Antiulcer Agents. III. Synthesis and Antiulcer Activity of *N*-[3-(3-Piperidinomethylphenoxy)propyl]pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]-octane Carboxamides and Related Compounds

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The synthesis and antiulcer activity of highly strained cage compounds such as pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]-octane (cubane), pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (homocubane) and pentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane are described. Of the compounds obtained, *N*-[3-(3-piperidinomethylphenoxy)propyl]-4-piperidinocarbonylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane carboxamide (26a) and *N*-[3′-(3′-piperidinomethylphenoxy)propyl]-1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane]-4-carboxamide (26q) showed more potent antiulcer activity with very good cytoprotective ability in the HCl·ethanol-treated rat model. Compounds 26a and 26q exhibited H_2-receptor antagonist potency (*in vitro*) comparable to that of ranitidine, but did not inhibit histamine-stimulated acid secretion (*in vivo*) in the gastric fistula rat model, when orally administered in the dose range at which antiulcer and cytoprotective activities were seen. The structure–activity relationships are discussed.

Keywords highly strained cage compound; cubane; homocubane; antiulcer activity; cytoprotective action; *N*-[3-(3-piperidinomethylphenoxy)propyl]pentacyclooctane carboxamide

There has been considerable interest in the development of histamine H_2-receptor antagonists for the treatment of peptic ulcers. This is because peptic ulcers are still a major medical problem and new drugs, particularly non-toxic drugs with a prophylactic effect, are required to prevent ulcer reoccurrence. As part of a continuing effort to prepare antiulcer agents with potent gastric acid antisecretory and gastrointestinal cytoprotective activities and lower toxicity, several compounds having the 3-(3-piperidinomethylphenoxy)propyl moiety as a lead moiety were synthesized (Chart 1).[1] In the present paper, we describe the synthesis of highly strained cage compounds such as pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane (cubane: **3** and **4**), pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (homocubane: **2a** and **2b**) and pentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane (**9**) and their *N*-[3-(3-piperidinomethylphenoxy)propyl]carboxamide derivatives (**26**) along with pharmacological evaluation of these compounds as antiulcer agents.

Chemistry Cubane-1,4-dicarboxylic acid (**3**) and its dimethyl ester **5** could be obtained by either the original method of Eaton and Cole[2a] or the method of Chapman *et al.*[3] Although cubane-1,3-dicarboxylic acid (**4**) and its dimethyl ester **6** have been prepared by Barborak *et al.*,[4] we have developed a new procedure for the preparation of **4** *via* intermediates **1b** and **2b** from **7**.[5] A novel cage compound, 10-oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]-decane-3-carboxylic acid (**9**) was prepared by treating **8** with 5% aqueous potassium hydroxide at 80 °C for 15 min.[6]

The dimethyl esters **5** and **6** were hydrolyzed into mono

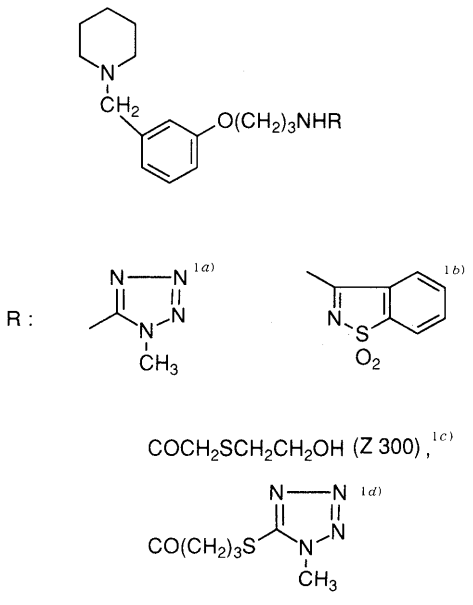

Chart 1

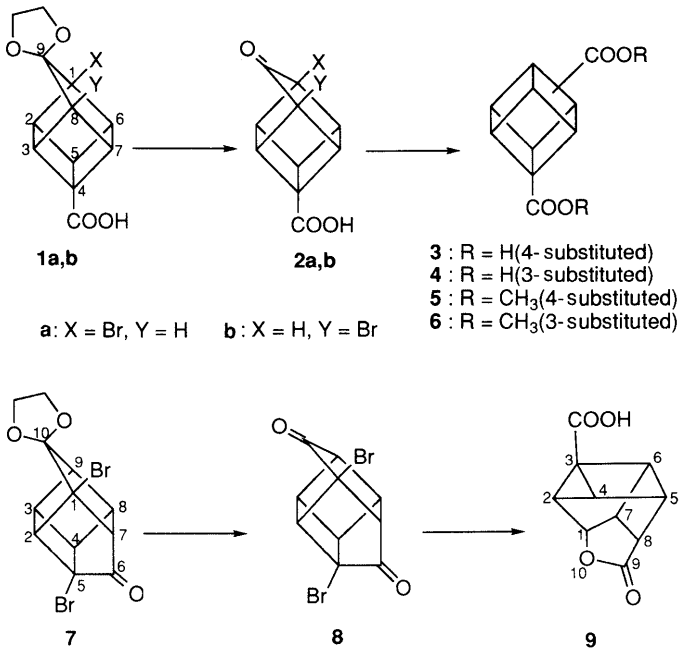

Chart 2

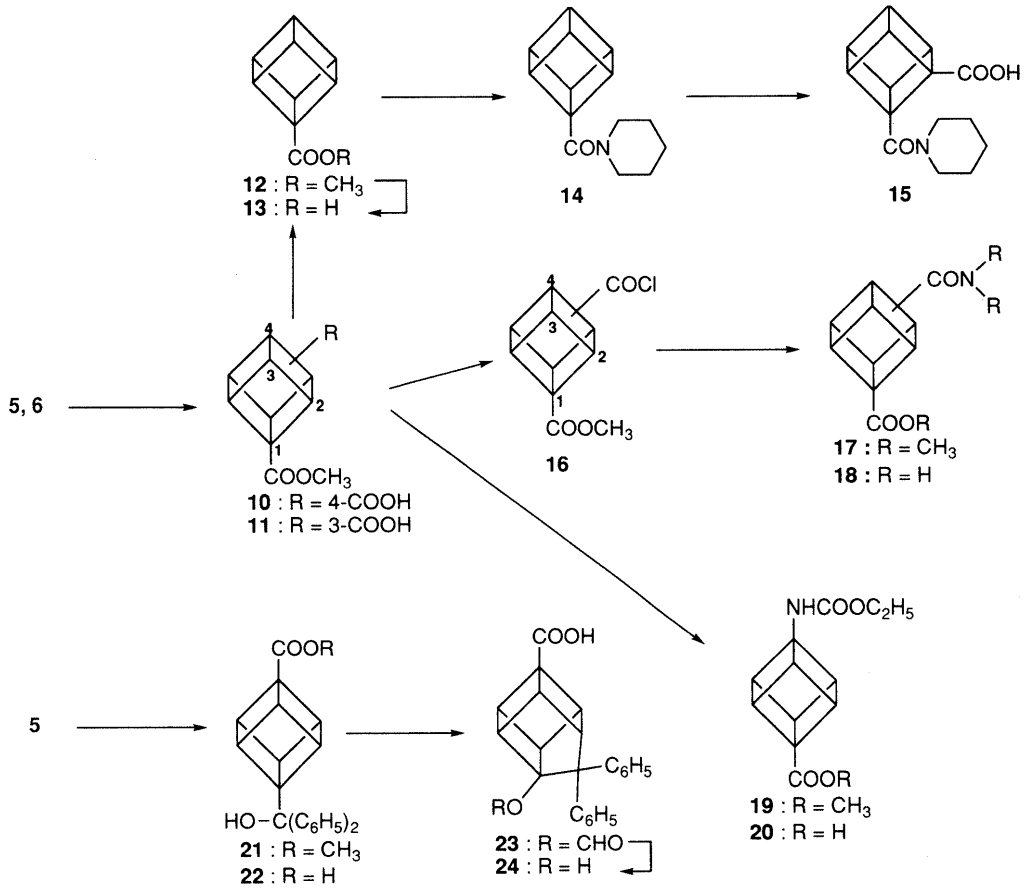

Chart 3

esters **10** and **11**, which were converted into **12** by Barton's decarboxylation procedure.[7] Hydrolysis of **12** with 1 N sodium hydroxide, followed by amidation gave **14**. Lithiation and carboxylation of **14** by the method of Bottaro *et al.*[8] gave **15** in 12% yield.

