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Studies on Uricosuric Diuretics. I. 6,7-Dichloro-5-sulfamoyl-2,3-dihydrobenzofuran-2-carboxylic Acids

HIROSHI HARADA,* YOSHIHIRO MATSUSHITA, MITSUAKI YODO, MASUHISA NAKAMURA and YUKIO YONETANI

Shionogi Research Laboratories, Shionogi & Co., Ltd., Sagisu 5-12-4, Fukushima-ku, Osaka 553, Japan

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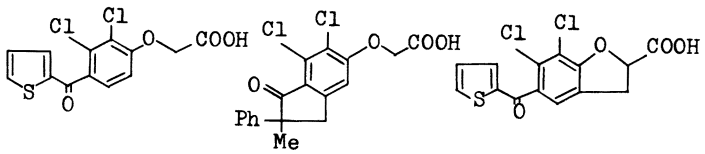
2,3-Dihydrobenzofuran derivatives having various sulfamoyl groups at the 5-position were synthesized and tested for oral diuretic and saluretic activities in rats and mice. Intraperitoneal uricosuric activity was also tested by a clearance method using oxonate-treated rats. Structure–activity relationships are presented. The 6,7-dichloro-5-*N*,*N*-disubstituted sulfamoyl-2,3-dihydrobenzofuran-2-carboxylic acids (**9ab**, **ac**, **13a** and **b**) having lower alkyl substituents showed the most potent diuretic and saluretic activities among the compounds synthesized. Hyperuricosuric activity was observed in 6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acids and 2-hydroxymethyl-6,7-dichloro-2,3-dihydrobenzofurans having a 5-sulfamoyl group, with relatively small substituents (**9aa**—**ac**, **af**, **ak**, **al**, **an**, **ao** and **16a**—**c**). The saluretic activity of **9ab** showed a high-ceiling profile. Examination of the enantiomers of **9ab** revealed that the (−)-enantiomer is responsible for most of the diuretic and saluretic activities, while the (+)-enantiomer is responsible for most of the uricosuric activity.

Keywords——diuretic activity; saluretic activity; uricosuric activity; antihypertensive activity; 2,3-dihydrobenzofuran-5-sulfonamide; structure–activity relationship; S-8666

Diuretics are widely used as the agents of choice in hypertension therapy. Thiazide drugs, which are most frequently used other than antialdosterone-type compounds, accelerate excretion of Na and Cl by restraining their reabsorption at the nephron: this action is favorable with respect to the diuretic effect, but frequently causes side effects such as hypokalemia, glycohemia and hyperuricemia. Loop diuretics, which cause potent but



1 tienilic acid 2 indacrinone 3

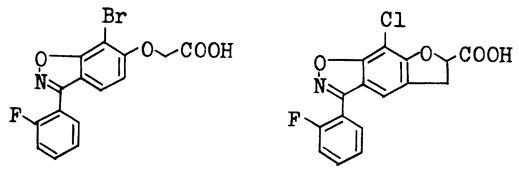


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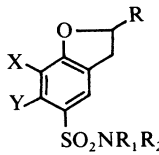
Chart 1

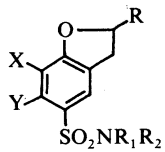
TABLE I. Substituted 2,3-Dihydrobenzofuran-5-sulfonamides



No.	X	Y	R_1	R_2	R	Yield (%)	mp (°C)	Recrystn. solvent[a)]	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
9aa	Cl	Cl	H	H	COOH	91	227—229	EA–E	$C_9H_7Cl_2NO_5S$	34.63	2.26	22.72	4.49	10.27
										(34.73	2.49	22.78	4.45	10.09)
9ab	Cl	Cl	CH_3	CH_3	COOH	94	155—156	D–E–H	$C_{11}H_{11}Cl_2NO_5S$	38.84	3.26	20.84	4.12	9.43
										(38.64	2.99	20.92	4.31	9.66)
(−)-**9ab**							130—131	EA–H		(38.87	3.32	20.79	4.17	9.28)
(+)-**9ab**							130—131	EA–H		(39.07	3.43	20.55	4.03	9.17)
9ac	Cl	Cl	C_2H_5	C_2H_5	COOK	96	235—236	EL–W	$C_{13}H_{14}Cl_2KNO_5S \cdot H_2O$	36.79	3.80	16.70	3.30	7.56
										(36.64	3.81	16.92	3.29	7.89)
9ad	Cl	Cl	*n*-C_3H_7	*n*-C_3H_7	COOH	84	120—121	EA–E	$C_{15}H_{19}Cl_2NO_5S$	45.46	4.83	17.89	3.53	8.09
										(45.36	4.80	17.83	3.25	8.12)
9ae	Cl	Cl	iso-C_3H_7	iso-C_3H_7	COOH	80	176—177	EA–E	$C_{15}H_{19}Cl_2NO_5S$	45.46	4.83	17.89	3.53	8.09
										(45.23	4.75	17.95	3.48	7.91)
9af	Cl	Cl	CH_3	*n*-C_4H_9	COOH	76	92—93	EA–H	$C_{14}H_{17}Cl_2NO_5S$	43.99	4.48	18.55	3.66	8.39
										(43.85	4.35	18.43	3.77	8.33)
9ag	Cl	Cl	$PhCH_2$	$PhCH_2$	COOH	72	127—128	EA–E	$C_{23}H_{19}Cl_2NO_5S$	56.11	3.89	14.40	2.84	6.51
										(56.01	3.81	14.62	2.83	6.31)
9ah	Cl	Cl	CH_3	$PhCH_2$	COOH	80	148—149	EA–E	$C_{17}H_{15}Cl_2NO_5S$	49.05	3.63	17.03	3.36	7.70
										(48.90	3.72	17.20	3.42	7.56)
9ai	Cl	Cl	CH_3	Ph	COOK	80	194—195	EL–W	$C_{16}H_{12}Cl_2KNO_5S \cdot H_2O$	41.93	3.08	15.46	3.05	6.99
										(41.73	3.14	15.75	3.30	7.06)
9aj	Cl	Cl	CH_3	*cyclo*-C_6H_{11}	COOH	52	148—149	D–E–H	$C_{16}H_{19}Cl_2NO_5S$	47.07	4.69	17.37	3.43	7.85
										(47.34	4.73	17.12	3.41	7.50)
9ak	Cl	Cl		$-(CH_2)_4-$	COOH	99	181—182	EA–E	$C_{13}H_{13}Cl_2NO_5S$	42.64	3.58	19.36	3.82	8.76
										(42.44	3.59	19.20	3.77	8.56)
9al	Cl	Cl		$-(CH_2)_5-$	COOH	99	199—200	EA–E	$C_{14}H_{15}Cl_2NO_5S$	44.22	3.98	18.65	3.68	8.43
										(44.17	3.95	18.57	3.71	8.23)
9am	Cl	Cl		$-(CH_2)_2O(CH_2)_2-$	COOH	89	228—229	EA–E	$C_{13}H_{13}Cl_2NO_6S$	40.85	3.43	18.55	3.66	8.39
										(40.43	3.39	18.37	3.60	8.28)
9an	Cl	Cl	H	CH_3	COOH	88	215—216	EA–E	$C_{10}H_9Cl_2NO_5S$	36.83	2.78	21.74	4.29	9.83
										(36.93	3.04	21.09	4.17	9.51)
9ao	Cl	Cl	H	*n*-C_3H_7	COOH	95	200—201	EA–E	$C_{12}H_{13}Cl_2NO_5S$	40.69	3.70	20.02	3.95	9.05
										(40.52	3.73	19.96	3.91	8.82)

9ap	Cl	Cl	H	iso-C_3H_7	COOH	95	184—185	EA–E	$C_{12}H_{13}Cl_2NO_5S$	40.69	3.70	20.02	3.95	9.05
										(40.53	3.68	19.72	4.00	8.89)
9aq	Cl	Cl	H	$PhCH_2$	COOH	85	199—200	EA–E	$C_{16}H_{13}Cl_2NO_5S$	47.78	3.26	17.63	3.48	7.97
										(47.90	3.47	17.68	3.40	7.59)
9ar	Cl	Cl	H	Ph	COOH	86	201—202	EA–E	$C_{15}H_{11}Cl_2NO_5S$	46.41	2.86	18.26	3.61	8.26
										(46.31	2.92	17.96	3.61	8.06)
9as	Cl	Cl	H	4-Cl–Ph	COOH	94	189—190	EA–E	$C_{15}H_{10}Cl_3NO_5S$	42.63	2.38	25.16	3.31	7.59
										(42.93	2.71	24.55	3.20	7.42)
9at	Cl	Cl	H	4-CH_3O–Ph	COOH	91	173—174	E–H	$C_{16}H_{13}Cl_2NO_6S$	45.95	3.13	16.95	3.35	7.67
										(45.99	3.23	16.74	3.34	7.52)
9au[b]	Cl	Cl	H	O N$(CH_2)_2$	COOH	87	250—251	W	$C_{15}H_{18}Cl_2N_2O_6S\cdot$ HCl	39.01	4.15		6.07	6.94
										(38.96	4.17		6.06	7.07)
9av	Cl	H	CH_3	CH_3	COOH	97	164—166	A–H	$C_{11}H_{12}ClNO_5S$	43.21	3.96	11.60	4.58	10.49
										(43.01	4.00	11.51	4.57	10.21)
9aw	Cl	H	C_2H_5	C_2H_5	COOH	91	164—165	A–H	$C_{13}H_{16}ClNO_5S$	46.78	4.83	10.62	4.20	9.60
										(46.59	4.85	10.30	4.21	9.34)
9ax	H	Cl	CH_3	CH_3	COOH	94	145	A–H	$C_{11}H_{12}ClNO_5S$	43.21	3.96	11.60	4.58	10.49
										(42.85	4.02	11.75	4.59	10.30)
9ay	H	Cl	C_2H_5	C_2H_5	COOH	87	83—85	A–H	$C_{13}H_{16}ClNO_5S\cdot$ 3/4 H_2O	44.96	5.08	10.21	4.03	9.23
										(44.92	4.93	10.17	4.32	9.49)
9az	Br	H	CH_3	CH_3	COOH	93	194—195	A–H	$C_{11}H_{12}BrNO_5S\cdot$ 3/4 H_2O	37.73	3.45	22.82[c]	4.00	9.16
										(37.73	3.57	22.97[c]	3.87	9.20)
9ba	Br	H	C_2H_5	C_2H_5	COOH	99	161—162	A–H	$C_{13}H_{16}BrNO_5S\cdot$ 3/4 H_2O	41.28	4.26	21.13[c]	3.70	8.48
										(41.26	4.37	20.42[c]	3.78	8.35)
9bb	CH_3	CH_3	H	H	COOH	92	229—230	EA–E	$C_{11}H_{13}NO_5S$	48.70	4.83		5.16	11.82
										(48.41	4.85		5.19	11.18)
9bc	CH_3	CH_3	H	CH_3	COOH	87	179—180	EA–E	$C_{12}H_{15}NO_5S$	50.52	5.30		4.91	11.24
										(50.43	5.23		4.92	11.16)
9bd	CH_3	CH_3	CH_3	CH_3	COOH	87	127—128	EA–E	$C_{13}H_{17}NO_5S$	52.16	5.72		4.68	10.71
										(52.11	5.57		4.73	10.62)
10a	Cl	Cl	CH_3	CH_3	COOPht[d]	56	152—154	EA–H	$C_{19}H_{15}Cl_2NO_7S\cdot$ 1/3 H_2O	47.71	3.45	14.82	2.92	6.70
										(47.88	3.26	14.61	2.99	6.50)
10b	Cl	Cl	CH_3	CH_3	COOPOM[e]	69	113—114	EA–E	$C_{17}H_{21}Cl_2NO_7S\cdot$ 1/3 H_2O	44.94	4.66	15.61	3.08	7.06
										(44.93	4.65	15.73	3.14	6.98)
10c	Cl	Cl	CH_3	CH_3	$COOCH_2COOH$	85	149—150	A–E–H	$C_{13}H_{13}Cl_2NO_7S$	39.21	3.29	17.81	3.52	8.05
										(39.16	3.42	17.65	3.60	7.98)
10d	Cl	Cl	C_2H_5	C_2H_5	$COOCH_2COOH$	70	102—103	A–E–H	$C_{15}H_{17}Cl_2NO_7S$	42.27	4.02	16.63	3.29	7.52
										(42.03	4.04	16.80	3.32	7.45)
11a	Cl	Cl	CH_3	CH_3	$CONH_2$	97	209—210	EA–E	$C_{11}H_{12}Cl_2N_2O_4S$	38.95	3.57	20.90	8.26	9.45
										(38.70	3.62	21.16	8.22	9.52)
11b	Cl	Cl	CH_3	CH_3	$CONHCH_3$	98	182—184	EL–E	$C_{12}H_{14}Cl_2N_2O_4S$	40.80	4.00	20.07	7.93	9.08
										(40.59	4.01	20.03	7.91	8.96)

TABLE I. (continued)



