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Antivertigo Agents. I. Structure–Activity Relationships of 2-(2-Aminoethyl)pyridines[1)]

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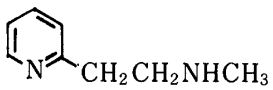
A series of 2-(2-aminoethyl)pyridines derived by the modification of the amine moiety in betahistine, 2-(2-methylaminoethyl)pyridine, was synthesized and evaluated for antivertigo action in terms of inhibitory activity against spontaneous nystagmus in cats. The structure–activity relationships between the amine moieties and antivertigo activities were investigated. The effects of substituents on the phenyl ring of the 4-phenylpiperazine moiety were investigated by means of quantitative regression analysis using various physicochemical parameters. The following equation gave the best correlation. $\log 1/ID_{30} = -0.417\ (\pm 0.322)\ \pi + 0.166\ (\pm 0.048)\ MR - 1.473\ (\pm 0.237)$ ($n=15$, $s=0.239$, $r=0.910$, $F_{12}^2=28.887$). In this series of compounds, 1-(2-methoxyphenyl)-4-[2-(2-pyridyl)ethyl]piperazine, 1-(2-methoxyphenyl)-4-[2-[2-(6-methyl)pyridyl]ethyl]-piperazine, and 1-(2-methoxyphenyl)-4-[2-[2-(5-ethyl)pyridyl]ethyl]piperazine were found to show more potent activity than betahistine. Thus, the 4-(2-methoxyphenyl)piperazine group was found to be the most effective amine moiety for activity against spontaneous nystagmus.

Keywords——antivertigo action; 2-(2-aminoethyl)pyridine; structure–activity relationship; spontaneous nystagmus; 1-(substituted phenyl)piperazine

Betahistine (**1a**), 2-(2-methylaminoethyl)pyridine, possesses a histamine-like action and has been clinically used as an antivertigo agent. Furthermore, a number of analogs of **1a** were synthesized mainly to investigate their histamine-like action[2)] and some of them were reported to have a tranquilizing[3)] or an antihypertensive[4)] action. In spite of these results, there have been no reports dealing with the relationships between the chemical structures and antivertigo activities of **1a** and related compounds.



1a

Chart 1

Thus, our interest was focused on modification of the amine moiety of **1a** to investigate the structure–activity relationships of these compounds as antivertigo agents. This paper deals with the synthesis of 2-(2-aminoethyl)pyridine derivatives and reports a quantitative regression analysis of their antivertigo activities.

Synthesis

According to the reported method,[5] 2-(2-aminoethyl)pyridine (**1b**) was obtained by the reaction of 2-vinylpyridine with ammonium chloride. Similarly, most of the 2-(2-alkylaminoethyl)pyridines (**1c**, **2a**, **b**, **d**—**f**, **3a**—**o**, and **5a**, **b**) were synthesized by the Michael reaction of 2-vinylpyridine with the corresponding aliphatic amine in the presence of an equivalent amount of acetic acid. The reaction of 2-vinylpyridine with a half molar equivalent of piperazine gave 1,4-bis[2-(2-pyridyl)ethyl]piperazine (**2g**)[6] selectively, whereas the reaction with excess piperazine afforded 1-[2-(2-pyridyl)ethyl]piperazine (**2c**). Compound **2c** readily reacted with acylating agents such as acyl chloride, alkyl isocyanate, and alkyl isothiocyanate to give the corresponding 4-substituted derivatives (**4a**—**d**). Compounds **6a** and **6b** were obtained by the reaction of 1-(2-methoxyphenyl)piperazine with 6-methyl- and 5-ethyl-2-