Acyl chlorides **16**, prepared from **10** and **11** with thionyl chloride, were allowed to react with various amines to give the corresponding amides **17**. The amides **17** were converted into the corresponding acids **18** by alkaline hydrolysis. Reaction of **10** with diphenylphosphoryl azide (DPPA) in the presence of triethylamine in ethanol gave **19** in 53% yield, and this product was converted into the acid **20** by alkaline hydrolysis.

Reaction of **5** with 2 eq of phenylmagnesium bromide in tetrahydrofuran (THF) gave **21** in 49% yield after purification by column chromatography on silica gel with chloroform. Compound **21** was hydrolyzed with 1 N sodium hydroxide to give the oxyacid **22** in 99% yield. Treatment of **22** with formic acid (Wagner–Meerwein rearrangement) gave **23** in 91% yield. Hydrolysis of **23** with 10% methanolic potassium hydroxide afforded **24** in a quantitative yield. The carboxylic acid derivatives (**1a**, **1b**, **9**, **13**, **15**, **18**, **20**, **22** and **24**) employed in this series are summarized with the elemental analysis data in Table I.

The amine derivatives **25** used in this study were prepared according to the literature.[1c,d] Compounds **26** were prepared from the carboxylic acids and the amines **25** by the usual procedure. The results are summarized in Tables II and III.

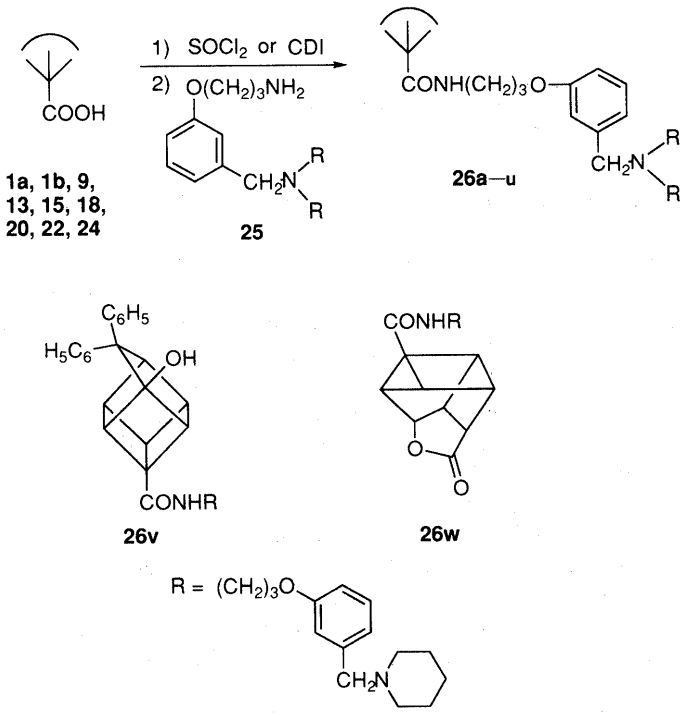

Chart 4

Biological Screening Methods The compounds were evaluated for gastric acid antisecretory, antiulcer and cytoprotective activities in animal models.

Gastric Acid Antisecretory Activity[9]: The conscious rat with gastric fistula was used for this test. Histamine

TABLE I. Carboxylic Acid Derivatives (**1a**, **1b**, **9**, **13**, **15**, **18**, **20**, **22** and **24**)

Compd. No.	R[a]	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd (Found)			
					C	H	N	Br
1a[c]		187.5—189.6 (lit.,[3] 187—189)	MeOH	$C_{12}H_{11}BrO_4$				
1b[c]		190.2—191.8	CH_2Cl_2	$C_{12}H_{11}BrO_4$	48.14 (47.99	3.71 3.52		26.71 26.49)
9[c]		121.1—122.2	AcOEt	$C_{10}H_8O_4$	62.50 (62.43	4.20 4.04)		
13	H	126.4—127.4 (lit.,[2b] 124—125)	CH_2Cl_2–Hex	$C_9H_8O_2$				
15	2-COP	176.0—177.3	CH_2Cl_2–Hex	$C_{15}H_{17}NO_3$	69.48 (69.51	6.61 6.56	5.40 5.48)	
18a	3-COP	200.9—201.6	CH_2Cl_2–Hex	$C_{15}H_{17}NO_3$	69.48 (69.75	6.61 6.33	5.40 5.28)	
18b	4-COP	216.0—217.0	$CHCl_3$–Hex	$C_{15}H_{17}NO_3$	69.48 (69.25	6.61 6.35	5.40 5.32)	
18c	4-COPy	209.0—211.0	$CHCl_3$–Hex	$C_{14}H_{15}NO_3$	68.56 (68.42	6.16 5.99	5.71 5.74)	
18d	4-COM	239.0—241.0	$CHCl_3$–Hex	$C_{14}H_{15}NO_4$	64.36 (64.41	5.79 5.66	5.36 5.20)	
18e	4-CON$(CH_3)_2$	210.0—212.0	$CHCl_3$–Hex	$C_{12}H_{13}NO_3$	65.74 (65.43	5.98 5.71	6.39 6.40)	
18f	4-CONHCH$_3$	180.0—182.0	$CHCl_3$–Hex	$C_{11}H_{11}NO_3$	64.38 (64.15	5.40 5.27	6.83 6.97)	
18g	4-CONH$_2$	252.0—254.0	MeOH–Et_2O	$C_{10}H_9NO_3$	62.82 (62.83	4.74 4.79	7.33 7.26)	
18h	4-COPz	125.0—126.0	B–Hex	$C_{16}H_{20}N_2O_3$	66.65 (66.60	6.99 6.76	9.72 9.81)	
18i	4-CONHDAE	76.0—78.0	Hex	$C_{17}H_{24}N_2O_3 \cdot 1/2H_2O$	65.15 (64.98	8.04 7.68	8.94 9.21)	
20	4-NHCOOC$_2$H$_5$	188.0—190.0	$CHCl_3$–Hex	$C_{12}H_{13}NO_4$	61.27 (60.98	5.57 5.40	5.95 5.74)	
22	4-C$(C_6H_5)_2$OH	198.0—199.0	MeOH–H_2O	$C_{22}H_{18}O_3$	79.98 (79.71	5.49 5.75)		
24[c]		239.7—241.7	Acetone–Hex	$C_{22}H_{18}O_3$	HRMS[d]	330.1256 (330.1281)		

a) P, piperidino; M, morpholino; Pz, 4-methylpiperazino; DAE, *N*,*N*-diethylaminoethyl. *b*) Hex, hexane; B, benzene. *c*) The structure is shown in the text. *d*) HRMS: high-resolution mass spectrum.

was empolyed as a gastric acid inducer. In this test, the compounds were administered intraduodenally (i.d.) at a 10 mg/kg dose and gastric juice was collected at 60-min intervals for 5 h following the start of histamine infusion. The reduction in acid output was determined from the total volume of gastric juice collected in 5 h.

Pepsin Activity in Gastric Juice: Each gastric juice collected at 60-min intervals in the above experiment was examined. The activity was measured by a modification of Anson's method.[10]

Antiulcer Activity: The compounds were tested in a water-immersion stress-induced ulcer model in the rat according to the method described in the literature.[11] In this test, the compounds were administered orally (*p.o.*) 5 min before stress loading and the effect of the compounds was measured in terms of the sum of the length (mm) of all lesions.

