paring the manuscript. This work was supported by the Auckland Division of the Cancer Society of New Zealand and by the Medical Research Council of New Zealand.

Registry No. 7, 112421-77-9; 8, 112421-78-0; 9, 112421-79-1; 10, 112421-80-4; 11, 112421-81-5; 12, 112421-82-6; 13, 112421-83-7; 14, 112421-84-8; 15, 112421-85-9; 16, 112421-86-0; 17, 112421-87-1; 18, 112421-88-2; 19, 112421-89-3; 20, 112421-90-6; 21, 112421-91-7; 22, 112421-92-8; 23, 112421-93-9; 24, 112421-94-0; 25, 112421-95-1; 25·3HCl, 112422-04-5; 26, 112421-96-2; 27, 112421-97-3; I, 601-87-6; II, 82617-45-6; III, 14294-33-8; IV, 14294-35-0; V (R = H), 112421-98-4; V (R = 2′-aza), 112422-05-6; V (R = 2′-Cl), 112422-06-7; V (R = 3′-aza), 112422-07-8; V (R = 3′-Cl), 112422-08-9; V (R = 4′-aza), 112422-09-0; V (R = 4′-Cl), 112422-11-4; V (R = 4′-F), 112422-10-3; V (R = 4′-Br), 112422-12-5; V (R = 4′-I), 112422-13-6; V (R = 4′-NO_2), 112422-14-7; V (R = 4′-OCH_3), 112422-15-8; VI, 14294-36-1; VII (R = H), 112421-99-5; VII (R = 2′-aza), 112422-16-9; VII (R = 2′-Cl), 112422-17-0; VII (R = 3′-aza), 112422-18-1; VII (R = 3′-Cl), 112422-19-2; VII (R = 4′-aza), 112422-20-5; VII (R = 4′-Cl), 112422-22-7; VII (R = 4′-F), 112422-21-6; VII (R = 4′-Br), 112422-23-8; VII (R = 4′-I), 112422-24-9; VII (R = 4′-NO_2), 112422-25-0; VII (R = 4′-OCH_3), 112422-26-1; VIII, 104728-15-6; IX (R = H), 112422-00-1; IX (R = 2′-aza), 112422-27-2; IX (R = 2′-Cl), 112422-28-3; IX (R = 3′-aza), 112481-47-7; IX (R = 3′-Cl), 112422-29-4; IX (R = 4′-aza), 112422-30-7; IX (R = 4′-F), 112422-31-8; IX (R = 4′-Cl), 112422-32-9; IX (R = 4′-Br), 112422-33-0; IX (R = 4′-I), 112422-34-1; IX (R = 4′-NO_2), 112422-35-2; IX (R = 4′-OCH_3), 112422-36-3; C_6H_6, 71-43-2; *N*-(2-carboxy-6-phenylphenyl)benzamide, 112422-01-2; *N*-[2-(methoxycarbonyl)-6-phenylphenyl]-benzamide, 112422-02-3; 2,8-diphenyl-3,1-benzoxain-4(4*H*)-one, 112422-03-4; *N*,*N*-dimethylethylenediamine, 108-00-9.

Synthesis and Antiulcer Activity of 5,11-Dihydro[1]benzoxepino[3,4-*b*]pyridines

Toshiaki Kumazawa, Hiroyuki Harakawa, Hiroyuki Obase,* Yoshimasa Oiji, Hiroshi Tanaka, Katsuichi Shuto, Akio Ishii, Tetsuo Oka, and Nobuhiro Nakamizo

Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka-ken, 411 Japan. *Received January 23, 1987*

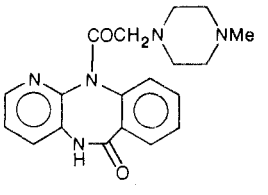
A series of substituted 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridines was synthesized and evaluated for antiulcer activity in water immersion/restrained stress ulcer assay in rats. Structure–activity relationships are described. Most of the tested compounds exhibited low affinity to the muscarinic acetylcholine receptor. The molecular features for the best activities are the 2-(diethylamino)ethylenediamine group at the 5-position of the oxepin ring and an oxepin skeleton rather than a thiepin or a pyran skeleton. Methyl and chlorine substitution on the benzene ring reduced the activity. Compound 11, 5-[[2-(diethylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine trihydrochloride was selected for further evaluation. Synthesis and antiulcer activity of optically active 11 is described. There were no statistically significant differences between (+)-, (−)-, and (±)-11. Compound 11 showed weak antisecretory activity in pylorus-ligated rats. It is now under clinical evaluation as KW 5805.

Peptic ulcers have been generally thought to result from an imbalance between the aggressive forces of acid and pepsin and the defensive forces of resistance.[1] Consequently, antiulcer therapy has been directed toward these two factors. The histamine (H_2) receptor antagonists, anticholinergics, and antacids are known to lower acid secretion.

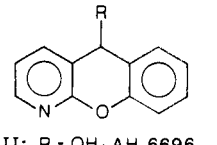
Some tricyclic compounds, I–IV, with a pyridine nucleus have been reported to inhibit gastric acid secretion in animals.[2–5] Pirenzepine is a recently introduced antimuscarinic drug with antiulcer activity.

We have prepared and tested (the objective being novel and potent antiulcer compounds with fewer side effects) a series of 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine derivatives (V) for antiulcer activity (preventive activity against gastric erosions induced by restraint and water immersion stress) and for anticholinergic effect (muscarinic receptor binding assay).

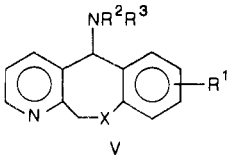
Little work has been reported on the 5,11-dihydro[1]-benzoxepino[3,4-*b*]pyridine structure, and none of the



I: pirenzepine



II: R = OH; AH 6696
III: R = $NR^1CONR^2R^3$
IV: R = $S(CH_2)_nNR^1R^2$



V

compounds possessing gastric antisecretory and/or antiulcer activities have been described.[6]

We found a novel antiulcer agent, 5-[[2-(diethylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]-pyridine trihydrochloride (compound 11) whose pharmacological profile is quite different from the known tricyclic compounds I–IV. The present compound elicits antiulcerogenic effects in various experimental models by mainly acting on the defensive mechanisms.

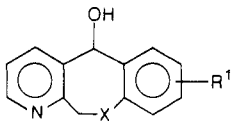
We report here the synthesis and antiulcer activity of 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine derivatives V.