No.	X	Y	R_1	R_2	R	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
11c	Cl	Cl	CH_3	CH_3	$CON(CH_3)_2$	70	171—172	A–E	$C_{13}H_{16}Cl_2N_2O_4S \cdot 1/4H_2O$	41.95 (42.26	4.28 4.48		7.54 7.53	8.63 8.62)
12	Cl	Cl	CH_3	$COOC_2H_5$	COOH	63	199—201	A–E–H	$C_{13}H_{13}Cl_2NO_7S$	39.21 (39.40	3.29 3.43	17.81 17.66	3.52 3.54	8.05 7.92)
13a	Cl	Cl	CH_3	C_2H_5	COONa	76	176—177	EL–W	$C_{12}H_{12}Cl_2NNaO_5S \cdot H_2O$	36.56 (36.58	3.58 3.47		3.55 3.41	8.13 8.37)
13b	Cl	Cl	CH_3	n-C_3H_7	COONa	73	162—163	EL–W	$C_{13}H_{14}Cl_2NNaO_5S \cdot 2H_2O$	36.63 (36.70	4.26 4.15	16.63 16.76	3.29 3.28	7.52 7.74)
16a	Cl	Cl	H	H	CH_2OH	99	183—186	EL–EA–E	$C_9H_9Cl_2NO_4S$	36.26 (36.09	3.06 3.12	23.78 23.48	4.70 4.70	10.75 10.57)
16b	Cl	Cl	CH_3	CH_3	CH_2OH	89	133—134	EA–E	$C_{11}H_{13}Cl_2NO_4S$	40.50 (40.32	4.02 3.98	21.74 21.56	4.29 4.21	9.83 9.71)
16c	Cl	Cl	CH_3	$PhCH_2$	CH_2OH	76	73—74	EA–E	$C_{17}H_{17}Cl_2NO_4S \cdot 1/4H_2O$	50.19 (50.11	4.34 4.33		3.44 3.62	7.88 7.76)
16d	Cl	Cl	CH_3	Ph	CH_2OH	87	117—118	EA–E	$C_{16}H_{15}Cl_2NO_4S$	49.50 (49.46	3.89 3.79	18.26 18.18	3.61 3.50	8.26 8.26)
16e	Cl	Cl	H	CH_3	CH_2OH	78	118—119	EA–E	$C_{10}H_{11}Cl_2NO_4S$	38.48 (38.36	3.55 3.50	22.71 22.72	4.49 4.41	10.27 10.00)
16f	Cl	Cl	H	$PhCH_2$	CH_2OH	91	55—56	A–E	$C_{16}H_{15}Cl_2NO_4S \cdot 1/4H_2O$	48.93 (49.06	3.98 4.09	18.05 17.60	3.57 3.45	8.16 7.60)
16g	Cl	Cl	H	Ph	CH_2OH	81	161—162	A–E	$C_{15}H_{13}Cl_2NO_4S$	48.14 (48.10	3.50 3.58	18.95 19.07	3.74 3.69	8.57 8.31)
17a	Cl	Cl	H	H	CH_2Cl	66	195—196	EA–E	$C_9H_8Cl_3NO_3S$	34.14 (34.09	2.55 2.71	33.60 33.22	4.42 4.40	10.13 10.20)
17b	Cl	Cl	CH_3	CH_3	CH_2Cl	63	77—78	D–H	$C_{11}H_{12}Cl_3NO_3S$	38.34 (38.09	3.51 3.54	30.86 30.63	4.06 4.10	9.30 9.22)
18a	Cl	Cl	H	H	$CH_2OC_2H_5$	24	148—149	EA–E	$C_{11}H_{13}Cl_2NO_4S$	40.50 (40.37	4.02 3.95	21.74 21.50	4.29 4.22	9.83 9.79)
18b	Cl	Cl	CH_3	CH_3	$CH_2OC_2H_5$	43	91—92	A–E	$C_{13}H_{17}Cl_2NO_4S$	44.08 (44.19	4.84 4.87	20.02 20.13	3.95 4.05	9.05 8.82)

a) A = acetone, D = dichloromethane, E = ether, EA = ethyl acetate, EL = ethanol, H = hexane, W = water. *b*) HCl salt. *c*) Br. *d*) Pht = phthalidyl. *e*) POM = pivaloyloxymethyl.

temporary diuresis, occasionally fail to decrease blood pressure because of their short action time. Recently, however, they have been used in sustained-release preparations in order to avoid the side effects caused by thiazides.

One large family of modern diuretics, first recognized with the discovery of ethacrynic acid, is that of aryloxyacetates.[1] Recently, many new compounds having interesting pharmacological actions, including uricosuric and diuretic activities have been reported from this family, *e.g.*, tienilic acid (**1**),[1] indacrinone (**2**),[1,2] **3**,[1,3] HP-522 (**4**),[4] and **5**[5] (Chart 1).

We tried to create a new type of uricosuric diuretic which would display temporary diuretic action and inhibit reabsorption of uric acid by renal tubules. The structure of 5-acyl-2,3-dihydrobenzofuran-2-carboxylic acid, found in compounds **3**—**5**, seemed to be a developed form of 4-acylphenoxyacetic acid. A promising substituent was considered to be the sulfamoyl group, which is found in thiazide diuretics and probenecid, a uricosuric drug. We therefore synthesized some dihydrobenzofuran derivatives with 5-sulfamoyl substituents and found that they display both actions.

Chemistry

The compounds prepared for this study are shown in Table I and their syntheses are outlined in Charts 2 and 3. The starting materials (**7a** and **14**,[3] **7b**, **c** and **e**,[6] **d**[7] are described in the literature.

5-Sulfamoyl-2,3-dihydrobenzofuran-2-carboxylic acids (**9aa**—**az** and **9ba**—**bd**) were obtained by chlorosulfonation of the corresponding esters (**7**) with chlorosulfonic acid and thionyl chloride followed by aminolysis and hydrolysis. The esters **10a** and **b** were prepared by alkylation of the potassium salt of **9ab** with phthalidyl bromide or iodomethyl pivalate. The esters **10c** and **d** were prepared by the reaction of diphenylmethyl glycolate with acid chlorides

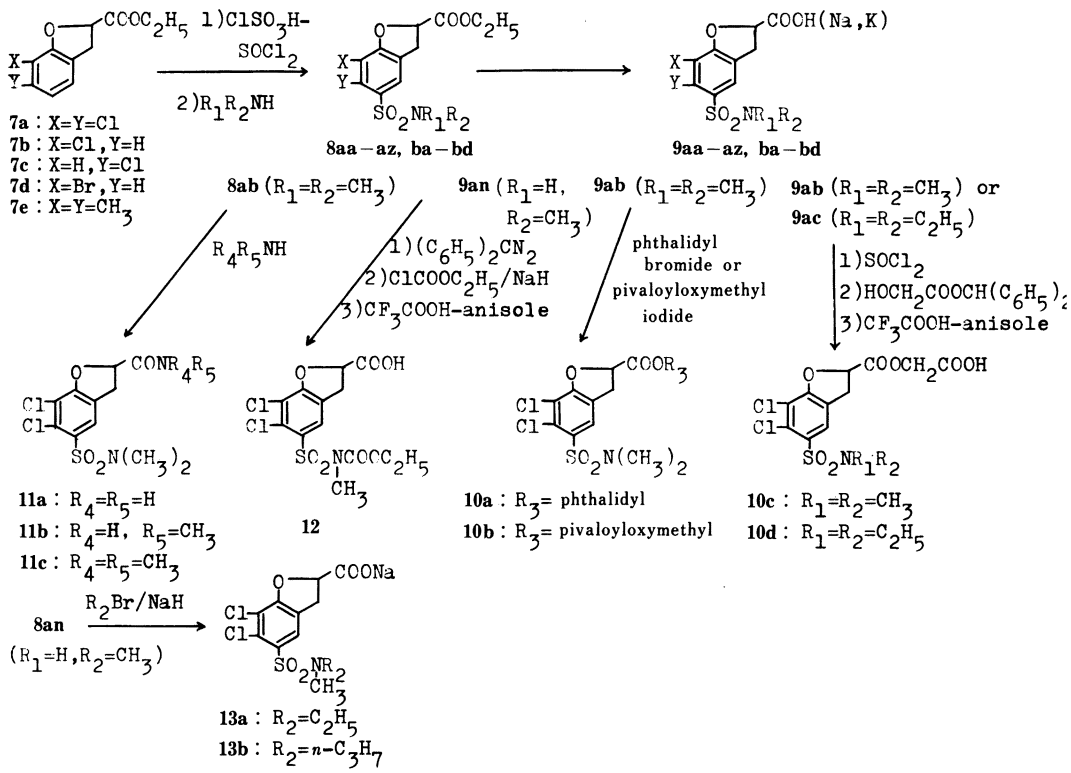


Chart 2

of **9ab** and **9ac** followed by hydrolysis with trifluoroacetic acid. The 2-carboxamides (**11a—c**) were obtained by aminolysis of the ethyl esters (**8ab**). The urethane (**12**) was prepared by ethoxycarbonylation of **9an** benzhydryl ester with ethyl chloroformate and sodium hydride followed by hydrolysis with trifluoroacetic acid and anisole. The 5-(*N*-ethyl-*N*-methyl)- and 5-(*N*-methyl-*N*-propyl)sulfamoyl derivatives (**13a** and **b**) were prepared by alkylation of **8an** with the corresponding alkyl halides in the presence of sodium hydride followed by alkaline hydrolysis (Chart 2).

The 2-hydroxymethyl-2,3-dihydrobenzofuran-5-sulfonamide derivatives (**16**) were prepared by sulfamoylation of the acetate of **14** followed by alkaline hydrolysis through a procedure similar to that described for the preparation of **9** (Chart 3). 2-Chloromethyl derivatives (**17a** and **b**) were obtained by chlorination of **16a** and **b**, and 2-ethoxymethyl derivatives (**18a** and **b**) were synthesized by sulfamoylation of the ethoxy derivative of **14** or by direct ethylation of **16b**, respectively. Intermediates to the above compounds are described in the experimental section.

Optical resolution of **9ab** was carried out as outlined in Chart 4. The diastereoisomeric amides (**19**) were obtained by the reaction of the acid chloride of **9ab** with L-proline *tert*-butyl ester in the presence of triethylamine and 4-*N*,*N*-dimethylaminopyridine in dry benzene under ice-cooling. One isomer (**19a**) was readily crystallized from the mixture and the resultant mother liquor was separated by silica gel column chromatography. The separated diastereoisomers (**19a** and **b**) were hydrolyzed in aqueous sulfuric acid–dioxane under reflux to give the optically active enantiomers [(−)- and (+)-**9ab**], which showed the same melting points and optical rotations (except for the sign).

