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Spirocyclopropane Compounds. IV.[1] Synthesis of 5-Acetylspiro-[benzofuran-2(3*H*),1′-cyclopropan]-3-one Related Compounds for Evaluation as Gastric Antisecretory and Antiulcer Agents

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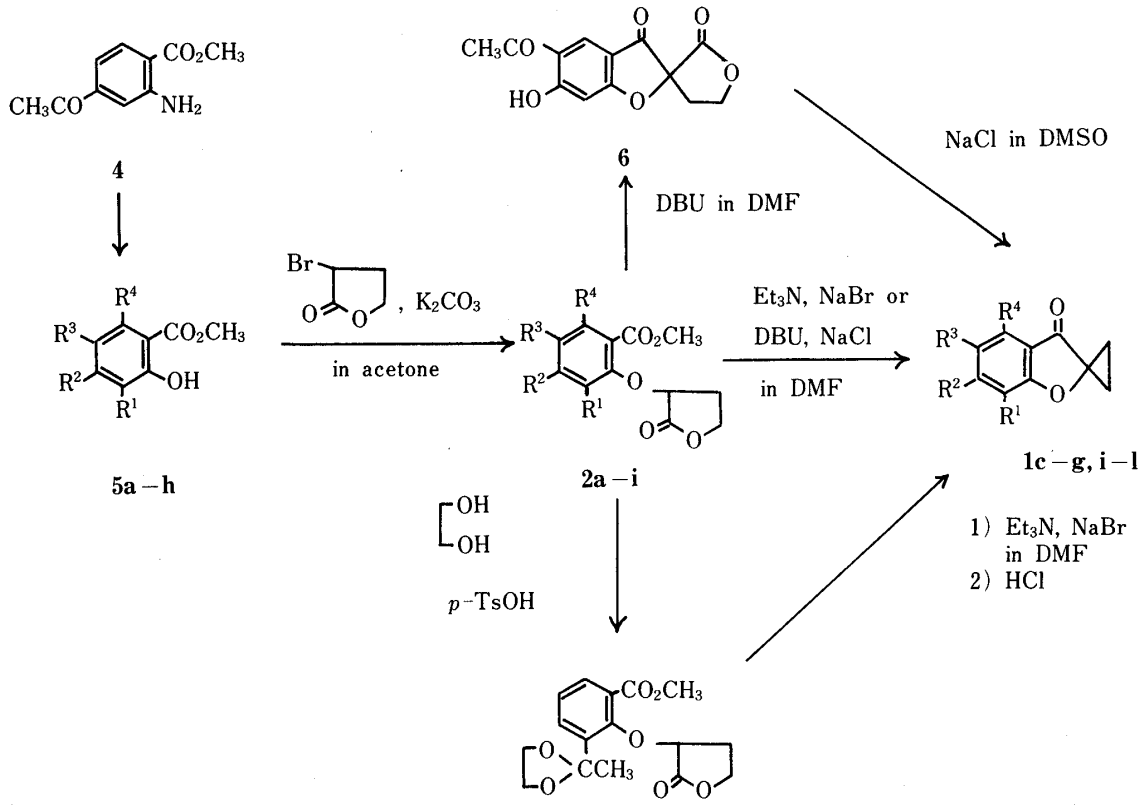
5-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (**1a**) shows potent gastric antisecretory and antiulcer activities in rats. In an attempt to improve the pharmacological profile of **1a**, we synthesized positional isomers, as well as the prenyloxy and oxime derivatives. Evaluation of their antisecretory activities and protective activities against gastric lesions induced by water-immersion restraint stress in the rat indicated that the 7-acetyl derivative (**1d**) was equipotent to **1a**.

Keywords——spirocyclopropane compound; prenyloxy derivative; oxime derivative; antisecretory activity; antiulcer activity

We have reported that 5-acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (**1a**) shows prominent prophylactic and curative effects on various experimental ulcers in animals,[2] and **1a** appears to be an antiulcer agent of a new structural type. Other compounds which have been reported to show antiulcer activities include gefarnate,[3] its analog,[4] ubiquinone[5] and isoprenyl chalcone,[6] and the isoprenyl group appears to exert a mucus-protecting activity. The antisecretory activity of chromone oxime derivatives is described in a U.S. patent.[7] On the basis of these reports, we modified the structure of **1a** in an attempt to improve its pharmacological profile. Here we describe the preparation of positional isomers, as well as prenyloxy and oxime derivatives of **1a**, and the determination of their antisecretory and antiulcer activities.

The positional isomers of **1a** and related compounds were prepared in a manner similar to that described in the following report[8] (Chart 1). The synthesis of **1d** by spiroannelation and subsequent decarboxylation of **2d** gave only a low yield. The ethyleneacetal derivative (**3**), in which the acetyl group was protected, gave a good yield of **1d**. Methyl 4-acetyl salicylate (**5c**) was prepared by diazotization and subsequent hydrolysis of **4**. Friedel–Crafts reaction of **2h** with acetic anhydride using boron trifluoride produced the 5-acetyl-6-hydroxy derivative (**2i**) accompanied by debenzylation (Table I). One-step synthesis of **1i** from **2i** gave a very low yield. Alternatively, the spirolactone (**6**) obtained by Dieckmann condensation of **2i** with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) was decarboxylated and afforded **1i** in good overall yield. The hydroxy derivatives (**1f** and **1i**) were isoprenylated with isoprenyl bromide, giving the 4-prenyloxy (**1j**) and 6-prenyloxy compounds (**1k** and **1l**), respectively (Table II).

The 7-acetyl derivative (**1d**) was converted into **7** and **8** by a method similar to one described in a previous report.[1] Sodium borohydride reduction of **1b** afforded **9**. Compound **9** is unstable to acid and is easily isomerized to **10**. The diastereoisomeric mixture (**11a, b**) was obtained by reduction of **1a**. Stereochemical assignment of **11a, b** was not attempted.



