Studies on Uricosuric Diuretics. III. Substituted 1,3-Dioxolo[4,5-*f*]-1,2-benzisoxazole-6-carboxylic Acids and 1,3-Dioxolo[4,5-*g*]-1,2-benzisoxazole-7-carboxylic Acids[1)]

Haruhiko SATO,* Takashi DAN, Etsuro ONUMA, Haruko TANAKA, Bunya AOKI, and Hiroshi KOGA*

Exploratory Research Laboratories, Chugai Pharmaceutical Co., Ltd., 135 Komakado 1-chome, Gotemba-shi, Shizuoka 412, Japan. *Received June 27, 1991*

A series of substituted 1,3-dioxolo[4,5-*f*]-1,2-benzisoxazole-6-carboxylic acids 13 and 1,3-dioxolo[4,5-*g*]-1,2-benzisoxazole-7-carboxylic acids 14 were synthesized and evaluated for diuretic and uricosuric activities in rats. Most of the benzisoxazole derivatives 13 and 14 showed potent diuretic activities. Moderate uricosuric activities were also found in 14a, 14b, and 14f.

Keywords diuretic activity; uricosuric activity; 1,3-dioxolo[4,5-*f*]-1,2-benzisoxazole-6-carboxylic acid; 1,3-dioxolo[4,5-*g*]-1,2-benzisoxazole-7-carboxylic acid

The discovery of tienilic acid (**1**),[2)] an uricosuric diuretic, coupled with the observation that annulation of **1** to indacrinone (**2**),[2,3)] a dihydrobenzofurancarboxylic acid **3**,[2,4)] and HP-522 (**4**)[2,5)] (Chart 1) enhanced diuretic activity, prompted us to design the annulated compounds **5**—**14** (Chart 2).

In previous papers,[6)] we reported the syntheses and diuretic and uricosuric activities of xanthones **5** and **6**, dihydrofuroxanthones **7** and **8**, and dihydrofurobenzisoxazoles **10** and dihydrofurobenzoxazoles **12** (Chart 2).

Herein we report the syntheses and biological activities of dioxolobenzisoxazoles **13** and **14**.

Chemistry The compounds prepared in this study are listed in Tables I and II, and their synthetic routes are outlined in Charts 3—4.

1,3-Dioxolo[4,5-*f*]-1,2-benzisoxazole-6-carboxylic acids

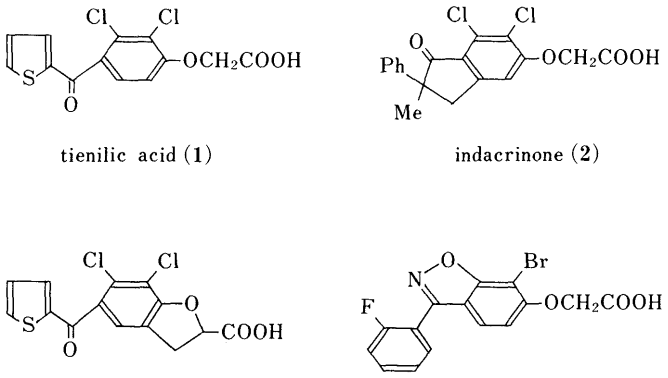


Chart 1

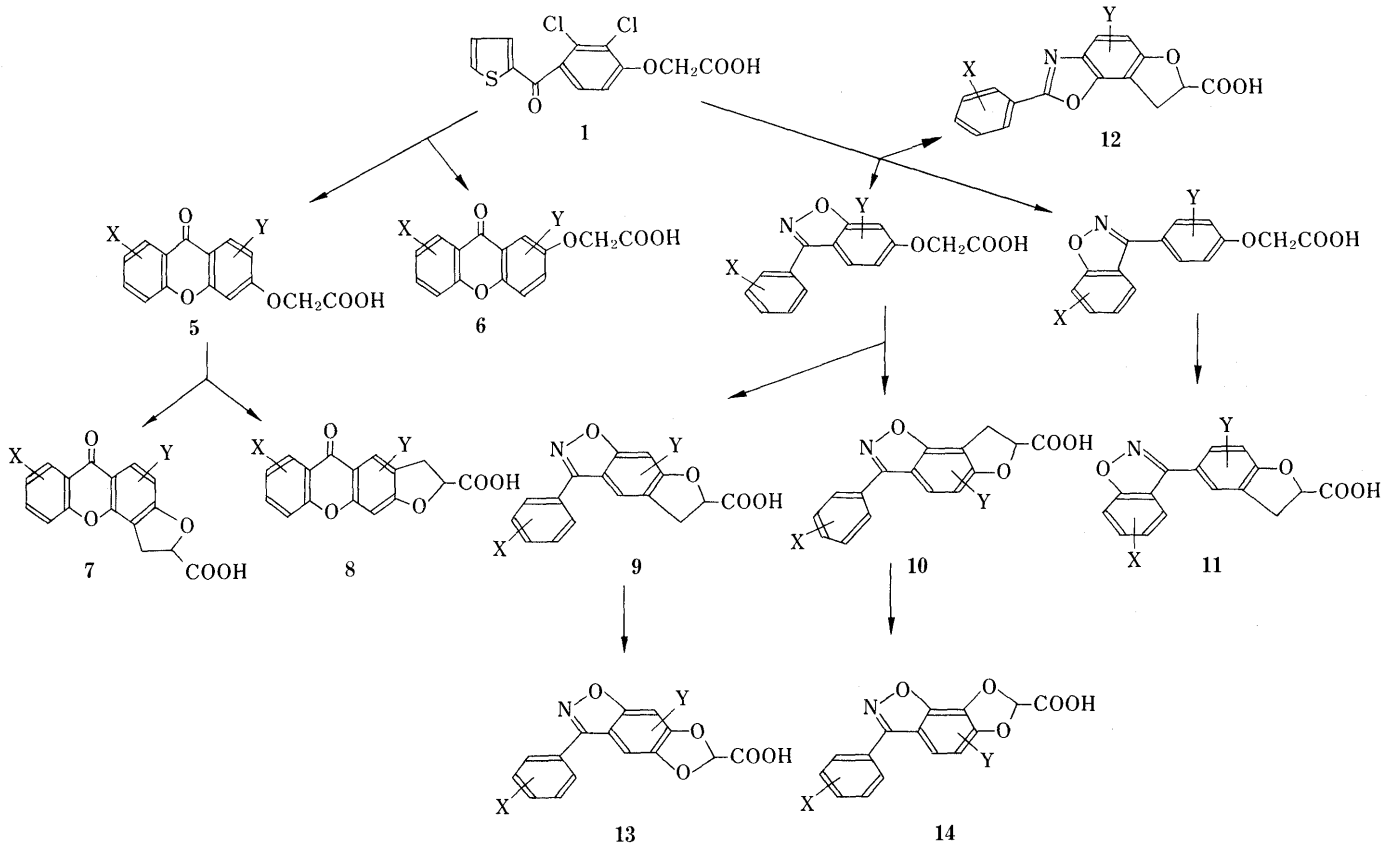
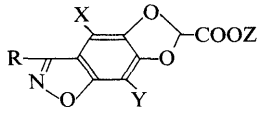