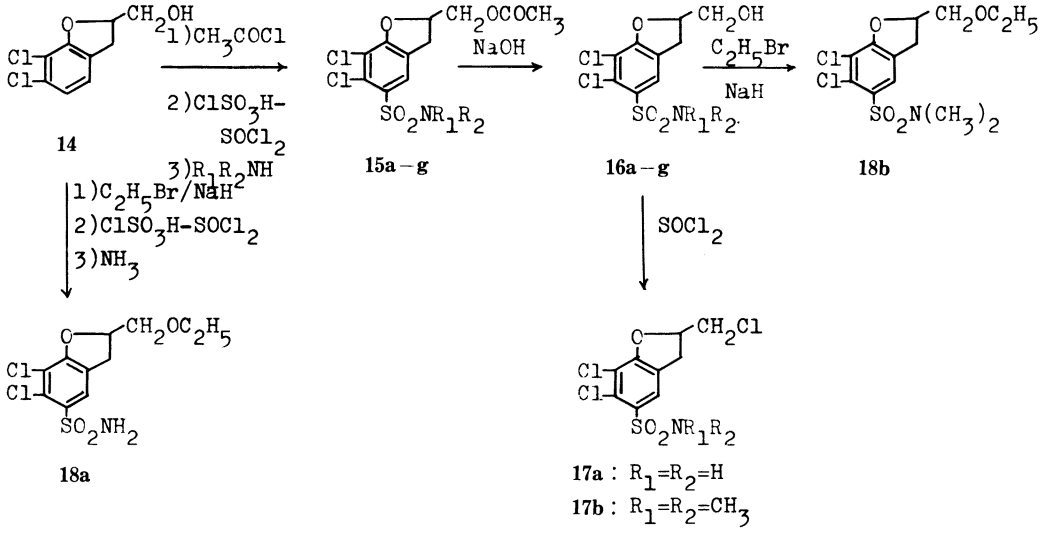


Chart 3

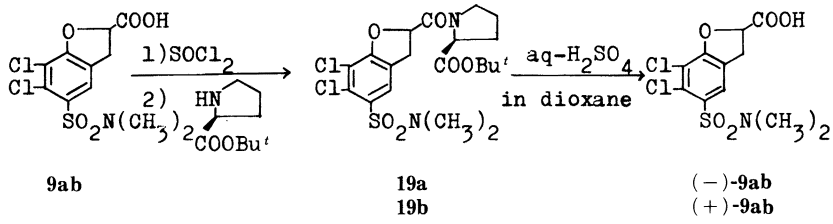


Chart 4

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

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.
9aa	50	26 (N)	0.88 (N)	0.28 (1.5)	30	27 (N)	0.83 (N)	0.92 (1.7)
9ab	50	39 (1.4)	3.0 (4.9)	0.87 (4.5)	30	48 (1.9)	4.7 (9.1)	1.2 (2.2)
(−)-**9ab**	50	47 (2.0)	3.8 (8.3)	1.2 (5.0)	30	73 (3.3)	7.8 (15)	1.8 (3.9)
(+)-**9ab**	50	28 (1.2)	0.53 (N)	0.32 (N)	30	28 (N)	1.3 (2.6)	0.85 (1.8)
9ac	50	40 (1.6)	3.0 (6.0)	1.1 (4.5)	30	85 (2.9)	9.3 (11)	2.1 (3.0)
9ad	50	28 (1.3)	1.3 (2.8)	0.37 (N)	30	41 (2.0)	3.8 (4.9)	1.0 (1.5)
9ae	50	25 (N)	0.77 (N)	0.23 (N)	30	29 (N)	2.3 (3.0)	0.96 (1.4)
9af	50	33 (1.4)	1.8 (3.6)	0.63 (2.5)	30	61 (2.3)	6.3 (8.0)	2.0 (2.5)
9ag	50	23 (N)	0.72 (1.5)	0.25 (N)	30	31 (N)	1.3 (N)	1.0 (N)
9ah	50	36 (1.6)	2.0 (4.1)	0.58 (2.5)	30	64 (2.3)	6.3 (7.5)	1.7 (2.1)
9ai	50	39 (1.6)	2.5 (5.1)	0.73 (2.9)	30	44 (1.7)	4.3 (5.4)	1.5 (1.7)
9aj	50	25 (N)	0.72 (N)	0.32 (N)	30	29 (N)	1.3 (N)	0.7 (N)
9ak	50	35 (1.6)	1.7 (3.5)	0.58 (N)	30	58 (2.1)	5.8 (6.8)	1.5 (1.9)
9al	50	29 (N)	1.3 (2.7)	0.50 (2.1)	30	66 (2.3)	6.7 (7.9)	1.9 (2.3)
9am	50	25 (N)	0.67 (1.5)	0.35 (N)	30	39 (1.4)	3.5 (4.1)	1.2 (1.5)
9an	50	30 (1.2)	1.3 (2.0)	0.54 (2.6)	30	34 (1.3)	2.7 (2.8)	1.0 (N)
9ao	50	28 (N)	1.1 (1.7)	0.42 (2.0)	30	47 (1.7)	4.3 (4.6)	1.2 (1.5)
9ap	50	26 (1.2)	1.0 (1.7)	0.38 (N)	30	38 (1.3)	2.6 (3.4)	1.2 (1.7)
9aq	50	24 (N)	0.71 (N)	0.26 (N)	30	26 (N)	0.79 (N)	0.84 (N)
9ar	50	26 (N)	0.75 (N)	0.30 (N)	30	39 (N)	2.9 (3.3)	0.97 (N)
9as	50	22 (N)	0.51 (N)	0.23 (N)	30	37 (1.3)	2.1 (2.4)	0.93 (N)
9at	50	26 (N)	0.92 (1.6)	0.40 (N)	30	36 (1.3)	1.8 (2.3)	0.88 (N)
9au	50	23 (N)	0.55 (N)	0.25 (N)				
9av	50	27 (N)	0.54 (N)	0.46 (N)	30	24 (N)	0.94 (N)	0.60 (N)
9aw	50	29 (N)	0.91 (1.8)	0.40 (1.5)	30	31 (1.6)	2.0 (2.4)	0.85 (1.4)
9ax	50	30 (N)	1.4 (2.3)	0.62 (2.2)	30	24 (N)	1.5 (2.4)	0.62 (N)
9ay	50	29 (N)	1.1 (2.1)	0.46 (1.8)	30	26 (1.4)	1.5 (2.4)	0.71 (1.9)
9az	50	29 (N)	0.78 (N)	0.25 (N)	30	29 (N)	1.2 (N)	0.91 (N)
9ba	50	27 (N)	0.75 (N)	0.29 (N)	30	28 (N)	1.6 (2.4)	1.1 (2.0)
9bb	50	26 (N)	0.51 (N)	0.27 (N)	30	27 (N)	0.8 (N)	0.62 (N)
9bc	50	27 (N)	0.72 (N)	0.36 (N)	30	30 (N)	1.5 (N)	0.83 (N)
9bd	50	32 (N)	1.5 (1.9)	0.49 (1.8)	30	36 (1.3)	2.4 (2.1)	0.96 (N)
10a	50	38 (N)	2.4 (3.1)	1.2 (1.7)	30	29 (1.2)	1.0 (1.6)	0.41 (2.0)
10b	50	34 (N)	1.4 (1.8)	0.74 (N)	30	29 (N)	0.81 (1.5)	0.30 (1.6)
10c	50	39 (1.7)	2.5 (4.1)	0.86 (4.1)	30	56 (1.6)	5.2 (5.9)	1.5 (2.2)
10d	50	39 (1.7)	2.8 (4.7)	1.1 (5.3)	30	82 (2.4)	8.3 (9.4)	1.9 (2.7)
11a	50	35 (1.5)	2.2 (5.4)	0.81 (3.7)	30	22 (N)	2.0 (2.5)	0.75 (1.3)
11b	50	31 (1.3)	2.6 (1.4)	0.51 (1.8)	30	26 (N)	1.5 (1.8)	1.1 (N)
11c	50	25 (N)	1.3 (3.2)	0.34 (N)				
12	50	32 (1.4)	1.7 (2.8)	0.67 (3.2)	30	35 (N)	1.8 (2.4)	0.92 (N)
13a	50	47 (1.6)	3.3 (5.0)	1.1 (3.7)	30	75 (3.8)	8.2 (9.6)	1.9 (3.1)
13b	50	44 (1.5)	3.2 (4.2)	0.85 (2.9)	30	75 (3.8)	8.2 (9.6)	1.9 (3.2)
16a	50	43 (1.6)	3.3 (5.3)	0.74 (4.4)	30	35 (1.3)	2.6 (4.6)	1.3 (2.1)
16b	50	37 (1.2)	2.4 (3.7)	0.56 (2.4)	30	26 (N)	3.3 (4.7)	0.90 (1.9)
16c	50	32 (1.5)	1.9 (4.3)	0.48 (1.6)	30	47 (1.9)	4.9 (5.9)	1.4 (1.9)
16d	50	20 (N)	0.27 (N)	0.21 (N)	30	25 (N)	1.1 (N)	0.57 (N)
16e	50	23 (N)	1.2 (2.9)	0.36 (1.6)	30	28 (N)	3.8 (4.3)	1.27 (N)
16f	50	31 (1.3)	1.7 (3.1)	0.68 (2.4)	30	31 (N)	1.2 (N)	0.97 (1.4)
16g	50	22 (N)	0.25 (N)	0.26 (N)	30	22 (N)	1.1 (N)	0.79 (N)
17a	50	26 (N)	0.93 (1.7)	0.23 (N)	30	30 (N)	1.6 (2.2)	1.1 (N)
17b	50	26 (N)	1.2 (2.2)	0.43 (2.1)	30	28 (N)	1.1 (N)	0.75 (N)
18a	50	35 (1.5)	2.0 (4.1)	0.69 (3.6)	30	46 (1.3)	2.9 (3.3)	1.6 (2.3)
18b	50	29 (1.6)	1.6 (3.0)	0.39 (1.6)	30	30 (N)	2.7 (3.3)	1.0 (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 procedures used for the diuretic and saluretic tests are described in Experimental. *b*) Ratio to the control is shown in parenthesis; N indicates that the difference from the control was not statistically significant.

Biological Activities

Saluresis and Diuresis——The compounds shown in Table I were evaluated for oral diuretic and saluretic activities in rats and mice. The results are listed in Table II. Tienilic acid and indacrinone were used as reference compounds. Diuretic and kaliuretic activities paralleled the natriuretic activity. Structural requirements for natriuretic activity within these compounds were evaluated at four positions (2, 5, 6 and 7 positions) of the 2,3-dihydrobenzofuran ring system. In variants of the X and Y groups at the 6- and 7-positions, the highest activity was found when X=Y=Cl, with lesser activities for X=H, Y=Cl (**9ax** and **ay**) and X=Y=CH_3 (**9bb**—**bd**). Among derivatives having the 2-COOH group, alkyl variants of the 5-sulfonamide group (R_1 and R_2) showed the most potent activities in the cases of the lower alkyl groups (**9ab**, **ac**, **13a** and **b**), while the unsubstituted and monoalkyl-substituted sulfonamides (**9aa** and **9an**—**au**) had completely lost the activities or exhibited only slight activities. Among derivatives having a 5-*N*,*N*-dimethylsulfamoyl substituent ($R_1=R_2=CH_3$), variants of the R group at the 2-position influenced the natriuretic activities. As shown in Fig. 1, compounds having a carboxyl group or substituent having a carboxyl group (**9ab** and **10c**) showed potent activities in rats when given orally. The relative effectiveness of other substituents at the 2-position in producing natriuretic activity was $CH_2OH \simeq CONH_2 > CH_2OC_2H_5 > CH_2Cl >$ esters.

The natriuretic dose response curves of a representative compound, **9ab**, in male rats and female mice after oral administration are shown in Figs. 2 and 3. Compound **9ab** displayed a typical high-ceiling curve like that of furosemide in both models, in contrast to tri-

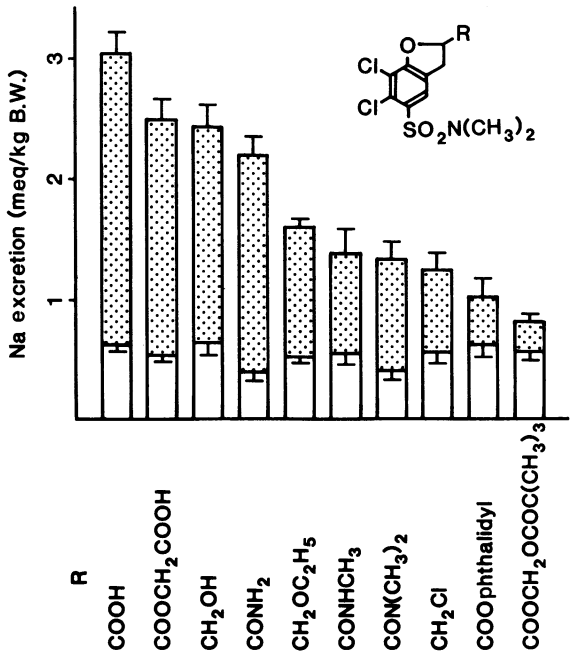


Fig. 1. Effect of the 2-Substituent in 6,7-Dichloro-5-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran on Na Excretion during a 5-h Period after Oral Administration (50 mg/kg) to Male Rats

Each column represents the mean±S.E. of 8 rats that received the test compound (shaded column) or the vehicle only (open column).

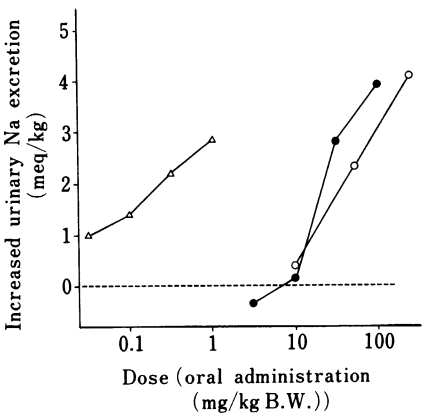


Fig. 2. Increase of Na Excretion during a 5-h Period after Oral Administration of **9ab**, Furosemide or Trichlormethiazide (TCM) to Male Rats

Excretion level of the control is shown by the dotted line.
△—△, TCM; ●—●, furosemide; ○—○, **9ab**.

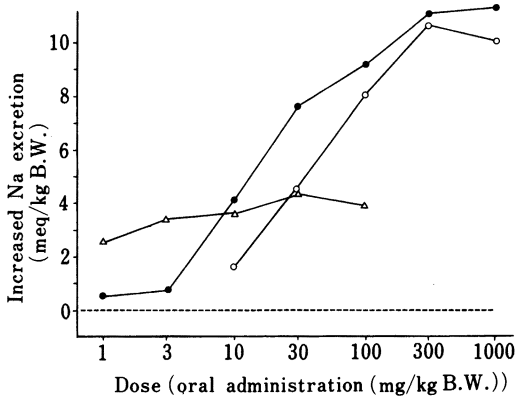


Fig. 3. Increase of Na Excretion during a 4-h Period after Oral Administration of **9ab**, Furosemide or TCM to Female Mice

Each point is the value of five mice/cage. Excretion level of the control is shown by the dotted line.
△—△, TCM; ●—●, furosemide; ○—○, **9ab**.

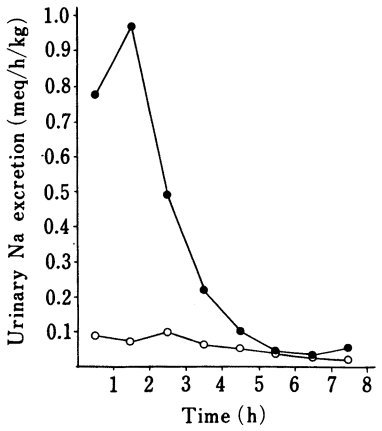


Fig. 4. Na Excretion after Oral Administration (50 mg/kg) of **9ab** to Male Rats

●—●, **9ab**; ○—○, control.

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
9aa	50	0.154	0.421
9ab	50	0.107	0.212
(−)-**9ab**	50	0.026	−0.040
(+)-**9ab**	50	0.018	0.123
9ac	50	0.047	0.092
9ad	50	0.046	=
9af	50	0.085	0.065
9ah	50	0.032	=
9ak	50	0.075	0.122
9al	50	0.110	0.202
9an	50	0.100	0.302
9ao	50	0.090	0.339
16a	50	0.058	0.172
16b	50	0.137	0.204
16c	50	0.045	0.115
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 value for 80 min after dosing. The symbol = means that there was no difference compared with the control.

chlormethiazide. The time course of natriuretic activity in rats administered **9ab** orally is shown in Fig. 4. Compound **9ab** showed temporary natriuresis. These data suggest that the main site of action of **9ab** inducing diuresis may be in the loop of Henle.

Optical isomers of **9ab**, resolved as shown in Chart 4, were tested in rats and mice in comparison with the racemate. The (−)-enantiomer possesses most of the saluretic activity

and its activity is approximately twice that of the racemate.

Uricosuric Activity——Mammals which excrete uric acid as an end product of purine metabolism are the Cebus monkey, chimpanzee and man. Thus, the activity usually cannot be tested in commonly used experimental animals such as rodents. Tienilic acid and indacrinone have been shown to have a hyperuricosuric character through inhibition of urate reabsorption by renal tubules in man and chimpanzee, respectively.

A method has been developed[8] to test uricosuric activity using rats treated with potassium oxonate which is known to be a uricase inhibitor. The test compounds were administered intraperitoneally and the uricosuric activity was evaluated in terms of the increase in fractional excretion of uric acid (FEua) and urine-excreted amounts of uric acid (UuaV) values. The results are listed in Table III.

Probenecid and tienilic acid, which were used as reference compounds, showed hyperuricosuric activities with increased FEua and UuaV values. Indacrinone, however, showed only an increase in UuaV. Furosemide showed a decrease of FEua, suggesting the possibility of hypouricosuric action.

Among 6,7-dichloro-2,3-dihydrobenzofuran derivatives having either a 2-carboxyl or a 2-hydroxymethyl group, marked increases of both FEua and UuaV were observed in variants having unsubstituted and mono- or disubstituted sulfonamides (**9aa**—**ac**, **af**, **ak**, **al**, **an**, **ao**, and **16a**—**c**) in which the substituents were lower alkyl groups. Accordingly, these compounds are expected to show a hyperuricosuric character in higher animals, including man.

The resolved enantiomers of **9ab** were tested for uricosuric activity. The (+) enantiomer had this activity, while the (−) enantiomer showed an increase in UuaV with a slight decrease of FEua.

Indacrinone (**2**) has been reported to show urate-retaining activity as a result of potent and long-lasting diuresis in clinical trials.[9] The diuretic potency of **9ab** seems to be intermediate between those of **2**—**5** and tienilic acid (**1**).[1,3,5] Thus, it should show both uricosuric and moderate diuretic actions, which would allow its use in clinical antihypertensive therapy. We therefore selected **9ab** for clinical evaluation, and further investigation is in progress.

