Amphoteric Drugs. 3. Synthesis and Antiallergic Activity of 3-[(5,11-Dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)piperidino]propionic Acid Derivatives and Related Compounds

Nobuhiko Iwasaki,* Tetsuo Ohashi, Keiichi Musoh, Hiroyuki Nishino, Noriyuki Kado, Shingo Yasuda, Hideo Kato, and Yasuo Ito

Research and Development Division, Hokuriku Seiyaku Co., Ltd., 37-1-1 Inokuchi, Katsuyama, Fukui, 911, Japan

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An important approach to the design of antiallergic agents with reduced penetration into the central nervous system (CNS) is described. A series of 3-[(5,11-dihydro[1]benzoxepino[4,3-*b*]-pyridin-11-ylidene)piperidino]propionic acid derivatives (**31**–**47**) and related compounds (**48**–**54**) were synthesized and evaluated for antiallergic activity and penetration of a compound into the CNS in comparison with the corresponding 6*H*-dibenz[*b*,*e*]oxepin derivative (**3**). Combination of zwitterionization and introduction of a pyridine component resulted in an increase in antiallergic activity and a great reduction of penetration into the CNS, which was evaluated by the selectivity (*B*/*A*) of antihistaminic activities in the central system [ID_{50} value (*B*) for *ex vivo* H_1 binding to mouse brain membranes] and in the peripheral system [ED_{50} value (*A*) for inhibitory effect on histamine-induced increase in vascular permeability in mice]. This surprising reduction of penetration into the CNS could be considered on the basis of an increase in hydrophilicity caused by both of the zwitterionization and the introduction of a pyridine component. 3-[4-(8-Fluoro-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)piperidino]propionic acid (**33**) exhibited a strong antiallergic effect in various experimental models and very low penetration into the CNS. Compound **33** (HSR-609) is now under clinical trial as a promising antiallergic agent with greatly reduced penetration into the CNS.

Introduction

There has been intense effort aimed at the development of nonsedative antiallergic agents, and several compounds have been shown to be effective clinically in the treatment of various allergic disorders.[1] These antiallergic agents could be classified into two groups by chemical structure.[2] One group is comprised of acidic antiallergic agents such as disodium cromoglycate (DSCG),[3] which show antiallergic activities by inhibiting release of various chemical mediators. The other is comprised of basic antiallergic agents such as ketotifen[4] and loratadine.[5] These agents possess strong antihistaminic activities in mice and guinea pigs but relatively weak effects in a rat model. Recently, a new class of compounds bearing both acidic and basic parts in their molecules have been reported (*e.g.*, acrivastine,[6] cetirizine,[7] KW-4679,[8] and AHR-13268D[9]). Agents of this type could be referred to as amphoteric or zwitterionized antiallergic agents.

We have synthesized many amphoteric compounds by conversion of *N*-alkyl (especially *N*-methyl) groups into *N*-alkylenecarboxy groups and examined modification of pharmacological activities, such as antiallergic activity and effects on the central nervous system (CNS). In our previous paper,[10] we described the possibility of converting classical tricyclic antihistaminic (cyproheptadine,[11] **1**) and related compounds into new amphoteric antiallergic agents. The results obtained by our study were as follows: (1) *N*-alkylenecarboxylic acids such as **3** exhibited stronger antiallergic activities in both rats and guinea pigs *in vivo* than the corresponding *N*-methyl derivatives such as **2**; (2) zwitterionization was capable of reducing undesirable CNS side effects, exemplified by prolongation of sleeping time on hexobarbital-induced anesthesia; (3) the optimum length of the alkylene chain between the nitrogen atom of the piperidine ring and the carboxyl group was shown to be two (propionic acid derivative), on the basis of a large safety area represented by the difference between the dose producing antiallergic effect and that causing undesirable CNS side effects; and (4) introduction of an oxygen atom into the central seven-membered ring in the tricyclic system leading to **3** enhanced antiallergic activity.

Further evaluation of **3** revealed, however, that the zwitterionization did not always reduce penetration of a compound into the CNS, which was evaluated by the selectivity (*B*/*A*) of antihistaminic activities in the central system [ID_{50} value (*B*) for *ex vivo* H_1 binding to mouse brain membranes] and in the peripheral system [ED_{50} value (*A*) for inhibitory effect on histamine-induced increase in vascular permeability in mice] (Table 3). Thus the reduction of the CNS side effects in the amphoteric compounds would not be attributed to reduction of the penetration into the CNS but to reduction of binding affinity for the receptors which were associated with the CNS action. This presumption was supported by our fundamental study[12] that zwitterionization was capable of maintaining H_1-antihistaminic activity while reducing other pharmacological activities such as anticholinergic activity *in vitro*.

Taking the above results into consideration, we carried out chemical modifications of **3** by replacement of one benzene ring of **3** by a pyridine ring and examined its physicochemical and pharmacological properties to

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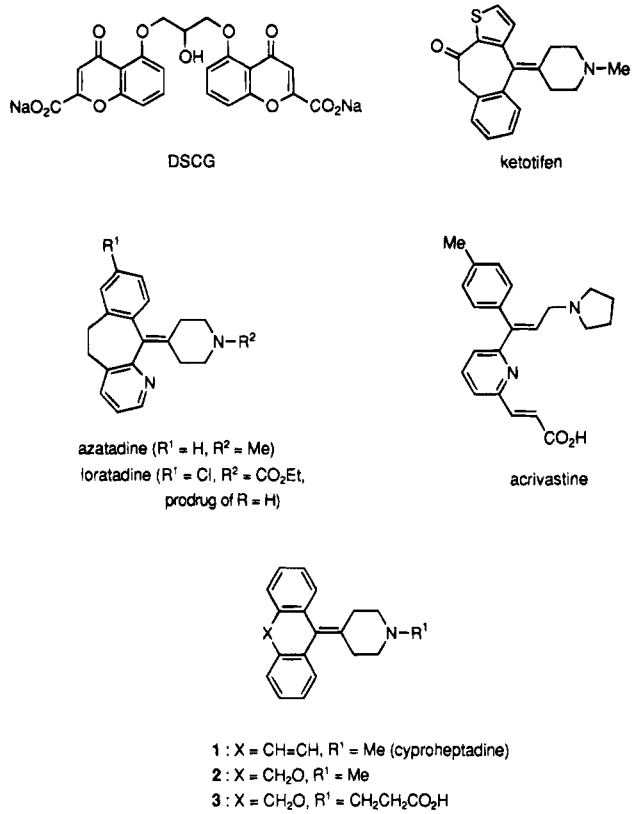
Chart 1



explore an amphoteric antiallergic agent with less penetration into the CNS. Such chemical modification has been known, exemplified by azatadine[13] and loratadine[5] (Chart 1); however, no reports on the introduction of a pyridine ring into tricyclic amphoteric compounds have been published. Thus, we selected (5,11-dihydro[1]benzoxepino[4,3-*b*]pyridine (type I) and (5,11-dihydro[1]benzoxepino[3,4-*b*]pyridine (type II) as tricyclic systems (Chart 2).

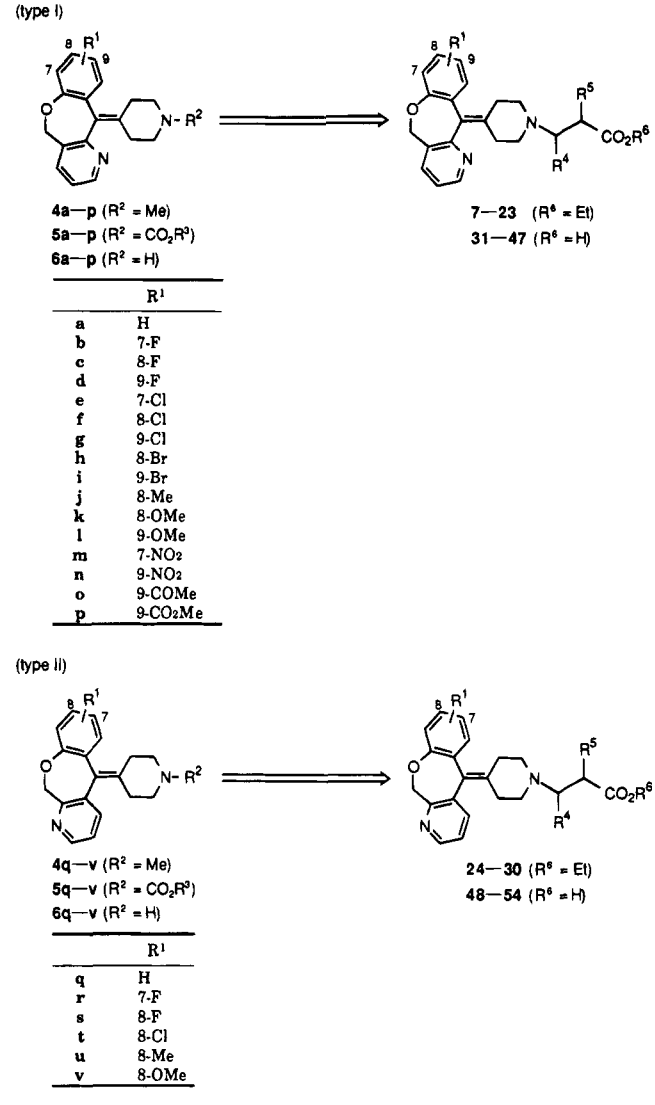
In the present paper, we describe the synthesis and antiallergic activity of 3-[(5,11-dihydro[1]benzoxepino-[4,3-*b*]pyridin-11-ylidene)piperidino]propionic acid derivatives (**31**–**47**) and related compounds (**48**–**54**) bearing structures isosteric to 6*H*-dibenz[*b*,*e*]oxepin derivatives (**3**). The influence of introducing a pyridine ring into the amphoteric compounds upon antiallergic activity and the penetration of a compound into the CNS is also discussed.