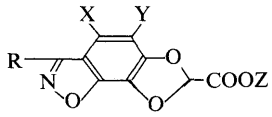
Chart 2

TABLE I. 1,3-Dioxolo[4,5-*f*]-1,2-benzisoxazole-6-carboxylic Acids **13**



Compd. No.	R	X	Y	Z	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
13a	C_6H_5	H	H	H	A (B)	54	203—204	CH_3CN	$C_{15}H_9NO_5$	63.61	3.20	4.95	63.79	3.26	5.02
13aa	C_6H_5	Cl	H	H	A (D)	58	246—248	CH_3CN–H_2O	$C_{15}H_8ClNO_5$	56.71	2.54	4.41	56.61	2.56	4.41
13ab	C_6H_5	H	Cl	H	A (C, D)	44	206—207	CH_3CN–H_2O	$C_{15}H_8ClNO_5$	56.71	2.54	4.41	56.66	2.59	4.39
13ac	C_6H_5	Cl	Cl	H	A (D)	9	231—232	Acetone–H_2O	$C_{15}H_7Cl_2NO_5$	51.16	2.00	3.98	51.14	2.16	4.00
13b	2-ClC_6H_4	H	H	H	A	51	229—230	CH_3CN	$C_{15}H_8ClNO_5$	56.71	2.54	4.41	56.62	2.48	4.54
13c	2-FC_6H_4	H	H	H	A	57	245—248	CH_3CN	$C_{15}H_8FNO_5$	59.81	2.68	4.65	59.70	2.70	4.65
13d	2-FC_6H_4	H	Cl	H	A (C)	29	212—214	CH_3CN	$C_{15}H_7ClFNO_5$	53.67	2.10	4.17	53.71	2.04	4.47
13e	2-$CH_3C_6H_4$	H	H	K	A (B)	51	166—170	EtOH	$C_{16}H_{10}KNO_5$	57.31	3.01	4.18	57.70	3.30	4.30
13f	2-Thienyl	H	H	H	A (B)	18	222—224	Acetone–H_2O	$C_{13}H_7NO_5S$	53.98	2.44	4.84	54.16	2.33	4.88

TABLE II. 1,3-Dioxolo[4,5-*g*]-1,2-benzisoxazole-7-carboxylic Acids **14**



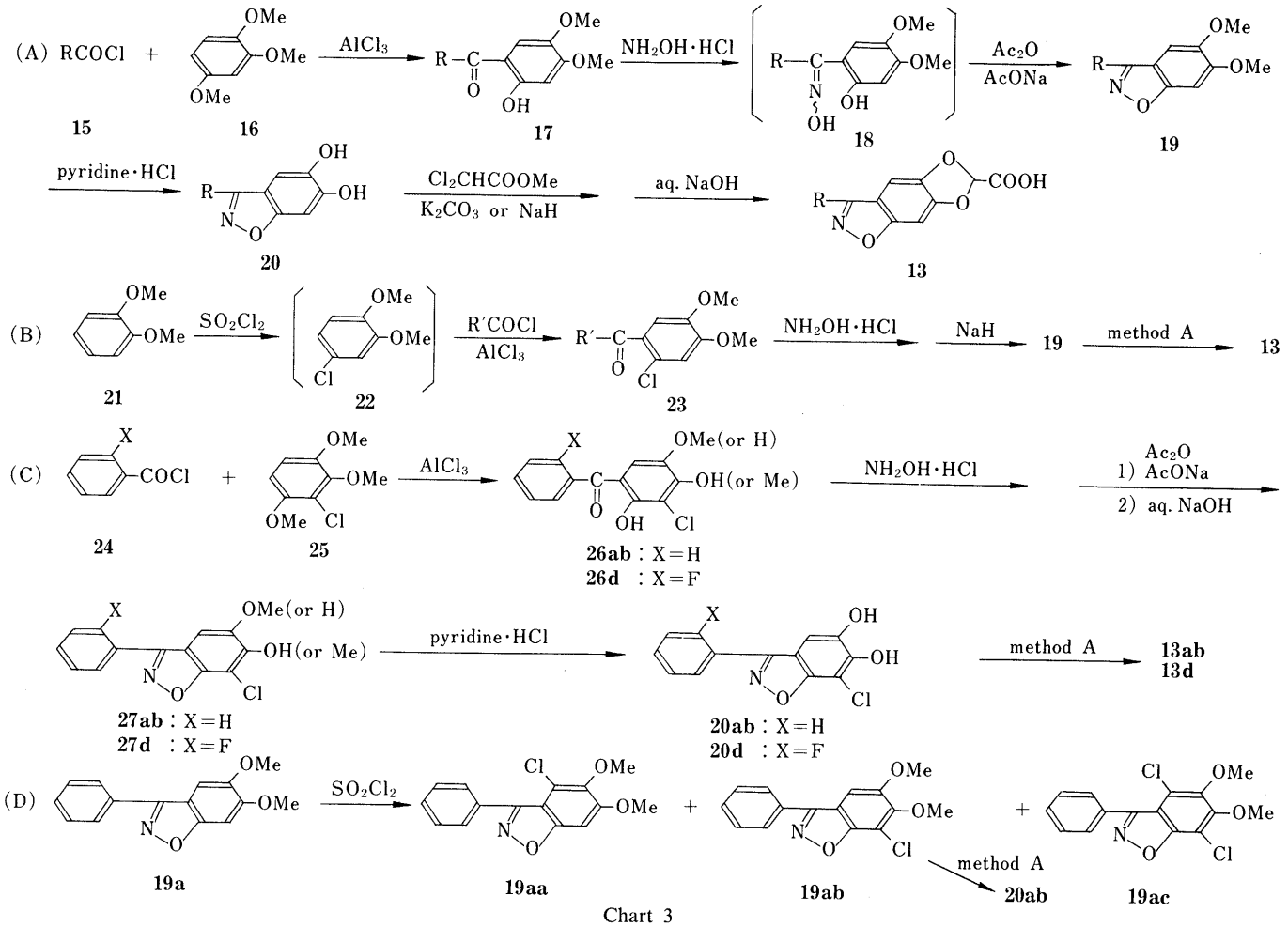
Compd. No.	R	X	Y	Z	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
14a	C_6H_5	H	H	H	E	58	187—190	Acetone–H_2O	$C_{15}H_9NO_5$	63.61	3.20	4.95	63.66	3.22	4.81
14aa	C_6H_5	Cl	H	H	E (F)	27	150—152	Benzene	$C_{15}H_8ClNO_5$	56.71	2.54	4.41	56.95	2.61	4.51
14ab	C_6H_5	H	Cl	H	E (G)	62	182—184	Acetone–H_2O	$C_{15}H_8ClNO_5$	56.71	2.54	4.41	56.22	2.60	4.31
14b	2-ClC_6H_4	H	H	K	E	83	222—225	H_2O	$C_{15}H_7ClKNO_5$	50.64	1.98	3.94	50.29	2.02	4.06
14c	4-ClC_6H_4	H	H	H	E	68	237—240	CH_3CN	$C_{15}H_8ClNO_5$	56.71	2.54	4.41	56.83	2.46	4.54
14d	2-FC_6H_4	H	H	H	E	47	164—166	CH_2Cl_2	$C_{15}H_8FNO_5$	59.81	2.68	4.65	59.93	2.70	4.75
14e	3-FC_6H_4	H	H	H	E	62	191—193	CH_3CN_2	$C_{15}H_8FNO_5$	59.81	2.68	4.65	59.99	2.70	4.64
14f	4-FC_6H_4	H	H	H	E	88	222—223	CH_3CN	$C_{15}H_8FNO_5$	59.81	2.68	4.65	59.77	2.65	4.73
14fa	4-FC_6H_4	H	Cl	H	E (G)	83	205—206	Acetone–H_2O	$C_{15}H_7ClFNO_5$	53.67	2.10	4.17	53.61	2.10	4.13
14g	2-$CH_3C_6H_4$	H	H	K	E	48	258—261	H_2O	$C_{16}H_{10}KNO_5$	57.30	3.01	4.18	57.43	3.01	4.24
14h	3-$CF_3C_6H_4$	H	H	H	E	20	194—197	CH_3CN	$C_{16}H_8F_3NO_5$	54.71	2.30	3.99	54.89	2.35	3.97
14i	2-Thienyl	H	H	H	E	73	226—228	CH_3CN	$C_{13}H_7NO_5S$	53.98	2.44	4.84	54.04	2.44	4.91

