H, arom. H), 8.11 (1H, d, t, J=1.8, 7.8, arom. H), 8.77 (1H, d, J=15.8, NH).

5-Acetamido-6,7-dichloro-4-nitro-2,3-dihydrobenzofuran-2-carboxylic Acid (11b)——A mixture of **11a** (0.40 g, 0.0011 mol), 7.5% aqueous potassium carbonate (10 ml), and THF (5 ml) was stirred for 20 h, then concentrated *in vacuo*. The reactant was diluted with water, washed with dichloromethane, acidified with 20% hydrochloric acid, then extracted with ethyl acetate. After evaporation of the ethyl acetate, the residue was treated with ether to give **11b** (0.34 g, 92%), mp 250—252 °C (dec.) (ethyl acetate–ether). ^{1}H-NMR (in acetone-d_6) δ: 2.10 (3H, s, COCH$_3$), 3.70 (1H, 2×d, J=17.4, 6.3, Ph–CH$_2$–CH), 4.04 (1H, 2×d, J=17.4, 10.2, Ph–CH$_2$–CH), 5.57 (1H, 2×d, J=10.2, 6.3, O–CH), 9.16 (1H, br s, NH).

Compound **12b** was obtained in a similar manner. Yield 88%. ^{1}H-NMR (in acetone-d_6) δ: 3.77 (1H, 2×d, J=18.0, 6.9, Ph–CH$_2$–CH), 4.10 (1H, 2×d, J=18.0, 10.1, Ph–CH$_2$–CH), 5.62 (1H, 2×d, J=10.1, 6.9, O–CH), 7.15—7.77 (3H, m, arom. H), 7.89 (1H, d, t, J=1.8, 7.5, arom. H), 9.34 (1H, d, J=7.5, NH).

Ethyl 5-Amino-6,7-dichloro-4-nitro-2,3-dihydrobenzofuran-2-carboxylate (13a)——Fuming nitric acid (d=1.50, 18 ml) was added to a solution of **8** (8.963 g, 0.032 mol) in dichloromethane (180 ml), and the mixture was allowed to react at 4—6 °C for 2 h with stirring. The reactant was poured into ice water, then extracted with dichloromethane. The organic layer was dried and evaporated. The residue was chromatographed and eluted with dichloromethane, giving **13a** (7.542 g, 72%), which was used for the next reaction without further purification. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.2, CH$_3$), 3.83 (1H, 2×d, J=18.7, 7.1, Ph–CH$_2$–CH), 4.12 (1H, 2×d, J=18.7, 7.1, Ph–CH$_2$–CH), 4.27 (2H, q, J=7.2, O–CH$_2$), 5.25 (1H, 2×d, J=9.8, 7.1, O–CH), 6.35 (2H, br s, NH$_2$).

Compound **26** was obtained in a similar manner. Dichloromethane–ethyl acetate (30 : 1) was used for the chromatographic separation. Yield 77%, mp 168—169 °C (ethyl acetate–ether). *Anal.* Calcd for $C_{11}H_{10}Cl_2N_2O_5$: C, 41.14; H, 3.14; Cl, 22.08; N, 8.72. Found: C, 41.15; H, 3.30; Cl, 22.09; N, 8.73. ^{1}H-NMR (in $CDCl_3$) δ: 2.10 (3H, s, COCH$_3$), 3.53 (1H, 2×d, J=17.0, 7.0, Ph–CH$_2$–CH), 3.90 (1H, 2×d, J=17.0, 9.0, Ph–CH$_2$–CH), 4.31 (2H, d, J=6.0, O–CH$_2$), 4.90—5.35 (1H, m, O–CH), 6.30 (2H, br, NH$_2$).

5-Amino-6,7-dichloro-4-nitro-2,3-dihydrobenzofuran-2-carboxylic Acid (13b)——A mixture of **11a** (3.05 g,

0.0084 mol), 20% hydrochloric acid (25 ml) and dioxane (25 ml) was refluxed for 1 h, then concentrated at atmospheric pressure. Precipitates formed by addition of water were filtered off and dried at room temperature to obtain **13b** (1.92 g, 78%). ^{1}H-NMR (in DMSO-d_6) δ: 3.68 (1H, 2×d, J=18.0, 6.8, Ph-CH$_2$-CH), 4.03 (1H, 2×d, J=18.0, 10.5, Ph-CH$_2$-CH), 5.33 (1H, 2×d, J=10.5, 6.8, O-CH), 6.90 (2H, br s, NH$_2$), 13.2 (1H, br, COOH).

Ethyl 6,7-Dichloro-4-nitro-2,3-dihydrobenzofuran-2-carboxylate (14a)——A 45% nitrosylsulfuric acid solution in sulfuric acid (22 g) was added to a solution of **13a** (10.47 g, 0.033 mol) in THF (440 ml) at −25—−18 °C over 1 h with stirring, then the reaction temperature was raised to −5 °C for 2.5 h. Next, 50% aqueous hypophosphorus acid (230 ml) was added at −14—15 °C over 1 h, then the reaction mixture was extracted with ether. The extract was dried and evaporated. The residue was chromatographed and eluted with dichloromethane to obtain **14a** (6.584 g, 66%), mp 104 °C (ether). *Anal.* Calcd for $C_{11}H_9Cl_2NO_5$: C, 43.16; H, 2.96; Cl, 23.16; N, 4.59. Found: C, 43.06; H, 3.16; Cl, 23.78; N, 4.46. ^{1}H-NMR (in $CDCl_3$) δ: 1.33 (3H, t, J=7.0, CH$_3$), 3.83 (1H, 2×d, J=18.9, 7.5, Ph-CH$_2$-CH), 4.08 (1H, 2×d, J=18.9, 9.8, Ph-CH$_2$-CH), 4.27 (2H, q, J=7.0, O-CH$_2$), 5.39 (1H, 2×d, J=9.8, 7.5, O-CH), 7.85 (1H, s, 5-H).