Chemistry. The 5,11-dihydro[1]benzepino[3,4-*b*]pyridine derivatives were synthesized by several routes with

(1) Shay, H.; Sun, D. C. H. In *Gastroenterology*; Bockus, H. L., Ed.; W. B. Saunders: Philadelphia, 1974; Vol. 1, p 579.
(2) Eberlein, V. G.; Schmidt, G.; Reuter, A.; Kutter, E. *Arzneim.-Forsch.* **1977**, *27*, 356.
(3) Ashby, P.; Curwain, B. P.; Daly, M. J.; Mclsaac, R. L. *Br. J. Pharmacol.* **1976**, 440P.
(4) Bristol, J. A.; Gold, E. H.; Lovey, R. G. *J. Med. Chem.* **1981**, *24*, 927.
(5) Bristol, J. A.; Gold, E. H.; Gross, I.; Lovey, R. G. *J. Med. Chem.* **1981**, *24*, 1010.
(6) Tagawa, H.; Kubo, S.; Ishikawa, F. *Chem. Pharm. Bull.* **1981**, *29*, 3515.

0022-2623/88/1831-0779$01.50/0

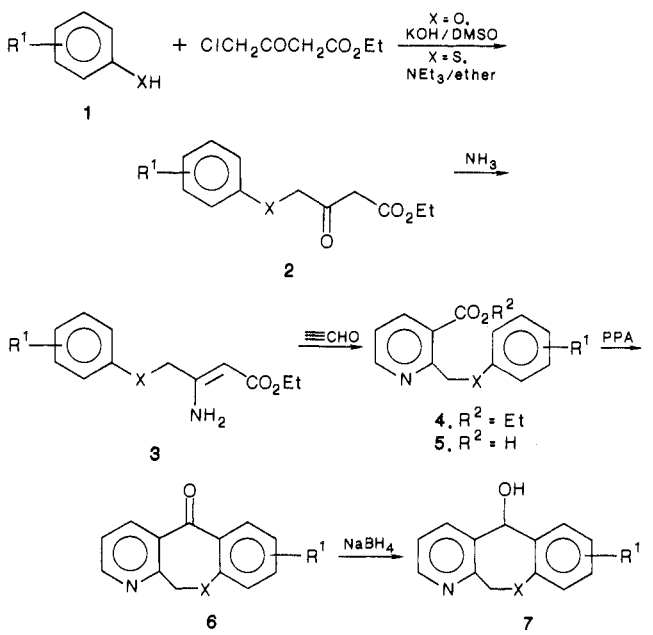
Table I. 5,11-Dihydro[1]benzepino[3,4-*b*]pyridin-5-ols (7)



compd	X	R^1	yield, %	mp, °C	formula[a]	recrystn, solvent
7a	O	H	85	143–144	$C_{13}H_{11}NO_2$	*i*-PrOH
7b	O	7-Me	66	141–142	$C_{14}H_{13}NO_2$	*i*-PrOH
7c	O	7-F	81	174–176	$C_{13}H_{10}NO_2F$	*i*-PrOH
7d	O	7-Cl	74	169–171	$C_{13}H_{10}NO_2Cl$	toluene
7e	O	9-Me	70	135–136	$C_{14}H_{13}NO_2$	toluene
7f	S	H	85	192–194	$C_{13}H_{11}NOS$	*i*-PrOH

[a] All new compounds had C, H, and N microanalyses within 0.4% of theoretical values.

Scheme I



the 5,11-dihydro[1]benzepino[3,4-*b*]pyridin-5-ones **6** and the 5,11-dihydro[1]benzepino[3,4-*b*]pyridin-5-ols **7** as starting materials, which were prepared by the $NaBH_4$ reduction of **6** (Scheme I). The physical properties of **7** are summarized in Table I.

In the reported route to **6** via the carboxylic acid **5**,[6] the yield of **5** was low, so an alternative route to **5** via the γ-keto ester **2** was developed (Scheme I).

4-Phenoxyacetoacetate **2**, which was prepared from the phenol **1** and ethyl 4-chloroacetoacetate, was aminated with NH_3 to give the enamino ester **3**. Condensation of the enamino ester **3** with propargylaldehyde followed by hydrolysis gave nicotinic acid **5**, which was cyclized to **6** with polyphosphoric acid according to the reported method.[6]

The general synthetic method for the compounds V listed in Table II was as found in Scheme II.

Method A. The alcohol **7** was chlorinated by $SOCl_2$ in CH_2Cl_2 to give the chloride, which was treated with amine in CH_2Cl_2 to give the diamines V-A (compounds **10–21** and **34–38**).

Method B. The chloride obtained in method A was aminated with NH_3 in CH_2Cl_2 to give the amine **8**, which was alkylated with chloride to give the diamines V-B (**22–26**).

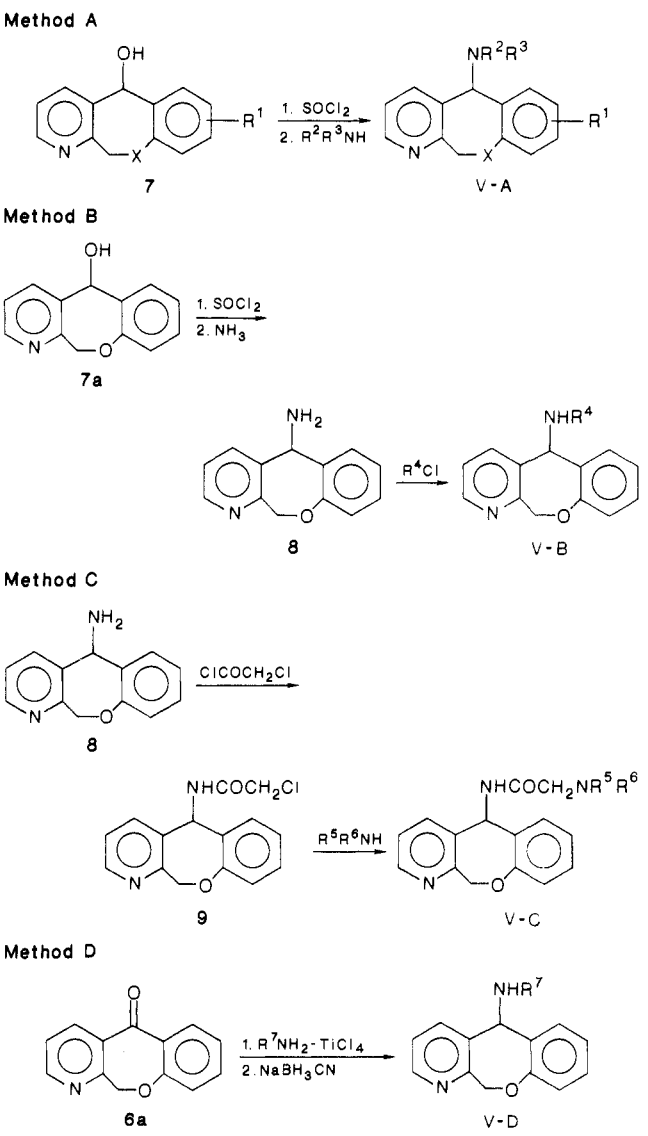
Method C. The amine **8** was acylated with α-chloroacetyl chloride to give **9**, which was treated with amine to give the amides V-C (**27–30**).