Chemistry

N-Methylpiperidines **4a**–**l** and **4q**–**v** as starting materials were synthesized according to the literature as illustrated in Schemes 1 and 2 (routes A[14] and C[15]). Intermediate ketones in type I were also prepared from furo[3,4-*b*]pyridin-7(5*H*)-one[16] (**55**) in moderate yield (route B). Treatment of compound **55**, derived from commercially available 2,3-pyridinedicarboxylic anhydride by two steps, with sodium 3-fluorophenoxide in the presence of NaCl gave the picolinic acid derivative (**56**) in 84% yield. Ring closure was accomplished by Friedel–Crafts reaction of the acid chloride of **56** giving the ketone in 50% yield.

The propionic acid derivatives (**31**–**54**) in Tables 1 and 2 were synthesized as shown in Schemes 3–6. *N*-Methylpiperidines (**4**) were treated with ethyl chloroformate (or 1-chloroethyl chloroformate) in 1,2-dichloroethane to give the corresponding 1-piperidinecarboxylates (**5**), which were subsequently hydrolyzed under strong alkali conditions (or refluxed in MeOH for 1-chloroethyl 1-piperidinecarboxylates) yielding unsubstituted piperidines (**6**). The various propionates (**7**–**30**) obtained by Michael addition of **6** were hydrolyzed with 2 N NaOH (or 25% HBr/AcOH for *tert*-butyl propionates) to afford the target amphoteric compounds (**31**–**54**).

Chart 2

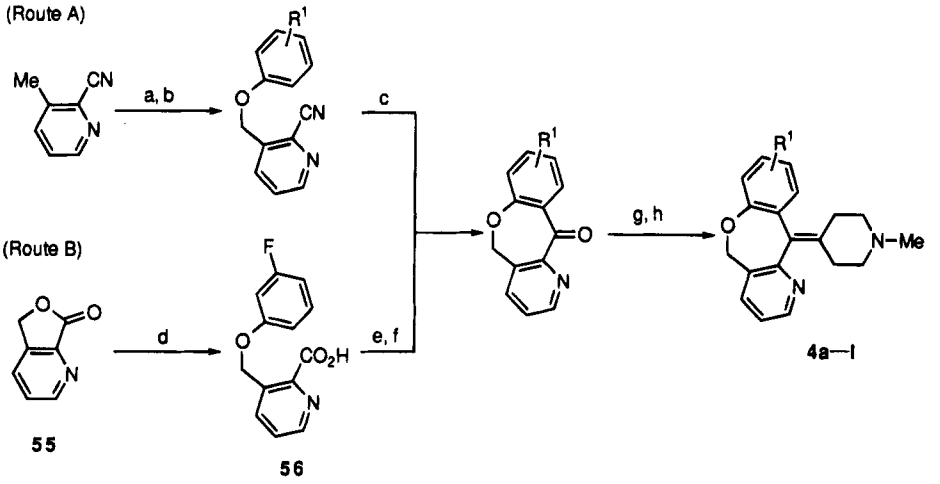


	R¹
a	H
b	7-F
c	8-F
d	9-F
e	7-Cl
f	8-Cl
g	9-Cl
h	8-Br
i	9-Br
j	8-Me
k	8-OMe
l	9-OMe
m	7-NO_2
n	9-NO_2
o	9-COMe
p	9-CO_2Me

	R¹
q	H
r	7-F
s	8-F
t	8-Cl
u	8-Me
v	8-OMe

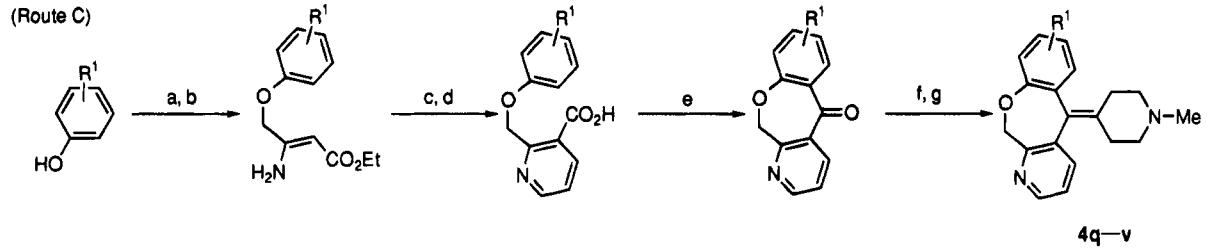
Nitro derivatives (**44** and **45**) in type I were prepared via nitration of unsubstituted 1-piperidinecarboxylates (**5a**) (Scheme 4). The nitration of **5a** using concentrated nitric acid and acetic anhydride gave a mixture of 7-NO_2 (**5m**) and 9-NO_2 derivative (**5n**), which was separated by column chromatography in 36% and 52% yield, respectively. 9-Acetylated compound (**46**) was prepared by Friedel–Crafts reaction (Scheme 5). Acetylation of **5a** proceeded regioselectively to give **5o** in 90% yield. Since hydrolysis of **5o** under a strong alkaline condition gave a complicated mixture, compound **6o** was alternatively obtained in good yield by a sequence of reaction: protection of **5o**, hydrolysis, and deprotection. The 9-carboxylated derivative (**47**) was prepared from the 9-bromo derivative (**4i**) as shown in Scheme 6. 9-Carboxylation was accomplished by halogen–metal ex-

Scheme 1. Type I[a]



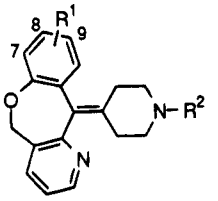
[a] (a) NBS, $(PhCOO)_2$, CCl_4, reflux; (b) $R^1C_6H_4OH$, NaOEt, EtOH, reflux; (c) CF_3SO_3H, 50 °C; (d) $3\text{-}FC_6H_4ONa$, NaCl, xylene, reflux; (e) $(COCl)_2$, CH_2Cl_2; (f) $AlCl_3$, 1,2-dichloroethane, reflux; (g) 4-chloro-1-methylpiperidine, Mg, THF; (h) CF_3SO_3H or MsCl.

Scheme 2. Type II[a]



[a] (a) $ClCH_2COCH_2CO_2Et$, KOH, DMSO; (b) NH_3(gas); (c) propargylaldehyde, toluene, 90 °C; (d) KOH, aqueous EtOH; (e) PPA, 165 °C; (f) 4-chloro-1-methylpiperidine, Mg, THF; (g) CF_3SO_3H or MsCl.

Table 1. Physicochemical Data for Propionic Acids **31**–**47** (Type I)



compd no.	R^1	R^2	yield[a] (%)	mp, °C	recryst solvent[b]	formula[c]
31	H	$(CH_2)_2CO_2H$	35	203–206	ET	$C_{21}H_{22}N_2O_3\cdot HCl\cdot H_2O$
32	7-F	$(CH_2)_2CO_2H$	68	205–208	ME	$C_{21}H_{21}FN_2O_3\cdot 0.5C_4H_4O_4$[e]$\cdot 0.25H_2O$
33	8-F	$(CH_2)_2CO_2H$	41	160–161	ME	$C_{21}H_{21}FN_2O_3$
34	8-F	$CH(Me)CH_2CO_2H$	67	oil[d]		[f]
35	8-F	$CH_2CH(Me)CO_2H$	76	192.5–194.5	IP	$C_{22}H_{23}FN_2O_3\cdot 0.25H_2O$
36	9-F	$(CH_2)_2CO_2H$	40	121–124	ET	$C_{21}H_{21}FN_2O_3\cdot 2.25H_2O$
37	7-Cl	$(CH_2)_2CO_2H$	79	250–253 dec	ET–W	$C_{21}H_{21}ClN_2O_3\cdot HCl$
38	8-Cl	$(CH_2)_2CO_2H$	60	257–260 dec	ME	$C_{21}H_{21}ClN_2O_3\cdot HCl$
39	9-Cl	$(CH_2)_2CO_2H$	74	198–199.5	ME	$C_{21}H_{21}ClN_2O_3\cdot 1.5H_2O$
40	8-Br	$(CH_2)_2CO_2H$	51	137–139	IP	$C_{21}H_{21}BrN_2O_4/_3H_2O$
41	8-Me	$(CH_2)_2CO_2H$	77	125–127	ET	$C_{22}H_{24}N_2O_3\cdot 2.75H_2O$
42	8-OMe	$(CH_2)_2CO_2H$	61	132–135	ET	$C_{22}H_{24}N_2O_4\cdot 1.75H_2O$
43	9-OMe	$(CH_2)_2CO_2H$	36	157–161	ME–IPE	$C_{22}H_{24}N_2O_4\cdot 0.5C_4H_4O_4$[e]$\cdot H_2O$
44	7-NO_2	$(CH_2)_2CO_2H$	46	233–240 dec	ME	$C_{21}H_{21}N_3O_5\cdot HCl\cdot 0.25H_2O$
45	9-NO_2	$(CH_2)_2CO_2H$	33	223–226 dec	ME	$C_{21}H_{21}N_3O_5\cdot 2HCl\cdot 0.4H_2O$
46	9-COMe	$(CH_2)_2CO_2H$	59	213–216 dec	ET	$C_{23}H_{24}N_2O_4\cdot HCl\cdot 0.25H_2O$
47	9-CO_2H	$(CH_2)_2CO_2H$	56	216–219	ME–W	$C_{22}H_{22}N_2O_5\cdot 1.25H_2O$

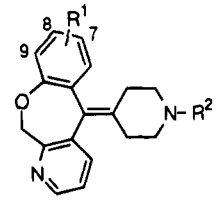
[a] Yields were calculated from the corresponding ethyl esters. [b] ET = EtOH, ME = MeOH, IP = *i*-PrOH, W = water, IPE = *i*-Pr_2O, DM = CH_2Cl_2, EE = Et_2O, EA= AcOEt, AN = acetonitrile, H = *n*-hexane, BE = benzene AC = acetone. [c] C,H,N analyses were within ± 0.4% of theoretical values. [d] Compound was purified by column chromatography on silica gel. [e] Fumaric acid. [f] High-resolution MS: calcd 382.1693, found 382.1696.

change reaction (using 2 equiv of *n*-BuLi) followed by the treatment with CO_2. Compound **47** was synthesized from **4p** by the method similar to that described in Scheme 3.