Compound **27** was obtained in a similar manner. Yield 77%, mp 100—101 °C (hexane–ether). *Anal.* Calcd for $C_{11}H_9Cl_2NO_5$: C, 43.16; H, 2.96; Cl, 23.16; N, 4.58. Found: C, 43.07; H, 3.09; Cl, 23.41; N, 4.63. ^{1}H-NMR (in $CDCl_3$) δ: 2.06 (3H, s, CH$_3$), 3.53 (1H, 2×d, J=18.0, 7.5, Ph-CH$_2$-CH), 3.90 (1H, 2×d, J=18.0, 10.5, Ph-CH$_2$-CH), 4.15—4.60 (2H, m, O-CH$_2$), 5.10—5.43 (1H, m, O-CH), 7.86 (1H, s, 5-H).

6,7-Dichloro-4-nitro-2,3-dihydrobenzofuran-2-carboxylic Acid (14b)——A mixture of **14a** (1.90 g, 0.0062 mol), THF (20 ml) and 7.5% aqueous potassium carbonate solution (20 ml) was stirred for 20 h, then concentrated *in vacuo*. The residue was acidified, then extracted with ethyl acetate. The extract was treated with ether to obtain **14b** (1.527 g, 88%), mp 169—170 °C (ethyl acetate–hexane).

Ethyl 4-Amino-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate (15) and 4-Amino-6,7-dichloro-2,3-dihydrobenzofuran-2-ylmethyl Acetate——Compounds **15** and **28** were obtained by a procedure similar to that described for **8**. Compound **15**: Yield 92%, mp 134—135 °C (ether). *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_3$: C, 47.85; H, 4.02; Cl, 25.68; N, 5.07. Found: C, 47.64; H, 3.97; Cl, 25.74; N, 5.08. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.2, CH$_3$), 3.17 (1H, 2×d, J=15.5, 7.2, Ph-CH$_2$-CH), 3.42 (1H, 2×d, J=15.5, 10.1, Ph-CH$_2$-CH), 3.0—3.7 (2H, br, NH$_2$), 4.26 (2H, q, J=7.2, O-CH$_2$), 5.28 (1H, 2×d, J=10.1, 7.2, O-CH), 6.36 (1H, s, 5-H). Compound **28**: Yield 45%, mp 96—97 °C (ethyl acetate–ether). *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_3$: C, 47.85; H, 4.02; Cl, 25.68; N, 5.07. Found: C, 47.95; H, 4.06; Cl, 25.21; N, 5.22. ^{1}H-NMR (in $CDCl_3$) δ: 2.07 (3H, s, COCH$_3$), 2.81 (1H, 2×d, J=15.0, 7.5, Ph-CH$_2$-CH), 3.16 (1H, 2×d, J=15.0, 9.0, Ph-CH$_2$-CH), 3.0—4.0 (2H, br, NH$_2$), 4.30 (2H, d, J=6.0, O-CH$_2$), 4.95—5.35 (1H, m, O-CH), 6.35 (1H, s, 5-H).

Ethyl 4-Acetamido-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate (16) and Ethyl 6,7-Dichloro-4-(*o*-fluorobenzoylamino)-2,3-dihydrobenzofuran-2-carboxylate (17)——Compounds **16** and **17** were obtained by a procedure similar to that described for **9** and **10**. Compound **16**: Yield 96%, mp 171—173 °C (ether). *Anal.* Calcd for $C_{13}H_{13}Cl_2NO_4$: C, 49.08; H, 4.12; Cl, 22.29; N, 4.40. Found: C, 48.71; H, 3.90; Cl, 22.13; N, 4.30. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.2, CH$_3$), 2.15 (3H, s, COCH$_3$), 3.25 (1H, 2×d, J=16.5, 7.5, Ph-CH$_2$-CH), 3.53 (1H, 2×d, J=16.5, 10.2, Ph-CH$_2$-CH), 4.23 (2H, q, J=7.2, O-CH$_2$), 5.26 (1H, 2×d, J=10.2, 7.5, O-CH), 7.14 (1H, br, NH), 7.30 (1H, s, 5-H). Compound **17**: Yield 97%. ^{1}H-NMR (in DMSO-d_6) δ: 1.22 (3H, t, J=7.0, CH$_3$), 3.40 (1H, 2×d, J=16.5, 6.8, Ph-CH$_2$-CH), 3.70 (1H, 2×d, J=16.5, 10.2, Ph-CH$_2$-CH), 4.20 (2H, q, J=7.0, O-CH$_2$), 5.55 (1H, 2×d, J=10.2, 6.8, O-CH), 7.23—7.83 (5H, m, 5-H, arom. H), 10.25 (1H, s, NH).