Method D. Condensation of the ketone **6** with amine in the presence of $TiCl_4$ in benzene or CH_2Cl_2,[7] followed by reduction with $NaBH_3CN$ in MeOH in weakly acidic media gave the diamines V-D (**31** and **32**).

The acylated analogue **33** was obtained by treatment of **11** with Ac_2O. In order to examine the effect of ring size, the pyran derivative **39** was synthesized from the corresponding alcohol in a similar manner to method A.

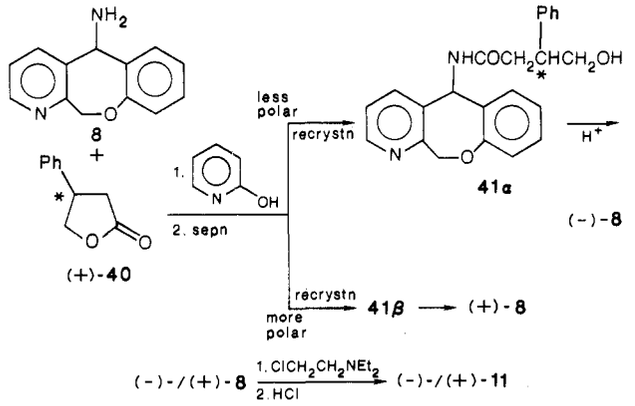
Since **11** possessed the most favorable combination of activity and low side effects, the optically active **11** was synthesized to examine the stereoisomeric effect.

Scheme II



(7) Moretti, I.; Torre, G. *Synthesis* **1970**, 141.

Scheme III



The optically active 8 was synthesized according to the method of Helmchen et al.[8] (Scheme III). Reaction of 8 with (+)-3-phenyl-γ-lactone (**40**) gave a diastereomeric mixture of amides (**41α** and **41β**), which was separated by preparative liquid chromatography to give **41α** (less polar fraction) and **41β** (more polar fraction). The separated **41α** and **41β** were hydrolyzed to (+)-8 and (-)-8,[9] which were alkylated with (*N*,*N*-diethylamino)ethyl chloride to give (+)-11 and (-)-11, respectively.

Larger amounts of (+)- and (-)-11 were obtained by the optical resolution of 11 with L- and D-tartaric acid. The precipitated salt obtained by treatment of the free base 11 with L-tartaric acid was recrystallized to give the L-tartarate of (+)-11, which was converted to its hydrochloride (+)-11. The mother liquor was basified and treated with D-tartaric acid to give the D-tartarate of (-)-11. The recrystallized salt was converted to (-)-11 in a manner similar to (+)-11.[11]

Biological Tests. The compounds were screened for gastric antiulcer activity in a water immersion/restrained stress ulcer in rats. In this test, the compounds were administered at doses of 10 and/or 30 mg/kg orally (po), and immersion was carried out for 7 h.[13]

The compounds were tested for muscarinic receptor binding assay to elucidate their antiulcer mechanisms. The binding assay was carried out as in a previously described method with a minor modification, the use of rat homogenated striatum.[14]

Results and Discussion

The results of antiulcer activity and muscarinic receptor binding assay are shown in Table III.

Most of the compounds tested had significant antiulcer activity against stress-induced ulcer in rats. The structure–activity relationships (SAR) in this model are as follows.

The nature of the side chain at position 5 was critical to activity. Lengthening the side chain of the ethylenediamine analogue **11** reduced activity (**12**). The substitution pattern of the terminal side chain amine at position 5 also profoundly influenced activity. Diethylamino, diisopropylamino, pyrrolidino, and *cis*-α,α′-dimethylpyrrolidino analogues (**11**, **22**, **17**, and **23**) showed the greatest activity. Decreasing the substitution on the terminal amine resulted in a marked loss of activity (**16** and **31**). Substitution of the secondary amine of **11** decreased the potency (**13** and **33**), while the acyl derivatives **27–30** were inactive. Among the compounds having a substituent in the benzene ring (**34–37**), only the 7-fluorine derivative **35** retained activity.

Thiepin **38** and pyran **39** exhibited reduced activity compared to oxepin **11**, so the oxepin skeleton is preferred for enhanced activity. Interestingly, our tricyclic compound **11** showed weak antisecretory activity in pylous-ligated rats (30 mg/kg, id) although tricyclic pyrans II–IV have been reported as potent inhibitors of gastric acid secretion in rats and dogs.

Among the compounds tested, compounds **11**, **17**, **22**, and **23** showed the most potent activity in our primary screening model. However, compounds **22** and **23** caused suppression of salivary secretion and mydriasis based on the anticholinergic effect at 25 mg/kg sc in the rats. At the same dose, compounds **11** and **17** did not show any sign of above anticholinergic side effects.

Structure–activity studies in this series led to the identification of two compounds, **11** and **17**. Of the two analogues, **11** was selected for further evaluation.

Antiulcer activity of optical isomers of **11** was examined in a stress-induced ulcer in rats (Table IV). Among the three isomers [(+)-, (-)- and (±)-11], there were no statistically significant differences.

Most of the tested compounds exhibited low affinity to the muscarinic receptor compared to the antiulcer drug pirenzepine, which has a similar tricyclic skeleton. Little correlation was found between the antiulcer activity and the affinity to the muscarinic receptor. Therefore, it can be presumed that the antiulcer activity of this class of compounds does not mainly result from their antimuscarinic activity.

In conclusion, we have described a new class of antiulcer agents, the 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine derivatives. Among the compounds tested, **11** has potent antiulcer activities and was selected for further development and clinical evaluation as KW 5805. The detailed pharmacology and mechanism of action of **11** will be published elsewhere.[15]

Experimental Section

Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a JEOL PMX-60 or a JEOL JNM GX-270 spectrometer with Me_4Si as internal standard. Elemental analyses were performed by the analytical department of our laboratories.