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 the coupling constants in Hz. 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-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran-2-carboxylate (8ab)——Chlorosulfonic acid (1.25 g, 0.0107 mol) was added dropwise to a solution of **7a** (1.0 g, 0.0038 mol) in thionyl chloride (2.5 ml) under ice-cooling, and the mixture was allowed to react at room temperature for 2 h. The reaction mixture was poured into ice water then extracted with ethyl acetate (60 ml). The organic layer was dried and evaporated *in vacuo*. A solution of the residue dissolved in dichloromethane (8 ml) was cooled to −20——10 °C, then 30% ethanolic dimethylamine (0.518 g, 3 × 0.0038 mol) was added dropwise, and the reaction was allowed to proceed for 1 h. The completion of the reaction was confirmed by thin layer chromatography (TLC) (silica gel/dichloromethane), then the reaction mixture was adjusted to about pH 5 and extracted with dichloromethane. When the organic layer was dried and evaporated *in vacuo*, it left an oily residue, which was chromatographed. Elution with dichloromethane gave **8ab** (1.0 g, 71%).

Compounds **8aa**, **8ac**—**az** and **8ba**—**bd** were obtained in a similar manner (Table IV). ^{1}H-NMR spectral data are given in Table V.

6,7-Dichloro-5-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran-2-carboxylic Acid (9ab)——A 15% aqueous potassium carbonate solution (14 ml) was added to a solution of **8ab** (1.0 g, 0.0029 mol) in tetrahydrofuran (9 ml), and the mixture was stirred for 72 h at room temperature. Concentration of the reaction mixture *in vacuo* left a residue,

which was acidified to pH 5, then extracted with ethyl acetate. The organic layer was dried and evaporated *in vacuo*, leaving an oil, which, when treated with ether, gave **9ab** (0.868 g, 94%).

Compounds **9aa**, **9ac**—**az** and **9ba**—**bd** were obtained in a similar manner. ^{1}H-NMR spectral data for **9aa**—**az** and **9ba**—**bd** are listed in Table VI.

Phthalidyl 6,7-Dichloro-5-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran-2-carboxylate (10a)——Potassium carbonate (0.425 g, 2.1 × 0.0029 mol) was added to a solution of **9ab** (1.0 g, 0.0029 mol) in acetonitrile (10 ml), and the mixture was stirred for 1 h at room temperature. After confirmation by TLC [silica gel; dichloromethane/ethanol (10 : 1)/1% acetic acid] that no free acid was left, the precipitated crystals (1.35 g) were collected by filtration. The crystals were dissolved in acetonitrile (20 ml), then cooled to −20 °C. Next, 1-phthalidyl bromide(1,3-dihydro-3-oxo-1-isobenzofuranyl bromide, 1.32 g, 2.1 × 0.0029 mol) was added, and the mixture was stirred at room temperature. *N*,*N*-Dimethylformamide (DMF) (6 ml) was added, and the resulting mixture was refluxed for 30 min. After removal of the insoluble matter by filtration, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated *in vacuo*. Chromatography of the resulting residue using dichloromethane as the eluant gave **10a** (0.77 g, 56%), mp 152—154 °C (ethyl acetate–hexane), which was a diastereoisomeric mixture according to its ^{1}H-NMR spectrum. ^{1}H-NMR spectral data are summarized in Table VI.

Pivaloyloxymethyl 6,7-Dichloro-5-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran-2-carboxylate (10b)——Pivaloyloxymethyl iodide (1.5 g, 2.1 × 0.0029 mol) was added dropwise to a solution of the potassium salt of **9ab** (1.0 g, 0.0029 mol) in acetonitrile (10 ml) at 20 °C, and the mixture was refluxed for 2.5 h. The insoluble matter was removed by filtration, and the reaction solution was extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated *in vacuo*, giving a crystalline residue. Chromatography of this residue using dichloromethane as the eluant gave **10b** (0.911 g, 69%). ^{1}H-NMR spectral data are given in Table VI.

6,7-Dichloro-5-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran-2-yl-carbonyloxyacetic Acid (10c)——The acid chloride of **9ab**, which was formed by treatment of **9ab** (1.0 g, 0.0029 mol) with thionyl chloride (1.5 ml) in benzene (5 ml) under reflux, was dissolved in benzene (8 ml). This solution was added dropwise at 0 °C to a solution of benzhydryl glycolate (0.855 g, 0.0035 mol), triethylamine (0.3 g) and 4-*N*,*N*-dimethylaminopyridine (35 mg, 0.0003 mol) in benzene (5 ml). The mixture was stirred for 1 h under ice-cooling and then extracted with dichloromethane. The organic layer was washed with water, dried and evaporated *in vacuo*, giving a residue. Chromatography of this residue using dichloromethane as the eluant gave diphenylmethoxycarbonylmethyl 5-(*N*,*N*-dimethylsulfamoyl)-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylate (1.35 g, 85%), mp 56—58 °C (ethyl acetate–hexane). *Anal.* Calcd for $C_{26}H_{23}Cl_2NO_7S$: C, 55.33; H, 4.11; Cl, 12.56; N, 2.48; S, 5.68. Found: C, 55.82; H, 4.22; Cl, 12.29; N, 2.60; S, 5.51. ^{1}H-NMR (in $CDCl_3$) δ: 2.82 (6H, s, 2 × C$\underline{H}_3$), 3.10—3.90 (2H, m, C$\underline{H}_2$), 4.67 and 4.92 (2H, ABq, J = 16.0, O–C$\underline{H}_2$–CO), 5.43 (1H, 2 × d, J = 10.0, 6.3, O–C$\underline{H}$), 6.87 (1H, s, O–C$\underline{H}$), 7.27 (10H, s, arom. H), 7.75 (1H, t, J = 1.0, arom. H). Trifluoroacetic acid (1 ml) was added to a stirred suspension of this compound (0.85 g) in anisole (1 ml) under ice-cooling. After being stirred for 1 h at room temperature, the reaction mixture was evaporated *in vacuo*. The residue was recrystallized from hexane–ether, giving **10c** (0.599 g, 100%).

Compound **10d** was obtained in a similar manner; yield 70%. ^{1}H-NMR spectral data for **10a**—**d** are given in Table VI.

6,7-Dichloro-5-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran-2-carboxamide (11a)——A solution of **8ab** (0.500 g, 0.0016 mol) in 20% ethanolic ammonia (50 ml) was stirred for 17 h at room temperature. Evaporation of the reaction mixture *in vacuo* gave a crystalline residue, which was washed with ether, giving **11a** (0.448 g, 97%).

Compounds **11b** and **11c** were obtained in a similar manner. Compound **11b**, yield 98%. Compound **11c**, yield 70%. ^{1}H-NMR spectral data for **11a**—**c** are listed in Table VI.

6,7-Dichloro-5-(*N*-ethoxycarbonyl-*N*-methylsulfamoyl)-2,3-dihydrobenzofuran-2-carboxylic Acid (12)——Diphenyl diazomethane (1.3 g, 0.0067 mol) was gently added to a solution of **9an** (1.5 g, 0.0046 mol) in dichloromethane (20 ml) under ice-cooling. The mixture was stirred for 2 h at room temperature, then the remaining reagent was decomposed by adding 10% hydrochloric acid. The mixture was extracted with dichloromethane (60 ml), then the organic layer was washed with water, dried and evaporated *in vacuo*. The residue was chromatographed using dichloromethane as the eluant to give benzhydryl 6,7-dichloro-5-*N*-methylsulfamoyl-2,3-dihydrobenzofuran-2-carboxylate (2.06 g, 91%), mp 132—133 °C (hexane–ether). Sodium hydride (50% suspension in oil, 0.180 g, 0.0038 mol) was gently added to a solution of the ester (1.655 g, 0.0034 mol) in DMF (20 ml) at 4 °C, and the mixture was stirred for 1 h at room temperature. Next, ethyl chloroformate (0.41 g, 0.0038 mol) was added, and the reaction was allowed to continue for 1 h. The reaction mixture was then poured into water and extracted with ether (300 ml). The organic layer was dried and evaporated *in vacuo*, giving an oily residue. Chromatography of this residue using dichloromethane as the eluant gave benzhydryl 6,7-dichloro-5-(*N*-ethoxycarbonyl-*N*-methylsulfamoyl)-2,3-dihydrobenzofuran-2-carboxylate (1.314 g, 69%), mp 111—112 °C (ethyl acetate–hexane). *Anal.* Calcd for $C_{26}H_{23}Cl_2NO_7S$: C, 55.33; H, 4.11; Cl, 12.56; N, 2.48; S, 5.58. Found: C, 55.50; H, 4.17; Cl, 12.54; N, 2.43; S, 5.61. ^{1}H-NMR (in $CDCl_3$) δ: 1.07 (3H, t, J = 7.0, C$\underline{H}_3$), 3.20—3.90 (2H, m, C$\underline{H}_2$), 3.42 (3H, s, N–C$\underline{H}_3$), 4.05 (2H, q, J = 7.0, O–C$\underline{H}_2$), 5.48 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 6.93 (1H, s, C$\underline{H}$), 7.30 (5H, s, arom. H), 7.36 (5H, s, arom. H), 7.96 (1H, t, J = 1.0, 4-$\underline{H}$). Trifluoroacetic acid (2.5 ml) was added dropwise to a solution of 1.314 g (0.0023 mol) of the urethane

TABLE IV. Compounds **8** and **15**

No.	X	Y	R_1	R_2	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula	Analysis (%) Calcd (Found)				
									C	H	Cl	N	S
8aa	Cl	Cl	H	H	50	167—168	A–E–H	$C_{11}H_{10}Cl_2NO_5S \cdot 1/2\,H_2O$	37.94 (38.27	3.18 3.09		4.09 4.13	9.21 9.18)
8ab	Cl	Cl	CH_3	CH_3	71	124—125	E–H	$C_{13}H_{15}Cl_2NO_5S$	42.40 (42.11	4.11 4.19	19.26 19.28	3.80 3.82	8.61 8.61)
8ac	Cl	Cl	C_2H_5	C_2H_5	70	Oil		$C_{15}H_{19}Cl_2NO_5S$	45.46 (45.08	4.83 4.76	17.89 18.56	3.53 3.58	8.09 8.21)
8ad	Cl	Cl	*n*-C_3H_7	*n*-C_3H_7	75	87—88	E–H	$C_{17}H_{23}Cl_2NO_5S$	48.12 (47.98	5.46 5.41	16.71 16.81	3.30 3.40	7.64 7.64)
8ae	Cl	Cl	iso-C_3H_7	iso-C_3H_7	28	Oil		$C_{17}H_{23}Cl_2NO_5S \cdot 1/2\,H_2O$	47.11 (47.24	5.58 5.36		3.23 3.38	7.40 7.45)
8af	Cl	Cl	CH_3	*n*-C_4H_9	85	Oil		$C_{16}H_{21}Cl_2NO_5S$	46.84 (46.77	5.16 5.21	17.28 17.47	3.41 3.32	7.81 7.54)
8ag	Cl	Cl	$PhCH_2$	$PhCH_2$	75	Oil		$C_{25}H_{23}Cl_2NO_5S \cdot 1/2\,H_2O$	56.71 (56.96	4.57 4.51		2.65 2.72	6.06 6.02)
8ah	Cl	Cl	CH_3	$PhCH_2$	76	102—103	E–H	$C_{19}H_{19}Cl_2NO_5S$	51.36 (51.11	4.31 4.18	15.96 16.13	3.15 3.21	7.22 7.38)
8ai	Cl	Cl	CH_3	Ph	50	Oil		$C_{18}H_{17}Cl_2NO_5S \cdot H_2O$	48.22 (48.47	4.27 3.95		3.12 3.24	7.15 6.97)
8aj	Cl	Cl	CH_3	*cyclo*-C_6H_{11}	73	Oil		$C_{18}H_{23}Cl_2NO_5S$	49.55 (49.37	5.31 5.28	16.25 16.24	3.21 3.29	7.35 7.17)
8ak	Cl	Cl	$-(CH_2)_4-$		56	135—136	E–H	$C_{15}H_{17}Cl_2NO_5S$	45.70 (45.40	4.35 4.27	17.98 18.24	3.55 3.52	8.13 7.95)
8al	Cl	Cl	$-(CH_2)_5-$		67	131—132	E–H	$C_{16}H_{19}Cl_2NO_5S$	47.07 (46.96	4.69 4.67	17.37 17.50	3.43 3.31	7.85 7.65)
8am	Cl	Cl	$-(CH_2)_2O(CH_2)_2-$		70	141—142	EA–H	$C_{15}H_{17}Cl_2NO_6S$	43.91 (43.45	4.18 4.03		3.41 3.48	7.82 7.76)
8an	Cl	Cl	H	CH_3	75	140—141	EA–E	$C_{12}H_{13}Cl_2NO_5S$	40.69 (40.62	3.70 3.70	20.02 20.13	3.95 3.96	9.05 9.00)
8ao	Cl	Cl	H	*n*-C_3H_7	70	102—103	EA–E	$C_{14}H_{17}Cl_2NO_5S$	43.99 (43.88	4.48 4.46	18.55 18.77	3.66 3.69	8.39 8.24)
8ap	Cl	Cl	H	iso-C_3H_7	80	169—170	EA–H	$C_{14}H_{17}Cl_2NO_5S$	43.99 (43.60	4.48 4.41	18.55 19.03	3.66 3.67	8.39 8.17)
8aq	Cl	Cl	H	$PhCH_2$	73	168—169	EA–E	$C_{18}H_{17}Cl_2NO_5S$	50.24 (49.96	3.98 3.98	16.48 16.80	3.26 3.27	7.45 7.33)