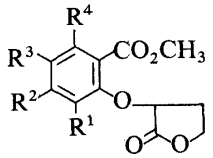
a: $R^1=R^2=R^4=H$, $R^3=COCH_3$
b: $R^1=R^2=R^3=R^4=H$
c: $R^1=R^3=R^4=H$, $R^2=COCH_3$
d: $R^1=COCH_3$, $R^2=R^3=R^4=H$
e: $R^1=COCH_3$, $R^2=R^4=H$, $R^3=CH_3$
f: $R^1=R^2=H$, $R^3=COCH_3$, $R^4=OH$
g: $R^1=R^3=R^4=H$, $R^2=OCH_2CH=C(CH_3)_2$
h: $R^1=R^3=R^4=H$, $R^2=OCH_2Ph$
i: $R^1=R^4=H$, $R^2=OH$, $R^3=COCH_3$
j: $R^1=R^2=H$, $R^3=COCH_3$, $R^4=OCH_2CH=C(CH_3)_2$
k: $R^1=R^4=H$, $R^2=OCH_2CH=C(CH_3)_2$, $R^3=COCH_3$
l: $R^1=R^4=H$, $R^2=O(CH_2CH=C(CH_3)CH_2)_3H$, $R^3=COCH_3$

Chart 1

Compound **14** was synthesized by reduction of the ethyleneacetal derivative (**12**) followed by deprotection of **13** using aqueous tartaric acid. Hydrolysis of **13** with *p*-toluenesulfonic acid gave isomerized products (**15a**, **b**). The reduction of **16** and **17** with sodium borohydride afforded **19** and **20**, respectively. The glycinate derivative (**20**) was obtained by the hydrolysis of **19** with sodium hydrogen carbonate. (Chart 2).

The reaction of **1b** and **12** with hydroxylamine hydrochloride in pyridine afforded a mixture of *syn* and *anti* isomers, **21** and **22**, respectively. The oxime (**22**) was alkylated with dimethyl sulfate and subsequently hydrolyzed to give a mixture of *syn* and *anti* O-methyl oximes (**23a**, **b**). Assignment of the *syn* and *anti* isomers was based on the chemical shifts of the 4-aromatic proton and methylene protons of cyclopropane in the ^{1}H-NMR spectrum (Table III). In similar alkylation of **22**, only the *syn* isomers (**24** and **25**) were isolated. Reaction of the oxime (**21**) with isocyanates afforded **26** and **27**. Similarly, **30** and **31** were prepared from **28** and **29**, respectively, which had been obtained from the reaction of **22** with isocyanates (Table IV). All the products isolated were *syn* isomers (Chart 3).

TABLE I. Methyl 2-[(Tetrahydro-2-oxo-3-furanyl)oxy]benzoates



Compd. No.	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H
2c	H	$COCH_3$	H	H	88	114—115 (AcOEt–hexane)[a]	$C_{14}H_{14}O_6$	60.43 (60.30	5.07 5.00)
2d	$COCH_3$	H	H	H	85	Oil	$C_{14}H_{14}O_6$	60.43 (60.21	5.07 5.02)
2e	$COCH_3$	H	CH_3	H	77	105—107 (AcOEt–hexane)	$C_{15}H_{16}O_6$	61.64 (61.72	5.52 5.43)
2f	H	H	$COCH_3$	OH	42	128—131 (AcOEt–hexane)	$C_{14}H_{14}O_7$	57.14 (57.22	4.80 4.76)
2g	H	$OCH_2CH=C(CH_3)CH_3$	H	H	73	59—61 (Et_2O–hexane)	$C_{17}H_{20}O_6$	63.74 (63.56	6.29 6.28)
2h	H	OCH_2Ph	H	H	73	90—92 (AcOEt–hexane)	$C_{19}H_{18}O_6$	66.66 (66.74	5.30 5.25)
2i	H	OH	$COCH_3$	H	32	129—131 (AcOEt–Et_2O)	$C_{14}H_{14}O_7$	57.14 (57.05	4.80 4.75)
3		H	H	H	b)	87—89 (MeOH)	$C_{16}H_{18}O_7$	59.62 (59.49	5.63 5.51)

a) Recrystallization solvents.
b) The crude product was used for the next step without further purification. Small samples were recrystallized for elemental analysis.

Biological Results

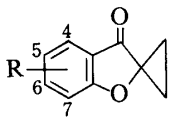
The biological results are listed in Tables V and VI. The compounds were evaluated for antisecretory and antiulcer activities using pylorus-ligated rats[9] and water-immersion restraint rats,[10] respectively. Most of the acetyl derivatives except **1i** and **1l** exhibited gastric antisecretory activity equal to or more potent than that of **1a** at the oral screening dose. Reduction of the carbonyl group of **1a** and **1b** to a hydroxy group (**14** and **9**) did not affect the activities. Prominent antisecretory activity was obtained with the oxime (**21**) and carbamoyl oximes (**26** and **27**) which have no substituent on the phenyl ring, although the oxime (**24**) and carbamoyl oximes (**30** and **31**) of the 5-acetyl derivative enhanced gastric secretion. The 7-acetyl derivative (**1d**) showed equal or greater potency as compared to **1a** for inhibition of ulcer formation in the water-immersion restraint rats. However, all other acetyl derivatives showed decreased antiulcer activity. No significant antiulcer activity was observed with oxime derivatives. Carbamoyl oximes (**26** and **31**) exhibited prominent antiulcer activity, but the corresponding **30** and **27** were inactive. In addition, all carbamoyl oximes were toxic and offered no advantage over **1a**.

