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Spirocyclopropane Compounds. III.[1,2] Synthesis of Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones for Evaluation as Gastric Antisecretory and Antiulcer Agents

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Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-1) and its derivatives (VI-2—VI-75) were synthesized in the same manner as described previously for the synthesis of spiro[cyclopropane-1,2′-[2*H*]indol]-3′(1′*H*)-ones (I). These spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones were evaluated for gastric antisecretory activity and protective activity against lesions induced by water-immersion restraint stress in the rat. The most potent antiulcer compounds (VI-17 and VI-55) were obtained by the introduction of an acetyl or dimethylamino group at the 5-position on the benzene ring. The most interesting member of the series, 5-acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-17, AG-629), was selected as a candidate for clinical studies.

Keywords——spirocyclopropane compound; spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one; gastric antisecretory activity; antiulcer activity

We are interested in the pharmacological activities of spiro compounds, and in previous reports,[1,2] we described the facile synthesis and biological activities of spiro[cyclopropane-1,2′-[2*H*]indol]-3′(1′*H*)-ones (I, Chart 1). In this report, we describe the synthesis of their 1′-oxa analogs, spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones (VI, Table I) and the effects of these compounds on gastric secretion as well as gastric lesions induced by water-immersion restraint stress in the rat.

Chemistry

Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one derivatives (VI) (Table I) were synthesized in a manner similar to that used for the synthesis of spiro[cyclopropane-1,2′-[2*H*]indol]-3′(1′*H*)-ones (I, Chart 1). Methyl salicylate compounds (II) were allowed to react with α-bromo-γ-butyrolactone to yield methyl 2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate compounds (III). Hydrolysis of III and subsequent lactonization afforded the corresponding 2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoic acid compounds (IV). Methyl 5-methylsulfonyl-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (IIIq) was prepared by oxidation of the 5-methylthio compound (IIIp) with *m*-chloroperbenzoic acid. 3-Methyl-5-nitro-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoic acid (IVt) was obtained by nitration of the 3-methyl compound (IVj) with fuming nitric acid. The physical constants of the resulting compounds III and IV are shown in Table II. Compounds III and IV were spiroannelated by heating with acetic anhydride and triethylamine to yield 4′,5′-dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-dione compounds (Va—t, Table III). Compound IIIa or IVa gave the 3,3-diacetoxy compound (VII, Chart 1) by this reaction as by-product. The formation of 3,3-diacetoxy compounds might be related to the low yield (less than 60%) of the desired spirolactones in this reaction. Condensation of methyl 4-acetylaminosalicylate (II, R=4-$NHCOCH_3$) with α-

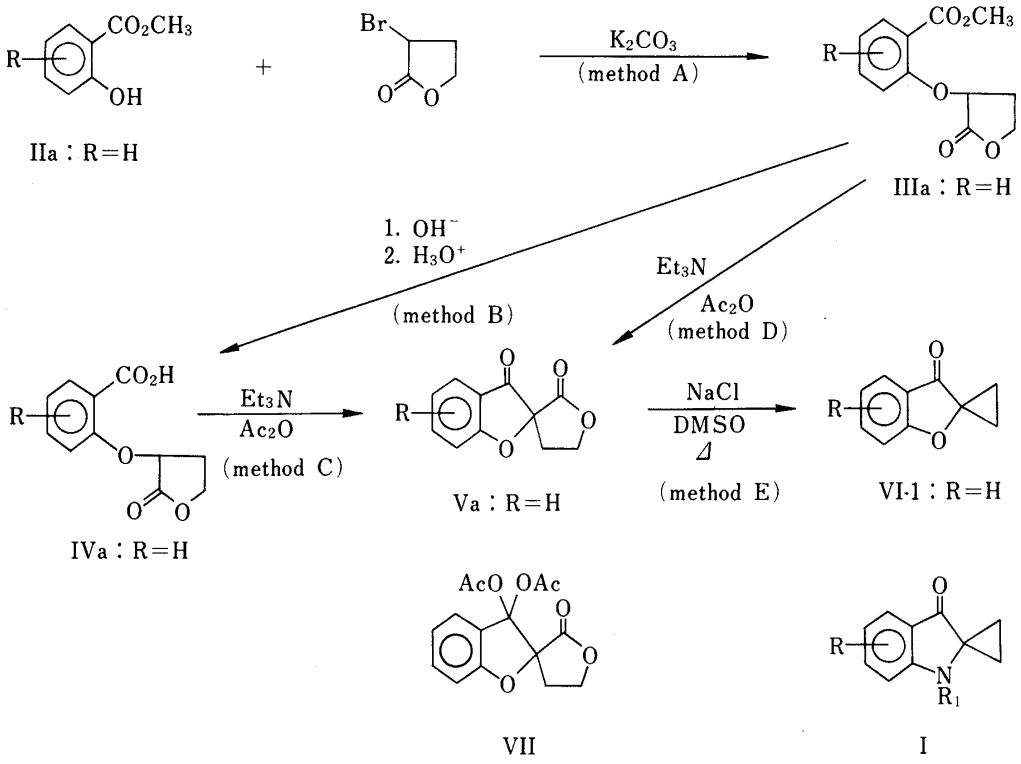


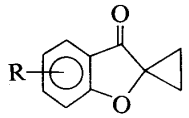
Chart 1

bromo-γ-butyrolactone at 80 °C afforded the condensation product (IIIr) and a small amount of the corresponding spirolactone (Vr), suggesting the feasibility of a one-step synthesis of V from II. Spiroannelation of III having electron-donating substituents on the benzene ring (*e.g.* alkyl, alkoxy and methylthio) did not proceed under the reaction conditions described above. Therefore these spirolactones were alternatively prepared from the corresponding IV (method C in Chart 1).

On the other hand, the presence of electron-attracting groups did not affect the spiroannelation. For example, Vm was obtained directly from the ester (IIIm) (method D in Chart 1) as well as from the carboxylic acid (IVm) (method C), in 47 and 55% yields, respectively. Spiroannelation of the 6-hydroxy, 4-acetylamino and 4-acetylamino-5-chloro compounds (IVi, IIIr and IIIs) was accompanied by O- or N-acetylation to give the corresponding *O*-acetyl and *N,N*-diacetyl spirolactones (Vi, Vr′ and Vs), respectively. The 5-sulfamoyl spirolactone (Vu) was prepared by chlorosulfonylation of Va, followed by amination. These spirolactone compounds (Va—Vr, Vs, Vt and Vu) were decarboxylated in the presence of sodium chloride in dimethyl sulfoxide (DMSO) to afford the desired spirocyclopropanes (VI-1—9, VI-14—22, VI-44, VI-67 and VI-75). The 4-hydroxy and 5-hydroxy spirocyclopropanes (VI-10 and VI-11) were prepared by alkaline hydrolysis of the 4-acetoxy derivative (VI-9) and catalytic hydrogenation of the 5-benzyloxy derivative (VI-8) using 5% palladium charcoal (Pd–C), respectively. Reaction of VI-10 and VI-11 with diethylaminoethylchloride led to the 4- and 5-(2-diethylaminoethyl)oxyspirocyclopropanes (VI-12 and VI-13), respectively. Oxidation of the 5-methylthio derivative (VI-20) with 2 eq and 1 eq of *m*-chloroperbenzoic acid afforded VI-21 and VI-23, respectively. Selective reduction of the 5-acetylspirocyclopropane (VI-17) with sodium borohydride in tetrahydrofuran (THF) containing isopropanol gave the 5-(1-hydroxyethyl) derivative (VI-24) in good yield.

Bromination of VI-17 with bromine resulted in the formation of VI-25 in low yield

TABLE I. Physical Properties of Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones (VI)



Compound No.	R	mp °C	Recrystallization solvent	Synthesis method[a]	Yield %	Formula	Analysis (%) Calcd (Found)		
							C	H	N
VI-1	H	89—91.5	EtOH–H_2O	E	94	$C_{10}H_8O_2$	74.99 (75.01	5.03 4.96)	
VI-2	5-Cl	120—121	EtOH–H_2O	E	93	$C_{10}H_7ClO_2$	61.71 (61.68	3.63 3.50)	
VI-3	5,7-Cl_2	116—118	EtOH	E	79	$C_{10}H_6Cl_2O_2$	52.43 (52.65	2.64 2.61)	
VI-4	5-Ph	118—119	MeOH	E	91	$C_{16}H_{12}O_2$	81.34 (81.65	5.12 5.00)	
VI-5	5,6-	127—129	MeOH	E	46	$C_{14}H_{10}O_2$	79.98 (79.89	4.79 4.65)	
VI-6	5-OCH_3	86—88	EtOH	E	94	$C_{11}H_{10}O_3$	69.46 (69.31	5.30 5.13)	
VI-7	6-OCH_3	95—97	EtOH	E	80	$C_{11}H_{10}O_3$	69.46 (69.35	5.30 5.30)	
VI-8	5-OCH_2Ph	114—116	EtOH	E	91	$C_{17}H_{14}O_3$	76.67 (76.53	5.30 5.18)	
VI-9	4-OAc	85—86.5	Et_2O	E	46	$C_{12}H_{10}O_4$	66.05 (65.89	4.62 4.52)	
VI-10	4-OH	107—108	Pet.ether	b)	86	$C_{10}H_8O_3$	68.18 (68.38	4.58 4.42)	
VI-11	5-OH	184—185	MeOH	b)	64	$C_{10}H_8O_3$	68.18 (68.12	4.58 4.44)	
VI-12 (HCl)	4-$OCH_2CH_2NEt_2$	167—168	EtOH–Et_2O	b)	80	$C_{16}H_{21}NO_3 \cdot HCl$	61.63 (61.38	7.11 7.23	4.49 4.38)
VI-13 (citrate)	5-$OCH_2CH_2NEt_2$	109—112	MeOH–Et_2O	b)	18	$C_{16}H_{21}NO_3 \cdot C_6H_8O_7 \cdot 3/2H_2O$	53.43 (53.44	6.52 6.21	2.83 2.89)
VI-14	7-CH_3	123—125	EtOH	E	76	$C_{11}H_{10}O_2$	75.84 (75.76	5.79 5.80)	