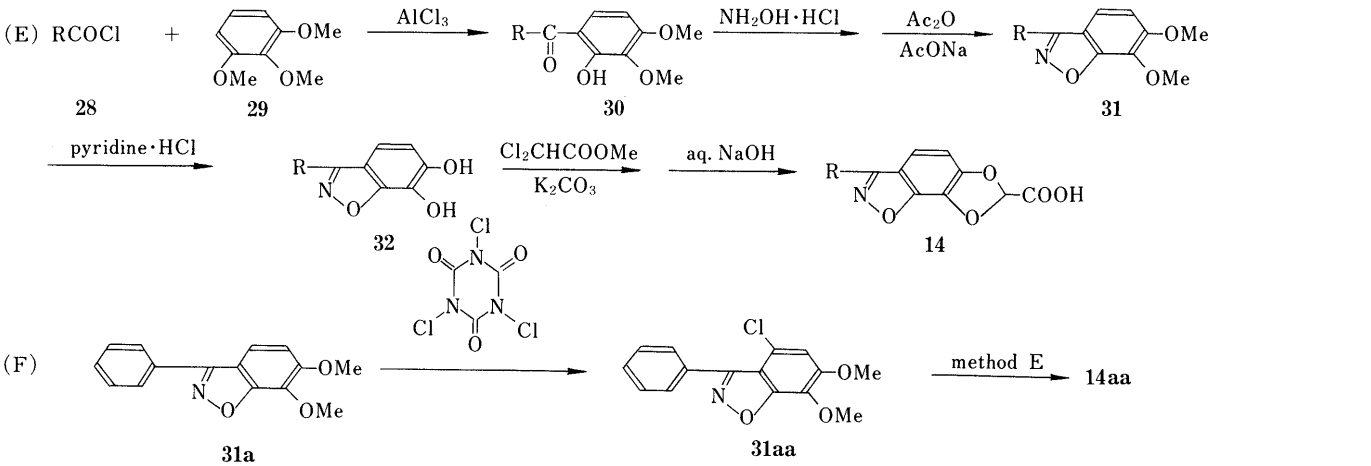
13 were synthesized by the four methods shown in Chart 3.

Method A was used for the preparation of **13**, which had no substituent at positions 4 and 8. 1,2,4-Trimethoxybenzene (**16**) was treated with an acyl chloride **15** (1 eq) and aluminum chloride (1 eq) in 1,2-dichloroethane at room temperature followed by heating at refluxing temperature to give the 2-hydroxy-4,5-dimethoxybenzophenone **17** (Table IV). Heating **17** with hydroxylamine hydrochloride in pyridine yielded the corresponding oxime **18**, which was cyclized to the 5,6-dimethoxy-1,2-benzisoxazole **19** by treatment with acetic anhydride and sodium acetate (Table V). The methyl ether in **19** was smoothly cleaved with pyridine hydrochloride at 170—180 °C, giving the corresponding 5,6-dihydroxy-1,2-benzisoxazole **20** (Table VI). Successive treatment of **20** with methyl dichloroacetate in the presence of anhydrous potassium carbonate or sodium hydride, followed by the action of aqueous sodium hydroxide, gave the desired carboxylic acid **13** (Table I).

The 5,6-dimethoxy-1,2-benzisoxazole **19** was also obtained by an alternative approach (method B). Chlorination of 1,2-dimethoxybenzene (**21**) with sulfuryl chloride gave 4-chloro-1,2-dimethoxybenzene (**22**), which was acylated with an acyl chloride in the presence of aluminum chloride to give the 4-acyl-5-chloro-1,2-dimethoxybenzene **23** (Table VII). Treatment of **23** with hydroxylamine hydrochloride in pyridine followed by the action of sodium hydride gave the benzisoxazole **19** (Table V). The compounds **19a**, **19e**, and **19f** were converted into the corresponding carboxylic acids **13a**, **13e**, and **13f** in the same way as method A (Table I).

The preparation of **13ab** and **13d**, having a chloro substituent at position 8, was performed by method C starting from 3-chloro-1,2,4-trimethoxybenzene (**25**). Treatment of **25** with an acyl chloride **24** (1 eq) and aluminum chloride (1 eq) in 1,2-dichloroethane under the controlled conditions (see Experimental section) gave the 3-chloro-2,4(or 2,5)-dihydroxy-5(or 4)-methoxybenzophenone **26**. Compound **26** was heated with hydroxylamine hydrochloride in pyridine to give the corresponding oxime which was successively treated with acetic anhydride and sodium acetate, followed by the action of aqueous sodium hydroxide, to afford the 7-chloro-6(or 5)-hydroxy-5(or





6)-methoxy-1,2-benzisoxazole **27**. Heating **27** with pyridine hydrochloride at 170—180 °C gave the corresponding 7-chloro-5,6-dihydroxy-1,2-benzisoxazole **20** (Table VI). Compounds **20ab** and **20d** were transformed into the corresponding 8-chloro **13**, **13ab** and **13d** respectively, in the same manner (Table I).

Chlorination of 5,6-dimethoxy-3-phenyl-1,2-benzisoxazole (**19a**) with sulfuryl chloride in dichloromethane provided the 4-chloro derivative **19aa**, the 7-chloro derivative **19ab** and the 4,7-dichloro derivative **19ac** (method D). These compounds were similarly converted into the corresponding chloro-substituted **13**, **13aa**, **13ab**, and **13ac** (Table I).

Synthesis of the 1,3-dioxolo[4,5-*g*]-1,2-benzisoxazole-7-carboxylic acids **14** were achieved by the three methods shown in Chart 4.

The preparation of **14**, which had no substituent at positions 4 and 5, was synthesized by method E, starting from 1,2,3-trimethoxybenzene (**29**) through the 2-acyl-5,6-dimethoxyphenol **30**, 6,7-dimethoxy-1,2-benzisoxazole **31**, and 6,7-dihydroxy-1,2-benzisoxazole **32**, quite similarly to method A (Tables II, VIII, IX, and X).

Treatment of 6,7-dimethoxy-3-phenyl-1,2-benzisoxazole (**31a**) with trichloroisocyanuric acid in *N*,*N*-dimethylformamide (DMF) afforded the 4-chloro derivative **31aa** as the sole product, with the 5-chloro isomer not formed (method F). Compound **31aa** was converted into the 4-chloro **14**, **14aa** in the same way as method E (Table II).

On the other hand, chlorination of 2-hydroxy-3,4-dimethoxybenzophenones, **30a** and **30f**, took place at position 5 to give the 5-chloro derivatives, **30ab** and **30fa**, respectively (method G). Thus, chlorination of **30a** with sulfuryl chloride in dichloromethane gave **30ab**, and **30f** afforded **30fa** with trichloroisocyanuric acid in DMF. These compounds, **30ab** and **30fa**, were led to the 5-chloro **14**, **14ab** and **14fa**, in the same manner (Table II).

TABLE III. Diuretic and Uricosuric Activities[a]

Compd. No.	No. of animals	Diuretic[b] (0—6 h)	Uricosuric[b] (0—6 h)
13a	5	156[c]	102
13aa	5	237[e]	98
13ab	5	422[e]	77
13ac	5	291[e]	91
13b	5	140[c]	72[c]
13c	5	193[d]	103
13d	5	328[e]	115
13e	5	143	99
13f	5	167[d]	74[c]
14a	15	181[e]	124[d]
14aa	10	157[e]	116
14ab	5	155[c]	99
14b	5	122	126[c]
14c	5	151[d]	112
14d	5	174[c]	119
14e	5	193[e]	106
14f	10	343[e]	132[c]
14fa	5	255[e]	110
14g	5	93	101
14i	5	145[d]	109
Tienilic acid	15	143[e]	118[c]
Indacrinone	19	265[e]	156[e]

a) Test compounds were administered at 100 mg/kg *p.o.* to Wistar–Imamichi rats and the activities are shown as relative activity (%) to the control (100%). Details of the test protocol are described in the experimental section. *b*) Student's *t*-test: *c*) $p<0.05$, *d*) $p<0.01$, *e*) $p<0.001$ *vs.* control; values without marks are not statistically significant.