Results and Discussion

To examine the influence of introducing a pyridine component into a tricyclic system upon antiallergic

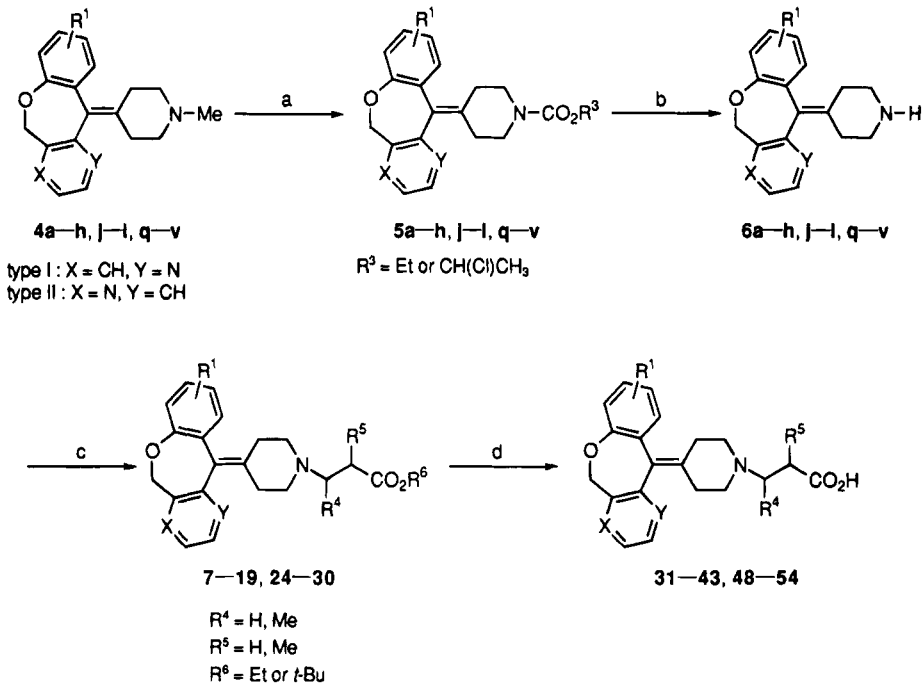
Table 2. Physicochemical Data for Propionic Acids **48**–**54** (Type II)



compd no.	R^1	R^2	yield[a] (%)	mp, °C	recryst solvent[b]	formula[c]
48	H	$(CH_2)_2CO_2H$	50	201.5–204.5	ET	$C_{21}H_{22}N_2O_3 \cdot 2.25H_2O$
49	7-F	$(CH_2)_2CO_2H$	85	101.5–103	ET	$C_{21}H_{21}FN_2O_3 \cdot 0.5H_2O$
50	8-F	$(CH_2)_2CO_2H$	64	222.5–224.5	ME	$C_{21}H_{21}FN_2O_3 \cdot 0.25H_2O$
51	8-F	$CH_2CH(Me)CO_2H$	47	149–152.5	DM–EE	$C_{22}H_{23}FN_2O_3 \cdot HCl$
52	8-Cl	$(CH_2)_2CO_2H$	42	139–143.5	ME	$C_{21}H_{21}ClN_2O_3 \cdot H_2O$
53	8-Me	$(CH_2)_2CO_2H$	77	250.5–252	ET–W	$C_{22}H_{24}N_2O_3 \cdot HCl \cdot 0.25H_2O$
54	8-OMe	$(CH_2)_2CO_2H$	56	182–184	ET–W	$C_{22}H_{24}N_2O_4 \cdot 2.25H_2O$

[a] Yields were calculated from the corresponding ethyl esters. [b] See footnote in Table 1. [c] C,H,N analyses were within ±0.4% of theoretical values.

Scheme 3[a]



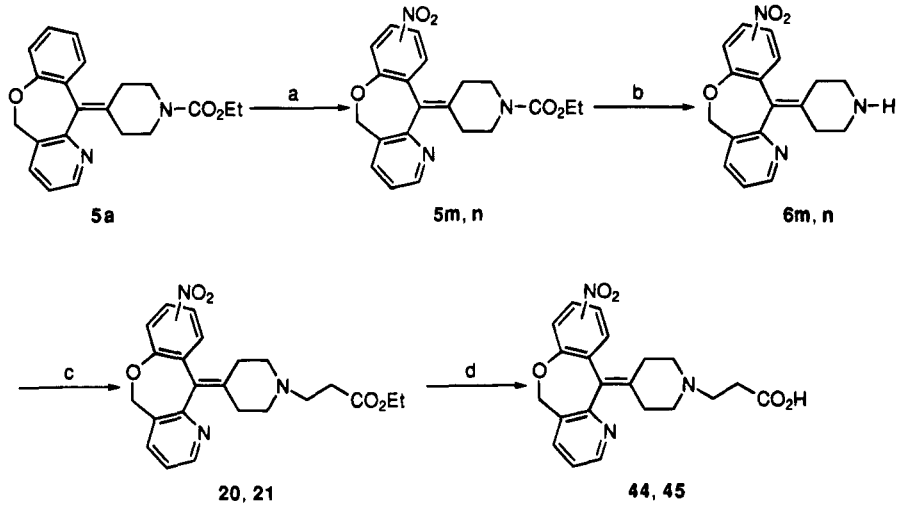
[a] (a) $ClCO_2Et$, 1,2-dichloroethane or $ClCO_2CH(Cl)CH_3$, 1,2-dichloroethane; (b) KOH, *i*-PrOH, reflux (R^3 = Et) or MeOH, reflux (R^3 = $CH(Cl)CH_3$); (c) $CH(R^4)=C(R^5)CO_2R^6$, EtOH or *i*-PrOH, reflux; (d) 2 N NaOH, MeOH (R^6 = Et) or 25% HBr/AcOH, 1,2-dichloroethane (R^6 = *t*-Bu).

activity and penetration of a compound into the CNS, we initially compared aza analogues (type I and II) of dibenz[*b*,*e*]oxepin with the parent compounds (**2** and **3**). Antiallergic activity was evaluated by inhibitory effect on compound 48/80-induced lethality in rats. The prolongation of sleeping time on hexobarbital-induced anesthesia in mice was considered as an index of the CNS side effects. The penetration of a compound into the CNS was employed by the selectivity which was represented by the ratio (*B*/*A*) of antihistaminic activities in the central system [ID_{50} value (*B*) for *ex vivo* H_1 binding to mouse brain membranes] and in the peripheral system [ED_{50} value (*A*) for inhibitory effect on histamine-induced increase in vascular permeability in mice]. The results are shown in Table 3.

Both type of amphoteric aza analogues (**31** and **48**) showed slightly weaker antiallergic activities than that of dibenz[*b*,*e*]oxepin derivatives (**3**). Additionally, compounds **31** and **48** had antiallergic activities similar to the corresponding *N*-methyl compounds (**4a** and **4q**). These results demonstrated that the zwitterionization did not appreciably contribute to enhancement in antiallergic activity in these aza analogues, in comparison with dibenz[*b*,*e*]oxepin derivatives.

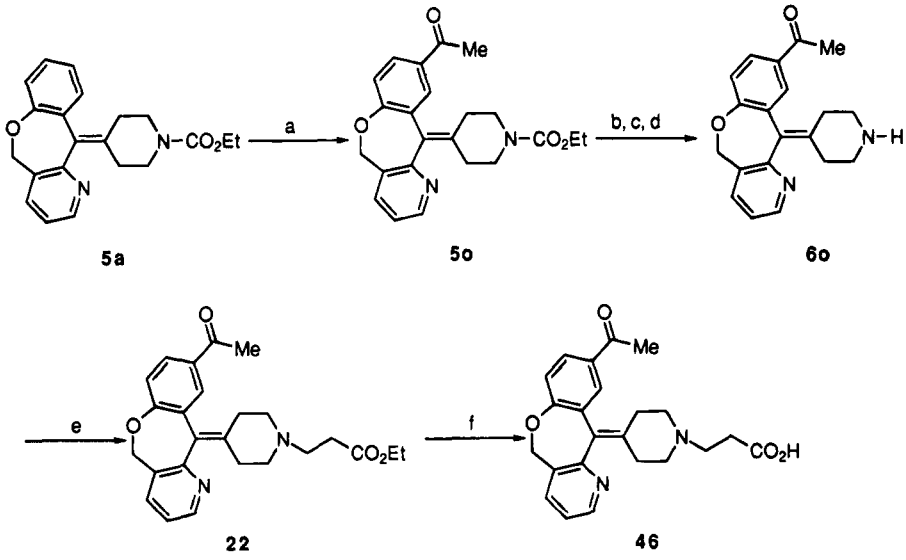
As for penetration of a compound into the CNS, introduction of a pyridine ring and zwitterionization was expected to reduce the penetration into the CNS. The selectivities (*B*/*A*) for the amphoteric compound **3** and the aza analogues (**4a** and **4q**) were as low as that for **2**, even though their CNS side effects such as the prolongation of sleeping time on hexobarbital-induced anesthesia reduced considerably in comparison with **2**. Thus the reduction of the CNS side effects in the amphoteric compounds **3** and the aza analogues (**4a** and **4q**) would not be attributed to reduction of the penetration into the CNS. Compounds **31** and **48** exhibited much higher selectivities and much lower values of partition coefficient (PC_{oct}), compared with the com-

Scheme 4[a]



[a] (a) concentrated HNO_3, Ac_2O, 10 °C, then separation by column chromatography; (b) KOH, *i*-PrOH, reflux; (c) CH_2=$CHCO_2Et$, EtOH, reflux; (d) 2 N NaOH, MeOH.

Scheme 5[a]



[a] (a) AcCl, $AlCl_3$, 1,2-dichloroethane, 5 °C; (b) ethylene glycol, TsOH, toluene; (c) KOH; *i*-PrOH, reflux; (d) 10% HCl, THF; (e) CH_2=$CHCO_2Et$, EtOH, reflux; (f) 2 N NaOH, MeOH.

pounds **3**, **4a**, and **4q**. Therefore, combination of zwitterionization and the introduction of a pyridine component were shown to be important to attain much higher hydrophilicity, which was considered as a factor of reducing the penetration into the CNS.