Ethyl 4-Acetamido-6,7-dichloro-5-nitro-2,3-dihydrobenzofuran-2-carboxylate (18a) and Ethyl 6,7-Dichloro-4-(*o*-fluorobenzoylamino)-5-nitro-2,3-dihydrobenzofuran-2-carboxylate (19a)——Compounds **18a** and **19a** were obtained by a procedure similar to that described for **11a** and **12a**. Compound **18a**: Yield 76%, mp 143 °C (hexane–ether). *Anal.* Calcd for $C_{13}H_{12}Cl_2N_2O_6$: C, 43.00; H, 3.33; Cl, 19.52; N, 7.71. Found: C, 43.01; H, 3.25; Cl, 19.80; N, 7.59. ^{1}H-NMR (in $CDCl_3$) δ: 1.31 (3H, t, J=7.0, CH$_3$), 2.15 (3H, s, COCH$_3$), 3.31 (1H, 2×d, J=17.0, 7.0, Ph-CH$_2$-CH), 3.66 (1H, 2×d, J=17.0, 10.2, Ph-CH$_2$-CH), 4.26 (2H, q, J=7.0, O-CH$_2$), 5.36 (1H, 2×d, J=10.2, 7.0, O-CH), 8.00 (1H, br s, NH).

Compound **19a**: Yield 55%, mp 126—128 °C (ethyl acetate–ether). *Anal.* Calcd for $C_{18}H_{13}Cl_2FN_2O_6$: C, 48.78; H, 2.96; Cl, 16.00; F, 4.29; N, 6.32. Found: C, 48.73; H, 3.01; Cl, 15.98; F, 4.27; N, 6.41. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.1, CH$_3$), 3.38 (1H, 2×d, J=17.4, 6.8, Ph-CH$_2$-CH), 3.79 (1H, 2×d, J=17.4, 10.5, Ph-CH$_2$-CH), 4.27 (2H, q, J=7.1, O-CH$_2$), 5.41 (1H, 2×d, J=10.5, 6.8, O-CH), 7.05—7.75 (3H, m, arom. H), 8.10 (1H, d, t, J=2.0, 8.1, arom. H), 9.07 (1H, d, J=15.3, NH).

4-Acetamido-6,7-dichloro-5-nitro-2,3-dihydrobenzofuran-2-carboxylic Acid (18b) and 6,7-Dichloro-4-(*o*-fluorobenzoylamino)-5-nitro-2,3-dihydrobenzofuran-2-carboxylic Acid (19b)——Compounds **18b** and **19b** were obtained by a procedure similar to that described for **11b** and **12b**. Compound **18b**: Yield 95%. ^{1}H-NMR (in acetone-d_6) δ: 2.10 (3H, s, COCH$_3$), 3.43 (1H, 2×d, J=17.1, 6.8, Ph-CH$_2$-CH), 3.76 (1H, 2×d, J=17.1, 10.4, Ph-CH$_2$-CH), 5.56 (1H, 2×d, J=10.4, 6.8, O-CH), 9.17 (1H, br, NH).

Compound **19b**: Yield 91%. ^{1}H-NMR (in acetone-d_6) δ: 3.57 (1H, 2×d, J=17.1, 6.8, Ph-CH$_2$-CH), 3.88 (1H, 2×d, J=17.1, 10.1, Ph-CH$_2$-CH), 5.65 (1H, 2×d, J=10.1, 6.8, O-CH), 7.15—7.80 (3H, m, arom. H), 7.89 (1H, d, t, J=2.3, 7.5, arom. H), 9.48 (1H, d, J=7.5, NH).

4-Amino-6,7-dichloro-5-nitro-2,3-dihydrobenzofuran-2-carboxylic Acid (20)——A mixture of **18a** (0.47 g, 0.0013 mol), 20% hydrochloric acid (10 ml) and THF (10 ml) was refluxed for 4 h. After cooling, the reaction mixture was extracted with ethyl acetate, then the organic layer was extracted with an aqueous sodium bicarbonate solution. The aqueous layer was acidified, then extracted with ethyl acetate, and the organic layer was dried and evaporated. The residue was treated with hexane–ether to obtain **20** (0.23 g, 63%). ^{1}H-NMR (in DMSO-d_6) δ: 3.22 (1H, 2×d, J=16.5, 6.8, Ph–CH$_2$–CH), 3.50 (1H, 2×d, J=16.5, 10.5, Ph–CH$_2$–CH), 5.46 (1H, 2×d, J=10.5, 6.8, O–CH), 6.30 (3H, br, NH$_2$, COOH).

Ethyl 6,7-Dichloro-4-sulfamoyl-2,3-dihydrobenzofuran-2-carboxylate (21a)——Sodium nitrite (0.376 g, 0.0054 mol) was added to a solution of **15** (1.0 g, 0.0036 mol), concentrated hydrochloric acid (15 ml) and acetic acid (15 ml) at −20 °C with stirring, then the reaction temperature was raised gradually to 0 °C over 2 h. The reaction mixture was cooled to −20 °C, then liquid sulfur dioxide (10 g) and a solution of cupric chloride (1.4 g, 0.0104 mol) in water (2 ml) and acetic acid (20 ml) were added. The reaction mixture was stirred at 0 °C for 20 min, at room temperature for 30 min, and finally at 50 °C for 1 h to drive out the sulfur dioxide. It was then poured into ice water and extracted with dichloromethane. The organic layer was washed with chilled water, dried and evaporated *in vacuo*. The residue was dissolved in dichloromethane (20 ml), and ammonia gas was passed through the solution at room temperature for 3 h. Next, the solution was evaporated *in vacuo*, and the resultant oily material was dissolved in ethyl acetate. This solution was washed with water, dried and evaporated. Ethereal diazomethane was added to the residue until evolution of nitrogen gas ceased. Evaporation and treatment with hexane–ether gave **21a** (0.81 g, 66%), mp 174—175 °C (acetone–hexane). *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_5S$: C, 38.84; H, 3.26; Cl, 20.84; N, 4.12; S, 9.42. Found: C, 38.89; H, 3.46; Cl, 20.63; N, 4.28; S, 9.19. ^{1}H-NMR (in acetone-d_6) δ: 1.25 (3H, t, J=7.0, CH$_3$), 3.66 (1H, 2×d, J=17.0, 7.0, Ph–CH$_2$–CH), 3.97 (1H, 2×d, J=17.0, 10.0, Ph–CH$_2$–CH), 4.21 (2H, q, J=7.0, O–CH$_2$), 5.52 (1H, 2×d, J=10.0, 7.0, O–CH), 6.80 (2H, br, NH$_2$), 7.48 (1H, s, 5-H).