Gastrointestinal Cytoprotective Activity[12]: This test was carried out in the HCl·ethanol-treated rat model. In this test, the compound was administered orally (*p.o.*) 30 min before oral administration of HCl·ethanol. The effect of the compounds was measured in terms of the sum of the length (mm) of all lesions.

Histamine H_2-Receptor Antagonistic Activity[13]: The gastric acid antisecretory efficacies of the compounds were further evaluated by measuring the H_2 antagonistic potencies against histamine-induced contraction of guinea pig atrium.

Results and Discussion

Compounds **26** were tested for gastric acid antisecretory activity in the rat model and antiulcer activities in stress-exposed rats and in HCl·ethanol-treated rats at the dose of 10 mg/kg as primary screening tests. The results are summarized in Table IV. The compounds prepared in this series exhibited very weak gastric antisecretory activity in the rat model. However, some compounds were shown to have significant cytoprotective activity, exhibiting 70 to 80% inhibition of ulcer formation in the HCl·ethanol-treated rat and relatively high antiulcer activity in the water-immersion stress-induced ulcer model in the rat. Of these compounds, **26a** and **26q** were more active in the primary screenings.

The efficacy of **26a**, in terms of ED_{50} value in the water-immersion stress-induced ulcer model, which is considered to resemble the human ulcer, was greater than that of ranitidine. The ED_{50} value for **26q** was not determined because the dose-response curve for this compound was

TABLE II. *N*-[3-(3-Aminomethylphenoxy)propyl]cubane Carboxamides (**26a—p**)

Compd. No.	R[1a]	R[2a]	Yield (%)	mp (°C) (Recryst. solv.)[b]	Formula	Analysis (%) Calcd (Found)		
						C	H	N
26a	4-COP	P	68.3	118—120 (B–Hex)	$C_{30}H_{39}N_3O_3$	73.59 (73.32	8.03 8.00	8.58 8.63)
26b	4-COPy	P	60.2	132—133 ($CHCl_3$–Hex)	$C_{29}H_{37}N_3O_3$	73.23 (73.01	7.84 7.58	8.83 8.82)
26c	4-COM	P	54.7	151—153 ($CHCl_3$–Hex)	$C_{29}H_{37}N_3O_4$	70.85 (70.73	7.59 7.38	8.55 8.55)
26d	4-CON(CH_3)$_2$	P	45.2	99—101 ($CHCl_3$–Hex)	$C_{27}H_{35}N_3O_3$	72.13 (72.08	7.85 7.95	9.35 9.24)
26e	4-CONHCH$_3$	P	55.7	180—182 ($CHCl_3$–Hex)	$C_{26}H_{33}N_3O_3$	71.70 (71.46	7.64 7.52	9.65 9.44)
26f	4-CONH$_2$	P	46.6	245—247 (MeOH–H_2O)	$C_{25}H_{31}N_3O_3$	71.23 (71.10	7.41 7.24	9.97 10.02)
26g	4-COPz	P	25.3	103—105 ($CHCl_3$–Hex)	$C_{30}H_{40}N_4O_3$	71.40 (71.49	7.99 7.75	11.10 11.09)
26h	4-CONHDEA	P	35.4	164—166 (B–Hex)	$C_{31}H_{44}N_4O_3$	71.51 (71.23	8.52 8.30	10.76 10.56)
26i	4-COP	Py	73.9	114—115 (B–Hex)	$C_{29}H_{37}N_3O_3$	73.23 (73.40	7.84 7.63	8.83 8.81)
26j[c]	4-COP	PyOH	56.7	Oil	$C_{29}H_{37}N_3O_4$			
26k	4-COP	N(CH_3)$_2$	64.4	127—128 (B–Hex)	$C_{27}H_{35}N_3O_3$	72.13 (71.84	7.85 7.60	9.35 9.56)
26l	4-COHPh$_2$	P	57.9	98—100 (B–Hex)	$C_{37}H_{40}N_2O_3$	79.25 (79.12	7.19 7.23	5.00 4.72)
26m	4-NHCOOC$_2$H$_5$	P	55.0	106—108 (B–Hex)	$C_{27}H_{35}N_3O_4$	69.65 (69.44	7.58 7.57	9.03 9.04)
26n	H	P		196.6—197.7	$C_{26}H_{32}N_2O_6$	66.65 (66.64	6.88 6.66	5.98 6.06)
26o	3-COP	P		Oil	$C_{30}H_{39}N_3O_3$	HRMS[d]	489.2989 (489.3008)	
26p	2-COP	P		156.0—158.0	$C_{30}H_{39}N_3O_3$	HRMS[d]	489.2989 (489.2979)	

a) P, piperidino; M, morpholino; Pz, 4-methylpiperazino; Py, pyrrolidino; PyOH, 3-hydroxypyrrolidino; DAE, *N*,*N*-diethylaminoethyl. *b*) B, benzene; Hex, hexane. *c*) The structure was established by NMR, IR and MS spectral data. *d*) HRMS: high-resolution mass spectrum.

TABLE III. *N*-[3-(3-Aminomethylphenoxy)propyl]homocubane Carboxamides (**26q—v**) and a Related Compound (**26w**)

Compd. No.	R[a]	R^1	R^2	Yield (%)	mp (°C) (Recryst. solv.)	Formula	Analysis (%) Calcd (Found)			
							C	H	N	Br
26q	P	Br	H	96.2	176.0—178.0 (MeOH–$CHCl_3$–AcOEt)	$C_{27}H_{33}BrN_2O_4 \cdot C_2H_2O_4$	56.22 (56.14	5.69 5.66	4.52 4.41	12.90 12.93)
26r	Py	Br	H	87.2	194.0—196.0 (MeOH–ether)	$C_{26}H_{31}BrN_2O_4 \cdot C_2H_2O_4$	55.54 (55.59	5.49 5.21	4.63 4.60	13.20 13.07)
26s	PyOH	Br	H	81.3	178.0—180.0 (MeOH–ether)	$C_{26}H_{31}BrN_2O_5 \cdot C_2H_2O_4$	54.11 (54.03	5.35 5.34	4.51 4.41	12.86 12.66)
26t	N(CH_3)$_2$	Br	H	80.0	205.0—207.0 (MeOH–ether)	$C_{24}H_{29}BrN_2O_4 \cdot C_2H_2O_4$	53.89 (53.83	5.39 5.24	4.83 4.69	13.79 13.71)
26u	P	H	Br	97.0	130.0—130.8	$C_{27}H_{33}BrN_2O_4$	61.25 (61.10	6.28 6.08	5.29 5.22	15.09 15.31)
26v				59.0	Oil	$C_{37}H_{40}N_2O_3$	HRMS[b]	560.3041 (560.3048)		
26w				83.6	Oil	$C_{25}H_{30}N_2O_3$	HRMS[b]	422.2207 (422.2198)		

a) P, piperidino; Py, pyrrolidino; PyOH, 3-hydroxypyrrolidino. *b*) HRMS: high-resolution mass spectrum.

not established. The cytoprotective activity of **26a** and **26q** was rather superior to that of ranitidine. The histamine H_2 receptor antagonistic activity of **26a**, in terms of pA_2 value, was found to be comparable with that of ranitidine, and the antagonistic activity of **26q** was clearly superior to that of ranitidine; pA_2 values determined were 6.55 for **26a**, 7.38 for **26q** and 6.60 for ranitidine. However, **26a** and **26b** did not inhibit histamine-stimulated acid secretion in the gastric fistula rat model, when orally administered in the dose range at which antiulcer and cytoprotective activities were seen. Interestingly, **26a** and **26q** were found to inhibit pepsin secretion when administered intraduodenally at the

dose of 10 mg/kg.

Structure–Activity Relationships The gastric acid antisecretory and antiulcer activities summarized in Tables IV and V suggested the following structure–activity relationships.