To optimize a series of aza analogues as antiallergic agents, we next introduced various substituents into the benzene ring of **4a** and **4q** and a methyl group into ethylene bridge between their piperidine ring and carboxyl group (Table 4).

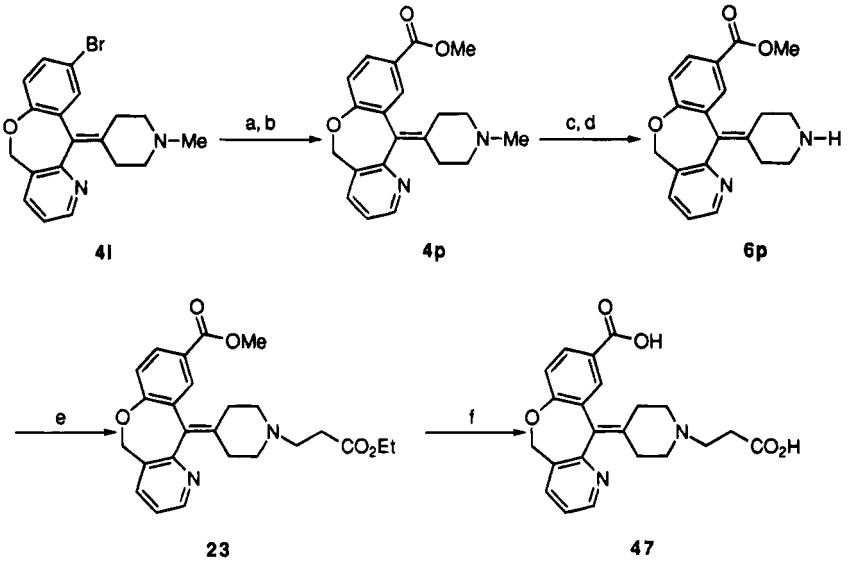
Except for the 8-fluorinated compound (**33**), substitution of a halogen atom in type I resulted in a slight loss of potency. This result was consistent with a report[13] that substitution of chlorine at the 8- and 9-position in 11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine system reduced antihistaminic and antiallergic activity. A different effect on substitution by fluorine and chlorine was observed. Compound **36**, bearing fluorine at the 9-position, showed lesser activity than 7-F (**32**) and 8-F derivatives (**33**), whereas the 9-chloro compound (**39**) was more potent than 7-Cl (**37**) and 8-Cl derivatives (**38**).

Substitution of electron-donating groups such as methyl (**41**) and methoxy group (**42** and **43**) or electron-withdrawing groups such as nitro (**44** and **45**) and acetyl group (**46**) caused a loss of antiallergic activity, regardless of the substitution position. An additional introduction of a carboxyl group in tricyclic system (**31** → **47**) led to great reduction of potency.

On the other hand, introduction of halogen atoms (**49**, **50**, and **52**) caused enhancement in antiallergic activity in respect of the aza analogues in type II. Compound **50**, in particular, exhibited the strongest antiallergic activity among all compounds synthesized. Substitution of methyl (**53**) and methoxy groups (**54**) did not contribute to enhancement in potency, as similarly observed in type I.

As for branching by a methyl group in ethylene bridge between the piperidine ring and the carboxyl group, a definite difference between two regioisomers (**34** and **35**) was observed. Methylation at α-position in propionic acid moiety (**33** → **35**) enhanced antiallergic activity, whereas a similar substitution at the β-position (**33** →

Scheme 6[a]



[a] (a) *n*-BuLi then CO_2(gas), THF, −72 °C; (b) MeOH, concentrated H_2SO_4, reflux; (c) $ClCO_2CH(Cl)CH_3$, 1,2-dichloroethane; (d) MeOH, reflux; (e) $CH_2{=}CHCO_2Et$, EtOH, reflux; (f) 2 N NaOH, MeOH.

Table 3. Comparison between 6*H*-Dibenz[*b*,*e*]oxepin Derivatives and Isosteric Aza Analogues

compd no.	compound 48/80-induced lethality in rats (mg/kg, po) inhibition, % (n = 5) 0.01	0.1	1	10	histamine-induced vascular permeability in mice (*A*) ED_{50}[a] (mg/kg, po)	ex vivo H_1-binding in mice (*B*) ID_{50}[b] (mg/kg, po)	selectivity (*B*/*A*)	hexobarbital-induced anesthesia in mice ID_{50}[b] (mg/kg, po)	PC_{oct}[c]
2		0	60	100	0.035 (0.0053−0.23)	0.77 (0.20−2.9)	22	0.73 (0.20−2.7)	∞
3	20	60	100		0.0038 (0.00080−0.018)	0.062 (0.013−0.29)	16	16 (6.4−37)	9.66
4a		0	100		0.011 (0.0019−0.069)	0.20 (0.063−0.61)	18	>100	28.4
31		0	100		0.012 (0.0026−0.053)	19 (6.4−58)	1600	>100	0.52
4q		0	100		0.025 (0.0045−0.14)	0.49 (0.15−1.6)	20	9.9 (2.7−36)	54.3
48	0	40	100		0.010 (0.0013−0.077)	3.4 (1.2−9.4)	340	>100	0.56

[a] ED_{50} and 95% confidence limits (in parentheses). [b] ID_{50} and 95% confidence limits (in parentheses). [c] 1-Octanol−buffer partition coefficient.

Table 4. Inhibitory Effects of Compounds **31**−**54** on Compound 48/80-Induced Lethality in Rats

compd no.	compound 48/80-induced lethality in rats (mg/kg, po) inhibition, % (n = 5) 0.01	0.1	1	10
31		0	100	
32	0	20	100	
33	0	40	100	
34			0	100
35	20	60	100	
36		0	20	100
37		0	60	100
38		0	80	100
39		0	100	
40	0	40	60	100
41	0	20	40	100
42		0	20	100
43	0	20	60	80
44			0	60
45		0	20	80
46		0	20	100
47			0	20
48	0	40	100	
49	0	60	100	
50	40	100		
51	20	100		
52	40	80	100	
53	0	20	60	100
54	0	40	100	

34) resulted in a great loss of activity. These results might suggested some binding features at the H_1 receptor.

We therefore selected three 8-fluoro derivatives (**33**, **35**, and **50**) having strong antiallergic effects and evaluated these compounds by further biological tests including duration of action and penetration of a compound into the CNS. Duration of action was evaluated by inhibitory effect on histamine-induced lethality in guinea pigs at 8 h after oral dose of 0.3 mg/kg. Ketotifen and loratadine bearing similar tricyclic systems and acrivastine bearing a similar amphoteric structure were used as reference compounds (Table 5).

Compound **50** of type II showed a stronger antiallergic activity in rats and mice than compound **33** of type I and high selectivity (*B*/*A*) of antihistaminic activities in the central system and in the peripheral system, but had shorter duration of action than that of **33**. Compound **35**, bearing a methyl group at the α-position of the propionic acid moiety, showed a low selectivity of antihistaminic activities in comparison with **33**. Compound **33** had a 5−10 times stronger antiallergic effect than the reference compounds in experimental models. Moreover, the selectivity of antihistaminic activities in the central system and in the peripheral system for **33** was much higher than that for ketotifen.

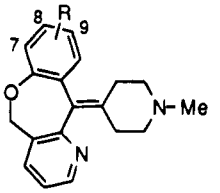
Additionally, compound **33** exhibited 90% inhibitory effect on histamine-induced lethality in guinea pigs, whereas unsubstituted compound (**31**) exhibited 30% inhibitory effect in the same test. Introduction of an 8-fluoro substituent contributed to longer duration of antiallergic activity.

Table 5. Biological Evaluation for Propionic Acid Derivatives of Aza Isosteres

	compound 48/80-induced lethality in rats (n = 7) ED_{50}[a] (mg/kg, po)	histamine-induced vascular permeability in mice (A) ED_{50}[a] (mg/kg, po)	ex vivo H_1-binding in mice (B) ID_{50}[b] (mg/kg, po)	selectivity (B/A)	histamine-induced lethality in guinea pigs (n = 10) inhibition[c] (%)
33	0.29 (0.12–0.69)	0.025 (0.0041–0.15)	14 (7.2–26)	560	90
35	NT[d]	0.011 (0.0024–0.049)	2.3 (1.4–3.7)	210	NT[d]
50	0.034 (0.011–0.11)	0.0037 (0.00048–0.028)	2.5 (0.84–7.3)	680	60
ketotifen	0.69 (0.29–1.6)	0.23 (0.022–2.4)	0.65 (0.33–1.3)	2.8	10[e]
loratadine	NT[d]	0.21 (0.034–1.2)	36 (10–120)	170	80
acrivastine	3.3 (0.98–11)	0.63 (0.11–3.7)	>300	>480	0[f]

[a] ED_{50} and 95% confidence limits (in parentheses). [b] ID_{50} and 95% confidence limits (in parentheses). [c] At 8 h after oral dose of 0.3 mg/kg. [d] Not tested. [e] Oral dose of 0.02 mg/kg. [f] Oral dose of 0.16 mg/kg.

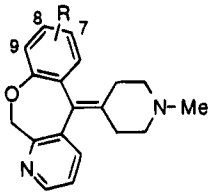
Table 6. Physicochemical Data for **4a–l** (Type I)



compd no.	R	mp, °C	recryst solvent[a]	formula[b]
4a	H	143–144	EA	$C_{19}H_{20}N_2O{\cdot}0.25H_2O$
4b	7-F	146–148	AN	$C_{19}H_{19}FN_2O$
4c	8-F	125–126	EA	$C_{19}H_{19}FN_2O$
4d	9-F	146–148	IPE	$C_{19}H_{19}FN_2O$
4e	7-Cl	169–170	IP	$C_{19}H_{19}ClN_2O$
4f[c]	8-Cl	167.5–170.5[d]	EA	$C_{19}H_{19}ClN_2O$
4g	9-Cl	274–276 dec	ET	$C_{19}H_{19}ClN_2O{\cdot}2HCl{\cdot}2H_2O$
4h	8-Br	176–178	EA	$C_{19}H_{19}BrN_2O$
4i	9-Br	170–172	IP	$C_{19}H_{19}BrN_2O$
4j	8-Me	238–241 dec	IP	$C_{20}H_{22}N_2O{\cdot}HCl{\cdot}H_2O$
4k	8-OMe	248–250	IP	$C_{20}H_{22}N_2O_2{\cdot}HCl{\cdot}2.5H_2O$
4l	9-OMe	121–123.5	AN	$C_{20}H_{22}N_2O_2$

[a] See footnote in Table 1. [b] C,H,N analyses within ±0.4% of theoretical values. [c] See ref 14. [d] Literature[14] mp 168–170 °C.