Chemistry. Ethyl 4-Phenoxyacetoacetate (2a). To a mixture of 13.1 g (0.2 mol) of potassium hydroxide in 200 mL of DMSO was added dropwise a solution of 9.4 g (0.1 mol) of phenol in 15 mL of DMSO. The mixture was stirred at room temperature

(8) Helmchen, G.; Nill, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 65.

(9) The enantiomeric excess was determined according to the reported method.[10] The amine 8 was acylated with (-)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride (MTPA-Cl) to give the amide derivative, which was analyzed by ^{1}H NMR spectroscopy. Both enantiomers were at least 95% ee.

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(11) The enantiomeric excess was determined according to the reported method.[12] The amine 11 was treated with (*R*)-(-)-[1-(1-naphthyl)ethyl]isocyanate to give the urea derivative, which was analyzed by HPLC. Both enantiomers were at least 97.5% ee.

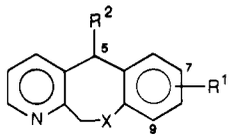
(12) Darmon, A.; Thenot, J. P. *J. Chromatogr.* **1986**, *374*, 321.

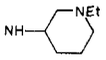
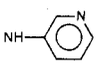
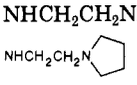
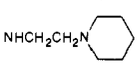
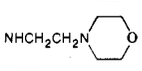
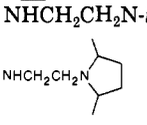
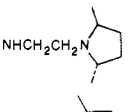
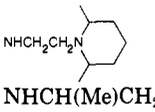
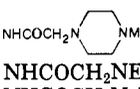
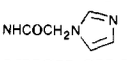
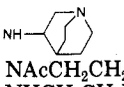
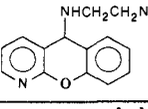
(13) Takagi, K.; Okabe, S. *Jpn. J. Pharmacol.* **1968**, *18*, 9.

(14) Laduron, P. M.; Verwimp, M.; Leysen, J. E. *J. Neurochem.* **1979**, *32*, 421.

(15) Presented in part: Tanaka, H.; Kosaka, N.; Shuto, K.; Oka, T.; Nakamizo, N. *Jpn. J. Pharmacol.* **1987**, *43*, 233 (supplement). Kosaka, N.; Tanaka, H.; Shuto, K. *Jpn. J. Pharmacol.* **1987**, *43*, 233 (supplement). Shuto, K.; Tanaka, H.; Kosaka, N.; Oka, T.; Nakamizo, N. 10th Internationl Congress of Pharmacology, Sydney, Australia, Aug. 1987, Abstracts P-1373.

Table II. Substituted 5,11-Dihydro[1]benzepino[3,4-*b*]pyridine Derivatives (V)



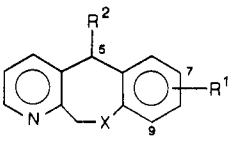
compd	X	R^1	R^2	method of synthesis	yield,[a] %	mp, °C	formula[b]	recrystn solvent[c]
10	O	H	$NHCH_2CH_2NMe_2$	A	49	170–175 dec	$C_{17}H_{21}N_3O{\cdot}3HCl{\cdot}0.5H_2O$	IPA
11	O	H	$NHCH_2CH_2NEt_2$	A	91	195–198 dec	$C_{19}H_{25}N_3O{\cdot}3HCl$	IPA–acetone
12	O	H	$NHCH_2CH_2CH_2NEt_2$	A	72	159–161 dec	$C_{20}H_{27}N_3O{\cdot}3HCl{\cdot}0.5H_2O$	MEK[d]
13	O	H	$NEtCH_2CH_2NEt_2$	A	75	126–129 dec	$C_{21}H_{29}N_3O{\cdot}3HCl{\cdot}H_2O$	IPA
14	O	H		A	76	165–170 dec	$C_{20}H_{25}N_3O{\cdot}3HCl{\cdot}2H_2O$	IPA
15	O	H		A	76	132–136	$C_{18}H_{15}N_3O$	IPE
16	O	H	$NHCH_2CH_2NH_2$	A	83	180 dec	$C_{15}H_{17}N_3O{\cdot}3HCl{\cdot}0.5H_2O$	IPA[d]
17	O	H		A	95	155–160 dec	$C_{19}H_{23}N_3O{\cdot}3HCl{\cdot}0.5H_2O$	IPA
18	O	H		A	68	190–195 dec	$C_{20}H_{25}N_3O{\cdot}3HCl{\cdot}H_2O$	IPA[d]
19	O	H		A	83	199–204 dec	$C_{19}H_{23}N_3O_2{\cdot}3HCl{\cdot}H_2O$	IPA
20	O	H		A	76	100–102	$C_{18}H_{21}N_3O$	*n*-hexane
21	O	7-Me		A	65	115–118	$C_{19}H_{23}N_3O$	*n*-hexane
22	O	H	$NHCH_2CH_2N$-*i*-Pr_2	B	68	190–200 dec	$C_{21}H_{29}N_3O{\cdot}3HCl{\cdot}0.5H_2O$	IPA
23	O	H		B	33	195–200 dec	$C_{21}H_{27}N_3O{\cdot}3HCl{\cdot}1.5H_2O$	IPA
24	O	H		B	18	185–192 dec	$C_{21}H_{27}N_3O{\cdot}3HCl{\cdot}0.5H_2O$	IPA
25	O	H		B	63	178–181 dec	$C_{22}H_{29}N_3O{\cdot}3HCl{\cdot}3H_2O$	IPA
26	O	H	$NHCH(Me)CH_2NEt_2$	B	24	168 dec	$C_{20}H_{27}N_3O{\cdot}C_6H_{14}O$[e]$\cdot 3HCl{\cdot}H_2O$	IPA–IPE
27	O	H		C	86	148–152 dec	$C_{20}H_{24}N_4O_2{\cdot}C_4H_4O_4$[f]$\cdot 1.5H_2O$	MEK[d]
28	O	H	$NHCOCH_2NEt_2$	C	97	148–153 dec	$C_{19}H_{23}N_3O_2{\cdot}C_4H_4O_4$[f]$\cdot 1.5H_2O$	acetone[d]
29	O	H	$NHCOCH_2N$-*i*-Pr_2	C	70	148–153	$C_{21}H_{27}N_3O_2$	*n*-hexane
30	O	H		C	84	184–186	$C_{18}H_{16}N_4O_2$	toluene
31	O	H	$NHCH_2CH_2NHEt$	D	96	172–175	$C_{17}H_{21}N_3O{\cdot}0.5C_3H_8O$[g]$\cdot 3HCl$	IPA
32	O	H		D	33	180 dec	$C_{20}H_{23}N_3O{\cdot}3HCl{\cdot}H_2O$	IPA–IPE
33	O	H	$NAcCH_2CH_2NEt_2$		77	87–89 dec	$C_{21}H_{27}N_3O_2{\cdot}2HCl{\cdot}xH_2O$[h]	IPA
34	O	7-Me	$NHCH_2CH_2NEt_2$	A	93	203–208 dec	$C_{20}H_{27}N_3O{\cdot}3HCl{\cdot}0.5H_2O$	IPA
35	O	7-F	$NHCH_2CH_2NEt_2$	A	62	212–215 dec	$C_{19}H_{24}N_3OF{\cdot}3HCl{\cdot}0.5H_2O$	IPA
36	O	7-Cl	$NHCH_2CH_2NEt_2$	A	83	211–215 dec	$C_{19}H_{24}N_3OCl{\cdot}3HCl{\cdot}0.5H_2O$	IPA–IPE
37	O	9-Me	$NHCH_2CH_2NEt_2$	A	55	180 dec	$C_{20}H_{27}N_3OCl{\cdot}3HCl{\cdot}xH_2O$[h]	IPA–IPE
38	S	H	$NHCH_2CH_2NEt_2$	A	79	175 dec	$C_{19}H_{25}N_3S{\cdot}3HCl{\cdot}H_2O$	IPA–IPE
39				A	85	170–171 dec	$C_{18}H_{23}N_3O{\cdot}3HCl$	IPA