Biological Activities Diuretic and uricosuric activities in rats of the compounds **13** and **14** are shown in Table III. Tienilic acid and indacrinone were used as the reference agents for the diuretic and uricosuric activities. Tienilic acid showed moderate diuretic and uricosuric activities, whereas indacrinone showed potent diuretic and uricosuric activities.

The diuretic activity of compounds **13** was comparable to, or more potent than, that of tienilic acid, but the uricosuric activity was only marginal. In particular, compounds **13ab**, **13ac**, and **13d** showed a high level of diuretic activity.

The diuretic activity of most of compounds **14** was comparable to, or more potent than, that of tienilic acid. Compound **14f** showed a high level of diuretic activity in particular. Compounds **14a**, **14b**, and **14f** possessed uricosuric activity. Among these compounds, **14a** and **14f** had both diuretic and uricosuric activities.

In a preliminary toxicological study, tienilic acid showed positive for urobilinogen in rat urine by BM test 6-III (Yamanouchi Pharmaceutical Co., Ltd.), while compounds **13** and **14** did not. These results seem to show that the liver toxicity of compounds **13** and **14** is weaker than that of tienilic acid.

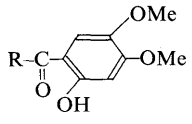
As a result, compound **14a** was found to possess diuretic and uricosuric activities more potent than those of tienilic acid and balanced diuretic and uricosuric activities, with a minimal effect on liver.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi 270-30 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-24B spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are given in Hertz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad. For column chromatography, Wakogel C-200 (Wako, 0.074—0.149 mm) was used.

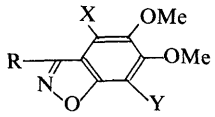
2-Hydroxy-4,5-dimethoxybenzophenone (17a) (General Procedure) Benzoyl chloride (2.64 g, 0.019 mmol) and 1,2,4-trimethoxybenzene (**16**) (3.0 g, 0.018 mol) were dissolved in 1,2-dichloroethane (30 ml) and the solution was cooled to 0—5 °C. $AlCl_3$ (2.63 g, 0.020 mol) was added portionwise to the solution, and the resulting mixture was warmed to room temperature over a 4 h period and then refluxed for 2 h. After cooling, ice-water and conc. HCl were added to the reaction mixture, and the whole mixture was stirred for 30 min. The slurry formed was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated.

TABLE IV. 2-Hydroxy-4,5-dimethoxybenzophenones **17**



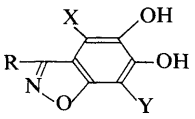
Compd. No.	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
17a	C_6H_5	97	109—110 (lit.[7] 106—107)	EtOH	$C_{15}H_{14}O_4$	69.76 (69.56)	5.46 (5.65)
17b	2-ClC_6H_4	60	75—77	EtOH	$C_{15}H_{13}ClO_4$	61.55 (61.58)	4.48 (4.53)
17c	2-FC_6H_4	95	89—90	EtOH	$C_{15}H_{13}FO_4$	65.22 (65.25)	4.74 (4.88)

TABLE V. 5,6-Dimethoxy-1,2-benzisoxazoles **19**



Compd. No.	R	X	Y	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
19a	C_6H_5	H	H	A, B	77, 99	108—109	EtOH	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	70.63	5.16	5.62
19aa	C_6H_5	Cl	H	D	43	171—172	EtOH	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.83	62.30	4.13	4.96
19ab	C_6H_5	H	Cl	D	5	129—130	EtOH	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.83	62.37	4.13	5.05
19ac	C_6H_5	Cl	Cl	D	45	121—123	EtOH	$C_{15}H_{11}Cl_2NO_3$	55.58	3.42	4.32	55.51	3.42	4.37
19b	2-ClC_6H_4	H	H	A	70	129—130	EtOH	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.83	61.94	4.24	4.66
19c	2-FC_6H_4	H	H	A	60	156—157	EtOH	$C_{15}H_{12}FNO_3$	65.93	4.43	5.13	65.89	4.41	5.02
19e	2-$CH_3C_6H_4$	H	H	B	64	69—70	EtOH	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.35	5.84	5.18
19f	2-Thienyl	H	H	B	20	146—147	EtOH	$C_{13}H_{11}NO_3S$	59.76	4.24	5.36	59.87	4.30	5.34

TABLE VI. 5,6-Dihydroxy-1,2-benzisoxazoles **20**



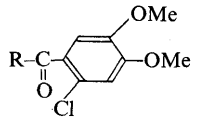
Compd. No.	R	X	Y	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
20a	C_6H_5	H	H	A	91	195—196	EtOH–H_2O	$C_{13}H_9NO_3$	68.72	3.99	6.16	68.70	3.91	6.14
20aa	C_6H_5	Cl	H	A	84	180—183	AcOEt–hexane	$C_{13}H_8ClNO_3$	59.67	3.08	5.35	59.74	2.86	5.12
20ab	C_6H_5	H	Cl	A, C	80, 90	211—213	AcOEt–hexane	$C_{13}H_8ClNO_3$	59.67	3.08	5.35	59.35	3.30	5.65
20ac	C_6H_5	Cl	Cl	A	70	196—198	EtOH–H_2O	$C_{13}H_7Cl_2NO_3$	52.73	2.38	4.73	52.49	2.22	4.48
20b	2-ClC_6H_4	H	H	A	77	181—183	EtOH–H_2O	$C_{13}H_8ClNO_3$	59.67	3.08	5.35	59.29	2.96	5.24
20c	2-FC_6H_4	H	H	A	87	206—208	EtOH–H_2O	$C_{13}H_8FNO_3$	63.68	3.29	5.71	63.29	3.15	5.66
20d	2-FC_6H_4	H	Cl	C	77	197—199	EtOH–H_2O	$C_{13}H_7ClFNO_3$	55.83	2.52	5.01	55.43	2.63	4.85
20e	2-$CH_3C_6H_4$	H	H	A	74	167—168	Acetone–CH_2Cl_2	$C_{14}H_{11}NO_3$	69.70	4.59	5.80	69.34	4.42	5.73
20f	2-Thienyl	H	H	A	83	252—254	AcOEt–hexane	$C_{11}H_7NO_3S$	56.65	3.03	6.01	56.77	2.71	5.77

The resulting residue was chromatographed on silica gel with CH_2Cl_2 to give **17a** (4.46 g). Mass spectrum (MS) *m/z*: 258 (M^+), 243, 228. IR (KBr) cm^{-1}: 1630 (C=O), 1598. NMR ($CDCl_3$) δ: 3.69 (3H, s, $OC\underline{H}_3$), 3.91 (3H, s, $OC\underline{H}_3$), 6.55 (1H, s, 3-H), 7.00 (1H, s, 6-H), 7.37—7.86 (5H, m, arom. H), 12.63 (1H, s, O$\underline{H}$). Yields, melting points, recrystallization solvents, and microanalysis data for **17** are given in Table IV.

5,6-Dimethoxy-3-phenyl-1,2-benzisoxazole (19a) (General Procedure, Method A) A mixture of **17a** (4.00 g, 0.016 mol) and $NH_2OH \cdot HCl$ (4.32 g, 0.062 mol) in pyridine (40 ml) was refluxed for 2 h and evaporated. The resulting mixture was acidified with HCl and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 2-(α-hydroxyiminobenzyl)-4,5-dimethoxyphenol (**18a**). A mixture of this crude phenol, acetic anhydride (5.1 g, 0.050 mol), and sodium acetate (4.0 g, 0.049 mol) in DMF (60 ml) was refluxed for 2 h and evaporated. 5 N NaOH (200 ml) was added and the mixture was stirred at 50—60 °C for 30 min. After cooling, the deposited crystals were collected by filtration, washed with H_2O, dried, and chromatographed on silica gel with CH_2Cl_2 to give **19a** (3.04 g). MS *m/z*: 255 (M^+), 240. IR (KBr) cm^{-1}: 1620. NMR ($CDCl_3$) δ: 3.91 (3H, s, $OC\underline{H}_3$), 3.95 (3H, s, $OC\underline{H}_3$), 7.07 (1H, s, 7-H) 7.15 (1H, s, 4-H), 7.40—7.70 (3H, m, arom. H), 7.70—8.10 (2H, m, arom. H). Yields, melting points, recrystallization solvents, and microanalysis data for **19a**, **19b**, and **19c** are given in Table V.