Table 7. Physicochemical Data for **4q–v** (Type II)



compd no.	R	mp, °C	recryst solvent[a]	formula[b]
4q	H	144–145	EA	$C_{19}H_{20}N_2O$
4r	7-F	127–129	H	$C_{19}H_{19}FN_2O$
4s	8-F	177.5–178.5	EA	$C_{19}H_{19}FN_2O$
4t	8-Cl	160.5–161	EA	$C_{19}H_{19}ClN_2O$
4u	8-Me	145–146	EA	$C_{20}H_{22}N_2O$
4v	8-OMe	166–167	EA	$C_{20}H_{22}N_2O_2$

[a] See footnote in Table 1. [b] C,H,N analyses within ±0.4% of theoretical values.

In conclusion, it appears that the combination of zwitterionization and introduction of a pyridine component was a useful approach to antiallergic agents with less penetration into the CNS. A series of our study on amphoteric drugs provided us with potential compound (**33**). Compound **33** (HSR-609) had a strong antiallergic effect in various experimental animals and a long duration of its activity. This compound is now under clinical trial.

Experimental Section

All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Spectral data were obtained as follows: ^{1}H-NMR spectra with JEOL A-500 (500 MHz) spectrometers, with tetramethylsilane (TMS) as an internal standard; mass spectra (MS) with JEOL JMS-DX 300 mass spectrometer; IR spectra with Hitachi 270-30 spectrometer. Elemental analyses were performed with a Yanagimoto MT-3 or MT-5 elemental analysis apparatus on solid samples only; the analytical results (C, H, N) were within ±0.4% of the theoretical values. Column chromatography was carried out with silica gel [Kieselgel 60 (Merck)]. TLC was conducted on a 0.25 mm precoated silica gel plate ($60F_{254}$, Merck).

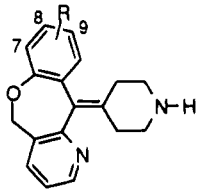
Routes A and C. *N*-Methylpiperidines (4a–l, q–v). These compounds as starting materials were prepared essentially according to the literature[14,15] as illustrated in Schemes 1 and 2. Physicochemical data were summarized in Tables 6 and 7.

Route B. a. Furo[3,4-*b*]pyridin-7(5*H*)-one (55). A suspension of 2,3-pyridinedicarboxylic anhydride (19.3 g, 0.13 mol) in dry EtOH (100 mL) was refluxed for 1 h. After removal of the solvent under reduced pressure, the crystalline residue was washed with Et_2O to give 2-(ethoxycarbonyl)nicotinic acid (17.0 g, 67%). ^{1}H-NMR ($CDCl_3$): δ 1.41 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.47 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 7.50 (1H, dd, J = 8.0, 5.0 Hz, C_5-H), 8.29 (1H, dd, J = 8.0, 2.0 Hz, C_4-H), 8.77 (1H, dd, J = 5.0, 2.0 Hz, C_6-H).

To a mixture of 2-(ethoxycarbonyl)nicotinic acid (27.5 g, 0.14 mol) and Et_3N (20.7 mL, 0.15 mol) in dry THF (400 mL) was added dropwise ethyl chloroformate (14.2 mL, 0.15 mol) at 5 °C, and then the mixture was stirred at 5 °C for 1.5 h. The resulting crystals were filtered off. A solution of lithium borohydride (3.1 g, 0.14 mol) in dry THF (70 mL) was added dropwise to the above filtrate at 5 °C, and then the mixture was stirred at the same temperature for 20 min. The reaction mixture was adjusted to pH 4 with dilute hydrochloric acid. After removal of the solvent under reduced pressure, the residue was diluted with water, made alkaline with aqueous K_2CO_3, and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give **55** as yellow crystals (10.1 g, 53%). Recrystallization from AcOEt afforded colorless needles, mp 162–162.5 °C (lit.[16] mp 158–160 °C). ^{1}H-NMR ($CDCl_3$): δ 5.41 (2H, s, C_5-H_2), 7.60 (1H, dd, J = 8.0, 5.0 Hz, C_3-H), 7.95 (1H, d, J = 8.0 Hz, C_4-H), 8.91 (1H, d, J = 5.0 Hz, C_2-H). IR (KBr): 1782 cm^{-1} (C=O). MS: m/z 135 (M^+). Anal. ($C_7H_5FNO_2$) C, H, N.

b. 3-(3-Fluorophenoxymethyl)picolinic Acid (56). A mixture of sodium 3-fluorophenoxide, prepared from 3-fluorophenol (7.2 g, 64 mmol) and Na metal (1.5 g, 65 mmol) in absolute EtOH, **55** (13.0 g, 96 mmol), and NaCl (6.4 g, 109 mmol) in dry xylene (200 mL) was refluxed for 1 h and then cooled to room temperature. The resulting crystals were collected by filtration. The crystals were dissolved in aqueous NaOH, and insoluble materials were filtered off. The filtrate was adjusted to pH 5 with dilute hydrochloric acid. The resulting crystals were collected by filtration and washed with water to give **56** as colorless crystals (13.3 g, 84%). ^{1}H-NMR (DMSO-d_6): 5.40 (2H, s, CH_2), 6.73–6.78 (1H, m, Ar-H), 6.82–6.88 (2H, m, Ar-H), 7.27–7.33 (1H, m, Ar-H), 7.42 (1H, dd, J = 8.0, 5.0 Hz, C_5-H), 7.90 (1H, d, J = 8.0 Hz, C_4-H), 8.47 (1H, d, J = 5.0 Hz, C_6-H). IR (KBr): 1616 cm^{-1} (C=O). MS: m/z 247 (M^+).

Table 8. Physicochemical Data for **6a–h,j–p** (Type I)



compd no.	R	mp, °C	recryst solvent[a]	formula[b]
6a	H	275–280 dec	IP	$C_{18}H_{18}N_2O{\cdot}2HCl{\cdot}0.5H_2O$
6b	7-F	222–226	ET–W	$C_{18}H_{17}FN_2O{\cdot}0.5C_4H_4O_4{\cdot}2.5H_2O$
6c	8-F	173–174	EA	$C_{18}H_{17}FN_2O$
6d	9-F	154–155	EA	$C_{18}H_{17}FN_2O$
6e	7-Cl	173–175	EA	$C_{18}H_{17}ClN_2O$
6f[c]	8-Cl	182.5–184.5[d]	IP	$C_{18}H_{17}ClN_2O$
6g	9-Cl	180–182	EA	$C_{18}H_{17}ClN_2O$
6h	8-Br	179–181	IP	$C_{18}H_{17}BrN_2O$
6j	8-Me	290–294 dec	ET	$C_{19}H_{20}N_2O{\cdot}HCl$
6k	8-OMe	168–170	EA	$C_{19}H_{20}N_2O_2{\cdot}0.5H_2O$
6l	9-OMe	190–192	ME	$C_{19}H_{20}N_2O_2{\cdot}C_4H_4O_4{\cdot}1.25H_2O$
6m	7-NO_2	98–101	EE[e]	*g*
6n	9-NO_2	173–176	IP	$C_{18}H_{17}N_3O_3{\cdot}0.25H_2O$
6o	9-COMe	282–285 dec	ET	$C_{20}H_{20}N_2O_2{\cdot}HCl{\cdot}0.25H_2O$
6p	9-CO_2Me	168–171	EA	$C_{20}H_{20}N_2O_3$

[a] See footnote in Table 1. [b] C,H,N analyses within ±0.4% of theoretical values. [c] See ref 14. [d] Literature[14] mp 166–176 °C. [e] Triturated solvent. [f] Furmaric acid. [g] High-resolution MS: calcd 323.1270, found 323.1274.

c. 8-Fluoro-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-one. To a suspension of **56** (1.0 g, 4 mmol) and dry DMF (1 drop) in CH_2Cl_2 (10 mL) was added dropwise oxalyl chloride (1.0 mL, 11 mmol) at room temperature, and the mixture was stirred for 2 h. The reaction mixture was evaporated to dryness to give the crude acid chloride of **56** (hydrochloride). To a suspension of crude acid chloride in 1,2-dichloroethane (12 mL) was added granulated anhydrous $AlCl_3$ (1.4 g, 10 mmol) by portions at 5 °C, and then the mixture was refluxed for 2 h. After being cooled, the reaction mixture was poured into ice–water, made alkaline with aqueous NaOH, and then extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and evaporated. The oily residue was purified by column chromatography [SiO_2, CH_2Cl_2–MeOH (20:1)] to afford the title compound as pale yellow crystals (0.5 g, 50%). Recrystallization from AcOEt afforded colorless needles, mp 144–145 °C. ^{1}H-NMR ($CDCl_3$): δ 5.21 (2H, s, C_5-H_2), 6.76 (1H, dd, J = 10.0, 2.5 Hz, C_7-H), 6.88 (1H, ddd, J = 9.0, 7.0, 2.5 Hz, C_9-H), 7.51 (1H, dd, J = 8.0, 5.0 Hz, C_3-H), 7.79 (1H, dd, J = 8.0, 2.0 Hz, C_4-H), 8.28 (1H, dd, J = 9.0, 7.0 Hz, C_{10}-H), 8.81 (1H, dd, J = 5.0, 2.0 Hz, C_2-H). MS: *m/z* 229 (M^+). Anal. ($C_{13}H_8FNO_2$) C, H, N.