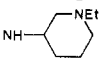
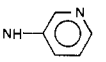
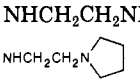
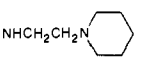
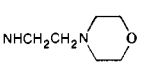
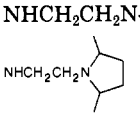
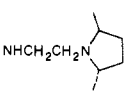
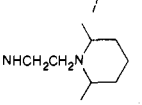
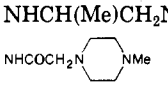
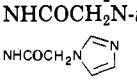
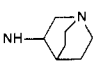
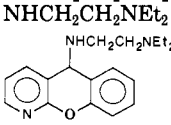
[a] As free base. [b] All new compounds had C, H, and N microanalyses within 0.4% of theoretical values, except **13** (H: calcd, 7.34; found, 7.93); **19** (C: calcd, 50.40; found, 50.86), **23** (N: calcd, 8.87; found, 8.45), and **27** (N: calcd, 11.31; found, 10.77). [c] IPA, isopropyl alcohol; MEK, methyl ethyl ketone; IPE, isopropyl ether. [d] Trituration solvent. [e] $C_6H_{14}O$, isopropyl ether. [f] $C_4H_4O_4$, fumaric acid. [g] C_3H_8O, 2-propanol. [h] Very hygroscopic. [i] Starting material was a mixture of cis and trans isomers.

for 15 min and then 16.5 g (0.1 mol) of ethyl 4-chloroacetoacetate was added. The mixture was stirred at room temperature overnight and then acidified with 4 N HCl. The mixture was extracted with ether, washed with water and brine, dried, and concentrated in vacuo. Vacuum distillation of the residue gave 13.4 g (60%) of ethyl 4-phenoxyacetoacetate (**2a**): bp 117–120 °C (0.7 mmHg); IR (liquid film), 1720, 1600, 1495 cm^{-1}; ^1H NMR (CCl_4) δ 1.20 (t, 3 H, J = 7), 3.43 (s, 2 H), 4.06 (q, 2 H, J = 7), 4.45 (s, 2 H), 6.62–7.35 (m, 5 H).

Ethyl 3-Amino-4-phenoxycrotonate (3a). NH_3 was introduced into 166.0 g (0.75 mol) of ethyl 4-phenoxyacetoacetate at room temperature for 2 h. The internal temperature reached 60 °C. The mixture was stirred at room temperature for 1 **h**, and then excess NH_3 was removed in vacuo. The mixture was dis-

Table III. Antiulcer Activities and Affinities to the Muscarinic Receptor of Compound V



compd	X	R^1	R^2	% inhibn of stress-induced ulcer in rats:[a] po dose, mg/kg		% inhibn of muscarinic receptor binding: concn, M	
				30	10	10^{-5}	10^{-6}
10	O	H	$NHCH_2CH_2NMe_2$	85**	24	36	11
11	O	H	$NHCH_2CH_2NEt_2$	85***	65***	26	4
12	O	H	$NHCH_2CH_2CH_2NEt_2$	55**	34	40	10
13	O	H	$NEtCH_2CH_2NEt_2$	33		15	3
14	O	H		67**		50	11
15	O	H		15		12	4
16	O	H	$NHCH_2CH_2NH_2$	19		0	−3
17	O	H		72**	68**	35	3
18	O	H		52**		33	6
19	O	H		73***	7	1	−1
20	O	H		76***	28	49	19
21	O	7-Me		7		16	2
22	O	H	$NHCH_2CH_2N$-*i*-Pr_2	88***	61**	39	5
23	O	H		94***	67***	29	6
24	O	H		69**	64*	32	3
25	O	H		64**		28	3
26	O	H	$NHCH(Me)CH_2NEt_2$	62*		56	11
27	O	H		56*	31	6	3
28	O	H	$NHCOCH_2NEt_2$	16	10	4	1
29	O	H	$NHCOCH_2N$-*i*-Pr_2	45*	17	12	3
30	O	H		12	6	5	0
31	O	H	$NHCH_2CH_2NHEt$	55*		10	2
32	O	H		36		79	27
33	O	H	$NAcCH_2CH_2NEt_2$	0		18	1
34	O	7-Me	$NHCH_2CH_2NEt_2$	40		38	8
35	O	7-F	$NHCH_2CH_2NEt_2$	87***	53*	37	4
36	O	7-Cl	$NHCH_2CH_2NEt_2$	30		46	10
37	O	9-Me	$NHCH_2CH_2NEt_2$	48*	36*	35	7
38	S	H	$NHCH_2CH_2NEt_2$	19		61	16
39				60**	18	0	−4
			pirenzepine	86***	67***	83	38
			cimetidine	39*	33	2	2

[a] Mean value from five determinations. The homogeneity in variance was verified by the *F* test. The significance of difference between means was verified by the Student's *t* test. When the variance was not homogeneous, the significance of difference between means was verified by the Aspin–Welch method. (***) $P < 0.001$, (**) $P < 0.01$, (*) $P < 0.05$ vs respective control value by the Student's *t* test.