Compounds **21b—e** and **29a** were obtained in a similar manner *via* reactions of methanol solutions of the corresponding amines at −20——10 °C instead of ammonia gas. For the synthesis of **29a**, the diazomethane treatment was omitted.

Compound **21b**: Yield 71%, mp 135—137 °C (hexane–ether). *Anal.* Calcd for $C_{12}H_{13}Cl_2NO_5S$: C, 40.69; H, 3.70; Cl, 20.02; N, 3.95; S, 9.05. Found: C, 40.55; H, 3.77; Cl, 19.98; N, 4.00; S, 8.95. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.0, CH$_3$), 2.68 (3H, d, J=5.0, NHCH$_3$), 3.64 (1H, 2×d, J=17.4, 7.5, Ph–CH$_2$–CH), 3.90 (1H, 2×d, J=17.4, 10.5, Ph–CH$_2$–CH), 4.27 (2H, q, J=7.0, O–CH$_2$), 4.75 (1H, br, NH), 5.35 (1H, 2×d, J=10.5, 7.5, O–CH), 7.47 (1H, s, 5-H).

Compound **21c**: Yield 68%, mp 93—94 °C (hexane–ether). *Anal.* Calcd for $C_{13}H_{15}Cl_2NO_5S$: C, 42.40; H, 4.11; Cl, 19.26; N, 3.80; S, 8.71. Found: C, 42.43; H, 4.09; Cl, 19.54; N, 3.78; S, 8.56. ^{1}H-NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7.0, CH$_3$), 2.80 (6H, s, 2×N–CH$_3$), 3.66 (1H, 2×d, J=18.0, 7.1, Ph–CH$_2$–CH), 3.93 (1H, 2×d, J=18.0, 10.2, Ph–CH$_2$–CH), 4.27 (2H, q, J=7.0, O–CH$_2$), 5.35 (1H, 2×d, J=10.2, 7.1, O–CH), 7.39 (1H, s, 5-H).

Compound **21d**: Yield 44%, mp 108—109 °C (hexane–ether). *Anal.* Calcd for $C_{19}H_{19}Cl_2NO_5S$: C, 51.36; H, 4.31; Cl, 15.96; N, 3.15; S, 7.22. Found: C, 51.23; H, 4.35; Cl, 15.84; N, 3.15; S, 7.13. ^{1}H-NMR (in $CDCl_3$) δ: 1.28 (3H, t, J=7.0, CH$_3$), 2.67 (3H, s, N–CH$_3$),3.66 (1H, 2×d, J=18.0, 7.5, Ph–CH$_2$–CH), 3.93 (1H, 2×d, J=18.0, 9.6, Ph–CH$_2$–CH), 4.25 (2H, s, Ph–CH$_2$), 4.28 (2H, q, J=7.0, O–CH$_2$), 5.33 (1H, 2×d, J=9.6, 7.5, O–CH), 7.33 (5H, s, arom. H), 7.41 (1H, s, 5-H).

Compound **21e**: Yield 67%, mp 145—146 °C (hexane–ether). *Anal.* Calcd for $C_{18}H_{17}Cl_2NO_5S$: C, 50.24; H, 3.98; Cl, 16.48; N, 3.26; S, 7.45. Found: C, 50.02; H, 4.06; Cl, 16.60; N, 3.32; S, 7.34. ^{1}H-NMR (in $CDCl_3$) δ: 1.26 (3H, t, J=7.0, CH$_3$), 2.72 (1H, 2×d, J=18.0, 7.1, Ph–CH$_2$–CH), 3.14 (1H, 2×d, J=18.0, 10.5, Ph–CH$_2$–CH), 3.23 (3H, s, NCH$_3$), 4.21 (2H, q, J=7.0, O–CH$_2$), 5.05 (1H, 2×d, J=10.5, 7.1, O–CH), 7.0—7.5 (5H, m, arom. H), 7.38 (1H, s, 5-H).

Compound **29a**: Yield 50%, mp 113—114 °C (ether). *Anal.* Calcd for $C_{13}H_{15}Cl_2NO_5S$: C, 42.40; H, 4.11; Cl, 19.26; N, 3.80; S, 8.71. Found: C, 42.35; H, 4.11; Cl, 19.26; N, 3.77; S, 8.58. ^{1}H-NMR (in $CDCl_3$) δ: 2.06 (3H, s, COCH$_3$), 2.80 (6H, s, 2×N–CH$_3$), 3.35 (1H, 2×d, J=18.0, 7.5, Ph–CH$_2$–CH), 3.70 (1H, 2×d, J=18.0, 9.0, Ph–CH$_2$–CH), 4.15—4.55 (2H, m, O–CH$_2$), 5.00—5.40 (1H, m, O–CH), 7.35 (1H, s, 5-H).