Ethyl 4-(8-Fluoro-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (5c, R^3 = Et). To a solution of **4c** (16.6 g, 53.5 mmol) in 1,2-dichloroethane (90 mL) was added dropwise ethyl chloroformate (51.2 mL, 535 mmol) at room temperature, and then the mixture was refluxed for 11 h. After being cooled, the reaction mixture was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated. The oily residue was purified by column chromatography [SiO_2, CH_2Cl_2–MeOH (10:1)] to afford **5c** (R^3 = Et) as a brown oil (19.4 g, 98%). ^{1}H-NMR ($CDCl_3$): δ 1.26 (3H, t, J = 7.5 Hz, $CO_2CH_2CH_3$), 2.28–2.64 (4H, m, CH_2 × 2), 3.08–3.29 (2H, m, CH_2), 3.49–3.85 (2H, m, CH_2), 4.15 (2H, q, J = 7.5 Hz, $CO_2CH_2CH_3$), 4.85 (1H, d, J = 12.5 Hz, C_5-*H*H), 5.61 (1H, d, J = 12.5 Hz, C_5-H*H*), 6.52 (1H, dd, J = 10.5, 2.5 Hz, C_7-H), 6.59–6.62 (1H, m, C_9-H), 7.05 (1H, dd, J = 8.5, 6.5 Hz, C_{10}-H), 7.26 (1H, dd, J = 7.5, 5.0 Hz, C_3-H), 7.69–7.71 (1H, m, C_4-H), 8.56 (1H, dd, J = 5.0, 1.0 Hz, C_2-H). IR (liquid): 1698 cm^{-1} (C=O). High-resolution MS: *m/z* calcd for $C_{21}H_{21}FN_2O_3$ 368.1536, found 368.1526.

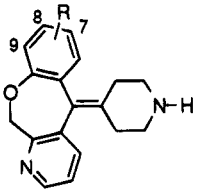
8-Fluoro-5,11-dihydro-11-(4-piperidylidene)[1]benzoxepino[4,3-*b*]pyridine (6c). A mixture of **5c** (R^3 = Et) (19.1 g, 51.8 mmol) and KOH (17.1 g, 305 mmol) in *i*-PrOH (130 mL) was refluxed for 6 h and then evaporated. The residue was diluted with water and extracted with Et_2O. The ethereal layer was washed with water, dried over Na_2SO_4, and evaporated. The resulting solid was recrystallized from AcOEt to afford **6c** as pale brown crystals (9.9 g, 65%), mp 173–174 °C. ^{1}H-NMR ($CDCl_3$): δ 2.15 (1H, br s, NH), 2.30–3.14 (8H, m, CH_2 × 4), 4.83 (1H, d, J = 13.0 Hz, C_5-*H*H), 5.66 (1H, d, J = 13.0 Hz, C_5-H*H*), 6.51 (1H, dd, J = 10.5, 3.0 Hz, C_7-H), 6.57-6.61 (1H, m, C_9-H), 7.06 (1H, dd, J = 9.0, 7.5 Hz, C_{10}-H), 7.23 (1H, dd, J = 7.5, 5.0 Hz, C_3-H), 7.68 (1H, dd, J = 7.5, 2.0 Hz, C_4-H), 8.56 (1H, dd, J = 5.0, 2.0 Hz, C_2-H). MS: *m/z* 296 (M^+). Anal. ($C_{18}H_{17}FN_2O$) C, H, N.

7-Fluoro-5,11-dihydro-11-(4-piperidylidene)[1]benzoxepino[4,3-*b*]pyridine Fumarate (6b). To a solution of **4b** (4.0 g, 12.9 mmol) and Et_3N (2.3 mL, 16.8 mmol) in 1,2-dichloroethane (40 mL) was added dropwise 1-chloroethyl chloroformate (4.2 mL, 38.7 mmol) at room temperature, and then the mixture was stirred at the same temperature for 1.5 h. The reaction mixture was washed with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to give crude **5b** (R^3 = CH(Cl)CH_3) as a brown oil. A solution of crude **5b** (R^3 = CH(Cl)CH_3) in MeOH (40 mL) was refluxed for 1 h and then evaporated. The residue was diluted with water, made alkaline with aqueous $NaHCO_3$, and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give crude free base of **6b** as a pale brown oil. The free base was converted to the fumarate (4.1 g, 76%) by the usual method. Fumarate: colorless prisms, mp 222–226 °C (aqueous EtOH). ^{1}H-NMR (CD_3OD): δ 2.15–3.39 (8H, m, CH_2 × 4), 5.07 (1H, d, J = 13.0 Hz, C_5-*H*H), 5.70 (1H, d, J = 13.0 Hz, C_5-H*H*), 6.64 (1H, s, 0.5 fumarate), 6.84–6.92 (2H, m, C_9-H and C_{10}-H), 7.02 (1H, ddd, J = 10.5, 7.5, 2.0 Hz, C_8-H), 7.44 (1H, dd, J = 8.0, 5.0 Hz, C_3-H), 7.95 (1H, dd, J = 8.0, 2.0 Hz, C_4-H), 8.52 (1H, dd, J = 5.0, 2.0 Hz, C_2-H). MS: *m/z* 296 (M^+(free base)). Anal. ($C_{18}H_{17}FN_2O{\cdot}0.5C_4H_4O_4{\cdot}2.5H_2O$) C, H, N.

Other unsubstituted piperidine (**6**) were prepared in a manner similar to that described for **6c** or **6b** from the corresponding *N*-methylpiperidines. Physicochemical data are summarized in Tables 8 and 9.

Ethyl 3-[4-(8-Fluoro-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)piperidino]propionate (9). A solution of **6c** (7.7 g, 26.0 mmol) and ethyl acrylate (3.6 mL, 32.5 mmol) in EtOH (50 mL) was refluxed for 2 h and then evaporated. The oily residue was separated by column chromatography [SiO_2, CH_2Cl_2–MeOH (40:1)] to afford **9** as a brown oil (10.0 g, 98%). ^{1}H-NMR ($CDCl_3$): δ 1.26 (3H, t, J = 7.5 Hz, $CO_2CH_2CH_3$), 2.11–2.73 (12H, m, CH_2, × 6), 4.14 (2H, q, J = 7.5 Hz, $CO_2CH_2CH_3$), 4.83 (1H, d, J = 12.5 Hz, C_5-*H*H), 5.63 (1H, d, J = 12.5 Hz, C_5-H*H*), 6.51 (1H, dd, J = 10.5, 2.5

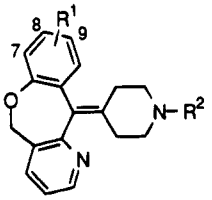
Table 9. Physicochemical Data for **6q–v** (Type II)



compd no.	R	mp, °C	recryst solvent[a]	formula[b]
6q	H	192–194	ME	$C_{18}H_{18}N_2O{\cdot}C_4H_4O_4{}^c{\cdot}0.25H_2O$
6r	7-F	180–182	ME	$C_{18}H_{17}FN_2O{\cdot}C_4H_4O_4{}^c{\cdot}0.5H_2O$
6s	8-F	174.5–178	ET	$C_{18}H_{17}FN_2O{\cdot}0.5C_4H_4O_4{}^c{\cdot}0.75H_2O$
6t	8-Cl	199.5–200.5	ME	$C_{18}H_{17}ClN_2O{\cdot}C_4H_4O_4{}^c{\cdot}H_2O$
6u	8-Me	242–244	W	$C_{19}H_{20}N_2O{\cdot}HCl$
6v	8-OMe	216–218	ET	$C_{19}H_{20}N_2O_2{\cdot}0.5C_4H_4O_4{}^c$

[a] See footnote in Table. [b] C,H,N analyses within ±0.4% of theoretical values. [c] Fumaric acid.

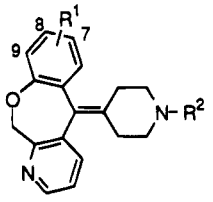
Table 10. Physicochemical Data for **7–23** (Type I)



compd no.	R^1	R^2	yield (%)	mp, °C	recryst solvent[a]	formula[b]
7	H	$(CH_2)_2CO_2Et$	94	120–121	BE	$C_{23}H_{26}N_2O_3$
8	7-F	$(CH_2)_2CO_2Et$	96	oil[c]		
9	8-F	$(CH_2)_2CO_2Et$	98	oil[c]		
10	8-F	$CH(Me)CH_2CO_2Et$	83	oil[c]		
11	8-F	$CH_2CH(Me)CO_2Et$	100	oil[c]		
12	9-F	$(CH_2)_2CO_2Et$	100	100–105	IPE	$C_{23}H_{25}FN_2O_3$
13	7-Cl	$(CH_2)_2CO_2Et$	98	110.5–111.5	AC-EE	$C_{23}H_{25}ClN_2O_3$
14	8-Cl	$(CH_2)_2CO_2Et$	100	210–213 dec	IP	$C_{23}H_{25}ClN_2O_3{\cdot}HCl$
15	9-Cl	$(CH_2)_2CO_2Et$	87	118–119	EA-IPE	$C_{23}H_{25}ClN_2O_3$
16	8-Br	$(CH_2)_2CO_2Et$	83	oil[c]		
17	8-Me	$(CH_2)_2CO_2Et$	69	oil[c]		
18	8-OMe	$(CH_2)_2CO_2Et$	99	oil[c]		
19	9-OMe	$(CH_2)_2CO_2Et$	74	oil[c]		
20	7-NO_2	$(CH_2)_2CO_2Et$	95	137–139.5	EA–IPE	$C_{23}H_{25}N_3O_5$
21	9-NO_2	$(CH_2)_2CO_2Et$	95	151–153	EA	$C_{23}H_{25}N_3O_5$
22	9-COMe	$(CH_2)_2CO_2Et$	67	oil[c]		
23	9-CO_2Me	$(CH_2)_2CO_2Et$	95	167–170	ET	$C_{25}H_{28}N_2O_5{\cdot}C_4H_4O_4{}^d{\cdot}H_2O$

[a] See footnote in Table 1. [b] C,H,N analyses were within ±0.4% of theoretical values. [c] Compounds were purified by column chromatography on silica gel. [d] Fumaric acid.