8ar	Cl	Cl	H	Ph	64	141—142	EA–E	$C_{17}H_{15}Cl_2NO_5S$	49.05 (48.93	3.63 3.66	17.03 17.37	3.36 3.43	7.70 7.61)
8as	Cl	Cl	H	4-Cl–Ph	58	164—165	EA–E	$C_{17}H_{14}Cl_3NO_5S$	45.30 (44.91	3.13 3.13	23.60 23.89	3.11 2.94	7.11 7.05)
8at	Cl	Cl	H	4-CH_3O–Ph	80	109—110	EA–H	$C_{18}H_{17}Cl_2NO_6S$	48.44 (48.33	3.84 3.84	15.89 15.92	3.14 3.15	7.18 7.11)
8au	Cl	Cl	H	O⌒N(CH_2)$_2$	53	Oil		$C_{17}H_{22}Cl_2N_2O_6S \cdot 1/2\,H_2O$	44.16 (44.04	5.04 4.87		6.05 5.88)	
8av	Cl	H	CH_3	CH_3	81	74—75	EA–E–H	$C_{13}H_{16}ClNO_5S$	46.78 (46.74	4.83 4.80	10.62 10.39	4.20 4.06	9.60 9.84)
8aw	Cl	H	C_2H_5	C_2H_5	76	Oil		$C_{15}H_{20}ClNO_5S$	49.79 (49.62	5.57 5.56	9.80 9.99	3.87 3.85	8.86 8.72)
8ax	H	Cl	CH_3	CH_3	36	42—43	EA–E–H	$C_{13}H_{16}ClNO_5S$	46.78 (46.69	4.83 4.61	10.62 10.80	4.20 4.22	9.61 9.59)
8ay	H	Cl	C_2H_5	C_2H_5	37	Oil		$C_{15}H_{20}ClNO_5S$	49.79 (49.66	5.57 5.29	9.80 9.96	3.87 3.89	8.86 8.84)
8az	Br	H	CH_3	CH_3	81	97—98	EA–H	$C_{13}H_{16}BrNO_5S$	41.28 (41.19	4.26 4.19	21.13[b] 21.04[b]	3.70 3.78	8.48 8.40)
8ba	Br	H	C_2H_5	C_2H_5	79	Oil		$C_{15}H_{20}BrNO_5S$	44.34 (44.34	4.96 4.96	19.67[b] 20.00[b]	3.45 3.53	7.89 7.76)
8bb	CH_3	CH_3	H	H	87	154—155	EA–E	$C_{13}H_{17}NO_5S$	52.16 (52.22	5.72 5.66		4.68 4.70	10.71 10.49)
8bc	CH_3	CH_3	H	CH_3	68	80—81	EA–E	$C_{14}H_{19}NO_5S$	53.66 (53.47	6.11 6.03		4.47 4.65	10.23 10.06)
8bd	CH_3	CH_3	CH_3	CH_3	89	110—111	EA–E	$C_{15}H_{21}NO_5S$	55.03 (54.76	6.47 6.41		4.28 4.27	9.79 9.61)
15a	Cl	Cl	H	H	51	164—166	EA–E	$C_{11}H_{11}Cl_2NO_5S$	38.84 (38.64	3.26 3.11	20.84 21.03	4.12 4.07	9.43 9.25)
15b	Cl	Cl	CH_3	CH_3	82	159—160	E	$C_{13}H_{15}Cl_2NO_5S$	42.40 (42.27	4.11 4.05	19.26 19.49	3.80 3.67	8.71 8.52)
15c	Cl	Cl	CH_3	$PhCH_2$	70	106—107	E	$C_{19}H_{18}Cl_2NO_5S \cdot 1/4\,H_2O$	51.16 (50.96	4.34 4.16	15.92 15.83	3.24 3.13	7.16 7.16)
15d	Cl	Cl	CH_3	Ph	51	Oil		$C_{18}H_{17}Cl_2NO_5S$	50.24 (49.98	3.98 3.99		3.26 3.16	7.45 7.25)
15e	Cl	Cl	H	CH_3	51	121—122	EA–E	$C_{12}H_{13}Cl_2NO_5S$	40.69 (40.43	3.70 3.71	20.02 20.34	3.95 3.95	9.05 8.89)
15f	Cl	Cl	H	$PhCH_2$	51	122—123	EA–E	$C_{18}H_{17}Cl_2NO_5S$	50.24 (49.95	3.98 4.09	16.48 16.87	3.26 3.27	7.45 7.26)
15g	Cl	Cl	H	Ph	86	169—170	EA–E	$C_{17}H_{15}Cl_2NO_5S \cdot 1/2\,H_2O$	48.01 (47.88	3.79 3.57		3.29 3.18	7.54 7.42)

a) See ref. *a* in Table I for abbreviations for the solvents used. *b*) Br.

TABLE V. ^{1}H-NMR Data for **8** and **15** in $CDCl_3$ Solution

8aa[a] 1.25 (3H, t, J=7.2, CH_3), 3.45—4.05 (2H, m, Ph–CH_2–CH), 4.21 (2H, q, J=7.2, CH_2), 5.51 (1H, 2×d, J=10.1, 6.5, O–CH), 6.62 (2H, br s, NH_2), 7.87 (1H, t, J=1.2, 4-H)

8ab 1.33 (3H, t, J=7.0, CH_3), 2.90 (6H, s, 2×CH_3), 3.30—3.90 (2H, m, Ph–CH_2–CH), 4.31 (2H, q, J=7.2, CH_2), 5.40 (1H, 2×d, J=10.0, 7.0, O–CH), 7.88 (1H, t, J=1.0, 4-H)

8ac 1.12 (6H, t, J=7.0, 2×CH_3), 1.30 (3H, t, J=7.0, CH_3), 3.32 (4H, q, J=7.0, 2×CH_2), 3.10—3.90 (2H, m, Ph–CH_2–CH), 4.25 (2H, q, J=7.0, CH_2), 5.35 (1H, 2×d, J=10.0, 7.0, O–CH), 7.86 (1H, t, J=1.0, 4-H)

8ad 0.83 (6H, t, J=7.0, 2×CH_3), 1.31 (3H, t, J=7.0, CH_3), 1.40—1.80 (4H, m, 2×CH_2), 3.24 (4H, t, J=7.0, 2×CH_2), 3.00—4.00 (2H, m, Ph–CH_2–CH), 4.30 (2H, q, J=7.0, CH_2), 5.38 (1H, 2×d, J=10.0, 7.0, O–CH), 7.92 (1H, t, J=1.0, 4-H)

8ae 1.28 (12H, d, J=7.0, 4×CH_3), 1.30 (3H, t, J=7.0, CH_3), 3.25—4.00 (4H, m, Ph–CH_2–CH, 2×CH), 4.26 (2H, q, J=7.0, CH_2), 5.35 (1H, 2×d, J=10.0, 7.0, O–CH), 7.90 (1H, t, J=1.0, 4-H)

8af 0.90 (3H, t, J=7.0, CH_3), 1.31 (3H, t, J=7.0, CH_3), 1.10—1.75 (4H, m, 2×CH_2), 2.85 (3H, s, CH_3), 3.22 (2H, t, J=7.0, CH_2), 3.30—3.85 (2H, m, Ph–CH_2–CH), 4.28 (2H, q, J=7.0, CH_2), 5.37 (1H, 2×d, J=10.0, 7.0, O–CH), 7.88 (1H, t, J=1.0, 4-H)

8ag 1.31 (3H, t, J=7.0, CH_3), 3.20—3.80 (2H, m, Ph–CH_2–CH), 4.26 (2H, q, J=7.0, CH_2), 4.37 (4H, s, 2× Ph–CH_2), 5.35 (1H, 2×d, J=10.0, 7.0, O–CH), 7.00—7.36 (10H, m, arom. H), 7.78 (1H, t, J=1.0, 4-H)

8ah 1.32 (3H, t, J=7.0, CH_3), 2.75 (3H, s, CH_3), 3.26—3.93 (2H, m, Ph–CH_2–CH), 4.30 (2H, q, J=7.0, O–CH_2), 4.42 (2H, s, Ph–CH_2), 5.38 (1H, 2×d, J=10.0, 7.0, O–CH), 7.35 (5H, s, arom. H), 7.92 (1H, t, J=1.0, 4-H)

8ai 1.28 (3H, t, J=7.0, CH_3), 3.13—3.80 (2H, m, Ph–CH_2–CH), 3.38 (3H, s, CH_3), 4.24 (2H, q, J=7.0, O–CH_2), 5.32 (1H, 2×d, J=10.0, 7.0, O–CH), 7.25 (5H, s, arom. H), 7.63 (1H, t, J=1.0, 4-H)

8aj 1.30 (3H, t, J=7.0, CH_3), 0.80—1.90 (10H, m, 5×CH_2), 2.77 (3H, s, CH_3), 3.20—3.86 (3H, m, Ph–CH_2–CH, CH), 4.25 (2H, q, J=7.0, O–CH_2), 5.35 (1H, 2×d, J=10.0, 7.0, O–CH), 7.86 (1H, t, J=1.0, 4-H)

8ak 1.31 (3H, t, J=7.0, CH_3), 1.80—2.10 (4H, m, 2×CH_2), 3.30—3.90 (6H, m, Ph–CH_2–CH, 2×N–CH_2), 4.28 (2H, q, J=7.0, O–CH_2), 5.37 (1H, 2×d, J=10.0, 7.0, O–CH), 7.88 (1H, t, J=1.0, 4-H)

8al 1.33 (3H, t, J=7.0, CH_3), 1.59 (6H, br, 3×CH_2), 3.26 (4H, br, 2×N–CH_2), 3.30—3.93 (2H, m, Ph–CH_2–CH), 4.30 (2H, q, J=7.0, O–CH_2), 5.38 (1H, 2×d, J=10.0, 7.0, O–CH), 7.86 (1H, t, J=1.0, 4-H)

8am 1.32 (3H, t, J=7.0, CH_3), 3.20—4.00 (10H, m, 5×CH_2), 4.30 (2H, q, J=7.0, O–CH_2), 5.40 (1H, 2×d, J=10.0, 7.0, O–CH), 7.84 (1H, t, J=1.0, 4-H)

8an 1.31 (3H, t, J=7.0, CH_3), 2.63 (3H, d, J=5.0, NH–CH_3), 3.30—3.93 (2H, m, Ph–CH_2–CH), 4.30 (2H, q, J=7.0, O–CH_2), 5.03 (1H, q, J=5.0, NH), 5.41 (1H, 2×d, J=10.0, 7.0, O–CH), 7.88 (1H, t, J=1.0, 4-H)

8ao 0.88 (3H, t, J=7.0, CH_3), 1.33 (3H, t, J=7.0, CH_3), 1.20—1.70 (2H, m, CH_2), 2.78 (2H, q, J=7.0, CH_2), 3.30—3.90 (2H, m, Ph–CH_2–CH), 4.30 (2H, q, J=7.0, O–CH_2), 5.05 (1H, t, J=7.0, NH), 5.41 (1H, 2×d, J=10.0, 7.0, O–CH), 7.90 (1H, t, J=1.0, 4-H)

8ap[a] 1.06 (6H, d, J=7.0, 2×CH_3), 1.26 (3H, t, J=7.0, CH_3), 3.20—4.00 (3H, m, Ph–CH_2–CH, CH), 4.25 (2H, q, J=7.0, O–CH_2), 5.56 (1H, 2×d, J=10.0, 7.0, O–CH), 6.53 (1H, br d, J=7.0, NH), 7.92 (1H, t, J=1.0, 4-H)

8aq 1.33 (3H, t, J=7.0, CH_3), 3.23—3.86 (2H, m, Ph–CH_2–CH), 4.10 (2H, d, J=5.0, Ph–CH_2), 4.31 (2H, q, J=7.0, O–CH_2), 5.35 (1H, t, J=5.0, NH), 5.38 (1H, 2×d, J=10.0, 7.0, O–CH), 7.25 (5H, s, arom. H), 7.80 (1H, t, J=1.0, 4-H)

8ar[a] 1.23 (3H, t, J=7.0, CH_3), 3.30—3.97 (2H, m, Ph–CH_2–CH), 4.23 (2H, q, J=7.0, O–CH_2), 5.53 (1H, 2×d, J=10.0, 7.0, O–CH), 6.90—7.50 (5H, m, arom. H), 7.95 (1H, t, J=1.0, 4-H)

8as[a] 1.26 (3H, t, J=7.0, CH_3), 3.20—4.00 (2H, m, Ph–CH_2–CH), 4.20 (2H, q, J=7.0, O–CH_2), 5.52 (1H, 2×d, J=10.0, 7.0, O–CH), 7.25 (4H, s, arom. H), 7.91 (1H, t, J=1.0, 4-H)

8at[a] 1.23 (3H, t, J=7.0, CH_3), 3.20—3.95 (2H, m, Ph–CH_2–CH), 3.70 (3H, s, O–CH_3), 4.18 (2H, q, J=7.0, O–CH_2), 5.50 (1H, 2×d, J=10.0, 7.0, O–CH), 6.75, 7.14 (4H, ABq, J=9.0, arom. H), 7.77 (1H, t, J=1.0, 4-H), 8.90 (1H, br, NH)

8au 1.31 (3H, t, J=7.0, CH_3), 2.20—2.60 (6H, m, 3×N–CH_2), 3.00 (2H, t, J=5.0, N–CH_2), 3.25—4.00 (6H, m, Ph–CH_2–CH, 2×O–CH_2), 4.30 (2H, q, J=7.0, O–CH_2), 5.42 (1H, 2×d, J=10.0, 7.0, O–CH), 5.85 (1H, br, NH), 7.87 (1H, t, J=1.0, 4-H)

8av 1.31 (3H, t, J=7.0, CH_3), 2.71 (6H, s, 2×CH_3), 3.46 (1H, 2×d, J=16.6, 7.5, Ph–CH_2–CH), 3.71 (1H, 2×d, J=16.6, 9.8, Ph–CH_2–CH), 4.28 (2H, q, J=7.0, O–CH_2), 5.36 (1H, 2×d, J=9.8, 7.5, O–CH), 7.49 (1H, br s, 6- or 4-H), 7.64 (1H, br s, 4- or 6-H)

8aw 1.13 (6H, t, J=7.2, 2×CH_3), 1.30 (3H, t, J=7.1, CH_3), 3.22 (4H, q, J=7.2, 2×CH_2), 3.44 (1H, 2×d, J=17.4, 7.5, Ph–CH_2–CH), 3.70 (1H, 2×d, J=17.4, 10.0, Ph–CH_2–CH), 4.28 (2H, q, J=7.1, O–CH_2), 5.34 (1H, 2×d, J=10.0, 7.5, O–CH), 7.51 (1H, br s, 6- or 4-H), 7.67 (1H, br s, 4- or 6-H)

TABLE V. (continued)