Table IV. Antiulcer Activities and Affinities to the Muscarinic Receptor of Optically Active 11

compd	% inhibn of stress-induced ulcer in rats: po,[a] 10 mg/kg	% inhibn muscarinic receptor binding: concn, M		K_i, μM
		10^{-5}	10^{-6}	
(+)-11	63**	21	2	3.0
(−)-11	55**	38	3	1.1
(±)-11	57*	26	4	1.6

[a] Mean value from five determinations. (**) $P < 0.01$, (*) $P < 0.05$ vs control.

solved in ether, washed with water and brine, dried, and concentrated in vacuo to give 158.9 g (96%) of ethyl 3-amino-4-phenoxycrotonate (**3a**): IR (liquid film) 3470, 3300, 1670, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7), 4.05 (q, 2 H, J = 7), 4.43 (s, 2 H), 4.62 (s, 1 H), 6.1–7.5 (m, 7 H).

Ethyl 2-(Phenoxymethyl)nicotinate (4a). To a solution of 140.8 g (0.64 mol) of **3** in 150 mL of toluene was added a solution of 34.4 g (0.64 mol) of propargylaldehyde in 60 mL of toluene. The temperature kept below 35 °C. The mixture was stirred at room temperature for 1 h and then at 90 °C for 3 h. Upon cooling, 700 mL of ether was added, and the ether solution was washed with 1 N NaOH and water and then extracted with 4 N HCl twice. The combined aqueous layer was washed with ether, basified with 10 N NaOH, and extracted with ether. The ether layer was washed with water and brine, dried, and concentrated in vacuo to give 117.0 g (71.5%) of **4a** as an oil: ^1H NMR (CCl_4) δ 1.20 (t, 3 H, J = 7), 4.19 (q, 2 H, J = 7), 5.33 (s, 2 H), 6.52–7.33 (m, 5 H), 7.92 (dd, 1 H, J = 1.5 and 7), 8.43 (dd, 1 H, J = 1.5 and 5).

5,11-Dihydro[1]benzoxepino[3,4-*b*]pyridin-5-one (6a). The obtained **4a** was converted to 5,11-dihydro[1]benzoxepino[3,4-*b*]pyridin-5-one according to the reported method.[6]

5,11-Dihydro[1]benzoxepino[3,4-*b*]pyridin-5-ol (7a). To a solution of 11.1 g (53 mmol) of **6a** in 160 mL of EtOH was added 1.3 g (34 mmol) of NaBH at 0 °C, and the mixture was stirred at room temperature for 3 h. After concentration in vacuo, 50 mL of water was added, and the mixture was extracted with AcOEt, dried, and concentrated in vacuo to give crude **7a** (10.5 g). Recrystallization from i-PrOH gave 9.5 g (85%) of **7a** (Table I): mp 143–144 °C; IR (KBr) 3250, 1590, 1580, 1485, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.19 and 5.42 (q, 2 H, AB type, J = 16), 5.78 (s, 1 H), 6.95–7.6 (m, 5 H), 7.80 (dd, 1 H, J = 2 and 8), 8.33 (dd, 1 H, J = 2 and 5). Anal. ($C_{13}H_{11}NO_2$) C, H, N.

Method A. 5-[[2-(Dimethylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine Trihydrochloride (10). To a solution of 1.0 g (4.7 mmol) of **7a** in 15 mL of CH_2Cl_2 was added a solution of 0.67 mL (9.2 mmol) of $SOCl_2$ in 5 mL of CH_2Cl_2 at 0 °C. After being stirred at 0 °C for 30 min and then at room temperature for 1 h, the mixture was concentrated in vacuo. The residue was dissolved in 10 mL of CH_2Cl_2 and added to a solution of 2.1 g (23.5 mmol) of *N,N*-dimethylethylenediamine in 10 mL of CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. After addition of 20 mL of CH_2Cl_2, the mixture was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on silica gel eluted with AcOEt–Et_3N–MeOH (100:5:4) to give 0.65 g (49%) of the free base of **10** as an oil: IR (liquid film) 3300, 2930, 2820, 1590, 1580, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 6 H), 2.30–2.83 (m, 4 H), 4.52 (s, 1 H), 5.03 and 5.74 (q, 2 H, AB type, J = 15), 6.80–7.33 (m, 5 H), 7.60 (dd, 1 H, J = 2 and 8), 8.38 (dd, 1 H, J = 2 and 4.5). This oil (0.65 g, 2.3 mmol) was dissolved in 10 mL of i-PrOH and 1.5 mL of 7 M HCl–i-PrOH was added to form crystals. Recrystallization from i-PrOH gave 0.43 g (23%) of **10** (Table II).

Method B. 5-[[2-(Diisopropylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine Trihydrochloride (22). To a solution of 4.3 g (20 mmol) of **7a** in 60 mL of CH_2Cl_2 was added a solution of 1.6 mL (22 mmol) of $SOCl_2$ in 20 mL of CH_2Cl_2 at 0 °C. After being stirred at 0 °C for 30 min and then at room temperature for 1 h, the mixture was concentrated in vacuo. The residue was dissolved in 50 mL of CH_2Cl_2 and added to 200 mL of saturated NH_3–CH_2Cl_2 at 0 °C. After being stirred at 0 °C for 1 h and then at room temperature for 2 h, the mixture was washed with water, dried, and concentrated in vacuo. Trituration of the residue with i-Pr_2O gave the crystalline product. Recrystallization from i-Pr_2O gave 3.62 g (85%) of **8** as colorless crystals: mp 72–73 °C; IR (KBr) 3280, 1549, 1490, 1430, 1220, 1050, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.92 (s, 1 H), 5.11 and 5.52 (q, 2 H, AB type, J = 16), 6.90–7.47 (m, 5 H), 7.65 (dd, 1 H, J = 2 and 8), 8.37 (dd, 1 H, J = 2 and 5). Anal. ($C_{13}H_{12}N_2O$) C, H, N.