VI-15	5-$CH(CH_3)_2$	113 (0.4 mmHg)[c]		E	75	$C_{13}H_{14}O_2$	77.20 (77.43	6.98 7.11)	
VI-16	5-C_6H_{13}	100—110 (0.2 mmHg)[c]		E	76	$C_{16}H_{20}O_2$	78.65 (78.88	8.25 8.37)	
VI-17	5-$COCH_3$	102—104	EtOH	E	88	$C_{12}H_{10}O_3$	71.28 (71.33	4.99 4.94)	
VI-18	5-COC_2H_5	75—77	EtOH	E	64	$C_{13}H_{12}O_3$	72.21 (72.16	5.59 5.52)	
VI-19	5-COPh	89—91	Et_2O	E	80	$C_{17}H_{12}O_3$	77.26 (77.30	4.58 4.33)	
VI-20	5-SCH_3	64—66	EtOH–H_2O	E	77	$C_{11}H_{10}O_2S$	64.06 (63.79	4.89 4.76)	
VI-21	5-SO_2CH_3	157—159	EtOH–H_2O	E	74	$C_{11}H_{10}O_4S$	55.45 (55.37	4.23 4.16)	
VI-22	5-SO_2NH_2	236—237.5	EtOH	E	56	$C_{10}H_9NO_4S$	50.20 (50.19	3.79 3.71	5.86 5.79)
VI-23	5-$SOCH_3$	87—89	AcOEt–hexane	b)	76	$C_{11}H_{10}O_3S$	59.44 (59.31	4.54 4.57)	
VI-24	5-$CH(OH)CH_3$	110 (0.05 mmHg)[c]		b)	85	$C_{12}H_{12}O_3$	70.57 (70.47	5.92 6.05)	
VI-25	5-$COCH_2Br$	139—140.5	EtOH	b)	75	$C_{12}H_9BrO_3$	51.28 (51.24	3.23 3.11)	
VI-26	5-CO_2H	225—227.5	EtOH	b)	93	$C_{11}H_8O_4$	64.70 (64.75	3.95 3.84)	
VI-27	5-CO_2CH_3	89—91	MeOH	b)	70	$C_{12}H_{10}O_4$	66.05 (66.19	4.62 4.62)	
VI-28	5-CO_2Et	97—98	EtOH	b)	87	$C_{13}H_{12}O_4$	67.23 (67.40	5.21 5.24)	
VI-29	5-$COCO_2CH_3$	57—58	Et_2O–hexane	b)	53	$C_{13}H_{10}O_5$	63.41 (63.63	4.09 4.21)	
VI-30	5-$CH(OH)CO_2CH_3$	112—113	AcOEt	b)	53	$C_{13}H_{12}O_5$	62.90 (62.80	4.87 4.82)	
VI-31	5-$CH(OH)CO_2H$	138—139	AcOEt–hexane	b)	66	$C_{12}H_{10}O_5$	61.54 (61.37	4.30 4.28)	
VI-32	5-$CONH_2$	243—244	EtOH	b)	81	$C_{11}H_9NO_3$	65.02 (64.92	4.46 4.42	6.89 6.86)
VI-33 (oxalate)	5-$CONHCH_2CH_2NEt_2$	178—179	EtOH	b)	28	$C_{17}H_{22}N_2O_3 \cdot C_2H_2O_4$	58.15 (57.92	6.17 6.27	7.14 7.15)

TABLE I. (continued)

Compound No.	R	mp °C	Recrystallization solvent	Synthesis method[a]	Yield %	Formula	Analysis (%) Calcd (Found)		
							C	H	N
VI-34 (oxalate)	5-CONHCH$_2$-  Et	165—167	EtOH	b)	39	$C_{18}H_{22}N_2O_3 \cdot C_2H_2O_4$	59.40 (59.13	5.98 6.02	6.93 6.75)
VI-35	5-CONHCH$_2$CO$_2$Et	142—143	AcOEt–hexane	b)	91	$C_{15}H_{15}NO_5$	62.28 (62.55	5.23 5.29	4.84 4.71)
VI-36	5-CONHCH$_2$CO$_2$H	250.5—251.5	EtOH–H$_2$O	b)	86	$C_{13}H_{11}NO_5$	59.77 (59.78	4.24 4.32	5.36 5.16)
VI-37	5-CN	148—149	EtOH	b)	76	$C_{11}H_7NO_2$	71.35 (71.13	3.81 3.70	7.56 7.39)
VI-38 (oxalate)	5-CH$_2$NH$_2$	191.5—192	MeOH–AcOEt	b)	36	$C_{11}H_{11}NO_2 \cdot C_2H_2O_4$	55.91 (55.74	4.69 4.60	5.02 4.93)
VI-39	5-NO$_2$	109—110	EtOH	b)	88	$C_{10}H_7NO_4$	58.54 (58.85	3.44 3.50	6.83 6.68)
VI-40	7-NO$_2$	135—136	AcOEt–hexane	b)	d)	$C_{10}H_7NO_4$	58.54 (58.42	3.44 3.37	6.83 6.65)
VI-41	5,7-(NO$_2$)$_2$	158—161	MeOH	b)	d)	$C_{10}H_6N_2O_6$	48.01 (48.03	2.42 2.33	11.20 11.01)
VI-42	5,7-(NO$_2$)$_2$, 6-OCH$_3$	121—124	MeOH	b)	71	$C_{11}H_8N_2O_7$	47.15 (46.86	2.88 2.79	10.00 9.83)
VI-43	5-NO$_2$, 6-OCH$_3$	160—163	EtOH	b)	67	$C_{11}H_9NO_5$	56.17 (56.44	3.86 3.76	5.96 5.80)
VI-44	5-NO$_2$, 7-CH$_3$	160—162	EtOH	b)	70	$C_{11}H_9NO_4$	60.27 (60.17	4.14 4.14	6.39 6.48)
VI-45	5-NH$_2$	130—132.5	AcOEt–hexane	b)	81	$C_{10}H_9NO_2$	58.56 (68.54	5.18 4.93	8.00 7.93)
VI-45 (HCl)	5-NH$_2$	139—142	EtOH–Et$_2$O			$C_{10}H_9NO_2 \cdot HCl$	56.75 (56.67	4.76 4.83	6.62 6.67)
VI-46	6-NH$_2$	188—189	MeOH	b)	68	$C_{10}H_9NO_2$	68.56 (68.34	5.18 5.05	8.00 7.88)
VI-47	7-NH$_2$	131—133	EtOH	b)	82	$C_{10}H_9NO_2$	68.56 (68.42	5.18 5.11	8.00 7.74)
VI-48 (HCl)	5,7-(NH$_2$)$_2$	>300	MeOH–Et$_2$O	b)	38	$C_{10}H_{10}N_2O_2 \cdot HCl \cdot H_2O$	49.08 (48.80	5.35 5.13	11.45 11.64)

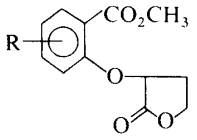
VI-49	5-NH_2, 6-OCH_3	175—177	EtOH	b)	48	$C_{11}H_{11}NO_3$	64.38	5.40	6.83
							(64.39	5.49	6.71)
VI-50	5-NH_2, 7-CH_3	138—140	EtOH–H_2O	b)	39	$C_{11}H_{11}NO_2$	68.82	5.86	7.40
							(69.66	5.71	7.43)
VI-51 (HCl)	5-$NHCH_3$	141—144	EtOH–H_2O	b)	51	$C_{11}H_{11}NO_2 \cdot HCl \cdot 1/2H_2O$	56.29	5.58	5.97
							(56.38	5.15	6.07)
VI-52	5-NHEt	102—104	AcOEt–hexane	b)	d)	$C_{12}H_{13}NO_2$	70.91	6.45	6.89
							(71.12	6.37	6.83)
VI-53	5-$NHCH(CH_3)_2$	69—71	EtOH–H_2O	b)	52	$C_{13}H_{15}NO_2$	71.86	6.96	6.45
							(71.77	6.82	6.59)
VI-54	5-$NHCH_2CH_2OH$	74—75	AcOEt–hexane	b)	d)	$C_{12}H_{13}NO_3$	65.74	5.98	6.39
							(65.71	6.02	6.23)
VI-55	5-$N(CH_3)_2$	96—97	EtOH	b)	82	$C_{12}H_{13}NO_2$	70.91	6.45	6.89
							(70.94	6.36	6.74)
VI-55 (HCl)	5-$N(CH_3)_2$	156—157	MeOH–AcOEt			$C_{12}H_{13}NO_2 \cdot HCl$	60.13	5.89	5.84
							(59.99	5.96	5.83)
VI-56 (oxalate)	5-NEt_2	127—131	Acetone	b)	61	$C_{14}H_{17}NO_2 \cdot C_2H_2O_4$	59.80	5.96	4.36
							(59.80	5.87	4.28)
VI-56 (HCl)	5-NEt_2	171—171.5	EtOH–Et_2O			$C_{14}H_{17}NO_2 \cdot HCl$	62.80	6.78	5.23
							(62.79	6.85	5.10)
VI-57	5-	102—103.5	EtOH	b)	44	$C_{14}H_{15}NO_2$	73.34	6.59	6.11
							(73.15	6.45	5.94)
VI-57 (HCl)	5-	146—148	EtOH–Et_2O			$C_{14}H_{15}NO_2 \cdot HCl$	63.27	6.07	5.27
							(63.26	6.10	5.26)
VI-58 (HCl)	5-	128—131	EtOH–Et_2O	b)	22	$C_{14}H_{15}NO_3 \cdot HCl$	59.68	5.73	4.97
							(59.59	5.60	4.95)
VI-59	5-	125—125.5	EtOH	b)	19	$C_{21}H_{22}N_2O_2$	75.42	6.63	8.38
							(75.26	6.78	8.41)
VI-60 (oxalate)	5-	195—197	EtOH	b)	65	$C_{16}H_{20}N_2O_2 \cdot C_2H_2O_4$	59.66	6.12	7.73
							(59.39	6.17	7.50)
VI-61	5-$N(CH_2CH_2OH)_2$	96—97	AcOEt–hexane	b)	86	$C_{14}H_{17}NO_4$	63.86	6.51	5.32
							(63.75	6.54	5.23)
VI-62	7-$NHCH_2CH_2OH$	76—76.5	AcOEt–hexane	b)	d)	$C_{12}H_{13}NO_3$	65.74	5.98	6.39
							(65.51	5.96	6.58)
VI-63	7-$N(CH_2CH_2OH)_2$	74—76	AcOEt–hexane	b)	80	$C_{14}H_{17}NO_4$	63.86	6.51	5.32
							(63.67	6.51	5.35)
VI-64	5-NHAc	211—212	EtOH	b)	39	$C_{12}H_{11}NO_3$	66.35	5.10	6.45
							(66.37	5.12	6.38)

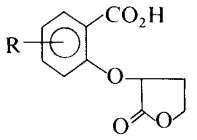
TABLE I. (continued)

Compound No.	R	mp °C	Recrystallization solvent	Synthesis method[a]	Yield %	Formula	Analysis (%) Calcd (Found)		
							C	H	N
VI-65	5-$NHSO_2CH_3$	152—154	EtOH	*b*)	51	$C_{11}H_{11}NO_4S$	52.16	4.38	5.53
							(52.20	4.37	5.32)
VI-66	5-$N(CH_3)CO_2CH_2Ph$	79—81	EtOH	*b*)	56	$C_{19}H_{17}NO_4$	70.57	5.30	4.33
							(70.54	5.26	4.19)
VI-67	6-NHAc	176—177	AcOEt	E	84	$C_{12}H_{11}NO_3$	66.35	5.10	6.45
							(66.30	5.00	6.20)
VI-68	5-$NHCONH_2$	250—252	DMF–EtOH	*b*)	34	$C_{11}H_{10}N_2O_3$	60.54	4.62	12.84
							(60.42	4.42	12.94)
VI-69	5-$NHCONHCH_3$	206—208	EtOH	*b*)	46	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06
							(61.87	5.11	11.67)
VI-70	5-$NHCSNHCH_3$	194—196	MeOH	*b*)	65	$C_{12}H_{12}N_2O_2S$	58.04	4.87	11.28
							(58.07	4.87	11.00)
VI-71 (HCl)	5-$NH(=NH)NH_2$	236—237	EtOH	*b*)	26	$C_{11}H_{11}N_3O_2 \cdot HCl$	52.08	4.77	16.57
							(52.15	4.77	16.84)
VI-72	4-Br, 5-NH_2	167—170	EtOH–H_2O	*b*)	55	$C_{10}H_8BrNO_2$	47.27	3.17	5.51
							(47.58	3.12	5.64)
VI-73	4-Br, 5-$N(CH_3)_2$	79—81	EtOH–H_2O	*b*)	34	$C_{12}H_{12}BrNO_2$	51.08	4.29	4.97
							(50.87	4.13	5.03)
VI-74	5-Cl, 6-NH_2	201	MeOH	*b*)	86	$C_{10}H_8ClNO_2$	57.29	3.85	6.68
							(57.24	3.74	6.67)
VI-75	5-Cl, 6-NHAc	185—187.5	MeOH	E	43	$C_{12}H_{10}ClNO_3$	57.27	4.01	5.57
							(57.03	3.86	5.46)

a) Shown in Chart 1. See Experimental.
b) See Experimental.
c) The oil was purified by distillation under reduced pressure and the boiling point is given as the bath temperature.
d) Obtained as a by-product.