In conclusion, the 7-acetyl derivative (**1d**) was found to be equipotent to **1a**.

Experimental

All melting points are uncorrected and were taken on a Yanagimoto micromelting point apparatus. Infrared (IR) spectra were taken on a Hitachi 260-10 infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra

TABLE II. Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones



Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)	
					C	H
1c	6-$COCH_3$	69	122—124 (AcOEt–hexane)[a]	$C_{12}H_{10}O_3$	71.28	4.99
					(71.23	4.91)
1d	7-$COCH_3$	9 (68)[b]	114—116 (EtOH)	$C_{12}H_{10}O_3$	71.28	4.99
					(71.39	4.96)
1e	5-CH_3, 7-$COCH_3$	11	90—92 (MeOH)	$C_{13}H_{12}O_3$	72.21	5.59
					(72.18	5.46)
1f	4-OH, 5-$COCH_3$	60	209—211 (AcOEt)	$C_{12}H_{10}O_4$	66.05	4.62
					(66.18	4.37)
1g	6-$OCH_2CH{=}C(CH_3)CH_3$	43	90—92 (Hexane)	$C_{15}H_{10}O_4$	73.75	6.60
					(73.65	6.59)
1i	5-$COCH_3$, 6-OH	15 (41)	161—162 (MeOH)	$C_{12}H_{10}O_4$	66.05	4.62
					(65.94	4.74)
1j	4-$OCH_2CH{=}C(CH_3)CH_3$, 5-$COCH_3$	72	72—73 (MeOH)	$C_{17}H_{18}O_4$	71.31	6.34
					(71.36	6.27)
1k	5-$COCH_3$, 6-$OCH_2CH{=}C(CH_3)CH_3$	78	137—139 (EtOH)	$C_{17}H_{18}O_4$	71.31	6.34
					(71.56	6.42)
1l	5-$COCH_3$, 6-$O(CH_2{=}C(CH_3)CH_2)_3H$	85	Oil	$C_{27}H_{34}O_4$	76.74	8.11
					(76.67	8.22)

a) Recrystallization solvents.
b) Yields reported in parentheses are the yields of **1d** and **1i** from **3** and **6**, respectively.

were obtained on Varian EM-360 60 MHz and XL-100A spectrometers with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm): s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet.

6-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (1c)——A solution of methyl 4-acetyl-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (**2c**) (3.8 g) in dimethylformamide (DMF) (38 ml) was added dropwise to a mixture of DBU (190 mg), NaBr (2.7 g) and DMF (38 ml) under stirring at 150 °C. Stirring was continued for 1 h, then the reaction mixture was poured into ice-H_2O. The aqueous solution was extracted with AcOEt. The extract was washed, dried and evaporated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ and the product was recrystallized to give **1c** (1.9 g) (Table II).

Compounds **1d**—**1g** and **1i** were similarly prepared and are included in Table II.

Methyl 3-Acetyl-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (2d)——A mixture of methyl 3-acetylsalicylate (**5d**) (16.5 g, 85.0 mmol), α-bromo-γ-butyrolactone (28 g) and K_2CO_3 (35.2 g) in acetone (200 ml) was refluxed with stirring for 11 h. A precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt and the solution was washed, dried and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ to afford **2d** (20.2 g). ^{1}H-NMR ($CDCl_3$): 2.57 (3H, s, $COCH_3$), 2.35—2.80 (2H, m, CH_2), 3.87 (3H, s, CO_2CH_3), 4.37 (2H, q, J=7 Hz, OCH_2), 4.72 (2H, t, J=7 Hz, CHCO), 7.15 (1H, t, J=7 Hz, 5-aromat. H), 7.65 (1H, dd, J=2 and 7 Hz, 4- or 6-aromat. H), 7.88 (1H, dd, J=2 and 7 Hz, 4- or 6-aromat. H) (Table I).

Compounds **2c**, **2e**, **2f**, **2g** and **2h** were similarly prepared and are included in Table I.

Methyl 5-Acetyl-4-hydroxy-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (2i)——BF_3 gas was bubbled into a solution of **2h** (6.8 g, 19.9 mmol) in Ac_2O (10 ml) and the solution was stirred at 60 °C for 0.5 h. The reaction mixture was diluted with ice-H_2O and extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The residue was crystallized to give **2i**. IR ν_{max}^{KBr} cm^{-1}: 1770 (γ-lactone), 1720 (CO_2CH_3), 1630 ($COCH_3$). ^{1}H-NMR ($CDCl_3$): 2.62 (3H, s, $COCH_3$), 2.6—3.0 (2H, m, CH_2), 3.88 (3H, s, CO_2CH_3), 4.2—4.8 (2H, m, CH_2O), 5.13 (1H, t, J=7 Hz, CHCO), 6.73 (1H, s, 6-aromat. H), 8.43 (1H, s, 3-aromat. H) (Table I).

5-Acetyl-6-hydroxy-4′,5′-dihydrospiro[benzofuran-2(3*H*),3′(2′*H*)-furan]-2′,3-dione (6)——A solution of **2i** (4.8 g,