5,6-Dihydroxy-3-phenyl-1,2-benzisoxazole (20a) (General Procedure, Method A) Compound **19a** (1.0 g, 3.9 mmol) was heated with pyridine hydrochloride (20 g) at 170—180 °C for 3 h and then cooled to 70 °C. The product crystallized upon the addition of H_2O was collected by filtration and washed with H_2O to give **20a** (0.81 g). MS *m/z*: 227 (M^+). IR (KBr) cm^{-1}: 1624. NMR ($CDCl_3$–dimethylsulfoxide (DMSO)-d_6) δ: 7.07 (1H, s, 7-H), 7.26 (1H, s, 4-H), 7.38—7.70 (3H, m, arom. H), 7.50 (2H, br s, O$\underline{H}$ × 2), 7.70—8.06 (2H, m, arom. H). Yields, melting points, recrystallization solvents, and microanalysis data for **20a**, **20aa—ac**, **20b—c**, and **20e—f** are given in Table VI.

TABLE VII. 4-Acyl-5-chloro-1,2-dimethoxybenzenes **23**



Compd. No.	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H
23a	C_6H_5	47	46—47	EtOH	$C_{15}H_{13}ClO_3$	65.11 (64.88)	4.74 (4.94)
23e	2-$CH_3C_6H_4$	80	67—69	EtOH	$C_{16}H_{15}ClO_3$	66.10 (66.08)	5.20 (5.36)
23f	2-Thienyl	91	99—101	EtOH	$C_{13}H_{11}ClO_3S$	55.23 (55.37)	3.92 (4.13)

1,3-Dioxolo[4,5-*f*]-3-phenyl-1,2-benzisoxazole-6-carboxylic Acid (13a) (General Procedure) A mixture of **20a** (2.9 g, 0.013 mol), methyl dichloroacetate (3.7 g, 0.026 mol), and anhyd. K_2CO_3 (10.7 g, 0.078 mol) in DMF (50 ml) was stirred at 90—100 °C under N_2 for 2.5 h. After cooling the mixture, H_2O (50 ml) was added, and the mixture was stirred at 90—100°C for 40 min. After cooling, the mixture was weakly acidified with 2 N HCl and then weakly basified with saturated $NaHCO_3$, and washed with Et_2O. The aqueous layer was acidified with 2 N HCl and extracted with Et_2O. The extract was washed with H_2O, dried over

Na_2SO_4, and evaporated. After trituration of the resulting residue with CH_2Cl_2, the crystals were collected by filtration, washed with CH_2Cl_2, and dried to give **13a** (1.95 g). MS *m/z*: 283 (M^+), 238. IR (KBr) cm^{-1}: 1722 (COOH). NMR ($CDCl_3$–DMSO-d_6) δ: 6.42 (1H, s, Ph–O–CH), 7.10 (1H, s, 8-H), 7.17 (1H, s, 4-H), 7.27—7.59 (3H, m, arom. H), 7.59—7.97 (2H, m, arom. H), 11.90 (1H, br s, COOH). Yields, melting points, recrystallization solvens, and microanalysis data for **13** are given in Table I.

2-Chloro-4,5-dimethoxybenzophenone (23a) (General Procedure) 1,2-Dimethoxybenzene (**21**) (3.0 g, 0.022 mol) was dissolved in $CHCl_3$ (30 ml) and the solution was cooled to 0—5 °C. SO_2Cl_2 (3.1 g, 0.023 mol) was added portionwise to the solution and the resulting mixture was warmed to room temperature over a 5 h period and left to stand overnight, then evaporated to give crude 4-chloro-1,2-dimethoxybenzene (**22**). This crude **22** and benzoly chloride (3.2 g, 0.023 mol) were dissolved in 1,2-dichloroethane (30 ml) and the solution was cooled to 0—5 °C. $AlCl_3$ (3.3 g, 0.025 mol) was added portionwise to the solution, and the resulting mixture was warmed to room temperature over a 9 h period. The reaction mixture was added to aq. HCl, and the whole mixture was stirred for 30 min. The slurry formed was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The resulting residue was chromatographed on silica gel with CH_2Cl_2 to give **23a** (2.8 g). MS *m/z*: 276 (M^+), 199. IR (KBr) cm^{-1}: 1658 (C=O). NMR ($CDCl_3$) δ: 3.85 (3H, s, OCH$_3$), 3.93 (3H, s, OCH$_3$), 6.90 (1H, s, 3-H; 1H, s, 6-H), 7.38—7.65 (3H, m, arom. H), 7.71—7.96 (2H, m, arom. H). Yields, melting points, recrystallization solvents, and microanalysis data for **23a**, **23e**, and **23f** are given in Table VII.

5,6-Dimethoxy-3-phenyl-1,2-benzisoxazole (19a) (General Procedure, Method B) A mixture of **23a** (2.2 g, 8.0 mmol) and $NH_2OH \cdot HCl$ (2.3 g, 0.033 mol) in pyridine (30 ml) was refluxed for 3 h, and evaporated. The resulting mixture was acidified with HCl and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 4-chloro-5-(α-hydroxyiminobenzyl)-1,2-dimethoxybenzene. To a solution of this crude benzene in DMF (40 ml), 60% NaH (0.40 g, 0.010 mol) was added and the mixture was stirred at 80—90 °C for 4 h. The product crystallized upon the addition of H_2O was collected by filtration, washed with H_2O, dried, and chromatographed on silica gel with CH_2Cl_2 to give **19a** (2.0 g). Yields, melting points, recrystallization solvents, and microanalysis data for **19a**, **19e**, and **19f** are given in Table V.

3-Chloro-2,4(or 2,5)-dihydroxy-5(or 4)-methoxybenzophenone (26ab) Benzoyl chloride (7.3 g, 0.052 mol) and 3-chloro-1,2,4-trimethoxybenzene (**25**) (10.1 g, 0.050 mol) were dissolved in 1,2-dichloroethane (100 ml) and the solution was cooled to 0—5 °C. $AlCl_3$ (7.3 g, 0.055 mol) was added portionwise to the solution, and the resulting mixture was warmed to room temperature over a 8 h period and then refluxed for 1.5 h. After cooling, the reaction mixture was added to aq. HCl, and the whole mixture was stirred for 30 min. The slurry formed was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The resulting residue was chromatographed on silica gel with CH_2Cl_2 to give **26ab** (8.0 g, 58%) as crystals ($CHCl_3$), mp 181—182 °C. *Anal.* Calcd for $C_{14}H_{11}ClO_4$: C, 60.34; H, 3.98. Found: C, 60.08; H, 4.01. MS *m/z*: 278 (M^+), 277, 263. IR (KBr) cm^{-1}: 1626 (C=O), 1590. NMR ($CDCl_3$) δ: 3.76 (3H, s, OCH$_3$), 3.85 (1H, br s, OH), 6.97 (1H, s, 6-H), 7.40—7.93 (5H, m, arom. H), 13.08 (1H, s, OH).

3-Chloro-2′-fluoro-2,4-(or 2,5)-dihydroxy-5(or 4)-methoxybenzophenone (**26d**) was obtained from 3-chloro-1,2,4-trimethoxybenzene (**25**) and 2-fluorobenzoyl chloride in the same manner as **26ab** in 71% yield, mp 136—137 °C (CH_2Cl_2). *Anal.* Calcd for $C_{14}H_{10}ClFO_4$: C, 56.68; H, 3.40. Found: C, 56.65; H, 3.30.