8ax	1.30 (3H, t, J=7.2, CH_3), 2.86 (6H, s, 2×CH_3), 3.20—3.80 (2H, m, Ph–CH_2–CH), 4.27 (2H, q, J=7.2, O–CH_2), 5.30 (1H, 2×d, J=10.2, 7.0, O–CH), 7.01 (1H, s, 7-H), 7.88 (1H, t, J=1.2, 4-H)
8ay	1.11 (6H, t, J=7.1, 2×CH_3), 1.30 (3H, t, J=7.1, CH_3), 3.17—3.75 (6H, m, Ph–CH_2–CH, 2×CH_2), 4.25 (2H, q, J=7.1, O–CH_2), 5.27 (1H, 2×d, J=10.2, 7.5, O–CH), 6.97 (1H, s, 7-H), 7.91 (1H, t, J=1.2, 4-H)
8az	1.31 (3H, t, J=7.1, CH_3), 2.72 (6H, s, 2×CH_3), 3.49 (1H, 2×d, J=16.3, 7.2, Ph–CH_2–CH), 3.75 (1H, 2×d, J=16.3, 9.9, Ph–CH_2–CH), 4.28 (2H, q, J=7.1, O–CH_2), 5.36 (1H, 2×d, J=9.9, 7.2, O–CH), 7.53 (1H, br s, 6- or 4-H), 7.79 (1H, br s, 4- or 6-H)
8ba	1.13 (6H, t, J=7.0, 2×CH_3), 1.30 (3H, t, J=7.2, CH_3), 3.22 (4H, q, J=7.0, 2×CH_2), 3.47 (1H, 2×d, J=16.2, 7.3, Ph–CH_2–CH), 3.72 (1H, 2×d, J=16.2, 9.9, Ph–CH_2–CH), 4.28 (2H, q, J=7.2, O–CH_2), 5.34 (1H, 2×d, J=9.9, 7.3, O–CH), 7.55 (1H, br s, 6- or 4-H), 7.81 (1H, br s, 4- or 6-H)
8bb	1.28 (3H, t, J=7.0, CH_3), 2.20, 2.54 (2×3H, 2×s, 2×CH_3), 3.10—3.75 (2H, m, Ph–CH_2–CH), 4.22 (2H, q, J=7.0, O–CH_2), 4.90 (2H, br, NH_2), 5.18 (1H, 2×d, J=10.5, 7.5, O–CH), 7.72 (1H, br s, 4-H)
8bc	1.28 (3H, t, J=7.0, CH_3), 2.20, 2.50 (2×3H, 2×s, 2×CH_3), 2.56 (3H, d, J=7.0, NH–CH_3), 3.10—3.80 (2H, m, Ph–CH_2–CH), 4.24 (2H, q, J=7.0, O–CH_2), 4.47 (1H, d, J=7.0, NH), 5.21 (1H, 2×d, J=10.5, 7.5, O–CH), 7.70 (1H, br s, 4-H)
8bd	1.28 (3H, t, J=7.0, CH_3), 2.20, 2.48 (2×3H, 2×s, 2×CH_3), 2.74 (6H, s, 2×CH_3), 3.10—3.75 (2H, m, Ph–CH_2–CH), 4.23 (2H, q, J=7.0, O–CH_2), 5.20 (1H, 2×d, J=10.5, 7.5, O–CH), 7.65 (1H, br s, 4-H)
15a[a]	2.00 (3H, s, $COCH_3$), 3.07—3.77 (2H, m, Ph–CH_2–CH), 4.15—4.56 (2H, m, O–CH_2), 5.16—5.53 (1H, m, O–CH), 6.64 (2H, br s, NH_2), 7.87 (1H, t, J=1.2, 4-H)
15b	1.97 (3H, s, $COCH_3$), 2.83 (6H, s, 2×CH_3), 2.95—3.70 (2H, m, Ph–CH_2–CH), 4.10—4.65 (2H, m, O–CH_2), 5.17—5.53 (1H, m, O–CH), 7.85 (1H, t, J=1.2, 4-H)
15c	2.07 (3H, s, $COCH_3$), 2.75 (3H, s, CH_3), 2.95—3.70 (2H, m, Ph–CH_2–CH), 4.35 (2H, d, J=5.0, O–CH_2), 4.32 (2H, s, Ph–CH_2), 5.05—5.45 (1H, m, O–CH), 7.35 (5H, s, arom. H), 7.91 (1H, t, J=1.0, 4-H)
15d	2.03 (3H, s, $COCH_3$), 3.30 (3H, s, CH_3), 2.80—3.60 (2H, m, Ph–CH_2–CH), 4.27 (2H, d, J=5.0, O–CH_2), 5.00—5.37 (1H, m, O–CH), 7.25 (5H, s, arom. H), 7.64 (1H, t, J=1.0, 4-H)
15e	2.07 (3H, s, $COCH_3$), 2.60 (3H, d, J=5.0, NH–CH_3), 3.00—3.70 (2H, m, Ph–CH_2–CH), 4.34 (2H, d, J=5.0, O–CH_2), 5.00 (1H, q, J=5.0, NH), 5.00—5.43 (1H, m, O–CH), 7.86 (1H, t, J=1.0, 4-H)
15f	2.08 (3H, s, $COCH_3$), 2.90—3.60 (2H, m, Ph–CH_2–CH), 4.10 (2H, d, J=6.0, NH–CH_2), 4.33 (2H, d, J=5.0, O–CH_2), 5.05—5.45 (2H, m, O–CH, NH), 7.24 (5H, s, arom. H), 7.80 (1H, t, J=1.0, 4-H)
15g	1.97 (3H, s, $COCH_3$), 2.85—3.60 (2H, m, Ph–CH_2–CH), 4.25 (2H, d, J=5.0, O–CH_2), 4.95—5.30 (1H, m, O–CH), 6.80—7.50 (1H, br, NH), 7.13 (5H, s, arom. H), 7.73 (1H, t, J=1.0, 4-H)

a) In acetone-d_6 solution.

compound obtained above in anisole (3 ml) under ice-cooling, and the mixture was stirred at room temperature for 1 h. Evaporation of the reaction mixture *in vacuo* gave a residue, which, when treated with hexane, gave **12** (0.942 g, 100%). Recrystallization from hexane–ether–acetone gave colorless crystals, mp 199—201 °C, ^{1}H-NMR spectral data of which are given in Table VI.

6,7-Dichloro-5-(*N*-ethyl-*N*-methylsulfamoyl)-2,3-dihydrobenzofuran-2-carboxylic Acid (13a)——Sodium hydride 50%; (0.150 g, 0.0031 mol) was added to a solution of **8an** (1.0 g, 0.0031 mol) in anhydrous DMF (10 ml) and the mixture was stirred for 30 min. After addition of ethyl bromide (0.40 g, 0.0036 mol) under ice-cooling, the mixture was stirred for 30 min under ice-cooling and then for another 30 min at room temperature. Next, 10% hydrochloric acid (1.0 ml) and water (10 ml) were added to the reaction mixture, which was then extracted with ether (80 ml). The ether layer was dried and evaporated *in vacuo*, giving a residue. A solution of the residue in ether was combined with an ethereal solution of diazomethane and allowed to react for 30 min. Evaporation of the reaction mixture *in vacuo* gave a residue, which, when chromatographed using dichloromethane–ether as the eluant, gave ethyl 6,7-dichloro-5-(*N*-ethyl-*N*-methylsulfamoyl)-2,3-dihydrobenzofuran-2-carboxylate (0.905 g, 84%), mp 80—81 °C (hexane–ether). *Anal.* Calcd for $C_{14}H_{17}Cl_2NO_5S$: C, 43.99; H, 4.48; Cl, 18.55; N, 3.66; S, 8.39. Found: C, 43.77; H, 4.47; Cl, 18.71; N, 3.84; S, 8.41. ^{1}H-NMR (in $CDCl_3$) δ: 1.16 (3H, t, J=7.0, CH_3), 1.30 (3H, t, J=7.0, CH_3), 2.86 (3H, s, N–CH_3), 3.27 (2H, q, J=7.0, N–CH_2), 3.20—3.90 (2H, m, CH_2), 4.28 (2H, q, J=7.0, O–CH_2), 5.38 (1H, 2×d, J=10.0, 7.0, O–CH), 7.87 (1H, t, J=1.0, arom. H). A 1 N sodium hydroxide solution (1.65 ml) was added to a solution of the ester (0.60 g, 0.0016 mol) obtained above in acetonitrile (2 ml), and the mixture was stirred for 30 min. Evaporation of the reaction mixture *in vacuo* gave a residue, which was acidified with 10% hydrochloric acid and extracted with ethyl acetate (50 ml). The ethyl acetate layer was dried and evaporated, giving a viscous residue. The residue was dissolved in acetonitrile (10 ml), then combined with 1 N sodium hydroxide (1.6 ml), and the mixture was stirred for 30 min under ice-cooling. The precipitated crystals were collected by filtration, then recrystallized from aqueous ethanol, giving **13a**

TABLE VI. ^{1}H-NMR Data for Compounds **9**—**13** and **16**—**18** in d_6-Acetone Solution

9aa	3.27—4.55 (2H, m, Ph–C$\underline{H}_2$–CH), 5.55 (1H, 2 × d, J = 10.2, 6.6, O–C$\underline{H}$), 6.4 (1H, br, COO$\underline{H}$), 6.67 (2H, br s, N$\underline{H}_2$), 7.90 (1H, t, J = 1.2, 4-H)
9ab	2.85 (6H, s, 2 × C$\underline{H}_3$), 3.30—4.00 (2H, m, Ph–C$\underline{H}_2$–CH), 5.55 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.87 (1H, t, J = 1.0, 4-H), 8.40 (1H, br, COO$\underline{H}$)
9ac[a)]	1.03 (6H, t, J = 7.0, 2 × C$\underline{H}_3$), 3.26 (4H, q, J = 7.0, 2 × C$\underline{H}_2$), 3.00—3.70 (2H, m, Ph–C$\underline{H}_2$–CH), 4.95 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.71 (1H, t, J = 1.0, 4-H)
9ad	0.80 (6H, t, J = 7.0, 2 × C$\underline{H}_3$), 1.00—1.80 (4H, m, 2 × C$\underline{H}_2$), 3.26 (4H, t, J = 7.0, 2 × C$\underline{H}_2$), 3.25—4.20 (2H, m, Ph–C$\underline{H}_2$–CH), 5.57 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.94 (1H, t, J = 1.0, 4-H), 8.93 (1H, br, COO$\underline{H}$)
9ae	1.27 (12H, d, J = 7.0, 4 × C$\underline{H}_3$), 3.40—4.10 (4H, m, Ph–C$\underline{H}_2$–CH, 2 × C$\underline{H}$), 5.57 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 8.00 (1H, t, J = 1.0, 4-H)
9af	0.87 (3H, t, J = 7.0, C$\underline{H}_3$), 1.05—1.80 (4H, m, 2 × C$\underline{H}_2$), 2.85 (3H, s, C$\underline{H}_3$), 3.25 (2H, t, J = 7.0, C$\underline{H}_2$), 3.40—4.10 (2H, m, Ph–C$\underline{H}_2$–CH), 5.60 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.93 (1H, t, J = 1.0, 4-H), 8.00—9.80 (1H, br, COO$\underline{H}$)
9ag	3.30—4.05 (2H, m, Ph–C$\underline{H}_2$–CH), 4.44 (4H, s, 2 × Ph–C$\underline{H}_2$), 5.55 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.00—7.35 (10H, s, arom. H), 7.85 (1H, t, J = 1.0, 4-H), 7.30—8.50 (1H, br, COO$\underline{H}$)
9ah	2.73 (3H, s, C$\underline{H}_3$), 3.30—4.05 (2H, m, Ph–C$\underline{H}_2$–CH), 4.43 (2H, s, Ph–C$\underline{H}_2$), 5.57 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.32 (5H, s, arom. H), 7.95 (1H, t, J = 1.0, 4-H), 9.37 (1H, br, COO$\underline{H}$)
9ai[a)]	3.00—3.70 (2H, m, Ph–C$\underline{H}_2$–CH), 3.28 (3H, s, C$\underline{H}_3$), 4.96 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.10—7.50 (5H, m, arom. H), 7.62 (1H, t, J = 1.0, 4-H)
9aj	0.70—1.90 (10H, m, 5 × C$\underline{H}_2$), 2.80 (3H, s, C$\underline{H}_3$), 3.00—4.10 (3H, m, Ph–C$\underline{H}_2$–CH, C$\underline{H}$), 5.51 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 6.10 (1H, br, COO$\underline{H}$), 7.91 (1H, br s, 4-H)
9ak	1.65—2.15 (4H, m, 2 × C$\underline{H}_2$), 3.10—4.25 (6H, m, Ph–C$\underline{H}_2$–CH, 2 × N–C$\underline{H}_2$), 5.56 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.90 (1H, t, J = 1.0, 4-H), 8.86 (1H, br, COO$\underline{H}$)
9al[a)]	1.50 (6H, br, 3 × C$\underline{H}_2$), 3.15 (4H, br, 2 × N–C$\underline{H}_2$), 3.10—3.85 (2H, m, Ph–C$\underline{H}_2$–CH), 5.05 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.76 (1H, t, J = 1.0, 4-H)
9am[a)]	2.80—3.40 (4H, m, 2 × C$\underline{H}_2$), 3.49—4.10 (6H, m, 3 × C$\underline{H}_2$), 5.52 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.83 (1H, t, J = 1.0, 4-H)
9an	2.57 (3H, d, J = 5.0, NH–C$\underline{H}_3$), 3.35—4.20 (2H, m, Ph–C$\underline{H}_2$–CH), 5.57 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 6.50 (1H, q, J = 5.0, N$\underline{H}$), 7.92 (1H, t, J = 1.0, 4-H), 7.90—8.95 (1H, br, COO$\underline{H}$)
9ao	0.83 (3H, t, J = 7.0, C$\underline{H}_3$), 1.25—1.70 (2H, m, C$\underline{H}_2$), 2.86 (2H, q, J = 7.0, C$\underline{H}_2$), 3.30—4.05 (2H, m, Ph–C$\underline{H}_2$–CH), 5.55 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 6.85 (1H, br t, N$\underline{H}$), 7.90 (1H, t, J = 1.0, 4-H)
9ap	1.06 (6H, d, J = 7.0, 2 × C$\underline{H}_3$), 3.20—4.10 (3H, m, Ph–C$\underline{H}_2$–CH, C$\underline{H}$), 5.60 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 6.52 (1H, br d, J = 7.0, N$\underline{H}$), 7.95 (1H, t, J = 1.0, 4-H), 9.25—10.05 (1H, br, COO$\underline{H}$)
9aq	3.25—4.10 (2H, m, Ph–C$\underline{H}_2$–CH), 4.15 (2H, d, J = 6.0, Ph–C$\underline{H}_2$), 5.52 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.17 (5H, s, arom. H), 7.75 (1H, t, J = 1.0, 4-H), 7.30—9.10 (1H, br, COO$\underline{H}$)
9ar	3.30—4.00 (2H, m, Ph–C$\underline{H}_2$–CH), 5.51 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 6.85—7.35 (5H, m, arom. H), 7.93 (1H, t, J = 1.0, 4-H), 8.60 (1H, br, COO$\underline{H}$), 9.20 (1H, br s, N$\underline{H}$)
9as	3.35—4.10 (2H, m, Ph–C$\underline{H}_2$–CH), 5.56 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.27 (4H, s, arom. H), 7.93 (1H, t, J = 1.0, 4-H), 7.50—9.30 (1H, br, COO$\underline{H}$), 9.40 (1H, br, N$\underline{H}$)
9at	3.30—4.20 (2H, m, Ph–C$\underline{H}_2$–CH), 3.67 (3H, s, O–C$\underline{H}_3$), 5.53 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 6.77, 7.27 (4H, ABq, J = 9.0, arom. H), 7.82 (1H, t, J = 1.0, 4-H), 8.75 (1H, br, COO$\underline{H}$), 8.92 (1H, br s, N$\underline{H}$)
9au[a)]	2.80—3.40 (8H, m, 4 × N–C$\underline{H}_2$), 3.40—4.10 (6H, m, Ph–C$\underline{H}_2$–CH, 2 × O–C$\underline{H}_2$), 5.53 (1H, 2 × d, J = 10.0, 7.0, O–C$\underline{H}$), 7.86 (1H, t, J = 1.0, 4-H), 8.10 (1H, t, J = 5.0, N$\underline{H}$)
9av	2.70 (6H, s, 2 × C$\underline{H}_3$), 3.58 (1H, 2 × d, J = 16.8, 6.9, Ph–C$\underline{H}_2$–CH), 3.90 (1H, 2 × d, J = 16.8, 10.2, Ph–C$\underline{H}_2$–CH), 5.56 (1H, 2 × d, J = 10.2, 6.9, O–C$\underline{H}$), 7.63 (2H, s, 4-H, 6-H), 7.6—9.3 (1H, br, COO$\underline{H}$)
9aw	1.11 (6H, t, J = 7.0, 2 × C$\underline{H}_3$), 3.23 (4H, q, J = 7.0, 2 × C$\underline{H}_2$), 3.55 (1H, 2 × d, J = 16.5, 6.8, Ph–C$\underline{H}_2$–CH), 3.89 (1H, 2 × d, J = 16.5, 10.5, Ph–C$\underline{H}_2$–CH), 5.53 (1H, 2 × d, J = 10.5, 6.8, O–C$\underline{H}$), 7.66 (2H, s, 4-H, 6-H)
9ax	2.80 (6H, s, 2 × C$\underline{H}_3$), 3.25—3.93 (2H, m, Ph–C$\underline{H}_2$–CH), 5.43 (1H, 2 × d, J = 10.2, 6.8, O–C$\underline{H}$), 7.03 (1H, s, 7-H), 7.88 (1H, t, J = 1.2, 4-H)
9ay	1.08 (6H, t, J = 7.2, 2 × C$\underline{H}_3$), 3.20—3.90 (6H, m, Ph–C$\underline{H}_2$–CH, 2 × C$\underline{H}_2$), 4.2—5.3 (br, COO$\underline{H}$), 5.43 (1H, 2 × d, J = 10.5, 7.0, O–C$\underline{H}$), 7.00 (1H, s, 7-H), 7.91 (1H, t, J = 1.2, 4-H)
9az	2.70 (6H, s, 2 × C$\underline{H}_3$), 3.60 (1H, 2 × d, J = 16.6, 7.0, Ph–C$\underline{H}_2$–CH), 3.93 (1H, 2 × d, J = 16.6, 10.5, Ph–C$\underline{H}_2$–CH), 5.54 (1H, 2 × d, J = 10.5, 7.0, O–C$\underline{H}$), 7.66 (1H, m, 6- or 4-H), 7.75 (1H, m, 4- or 6-H), 7.2—8.5 (1H, br, COO$\underline{H}$)
9ba	1.10 (6H, t, J = 7.1, 2 × C$\underline{H}_3$), 3.22 (4H, q, J = 7.1, 2 × C$\underline{H}_2$), 3.57 (1H, 2 × d, J = 16.5, 6.8, Ph–C$\underline{H}_2$–CH), 3.90 (1H, 2 × d, J = 16.5, 10.5, Ph–C$\underline{H}_2$–CH), 5.52 (1H, 2 × d, J = 10.5, 6.8, O–C$\underline{H}$), 7.70 (1H, m, 6- or 4-H), 7.79 (1H, m, 4- or 6-H), 7.2—8.5 (1H, br, COO$\underline{H}$)