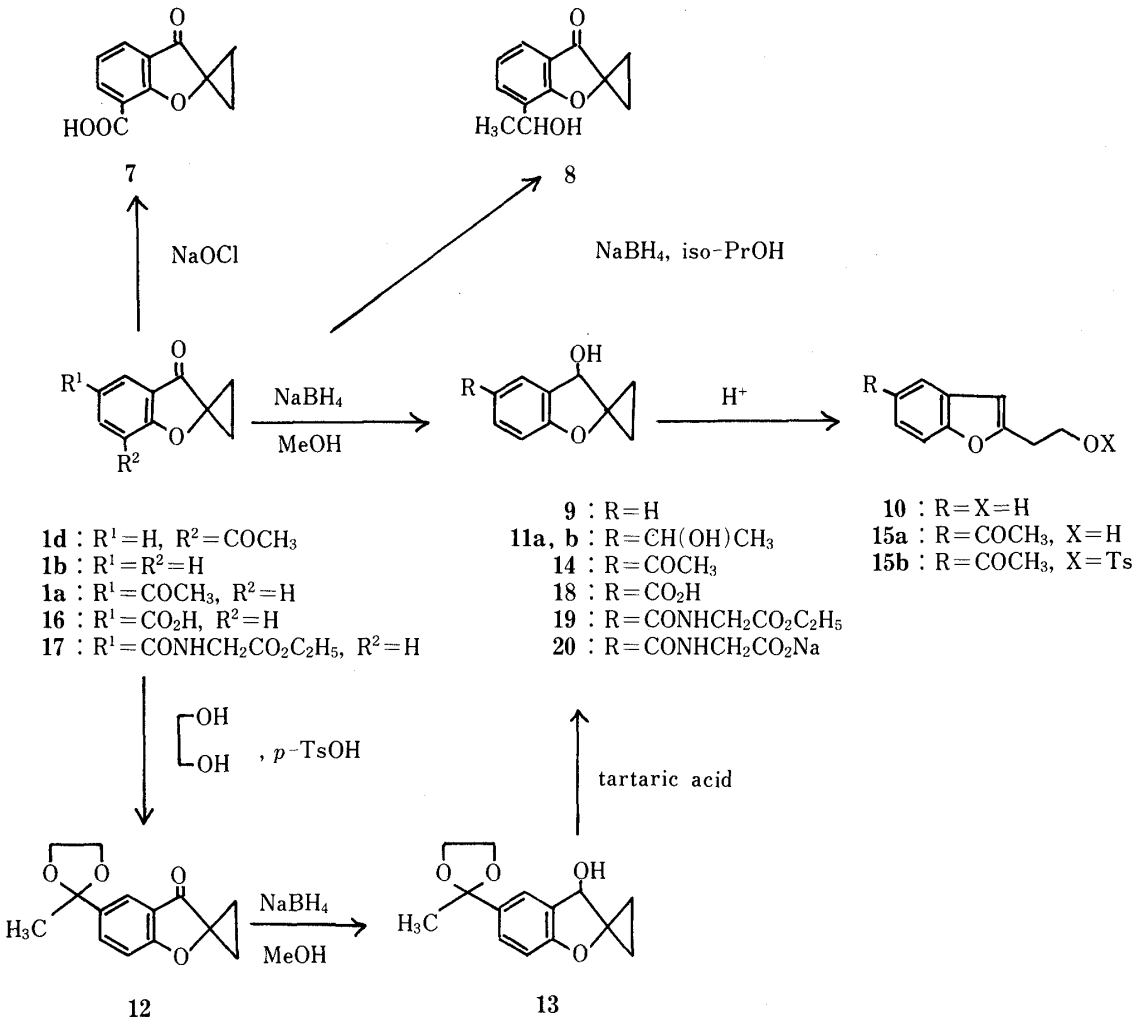


Chart 2

16.3 mmol) in DMF (30 ml) was added to a solution of DBU (2.5 g) in DMF (25 ml) at 130 °C. The reaction solution was stirred at the same temperature for 1 h and poured into ice-H_2O. The crystals that separated were recrystallized from AcOEt to afford **6** (3.6 g, 84%), mp 210—212 °C. *Anal.* Calcd for $C_{13}H_{10}O_6$: C, 59.54; H, 3.84. Found: C, 59.66; H, 3.79.

5-Acetyl-6-hydroxyspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (1i)——A mixture of **6** (3.5 g, 13.3 mmol), NaCl (0.9 g) and DMSO (15 ml) was heated at 150 °C for 1.5 h. After cooling, the reaction mixture was diluted with H_2O and extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel and recrystallized from EtOH to give **1i** (1.2 g) (Table II).

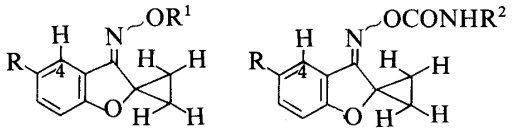
5-Acetyl-4-(3-methyl-2-butenyloxy)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (1j)——3-Methyl-2-butenyl-bromide (1.794 g) was added dropwise to a stirred mixture of **1f** (0.436 g, 2.0 mmol) and K_2CO_3 (1.3 g) in acetone (40 ml) at 50 °C. The whole was refluxed for 5.5 h, then the precipitates were filtered off and the filtrate was concentrated *in vacuo*. The residue was crystallized to afford **1j** (Table II).

Compounds **1k** and **1l** were prepared in a similar manner from **1i** and are included in Table II.

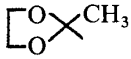
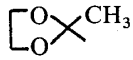
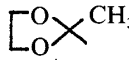
Methyl 4-Acetylsalicylate (5c)——A solution of $NaNO_2$ (6.7 g) in H_2O (62 ml) was added to a solution of methyl 4-acetyl-2-aminobenzoate (**4**)[11] (12.4 g, 64.2 mmol) in a mixture of AcOH (124 ml), conc. HCl (15.5 ml) and H_2O (62 ml) under cooling in an ice-bath. The mixture was stirred for 0.5 h, then urea (744 mg) was added to decompose the excess $NaNO_2$. The reaction solution was poured into 10% H_2SO_4 (200 ml), heated at 100 °C for 1 h, then cooled. The crystals that separated were recrystallized from MeOH to afford **5c** (7.6 g, 61%), mp 120—122 °C. *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.77; H, 5.21.