7-Chloro-6(or 5)-hydroxy-5(or 6)-methoxy-3-phenyl-1,2-benzisoxazole (27ab) A mixture of **26ab** (0.90 g, 3.2 mmol) and $NH_2OH \cdot HCl$ (1.21 g, 0.017 mol) in pyridine (10 ml) was refluxed for 3 h and evaporated. The resulting mixture was acidified with HCl and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 6-chloro-5(or 4)-hydroxy-2-(α-hydroxyiminobenzyl)-4(or 5)-methoxyphenol. A mixture of this crude phenol, acetic anhydride (1.38 g, 0.013 mol) and sodium acetate (1.08 g, 0.013 mol) in DMF (15 ml) was refluxed for 30 min and evaporated. 2 N NaOH (50 ml) was added and the mixture was stirred at 50—60 °C for 1 h. After cooling, the reaction mixture was acidified with aq. HCl and the deposited crystals were collected by filtration, washed with H_2O, dried, and chromatographed on silica gel with CH_2Cl_2 to give **27ab** (0.28 g, overall 31%) as crystals (CH_2Cl_2), mp 201—202 °C. *Anal.* Calcd for $C_{14}H_{10}ClNO_3$: C, 60.99; H, 3.66; N, 5.08. Found: C, 61.02; H, 3.64; N, 5.14. MS *m/z*: 275 (M^+), 260. IR (KBr) cm^{-1}: 3200 (OH), 1484. NMR ($CDCl_3$–DMSO-d_6) δ: 3.84 (1H, s, OH), 4.00 (3H, s, OCH$_3$), 7.16 (1H, s, 4-H), 7.52—7.76 (3H, m, arom. H), 7.82—8.12 (2H, m, arom. H).

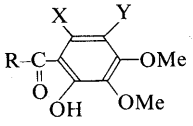
7-Chloro-3-(2-fluorophenyl)-6(or 5)-hydroxy-5(or 6)-methoxy-1,2-benzisoxazole (**27d**) was obtained from **26d** in the same manner as **27ab** in 56% yield, mp 178—179 °C (EtOH). *Anal.* Calcd for $C_{14}H_9ClFNO_3$: C, 57.26; H, 3.09; N, 4.77. Found: C, 57.29; H, 2.99; N, 4.77.

7-Chloro-5,6-dihydroxy-3-phenyl-1,2-benzisoxazole (20ab) (Method C) Compound **27ab** (0.20 g, 0.73 mmol) was heated with pyridine hydrochloride (10 g) at 180—190 °C for 1.5 h and then cooled to 70 °C. The poduct crystallized upon the addition of H_2O was collected by filtration and washed with H_2O to give **20ab** (0.17 g). MS *m/z*: 261 (M^+). IR (KBr) cm^{-1}: 1448. NMR ($CDCl_3$–DMSO-d_6) δ: 7.17 (1H, s, 4-H), 7.37—7.65 (3H, m, arom. H), 7.70 (2H, br s, OH × 2), 7.75—8.04 (2H, m, arom. H).

7-Chloro-3-(2-fluorophenyl)-5,6-dihydroxy-1,2-benzisoxazole (**20d**) was obtained from **27d** in the same manner as **20ab**. Yields, melting points, recrystallization solvents, and microanalysis data for **20ab** and **20d** are given in Table VI.

4-Chloro-5,6-dimethoxy-3-phenyl-1,2-benzisoxazole (19aa), 7-Chloro-5,6-dimethoxy-3-phenyl-1,2-benzisoxazole (19ab) and 4,7-Dichloro-5,6-dimethoxy-3-phenyl-1,2-benzisoxazole (19ac) (Method D) To a stirred solution of **19a** (8.9 g, 0.035 mol) in 1,2-dichloroethane (50 ml), a solution of SO_2Cl_2 (5.2 g, 0.039 mol) in 1,2-dichloroethane (10 ml) was added portionwise at room temperature. The resulting mixture was stirred for 4 h. After addition of a solution of SO_2Cl_2 (1.8 g, 0.013 mol) in 1,2-dichloroethane (10 ml) to

TABLE VIII. 2-Acyl-5,6-dimethoxyphenols **30**



Compd. No.	R	X	Y	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Found C	Found H
30a	C_6H_5	H	H	E	96	132—134[a)]	EtOH	$C_{15}H_{14}O_4$	69.76	5.46	69.64	5.64
30ab	C_6H_5	H	Cl	G	70	84—85	EtOH	$C_{15}H_{13}ClO_4$	61.55	4.48	61.51	4.08
30b	2-ClC_6H_4	H	H	E	86	115—117	EtOH	$C_{15}H_{13}ClO_4$	61.55	4.48	61.54	4.75
30c	4-ClC_6H_4	H	H	E	54	148—149	EtOH	$C_{15}H_{13}ClO_4$	61.55	4.48	61.60	4.43
30d	2-FC_6H_4	H	H	E	95	97—99	EtOH	$C_{15}H_{13}FO_4$	65.22	4.74	65.15	4.80
30e	3-FC_6H_4	H	H	E	80	84—85	EtOH	$C_{15}H_{13}FO_4$	65.22	4.74	65.35	4.71
30f	4-FC_6H_4	H	H	E	79	144—146	EtOH	$C_{15}H_{13}FO_4$	65.22	4.74	65.35	4.71
30fa	4-FC_6H_4	H	Cl	G	69	130—131	EtOH	$C_{15}H_{12}ClFO_4$	57.99	3.89	58.07	3.66
30g	2-$CH_3C_6H_4$	H	H	E	63	93—95	EtOH	$C_{16}H_{16}O_4$	70.58	5.92	70.51	5.96
30h	3-$CF_3C_6H_4$	H	H	E	33	124—126	EtOH	$C_{16}H_{13}F_3O_4$	58.90	4.02	58.55	4.34
30i	2-Thienyl	H	H	E	67	143—144[b)]	EtOH	$C_{13}H_{12}O_4S$	59.08	4.58	58.98	4.56

a) Lit.[8a)] 120—121 °C, lit.[8b,8c)] 131 °C. *b*) Lit.[8c,9)] 140 °C.

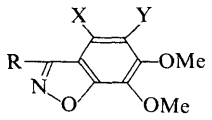
the reaction mixture, the mixture was further stirred for 10 h. The resulting mixture was evaporated and chromatographed on silica gel with CH_2Cl_2–hexane to give **19aa** (4.36 g), **19ab** (0.46 g) and **19ac** (5.08 g). Product **19aa**: MS *m/z*: 289 (M^+), 274. IR (KBr) cm^{-1}: 1614. NMR ($CDCl_3$) δ: 3.85 (3H, s, $OC\underline{H}_3$), 3.97 (3H, s, $OC\underline{H}_3$), 7.01 (1H, s, 7-H), 7.32—7.87 (5H, m, arom. H). Product **19ab**: *m/z*: 289 (M^+), 274. IR (KBr) cm^{-1}: 1494. NMR ($CDCl_3$) δ: 3.87 (3H, s, $OC\underline{H}_3$), 3.92 (3H, s, $OC\underline{H}_3$), 7.04 (1H, s, 4-H), 7.34—7.60 (3H, m, arom. H), 7.67—7.89 (2H, m, arom. H). Product **19ac**: MS *m/z*: 323 (M^+), 308. IR (KBr) cm^{-1}: 1384. NMR ($CDCl_3$) δ: 3.87 (3H, s, $OC\underline{H}_3$), 4.01 (3H, s, $OC\underline{H}_3$), 7.32—7.87 (5H, m, arom. H). Yields, melting points, recrystallization solvents, and microanalysis data for **19aa**, **19ab**, and **19ac** are given in Table V.