In the cubane system, the presence of a -CON< group on the cubane ring appeared to be necessary to maintain the antiulcer potency. The piperidinocarbonyl (**26a**), pyrrolidinocarbonyl (**26b**) and 4-ethoxycarbonylamino (**26m**) analogues exhibited comparable oral antiulcer activities in the rat. The aminocarbonyl compound (**26f**) exhibited reduced antiulcer activity relative to that of **26a**. Introduction of other CON< groups resulted in a reduction of the antiulcer activity relative to either **26a**, **26b**, **26f** or **26m**. Introduction of the piperidinocarbonyl group (**26o** and **26p**) at the 2- or 3-position of the cubane ring resulted in a marked reduction of the antiulcer activity, compared with that of **26a**. Although the pA_2 value of **26a** was comparable to that of ranitidine, **26a** did not exhibit gastric acid antisecretory activity in the gastric fistula rat model.

TABLE IV. Antiulcer Activity of **26**

Compd. No.	Gastric acid antisecretory activity[a] in the conscious rat with gastric fistula, i.d.	Antiulcer activity[a] in	
		Stress-exposed rat, *p.o.*	HCl·EtOH-treated rat, *p.o.*
26a	17.2	64.2	70.9
26b	35.5	33.5	75.9
26c	22.7	−15.8	35.6
26d	23.3	45.7	34.3
26e	−0.8	48.3	16.6
26f	24.1	8.4	42.8
26g	15.4	15.6	24.3
26h	13.4	23.6	16.1
26i	−14.9	21.3	31.9
26j	−23.1	−49.1	—[c]
26k	−28.7	−6.8	14.1
26l	5.8	30.8	42.2
26m	1.4	16.0	76.4
26n	23.9	44.5	34.6
26o	76.8[b]	—[c]	—[c]
26p	10.1[b]	45.4[b]	98.7[b]
26q	43.2	43.0	77.4
26r	−1.5	10.0	21.1
26s	−6.8	26.7	13.1
26t	11.7	26.1	−57.9
26u	11.7	−6.0	73.3
26v	18.5	16.5	43.4
26w	18.8[b]	36.8[b]	77.2[b]

a) % inhibition at the dose of 10 mg/kg. *b*) % inhibition at the dose of 30 mg/kg. *c*) Not detected. Each value represents the mean of five rats.

In the homocubane system, **26q** and **26u** exhibited comparable antiulcer activities. Replacement of the piperidinomethyl group in **26q** with other aminomethyl groups such as 3-hydroxypyrrolidinomethyl and dimethylaminomethyl groups resulted in a marked reduction of the antiulcer activity. Compound **26q** weakly inhibited histamine-stimulated acid secretion in the gastric fistula rat model.

As regards the substituent on the benzene ring, the aminomethyl group at the *meta*-position of the benzene ring plays an important role in imparting the desired level of antiulcer activity. In this series, the piperidinomethyl group (**26a**, **26o** or **26p**) provided antiulcer activity, but the pyrrolidinomethyl group (**26i**) was less effective. The 3-hydroxypyrrolidinomethyl group (**26j** or **26s**) and dimethylaminomethyl group (**26k** or **26t**) resulted in no significant antiulcer activity.

In conclusion, a series of highly strained cage compounds were synthesized, and one of them (**26a**) exhibited significant cytoprotective and antiulcer activities. The cubane and homocubane structures may be new pharmacophores.

Experimental

Melting points were measured in a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi model 260-30 infrared spectrophotometer and ^1H- and ^{13}C-NMR spectra were measured on Hitachi R-90H (90 MHz), JEOL JNM-EX 270 (270 MHz), Varian Gemini 300 (300 MHz) and Bruker AM 360 (360 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are given as δ values (ppm); s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; br, broad; m, multiplet. All spectra were consistent with the assigned structures. Mass spectra (MS) were obtained on a JMS-DX 300 spectrometer. Combustion analyses were performed on a Perkin-Elmer model 240C elemental analyzer and high-resolution MS (HRMS) analyses were used for oily products.

THF was dried over CaH_2 and distilled before use. Other solvents were dried over molecular sieves 4A overnight. Reagents employed in this study were commercial products.

Cubane derivatives are quite stable. However, as they are all high energy content materials, great care should be taken to assure that crude reaction products are not concentrated at elevated temperature, particularly in the presence of acidic contaminants.

1-Bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (1a) This compound was prepared by the procedure of Chapman *et al.*[3] Yield: 92.0%; mp 188—189 °C (lit., 187—189 °C).

8-Bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (1b) A solution of **7** (2.0 g, 5.52 mmol) in 10% KOH (50 ml) was stirred for 2.5 h in refluxing water, cooled below 10 °C and acidified with conc. HCl to below pH 1. The precipitates were extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to give a pale yellow solid. The solid was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **1b**, which was recrystallized from CH_2Cl_2 to give colorless needles. Yield: 1.5 g (92%).

1-Bromo-9-oxopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid

TABLE V. Pharmacological Properties of **26a** and **26q**

Compd. No.	Gastric acid antisecretory activity[a] in the conscious rat with gastric fistula, i.d. ED_{50} mg/kg	Antiulcer activity[a] in		% secretory inhibition[a] of pepsin at the dose of 10 mg/kg, *p.o.* in rat	H_2-Receptor antagonist activity (guinea pig atrium) pA_2
		Stress-exposed rat, *p.o.* ED_{50} mg/kg	HCl·EtOH-treated rat, *p.o.* ED_{50} mg/kg		
26a	—[b]	1.1[c]	4.2[c]	30.6[c]	6.55[d]
26q	—[b]	—[b]	7.5[d]	30.5[d]	7.38[d]
Ranitidine[e]	17.7	22.0	284.0	—[b]	6.60

a) Five rats were used for each experiment. *b*) Not detected. *c*) Free base was employed for the test. *d*) Oxalate was employed for the test. *e*) See ref. 1c.

(2a) This compound was prepared by the procedure described in the literature.[3] Yield: 76%; mp 221.5—222.5 °C (lit., 219—220 °C).

8-Bromo-9-oxopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (2b) A solution of **1b** (1.0 g, 3.34 mmol) in 75% H_2SO_4 (30 ml) was stirred for 24 h at room temperature and poured into ice-water (400 ml). The resulting aqueous layer was saturated with $(NH_4)_2SO_4$ and extracted with AcOEt. After removal of the solvent, the residue was dissolved in saturated aqueous $NaHCO_3$ (20 ml). The aqueous layer was washed with CH_2Cl_2, acidified with conc. HCl, washed with CH_2Cl_2, saturated with $(NH_4)_2SO_4$ and then extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated to give pure **2b** as a colorless solid. Yield: 0.77 g (92%); mp 236.7—239 °C (dec.). ^{1}H-NMR (360 MHz, DMSO-d_6) δ: 3.18 (1H, t, J=5 Hz), 3.74 (2H, m), 3.80 (1H, m), 3.90 (2H, m), 12.6 (1H, br s). ^{13}C-NMR (90 MHz, DMSO-d_6) δ: 37.2, 38.8, 45.6, 48.8, 54.3, 57.4, 170.6, 204.4. IR (KBr): 1770, 1690 cm^{-1}. MS m/z: 254 (M^+). *Anal.* Calcd for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77; Br, 18.82. Found: C, 47.34; H, 2.89; Br, 18.62.

Dimethyl Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1,4-dicarboxylate (5) This compound was prepared by the procedure described in the literature.[3] Yield: 44%; mp 162.3—164.1 °C (from MeOH) (lit., 161—162 °C).

Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1,3-dicarboxylic Acid (4) and Its Dimethyl Ester (6) A solution of **2b** (284 mg, 1.11 mmol) in 25% KOH (3 ml) was stirred for 3.5 h in refluxing water and acidified with conc. HCl to below pH 1 under cooling with ice-water. The aqueous layer was saturated with $(NH_4)_2SO_4$ and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated to give crude **4**. Crude **4** was treated with diazomethane in MeOH by the usual procedure to afford to dimethyl ester **6**, which was purified by column chromatography on slica gel with $CHCl_3$ as an eluent to afford an oily product. The oil was triturated with pentane to give pure **6**. Yield: 61 mg (25%); mp 56.2—58.6 °C. ^{1}H-NMR (360 MHz, $CDCl_3$) δ: 3.72 (6H, s), 4.00 (2H, q, J=5 Hz), 4.22 (2H, sept, J=3 Hz), 4.46 (2H, m). ^{13}C-NMR (90 MHz, $CDCl_3$) δ: 42.8, 49.8, 51.1, 51.6, 53.2, 171.5.