Methyl 3-(1-Ethylenedioxy)ethyl-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (3)——A mixture of ethylene glycol (71 ml) and *p*-TsOH (4.8 g) in benzene (500 ml) was refluxed under a Dean–Stark water separator. Then **2d** (48 g, 172.5 mmol) was added and the whole was refluxed for 6 h while the H_2O produced was removed. After cooling, the solution was washed with aq. $NaHCO_3$ and H_2O, and concentrated *in vacuo* to give crude **3**. The product was used for the next step without further purification. An analytical sample was recrystallized from MeOH to give colorless

TABLE III. ^{1}H-NMR Spectral Data for Oxime Derivatives of **1**



21—25 **26—31**

Compd. No.	R	R^1	R^2	δ (ppm)[a) 4-H	4-H
21 (*syn*)	H	H	—	8.18	1.42
21 (*anti*)				7.50	2.23
22 (*syn*)		H	—	8.53	1.30
22 (*anti*)				7.42	2.15
23a (*syn*)				8.55	1.28
23b (*anti*)	$COCH_3$	CH_3	—	8.15	2.10
24	$COCH_3$	$CH_2CH=C(CH_3)_2$	—	8.65	1.17
25	$COCH_3$	$CH_2CH_2N(C_2H_5)_2HCl$	—	8.52	1.23
26	H	—	CH_3	8.47	1.42
27	H	—	$CH_2CH=CH_2$	8.25	1.33
28		—	CH_3	8.25	1.33
29		—	$CH_2CH=CH_2$	8.28	1.33
30	$COCH_3$	—	CH_3	8.73	1.42
31	$COCH_3$	—	$CH_2CH=CH_2$	8.77	1.40

a) Measured at 60 MHz with TMS as an internal standard in $CDCl_3$.

needles (Table I).

3-Oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-7-carboxylic Acid (7)——Compound **1d** (1.4 g, 6.9 mmol) was added portionwise to a well stirred solution of aq. NaOCl (40 ml) containing a small amount of detergent (OP-10) at 60 °C. After being stirred for 2 h, the reaction solution was diluted with ice-H_2O and the excess NaOCl was decomposed with aq. $NaHSO_3$. The crystals that separated were recrystallized from EtOH to afford **7** (0.97 g, 68%), mp 259—262 °C (dec.). *Anal.* Calcd for $C_{11}H_8O_4$: C, 64.70; H, 3.95. Found: C, 64.53; H, 4.00.

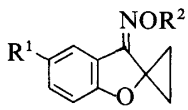
7-(1-Hydroxyethyl)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (8)——A stirred solution of **1d** (1 g, 4.9 mmol) in THF (20 ml) and iso-PrOH (3 ml) was treated with $NaBH_4$ (0.4 g) under cooling in an ice-bath. The mixture was stirred overnight at 5 °C, then acetone was added to decompose the excess $NaBH_4$. The solvents were removed *in vacuo* and the residue was diluted with H_2O and extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The residue was crystallized from Et_2O–hexane to afford **8** (0.7 g, 69%), mp 88—91 °C. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1700 (CO). ^{1}H-NMR ($CDCl_3$): 1.05—1.80 (4H, m, CH_2CH_2), 1.52 (3H, d, J=6 Hz, CH_3), 3.33 (1H, br, OH), 5.13 (1H, q, J=7 Hz, C<u>H</u>OH), 7.00 (1H, t, J=7 Hz, 5-aromat. H), 7.50 (1H, d, J=7 Hz, 4- or 6-aromat. H), 7.62 (1H, d, J=7 Hz, 4- or 6-aromat. H). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.59; H, 6.23.

Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ol (9)——$NaBH_4$ (1 g) was added portionwise to a stirred solution of **1b** (1.6 g, 10.0 mmol) in MeOH (30 ml) at room temperature. The mixture was stirred for 1 h, then the solvent was removed *in vacuo* and the residue was diluted with H_2O. The aqueous solution was extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The residue was crystallized from ligroin to afford **9** (1.49 g, 92%), mp 61—63 °C. *Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 73.97; H, 6.15.

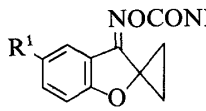
2-(2-Benzofuranyl)ethanol (**10**) was obtained as an oil from **9** by allowing an AcOH solution of **9** to stand at room temperature. IR ν_{max}^{neat} cm^{-1}: 3300 (OH). ^{1}H-NMR ($CDCl_3$): 2.87 (2H, t, J=6 Hz, CH_2), 3.80 (2H, t, J=6 Hz, C<u>H</u>$_2$OH), 6.32 (1H, s, CH). *Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 73.95; H, 6.30.

5-(1-Hydroxyethyl)spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ol (11a, b)——A solution of **1a** (2 g, 9.9 mmol) in THF (10 ml) and MeOH (50 ml) was reacted with $NaBH_4$ in the same manner as described for the synthesis of **9**, and the product was recrystallized from AcOEt to afford colorless needles of **11a**, mp 128—131 °C. ^{1}H-NMR ($CD_3OD+CDCl_3$): 0.60—1.32 (4H, m, CH_2CH_2), 1.45 (3H, d, J=6 Hz, CH_3), 4.78 (1H, q, J=6 Hz, CH_3C<u>H</u>OH),

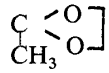
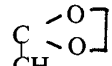
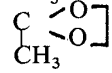
TABLE IV. Oxime Derivatives of **1**