A mixture of 2.0 g (9.4 mmol) of **8**, 2.83 g (14.1 mmol) of (*N,N*-diisopropylamino)ethyl chloride hydrochloride, 3.9 mL of NEt_3, and 0.2 g of KI in 35 mL of toluene was refluxed for 3 h. Upon cooling, 50 mL of toluene was added, and the mixture was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on silica gel with toluene–Et_3N (10:1) as eluent to give 2.17 g (68%) of free base of **22** as an oil. This was converted to its hydrochloride in a similar manner to that of **10**.

Method C. 5-[[(*N,N*-Diisopropylamino)acetyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine (29). To a solution of 1.87 g (8.8 mmol) of **8** and 1.2 mL (8.8 mmol) of NEt_3 in 30 mL of CH_2Cl_2 was added dropwise a solution of 1.0 g (8.8 mmol) of α-chloroacetyl chloride in 5 mL of CH_2Cl_2 at 0 °C, and the mixture was stirred at 0 °C for 2 h. After concentration in vacuo to one-third volume, 40 mL of i-Pr_2O and 10 mL of water were added. The resultant crystalline product was collected by filtration and dried to give 2.39 g (94%) of **9** as colorless crystals. An analytical sample was obtained by recrystallization from i-PrOH: mp 184 °C dec; IR (KBr) 3430, 3150, 2950, 1680, 1550, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 2 H), 5.03 and 5.53 (q, 2 H, AB type, J = 16), 6.00 (d, 1 H, J = 9), 6.92–7.60 (m, 5 H), 7.71 (m, 2 H), 8.42 (dd, 1 H, J = 1 and 4.5). Anal. ($C_{15}H_{13}N_2O_2Cl$) C, H, N.

A mixture of 2.16 g (7.5 mmol) of **9**, 5.4 mL (38.5 mmol) of diisopropylamine, and 0.25 g of KI in 40 mL of toluene was refluxed for 13 h. Upon cooling, 30 mL of AcOEt was added, and the mixture was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–Et_3N (20:1) as eluent to give a solid, which was recrystallized from n-hexane to afford 1.86 g (70%) of **29** as colorless needles (Table II).

Method D. 5-[[2-(Ethylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine Trihydrochloride (31). To a solution of 14.6 g (69 mmol) of **6a** and 60.8 g (690 mmol) of *N*-ethylethylenediamine in 350 mL of CH_2Cl_2 was added dropwise a solution of 7.6 mL (69 mmol) of $TiCl_4$ in 50 mL of CH_2Cl_2 at 0 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0 °C, and a solution of 7.6 mL of $TiCl_4$ in 50 mL of CH_2Cl_2 was added. After being stirred at room temperature for 2 days, the reaction mixture was poured into cooled 0.5 N NaOH and then filtered. The filtrate was separated, and the organic layer was dried and concentrated in vacuo. The residue was chromatographed on silica gel with AcOEt–Et_3N–MeOH (10:1:1) as eluent to give 18.0 g of the imine (*E,Z* mixture) as an oil (93%): IR (liquid film) 3300, 2962, 1624, 1479, 1440, 1306 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, 3 H, J = 7), 1.38 (br s, 1 H), 2.64 (q, 2 H, J = 7), 2.94 (t, 2 H, J = 6), 3.53–3.85 (m, 2 H), 5.24 (s, 2 H), 6.73–8.12 (m, 6 H), 8.38–8.61 (m, 1 H).

To a solution of 17.9 g (63.6 mmol) of the imine and a small amount of bromocresol green was added HCl–i-PrOH until the solution became yellow. Then, 6.0 g (96 mmol) of $NaBH_3CN$ was added, and the mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo, and CH_2Cl_2 and 0.5 N NaOH were added. The organic layer was separated, dried, and concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH–Et_3N (10:1:1) as eluent to give 17.9 g (99%) of the free base of **31** as an oil. This was converted to its hydrochloride in a similar manner to that of **10**.

5-[*N*-Acetyl-*N*-[2-(diethylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine Dihydrochloride (33). To a solution of 2.8 g (6.6 mmol) of **11** (free amine) and 3.7 mL (26.8 mmol) of NEt_3 in 50 mL of CH_2Cl_2 was added dropwise a solution of 0.63 g (8.0 mmol) of acetyl chloride in 5 mL of CH_2Cl_2 at 0 °C. After the mixture was stirred at room temperature for 2 h, 30 mL of CH_2Cl_2 was added, and the mixture was washed with aqueous $NaHCO_3$ and water, dried, and concentrated in vacuo. The residue was chromatographed on silica gel with

AcOEt–NEt (100:8) as eluents to give 1.81 g of the free base of **33** as an oil (77%). This was converted to its hydrochloride in a similar manner to that of **10**.

Optical Resolution of 8. A solution of 4.88 g (23.0 mmol) of **8**, 4.98 g (30.7 mmol) of (+)-**40** [$[\alpha]^{20}_D$ +53.3° (*c* 2, MeOH)], and 2.95 g (30.7 mmol) of 2-hydroxypyridine was refluxed for 24 h under an Ar atmosphere. Upon cooling, 200 mL of CH_2Cl_2 was added, and the mixture was washed with water, dried, and concentrated in vacuo. The residue was chromatographed with use of a preparative liquid chromatography [system-500 (Waters Ltd.); column, silica gel; eluent, AcOEt–Et_3N–EtOH (200:10:1)] to give 3.15 g of 41α (less polar fraction) (37%) and 3.50 g of 41β (more polar fraction) (41%), which were recrystallized from toluene to give 2.76 g of 41α and 3.09 g of 41β, respectively, as colorless crystals.

41α: mp 159.5–160 °C; IR (KBr) 3400, 1640, 1590, 1220 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.40 (dd, 1 H, J = 7.5 and 14), 2.67 (dd, 1 H, J = 6.5 and 14), 3.15–3.25 (m, 1 H), 3.73 (dd, 1 H, J = 1 and 6.5), 4.94 and 5.31 (q, 2 H, AB type, J = 16.5), 5.93 (d, 1 H, J = 9), 6.76 (d, 1 H, J = 9), 7.02–7.36 (m, 10 H), 7.78 (dd, 1 H, J = 1.5 and 8), 8.43 (dd, 1 H, J = 1.5 and 5).

41β: mp 157–159 °C; IR (KBr) 3370, 1640, 1590, 1225 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.52 (dd, 1 H, J = 6.5 and 4.5), 2.66 (dd, 1 H, J = 7 and 14.5), 3.18–3.28 (m, 1 H), 3.72 (d, 1 H, J = 6), 4.99 and 5.43 (q, 2 H, AB type, J = 9), 7.04–7.36 (m, 10 H), 7.86 (dd, 1 H, J = 1.5 and 7.5), 8.45 (d, 1 H, J = 4.5).