6,7-Dichloro-4-sulfamoyl-2,3-dihydrobenzofuran-2-carboxylic Acid (22a)——A mixture of **21a** (0.34 g, 0.0011 mol), 1 N sodium hydroxide solution (1.5 ml) and acetonitrile (5 ml) was stirred for 1 h, then evaporated *in vacuo*. The residue was mixed with 10% hydrochloric acid (1.5 ml) and this mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. Treatment of the residue with ether gave **22a** (0.23 g, 73%). ^{1}H-NMR (in acetone-d_6) δ: 3.67 (1H, 2×d, J=18.0, 7.0, Ph–CH$_2$–CH), 4.00 (1H, 2×d, J=18.0, 9.6, Ph–CH$_2$–CH), 5.52 (1H, 2×d, J=9.6, 7.0, O–CH), 6.83 (2H, br, NH$_2$), 7.47 (1H, s, 5-H).

Compounds **22b—e** and **29b** were obtained in a similar manner.

Compound **22b**: Yield 97%. ^{1}H-NMR (in acetone-d_6) δ: 2.62 (3H, d, J=5.0, N–CH$_3$), 3.67 (1H, 2×d, J=18.0, 7.2, Ph–CH$_2$–CH), 3.99 (1H, 2×d, J=18.0, 10.5, Ph–CH$_2$–CH), 5.52 (1H, 2×d, J=10.5, 7.2, O–CH), 6.60 (1H, br, NH), 7.44 (1H, s, 5-H).

Compound **22c**: Yield 79%. ^{1}H-NMR (in acetone-d_6) δ: 2.82 (6H, s, 2×N–CH$_3$), 3.73 (1H, 2×d, J=18.0, 6.8, Ph–CH$_2$–CH), 4.05 (1H, 2×d, J=18.0, 10.0, Ph–CH$_2$–CH), 5.55 (1H, 2×d, J=10.0, 6.8, O–CH), 7.40 (1H, s, 5-H).

Compound **22d**: Yield 94%. ^{1}H-NMR (in acetone-d_6) δ: 2.72 (3H, s, N–C$\underline{H}_3$), 3.76 (1H, 2×d, J=18.0, 7.2, Ph–C$\underline{H}_2$–CH), 4.07 (1H, 2×d, J=18.0, 9.8, Ph–C$\underline{H}_2$–CH), 4.33 (2H, s, Ph–C$\underline{H}_2$), 5.54 (1H, 2×d, J=9.8, 7.2, O–C$\underline{H}$), 7.33 (5H, s, arom. H), 7.46 (1H, s, 5-H).

Compound **22e**: Yield 99%. ^{1}H-NMR (in acetone-d_6) δ: 3.31 (3H, s, N–C$\underline{H}_3$), 2.77 (1H, 2×d, J=17.4, 7.0, Ph–C$\underline{H}_2$–CH), 3.30 (1H, 2×d, J=17.4, 10.5, Ph–C$\underline{H}_2$–CH), 5.28 (1H, 2×d, J=10.5, 7.0, O–C$\underline{H}$), 7.1—7.5 (6H, m, 5-H, arom. H).

Compound **29b**: Yield 90%. ^{1}H-NMR (in $CDCl_3$) δ: 2.04 (1H, t, J=7.0, O$\underline{H}$), 2.80 (6H, s, 2×N–C$\underline{H}_3$), 3.42 (1H, 2×d, J=16.0, 7.5, Ph–C$\underline{H}_2$–CH), 3.68 (1H, 2×d, J=16.0, 9.0, Ph–C$\underline{H}_2$–CH), 3.70—4.20 (2H, m, O–C$\underline{H}_2$), 4.90—5.30 (1H, m, O–C$\underline{H}$), 7.35 (1H, s, 5-H).

2,3-Dichloro-4-nitrophenol (31)——A solution of 2,3-dichlorophenol (**30**, 48 g, 0.245 mol) in acetic anhydride (100 ml) was added to a solution of nitric acid (d=1.38, 200 ml) in acetic acid (100 ml) dropwise at 4—8 °C with stirring. The mixture was kept for 1 h at the same temperature, then poured into ice water. The precipitated crystalline material was collected by filtration and washed with dichloromethane to obtain **31** as pale yellow crystals (25.6 g, 42%), mp 154 °C (dichloromethane–ether). *Anal.* Calcd for $C_6H_3Cl_2NO_3$: C, 34.65; H, 1.45; Cl, 34.09; N, 6.73. Found: C, 34.61; H, 1.54; Cl, 33.73; N, 6.85. ^{1}H-NMR (in acetone-d_6) δ: 3.3—5.5 (br, O$\underline{H}$), 7.18 and 7.93 (2H, AB, J=9.0, arom. H).

2,3-Dichloro-4-nitroanisole (32)——A mixture of **31** (11.9 g, 0.0572 mol), methyl iodide (32.5 g, 0.229 mol), and potassium carbonate (8 g, 0.058 mol) in *N*,*N*-dimethylformamide (DMF) (50 ml) was refluxed for 40 min, then evaporated *in vacuo*. The residue was dissolved in dichloromethane and the solution was washed, dried, and evaporated. The residue was chromatographed. Elution with dichloromethane gave **32** (12.38 g, 97%), which was used for the next reaction without further purification.