21—25



26—31

Compd. No.	R^1	R^2	R^3	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
21	H	H	—	66	96—114[a] (EtOH)[b]	$C_{10}H_9NO_2$	68.50 (68.52)	5.18 4.99	8.00 7.93)
22		H	—	39	167—180[a] (EtOH)	$C_{14}H_{15}NO_4$	64.36 (64.37)	5.79 5.61	5.36 5.55)
23a	$COCH_3$	CH_3	—	53	56—57 ($CHCl_3$–hexane)	$C_{13}H_{13}NO_3$	67.52 (67.54)	5.67 5.61	6.06 6.07)
23b	$COCH_3$	CH_3	—	6[c]	96—100 (EtOH–hexane)	$C_{13}H_{13}NO_3$	67.52 (67.34)	5.67 5.70	6.06 6.35)
24	$COCH_3$	$CH_2CH=C(CH_3)$	—	81	Oil	$C_{17}H_{19}NO_3$	71.56 (71.82)	6.71 6.99	4.91 5.04)
25	$COCH_3$	$CH_2CH_2N(C_2H_5)_2$	—	38	152—154 (MeOH–hexane)	$C_{18}H_{24}N_2O_3$ HCl	61.27 (61.46)	7.14 7.08	7.94 8.21)
26	H	—	CH_3	61	161—163 (EtOH)	$C_{12}H_{12}N_2O_3$ HCl	62.06 (62.17)	5.21 5.11	12.06 11.97)
27	H	—	$CH_2CH=CH_2$	69	101—103 (EtOH)	$C_{14}H_{14}N_2O_3$	65.10 (65.17)	5.46 5.31	10.85 10.80)
28		—	CH_3	69	188—191 (AcOEt)	$C_{16}H_{18}N_2O_5$	60.37 (60.45)	5.70 5.47	8.80 8.67)
29		—	$CH_2CH=CH_2$	68	90—91.5 (Et_2O–hexane)	$C_{18}H_{20}N_2O_5$	62.78 (62.93)	5.85 5.96	8.14 8.09)
30	$COCH_3$	—	CH_3	73	166—169 (EtOH)	$C_{14}H_{14}N_2O_4$	61.31 (61.49)	5.15 4.87	10.21 10.49)
31	$COCH_3$	—	$CH_2CH=CH_2$	75	134—136 (AcOEt–hexane)	$C_{16}H_{16}N_2O_4$	63.99 (64.10)	5.37 5.35	9.33 9.43)

a) Mixture of *syn* and *anti* isomers.
b) Recrystallization solvents.
c) The *syn* isomer (**23b**) was isolated as a by-product.

4.90 (1H, s, CHOH), 6.67 (1H, d, $J=7$ Hz, 7-aromat. H), 7.10 (1H, dd, $J=2$ and 7 Hz, 6-aromat. H), 7.37 (1H, d, $J=2$ Hz, 4-aromat. H). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.11; H, 6.76. The mother liquor from recrystallization of **11a** was concentrated and the residue was crystallized from Et_2O to afford colorless crystals of **11b**, mp 106—110 °C. *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.22; H, 6.90.

5-(1-Ethylenedioxy)ethylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (12)——A solution of **1a** (1.2 g, 5.9 mmol), *p*-TsOH (1.2 g) and ethylene glycol (16 ml) in benzene (400 ml) was reacted in the manner described for the synthesis of **3**. The product was recrystallized from EtOH to afford **12** (9.23 g, 63%), mp 76—77 °C. IR ν_{max}^{KBr} cm^{-1}: 1700 (CO), 1020 (). ^{1}H-NMR ($CDCl_3$): 1.63 (4H, m, CH_2CH_2), 1.66 (3H, s, CH_3), 3.97 (4H, m, OCH_2CH_2O), 7.18 (1H, d, $J=8$ Hz, 7-aromat. H), 7.65 (1H, dd, $J=2$ and 8 Hz, 6-aromat. H), 7.92 (1H, d, $J=2$ Hz, 4-aromat. H). *Anal.* Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.15; H, 5.60.

5-(1-Ethylenedioxy)ethylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ol (13)——A stirred solution of **12** (3.7 g, 15.0 mmol) in MeOH (100 ml) was treated portionwise with $NaBH_4$ (1.7 g) at room temperature. The mixture was stirred for 1 h, then MeOH was removed *in vacuo* and the residue was diluted with H_2O. The aqueous solution was extracted with Et_2O. The extract was washed, dried and concentrated *in vacuo*. The residue was crystallized from Et_2O–ligroin to afford **13** (3.14 g, 85%), mp 65—69 °C. ^{1}H-NMR ($CDCl_3$): 1.23 (4H, m, CH_2), 1.65 (3H, s, CH_3), 3.97 (4H, m, OCH_2CH_2O), 5.03 (1H, s, CHOH), 6.90 (1H, d, $J=8$ Hz, 7-aromat. H), 7.50 (1H, dd, $J=2$ and 8 Hz, 6-aromat. H), 7.70 (1H, dd, $J=2$ and 8 Hz, 4-aromat. H). *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.94;