The mixture of 2.72 g (7.3 mmol) of 41α and 14.6 mL of 1 N H_2SO_4 in dioxane–water (1:1) was stirred at 90 °C for 15 h. Upon cooling, 50 mL of water was added, and the aqueous layer was washed with 30 mL of toluene–AcOEt (3:1). The aqueous layer was basified with 10 N NaOH and extracted with AcOEt. The AcOEt extract was dried and concentrated in vacuo. The residue was chromatographed on silica gel with toluene–AcOEt–Et_3N (30:10:2) as eluents to give 1.30 g of (–)-**8** as a viscous oil, which was treated with i-Pr_2O to give a solid. Recrystallization from i-Pr_2O gave 0.92 g (59%) of (–)-**8** as colorless crystals. (+)-**8** was obtained from 41β in a similar manner (61%). (–)-**8**: mp 89.5–91.5 °C; $[\alpha]^{20}_D$ –179.1° (*c* 0.80, MeOH). (+)-**8**: mp 89.5–91 °C; $[\alpha]^{20}_D$ +173.8° (*c* 0.80, MeOH).

(–)-5-[[2-(Diethylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine Trihydrochloride [(–)-11]. A mixture of 0.85 g (4 mmol) of (–)-**8**, 0.72 g (4.2 mmol) of 2-(diethylamino)ethyl chloride hydrochloride, 0.7 mL of diisopropylethylamine, and a catalytic amount of KI in 16 mL of acetonitrile was refluxed for 8 h. Upon cooling, 50 mL of AcOEt was added, and the mixture was washed with 1 N NaOH and water, dried, and concentrated in vacuo. The residue oil was chromatographed on silica gel with n-hexane–AcOEt–Et_3N (40:20:3) and then AcOEt–Et_3N (20:1) as eluents to give 0.68 g (55%) of the free base of (–)-11 as an oil. This was converted to the trihydrochloride in a similar manner to that of **10**. Recrystallization from i-PrOH gave 0.66 g of (–)-11. mp 185 °C dec; $[\alpha]^{20}_D$ –136.7° (*c* 0.66, MeOH).

(+)-5-[[2-(Diethylamino)ethyl]amino]-5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine Trihydrochloride [(+)-11]. (+)-11 was obtained from (+)-8 in a similar manner to that of (–)-11: mp 186 °C; $[\alpha]^{20}_D$ +135.6° (*c* 0.73, MeOH).

Optical Resolution of 11. To a solution of 148.0 g (0.475 mol) of the free base of 11 in 3.5 L of MeOH was added 142.6 g (0.95 mol) of L-tartaric acid, and the mixture was stirred at 60 °C. Upon cooling, the resultant crystals were collected by filtration and dried. Recrystallization from MeOH three times gave 90.7 g (31%) of (+)-11 di-L-tartarate, $[\alpha]^{20}_D$ +100.5° (*c* 1, H_2O). The di-L-tartarate of (+)-11 (89.7 g, 0.417 mol) was neutralized with aqueous KOH and extracted with CH_2Cl_2. The extracts were washed with water, dried, and concentrated in vacuo to give 43.9 og the free base of (+)-11. This was dissolved in 370 mL of i-PrOH, and 35.9 mL of concentrated HCl was added. The mixture was refluxed until dissolved, and then 300 mL of acetone was added. The mixture was stirred at room temperature overnight. The resulting crystals were collected by filtration, washed with i-PrOH and acetone, and dried to give 46.5 g (75%) of (+)-11 trihydrochloride: mp 185 °C dec; $[\alpha]^{20}_D$ +132° (*c* 1, H_2O).

The filtrate of the di-L-tartarate was neutralized and extracted with CH_2Cl_2 to give 68.2 g of (–)-rich free base of 11. This was dissolved in 1.9 L of MeOH, and 63.0 g (0.42 mol) of D-tartaric acid was added. The mixture was heated to reflux. Upon cooling, the resulting crystals were collected by filtration and dried. Recrystallization from MeOH gave 101.1 g (35% from the free base of 11) of (–)-11 di-D-tartarate: $[\alpha]^{20}_C$ –101.1° (*c* 1, H_2O). This salt was converted to 49.3 g (71%) of (–)-11 in a similar manner as (+)-11: mp 186 °C dec; $[\alpha]^{20}_D$ –132° (*c* 1, H_2O).

Biology. Stress-Induced Ulcer (Restraint and Water Immersion) in the Rat.[13] The compounds were administered at doses of 10 and/or 30 mg/kg. Rats, 190–210 g, were deprived of food but allowed free access to water for 17 h before the experiment. They were placed in the stress cage and immersed in a water bath (23 ± 1 °C) for 7 h, during which time food and water were withheld. The animals were then immediately killed by inhalation of CO_2. The stomach of each was removed. The stomach was then incised along the greater curvature and examined for ulcers developed in the glandular portion. The test compounds were given to the rats 10 min before the water immersion in a volume of 0.5 mL/100 g of body weight. The gastric ulcers were observed, and the total length (mm) was measured. The percent (%) inhibition was obtained by the following formula:

$$\% \text{ inhibition} = [[\text{ulcer length (control)} - \text{ulcer length (treated)}]/\text{ulcer length (control)}] \times 100$$

Muscarinic Acetylcholine Receptor Binding Assay. The binding assay was carried out as in the previously described method with minor modification.[14] The striatum of the rat was homogenized in 10 volumes of distilled water with a Potter–Elvehjem homogenizer. This homogenate preparation was diluted to 200 volumes of the wet tissue weight with 50 mM sodium–potassium phosphate buffer solution (pH 7.4). Next, 50 μL of ^3H-quinuclidinyl benzilate solution (final concentration 1.26 nM) and the drug solution (10% ethanol, 50 μL) were added to 1 mL of the homogenate (corresponds to 5 mg of wet tissue) and incubated at 37 °C for 60 min. Nonspecific binding was determined by addition of unlabeled dexetimide (10% ethanol solution, final concentration 1 μM). The assay was terminated by rapid filtration under reduced pressure over Whatman GF/B filter. The filters were rinsed three times with 5 mL of ice-cold 50 mM sodium–potassium phosphate buffer (pH 7.4), transferred to counting vials containing 7 mL of cintillator (Scintisole EX-H, Wako), and counted by liquid scintillation spectrometry (Packard Tri-Carb 330).

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