TABLE II. Physical Properties of Methyl 2-[(Tetrahydro-2-oxo-3-furanyl)oxy]benzoates (III) and 2-[(Tetrahydro-2-oxo-3-furanyl)oxy]benzoic Acids (IV)

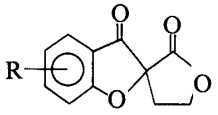

III


IV

Compound No.	R	mp °C	Recrystallization solvent	Synthesis method[a]	Yield %	Formula	Analysis (%) Calcd (Found) C	H	N
IIIa	H	66—68	MeOH	A	36	$C_{12}H_{12}O_5$	61.01 (60.98)	5.12 (4.99)	
IVa	H	113—115	AcOEt	B	36	$C_{11}H_{10}O_5$	59.46 (59.21)	4.54 (4.51)	
IVb	5-Cl	159—160.5[c]	AcOEt–hexane	B	36	$C_{11}H_9ClO_5$	51.48 (51.22)	3.53 (3.50)	
IVc	3,5-Cl_2	118.5—119.5	AcOEt	B	69	$C_{11}H_8Cl_2O_5$	45.38 (45.43)	2.72 (2.66)	
IIId	5-Ph	112—114	MeOH	A	38	$C_{18}H_{16}O_5$	69.22 (69.41)	5.16 (5.07)	
IIIe	4,5-	119—120	EtOH	A	42	$C_{16}H_{14}O_5$	67.12 (67.12)	4.93 (4.83)	
IVe	4,5-	185—186	AcOEt	B	63	$C_{15}H_{12}O_5$	66.17 (66.06)	4.44 (4.22)	
IVf	5-OCH_3	129—132	AcOEt	B	30	$C_{12}H_{12}O_6$	57.14 (57.04)	4.80 (4.78)	
IVg	4-OCH_3	130—133	AcOEt	B	15	$C_{12}H_{12}O_6$	57.14 (57.08)	4.80 (4.75)	
IVh	5-OCH_2Ph	120—122	AcOEt	B	53	$C_{18}H_{16}O_6$	65.85 (65.86)	4.91 (4.96)	
IVi	6-OH	199—201.5	AcOEt	B	18	$C_{11}H_{10}O_6$	55.46 (55.51)	4.23 (4.10)	
IVj	3-CH_3	129—131	AcOEt–hexane	B	51	$C_{12}H_{12}O_5$	61.01 (61.00)	5.12 (5.12)	
IVk	5-$CH(CH_3)_2$	124—126	AcOEt–hexane	B	30	$C_{14}H_{16}O_5$	63.62 (63.60)	6.10 (6.18)	
IVl	5-C_6H_{13}	98—100	Benzene–Et_2O	B	47	$C_{17}H_{22}O_5$	66.65 (66.50)	7.24 (7.28)	
IIIm	5-$COCH_3$	112—113	MeOH	A	84	$C_{14}H_{14}O_6$	60.43 (60.39)	5.07 (4.96)	
IVm	5-$COCH_3$	155—158	Me_2CO–MeOH	B	45	$C_{13}H_{12}O_6$	59.09 (58.98)	4.58 (4.48)	
IIIn	5-COC_2H_5	109—111	AcOEt–hexane	A	50	$C_{15}H_{16}O_6$	61.64 (61.63)	5.52 (5.56)	
IIIo	5-COPh	100.5—102	EtOH	A	44	$C_{19}H_{16}O_6$	67.05 (67.32)	4.75 (4.77)	
IIIp	5-SCH_3	60—63	AcOEt–hexane	A	64	$C_{13}H_{14}O_5S$	55.30 (55.09)	5.00 (4.93)	
IIIq	5-SO_2CH_3	102—105	AcOEt–hexane	b)	99	$C_{13}H_{14}O_7S$	49.68 (49.67)	4.49 (4.42)	
IIIr	4-NHAc	Oil		A	39	$C_{14}H_{15}NO_6$[d]			
IIIs	4-NHAc, 5-Cl	118—119	MeOH	A[e]	44	$C_{14}H_{14}ClNO_6$	51.31 (51.24)	4.31 (4.26)	4.27 (4.16)
IVt	3-CH_3, 5-NO_2	210 (dec.)	MeOH	b)	70	$C_{12}H_{11}NO_7$	51.25 (51.16)	3.94 (3.93)	4.98 (4.82)

a) Shown in Chart 1. See Experimental.
b) See Experimental.
c) D. T. Witiak *et al.*, *J. Med. Chem.*, **21**, 1198 (1978). mp 157—159 °C.
d) Not purified.
e) DMF was used as the solvent instead of acetone.

TABLE III. Physical Properties of 4′,5′-Dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (V)



Compound No.	R	mp °C	Recrystallization solvent	Synthesis method[a]	Yield %	Formula	Analysis (%) Calcd (Found)		
							C	H	N
Va	H	110—112	EtOH	C	60	$C_{11}H_8O_4$	64.70	3.95	
				D	35		(64.74	3.70)	
Vb	5-Cl	132.5—133	AcOEt–hexane	C	59	$C_{11}H_7ClO_4$	55.36	2.96	
							(55.49	2.79)	
Vc	5,7-Cl_2	157—159	AcOEt	C	13	$C_{11}H_6Cl_2O_4$	48.38	2.21	
							(48.47	2.14)	
Vd	5-Ph	193—195	AcOEt	D	48	$C_{17}H_{12}O_4$	72.85	4.32	
							(72.82	4.19)	
Ve	5,6-	168—170	MeOH	C	50	$C_{15}H_{10}O_4$	70.86	3.96	
							(70.83	3.63)	
Vf	5-OCH_3	120—122	AcOEt–hexane	C	25	$C_{12}H_{10}O_5$	61.54	4.30	
							(61.31	4.24)	
Vg	6-OCH_3	106—108	AcOEt	C	35	$C_{12}H_{10}O_5$	61.54	4.30	
							(61.62	4.22)	
Vh	5-OCH_2Ph	138—139	MeOH	C	38	$C_{18}H_{14}O_5$	69.67	4.55	
							(69.67	4.39)	
Vi	4-OAc	135—137	AcOEt–hexane	C	39	$C_{13}H_{10}O_6$	59.54	3.84	
							(59.55	3.68)	
Vj	7-CH_3	103—104	AcOEt–hexane	C	19	$C_{12}H_{10}O_4$	66.05	4.62	
							(66.31	4.63)	
Vk	5-$CH(CH_3)_2$	71	AcOEt–hexane	C	41	$C_{14}H_{14}O_4$	68.28	5.73	
							(68.39	5.67)	
Vl	5-C_6H_{13}	126—130[d] (0.02 mmHg)		C	66	$C_{17}H_{20}O_4$	70.81	6.99	
							(71.14	6.99)	
Vm	5-$COCH_3$	132—134	MeOH	C	55	$C_{13}H_{10}O_5$	63.41	4.09	
				D	47		(63.57	4.02)	
Vn	5-COC_2H_5	163—165	AcOEt	D	49	$C_{14}H_{12}O_5$	64.61	4.65	
							(64.70	4.57)	
Vo	5-COPh	199—201	AcOEt	D	52	$C_{18}H_{12}O_5$	70.13	3.92	
							(69.95	3.78)	
Vp	5-SCH_3	100—102	AcOEt–hexane	D	28	$C_{12}H_{10}O_4S$	57.59	4.03	
							(57.82	3.90)	
Vq	5-SO_2CH_3	220—222	AcOEt	D	47	$C_{12}H_{10}O_6S$	51.06	3.57	
							(50.97	3.52)	
Vr	6-NHAc	230—232	MeOH	b)	1.8[c]	$C_{13}H_{11}NO_5$	59.77	4.24	5.36
							(59.71	4.21	5.28)
Vr′	6-$N(Ac)_2$	172—174	AcOEt	D	12	$C_{15}H_{13}NO_6$	59.40	4.32	4.62
							(59.49	4.21	4.34)
Vs	5-Cl, 6-$N(Ac)_2$	183—184	AcOEt	D	29	$C_{15}H_{12}ClNO_6$	53.34	3.58	4.15
							(53.08	3.49	4.12)
Vt	5-NO_2, 7-CH_3	127—130	EtOH	C	14	$C_{12}H_9NO_6$	54.76	3.45	5.32
							(55.00	3.24	5.36)
Vu	5-SO_2NH_2	200—202	EtOH–H_2O	b)	68	$C_{11}H_9NO_6S$	46.64	3.20	4.95
							(46.39	3.14	4.87)

a) Shown in Chart 1. See Experimental.
b) See Experimental.
c) Obtained as a by-product in the synthesis of IIIr.
d) The oil was purified by distillation under reduced pressure and the boiling point is given as the bath temperature.

accompanied by ring-opening of the cyclopropane ring to give VIII (Chart 2).[1,3] Bromination of VI-17 with cupric bromide in a mixture of ethyl acetate and chloroform in the presence of calcium carbonate gave only the cyclopropane ring-opened product (IX, Chart 2).[1,3] Compound VI-25 was prepared by bromination with pyrrolidinone hydrotribromide[4] (Chart 2). In an attempt to synthesize the 5-diethylaminoacetyl spirocyclopropane, the reaction of VI-25 with diethylamine did not afford the expected product, but gave the 5-carboxy derivative (VI-26) in good yield.[5] Compound VI-26 could be alternatively prepared in 93% yield by haloform reaction of VI-17 with sodium hypochlorite (Chart 2). Oxidation of VI-17