1,5-Dibromo-10,10-ethylenedioxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (7) This compound was prepared by the method described in the literature.[6] Yield: 100%; mp 169.8—171.1 °C (from a mixture of AcOEt and hexane) (lit., 169.8—171.1 °C).

1,5-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (8) A solution of **7** (500 mg, 1.38 mmol) in conc. H_2SO_4 (5 ml) was stirred at room temperature and poured into ice-water (*ca.* 50 ml). The aqueous layer was diluted with chilled water in a volume of 100 ml, then saturated with $(NH_4)_2SO_4$ and extracted several times with AcOEt. The combined AcOEt layer was dried over $MgSO_4$ and evaporated to give a colorless solid. The solid was purified by column chromatography on silica gel with a (5 : 1) mixture of hexane and AcOEt as an eluent to give the pure monohydrate of **8**, which was recrystallized from a mixtue of AcOEt and hexane to give colorless plates. Yield: 441 mg (95%); mp 155.7—156.4 °C. The monohydrate of **8** was treated with molecular sieves 4A for 2 h in refluxing C_6H_6. The solvent was removed *in vacuo* to give pure **8** as a colorless powder. Yield: 417 mg (100%); mp 161.0—162.5 °C. ^{1}H-NMR (360 MHz, $CDCl_3$) δ: 3.00 (1H, m), 3.10 (1H, t, J=5 Hz), 3.51—3.54 (2H, m), 3.61 (1H, m), 3.72 (1H, m). ^{13}C-NMR (90 MHz, $CDCl_3$) δ: 35.5, 37.2, 39.2, 44.0, 47.8, 51.2, 54.1, 56.9, 201.9, 202.8. IR ($CHCl_3$): 3060, 3020, 1795, 1765 cm^{-1}. MS m/z: 316 (M^+). *Anal.* Calcd for $C_{10}H_6Br_2O_2$: C, 37.77; H, 1.90; Br, 50.26. Found: C, 37.62; H, 1.79; Br, 50.38.

10-Oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxylic Acid (9) A solution of **8** (100 mg, 0.314 mmol) in 5% KOH (8 ml) was stirred at 80 °C for 15 min. The mixture was cooled and acidified with conc. HCl to below pH 1 at below 10 °C. The resulting mixture was saturated with NaCl and extracted several times with AcOEt. The AcOEt layers were combined and dried over $MgSO_4$. After removal of the solvent, the solid was purified by column chromatography on slica gel with $CHCl_3$ as an eluent. Recrystallization from AcOEt gave analytically pure **9** as colorless scales. Yield: 53 mg (87%); mp 121.1—122.2 °C (lit.,[6] 121.1—122.2 °C).

4-Methoxycarbonylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylic Acid (10) Normal sodium hydroxide (38.6 ml) was added dropwise to a solution of **5** (8.5 g, 38.6 mmol) in MeOH (300 ml) over a period of 2 h, the temperature being kept in the range of 50 to 55 °C. Water (200 ml) was added to the resulting solution. After removal of the MeOH, the solution was diluted with additional water (300 ml) and extracted with CH_2Cl_2. The aqueous solution was acidified with conc. HCl to pH 5. The precipitated solid was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated to give a colorless solid. The solid was recrystallized from a mixture of CH_2Cl_2 and hexane to give analytically pure **10**. Yield: 5.2 g (66%); mp 183.8—185.2 °C (lit.,[14] 182—183 °C).

3-Methoxycarbonylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylic Acid (11) This compound was obtained as an oil in 58% yield from **6** according to the method described for **10**. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.72 (3H, s), 4.02 (2H, m), 4.24 (2H, m), 4.50 (2H, m), 7.20 (1H, br s). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 42.7, 49.7, 50.9, 51.7, 53.0, 53.1, 171.7, 176.6. MS m/z: 206 (M^+).

Methyl Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylate (12) and Its Carboxylic Acid (13) Thionyl chloride (1 ml) was added to a suspension of **10** (300 mg, 1.45 mmol) in dry C_6H_6 (2 ml). The mixture was stirred for 2 h in refluxing C_6H_6 and evaporated to give an oil. The sodium salt of *N*-hydroxypyridine-2(1*H*)-thione (239 mg, 1.60 mmol) and 4-dimethylaminopyridine (DMAP, 3 mg) were added to a solution of the oil in dry C_6H_6. The mixture was refluxed for 1 h under shielding from light and cooled to room temperature. *tert*-Butylmercaptan (0.4 ml, 3.5 mmol) and 2,2′-azobisisobutyronitrile (AIBN, 5 mg) were added, and the resulting mixture was refluxed for 2 h, cooled to room temperature. Ether (20 ml) was added to the mixture and then ethereal solution was washed with 10% $NaHCO_3$ and brine. The aqueous layer was extracted with ether. The ethereal extracts were combined, dried over $MgSO_4$ and evaporated to give **12** as a yellow oil. NaOH (88 mg) in MeOH (4 ml) was added to a solution of the oil in MeOH (4 ml). The resulting mixture was refluxed for 4 h and diluted with water (10 ml). After removal of the MeOH, the aqueous layer was acidified with conc. HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated to give a solid. The solid was recrystallized from hexane to give pure **13** as colorless plates. Yield: 0.89 mg (61%); mp 126.4—127.4 °C (lit.,[2b] 124-125 °C).

Piperidinopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane Carboxamide (14) A mixture of **13** (400 mg, 2.70 mmol) and $SOCl_2$ (5 ml) was refluxed for 15 min. After removal of the residual $SOCl_2$, the oil was dissolved in CH_2Cl_2. Piperidine (500 mg, 5.88 mmol) was added. The resulting mixture was stirred for 30 min at room temperature, and washed with 2 N HCl and brine, successively. The CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated to give a solid. The solid was recrystallized from a mixture of CH_2Cl_2 and hexane to give **14**. Yield: 480 mg (83%); mp 99.2—100.4 °C. ^{1}H-NMR (360 MHz, $CDCl_3$) δ: 1.56 (4H, m), 1.65 (2H, m), 3.18 (2H, t, J=5.3 Hz), 3.53 (2H, t, J=5.3 Hz), 3.99 (4H, m), 4.22 (3H, m). ^{13}C-NMR (90 MHz, $CDCl_3$) δ: 24.7, 25.5, 26.8, 42.7, 44.5, 45.8, 46.7, 49.4, 58.2, 170.1. IR (KBr): 2950, 2850, 1625, 1440, 1295, 1255, 1230 cm^{-1}. MS m/z: 215 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.19; H, 7.91; N, 6.56.

2-Piperidinocarbonylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylic Acid (15) All procedures were carried out under an argon atmosphere. Commercially available *n*-butyllithium hexane solution (concentration: 1.6 M; 14.6 ml, 23.3 mmol) was added to a solution of freshly distilled 2,2,6,6-tetramethylpiperidine (3.29 g, 23.3 mmol) in THF (15 ml) chilled to −78 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was cooled to −78 °C again and **14** (1.0 g, 4.65 mmol) and magnesium bromide etherate (3.02 g, 11.7 mmol) were added in one portion. The temperature of the reaction mixture was raised to 0 °C. The mixture was stirred for 5 h and then the temperature was dropped to −40 °C. Dry gasous carbon dioxide was bubbling through the reaction mixture. After being stirred for 1 h, the mixture was poured into ice-water containing HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to give a solid, which was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **15**. Recrystallization from a mixture of CH_2Cl_2 and hexane gave **15** as colorless prisms. Yield: 142 mg (12%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.64 (6H, m), 3.25 (2H, t, J=5 Hz), 3.57 (2H, t, J=5 Hz), 4.06 (2H, m), 4.28 (4H, m). ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 23.8, 25.0, 26.3, 43.0, 44.1, 44.5, 45.6, 47.8, 57.3, 60.2, 170.7, 172.6. IR ($CHCl_3$): 2975, 2925, 2850, 1700, 1560, 1485, 1465, 1290 cm^{-1}. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.51; H, 6.56; N, 5.48.