TABLE VI. (continued)

9bb	2.20, 2.56 (2 × 3H, 2 × s, 2 × CH_3), 3.20—3.90 (2H, m, Ph–CH_2–CH), 5.38 (1H, 2 × d, J = 10.8, 7.0, O–CH), 6.33 (2H, br, NH_2), 7.74 (1H, br s, 4-H)
9bc	2.20, 2.50 (2 × 3H, 2 × s, 2 × CH_3), 2.50 (3H, d, J = 5.0, NH–CH_3), 3.20—4.00 (2H, m, Ph–CH_2–CH), 5.37 (1H, 2 × d, J = 10.8, 7.0, O–CH), 6.10 (1H, br, NH), 7.71 (1H, br s, 4-H)
9bd	2.20, 2.50 (2 × 3H, 2 × s, 2 × CH_3), 2.70 (6H, s, 2 × CH_3), 3.25—4.00 (2H, m, Ph–CH_2–CH), 5.38 (1H, 2 × d, J = 10.8, 7.0, O–CH), 7.67 (1H, br s, 4-H)
10a	2.83 (6H, s, 2 × CH_3), 3.15—4.15 (2H, m, Ph–CH_2–CH), 5.60—5.90 (1H, m, O–CH), 7.54 (1H, s, O–CH–O), 7.60—8.00 (5H, arom. H)
10b	1.16 (9H, s, 3 × CH_3), 2.84 (6H, s, 2 × CH_3), 3.10—4.10 (2H, m, Ph–CH_2–CH), 5.62 (1H, 2 × d, J = 10.0, 7.0, O–CH), 5.84 (2H, s, O–CH_2–O), 7.88 (1H, t, J = 1.0, 4-H)
10c	2.85 (6H, s, 2 × CH_3), 3.30—4.15 (2H, m, Ph–CH_2–CH), 4.67, 4.87 (2H, ABq, J = 16.0, O–CH_2–CO), 5.67 (1H, 2 × d, J = 10.0, 6.3, O–CH), 7.88 (1H, t, J = 1.0, 4-H)
10d	1.10 (6H, t, J = 7.0, 2 × CH_3), 3.35 (4H, q, J = 7.0, 2 × CH_2), 3.40—4.20 (2H, m, Ph–CH_2–CH), 4.67, 4.86 (2H, ABq, J = 15.0, O–CH_2–CO), 5.68 (1H, 2 × d, J = 10.0, 7.0, O–CH), 7.93 (1H, t, J = 1.0, 4-H)
11a	2.86 (6H, s, 2 × CH_3), 3.25—3.96 (2H, m, Ph–CH_2–CH), 5.45 (1H, 2 × d, J = 10.0, 7.0, O–CH), 6.50—7.50 (2H, br, NH_2), 7.90 (1H, t, J = 1.0, 4-H)
11b[b]	2.85 (6H, s, 2 × CH_3), 2.87 (3H, d, J = 7.0, NH–CH_3), 3.30—4.00 (2H, m, Ph–CH_2–CH), 5.35 (1H, 2 × d, J = 10.0, 7.0, O–CH), 6.60 (1H, br, NH), 7.84 (1H, t, J = 1.0, 4-H)
11c[b]	2.78 (6H, s, 2 × CH_3), 3.05, 3.25 (2 × 3H, 2 × s, 2 × NCH_3), 3.20—4.15 (2H, m, Ph–CH_2–CH), 5.67 (1H, 2 × d, J = 10.0, 7.0, O–CH), 7.77 (1H, t, J = 1.0, 4-H)
12	1.07 (3H, t, J = 7.0, CH_3), 3.40 (3H, s, CH_3), 3.40—4.05 (2H, m, Ph–CH_2–CH), 4.05 (2H, q, J = 7.0, O–CH_2), 5.62 (1H, 2 × d, J = 10.0, 7.0, O–CH), 8.03 (1H, t, J = 1.0, 4-H), 9.30—10.20 (1H, br, COOH)
13a[a]	1.06 (3H, t, J = 7.0, CH_3), 2.80 (3H, s, CH_3), 3.20 (2H, q, J = 7.0, N–CH_2), 3.20—3.75 (2H, m, Ph–CH_2–CH), 5.06 (1H, 2 × d, J = 11.0, 7.0, O–CH), 7.76 (1H, t, J = 1.0, 4-H)
13b[a]	0.80 (3H, t, J = 7.0, CH_3), 1.25—1.80 (2H, m, CH_2), 2.77 (3H, s, CH_3), 3.12 (2H, t, J = 7.0, N–CH_2), 3.10—3.75 (2H, m, Ph–CH_2–CH), 5.04 (1H, 2 × d, J = 10.0, 7.0, O–CH), 7.74 (1H, t, J = 1.0, 4-H)
16a	3.13—4.17 (4H, m, Ph–CH_2–CH, O–CH_2), 4.21 (1H, 2 × d, J = 6.2, 5.3, OH), 5.00—5.35 (1H, m, O–CH), 6.62 (2H, br s, NH_2), 7.83 (1H, t, J = 1.2, 4-H)
16b	2.83 (6H, s, 2 × CH_3), 3.13—4.10 (4H, m, Ph–CH_2–CH, O–CH_2), 4.20 (1H, 2 × d, J = 6.3, 5.9, OH), 5.00—5.33 (1H, m, O–CH), 7.80 (1H, t, J = 1.2, 4-H)
16c[b]	2.35 (3H, s, CH_3), 3.00—4.15 (4H, m, Ph–CH_2–CH, O–CH_2), 4.38 (2H, s, Ph–CH_2), 4.38 (1H, t, J = 7.0, OH), 4.95—5.35 (1H, m, O–CH), 7.35 (5H, s, arom. H), 7.87 (1H, t, J = 1.0, 4-H)
16d	3.20—4.00 (4H, m, Ph–CH_2–CH, O–CH_2), 3.37 (3H, s, CH_3), 4.21 (1H, t, J = 6.0, OH), 5.00—5.35 (1H, m, O–CH), 7.31 (5H, s, arom. H), 7.68 (1H, t, J = 1.0, 4-H)
16e	2.56 (3H, d, J = 6.0, NH–CH_3), 3.10—4.00 (4H, m, Ph–CH_2–CH, O–CH_2), 4.20 (1H, t, J = 7.0, OH), 5.00—5.33 (1H, m, O–CH), 6.42 (1H, br, NH), 7.83 (1H, t, J = 1.0, 4-H)
16f	3.00—4.30 (4H, m, Ph–CH_2–CH, O–CH_2), 4.25 (2H, d, J = 7.0, Ph–CH_2), 5.00—5.35 (1H, m, O–CH), 7.21 (5H, s, arom. H), 7.73 (1H, t, J = 1.0, 4-H)
16g	3.15—4.05 (4H, m, Ph–CH_2–CH, O–CH_2), 4.90—5.40 (1H, m, O–CH), 6.70—7.40 (5H, m, arom. H), 7.90 (1H, t, J = 1.0, 4-H), 8.40—9.80 (1H, br, NH)
17a	3.15—4.20 (4H, m, Ph–CH_2–CH, Cl–CH_2), 5.15—5.60 (1H, m, O–CH), 6.67 (2H, br s, NH_2), 7.87 (1H, t, J = 1.0, 4-H)
17b[b]	2.87 (6H, s, 2 × CH_3), 3.05—3.85 (2H, m, Ph–CH_2–CH), 3.81 (2H, d, J = 5.0, Cl–CH_2), 5.10—5.45 (1H, m, O–CH), 7.85 (1H, t, J = 1.0, 4-H)
18a	1.12 (3H, t, J = 7.0, CH_3), 3.05—3.75 (2H, m, Ph–CH_2–CH), 3.71 (2H, d, J = 5.0, O–CH_2), 5.05—5.45 (1H, m, O–CH), 6.60 (2H, br, NH_2), 7.82 (1H, t, J = 1.0, 4-H)
18b[b]	1.20 (3H, t, J = 7.0, CH_3), 2.87 (6H, s, 2 × CH_3), 3.10—3.55 (2H, m, Ph–CH_2–CH), 3.60 (2H, q, J = 7.0, O–CH_2), 3.70 (2H, d, J = 5.0, O–CH_2), 5.00—5.35 (1H, m, O–CH), 7.83 (1H, t, J = 1.0, 4-H)

a) In DMSO-d_6 solution. *b*) In $CDCl_3$ solution.

(0.591 g, 91%).

Compound **13b** was obtained in a similar manner. Ethyl 6,7-dichloro-5-(*N*-methyl-*N*-propylsulfamoyl)-2,3-dihydrobenzofuran-2-carboxylate; yield 85%, mp 70—71 °C (hexane–ether). *Anal.* Calcd for $C_{15}H_{19}Cl_2NO_5S$: C, 45.46; H, 4.83; Cl, 17.89; N, 3.53; S, 8.09. Found: C, 45.41; H, 4.75; Cl, 18.10; N, 3.63; S, 8.10. ^{1}H-NMR (in $CDCl_3$) δ: 0.87 (3H, t, J = 7.0, CH_3), 1.30 (3H, t, J = 7.0, CH_3), 1.30—1.90 (2H, m, CH_2), 2.84 (3H, s, N–CH_3), 3.19 (2H, q, J = 7.0, N–CH_2), 3.20—3.85 (2H, m, CH_2), 4.27 (2H, q, J = 7.0, O–CH_2), 5.37 (1H, 2 × d, J = 10.0, 7.0, O–CH), 7.87

(1H, t, $J=1.0$, arom. H). Compound **13b**, yield 86%. ^{1}H-NMR spectral data for **13a**, **b** are given in Table VI.