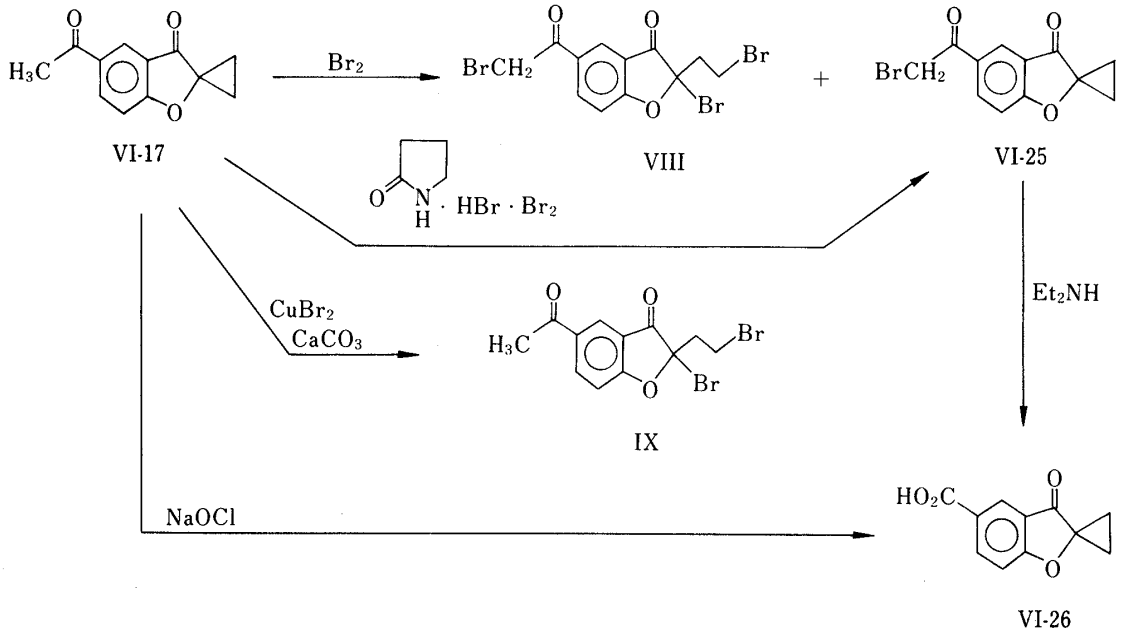


Chart 2

with selenium dioxide in dioxane and then with manganese dioxide in the presence of potassium cyanide in methanol afforded the methyl 5-oxalate derivative (VI-29). Compound VI-29 was converted into the 5-hydroxyacetic acid derivative (VI-31) by reduction with sodium borohydride, followed by hydrolysis.

The 5-alkoxycarbonyl (VI-27 and VI-28) and 5-amido (VI-33—VI-36) derivatives were obtained by esterification and amidation of VI-26. The 5-amino derivative (VI-45, described below) was converted into the 5-cyano derivative (VI-37) by diazotization, followed by cyanation with cuprous cyanide. The 5-cyano derivative (VI-37) was hydrolyzed to the 5-amido derivative (VI-32). The 5-aminomethyl derivative (VI-38) was obtained by catalytic hydrogenation of the 5-cyano compound (VI-37) using Raney-Nickel (Raney Ni) in a basic medium.

Nitration of VI-1 with cupric nitrate in acetic anhydride afforded a mixture of 5- and 7-nitro derivatives (VI-39 and VI-40) in low yields. The 5-nitro derivative (VI-39) was obtained by nitration with fuming nitric acid at -50——-40 °C in 88% yield. Small amounts of the 7-nitro (VI-40) and 5,7-dinitro (VI-41) derivatives were obtained as by-products. Nitration of the 6-methoxy derivative (VI-7) with fuming nitric acid afforded the 6-methoxy-5,7-dinitro derivative (VI-42). On the other hand, nitration of VI-7 with fuming nitric acid in a mixture of acetic anhydride and acetic acid exclusively gave the 6-methoxy-5-nitro derivative (VI-43) in good yield. These nitro compounds (VI-39—VI-41, VI-43 and VI-44) were readily converted into the corresponding amino derivatives (VI-45, VI-47—VI-49 and VI-50, respectively) by catalytic hydrogenation using either platinum oxide or Raney Ni as a catalyst.

The 5-methylamino and 5-ethylamino derivatives (VI-51 and VI-52) were prepared by protecting the amino group of VI-45 with the carbobenzyloxy group, followed by alkylation and subsequent deprotection. Reductive alkylation of VI-45 with acetone and sodium cyanoborohydride, formaldehyde, or acetaldehyde and platinum oxide afforded the 5-isopropylamino (VI-53), 5-dimethylamino (VI-55), or 5-diethylamino (VI-56) derivative, respectively. Compound VI-55 was also prepared in over 90% yield by reductive alkylation of the 5-nitro derivative (VI-39) using formalin in the presence of Raney Ni at a high pressure (100 kg/cm^2) of hydrogen gas. Alkylation of VI-45 with 1,4-dibromobutane in the presence of sodium hydrogencarbonate afforded the 5-pyrollidinyl derivative (VI-57). When bis(2-iodoethyl)ether, *N*-benzyl-2,2′-diiododiethylamine, or *N*-ethyl-2,2′-diiododiethylamine was used instead of 1,4-dibromobutane, the 5-morpholino (VI-58), 5-(4-benzyl-1-piperadinyl) (VI-59) and 5-(4-ethyl-1-piperadinyl) (VI-60) derivatives were obtained, respectively. The reaction of VI-45 and VI-47 with ethylene oxide afforded the diethanolamino (VI-61 and VI-63) and

TABLE IV. Effects of Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones (VI) on Gastric Secretion in Pylorus-Ligated Rats and on Gastric Lesions Induced by Water-Immersion Restraint Stress in Rats

Compound No.	R in VI (Chart 1)	Antisecretory activity[a]	Antiulcer activity[a]
VI-1	H	91^{++}	58
VI-2	5-Cl	48^{++}	60
VI-4	5-Ph	43	34
VI-14	7-CH_3	33	36
VI-17	5-$COCH_3$	42^{++}	66^{++}
VI-18	5-COC_2H_5	37^{++}	29
VI-19	5-COPh	27	44
VI-21	5-SO_2CH_3	0	71^{+}
VI-23	5-$SOCH_3$	24	84^{+}
VI-26	5-CO_2H	16	45
VI-32	5-$CONH_2$	26	45
VI-39	5-NO_2	57^{+}	86^{+}
VI-45	5-NH_2	78^{+}	45
VI-46	6-NH_2	61^{+}	27
VI-47	7-NH_2	82^{++}	11
VI-51·HCl	5-$NHCH_3$·HCl	76^{+++}	57^{++}
VI-52	5-NHEt	76^{++}	68^{+}
VI-53	5-$NHCH(CH_3)_2$	63^{++}	51
VI-54	5-$NHCH_2CH_2OH$	77^{+++}	68^{+}
VI-55·HCl	5-$N(CH_3)_2$·HCl	78^{++}	69^{++}
VI-56	5-NEt_2	78^{++}	64^{+}
VI-57	5-N⟨ ⟩	65^{+++}	71^{+}
VI-58	5-N⟨ O ⟩	71^{++}	30
VI-64	5-$NHCOCH_3$	61^{++}	43
VI-65	5-$NHSO_2CH_3$	68^{+}	7
VI-68	5-$NHCONH_2$	54^{+}	53
VI-69	5-$NHCONHCH_3$	59^{+}	54
VI-70	5-$NHCSNHCH_3$	4	52
Ranitidine		65^{+}	71^{+}

a) % inhibition of gastric juice volume (ml) in the pylorus-ligated rat for 3 h. +: $p<0.05$, ++: $p<0.01$, +++: $p<0.001$ *vs.* control value. 50 mg/kg *i.d.*

b) % inhibition of ulcer formation induced by water-immersion. +: $p<0.05$, ++: $p<0.01$ *vs.* control value. 50 mg/kg *p.o.*

ethanolamino (VI-54 and VI-62) derivatives. Alkaline hydrolysis of the 6-acetylamino (VI-67) and 6-acetylamino-5-chloro (VI-75) derivatives afforded the 6-amino (VI-46) and 6-amino-5-chloro (VI-74) derivatives, respectively. Acetylation or sulfonylation of VI-45 afforded the 5-acetylamino (VI-64) or 5-methylsulfonylamino (VI-65) derivatives, respectively. The 5-ureido (VI-68, VI-69 and VI-70) and 5-guanidino (VI-71) derivatives were prepared by treating VI-45 with sodium cyanate, methyl isocyanate, methyl isothiocyanate, or cyanamide, respectively. Bromination of VI-45 and VI-55 with bromine in the presence of calcium carbonate exclusively gave the 4-bromo derivatives (VI-72 and VI-73, respectively).

Biological Results and Discussion

The results of the evaluation of selected spirocyclopropane compounds (VI) at 50 mg/kg i.d. in the pylorus-ligated rat for gastric antisecretory activity[6] and in the water-immersion restraint rat for antiulcer activity[7] are summarized in Table IV.

Potent antisecretory activity was found in the parent compound (IV-1) at the screening dose. Some other members of the series, for example, compounds with an amino (VI-45, VI-46 and VI-47) and substituted amino (VI-51—VI-58, VI-64, VI-65, VI-68 and VI-69) group at the 5-, 6-, or 7-position on the benzene ring, exhibited significant antisecretory activity. Introduction of an electron-withdrawing group, such as chloro (VI-2), acetyl (VI-17), propionyl (VI-18) or nitro (VI-39) at the 5-position on the benzene ring did not abolish the activity. However, no clear structure–activity relationship was obtained between either the electronegativity of substituents or the lipophilicity of these spirocyclopropane compounds and antisecretory activity.

The antiulcer activity of spirocyclopropane compounds did not necessarily parallel the antisecretory activity. The 5-methylsulfonyl (VI-21) and 5-methylsulfinyl (VI-23) derivatives showed only moderate antisecretory activity, although they provided significant protection against gastric lesions induced by water-immersion restraint stress in the rat. On the other hand, amino derivatives (VI-45, VI-46 and VI-47) and acylamino derivatives (VI-64 and VI-65) did not exhibit significant antiulcer activity at the antisecretory activity–exhibiting dose. Therefore, the antiulcer activity of spirocyclopropane compounds seems to be due to mechanism other than the inhibition of gastric secretion. Some of the alkylamino derivatives (VI-51, VI-52, VI-54, VI-55 and VI-57) showed potent antiulcer activity as well as antisecretory activity. The most potent compound was the 5-dimethylamino derivative (VI-55). The ED_{50} values of VI-55 for the antisecretory and antiulcer activities were 2.8 mg/kg *i.d.* and 6.0 mg/kg *p.o.*, respectively. However, preliminary toxicological tests revealed that a high dose of VI-55 in rats suppressed body weight gain.

Further studies of related componds showed that the most promising potential antiulcer agent is the 5-acetyl derivative (VI-17). It is superior to VI-55 because it apparently lacks the undesirable side effects. The minimum effective oral dose of VI-17 for protection against gastric lesions induced by water-immersion restraint stress was 6.2 mg/kg *p.o.* Studies on VI-17 (AG-629) are continuing.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The following instruments were used for obtaining the spectral data: Proton nuclear magnetic resonance (^{1}H-NMR) spectra, Varian A-60A and Varian HA-100 spectrometers; infrared (IR) spectra, a Hitachi 215 grating infrared spectrophotometer; mass spectra, a Hitachi RMU-6D mass spectrometer.