4-Piperidinocarbonylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylic Acid (18b) A typical example is given to illustrate the general procedure. Thionyl chloride (6 ml) was added to a suspension of **10** (6.43 g, 31.2 mmol) in dry C_6H_6 (30 ml). The mixture was refluxed for 1 h and the excess $SOCl_2$ was removed as the toluene azeotrope *in vacuo* to give the corresponding acid chloride **16** as colorless crystals. The acid chloride was dissolved in dry CH_2Cl_2 and a solution of piperidine (9.27 ml, 93.6 mmol) in CH_2Cl_2 (30 ml) was added to it under ice-water cooling. The resulting mixture was stirred for 1 h at room temperatue, washed with water, 2 N HCl, water and 1 N NaOH, successively, and dried over $MgSO_4$. After removal of the solvent, the methyl ester **17b** (8.22 g) was obtained. A mixture of the methyl ester **17b** (8.22 g) and 1 N NaOH (60 ml) in MeOH (50 ml) was refluxed for 1 h. After removal of the MeOH, the aqueous

layer was diluted with water (200 ml) and extracted with AcOEt in order to remove impurities. The separated aqueous layer was acidified with 2 N HCl to pH 2 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over $MgSO_4$ and evaporated to give colorless crystals. The crystals were recrystallized from a mixture of $CHCl_3$ and hexane to give pure **18b** as colorless crystals.

The other compounds, **18a** and **18c—i**, were similarly prepared. Analytical data for **18** are summarized in Table I.

Methyl 4-Ethoxycarbonylaminopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane-1-carboxylate (19) and Its Carboxylic Acid (20) Triethylamine (0.354 ml, 2.54 mmol) and DPPA (0.547 ml, 2.54 mmol) were successively added to a suspension of **11** (500 mg, 2.42 mmol) in dry EtOH (10 ml). The resulting mixture was refluxed for 16 h, poured into chilled saturated $NaHCO_3$ aqueous solution and extracted with AcOEt. The AcOEt layer was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with a (8 : 2) mixture of C_6H_6 and AcOEt to give **19** as a colorless solid. This solid was used for the following step without purification. A mixture of the solid (320 mg) and 1 N NaOH (1.41 ml) in MeOH (10 ml) was heated for 0.5 h at 60 °C. After removal of the solvent, the residue was diluted with water (30 ml) and the resulting aqueous layer was washed with AcOEt and acidified with 2 N HCl to pH 2. The solid was collected, washed with water, dried and recrystallized from a mixture of $CHCl_3$ and hexane to give pure **20** as a colorless powder. Yield: 266 mg (47%).

Methyl 4-(α,α-Diphenylhydroxymethyl)pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]-octane-1-carboxylate (21) and Its Carboxylic Acid (22) Grignard reagent [prepared from Mg (1.1 g, 45.4 atom) and bromobenzene (7.13 g, 45.4 mmol)] in dry THF (20 ml) was added to a solution of **6** (5.0g, 22.7 mmol) in dry THF (100 ml) over a period of 15 min. The mixture was refluxed for 2 h, poured into ice-water saturated with NH_4Cl and extracted with ether. The ethereal layer was washed with water and brine successively, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent. The solid was recrystallized from $CHCl_3$ to give the pure methyl ester **21**. Yield: 3.8 g (49%); mp 168.0—169.5 °C (from $CHCl_3$).

A mixture of **21** (632 mg, 1.84 mmol) and 1 N NaOH (2.76 ml) in MeOH (20 ml) was stirred for 1 h in refluxing MeOH and then the MeOH was removed. The residue was poured into ice-water, and the solution was washed with CH_2Cl_2 and acidified with 2 N HCl to pH 2. The precipitated solid was collected, dried and recrystallized from a mixture of MeOH and water to give pure **22**. Yield: 600 mg (99%).

9,9-Diphenyl-1-formyloxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (23) A solution of **22** (570 mg, 1.73 mmol) in 99% HCOOH (10 ml) was stirred for 12 h at room temperature and poured into ice-water (10 ml). The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ aqueous solution and brine, successively, dried over $MgSO_4$ and evaporated to give **23**. Yield: 592 mg (95%). This compound was used for the following step without further purification.

9,9-Diphenyl-1-hydroxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (24) A solution of **23** (592 mg, 1.65 mmol) in 10% methanolic KOH (10 ml) containing water (2 ml) was stirred for 10 min in refluxing MeOH, acidified with 1 N HCl to pH 1 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to give **24**. Yield: 520 mg (100%).

The carboxylic acid derivatives synthesized (**1a**, **1b**, **9**, **13**, **15**, **18**, **20**, **22** and **24**) are listed together with their melting points and elemental analysis data in Table I.

***N*-[3-(3-Piperidinomethylphenoxy)propyl]-4-piperidinocarbonylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane Carboxamide (26a)** A typical example is given to illustrate the general procedure.

Method 1: *N*,*N*′-Carbonyldiimidazole (1.97 g, 12.2 mmol) was added to a suspension of **18b** (3.0 g, 11.6 mmol) in dry CH_2Cl_2 (30 ml). The mixture was stirred for 10 min at room temperature and for an additional 10 min in CH_2Cl_2 under reflux. It was cooled to room temperature, then a solution of 3-(3-piperidinomethylphenoxy)propanamine[1c] (2.87 g, 11.6 mmol) in dry CH_2Cl_2 (30 ml) was added. The reaction mixture was stirred for 1.5 h at room temperature, diluted with CH_2Cl_2 (200 ml), washed twice with water and dried over $MgSO_4$. After removal of the solvent, the residue obtained was recrystallized from a mixture of $CHCl_3$ and ether to give pure **26a**.

Method 2: A mixture of **18b** (2.1 g, 6.69 mmol) and $SOCl_2$ (2 ml) in dry C_6H_6 (3 ml) was refluxed for 1 h. The excess $SOCl_2$ was removed as the toluene azeotrope. A solution of the acid chloride in dry CH_2Cl_2 (10 ml) was added to a mixture of 3-(3-piperidinomethylphenoxy)propanamine (2.0 g, 8.03 mmol) and triethylamine (0.93 g, 6.69 mmol) in dry CH_2Cl_2 (15 ml) under ice-cooling. The resulting mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2, washed with water and brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with a (9 : 1) mixture of $CHCl_3$ and MeOH to give pure **26a**.

Other compounds in this series prepared by method 1 or 2 are listed together with elemental or HRMS analysis data and melting points in Tables II and III. Spectral data for **26** are given in Table VI.

Biological Screening Methods The free base or oxalate of each compound was used for the tests. The compounds were administered at a dose of 10 mg/kg in the primary screening.

Animals: Male Sprague Dawley rats weighing 190—220 g and male Hartley strain guinea pigs weighing 350—550 g were used. Rats were deprived of food, but allowed free access to water, for 24 h prior to the experiments.

Gastric Acid Antisecretory Activity in the Conscious Rat with Gastric Fistula[9] Rats were divided into groups of 5 animals each and anesthetized with ether. The abdomen was opened and an acute gastric fistula was prepared by placing polyethylene tubing in the forestomach with a ligature around the neck of the pylorus. The incision was closed, and the rats were allowed to recover from the anesthesia. The animals were first administered histamine by i.v. infusion. A dose of histamine of 8 mg/kg per hour was selected as the most appropriate stimulant. The aminals were administered a test compound at a dose of 10 mg/kg or vehicle (control) alone, *via* the i.d. route of administration, at 60 min following the start of the histamine infusion. Gastric juice was collected at 60-min intervals for 5 h following the start of histamine infusion. The volume of each 60-min collection was recorded and an aliquot was taken to determine the acid concentration; for this purpose, 0.1 ml of gastric juice was titrated to a pH value of 7.0 with 0.1 aqueous NaOH. The acid output was calculated as follows. The volume of gastric juice (V) collected over the 5-h period after drug administration was divided by the volume (V_0) collected over the 5-h period in the control experiments. This value (V/V_0) multipled by 100 gives the percentage of the observed acid output. Percent inhibition was calculated as follows: percent inhibition = 100 − percent of observed acid output ($V/V_0 \times 100$). The doses giving 50% inhibition of histamine-stimulated gastric acid secretion (ED_{50}) were calculated by linear regression analysis.