2,3-Dichloro-4-methoxyaniline (33)——A solution of **32** (25.17 g, 0.113 mol) in ethyl acetate (300 ml) was hydrogenated over 10% palladium–carbon catalyst (1.1 g). The catalyst was removed by filtration, and the filtrate was washed with 5% sodium hydroxide and brine, then dried and evaporated *in vacuo*. The residue was used for the next reaction without further purification.

2-Amino-3,4-dichloro-5-methoxybenzophenone (34a)——A solution of **33** (1.92 g, 0.01 mol) in dichloromethane (6 ml) and a solution of benzonitrile (1.53 g, 0.0149 mol) in dichloromethane (2 ml) were added dropwise to 2.0 mol of boron trichloride in dichloromethane (6.3 ml). Next, solid aluminum trichloride (1.5 g, 0.0112 mol) was added at 5-12 °C with stirring. The mixture was stirred at room temperature for 30 min, refluxed for 2 h, then left standing overnight. Next, 20% hydrochloric acid (10 ml) was added, and the mixture was hydrolyzed at 70 °C for 10 min, then filtered. The filtrate was extracted with dichloromethane and the organic layer was dried, then evaporated *in vacuo*. Chromatography of the residue with dichloromethane as the eluant gave **34a** (0.677 g, 23%), mp 81—83 °C (ether). *Anal.* Calcd for $C_{14}H_{11}Cl_2NO_2$: C, 56.78; H, 3.74; Cl, 23.94; N, 4.73. Found: C, 56.47; H, 3.92; Cl, 23.73; N, 4.89. ^{1}H-NMR (in $CDCl_3$) δ: 3.67 (3H, s, O–C$\underline{H}_3$), 6.1 (2H, br, N$\underline{H}_2$), 7.00 (1H, s, arom. H), 7.30—7.75 (5H, m, arom. H).

Compound **34b** was obtained in a similar manner with heating at 75 °C for 90 h using propionitrile instead of refluxing for 7 h with benzonitrile. Compound **34b**: Yield 34%, mp 86 °C (hexane–ether). *Anal.* Calcd for $C_{10}H_{11}Cl_2NO_2$: C, 48.41; H, 4.47; Cl, 28.58; N, 5.65. Found: C, 48.24; H, 4.46; Cl, 28.40; N, 5.74. ^{1}H-NMR (in $CDCl_3$) δ: 1.22 (3H, t, J=7.1, C$\underline{H}_3$), 2.95 (2H, q, J=7.1, COC$\underline{H}_2$), 3.85 (3H, s, O–C$\underline{H}_3$), 6.66 (2H, br, N$\underline{H}_2$), 7.25 (2H, s, arom. H).

3,4-Dichloro-5-methoxybenzophenone (35a)——A solution of 45% nitrosylsulfuric acid in sulfuric acid (2.0 g) was added dropwise to a solution of **34a** (0.975 g, 0.0033 mol) in THF (15 ml) at −25——16 °C over 7 min with stirring, then the reaction temperature was raised gradually to 0 °C over 1.5 h. Next, 45—50% aqueous hypophosphorus acid (25 ml) was added at 0—9 °C over 30 min and the solution was stirred at 6—10 °C for 2 h. Dichloromethane was added to the reactant, then the mixture was extracted, dried and evaporated *in vacuo*. Chromatography of the residue using hexane–dichloromethane (1 : 4) as the eluant gave **35a** (0.868 g, 94%), mp 85 °C (hexane–ether). *Anal.* Calcd for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59; Cl, 25.22. Found: C, 59.83; H, 3.58; Cl, 25.50. ^{1}H-NMR (in $CDCl_3$) δ: 3.96 (3H, s, O–C$\underline{H}_3$), 7.25—7.87 (7H, m, arom. H).

Compound **35b** was obtained in a similar manner. Compound **35b**: Yield 93%, mp 85 °C (hexane–ether). *Anal.* Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; Cl, 30.42. Found: C, 51.31; H, 4.34; Cl, 30.38. ^{1}H-NMR (in $CDCl_3$) δ: 1.22 (3H, t, J=7.2, C$\underline{H}_3$), 2.95 (2H, q, J=7.2, C$\underline{H}_2$), 3.95 (3H, s, O–C$\underline{H}_3$), 7.42 and 7.61 (2H, AB, J=1.8, arom. H).

3,4-Dichloro-5-hydroxybenzophenone (36a)——Boron tribromide (2.40 g, 0.0096 mol) was added to a solution of **35a** (1.627 g, 0.0058 mol) in dichloromethane (10 ml) at 5 °C with stirring. The mixture was maintained at the same temperature for 1 h, than allowed to react at room temperature for 20 min. The reactant was poured into ice-cooled 4% hydrochloric acid (50 ml), then extracted with dichloromethane. The organic layer was washed with 4% hydrochloric acid then brine, dried and evaporated *in vacuo*. Treatment of the residue with dichloromethane gave **36a** (1.513 g, 98%), mp 177 °C (dichloromethane). *Anal.* Calcd for $C_{13}H_8Cl_2O_2 \cdot 1/2H_2O$: C, 56.55; H, 3.29; Cl, 25.68. Found: C, 56.69; H, 3.17; Cl, 25.55. ^{1}H-NMR (in DMSO-d_6) δ: 7.30 and 7.34 (2H, ABq, J=1.8, arom. H), 7.45—7.85 (5H, m, arom. H), 11.13 (1H, s, O$\underline{H}$).