Methyl 2-[(Tetrahydro-2-oxo-3-furanyl)oxy]benzoate (IIIa). Method A——α-Bromo-γ-butyrolactone (220 g) was added in portions to a mixture of methyl salicylate (IIa, 152 g, 1.0 mol) and K_2CO_3 (173 g) in acetone (500 ml) at room temperature with stirring. After being stirred at 60 °C for 36 h, the mixture was cooled and filtered to remove the insoluble materials. The filtrate was concentrated *in vacuo*, dried and recrystallized to give IIIa (84 g) as colorless needles.

Other methyl 2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoates (IIId, IIIm, IIIn, IIIo, IIIp, IIIr and IIIs) were also prepared from the corresponding substituted methyl salicylates (II) according to the above procedure for the synthesis of IIIa, with the following exceptions.

Methyl 3-[(Tetrahydro-2-oxo-3-furanyl)oxy]naphthoate (IIIe)——α-Bromo-γ-butyrolactone was added to a mixture of 50% NaH (5.8 g) and methyl 3-hydroxy-2-naphthoate (IIe, 20 g, 99 mmol) in dimethylformamide (DMF) (150 ml) and toluene (50 ml) at room temperature with stirring. After being stirred at room temperature for 51 h, the mixture was concentrated *in vacuo*, and the residue was poured into ice-H_2O. The resulting mixture was acidified with dil. HCl and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was recrystallized to give IIIe (11.9 g) as colorless crystals.

Compound IIIj was prepared from methyl 2-hydroxy-3-methylbenzoate (IIj) according to the above procedure for the synthesis of IIIe. Without purification, IIIj was subjected to alkaline hydrolysis to afford the corresponding acid IVj.

Methyl 5-Methylsulfonyl-3-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (IIIg)——*m*-Chloroperbenzoic acid (1.72 g) was added in portions to a solution of IIIp (1.128 g, 4.0 mmol) in CH_2Cl_2 (24 ml) at room temperature with stirring. After being stirred at room temperature for 1 h, the mixture was diluted with water and extracted with $CHCl_3$. The extract was washed successively with water, aqueous $NaHCO_3$, aqueous $Na_2S_2O_4$ and water, then dried and concentrated *in vacuo*. The resulting residue was recrystallized to give IIIq (1.09 g) as colorless needles.

Method B. 2-[(Tetrahydro-2-oxo-3-furanyl)oxy]benzoic Acid (IVa)——Methyl salicylate (IIa, 1.217 kg, 8.0 mol) was added to a suspension of K_2CO_3 (1.216 kg) in DMF (2.0 l) at room temperature with stirring. The mixture was warmed at 60 °C for 1 h, then α-bromo-γ-butyrolactone (1.32 kg) was added at 5 °C over 3 h. The mixture was warmed at 45 °C for 10 h. The mixture was filtered to remove inorganic salts and the filtrate was concentrated *in vacuo*. The residue was subjected to distillation under reduced pressure to remove unreacted methyl salicylate. The residue (crude IIIa, 1.417 kg, 6.0 mol) was dissolved in MeOH (2 l) and 50% aqueous NaOH (2 l). The mixture was warmed to 60 °C. After being cooled, the mixture was poured into ice-H_2O (1.5 l) and acidified with conc. HCl (2.2 l). The resulting precipitates were collected, washed with water, dried and dissolved in dioxane (1 l) and toluene (1 l). *p*-Toluenesulfonic acid (400 g) was added to the above solution and the mixture was heated under reflux for 8.5 h in an apparatus equipped with a Dean–Stark water separator. The mixture was concentrated *in vacuo* and the resulting residue was poured into ice-H_2O (10 l). The resulting precipitates (crude IVa) were collected, washed with water, dried and dissolved in AcOEt. The solution was dried and concentrated *in vacuo*. The resulting residue was recrystallized to give pure IVa (648 g) as colorless needles.

Other 2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoic acids (IVb, IVc, IVe—IVi, IVk, IVl and IVm) were also prepared from the corresponding substituted methyl salicylates (II) according to the above procedure for the synthesis of IVa, with the following exception (IVt).

3-Methyl-4-nitro-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoic Acid (IVt)——3-Methyl-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoic acid (IVj, 24.4 g, 0.1 mol) was added in small portions to fuming HNO_3 ($d=1.52$, 120 ml) at 40 °C with stirring. When the addition was complete, the mixture was poured into ice-H_2O and the resulting pale yellow precipitates were collected, washed with water, dreid and recrystallized to give IVt (20.3 g) as pale yellow prisms.

4′,5′-Dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-dione (Va). Method C——A solution of IVa (280 g, 1.26 mol) in Ac_2O (2.8 l) and Et_3N (560 ml) was heated under reflux. The mixture was concentrated *in vacuo* and the resulting residue was poured into ice-H_2O (3 l). The resulting precipitates were collected, washed and recrystallized to give Va (155 g) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1780 (γ-lactone), 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.62—2.97 (2H, m, $C\underline{H}_2CH_2O$), 4.36—5.00 (2H, m, $CH_2C\underline{H}_2O$).

Other 4′,5′-dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (Vb, Vc, Ve, Vf, Vg, Vh, Vj, Vk, Vl, Vm and Vt) were prepared from the corresponding substituted 2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoic acids (IV) according to the above procedure for the synthesis of Va, with the following exceptions.

Method D——A solution of IIIa (1.1 g, 4.7 mmol) in Ac_2O (15 ml) and Et_3N (3 ml) was heated under reflux for 10 h. The mixture was concentrated *in vacuo*. The resulting residue was poured into ice-H_2O and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel with CCl_4–acetone (5:1, v/v). The first fraction provided 3,3-diacetoxy-4′,5′-dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′-one (VII, 0.32 g, 22%) as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1780 (γ-lactone), 1765, 1740 ($OCOCH_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, $OCOCH_3$), 2.34 (3H, s, $OCOCH_3$), 3.05 (2H, t, $J=7$ Hz, $C\underline{H}_2CH_2O$), 4.38 (2H, t, $J=7$ Hz, $CH_2C\underline{H}_2O$), 7.0—7.5 (4H, m, aromatic H). MS *m/e*: 306 (M^+).

The second fraction gave Va (0.33 g, 35%).

Other 4′,5′-dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (Vd, Vm, Vn, Vo, Vp, Vq, Vr′, Vs and Vt) were prepared from the corresponding substituted methyl 2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoates (III) according to method D for the synthesis of Va, with the exception of Vu.

5-Sulfamoyl-4′,5′-dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-dione (Vu)——Compound Va (3 g, 14.7 mmol) was added to $ClSO_3H$ (16 ml) in small portions at 0 °C with stirring. After being stirred at room temperature for 1 h and then at 4 °C for 70 min, the mixture was poured into ice-H_2O. The resulting precipitates were collected, washed with water and dried to give crude 5-chlorosulfonylspirolactone (4.08 g, 91%). This crude product

(1.71 g) was dissolved in THF (25 ml) and 28% NH_4OH (0.9 ml) was added at 0 °C with stirring. After being stirred at 0 °C for 5 min, the mixture was filtered to remove inorganic salts. The filtrate was concentrated *in vacuo* and the residue was recrystallized to give Vu (1.18 g) as colorless needles. ^{1}H-NMR (DMSO-d_6) δ: 2.92 (2H, t, J=7 Hz, CH_2CH_2O), 4.64 (2H, t, J=7 Hz, CH_2CH_2O), 7.48 (2H, s, NH_2), 7.61 (1H, d, J=9 Hz, 7-aromatic H), 8.11 (1H, d, J=2 Hz, 4-aromatic H), 8.15 (1H, dd, J=9 and 2 Hz, 6-aromatic H).

Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-1). Method E——A mixture of Va (1.5 kg, 7.4 mol) and NaCl (94 g) in DMSO (1.5 l) was heated at 150 °C for 1.5 h with stirring. After being cooled, the mixture was poured into ice-H_2O. The resulting precipitates were collected, washed with water, dried and recrystallized to give VI-1 (220 g) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.64 (4H, m, cyclopropane CH_2), 7.04—7.30 (2H, m, aromatic H), 7.50—7.80 (2H, m, aromatic H).

Other spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones (VI-2—9, VI-14—22, VI-44, VI-67 and VI-75) were prepared from the corresponding substituted 4′,5′-dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (V) according to method E for the synthesis of VI-1, with the following exceptions.

4-Hydroxyspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-10)——Compound VI-10 was prepared by usual alkaline hydrolysis of the 4-acetoxy compound (VI-9).

5-Hydroxyspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-11)——Compound VI-8 (3.3 g, 10 mmol) was hydrogenated in MeOH (250 ml) in the presence of 5% Pd–C (wet, 0.7 g) at room temperature under atmospheric pressure of H_2 gas with stirring. After the uptake of H_2 gas had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was recrystallized to give VI-11 (1.78 g) as pale yellow needles.

4-(2-Diethylaminoethyloxy)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-12) Hydrochloride——β-Diethylaminoethylchloride (172 mg) was added to a mixture of VI-10 (176 mg, 1.0 mmol) and K_2CO_3 (276 mg) at room temperature with stirring. After stirring of the mixture at room temperature for 30 min, further β-diethylaminoethylchloride (43 mg) was added. The whole was stirred at room temperature for 1 h, then diluted with water, made alkaline with aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel with $CHCl_3$. The desired eluate was concentrated *in vacuo* and the resulting residue was dissolved in EtOH. This solution was treated with EtOH containing HCl gas and the product was recrystallized to give VI-12·HCl (221 mg) as colorless needles.

5-(2-Diethylaminoethyloxy)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-13) Citrate——This compound was prepared from VI-11 according to the procedure described for the synthesis of VI-12. The free base of the product was converted to the citrate, which was recrystallized to give pure VI-13·citrate as a crystalline powder.

5-Methylsulfonylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-21)——Compound VI-21 was alternatively prepared from VI-20 by oxidation with two equivalents of *m*-chloroperbenzoic acid in CH_2Cl_2 instead of by method E.

5-Methylsulfinylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-23)——*m*-Chloroperbenzoic acid (210 mg) was added in portions to a solution of VI-20 (206 mg, 1.0 mmol) in CH_2Cl_2 (4 ml) at room temperature with stirring. After being stirred at room temperature for 1 h, the mixture was diluted with water and extracted with $CHCl_3$. The extract was washed successively with water, aqueous $NaHCO_3$, aqueous $Na_2S_2O_4$ and water, then dried and concentrated *in vacuo*. The resulting residue was recrystallized to give VI-23 (120 mg) as colorless needles.

5-(1-Hydroxyethyl)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-24)——$NaBH_4$ (0.9 g) was added in portions to a solution of VI-17 (1.0 g, 4.9 mmol) in THF (25 ml) containing iso-PrOH (3 ml) at −50 °C with stirring. After being stirred at room temperature for 30 min, the mixture was diluted with water, acidified with aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel with $CHCl_3$. The desired eluate was concentrated *in vacuo* and distilled under reduced pressure (0.05 mmHg) at 110 °C (bath temperature) to give VI-24 (0.861 g) as a colorless oil.