Table 11. Physicochemical Data for **24–30** (Type II)



compd no.	R^1	R^2	yield, %	appearance[a]
24	H	$(CH_2)_2CO_2Et$	100	oil
25	7-F	$(CH_2)_2CO_2Et$	92	oil
26	8-F	$(CH_2)_2CO_2Et$	100	oil
27	8-F	$CH_2CH(Me)CO_2Et$	41	oil
28	8-Cl	$(CH_2)_2CO_2Et$	100	oil
29	8-Me	$(CH_2)_2CO_2Et$	93	oil
30	8-OMe	$(CH_2)_2CO_2Et$	69	oil

[a] All compounds were purified by column chromatography on silica gel.

Hz, C_7-H), 6.57–6.61 (1H, m, C_9-H), 7.03–7.06 (1H, m, C_{10}-H), 7.22 (1H, dd, J = 7.5, 5.0 Hz, C_3-H), 7.68 (1H, dd, J = 7.5, 2.0 Hz, C_4-H), 8.55 (1H, dd, J = 5.0, 2.0 Hz, C_2-H). IR (liquid): 1732 cm^{-1} (C=O). High-resolution MS: *m/z* calcd for $C_{23}H_{25}FN_2O_3$ 396.1849, found 396.1852.

Other ethyl propionates (**7–30**) were prepared in a manner similar to that described for **9** from corresponding unsubstituted piperidine (**6**). Physicochemical data for ethyl propionates (**7–30**) are summarized in Tables 10 and 11.

3-[4-(8-Fluoro-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)piperidino]propionic Acid (33). A mixture of **9** (9.8 g, 24.7 mmol) and 2 N NaOH (24.7 mL, 49.4 mmol) in MeOH (66 mL) was refluxed for 1.5 h. The solution was neutralized with dilute hydrochloric acid and then evaporated to dryness. The residue was extracted with CH_2Cl_2–MeOH (1:1). The extract was dried over Na_2SO_4 and evaporated. The resulting solid was washed with *i*-Pr_2O to give **33** as pale red crystals (2.85 g, 41%). Recrystallization from MeOH afforded slightly red crystals, mp 160–161 °C. ^{1}H-NMR ($CDCl_3$): δ 2.43–3.00 (12H, m, CH_2 × 6), 4.85 (1H, d, J = 12.0 Hz, C_5-*H*H), 5.58 (1H, d, J = 12.0 Hz, C_5-H*H*), 6.53 (1H, dd, J = 10.0, 2.5 Hz, C_7-H), 6.59–6.63 (1H, m, C_9-H), 7.03 (1H, dd, J = 8.5, 6.5 Hz, C_{10}-H), 7.26 (1H, dd, J = 7.5, 5.0 Hz, C_3-H), 7.70 (1H, dd, J = 7.5, 2.0 Hz, C_4-H), 8.56 (1H, dd, J = 5.0, 2.0 Hz, C_2-H). IR (KBr): 1612 cm^{-1} (C=O). MS: *m/z* 368 (M^+). Anal. ($C_{21}H_{21}FN_2O_3$) C, H, N.

3-[4-(8-Fluoro-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)piperidino]propionic Acid Dihydrobro-

mide (33·2HBr). A mixture of **6c** (4.4 g, 14.8 mmol) and *tert*-butyl acrylate (3.3 mL, 22.3 mmol) in *i*-PrOH (26.4 mL) was refluxed for 2 h and then evaporated to leave pale brown amorphous. To a solution of the above residue in 1,2-dichloroethane (25 mL) was added dropwise 25% HBr/AcOH (25 mL) at room temperature, and the mixture was stirred at the same temperature for 30 min. The resulting precipitate was collected by filtration and washed with acetone twice to afford **33**·2HBr as colorless crystals (7.32 g, 90%), mp 204.5–207.5 °C. Anal. ($C_{21}H_{21}FN_2O_3$·2HBr·H_2O) C, H, N.

Other propionic acids (**31**–**54**) were prepared in a manner similar to that described for **33** or **33·2HBr** from corresponding unsubstituted piperidines (**6**).

Ethyl 4-(5,11-Dihydro-7-nitro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (5m) and Ethyl 4-(5,11-Dihydro-9-nitro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (5n). To a suspension of **5a** (9.5 g, 27.1 mmol) in acetic anhydride (25.7 mL, 271 mmol) was added dropwise concentrated nitric acid (6.4 mL, 101 mmol) at 5 °C, and the mixture was stirred at 5 °C for 4.5 h. The reaction mixture was poured into ice–water, made alkaline to pH 10 with 10 N NaOH, and then extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was separated by column chromatography [SiO_2, CH_2Cl_2–AcOEt–*n*-hexane (1:1:1)] to afford pure **5m** (3.8 g, 36%) and **5n** (5.6 g, 52%).

5m: pale yellow crystals, mp 161–162.5 °C (AcOEt–*i*-Pr_2O). ^{1}H-NMR ($CDCl_3$): δ 1.27 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 2.28–2.58 (4H, m, CH_2, × 2), 3.09–3.34 (2H, m, CH_2), 3.75–3.92 (2H, m, CH_2), 4.16 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 5.07 (1H, d, J = 13.0 Hz, C_5-*H*H), 5.73 (1H, d, J = 13.0 Hz, C_5-H*H*), 6.96 (1H, t, J = 8.0 Hz, C_9-H), 7.26–7.31 (2H, m, C_3-H and C_8-H), 7.56 (1H, dd, J = 8.0, 1.5 Hz, C_{10}-H), 7.70 (1H, dd, J = 7.5, 2.0 Hz, C_4-H), 8.58 (1H, dd, J = 5.0, 2.0 Hz, C_2-H). IR (KBr): 1696 cm^{-1} (C=O). MS: *m/z* 395 (M^+). Anal. ($C_{21}H_{21}N_3O_5$) C, H, N.

5n: pale yellow crystals, mp 199.5–200 °C (AcOEt). ^{1}H-NMR ($CDCl_3$): δ 1.27 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 2.26–2.72 (4H, m, CH_2 × 2), 3.14–3.38 (2H, m, CH_2), 3.74–3.95 (2H, m, CH_2), 4.16 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.95 (1H, d, J = 13.0 Hz, C_5-*H*H), 5.70 (1H, d, J = 13.0 Hz, C_5-H*H*), 6.87 (1H, d, J = 9.0 Hz, C_7-H), 7.29 (1H, dd, J = 8.0, 5.0 Hz, C_3-H), 7.73 (1H, dd, J = 8.0, 1.5 Hz, C_4-H), 8.00 (1H, dd, J = 9.0, 3.0 Hz, C_8-H), 8.06 (1H, d, J = 3.0 Hz, C_{10}-H), 8.61 (1H, dd, J = 5.0, 1.5 Hz, C_2-H). IR (KBr): 1696 cm^{-1} (C=O). MS: *m/z* 395 (M^+). Anal. ($C_{21}H_{21}N_3O_5$) C, H, N.

Ethyl 4-(9-Acetyl-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (5o). To a suspension of granulated anhydrous $AlCl_3$ (5.8 g, 43.2 mmol) in 1,2-dichloroethane (10 mL) was added dropwise a solution of **5a** (3.8 g, 10.8 mmol) in 1,2-dichloroethane (38 mL) at 5 °C. Acetyl chloride (1.6 mL, 22.7 mmol) was added dropwise to the above mixture at 5 °C, and then the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into ice–water and then extracted with CH_2Cl_2. The organic layer was washed with aqueous NaOH and water, dried over Na_2SO_4, and evaporated. The resulting solid was washed with *i*-Pr_2O to give **5o** as pale brown crystals (3.8 g, 90%). Recrystallization from EtOH afforded slightly brown crystals, mp 200–201 °C. ^{1}H-NMR ($CDCl_3$): δ 1.27 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 2.27–2.67 (4H, m, CH_2 × 2), 2.50 (3H, s, $COCH_3$), 3.10–3.34 (2H, m, CH_2), 3.74–3.95 (2H, m, CH_2), 4.16 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.91 (1H, d, J = 12.5 Hz, C_5-*H*H), 5.68 (1H, d, J = 12.5 Hz, C_5-H*H*), 6.84 (1H, d, J = 8.5 Hz, C_7-H), 7.27 (1H, dd, J = 8.0, 5.0 Hz, C_3-H), 7.72 (1H, dd, J = 8.0, 2.0 Hz, C_4-H), 7.75 (1H, d, J = 2.0 Hz, C_{10}-H), 7.77 (1H, dd, J = 8.5, 2.0 Hz, C_8-H), 8.58 (1H, dd, J = 5.0, 2.0 Hz, C_2-H). IR (KBr): 1694, 1684 cm^{-1} (C=O). MS: *m/z* 392 (M^+). Anal. ($C_{23}H_{24}N_2O_4$) C, H, N.

9-Acetyl-5,11-dihydro-11-(4-piperidylidene)[1]benzoxepino[4,3-*b*]pyridine Hydrochloride (6o). (1) Ethyl 4-(9-Acetyl-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate Ethylene Acetal. A mixture of **5o** (11.2 g, 28.5 mmol), ethylene glycol (15.9 mL, 285 mmol), and TsOH·H_2O (2.71 g, 14.2 mmol) in dry toluene (340 mL) was refluxed for 17.5 h with a Dean–Stark trap. The reaction solution was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The resulting solid was washed with AcOEt–*n*-hexane (1:1) to give the title compound as colorless crystals (11.3 g, 91%). Recrystallization from AcOEt afforded colorless prisms, mp 157–158 °C. ^{1}H-NMR ($CDCl_3$): δ 1.27 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 1.60 (3H, s, CH_3), 2.26–2.68 (4H, m, CH_2 × 2), 3.08–4.03 (8H, m, CH_2 × 4), 4.15 (2H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.84 (1H, d, J = 12.5 Hz, C_5-*H*H), 5.60 (1H, d, J = 12.5 Hz, C_5-H*H*), 6.77 (1H, d, J = 9.0 Hz, C_7-H), 7.21–7.27 (3H, m, C_3-H, C_8-H, and C_{10}-H), 7.68 (1H, dd, J = 7.5, 1.5 Hz, C_4-H), 8.56 (1H, dd, J = 5.0, 1.5 Hz, C_2-H). IR (KBr): 1690 cm^{-1} (C=O). MS: *m/z* 436 (M^+). Anal. ($C_{25}H_{28}N_2O_5$) C, H, N.