6,7-Dichloro-5-*N*,*N*-dimethylsulfamoyl-2,3-dihydrobenzofuran-2-ylmethyl Acetate (15b)——Acetyl chloride (5.37 g, 1.5 × 0.0457 mol) was added dropwise to a solution of **14** (10.0 g, 0.0457 mol) and 4-*N*,*N*-dimethylaminopyridine (11.13 g, 2 × 0.0457 mol) in dichloromethane (100 ml) under ice-cooling, and the reaction mixture was stirred for 1 h. Next, dichloromethane (100 ml) was added, and the organic layer was washed several times with water, then dried and evaporated. The residue was chromatographed and eluted with dichloromethane, giving oily 6,7-dichloro-2,3-dihydrobenzofuran-2-ylmethyl acetate (11.04 g, 93%). ^{1}H-NMR (in $CDCl_3$) δ: 2.06 (3H, s, $COCH_3$), 3.01 (1H, 2 × d, $J=16.0$, 7.5, Ph–CH_2–CH), 3.35 (1H, 2 × d, $J=16.0$, 9.5, Ph–CH_2–CH), 4.09—4.45 (2H, m, O–CH_2), 4.93—5.30 (1H, m, O–CH), 6.93 (2H, s, arom. H). Chlorosulfonic acid (1.25 ml) was added to a solution of this oily acetate (1.0 g, 0.0038 mol) in thionyl chloride (2 ml) under ice-cooling, and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice water and extracted with ether. The ethereal layer was washed with water, then dried and evaporated *in vacuo*. A 30% ethanolic solution of dimethylamine (1.8 ml, 3 × 0.0038 mol) was added dropwise to a solution of this oily chlorosulfonate in dichloromethane (10 ml) at −30 °C, and the mixture was stirred for 2 h. Next, dichloromethane was added, then the reaction mixture was washed with 10% hydrochloric acid. The organic layer was dried, evaporated *in vacuo* and treated with ether, giving **15b** (1.24 g, 88%).

Compounds **15a** and **15c**—**g** were obtained in a similar manner (Table IV). ^{1}H-NMR spectral data for **15a**—**g** are given in Table V.

6,7-Dichloro-2-hydroxymethyl-*N*,*N*-dimethyl-2,3-dihydrobenzofuran-5-sulfonamide (16b)——A solution of **15b** (2.94 g, 0.0080 mol) in tetrahydrofuran (15 ml) was stirred with 5% sodium hydroxide (7.5 ml) at room temperature for 2 h. The reaction mixture became transparent. After removal of tetrahydrofuran by evaporation *in vacuo*, the reaction mixture was acidified and extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated *in vacuo*. The residue was treated with ether–ethyl acetate, giving **16b** (2.15 g, 89%).

Compounds **16a** and **16c**—**g** were obtained in a similar manner. ^{1}H-NMR spectral data for **16a**—**g** are given in Table VI.

2-Chloromethyl-6,7-dichloro-*N*,*N*-dimethyl-2,3-dihydrobenzofuran-5-sulfonamide (17b)——Thionyl chloride (1 ml) was added dropwise to a solution of **16b** (1.0 g, 0.0031 mol) in pyridine (10 ml) at 4 °C, and the mixture was stirred at room temperature for 21 h. Next, 10% hydrochloric acid was added, and the mixture was extracted with ethyl acetate (200 ml). The organic layer was washed with 10% hydrochloric acid and then water, dried and evaporated *in vacuo*. Chromatography of the residue using dichloromethane as the eluant gave **17b** (0.663 g, 63%).

Compound **17a** was obtained in a similar manner. Yield 66%. ^{1}H-NMR spectral data for **17a**, **b** are given in Table VI.

6,7-Dichloro-2-ethoxymethyl-2,3-dihydrobenzofuran-5-sulfonamide (18a)——Sodium hydride 50%; (0.790 g, 0.0165 mol) was added to a solution of **14** (2.88 g, 0.0132 mol) in DMF (22 ml), and the mixture was stirred at room temperature for 30 min. Next, ethyl bromide (1.73 g, 0.0159 mol) was added, and the mixture was allowed to react at room temperature for 17 h. After decomposition of sodium hydride by addition of water, the reactant was extracted with ether. The ether layer was washed with water, dried and evaporated *in vacuo*, giving a residue, which, when chromatographed with dichloromethane, gave oily 6,7-dichloro-2-ethoxymethyl-2,3-dihydrobenzofuran (2.0 g, 62%).

Chlorosulfonic acid (3.0 g, 0.0258 mol) was added dropwise to a solution of this compound (2.0 g, 0.0081 mol) in thionyl chloride (5 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 2 h, poured into ice water, and then extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated *in vacuo*, giving an oil, which was then dissolved in dichloromethane (30 ml). After introduction of gaseous ammonia at −30——20 °C, the mixture was allowed to stand overnight at room temperature. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with water, dried and evaporated *in vacuo*, leaving an oily residue, which, when chromatographed with dichloromethane–acetone (20 : 1), gave **18a** (0.900 g, 24%).

6,7-Dichloro-*N*,*N*-dimethyl-2-ethoxymethyl-2,3-dihydrobenzofuran-5-sulfonamide (18b)——Sodium hydride 50%; (0.200 g, 0.0031 mol) was added to a solution of **16b** (1.0 g, 0.0031 mol) in DMF (8 ml), and the mixture was stirred at room temperature for 30 min. After addition of ethyl bromide (0.450 g, 1.3 × 0.0031 mol), the reaction mixture was stirred at room temperature for 24 h and then combined with water and ether. The organic layer was washed twice with water, dried and evaporated *in vacuo*, leaving an oily residue, which, when chromatographed with dichloromethane–acetone (20 : 1), gave **18b** (0.464 g, 43%). ^{1}H-NMR spectral data for **18a**, **b** are given in Table VI.

Resolution of the Optical Isomers of 9ab——Thionyl chloride (2.5 ml) was added to a stirred solution of **9ab** (1.50 g, 0.0044 mol) in absolute benzene (10 ml), and the solution was refluxed for 1 h, then evaporated *in vacuo*. The resulting oily acid chloride was dissolved in benzene (5 ml), and a solution of L-proline *tert*-butyl ester (0.90 g, 0.0053 mol), triethylamine (0.88 g, 0.0088 mol) and 4-*N*,*N*-dimethylaminopyridine (0.053 g, 0.0004 mol) in benzene (10 ml) was added dropwise with stirring at 4 °C. The mixture was allowed to react for 1 h, then evaporated *in vacuo*. The residue was dissolved in ethyl acetate (150 ml), and the solution was washed successively with 10% hydrochloric acid and water, dried and evaporated *in vacuo*. Treatment of the oily residue with ether gave colorless crystals of a diastereomer, **19a** (0.924 g, 44%). The mother liquor was chromatographed with a silica gel Lobar column (E. Merck, size B), which was eluted with dichloromethane–acetone (20 : 1). After separation of small amounts of **19a**, collection

of the subsequent fractions gave oily **19b** (0.89 g, 42%), which crystallized in a refrigerator at −20 °C. Compound **19a**: mp 177—178 °C (ethyl acetate–ether). *Anal.* Calcd for $C_{20}H_{26}Cl_2N_2O_6S$: C, 48.69; H, 5.31; Cl, 14.37; N, 5.68; S, 6.50. Found: C, 48.72; H, 5.22; Cl, 14.44; N, 5.68; S, 6.47. ^{1}H-NMR (in $CDCl_3$) δ: 1.31 and 1.46 (9H, 2 × s, 3 × C<u>H</u>$_3$), 1.80—2.45 (4H, m, 2 × C<u>H</u>$_2$), 2.86 (6H, s, 2 × C<u>H</u>$_3$), 3.30—4.20 (4H, m, N–C<u>H</u>$_2$, Ph–C<u>H</u>$_2$–CH), 4.20—5.00 (1H, m, N–C<u>H</u>), 5.60 (1H, 2 × d, J = 10.0, 7.0, O–C<u>H</u>), 7.84 (1H, t, J = 1.2, arom. H). Compound **19b**: mp 96—98 °C (hexane–ether). *Anal.* Calcd for $C_{20}H_{26}Cl_2N_2O_6S$: C, 48.69; H, 5.31; Cl, 14.37; N, 5.68; S, 6.50. Found: C, 48.28; H, 5.19; Cl, 14.59; N, 5.78; S, 6.37. ^{1}H-NMR (in $CDCl_3$) δ: 1.40 and 1.50 (9H, 2 × s, 3 × C<u>H</u>$_3$), 1.70—2.50 (4H, m, 2 × C<u>H</u>$_2$), 2.88 (6H, s, 2 × C<u>H</u>$_3$), 3.20—4.10 (4H, m, N–C<u>H</u>$_2$, Ph–C<u>H</u>$_2$–CH), 4.30—4.90 [1H, 2 sets of m and 2 × d (J = 7.5, 4.5), N–C<u>H</u>], 5.43 and 5.55 (1H, 2 sets of 2 × d, J = 10.2, 6.8, O–C<u>H</u>), 7.75 (1H, br s, arom. H).

A solution of **19a** (11.8 g, 0.0239 mol) in water (10 ml), concentrated sulfuric acid (25 g) and dioxane (225 ml) was heated at 90 °C with stirring for 17 h. After addition of water (200 ml), the solution was extracted with ethyl acetate (800 ml), then the organic layer was washed with water three times, dried and evaporated *in vacuo*. The residue was dissolved in a solution of sodium hydroxide (95%, 1.1 g, 0.0261 mol) and water (20 ml), and then acetonitrile (40 ml) was added. The precipitated crystalline material was collected by filtration and suspended in 10% hydrochloric acid. The suspension was extracted with ethyl acetate and the organic layer was washed with water, dried and evaporated *in vacuo*. Treatment of the residue with hexane–ethyl acetate gave (−)-**9ab** (7.43 g, 91%), mp 130—131 °C (ethyl acetate–hexane). *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_5S$: C, 38.84; H, 3.26; Cl, 20.84; N, 4.12; S, 9.43. Found: C, 38.87; H, 3.32; Cl, 20.79; N, 4.17; S, 9.28. ^{1}H-NMR (in acetone-d_6) δ: 2.83 (6H, s, 2 × C<u>H</u>$_3$), 3.53 (1H, 3 × d, J = 16.0, 7.0, 1.0, Ph–C<u>H</u>$_2$–CH), 3.86 (1H, 3 × d, J = 16.0, 10.0, 1.0, Ph–C<u>H</u>$_2$–CH), 5.55 (1H, 2 × d, J = 10.0, 7.0, O–C<u>H</u>), 7.10—8.20 (1H, br, COO<u>H</u>), 7.86 (1H, t, J = 1.0, 4-<u>H</u>). $[\alpha]_D$ −18.7 ± 0.6° (c = 1.0, acetone). Compound (+)-**9ab** was obtained from **19b** in a similar manner. Yield 86%, mp 130—131 °C. *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_5S$: C, 38.84; H, 3.26; Cl, 20.84; N, 4.12; S, 9.43. Found: C, 39.07; H, 3.43; Cl, 20.55; N, 4.03; S, 9.17. The ^{1}H-NMR spectrum in acetone-d_6 was the same as that of (−)-**9ab**, except for the signal of COOH, which appeared at 5.70—6.80 as a broad signal. $[\alpha]_D$ +17.6 ± 0.6° (c = 1.0, acetone).

Diuretic Effect on Rats——Male Sprague-Dawley rats, weighing about 250 g, at 8 weeks of age, were used in this test. A few lumps of sugar in place of ordinary diet were given on the morning of the day before the test day and 20 ml/kg of 5% glucose solution was given orally at approximately 4 p.m. On the morning of the test day, a suspension or solution of the test compound in 2% gum arabic was orally administered to each rat at a dose of 20 ml/kg. The control group received only 2% gum arabic orally at 20 ml/kg. Immediately after the administration, the test animals were put in plastic cages for the metabolic tests and urine samples were collected for 5 h. The cumulative urine volume, urinary sodium, and urinary potassium were quantitated.

Diuretic Effect on Mice——Female ddY mice, weighing about 20 g, were used for the test. The mice were fasted overnight, but were allowed free access to water. On the morning of the test day, a suspension or solution of the test compound in 2% gum arabic was orally administered to each mouse at 30 ml/kg. The control mice received only the vehicle. Immediately after the administration, five mice of the treated group were put together in a plastic cage for the metabolic tests and urine was collected for 4 h. The cumulative urine volume, urinary sodium, and urinary potassium were quantitated.

Uricosuric Effect on Rats——Nine-week-old male rats were employed for the test. Potassium oxonate was intraperitoneally administered to the animals at a dose of 250 mg/kg to measure uric acid clearance and inulin clearance. Within 2 h after the administration of the potassium oxonate, cannulae were placed in the right femoral artery, left femoral vein, and urinary bladder of each animal under pentobarbital anesthesia for blood collection, drug infusion, and urine collection, respectively. At 2 h after the first administration, potassium oxonate was administered again at the same dosage and then 60% urethane (2 ml/kg) and 15% inulin (4 ml/kg) were subcutaneously injected. A mixture of 4% mannitol–1.5% inulin–0.9% saline was infused at the flow rate of 0.1 ml/min into each animal on a plate kept at 30 °C. The animal was allowed 40 min to reach an equilibrium state, then arterial blood (0.2 ml each) samples were collected six times at 20-min intervals, and five 20-min urine samples were collected. Immediately after the collection of each blood sample, the serum was separated. The serum and urine samples were stored in a refrigerator.

Immediately after collection of the first urine sample, a test compound suspended in 1% gum arabic was intraperitoneally administered at 2 ml/kg. Uric acid levels in the serum and the urine were quantitated by the method of Yonetani *et al.*[10] Inulin was measured essentially by the method of Vurek and Pegram.[11] To analyze uric acid, 0.1 ml of a diluted solution of deproteinized serum or urine was admixed with a 1% dimedone–phosphoric acid solution and the resulting mixture was heated for 5 min. The mixture was then cooled in iced water and combined with 2.0 ml of acetic acid. The fluorescence was measured at 410 nm with excitation at 360 nm.

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