2-Bromo-5-bromoacetyl-2-(2-bromoethyl)-3(2*H*)-benzofuranone (VIII) and 5-Bromoacetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-25)——Experiment 1: A solution of Br_2 (0.48 g) in $CHCl_3$ (10 ml) was added dropwise to a solution of VI-17 (0.606 g, 3.0 mmol) and $CaCO_3$ (0.36 g) in $CHCl_3$ (15 ml) at room temperature with stirring. After being stirred at room temperature for 2 h, the mixture was filtered to remove inorganic salts. The filtrate was concentrated *in vacuo* and the resulting residue was subjected to column chromatography on silica gel with $CHCl_3$. Compound VIII (50 mg, 4%) was obtained from the first fraction as colorless needles (recrystallized from AcOEt–hexane), mp 135—138 °C. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O), 1680 ($COCH_2Br$). ^{1}H-NMR ($CDCl_3$) δ: 2.57—3.17 (2H, m, CH_2CH_2Br), 3.23—3.83 (2H, m, CH_2CH_2Br), 4.40 (2H, s, $COCH_2Br$), 7.18 (1H, d, J=9 Hz, 7-aromatic H), 8.30 (1H, dd, J=9 and 2 Hz, 6-aromatic H), 8.32 (1H, d, J=2 Hz, 4-aromatic H). *Anal.* Calcd for $C_{12}H_9BrO_3$: C, 32.68; H, 2.06. Found: C, 32.94; H, 2.12.

The second fraction yielded compound VI-25 (153 mg, 18%) as colorless plates. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O), 1680 ($COCH_2Br$). ^{1}H-NMR ($CDCl_3$) δ: 1.76 (4H, m, cyclopropane CH_2), 4.50 (2H, s, $COCH_2Br$), 7.35 (1H, d, J=9 Hz, 7-aromatic H), 8.40 (1H, dd, J=9 and 2 Hz, 6-aromatic H), 8.42 (1H, d, J=2 Hz, 4-aromatic H). From the third fraction, the starting material VI-17 (172 mg, 28%) was recovered.

Experiment 2: Pyrrolidinone hydrotribromide (5.0 g) and 2-pyrrolidinone (0.76 ml) were added to a solution of

VI-17 (2.0 g, 9.9 mmol) in THF (20 ml) at room temperature with stirring. After being stirred at room temperature for 84 h, the mixture was worked up in the usual manner to give VI-25 (2.1 g, 75%).

5-Acetyl-2-bromo-2-(2-bromoethyl)-3(2*H*)-benzofuranone (IX)——A mixture of VI-17 (10.0 g, 49 mmol), $CuBr_2$ (11.0 g) and $CaCO_3$ (5.0 g) in $CHCl_3$ (25 ml) and AcOEt (25 ml) was heated under reflux. During the reaction, additional $CuBr_2$ (3.0 g) and $CaCO_3$ (1.25 g) were added three times. After being heated under reflux for 5 h, the mixture was cooled and filtered to remove inorganic salts. The filtrate was diluted with $CHCl_3$, washed with water, dried and concentrated *in vacuo*. The resulting residue was recrystallized from acetone to give IX (8.7 g, 63%) as colorless plates, mp 104—110 °C. IR ν_{max}^{KBr} cm^{-1}: 1780 (C=O), 1670 ($COCH_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s, $COCH_3$), 2.9—3.2 (2H, m, CH_2CH_2Br), 3.4—3.9 (2H, m, CH_2CH_2Br), 7.30 (1H, d, J=9 Hz, 7-aromatic H), 8.4—8.6 (2H, m, 4- and 6-aromatic H). *Anal.* Calcd for $C_{12}H_{10}Br_2O_3$: C, 39.81; H, 2.78. Found: C, 40.10; H, 2.72.

3-Oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carboxylic Acid (VI-26)——Experiment 1: Compound VI-17 (13.5 g, 67 mmol) was added in portions to aqueous NaClO (300 ml) containing an interfacial activating agent (polyoxyethyleneoctylphenyl ether) at 60 °C with stirring. After being stirred at 60 °C for 3 h, the mixtur was cooled, diluted with water and 40% aqueous $NaHSO_3$ to decompose excess NaClO, and acidified with conc. HCl. The resulting precipitates were collected, washed with water, dried and recrystallized to give VI-26 (12.7 g) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3000—2500, 1710, 1690 (CO_2H), 1670 (C=O). ^{1}H-NMR ($CDCl_3+CD_3OD$) δ: 1.75 (4H, m, cyclopropane CH_2), 7.28 (1H, d, J=4 Hz, 7-aromatic H), 8.43 (1H, d, J=4 Hz, 6-aromatic H), 8.52 (1H, s, 4-aromatic H).

Experiment 2: A solution of VI-25 (0.843 g, 3.0 mmol) in CH_3CN (20 ml) was treated with Et_2NH (0.6 ml) at room temperature with stirring. After being stirred at room temperature for 3 h, the mixture was concentrated *in vacuo*. The resulting residue was diluted with AcOEt and extracted with aqueous Na_2CO_3. The aqueous layer was acidified with conc. HCl and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was recrystallized to give VI-26 (0.35 g, 57%).

Methyl 3-Oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carboxylate (VI-27)——Compound VI-27 was prepared from VI-26 by usual esterification using $(CH_3)_2SO_4$ and $NaHCO_3$ in acetone.

Ethyl 3-Oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carboxylate (VI-28)——Compound VI-28 was prepared from VI-26 by usual esterification using $(CH_3CH_2)_2SO_4$ and Na_2CO_3 in DMF.

Methyl 3-Oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-oxalate (VI-29)——A mixture of VI-17 (20.0 g, 99 mmol) and SeO_2 (20.0 g) in dioxane (200 ml) containing H_2O (20 ml) was heated under reflux for 24 h, then cooled. The insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (300 ml), then KCN (1.0 g) and active MnO_2 (30.0 g) were added in portions at room temperature with stirring. After being stirred at room temperature for 30 min, the mixture was filtered to remove inorganic salts. The filtrate was concentrated *in vacuo*, diluted with water and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel with hexane–AcOEt (3:1, v/v) to give VI-29 (13 g) as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 1775, 1705, 1675.

Methyl 2-Hydroxy-2-{3-oxospiro[benzofuran-2(3*H*),1′-cyclopropan]}-5-acetate (VI-30)——A solution of VI-29 (6.0 g, 24 mmol) in THF (60 ml) was treated with $NaBH_4$ (300 mg) in small portions at −20——−30 °C with stirring. After stirring of the mixture at room temperature for 30 min, acetone was added at room temperature. Stirring was continued at room temperature for 30 min, then the mixture was concentrated *in vacuo*. The resulting residue was diluted with water, acidified with dil. HCl and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo* to give VI-30 (3.2 g) as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3350, 1740, 1690, 1620. ^{1}H-NMR ($CDCl_3+D_2O$) δ: 1.41—1.8 (4H, m, cyclopropane CH_2), 3.74 (3H, s, CO_2CH_3), 5.23 (1H, s, CHOH), 7.13 (1H, d, J=5 Hz, aromatic H), 7.6—7.8 (2H, m, aromatic H).

2-Hydroxy-2-{3-oxospiro[benzofuran-2(3*H*),1′-cyclopropan]}-5-acetic Acid (VI-31)——A mixture of VI-30 (3.2 g, 13 mmol) and $NaHCO_3$ (3.0 g) in H_2O (30 ml), MeOH (30 ml) and THF (60 ml) was heated at 60 °C for 20 h with stirring. The mixture was concentrated *in vacuo*, diluted with water and extracted with AcOEt. The aqueous layer was acidified with dil. HCl and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was recrystallized to give pure VI-31 (2.0 g) as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3460, 3200—2500, 1740, 1675, 1660, 1625. ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 1.3—1.8 (4H, m, cyclopropane CH_2), 5.17 (1H, s, CHOH), 7.13 (1H, d, J=6 Hz, 7-aromatic H), 7.80 (1H, d, J=6 Hz, 6-aromatic H), 7.82 (1H, s, 4-aromatic H).

5-Carbamoylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-32)——A mixture of 7% aqueous H_2O_2 (33 ml) and EtOH (22.2 ml) was added to a solution of VI-37 (1.1 g, 5.9 mmol) in EtOH (110 ml) at 0 °C with stirring. The mixture was made alkaline with aqueous NaOH, stirred at 60 °C for 30 min, cooled and acidified with 3 N HCl. The resulting precipitates were collected, washed with water and recrystallized to give VI-32 (0.973 g) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3430, 1700, 1640 ($CONH_2$), 1680 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.67 (4H, m, cyclopropane CH_2), 7.17 (1H, d, J=5 Hz, 7-aromatic H), 8.23 (1H, d, J=5 Hz, 6-aromatic H), 8.30 (1H, s, 4-aromatic H).

5-(2-Diethylaminoethylcarbamoyl)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-33) Oxalate——Isobutylchloroformate (0.75 g) was added to a solution of VI-26 (1.02 g, 5.0 mmol) and Et_3N (0.7 ml) in THF (30 ml) at −18——−15 °C with stirring. Stirring was continued at the same temperature for 30 min, then diethylaminoethyl-

amine (0.58 g) was added at −18——15 °C with stirring. After being stirred at room temperature for 30 min, the mixture was concentrated *in vacuo* to give crude VI-33 (free base). The free base of VI-33 was converted to the oxalate in a usual manner and recrystallized to give pure VI-33 oxalate (1.083 g) as colorless prisms. ^{1}H-NMR (D_2O) δ: 1.33 (6H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.68 (4H, m, cyclopropane CH_2), 3.63—4.17 (6H, m, N–CH_2), 3.70—4.06 (2H, m, $C\underline{H}_2NHCO$), 7.11 (1H, d, J=9 Hz, 7-aromatic H), 7.80 (1H, d, J=2 Hz, 4-aromatic H), 8.03 (1H, dd, J=9 and 2 Hz, 6-aromatic H).

5-(1-Ethyl-2-pyrrolidinyl)methylcarbamoylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-34) Oxalate——Compound VI-34 oxalate was prepared from VI-26 according to the above procedure for the synthesis of VI-33·oxalate except for the use of *N*-ethyl-2-aminomethylpyrrolidine instead of diethylaminoethylamine. Colorless prisms.