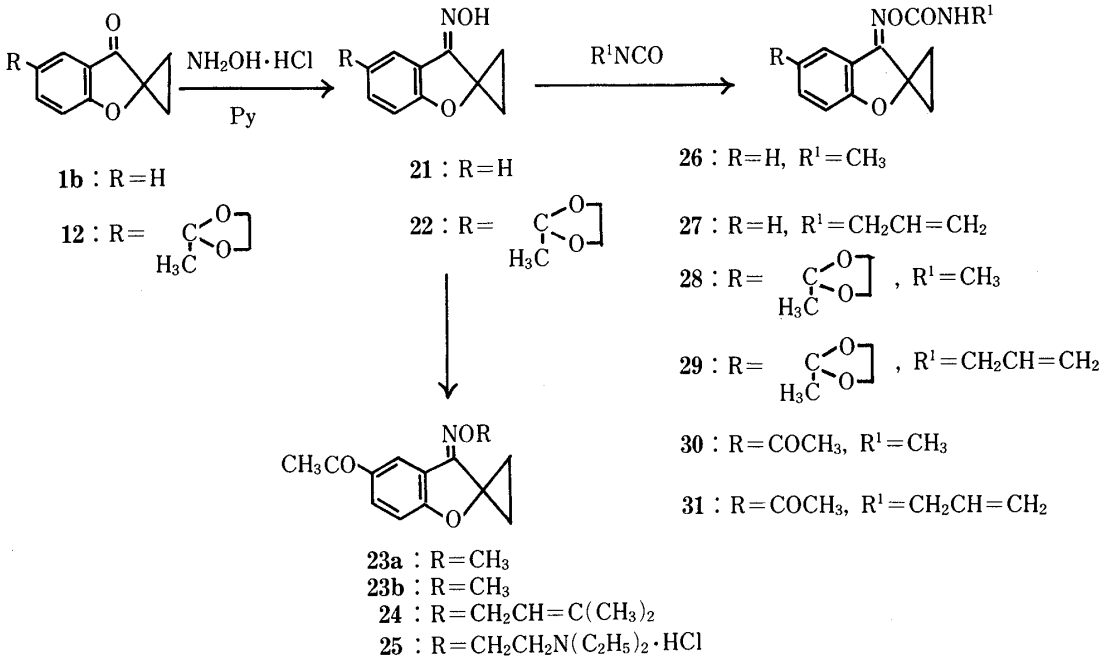
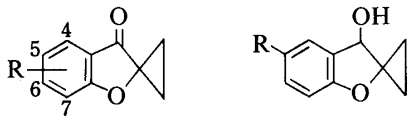


Chart 3

TABLE V. Antisecretory and Antiulcer Activities of Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ones and -3-ols

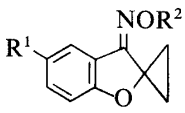


1 **9, 14**

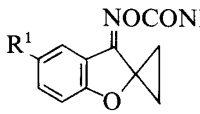
Compd. No.	R	Antisecretory activity[a]	Antiulcer activity[b]	Toxicity[c] (500 mg/kg, *i.p.*)
1a	5-$COCH_3$	42^{++}	66^{++}	0/5
1b	H	91^{++}	58	5/5
1c	6-$COCH_3$	41	9	—[d]
1d	7-$COCH_3$	67^{++}	81^{+}	0/5
1e	5-CH_3, 7-$COCH_3$	51	−41	—
1f	4-OH, 5-$COCH_3$	45^{+}	−3	0/5
1g	6-$OCH_2CH=C(CH_3)_2$	6	80^{+}	—
1i	5-$COCH_3$, 6-OH	9	44	0/5
1j	4-$OCH_2CH=C(CH_3)_2$, 5-$COCH_3$	50^{+}	−12	0/5
1k	5-$COCH_3$, 6-$OCH_2CH=C(CH_3)_2$	29^{+}	54	0/5
1l	5-$COCH_3$, 6-$O[CH_2CH=C(CH_3)CH_2]_3H$	15	56	0/5
9	H	83^{+}	48	1/5
14	5-$COCH_3$	36	36	0/5

a) % inhibition of gastric juice volume after administration of the compound at 50 mg/kg *i.d.* in pylorus-ligated rats during 3 h ligation periods. +: $p<0.05$; ++: $p<0.01$; +++: $p<0.001$ *vs.* control value.
b) % inhibition of ulcer formation after administration of the compound at 50 mg/kg *p.o.* in water-immersion restraint rats. +: $p<0.05$; ++: $p<0.01$ *vs.* control value.
c) The toxicity was expressed as the number of dead animals/the number treated.
d) Not tested.

TABLE VI. Antisecretory and Antiulcer Activities of Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one Oximes



21, 23a,



26, 27, 30, 31

Compd. No.	R^1	R^2	R^3	Antisecretory activity[a]	Antiulcer activity[a]	Toxicity[b]
21	H	H	—	66^{+}	−23	0/5
23a	$COCH_3$	CH_3	—	61^{+}	7	—
26	H	—	CH_3	68^{++}	89^{++}	2/5
27	H	—	$CH_2CH=CH_2$	79^{++}	−20	5/5
30	$COCH_3$	—	CH_3	−70	−1	c)
31	$COCH_3$	—	$CH_2CH=CH_2$	−28	98^{++}	5/5

a) See footnote to Table V.
b) Compound (500 mg/kg) was administered *i.p.* unless otherwise noted.
c) 3/5 at 50 mg/kg, *p.o.*

H, 6.49.

5-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-ol (14)——Aqueous tartaric acid (22 ml) was added to a solution of **13** (7.2 g, 29.0 mmol) in Et_2O (22 ml) with cooling in an ice-bath. After being stirred for 15 min, the reaction solution was neutralized with aqueous K_2CO_3 and extracted with Et_2O. The extract was washed, dried and concentrated *in vacuo*. The residue was crystallized from Et_2O–ligroin to afford **14** (4.6 g, 64%), mp 95—97 °C. ^{1}H-NMR ($CDCl_3$): 0.60—1.40 (4H, m, CH_2CH_2), 2.57 (3H, s, $COCH_3$), 5.13 (1H, s, CHOH), 6.93 (1H, d, J=9 Hz, 7-aromat. H), 8.03 (1H, dd, J=2 and 9 Hz, 6-aromat. H), 8.20 (1H, d, J=2 Hz, 4-aromat. H). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.63; H, 5.99.

5-Acetyl-2-(2-benzofuranyl)ethanol (**15a**) and its *p*-toluene sulfonic acid ester (**15b**) were obtained from **14** by hydrolysis with *p*-TsOH.