3′,4′-Dichloro-5′-hydroxypropiophenone (36b)——A solution of **35b** (1.54 g, 0.0062 mol) in 30% hydrogen bromide in acetic acid (35 ml) was refluxed for 48 h, then evaporated *in vacuo*. The residue was treated with hexane–

ether to obtain **36b** (1.28 g, 88%), mp 133—134 °C (ether). *Anal.* Calcd for $C_9H_8Cl_2O_2$: C, 49.35; H, 3.68; Cl, 32.39. Found: C, 48.81; H, 3.69; Cl, 32.44. ^{1}H-NMR (in acetone-d_6) δ: 1.10 (3H, t, J=7.1, C$\underline{H}_3$), 3.00 (2H, q, J=7.1, C$\underline{H}_2$), 7.53 and 7.63 (2H, AB, J=1.8, arom. H), 9.0—10.0 (1H, br, O$\underline{H}$).

3,4-Dichloro-5-allyloxybenzophenone (37a)——A mixture of **36a** (1.433 g, 0.0054 mol), potassium carbonate (0.753 g, 0.0055 mol), DMF (15 ml) and allyl bromide (1.85 g, 0.0153 mol) was allowed to react with stirring at room temperature. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in ether. This solution was washed with 5% aqueous sodium hydroxide, 5% hydrochloric acid, then brine, and dried and evaporated *in vacuo*. Treatment of the residue with hexane–ether gave **37a** (1.596 g, 97%), mp 78 °C (hexane–ether). *Anal.* Calcd for $C_{16}H_{12}Cl_2O_2$: C, 62.56; H, 3.94; Cl, 23.08. Found: C, 62.43; H, 3.91; Cl, 22.89. ^{1}H-NMR (in $CDCl_3$) δ: 4.66 (2H, d, t, J=4.8, 1.5, O–C$\underline{H}_2$),5.23—5.60 (2H, m, C$\underline{H}_2$), 5.85—6.32 (1H, m, C$\underline{H}$), 7.23—7.88 (7H, m, arom. H).

Compound **37b** was obtained in a similar manner. Compound **37b**: Yield 94%, mp 50 °C (hexane–ether). *Anal.* Calcd for $C_{12}H_{12}Cl_2O_2$: C, 55.62; H, 4.67; Cl, 27.36. Found: C, 55.64; H, 4.53; Cl, 27.36. ^{1}H-NMR (in $CDCl_3$) δ: 1.21 (3H, t, J=7.1, C$\underline{H}_3$), 2.93 (2H, J=7.1, O–C$\underline{H}_2$), 4.65 (2H, d, t, J=5.1, 1.5, O–C$\underline{H}_2$), 5.22—5.60 (2H, m, C$\underline{H}_2$), 5.83—6.30 (1H, m, C$\underline{H}$), 7.41 and 7.62 (2H, AB, J=1.8, arom. H).

2-Allyl-4,5-dichloro-3-hydroxybenzophenone (38a)——**37a** (1.535 g, 0.005 mol) was heated on an oil bath at 235 °C for 8 min. After cooling, it was chromatographed and eluted with hexane–dichloromethane (1 : 1) to obtain **38a** (1.028 g, 67%), mp 105 °C (hexane–ether). *Anal.* Calcd for $C_{16}H_{12}Cl_2O_2$: C, 62.56; H, 3.94; Cl, 23.08. Found: C, 62.34; H, 3.89; Cl, 23.31. ^{1}H-NMR (in $CDCl_3$) δ: 3.42 (2H, d, t, J=6.0, 1.5, C$\underline{H}_2$), 4.75—5.05 (2H, m, C$\underline{H}_2$), 5.60—6.00 (1H, m, C$\underline{H}$), 6.03 (1H, s, O$\underline{H}$), 7.02 (1H, s, arom. H), 7.33—7.90 (5H, m, arom. H).

Compound **38b** was obtained in a similar manner. Compound **38b**: Yield 59%, mp 80 °C (hexane–ether). *Anal.* Calcd for $C_{12}H_{12}Cl_2O_2$: C, 55.62; H, 4.67; Cl, 27.36. Found: C, 55.30; H, 4.58; Cl, 27.13. ^{1}H-NMR (in $CDCl_3$) δ: 1.16 (3H, t, J=7.1, C$\underline{H}_3$), 2.80 (2H, q, J=7.1, C$\underline{H}_2$), 3.51 (2H, d, t, J=6.2, 1.5, C$\underline{H}_2$), 4.82—5.15 (2H, m, C$\underline{H}_2$), 5.65—6.10 (1H, m, C$\underline{H}$), 6.12 (1H, s, O$\underline{H}$), 7.15 (1H, s, arom. H).

6,7-Dichloro-2-hydroxymethyl-2,3-dihydrobenzofuran-4-yl Phenyl Ketone (39a)——*m*-Chloroperbenzoic acid (*m*-CPBA) (1.39 g, 0.0081 mol) and potassium fluoride (0.373 g, 0.0064 mol) were added to a solution of **38a** (0.986 g, 0.0032 mol) in dichloromethane (40 ml) with stirring, and the reaction was allowed to proceed for 17 h. The reactant was washed with 5% sodium hydroxide, then brine, and dried then evaporated *in vacuo*. The residue was chromatographed and eluted with dichloromethane–acetone (20 : 1) to obtain **39a** (0.793 g, 76%), mp 102—104 °C (hexane–ether). *Anal.* Calcd for $C_{16}H_{12}Cl_2O_3$: C, 59.47; H, 3.74; Cl, 21.94. Found: C, 59.35; H, 3.83; Cl, 21.90. ^{1}H-NMR (in $CDCl_3$) δ: 2.20 (1H, br, O$\underline{H}$), 3.28 (1H, 2 × d, J=17.3, 8.3, Ph–C$\underline{H}_2$–CH), 3.55 (1H, 2 × d, J=17.3, 9.0, Ph–C$\underline{H}_2$–CH), 3.60—4.15 (2H, m, O–C$\underline{H}_2$), 4.93—5.30 (1H, m, O–C$\underline{H}$), 7.20 (1H, s, arom. H), 7.37—7.90 (5H, m, arom. H).