Ethyl *N*-[3-Oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carbonyl]glycinate (VI-35)——Oxalyl chloride (13.6 g) was added to a mixture of VI-26 (10.0 g, 49 mmol) and K_2CO_3 (69 g) in hexamethylphosphoric triamide (HMPA) (200 ml) at 0 °C with stirring. Stirring was continued at 0 °C for 30 min and at room temperarure for 30 min, then ethyl glycinate hydrochloride (25 g) was added at room temperature with stirring. After being stirred at room temperature for 1 h, the mixture was cooled to 0 °C and diluted with ice-H_2O. The resulting precipitates were collected, washed with water, dried and recrystallized to give VI-35 (13.5 g) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1730 (CO_2Et), 1705 (5-membered ketone), 1665 (5-CONH). ^{1}H-NMR (DMSO-d_6) δ: 1.25 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 1.4—2.0 (4H, m, cyclopropane CH_2), 4.05 (2H, d, J=7.2 Hz, $NHC\underline{H}_2CO_2Et$), 4.17 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.41 (1H, d, J=8.4 Hz, 7-aromatic H), 8.1—8.5 (2H, m, aromatic H), 9.15 (1H, t, J=7.2 Hz, $N\underline{H}CH_2CO_2Et$).

***N*-[3-Oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carbonyl]glycine (VI-36)**——A solution of $NaHCO_3$ (10.7 g) in H_2O (150 ml) was added to a solution of VI-35 (6.7 g, 23 mmol) in EtOH (50 ml) at 70 °C with stirring. After being stirred at 70 °C for 12 h, the mixture was concentrated *in vacuo*. The resulting residue was diluted with ice-H_2O and acidified with dil. HCl at 0 °C. The resulting precipitates were collected, washed with water, dried and recrystallized to give VI-36 (5.2 g) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3370 (amide), 2600—2300 (CO_2H), 1750, 1695 (C=O).

5-Cyanospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-37)——A solution of $NaNO_2$ (0.7 g) in H_2O (2 ml) was added to a solution of VI-45 (1.75 g, 10 mmol) in H_2O (20 ml) containing conc. HCl (2.5 ml) at 0 °C with stirring. Stirring was continued at 0 °C for 1 h, then toluene (10 ml) was added. The mixture was neutralized with $NaHCO_3$ at −40 °C with stirring. This diazonium solution was then added to a stirred mixture of aqueous CuCN [prepared from KCN (4.4 g) and CuCl (2.4 g) in H_2O (18 ml)] and AcOEt (20 ml) at room temperature. After being stirred at room temperature for 30 min and then at 70 °C for 30 min, the mixture was filtered to remove insoluble materials and the filtrate was extracted with AcOEt. The extract was washed successively with water, aqueous Na_2CO_3, water, 3 N HCl and water, then dried and concentrated *in vacuo*. The resulting residue was recrystallized to give VI-37 (1.4 g) as colorless prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (4H, m, cyclopropane CH_2), 7.30 (1H, d, J=9 Hz, 7-aromatic H), 7.85 (1H, dd, J=9 and 2 Hz, 6-aromatic H), 8.00 (1H, d, J=2 Hz, 4-aromatic H).

5-Aminomethylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-38) Oxalate——VI-37 (0.82 g, 4.4 mmol) was hydrogenated in a mixture of EtOH (40 ml) and 2 N NaOH (40 ml) in the presence of Raney-Ni (wet, 1 g) under atmospheric pressure of H_2 gas at room temperature with stirring. After the uptake of H_2 gas had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in ether and extracted with 3 N HCl. The aqueous layer was made alkaline with aqueous NaOH and extracted with $CHCl_3$. The extract was washed with water, dried and concentrated *in vacuo* to give the free base of VI-38. The free base of VI-38 was converted to the oxalate in a usual manner to give pure VI-38·oxalate (0.45 g) as pale brown crystals. ^{1}H-NMR (D_2O) δ: 1.53 (2H, q, J=3 Hz, cyclopropane CH_2), 1.78 (2H, q, J=3 Hz, cyclopropane CH_2), 4.11 (2H, s, $C\underline{H}_2NH_2$), 7.11 (1H, d, J=9 Hz, 7-aromatic H), 7.53 (1H, s, 4-aromatic H), 7.60 (1H, d, J=9 Hz, 6-aromatic H).

5- and 7-Nitrospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones (VI-39 and VI-40) and 5,7-Dinitrospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-41)——Experiment 1: Compound VI-1 (213 g, 1.33 mol) was added in portions to fuming HNO_3 (d=1.52, 1 l) at −45——−40 °C with stirring. After the addition, the mixture was poured into ice-H_2O. The resulting precipitates were collected, washed with water and recrystallized to give VI-39 (242 g) as pale yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.87 (4H, m, cyclopropane CH_2), 7.20 (1H, d, J=9 Hz, 7-aromatic H), 8.42 (1H, d, J=9 Hz, 6-aromatic H), 8.52 (1H, s, 4-aromatic H).

Compound VI-41 was obtained from the mother liquor as pale yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.88 (2H, m, cyclopropane CH_2), 2.07 (2H, m, cyclopropane CH_2), 8.89 (1H, d, J=2 Hz, aromatic H), 9.13 (1H, d, J=2 Hz, aromatic H).

Experiment 2: $Cu(NO_3)_2$ (5.6 g) was added in small portions to a solution of VI-1 (0.94 g, 5.9 mmol) in Ac_2O (30 ml) at 60—70 °C with stirring. After being stirred at 60—70 °C overnight, the mixture was cooled and poured into ice-H_2O, then extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel with $CHCl_3$. Compound VI-39 (0.17 g 14%) was obtained from the first fraction. The crystals obtained from the second fraction were recrystallized to give pure VI-40 (24 mg, 2%) as colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 1.68—2.04 (4H, m, cyclopropane CH_2), 7.28 (1H, t, J=8 Hz, 5-aromatic H), 8.04 (1H, dd, J=8 and 1.5 Hz, aromatic H), 8.42 (1H, dd, J=8 and 1.5 Hz, aromatic H).

6-Methoxy-5,7-dinitrospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-42)——Compound VI-42 was prepared

from VI-7 according to the aforementioned procedure (experiment 1) for the synthesis of VI-40. Pale yellow needles. ^{1}H-NMR (CD_3OD) δ: 1.69 (2H, q, J=3 Hz, cyclopropane CH_2), 1.93 (2H, q, J=3 Hz, cyclopropane CH_2), 4.10 (3H, s, OCH_3), 8.51 (1H, s, aromatic H).

6-Methoxy-5-nitrospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-43)——Fuming HNO_3 (d=1.52, 3 ml) was added dropwise to a solution of VI-7 (5.4 g, 25 mmol) in Ac_2O (25 ml) and AcOH (7 ml) at 10—15 °C with stirring. After being stirred at 10—15 °C for 30 min, the mixture was poured into ice-H_2O. The resulting precipitates were collected, washed with water and recrystallized to give VI-43 (4.5 g) as pale yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.80 (4H, m, cyclopropane CH_2), 4.03 (3H, s, OCH_3), 6.75 (1H, s, aromatic H), 8.25 (1H, s, aromatic H).

5-Aminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-45)——Compound VI-39 (20.6 g, 0.10 mol) was hydrogenated in EtOH (1 l) in the presence of Raney Ni (wet, 10 g) under atmospheric pressure of H_2 gas at room temperature with stirring. After the uptake of H_2 gas had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was recrystallized to give VI-45 (4.2 g) as yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.68 (4H, m, cyclopropane CH_2), 3.60 (2H, br, NH_2), 6.98 (3H, s, aromatic H).

Compound VI-45 was converted to the HCl salt in a usual manner and recrystallized to give VI-45·HCl as pale yellow crystals.

6-Aminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-46)——A mixture of VI-67 (1.09 g, 5.0 mmol) and KOH (0.8 g) in MeOH (50 ml) was heated under reflux for 1 h. After cooling, the mixture was concentrated *in vacuo* and the residue was triturated with water. The resulting precipitates were collected, washed with water and recrystallized to give VI-46 (0.6 g) as colorless prisms.

7-Aminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-47)——Compound VI-40 (8.8 g, 43 mmol) was hydrogenated in EtOH (800 ml) in the presence of PtO_2 (0.8 g) under atmospheric pressure of H_2 gas at room temperature with stirring. After the uptake of H_2 gas had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was recrystallized to give VI-47 (5.6 g) as pale yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (4H, m, cyclopropane CH_2), 3.80 (2H, br, NH_2), 6.72—7.20 (3H, m, aromatic H).

5,7-Diamino-, 5-Amino-6-methoxy and 5-Amino-7-methylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones (VI-48, VI-49 and VI-50)——These compounds were prepared from the corresponding nitro compounds (VI-41, VI-43 and VI-44, respectively) according to the above procedure for the synthesis of VI-47.

5-Methylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-51) Hydrochloride——Carbobenzyloxychloride (30% in toluene, 7.0 g) was added to a solution of VI-45 (1.35 g, 7.7 mmol) in pyridine (13.5 ml) at 0 °C with stirring. After the addition, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was recrystallized from EtOH to give 5-benzyloxycarbonylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (1.57 g, 66%) as pale yellow needles, mp 118—119 °C. This product (1.57 g) was dissolved in acetone (39 ml), then KOH (0.57 g) and CH_3I (1.0 ml) were added at room temperature with stirring. After being stirred at room temperature for 4 h, the mixture was concentrated *in vacuo*. The resulting residue was diluted with water and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel to give 5-(*N*-benzyloxycarbonyl-*N*-methylamino)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-66) (1.44 g, 88%) as colorless needles. This compound (1.44 g) was hydrogenated in MeOH in the presence of 5% Pd–C under atmospheric pressure of H_2 gas at room temperature with stirring. After the uptake of H_2 gas had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo* to give the crude free base of VI-51 as a colorless oil. This free base of VI-51 was converted to the HCl salt in a usual manner and recrystallized to give VI-51·HCl (0.53 g) as yellow needles.

5-Ethylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-52) and 5-Diethylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-56)——Experiment 1: A mixture of VI-45 (10.0 g, 57 mmol), 90% CH_3CHO (20 ml) and Me_3N·HCl (5.0 g) in EtOH (500 ml) was hydrogenated over Raney-Ni (wet, 10 g) under 5 kg/cm^2 of H_2 gas at 40 °C for 6 h with stirring. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with aqueous Na_2CO_3 and then water, dried and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel to give the crude free base of VI-56 (8 g, 61%) as a yellow oil. This free base of VI-56 was converted to the oxalate in a usual manner to give VI-56·oxalate as pale yellow needles.

Experiment 2: A mixture of VI-45 (1.75 g, 10 mmol) and 90% CH_3CHO (3 ml) in MeOH (105 ml) was hydrogenated over PtO_2 (175 mg) under atmospheric pressure of H_2 gas at room temperature with stirring. After the uptake of H_2 gas had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel. The free base of VI-56 was obtained as an oil from the first fraction. This free base of VI-56 was converted to the HCl salt in a usual manner to give VI-56·HCl (0.86 g, 32%) as colorless needles.

The cystals obtained from the second fraction were recrystallized to give VI-52 (0.13 g, 6.4%) as yellow prisms.