3-Hydroxyspiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carboxylic Acid (18)——$NaBH_4$ (1.2 g) was added portionwise to a solution of 3-oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carboxylic acid (**16**) (2.04 g, 10.0 mmol) in 1 N methanolic NaOH (40 ml). The mixture was stirred for 1 h at room temperature, then MeOH was removed *in vacuo* and the residue was diluted with H_2O. The aqueous solution was acidified with 3 N HCl and extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The residue was crystallized from AcOEt to afford **18** (1.2 g, 58%), mp 148—149 °C. *Anal.* Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.86; H, 4.82.

Ethyl *N*-{3-Hydroxyspiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carbonyl}glycinate (19)——$NaBH_4$ (0.8 g) was added in small portions to a solution of ethyl *N*-{3-oxospiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carbonyl}glycinate (**17**) (3.6 g, 12.4 mmol) in EtOH (125 ml) at 0 °C with stirring. After being stirred at room temperature for 2 h, the reaction mixture was diluted with ice-H_2O and extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The resulting solids were recrystallized from AcOEt–hexane to give **19** (13 g, 83%), mp 139—140 °C. IR ν_{max}^{KBr} cm^{-1}: 3350, 3270 (NH and OH), 1750 (CO_2Et), 1635 (CONH). ^{1}H-NMR (DMSO-d_6): 0.65—1.35 (4H, m, CH_2), 1.2 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 3.95 (2H, d, J=6 Hz, $NHCH_2CO_2C_2H_5$), 4.12 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 5.00 (1H, s, CHOH), 5.60 (1H, br, CHOH), 6.85 (1H, d, J=9 Hz, 7-aromat. H), 7.8 (1H, d, J=9 Hz, 6-aromat. H), 7.95 (1H, s, 5-aromat. H), 8.75 (1H, t, J=6 Hz, CONH). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.93; H, 5.91; N, 4.87.

Sodium *N*-{3-Hydroxyspiro[benzofuran-2(3*H*),1′-cyclopropan]-5-carbonyl}glycinate (20)——A solution of $NaHCO_3$ (1.45 g) in H_2O (30 ml) was added to a solution of **19** (1 g, 3.4 mmol) in acetone (10 ml) at 60 °C. After being stirred for 18 h, the solution was diluted with H_2O and extracted with AcOEt to remove nonacidic substances. The aqueous solution was concentrated *in vacuo* and chromatographed on XAD-II. Elution with H_2O afforded **20** (949 mg, 94%) as a hygroscopic amorphous powder, mp 275—280 °C. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1625 (CONH), 1585 (CO_2Na). ^{1}H-NMR (D_2O): 0.6—1.5 (4H, m, CH_2), 3.95 (2H, s, $NHCH_2$), 5.05 (1H, s, CHOH), 6.89 (1H, d, J=8.4 Hz, 7-aromat. H), 7.60—7.95 (2H, m, 4- and 6-aromat. H). *Anal.* Calcd for $C_{13}H_{12}NO_5Na \cdot 1/2H_2O$: C, 53.06; H, 4.45; N, 4.76. Found: C, 52.85; H, 4.74; N, 4.67.

Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one Oxime (21)——A solution of **1b** (8 g, 50.0 mmol) and hydroxylamine hydrochloride (10.4 g) in pyridine (50 ml) was heated at 130 °C for 1 h. The solvent was removed *in vacuo* and the residue was poured into ice–H_2O. The crystals that separated were collected, washed and recrystallized to

afford **21** (5.8 g) (Table IV). IR ν_{max}^{KBr} cm^{-1}: 3150, 3050 (OH), 1650, 960 (=NOH). ^{1}H-NMR: see Table III.

The oxime derivative (**22**) was prepared in a similar manner, and is included in Tables III and IV.

***syn*-5-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one *O*-Methyloxime (23a) and Its *anti*-Isomer (23b)**——A solution of **22** (1.56 g, 6.0 mmol) in DMF (30 ml) was treated with NaH (50% in mineral oil, 0.864 g) with cooling in an ice-bath. A solution of Me_2SO_4 (1.8 ml) in DMF (15 ml) was added to the above reaction mixture and the whole was stirred at room temperature for 15 min, then diluted with ice-H_2O and extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel to give 5-(1-ethylenedioxy)ethylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one *O*-methyloxime (1.66 g). The product was hydrolyzed with aqueous tartaric acid and chromatographed on silica gel. The first fraction eluted with AcOEt–CCl_4 (97 : 3) was concentrated and the residue was recrystallized to afford **23a** (0.728 g, 53%). The second fraction was concentrated and the residue was recrystallized to afford **23b** (80 mg, 6%) (Tables III and IV).

O-(3-Methyl-2-butenyl)oxime (**24**) and *O*-(2-diethylaminoethyl)oxime hydrochloride (**25**) of **1a** were prepared from **12** in a similar manner, and are included in Tables III and IV.

Spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one *O*-(Methylaminocarbonyl)oxime (26)——A solution of **21** (1.75 g, 10 mmol), Et_3N (0.05 ml) and methyl isocyanate (0.6 ml) in benzene (20 ml) was heated at 80 °C for 1 h. The solvents were removed *in vacuo* and the residue was crystallized to afford **26** (1.411 g) (Tables III and IV).

Compounds **27**, **28** and **29** were prepared in a similar manner and are included in Tables III and IV. Compounds **30** and **31** were prepared by hydrolysis of **28** and **29**, respectively, and are included in Tables III and IV.

Gastric Secretion in the 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.*[9] Fifty mg/kg of compound suspended in 5% gum arabic solution was given intraduodenally immediately after ligation of the pylorus in a volume of 2 ml/kg of body weight. Three h 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 titrated 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.[10] Groups of five rats were given the test compounds 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. Fifty mg/kg of compound suspended in 5% gum arabic solution was given orally 30 min before the water-immersion stress. Five h later, each animal was taken out of the cage and injected with 1 ml of 0.5% Evans' blue solution (dissolved in saline) into the 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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