2-Hydroxy-3,4-dimethoxybenzophenone (30a) (General Procedure, Method E) Benzoyl chloride (14.1 g, 0.10 mol) and 1,2,3-trimethoxybenzene (**29**) (16.8 g, 0.10 mol) was dissolved in 1,2-dichloroethane (150 ml) and the solution was cooled to 0—5 °C. $AlCl_3$ (13.3 g, 0.10 mol) was added portionwise to the solution, and the rsulting mixture was warmed to room temperature over a 3 h period and then refluxed for 1 h. After cooling, ice-water and conc. HCl were added to the reaction mixture, and the whole mixture was stirred for 30 min. The slurry formed was extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give **30a** (24.7 g). MS *m/z*: 258 (M^+). IR (KBr) cm^{-1}: 1618 (C=O). NMR ($CDCl_3$) δ: 3.90 (6H, s, $OC\underline{H}_3 \times 2$), 6.40 (1H, d, J=9.0 Hz, 5-H), 7.30 (1H, d, J=9.0 Hz, 6-H), 7.41—7.75 (5H, m, arom. H), 12.40 (1H, s, O<u>H</u>). Yields, melting points, recrystallization solvents, and microanalysis data for **30a**, **30b—f**, and **30g—i** are given in Table VIII.

6,7-Dimethoxy-3-phenyl-1,2-benzisoxazole (31a) (General Procedure, Method E) A mixture of **30a** (24.0 g, 0.093 mol) and $NH_2OH \cdot HCl$ (52.1 g, 0.74 mol) in pyridine (200 ml) was refluxed for 8 h, then evaporated. The resulting mixture was acidified with HCl and extracted with Et_2O–AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 2-(α-hydroxyiminobenzyl)-5,6-dimethoxyphenol. A mixture of this crude phenol, acetic anhydride (26.9 g, 0.26 mol), and sodium acetate (21.3 g, 0.26 mol) in DMF (200 ml) was refluxed for 1 h and evaporated. 4 N NaOH (200 ml) was added and the mixture was stirred at 50—60 °C for 30 min. After cooling, the deposited crystals were collected by filtration, washed with H_2O, and dried. Recrystallization from EtOH gave **31a** (11.6 g). MS *m/z*: 255 (M^+), 240, 226. IR (KBr) cm^{-1}: 1614. NMR ($CDCl_3$) δ: 3.90 (3H, s, $OC\underline{H}_3$), 4.17 (3H, s, $OC\underline{H}_3$), 6.91 (1H, d, J=9.0 Hz, 5-H), 7.35—7.62 (3H, m, arom. H), 7.37 (1H, d, J=9.0 Hz, 4-H), 7.62—8.03 (2H, m, arom. H). Yields, melting points, recrystallization solvents, and microanalysis data for **31a**, **31ab**, and **31b—31i** are given in Table IX.

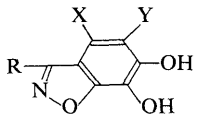
6,7-Dihydroxy-3-phenyl-1,2-benzisoxazole (32a) (General Procedure) Compound **31a** (2.55 g, 0.010 mol) was heated with pyridine hydrochloride (30 g) at 170—180 °C for 2 h and then cooled to 70 °C. The product crystallized upon the addition of H_2O was collected by filtration

TABLE IX. 6,7-Dimethoxy-1,2-benzisoxazoles **31**



Compd. No.	R	X	Y	Method	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
31a	C_6H_5	H	H	E	49	78—79	EtOH	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	70.56	5.11	5.52
31aa	C_6H_5	Cl	H	F	67	136—138	EtOH	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.83	62.13	4.17	4.65
31ab	C_6H_6	H	Cl	G	40	101—102	EtOH	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.83	62.14	4.14	4.74
31b	2-ClC_6H_4	H	H	E	69	99—101	EtOH	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.83	62.14	4.02	4.72
31c	4-ClC_6H_4	H	H	E	45	130—131	EtOH	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.83	62.42	4.10	4.76
31d	2-FC_6H_4	H	H	E	54	82—84	EtOH	$C_{15}H_{12}FNO_3$	65.93	4.43	5.13	65.80	4.31	5.13
31e	3-FC_6H_4	H	H	E	18	85—86	EtOH	$C_{15}H_{12}FNO_3$	65.93	4.43	5.13	66.03	4.34	5.12
31f	4-FC_6H_4	H	H	E	61	123—124	EtOH	$C_{15}H_{12}FNO_3$	65.93	4.43	5.13	65.87	4.36	5.27
31fa	4-FC_6H_4	H	Cl	G	59	128—129	EtOH	$C_{15}H_{11}ClFNO_3$	58.55	3.60	4.55	58.64	3.71	4.53
31g	2-$CH_3C_6H_4$	H	H	E	70	57—58	EtOH	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.49	5.61	5.09
31h	3-$CF_3C_6H_4$	H	H	E	51	75—76	EtOH	$C_{16}H_{12}F_3NO_3$	59.45	3.74	4.33	59.31	3.65	4.32
31i	2-Thienyl	H	H	E	37	86—87	EtOH	$C_{13}H_{11}NO_3S$	59.76	4.24	5.36	59.57	4.22	5.30

TABLE X. 6,7-Dihydroxy-1,2-benzisoxazoles **32**



Compd. No.	R	X	Y	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
32a	C_6H_5	H	H	97	205—206	EtOH–H_2O	$C_{13}H_9NO_3$	68.72	3.99	6.16	68.72	3.89	6.20
32aa	C_6H_5	Cl	H	93	205—207	EtOH–H_2O	$C_{13}H_8ClNO_3$	59.67	3.08	5.35	59.27	2.99	5.25
32ab	C_6H_5	H	Cl	95	181—182	EtOH–H_2O	$C_{13}H_8ClNO_3$	59.67	3.08	5.35	59.75	2.95	5.39
32b	2-ClC_6H_4	H	H	65	188—189	Acetone–CH_2Cl_2	$C_{13}H_8ClNO_3$	59.67	3.08	5.35	59.37	2.89	5.30
32c	4-ClC_6H_4	H	H	91	212—213	EtOH–H_2O	$C_{13}H_8ClNO_3$	59.67	3.08	5.35	59.28	3.09	5.25
32d	2-FC_6H_4	H	H	89	179—180	EtOH–H_2O	$C_{13}H_8FNO_3$	63.68	3.29	5.71	64.01	2.97	5.75
32e	3-FC_6H_4	H	H	58	209—212	EtOH–H_2O	$C_{13}H_8FNO_3$	63.68	3.29	5.71	63.62	3.21	5.64
32f	4-FC_6H_4	H	H	74	199—200	EtOH–H_2O	$C_{13}H_8FNO_3$	63.68	3.29	5.71	63.76	3.23	5.66
32fa	4-FC_6H_4	H	Cl	75	216—217	EtOH–H_2O	$C_{13}H_7ClFNO_3$	55.83	2.52	5.01	55.45	2.79	5.02
32g	2-$CH_3C_6H_4$	H	H	96	190—191	Acetone–CH_2Cl_2	$C_{14}H_{11}NO_3$	69.70	4.59	5.80	69.51	4.45	5.81
32h	3-$CF_3C_6H_4$	H	H	45	130—132	EtOH–H_2O	$C_{14}H_8F_3NO_3$	56.96	2.73	4.75	56.57	2.95	4.54
32i	2-Thienyl	H	H	67	204—206	EtOH–H_2O	$C_{11}H_7NO_3S$	56.65	3.03	6.01	56.27	2.97	5.87

and washed with H_2O to give **32a** (2.2 g). MS *m/z*: 227 (M^+). IR (KBr) cm^{-1}: 1638. NMR ($CDCl_3$–DMSO-d_6) δ: 6.90 (1H, d, J=9.0 Hz, 5-H), 7.17 (1H, d, J=9.0 Hz, 4-H), 7.33—7.65 (3H, m, arom. H), 7.65—8.05 (2H, m, arom, H), 8.80 (2H, br s, OH × 2). Yields, melting points, recrystallization solvents, and microanalysis data for **32** are given in Table X.