6,7-Dichloro-2-hydroxymethyl-2,3-dihydrobenzofuran-4-yl Ethyl Ketone (39b)——*m*-CPBA (1.78 g, 0.0103 mol) and potassium fluoride (0.48 g, 0.008 mol) were added to a soltuion of **38b** (1.055 g, 0.004 mol) in dichloromethane (25 ml) with stirring, which was continued for 20 h at room temperature. The reaction mixture was washed with an aqueous potassium carbonate solution, dried and evaporated *in vacuo*. The residue was chromatographed and eluted with dichloromethane–acetone (20 : 1). The first fractions were treated with ether to obtain **40** (0.500 g, 47%), mp 174 °C (ether). *Anal.* Calcd for $C_{12}H_{12}Cl_2O_3$: C, 52.39; H, 4.40; Cl, 25.77. Found: C, 52.15; H, 4.30; Cl, 25.61. ^{1}H-NMR (in acetone-d_6) δ: 0.99 (3H, t, J=7.3, C$\underline{H}_3$), 2.19 (2H, q, J=7.3, C$\underline{H}_2$), 2.68 (1H, d, J=18.0, Ph–C$\underline{H}_2$), 3.13 (1H, 3 × d, J=18.0, 4.5, 1.8, Ph–C$\underline{H}_2$), 3.66 (1H, 2 × d, J=7.5, 2.0, O–C$\underline{H}_2$), 3.97 (1H, 3 × d, J=7.5, 6.0, 1.8, O–C$\underline{H}_2$), 4.93 (1H, br t, J=5.5, O–C$\underline{H}$), 7.04 (1H, s, arom. H), 8.47 (1H, br s, O$\underline{H}$). The subsequent fractions eluted with the same solvent gave **39b** (0.494 g, 36%), mp 91—93 °C (ether). *Anal.* Calcd for $C_{12}H_{12}Cl_2O_3$: C, 52.39; H, 4.40; Cl, 25.77. Found: C, 52.13; H, 4.26; Cl, 25.71. ^{1}H-NMR (in $CDCl_3$) δ: 1.16 (3H, t, J=7.1, C$\underline{H}_3$), 2.53 (1H, br, O$\underline{H}$), 2.91 (2H, q, J=7.1, C$\underline{H}_2$), 3.38 (1H, 2 × d, J=18.0, 7.8, Ph–C$\underline{H}_2$–CH), 3.66 (1H, 2 × d, J=18.0, 9.0, Ph–C$\underline{H}_2$–CH), 3.74 (1H, 2 × d, J=12.3, 5.6, O–C$\underline{H}_2$), 3.95 (1H, 2 × d, J=12.3, 3.3, O–C$\underline{H}_2$), 4.90—5.25 (1H, m, O–C$\underline{H}$), 7.47 (1H, s, arom. H).

4-Benzoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic Acid (41a)——Jones reagent[10] (1.5 ml) was added to a solution of **39a** (0.682 g, 0.0021 mol) in acetone (12 ml) at 15 °C with stirring, which was continued for 7.5 h at the same temperature. The insoluble chromium salts were collected by filtration and washed with acetone. The washings and the filtrates were combined, then evaporated *in vacuo*. The residue was dissolved in ethyl acetate and the solution was washed with water, then extracted three times with 5% aqueous sodium hydroxide. The alkaline solution was acidified with concentrated hydrochloric acid, then extracted with ethyl acetate. The organic layer was washed with brine, dried, then evaporated *in vacuo*. The residue was chromatographed and eluted with dichloromethane–methanol–acetic acid (400 : 25 : 2) to obtain **41a** (0.385 g, 54%, from hexane–dichloromethane). ^{1}H-NMR (in acetone-d_6) δ: 3.55 (1H, 2 × d, J=17.8, 6.6, Ph–C$\underline{H}_2$–CH), 3.88 (1H, 2 × d, J=17.8, 10.2, Ph–C$\underline{H}_2$–CH), 5.50 (1H, 2 × d, J=10.2, 6.6, O–CH), 5.0—6.5 (br, COO$\underline{H}$), 7.26 (1H, s, arom. H), 7.42—7.90 (5H, m, arom. H).

Compound **41b** was obtained in a similar manner. Compound **41b**: Yield 76%. ^{1}H-NMR (in acetone-d_6) δ: 1.11 (3H, t, J=7.1, C$\underline{H}_3$), 3.01 (2H, q, J=7.1, C$\underline{H}_2$), 3.67 (1H, 2 × d, J=18.0, 7.1, Ph–C$\underline{H}_2$–CH), 3.99 (1H, 2 × d, J=18.0, 10.2, Ph–C$\underline{H}_2$–CH), 5.45 (1H, 2 × d, J=10.2, 6.7, 1.0, O–C$\underline{H}$), 7.0—9.5 (br, COO$\underline{H}$), 7.66 (1H, s, arom. H).

Biological Activities——Diuretic, saluretic and uricosuric activities were evaluated by the methods described in

the previous paper.[1)]

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