(2) 9-Acetyl-5,11-dihydro-11-(4-piperidylidene)[1]benzoxepino[4,3-*b*]pyridine Ethylene Acetal. The title compound was prepared from ethyl 4-(9-acetyl-5,11-dihydro[1]benzoxepino[4,3-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate ethylene acetal as described for **6c**. Pale yellow crystals, mp 176–177 °C (AcOEt). ^{1}H-NMR ($CDCl_3$): δ 1.61 (3H, s, CH_3), 2.28–3.17 (8H, m, CH_2 × 4), 3.69–4.03 (4H, m, CH_2 × 2), 4.83 (1H, d, J = 12.0 Hz, C_5-*H*H), 5.66 (1H, d, J = 12.0 Hz, C_5-H*H*), 6.76 (1H, d, J = 8.5 Hz, C_7-H), 7.19–7.28 (2H, m, C_8-H and C_{10}-H), 7.21 (1H, dd, J = 7.5, 5.0 Hz, C_3-H), 7.68 (1H, dd, J = 7.5, 1.5 Hz, C_4-H), 8.55 (1H, dd, J = 5.0, 1.5 Hz, C_2-H). MS: *m/z* 364 (M^+). Anal. ($C_{22}H_{24}N_2O_3$) C, H, N.

(3) 9-Acetyl-5,11-dihydro-11-(4-piperidylidene)[1]benzoxepino[4,3-*b*]pyridine Hydrochloride. A mixture of 9-acetyl-5,11-dihydro-11-(4-piperidylidene)[1]benzoxepino[4,3-*b*]pyridine ethylene acetal (8.46 g, 23.2 mmol) and 10% hydrochloric acid (17 mL) in THF (85 mL) was stirred at room temperature for 2 h and then evaporated. The residue was diluted with water, made alkaline with aqueous K_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to give the free base of **6o** as a pale yellow amorphous solid (7.86 g, quantitative). The free base was converted to the hydrochloride by the usual method.

Hydrochloride: slightly red needles, mp 282–285 °C dec (EtOH). ^{1}H-NMR (CD_3OD): δ 2.46–2.95 (4H, m, CH_2 × 2), 2.54 (3H, s, $COCH_3$), 3.08–3.49 (4H, m, CH_2 × 2), 5.06 (1H, d, J = 12.5 Hz, C_5-*H*H), 5.75 (1H, d, J = 12.5 Hz, C_5-H*H*), 6.91 (1H, d, J = 9.0 Hz, C_7-H), 7.46 (1H, dd, J = 7.5, 5.0 Hz, C_3-H), 7.78 (1H, d, J = 2.0 Hz, C_{10}-H), 7.84 (1H, dd, J = 9.0, 2.0 Hz, C_8-H), 7.98 (1H, dd, J = 7.5, 1.5 Hz, C_4-H), 8.55 (1H, dd, J = 5.0, 1.5 Hz, C_2-H). IR (KBr): 1674 (C=O). MS: *m/z* 320 (M^+-(free base)). Anal. ($C_{20}H_{20}N_2O_2$·HCl·0.25H_2O) C, H, N.

Methyl 5,11-Dihydro-11-(1-methylpiperidin-4-ylidene)-[1]benzoxepino[4,3-*b*]pyridine-9-carboxylate Hydrochloride (4p). To a solution of **4i** (11.8 g, 31.8 mmol) in dry THF (200 mL) was added dropwise 1.6 M *n*-BuLi-*n*-hexane (40 mL, 63.8 mmol) at −72 °C under N_2, and the mixture was stirred at the same temperature for 1 h. CO_2 was bubbled into the above mixture at −72 °C for 1 h. The reaction mixture was warmed gradually to room temperature and then evaporated. The residue was diluted with water and washed with Et_2O. The aqueous layer was acidified to pH 1 with dilute hydrochloric acid and then washed with Et_2O. The aqueous layer was neutralized with aqueous NaOH and evaporated to dryness. The residue was extracted with EtOH, and the extract was evaporated to leave an oil.

A mixture of above oil and concentrated H_2SO_4 (47.5 mL) in MeOH (600 mL) was refluxed for 1.5 h and then evaporated. The residue was diluted with water, made alkaline to pH 9 with 10 N NaOH, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography [SiO_2, CH_2Cl_2–MeOH (10:1)] to give free base of **4p** as a pale red amorphous solid (6.0 g, 54%). The free base was converted to the hydrochloride by the usual method.

Hydrochloride: colorless needles, mp 249–251 °C dec (*i*-PrOH). ^{1}H-NMR (DMSO-d_6): δ 2.27–3.65 (8H, m, CH_2 × 4), 3.22 (3H, s, NCH_3), 3.82 (3H, s, CO_2CH_3), 5.04–5.13 (1H, m, C_5-*H*H), 5.60–5.83 (1H, m, C_5-H*H*), 6.90 (1H, d, J = 7.0 Hz, C_7-H), 7.40 (1H, dd, J = 7.5, 5.0 Hz, C_3-H), 7.63 (1H, s, C_{10}-H), 7.75 (1H, dd, J = 7.5, 1.5 Hz, C_4-H), 7.96 (1H, d, J = 7.0 Hz, C_8-H), 8.55 (1H, dd, J = 5.0, 1.5 Hz, C_2-H). IR (KBr): 1718

cm^{-1} (C=O). MS: *m/z* 350 (M^+(free base)). Anal. ($C_{21}H_{22}N_2O_3 \cdot HCl \cdot 0.25H_2O$) C, H, N.

Determination of Octanol–Buffer Partition Coefficient (PC_{oct}). The procedure used involved dissolving an accurately weighed sample of compound in Sörensen buffer (pH 7.4) to give a concentration of 10 μg/mL. Equal volumes of buffer solution and 1-octanol were added to centrifuge tubes. The tubes were skaken for 24 h at 25 °C and then centrifuged. The organic and aqueous phases were pipetted into separate containers. The concentration of compound in each phase was quantitated by HPLC [apparatus, JASCO 880-PU (pump) and 870-UV (detector); detection, UV at 254 nm; column, Tosoh TSK-gel ODM-80TM 4.6 (i.d.) × 150 mm; mobile phase, 0.03 M phosphate buffer (pH 3.0)–CH_3CN (7:3); flow rate, 1.0 mL/min]. The value of PC_{oct} was calculated for each compound by dividing its equilibrium organic concentration by its aqueous concentration.

Pharmacological Evaluation Procedures. Effects on Compound 48/80-Induced Lethality in Rats.[17] Male Wistar rats (starved for 24 h, 6 weeks of age) were used. Compound 48/80 (formaldehyde condensation product of *p*-methoxy-*N*-methylphenethylamine) was administered intravenously at a lethal dose of 1 mg/kg. Survival for more than 2 h was selected as an all-or-none criterion. Test compounds were given orally 1 h before the compound 48/80 administration. ED_{50} values (doses which produced 50% inhibition of compound 48/80-induced lethality) were deduced from the number of survival animals at each dose by the method of Litchfield and Wilcoxon.[18]

Effect on Histamine-Induced Increase in Vascular Permeability in Mice. Male ICR mice (starved for 20 h, 6 weeks of age) were treated orally with the test compounds or vehicle. One hour later, the mice were lightly anesthetized with ether. The cutaneous reaction was induced by intradermal injection of 2.5 μg/site of histamine dihydrochloride and 25 μL/site of saline after an intraveneous injection of 0.2 mL of 1% Evans blue. Thirty minutes later, the mice were killed by cervical dislocation. The intensity of the response was evaluated by assaying the amount of extravasated dye according to the method of Katayama *et al.*[19] ED_{50} values (doses which produced 50% inhibition of histamine-induced increase in vascular permeability) were deduced from the relation between the dose and the percent inhibition (log–logit conversion) by the method of least squares.

***Ex vivo* Binding of [^{3}H]Mepyramine to Mouse Brain Membranes.** Male ICR mice (starved for 24 h, 6 weeks of age) were treated orally with the test compounds or vehicle. One hour later, the mice were killed by cervical dislocation, and the brain was rapidly removed and homogenized in 40 volumes of 50 mM phosphate buffer (pH 7.4). The [^{3}H]-mepyramine binding assay used was similar to that of Ahn and Barnett.[20] Each assay tube received 0.1 mL of 20 nM [^{3}H]-mepyramine, to a final concentration of 2 nM, 0.4 mL of buffer, and 0.5 mL of membrane suspension. The total incubation volume was 1 mL. The receptor–ligand binding reaction was initiated by adding the membrane suspension, and incubation was carried out at 25 °C for 30 min with shaking. Samples were subsequently filtered rapidly in vacuum through Whatman GF/B glass filter and washed with 5 mL of ice-cold buffer three times. The filters were dried and placed in 7 mL of Aquazol-2. Radioactivity was measured by a liquid scintillation counter. Inhibition effect of each test compound was represented as percent of control binding. ID_{50} values (doses which produced 50% inhibition of the specific binding of [^{3}H]-mepyramine) were deduced from the relation between the dose and the percent inhibition (log–logit conversion) by the method of least squares.

Effect on Hexobarbital-Induced Anesthesia in Mice. Male ICR mice (starved for 20–24 h, 5 weeks of age) were treated orally with test compounds or vehicle. One hour later, hexobarbital (80 mg/kg, ip) was injected into the animals, and the duration of loss of righting reflex was observed and taken as the sleeping time. The percent increase of sleeping time was calculated. Animals having more than 50% increase on the sleeping time compared to the control group were judged to respond. ID_{50} values (doses which produced 50% increase of the sleeping time) were deduced from the number of responded animals at each dose by the method of Litchfield and Wilcoxon.[18]

Effect on Histamine-Induced Lethality in Guinea Pigs. Male Hartley guinea pigs (starved for 24 h, 6 weeks of age) were treated orally with test compounds at a dose of 0.3 mg/kg. Eight hours later, histamine dihydrochloride was administered intravenously at a lethal dose of 1 mg/kg. Survival for more than 30 min was selected as an all-or-none criterion.

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