Pepsin Activity The pepsin activity in gastric juice was measured by a modification of Anson's method on the basis of excreted amount of pepsin (mg tyrosine per hour).[10]

Antiulcer Activity in Rats Rats were divided into groups of 5 animals each, immobilized in individual stress cages, and immersed in a water bath of which the temperature was thermostatically regulated at 23 ± 1 °C, up to the level of the xiphoid process according to the procedure of Takagi *et al.*[11] After exposure to stress for 7 h, the animals were immediately killed by cervical dislocation and the stomach of each was removed to evaluate the lesions. The ulcer index was expressed as the sum of the length (mm) of all lesions. The animals were orally given either a test compound at the dose of 10 mg/kg or the vechicle alone (control), 5 min before stress loading. The doses inhibiting gastric lesion formation by 50% (ED_{50}) were calculated by linear regression analysis in some case.

Gastrointestinal Cytoprotective Activity in Rats Rats were divided into groups of 5 amimals each. A test compound at the dose of 10 mg/kg or the vehicle alone (control) was orally given to rats 30 min prior to oral administration of 1 ml of a HCl·ethanol solution which was prepared according to the procedure described by Mizui and Doteuchi.[12] One hour after the administration of the HCl·ethanol solution the rats were killed with ether and the stomachs were removed to examine the lesions. The ulcer index was expressed as the sum of the length (mm) of all lesion. The doses inhibiting gastric lesions by 50% (ED_{50}) were calculated by linear regression analysis in some case.

Histamine H_2-Receptor Antagonist Activity The procedure is a modification of that described by Reinhardt *et al.*[13] Guinea pigs were stunned and bled from the femoral artery. The hearts were removed and the right atria were dissected out. Atria under a 0.5-g tension load were placed in a temperature-controlled (31 ± 1 °C) organ bath containing oxygenated (95% O_2 ± 5% CO_2) Krebs–Henseleit buffer of which the composition was as follows: 118 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM $NaHPO_4$, 25 mM $NaHCO_3$, 11 mM glucose. Individual atrial contractions were followed with a gross force-displacement transducer connected to a dynography recorder. A dose–response curve to histamine was obtained by cumulative additions of histamine to the organ bath. The test compounds were added to the organ bath