1,3-Dioxolo[4,5-*g*]-3-phenyl-1,2-benzisoxazole-7-carboxylic Acid (14a) (General Procedure) A mixture of **32a** (2.1 g, 9.3 mmol), methyl dichloroacetate (2.7 g, 0.019 mol), and anhyd. K_2CO_3 (7.7 g, 0.056 mol) in DMF (50 ml) was stirred at 90—100 °C under N_2 for 5 h. After cooling, H_2O (100 ml) was added, and the mixture was stirred at 90—100 °C for 30 min, and cooled. The mixture was acidified with 2 N HCl and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. Recrystallization gave **14a** (1.5 g). MS *m/z*: 283 (M^+), 238. IR (KBr) cm^{-1}: 1728 (COOH). NMR ($CDCl_3$–DMSO-d_6) δ: 6.68 (1H, s, Ph–O–CH), 6.72 (1H, br s, COOH), 7.15 (1H, d, J=9.0 Hz, 5-H), 7.55—7.80 (3H, m, arom. H), 7.58 (1H, d, J=9.0 Hz, 4-H), 7.80—8.16 (2H, m, arom. H). Yields, melting points, recrystallization solvents, and microanalysis data for **14** are given in Table II.

4-Chloro-6,7-dimethoxy-3-phenyl-1,2-benzisoxazole (31aa) (Method F) To a stirred solution of **31a** (120.2 g, 0.47 mol) in DMF (1000 ml), trichloroisocyanuric acid (50 g, 0.22 mol) was added portionwise at room temperature. The resulting mixture was stirred for 3 h. After cooling, 0.5 N NaOH (2000 ml) was added to the mixture and the resulting crystals were collected by filtration, washed with H_2O, and dried. Recrystallization from EtOH gave **31aa** (91.0 g). MS *m/z*: 289 (M^+), 274, 260. IR (KBr) cm^{-1}: 1612. NMR ($CDCl_3$) δ: 3.90 (3H, s, OCH_3), 4.15 (3H, s, OCH_3), 6.90 (1H, s, 5-H), 7.28—7.81 (5H, m, arom. H). Yield, melting point, recrystallization solvent, and microanalysis data for **31aa** are given in Table IX.

5-Chloro-2-hydroxy-3,4-dimethoxybenzophenone (30ab) (Method G) To a stirred solution of **30a** (26.0 g, 0.10 mol) in CH_2Cl_2 (250 ml), SO_2Cl_2 (15.0 g, 0.11 mol) was added portionwise at room temperature. The resulting mixture was stirred for 5 h and left to stand overnight. The resulting mixture was evaporated and chromatographed on silica gel with CH_2Cl_2 to give **30ab** (20.6 g). MS *m/z*: 292 (M^+). IR (KBr) cm^{-1}: 1620 (C=O). NMR ($CDCl_3$) δ: 3.90 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 7.28 (1H, s, 6-H), 7.37—7.69 (5H, m, arom. H), 12.38 (1H, s, OH).

5-Chloro-4′-fluoro-2-hydroxy-3,4-dimethoxybenzophenone (**30fa**) was obtained from **30f** in the same manner as **30ab**. Yields, melting points, recrystallization solvents, and microanalysis data for **30ab** and **30fa** are given in Table VIII.

5-Chloro-6,7-dimethoxy-3-phenyl-1,2-benzisoxazole (31ab) A mixture of **30ab** (19.0 g, 0.065 mol) and $NH_2OH \cdot HCl$ (36.4 g, 0.52 mol) in pyridine (200 ml) was refluxed for 8 h, and evaporated. The resulting mixture was acidified with HCl and extracted with Et_2O–AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 4-chloro-2-(α-hydroxyiminobenzyl)-5,6-dimethoxyphenol. A mixture of this crude phenol, acetic anhydride (19.9 g, 0.20 mol), and sodium acetate (16.0 g, 0.20 mol) in DMF (150 ml) was refluxed for 1 h and evaporated. 4 N NaOH (200 ml) was added and the mixture was stirred at 50—60 °C for 30 min. After cooling, the deposited crystals were collected hy filtration, washed with H_2O, and dried. Recrystallization from EtOH gave **31ab** (7.5 g). MS *m/z*: 289 (M^+), 274. IR (KBr) cm^{-1}: 1494. NMR ($CDCl_3$) δ: 3.97 (3H, s, OCH_3), 4.26 (3H, s, OCH_3), 7.30—7.68 (3H, m, arom. H), 7.52 (1H, s, 4-H), 7.68—8.08 (2H, m, arom. H).

5-Chloro-4′-fluoro-6,7-dimethoxy-3-phenyl-1,2-benzisoxazole (**31fa**) was obtained from **30fa** in the same manner as **31ab**. Yields, melting points, recrystallization solvents, and microanalysis data for **31ab** and **31fa** are given in Table IX.

Diuretic and Uricosuric Effects on Rats[10] Seven-week-old Wistar-Imamichi rats that had been fasted for 24 h were divided in groups of five so that the animals in each group would excrete almost the same amount of urine. After forced urination, the rats were orally administered the test compounds that were suspended in physiological saline containing 3% gum arabic in a dose volume of 25 ml per kg of body weight. The control rats were given only physiological saline containing 3% gum arabic. The animals were housed in seperate metabolic cages and the urine excreted from each animal was collected over a period of 6 h following the administration of the test compounds or physiological saline after complete starvation. The urine volume was directly read on a measuring cylinder after forced urination thereinto, and the amount of urine per kg of body weight was calculated. The amount of uric acid excreted in the urine was determined by the uricase–catalase method.

Acknowledgement The authors are indebted to Drs. S. Hata, I. Matsunaga, and T. Mori for valuable suggestions throughout this work. We are also grateful to Dr. M. Hamana, Professor emeritus of Kyushu University, for helpful discussions.

References

1) Portions of this work were presented at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1989, Abstract of Papers, IV, p. 5.
2) E. J. Cragoe, Jr., "Diuretics-Chemistry, Pharmacology, and Medicine," ed. by E. J. Cragoe, Jr., John Wiley and Sons, Inc., New York, 1983, p. 201.
3) S. J. deSolms, O. W. Woltersdorf, Jr., E. J. Cragoe, Jr., L. S. Watson, and G. M Fanelli, Jr., *J. Med. Chem.*, **21**, 437 (1978).
4) W. F. Hoffman, O. W. Woltersdorf, Jr., F. C. Novello, E. J. Cragoe, Jr., J. P. Springer, L. S. Watson, and G. M. Fanelli, Jr., *J. Med. Chem.*, **24**, 865 (1981).
5) G. M. Shutske, L. L. Setescak, R. C. Allen, L. Davis, R. C. Effland, K. Ranbom, J. M. Kitzen, J. C. Wilker, and W. J. Novick, Jr., *J. Med. Chem.*, **25**, 36 (1982).
6) H. Sato, T. Dan, E. Onuma, H. Tanaka, and H. Koga, *Chem. Pharm. Bull.*, **38**, 1266 (1990); H, Sato, T. Dan, E. Onuma, H. Tanaka, B. Aoki, and H. Koga, *ibid.*, **39**, 1760, (1991).
7) G. Bargellini and E. Martegiani, *Atti. Accad. Lincei*, **20**, 183 (1911); K. R. Laumas, S. Neelakantan, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **46A**, 343 (1957).
8) *a*) S. Motylewski, *Ber.*, **42**, 3148 (1909); *b*) R. A. de Lima and G. D. Monache, *Rend. Accad. Naz. 40* (*Quaranta*), **3**, 181 (1978); *c*) M. Varache-Beranger, A. Nuhrich, and G. Devaux, *Eur. J. Med. Chem.*, **23**, 501 (1988).
9) M. Varache-Beranger, A. Nuhrich, A. Carpy, J. P. Dupin, and G. Devaux, *Eur. J. Med. Chem.*, **21**, 255 (1986).
10) *a*) T. Dan, H. Koga, E. Onuma, H. Tanaka, H. Sato, and B. Aoki, *Adv. Exp. Med. Biol.*, **253A**, 301 (1989); *b*) T. Dan, H. Tanaka, and H. Koga, *J. Pharmacol. Exp. Ther.*, **253**, 437 (1990).