5-Isopropylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-53)——$NaBH_3CN$ (3.0 g) was added in small portions to a solution of VI-45 (2.0 g, 11 mmol) in CH_3CN (100 ml) containing acetone (5 ml) at room temperature with stirring. During the reaction, AcOH was added occasionally to keep the mixture neutral. After

being stirred at room temperature for 38 h, the mixtue was concentrated *in vacuo* and the resulting residue was dissolved in ether. The ether solution was washed with water, aqueous NaOH and then water, dried and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel and the crystals obtained were recrystallized to give VI-53 (1.3 g) as yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (6H, d, J=6 Hz, $CHC\underline{H}_3$), 1.62 (4H, m, cyclopropane CH_2), 3.60 (1H, m, $C\underline{H}CH_3$), 6.93 (2H, dd, J=9 and 2 Hz, 6- and 7-aromatic H), 7.0 (1H, d, J= 2 Hz, 4-aromatic H).

5-(β-Hydroxyethyl)aminospiro[benzofuran-2-(3*H*),1′-cyclopropan]3-one (VI-54) and 5-Bis(β-hydroxyethyl)-aminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-61)——A solution of VI-45 (10.0 g, 57 mmol) and ethylene oxide (10 ml) in MeOH (150 ml) was heated at 70 °C for 16 h in a sealed tube. After being cooled, the mixture was concentrated *in vacuo*. The resulting residue was recrystallized to give VI-61 (12.9 g) as yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (4H, m, cyclopropane CH_2), 3.52 (4H, t, J=5 Hz, NCH_2), 3.82 (4H, t, J=5 Hz, $C\underline{H}_2OH$), 6.8—7.2 (3H, m, aromatic H).

The mother liquor was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel. The crystals obtained were recrystallized to give VI-54 (1.6 g, 13%) as yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (4H, m, cyclopropane CH_2), 3.20 (2H, t, J=5 Hz, $NHC\underline{H}_2$), 3.82 (2H, t, J=5 Hz, $C\underline{H}_2OH$), 6.87 (2H, dd, J=9 and 2 Hz, 6- and 7-aromatic H).

7-(β-Hydroxyethyl)aminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-62) and 7-Bis(β-hydroxyethyl)-aminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-63)——These compounds were prepared from VI-47 according to the aforementioned procedure for the synthesis of VI-54 and VI-61.

5-Dimethylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-55)——A mixture of VI-39 (150 g, 0.73 mol), $Me_3N \cdot HCl$ (30 g) and 35% HCHO (300 ml) in EtOH (1 l) was hydrogenated over Raney Ni (wet, 150 g) under 50 kg/cm^2 of H_2 gas at 60 °C with stirring. After the uptake of H_2 gas had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with aqueous Na_2CO_3 and then water, dried and concentrated *in vacuo*. The resulting residue was recrystallized to give the free base of VI-55 (122 g) as green-yellow prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (2H, q, J=2 Hz, cyclopropane CH_2), 1.63 (2H, q, J=2 Hz, cyclopropane CH_2), 2.94 (6H, s, CH_3), 6.96 (1H, d, J=2 Hz, 7-aromatic H), 7.08 (1H, s, 4-aromatic H), 7.13 (1H, d, J=2 Hz, 6-aromatic H).

This free base of VI-55 was converted to the HCl salt in a usual manner and recrystallized to give VI-55 · HCl as colorless needles.

5-(1-Pyrrolidinyl)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-57)——A mixture of VI-45 (3.0 g, 17 mmol), 1,4-dibromobutane (3.7 g) and $NaHCO_3$ (2.89 g) in DMF (150 ml) was heated under reflux for 1 h. After being cooled, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel and the crystals obtained were recrystallized to give the free base of VI-57 (1.74 g) as yellow needles.

The free base of VI-57 was converted to the HCl salt in a usual manner and recrystallized to give VI-57 · HCl as colorless crystals.

5-Morpholinospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-58) Hydrochloride——Compound VI-58 · HCl was prepared from VI-45 according to the aforementioned procedure for the synthesis of VI-57 · HCl except for the use of bis(2-iodoethyl)ether instead of 1,4-dibromobutane. Pale brown needles.

5-(4-Benzyl-1-piperadinyl)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-59)——Compound VI-59 was prepared from VI-45 according to the aforementioned procedure for the synthesis of VI-57 except for the use of *N*-benzyl-β,β-diiododiethylamine instead of 1,4-dibromobutane. Yellow needles.

5-(4-Ethyl-1-piperadinyl)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-60) Oxalate——Compound VI-60 · oxalate was prepared from VI-45 according to the aforementioned procedure for the synthesis of VI-57 except for the use of *N*-ethyl-β,β-diiododiethylamine instead of 1,4-dibromobutane. Yellow needles.

5-Acetylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-64)——Compound VI-64 was prepared by acetylation of VI-45 using Ac_2O and AcOH. Yellow prisms.

5-Methylsulfonylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-65)——CH_3SO_2Cl (0.28 ml) was added to a solution of VI-45 (0.519 g, 3.0 mmol) in pyridine (5 ml) at 0 °C with stirring. After the addition, the mixture was poured into ice-H_2O containing HCl and extracted with AcOEt. The extract was washed with water, dried and concentrared *in vacuo*. The resulting residue was recrystallized to give VI-65 (0.38 g) as colorless needles.

5-Ureidospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-68)——A solution of sodium cyanate (130 mg) in H_2O (2 ml) was added to a solution of VI-45 (1.75 g, 10 mmol) in MeOH (10 ml) and AcOH (5 ml) at room temperature with stirring. After being stirred at room temperature for 1 h, the mixture was poured into ice-H_2O. The resulting precipitates were collected, washed with water and recrystallized to give VI-68 (0.74 g) as colorless needles. ^{1}H-NMR (DMSO-d_6) δ: 1.47 (2H, m, cyclopropane CH_2), 1.73 (2H, m, cyclopropane CH_2), 2.53 (1H, br, NH), 5.93 (2H, br, NH_2), 7.30 (1H, d, J=9 Hz, 7-aromatic H), 7.70 (1H, dd, J=9 and 2 Hz, 6-aromatic H), 7.95 (1H, d, J=2 Hz, 4-aromatic H).

5-Methylureidospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-69)——A solution of VI-45 (1.75 g, 10 mmol) and methyl isocyanate (1 ml) in THF (20 ml) was stirred at room temperature for 2 h. The mixture was concentrated

in vacuo and the resulting residue was recrystallized to give VI-69 (1.06 g) as yellow prisms. ^{1}H-NMR (DMSO-d_6) δ: 1.50 (2H, q, J=3 Hz, cyclopropane CH_2), 1.67 (2H, q, J=3 Hz, cyclopropane CH_2), 2.77 (3H, d, J=4 Hz, $NHCH_3$), 5.93 (1H, br, NH), 7.13 (1H, d, J=9 Hz, 7-aromatic H), 7.70 (1H, dd, J=9 and 2 Hz, 6-aromatic H), 7.87 (1H, d, J=2 Hz, 4-aromatic H), 8.60 (1H, br, NH).

5-Methylthioureidospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-70)——A solution of VI-45 (1.75 g, 10 mmol) and methyl isothiocyanate (1.1 g) in CH_3CN (60 ml) was stirred at room temperature for 15 h and then heated under reflux for 3 h. The mixture was concentrated *in vacuo* and the resulting residue was recrystallized to give VI-70 (1.62 g) as yellow prisms. ^{1}H-NMR (DMSO-d_6) δ: 1.50 (2H, q, J=3 Hz, cyclopropane CH_2), 1.70 (2H, q, J=3 Hz, cyclopropane CH_2), 3.00 (3H, d, J=5 Hz, CH_3), 7.10 (1H, d, J=10 Hz, 7-aromatic H), 7.5—7.7 (2H, m, 4- and 6-aromatic H).

5-Guanidinospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-71) Hydrochloride——NH_2CN (2.6 g) was added in small portions to a solution of VI-45 (1.75 g, 10 mmol) in EtOH (30 ml) containing 3.3 N HCl (4 ml) at room temperature with stirring. After being stirred at 50 °C for 60 h, the mixture was concentrated *in vacuo*. The resulting residue was recrystallized to give VI-71·HCl (0.661 g) as pale yellow plates. IR ν_{max}^{KBr} cm^{-1}: 3300, 1660, 1630 [NHC(=NH)NH_2], 1680 (C=O). ^{1}H-NMR (D_2O) δ: 1.6 (2H, q, J=3 Hz, cyclopropane CH_2), 1.86 (2H, q, J=3 Hz, cyclopropane CH_2), 7.20 (1H, d, J=9 Hz, 7-aromatic H), 7.46 (1H, s, 4-aromatic H), 7.53 (1H, d, J=9 Hz, 6-aromatic H).

5-Amino-4-bromospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-72)——A mixture of VI-45 (0.747 g, 4.3 mmol) and $CaCO_3$ (0.47 g) in CCl_4 (20 ml) and CH_2Cl_2 (5 ml) was treated dropwise with Br_2 (0.22 ml) at −17 °C with stirring. After being stirred at −17 °C for 45 min, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was recrystallized to give VI-72 (0.6 g) as yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (4H, m, cyclopropane CH_2), 3.94 (2H, br, NH_2), 6.90 (1H, d, J=9 Hz, 7-aromatic H), 7.09 (1H, d, J=9 Hz, 6-aromatic H).

4-Bromo-5-dimethylaminospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-73)——Compound VI-73 was prepared from VI-55 according to the aforementioned procedure for the synthesis of VI-72. Pale yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (4H, m, cyclopropane CH_2), 2.78 (6H, s, NCH_3), 7.04 (1H, d, J=9 Hz, 7-aromatic H), 7.42 (1H, d, J=9 Hz, 6-aromatic H).

6-Amino-5-chlorospiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (VI-74)——Compound VI-74 was prepared by alkaline hydrolysis of VI-75. Yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (4H, m, cyclopropane CH_2), 4.82 (2H, br, NH_2), 6.40 (1H, s, 7-aromatic H), 7.61 (1H, s, 4-aromatic H).

Gastric Secretion in Pylorus-Ligated Rats——Rats, 7 weeks old, were divided into groups of five animals each and fasted for 24 h with free access to water before the experiment. The animals were anesthetized with ether and the pylorus was ligated by the method of Shay *et al.*[6] Fifty mg/kg of a drug suspended in 5% gum arabic solution was given intraduodentally immediately after ligation of the pylorus in a volume of 2 ml/kg of body weight. Three hours later, the animals were given an overdose of ether. The gastric contents were centrifuged at 3000 rpm for 10 min, after which the volume of gastric juice was measured and the acidity was determined by titration with 0.1 N NaOH to pH 7.0 using an autoburette (Radiometer, Copenhagen).

Water-Immersion Stress Ulcer——Water-immersion stress ulcer was induced according to the method of Takagi and Okabe.[7] Groups of five rats were given a drug (50 mg/kg of drug suspended in 5% gum arabic solution) orally 30 min before being placed in a stress cage and immersed vertically to the level of the xiphoid process in a water bath maintained at 23 °C. Five hours later, each animal was taken out of the cage and injected with 1 ml of a 0.5% Evans' blue solution (dissolved in saline) into the tail vein to enhance the contrast of the mucosal lesions. Ten min later, the animals were sacrificed by ether overdose. The stomach was removed and examined for lesions.

Statistical Analysis——Statistical significance of differences between control and experimental groups was calculated by means of Student's t-test, and a p value of <0.05 was considered to be significant.

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