TABLE VI. MS, IR and ^{1}H-NMR Spectral Data for **26**

Compd. No.	Mass (M^+)	IR (cm^{-1})[a]	^{1}H-NMR ($CDCl_3$)[b] δ (ppm)
26a[d]	489	k: 3225, 1620	1.38—1.50 (2H, m), 1.50—1.72 (10H, m), 2.03 (2H, quin, J=6 Hz), 2.30—2.45 (4H, m), 3.18 (2H, t, J=5 Hz), 3.44 (2H, s), 3.47—3.58 (4H, m), 4.09 (2H, t, J=6 Hz), 4.13—4.23 (6H, m), 6.05—6.15 (1H, m), 6.73—6.79 (1H, m), 6.87—6.96 (2H, m), 7.22 (1H, t, J=8 Hz)
26b	475	k: 3325, 1610	1.38—1.50 (2H, m), 1.51—1.65 (4H, m), 1.80—2.10 (6H, m), 2.31—2.45 (4H, m), 3.36 (2H, t, J=7 Hz), 3.44 (2H, s), 3.43—3.56 (4H, m), 4.09 (2H, t, J=6 Hz), 4.12–4.22 (3H, m), 4.23—4.32 (3H, m), 6.03—6.14 (1H, m), 6.73–6.79 (1H, m), 6.87—6.96 (2H, m), 7.23 (1H, t, J=8 Hz)
26c	491	k: 3200, 1610	1.38—1.50 (2H, m), 1.50—1.65 (4H, m), 2.03 (2H, quin, J=6 Hz), 2.32—2.45 (4H, m), 3.26 (2H, t, J=5 Hz), 3.44 (2H, s), 3.53 (2H, q, J=6 Hz), 3.58—3.74 (6H, m), 4.09 (2H, t, J=6 Hz), 4.15—4.25 (6H, m), 6.04—6.14 (1H, m), 6.72—6.79 (1H, m), 6.86—6.96 (2H, m), 7.23 (1H, t, J=8 Hz)
26d	449	k: 3350, 1630	1.38—1.50 (2H, m), 1.52—1.64 (4H, m), 2.03 (2H, quin, J=6 Hz), 2.30—2.45 (4H, m), 2.91 (3H, s), 2.95 (3H, s), 3.44 (2H, s), 3.52 (2H, q, J=6 Hz), 4.09 (2H, t, J=6 Hz), 4.13—4.21 (3H, m), 4.21—4.28 (3H, m), 6.14 (1H, m), 6.72—6.78 (1H, m), 6.86—6.95 (2H, m), 7.22 (1H, t, J=8 Hz)
26e	435	k: 3250, 1620	1.38—1.50 (2H, m), 1.51—1.63 (4H, m), 2.03 (2H, quin, J=6 Hz), 2.30—2.45 (4H, m), 2.86 (3H, d, J=5 Hz), 3.44 (2H, s), 3.52 (2H, q, J=6 Hz), 4.09 (2H, t, J=6 Hz), 4.17 (6H, s), 5.46—5.60 (1H, m), 6.04—6.16 (1H, m), 6.72—6.79 (1H, m), 6.86—6.96 (2H, m), 7.23 (1H, t, J=8 Hz)
26f	421	k: 1640, 1610	1.32—1.43 (2H, m), 1.43—1.55 (4H, m), 1.86 (2H, quin, J=6 Hz), 2.23—2.35 (4H, m), 3.22 (2H, q, J=6 Hz), 3.37 (2H, s), 3.95 (2H, t, J=6 Hz), 4.03 (6H, s), 6.74—6.86 (3H, m), 6.94 (1H, br s), 7.20 (1H, t, J=8 Hz), 7.24 (1H, br s), 7.80 (1H, t, J=6 Hz)
26g	504	k: 3250, 1620	1.38—1.50 (2H, m), 1.52—1.64 (4H, m), 2.03 (2H, quin, J=6 Hz), 2.31 (3H, s), 2.32—2.45 (8H, m), 3.26 (2H, t, J=5 Hz), 3.44 (2H, s), 3.52 (2H, q, J=6 Hz), 3.62 (2H, t, J=5 Hz), 4.09 (2H, t, J=6 Hz), 4.14—4.25 (6H, m), 6.04—6.15 (1H, m), 6.76 (1H, dd, J=2, 8 Hz), 6.86—6.96 (2H, m), 7.22 (1H, t, J=8 Hz)
26h	520	k: 3250, 1610	1.01 (6H, t, J=7 Hz), 1.37—1.50 (2H, m), 1.50—1.63 (4H, m), 2.02 (2H, quin, J=6 Hz), 2.30—2.45 (4H, m), 2.53 (4H, q, J=7 Hz), 2.55 (2H, t, J=6 Hz), 3.30 (2H, q, J=6 Hz), 3.44 (2H, s), 3.51 (2H, q, J=6 Hz), 4.08 (2H, t, J=6 Hz), 4.16 (6H, s), 6.04—6.14 (1H, m), 6.17—6.28 (1H, m), 6.72—6.79 (1H, m), 6.86—6.94 (2H, m), 7.22 (1H, t, J=8 Hz)
26i	475	k: 3325, 1620	1.50—1.73 (6H, m), 1.73—1.87 (4H, m), 2.02 (2H, quin, J=6 Hz), 2.46—2.57 (4H, m), 3.17 (2H, t, J=5 Hz), 3.45—3.58 (4H, m), 3.59 (2H, s), 4.08 (2H, t, J=6 Hz), 4.13—4.25 (6H, m), 6.04—6.14 (1H, m), 6.73—6.80 (1H, m), 6.87—6.97 (2H, m), 7.23 (1H, t, J=8 Hz)
26j	491	k: 1620	1.49—1.82 (7H, m), 2.04 (2H, quin, J=6 Hz), 2.11—2.26 (1H, m), 2.30—2.40 (1H, m), 2.56 (1H, dd, J=5, 10 Hz), 2.65 (1H, dd, J=2, 10 Hz), 2.81—2.90 (1H, m), 3.17 (2H, t, J=5 Hz), 3.45—3.58 (4H, m), 3.60 (2H, d, J=4 Hz), 4.09 (2H, t, J=6 Hz), 4.12—4.25 (6H, m), 4.30—4.39 (1H, m), 6.17—6.28 (1H, m), 6.73—6.80 (1H, m), 6.89—6.97 (2H, m), 7.23 (1H, t, J=8 Hz)
26k	449	k: 3275, 1630	1.50—1.73 (6H, m), 2.04 (2H, quin, J=6 Hz), 2.24 (6H, s), 3.18 (2H, t, J=5 Hz), 3.40 (2H, s), 3.46—3.58 (4H, m), 4.09 (2H, t, J=6 Hz), 4.13—4.24 (6H, m), 6.02—6.13 (1H, m), 6.74—6.81 (1H, m), 6.85—6.94 (2H, m), 7.23 (1H, t, J=8 Hz)
26l	560	k: 3350, 1630	1.39—1.50 (2H, m), 1.52—1.70 (4H, m), 2.01 (2H, quin, J=6 Hz), 2.32—2.48 (4H, m), 3.44 (2H, s), 3.50 (2H, q, J=6 Hz), 4.03 (6H, s), 4.07 (2H, t, J=6 Hz), 5.95—6.05 (1H, m), 6.72—6.80 (1H, m), 6.85—6.95 (2H, m), 7.21 (1H, t, J=8 Hz), 7.22—7.40 (10H, m)
26m	465	k: 3250, 1680, 1620	1.26 (3H, t, J=7 Hz), 1.38—1.50 (2H, m), 1.51—1.68 (4H, m), 2.03 (2H, quin, J=6 Hz), 2.30—2.45 (4H, m), 3.44 (2H, s), 3.52 (2H, q, J=6 Hz), 4.00—4.20 (8H, m), 4.14 (2H, q, J=7 Hz), 5.20 (1H, br s), 6.00—6.10 (1H, m), 6.74—6.80 (1H, m), 6.89—6.96 (2H, m), 7.22 (1H, t, J=8 Hz)
26n[c]	378	c: 3450, 3000, 2945, 1645, 1520	1.44 (2H, m), 1.57 (4H, m), 2.02 (2H, m), 2.37 (4H, m), 3.44 (2H, s), 3.50 (2H, q), 3.99 (4H, m), 4.07 (2H, t, J=5.5 Hz), 4.20 (3H, m), 6.14 (1H, m), 6.76 (1H, m), 6.90 (2H, m), 7.21 (1H, t, J=8.6 Hz)
26o[c]	489	c: 3450, 3000, 2940, 2860, 1640, 1610	1.42—2.00 (12H, m), 2.02 (2H, m), 2.42 (4H, m), 3.25 (2H, m), 3.40—3.61 (6H, m), 3.92—4.00 (2H, m), 4.07 (2H, t, J=5.7 Hz), 4.21—4.24 (2H, m), 4.37—4.40 (2H, m), 6.27 (1H, m), 6.78—6.80 (1H, m), 6.81—6.95 (2H, m), 7.22 (1H, m)
26p[c]	489	c: 2950, 2930, 1630	1.57 (12H, m), 2.02 (2H, m), 2.36 (4H, m), 3.21 (2H, m), 3.44 (2H, s), 3.47 (2H, m), 3.49 (2H, m), 3.99 (2H, m), 4.04 (2H, m), 4.19 (4H, t, J=3.6 Hz), 6.78 (1H, m), 6.89 (2H, m), 7.19 (1H, m), 9.26 (1H, m)
26q[d]	528	n: 3280, 1620	1.30—1.80 (6H, m), 2.02 (2H, quin, J=6 Hz), 2.20—2.50 (4H, m), 2.90—3.10 (1H, m), 3.32—3.86 (7H, m), 3.45 (2H, s), 3.86—4.38 (6H, m), 5.82—6.10 (1H, m), 6.65—7.00 (3H, m), 7.24 (1H, t, J=8 Hz)
26r	514	n: 3300, 1630	1.68—2.20 (6H, m), 2.40—2.90 (4H, m), 2.90—3.12 (1H, m), 3.32—3.88 (9H, m), 3.90—4.40 (6H, m), 5.88—6.20 (1H, m), 6.68—7.05 (3H, m), 7.24 (1H, t, J=8 Hz)
26s	530	n: 3300, 1620	1.50—3.10 (9H, m), 3.30—4.50 (16H, m), 5.80—6.20 (1H, m), 6.65—7.00 (3H, m), 7.24 (1H, t, J=8 Hz)
26t	488	n: 3320, 1640	1.98 (2H, quin, J=6 Hz), 2.23 (6H, s), 2.89—3.10 (1H, m), 3.31—3.85 (7H, m), 3.39 (2H, s), 3.90—4.31 (6H, m), 5.80—6.10 (1H, m), 6.66—6.88 (3H, m), 7.24 (1H, t, J=8 Hz)
26u[c]	528	k: 3280, 2920, 1730, 1635	1.43 (2H, m), 1.58 (4H, m), 2.03 (2H, quin, J=5.6 Hz), 2.37 (4H, br s), 2.92 (1H, t, J=5.6 Hz), 3.43 (2H, s), 3.50—3.56 (4H, m), 3.60 (1H, m), 3.76 (2H, m), 4.00 (2H, m), 4.07 (2H, t, J=5.6 Hz), 4.25 (2H, m), 6.10 (1H, m), 6.78 (1H, m), 6.90 (1H, m), 6.91 (1H, s), 7.21 (1H, t, J=8 Hz)
26v[c]	560	c: 3560, 3440, 2980, 2930, 1645, 1600	1.42 (2H, m), 1.54 (4H, m), 1.95 (2H, quin, J=5 Hz), 2.35 (4H, m), 3.22 (2H, t, J=5.6 Hz), 3.41 (2H, s), 3.42 (2H, m), 3.52 (3H, m), 3.82 (1H, t, J=5.2 Hz), 4.02 (2H, t, J=5.6 Hz), 6.16 (2H, t, J=7.9 Hz), 6.72 (1H, m), 6.89 (2H, d, J=7.9 Hz), 7.10—7.24 (7H, m), 7.35 (4H, d, J=7.9 Hz)
26w[c]	422	c: 3450, 3020, 2955, 1780, 1660, 1610	1.44 (2H, m), 1.57 (4H, m), 2.01 (2H, m), 2.38 (4H, m), 2.76 (2H, t, J=6.4 Hz), 2.84 (2H, m), 3.28 (2H, m), 3.44 (2H, s), 3.48 (2H, m), 3.57 (1H, m), 4.07 (2H, t, J=5.6 Hz), 5.69 (1H, ddd, J=1.3, 2.3, 7.9 Hz), 6.20 (1H, m), 6.91 (2H, m), 7.23 (1H, t, J=7.9 Hz)

a) k, KBr; c, $CHCl_3$; n, neat. *b*) 300 MHz. *c*) 270 MHz. *d*) 360 MHz.

10 min before the application of histamine. Results were expressed as a percentage of the maximal response established in the absence of antagonists for each preparation. The H_2-receptor antagonist potency was represented as a pA_2 value determined from Schild plots.

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