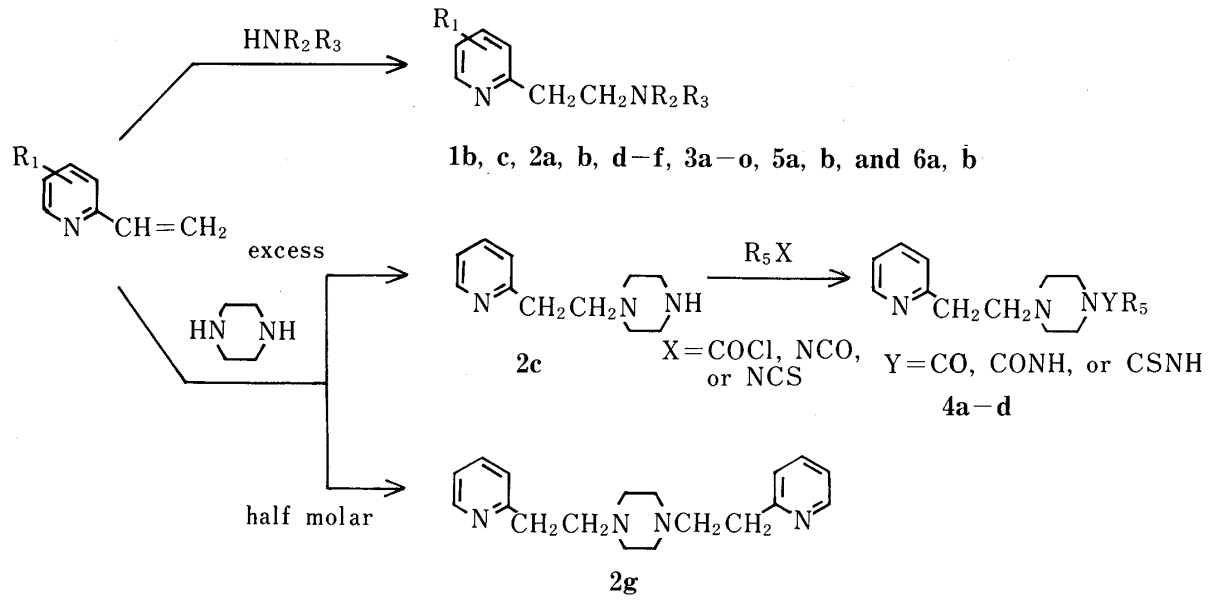


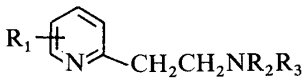
Chart 2

vinylpyridine, respectively. All the compounds thus obtained were transformed into the maleates or fumarates, whose melting points and yields are summarized in Table V.

Structure–Activity Relationships

We attempted to establish a reliable method for the screening of antivertigo activity, because there are few reliable methods for such screening. It is well known that diseases involving vertigo, such as Ménière's disease, are always accompanied by spontaneous nystagmus.[7] Thus, the inhibitory action of compounds against nystagmus induced by unilateral destruction of the labyrinth in a cat is considered to be a good index for the evaluation of the compounds.[8] Accordingly, the antivertigo action of these 2-(2-aminoethyl)pyridine derivatives was evaluated in terms of their inhibitory action against spontaneous nystagmus in cats. Table I shows the activities of 2-(2-aminoethyl)pyridines against spontaneous nystagmus in comparison with that of betahistine (**1a**). Table I indicates that the amine moiety in this series of compounds contributes greatly to the inhibitory action against spontaneous nystagmus. When a dimethylamino (**1c**), pyrrolidino (**2a**), or piperidino (**2b**) group was introduced as the amine moiety into the parent molecule (**1a**) instead of its methylamino group, the inhibitory activities were approximately comparable to that of **1a**, while an unsubstituted amine (**1b**) was less potent than **1a**. In the cases of the 4-unsubstituted (**2c**), 4-methyl (**2d**), and 4-benzyl (**2e**) piperazine analogs, in which the carbon atom at the 4-

TABLE I. Inhibitory Activities[a] of 2-(2-Aminoethyl)pyridines against Spontaneous Nystagmus in Cats



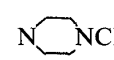
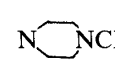
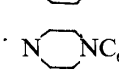
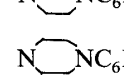
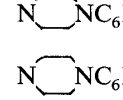
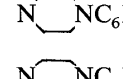
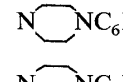
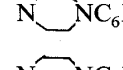
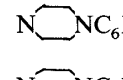
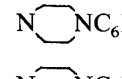
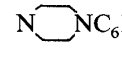
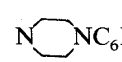
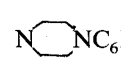
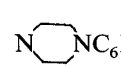
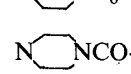
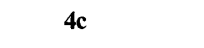
Compd. No.	R_1	NR_2R_3	ID_{30} (μmol/kg, *i.v.*)
1a	H	$NHCH_3$ (Betahistine)	100
1b	H	NH_2	185
1c	H	$N(CH_3)_2$	123
2a	H		105
2b	H		98.7
2c	H		Inact.[b]
2d	H		Inact.[b]
2e	H		Inact.[b]
2f	H		66.4
2g	H		85.3
3a	H		86.1
3b	H		3.75
3c	H		31.8
3d	H		34.7
3e	H		7.4
3f	H		21.4
3g	H		32.1
3h	H		79.3
3i	H		0.73
3j	H		38.7
3k	H		34.9
3l	H		11.0
3m	H		13.1
3n	H		20.2
3o	H		14.8
4a	H		54.1
4b	H		Inact.[b]

TABLE I. (continued)

Compd. No.	R_1	NR_2R_3	ID_{30} (μmol/kg, *i.v.*)
4c	H		Inact.[b]
4d	H		Inact.[b]
5a	H		19.4
5b	H		16.4
6a	6-CH_3		0.55
6b	5-C_2H_5		0.60

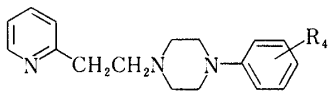
a) Each compound was injected as its salt (see Table V).
b) "Inact." indicates that the compound is inactive at the dose of 6 mg/kg, *i.v.*

position of piperidine (**2d**) can be considered to have been replaced with a nitrogen atom, the activity was lost. In contrast, compound **2g** with a 2-(2-pyridyl)ethyl group on the nitrogen atom of piperazine exhibited more potent activity than **1a**. Further increase in the activity was induced by the introduction of a 2-(3,4-dimethoxyphenyl)ethyl group (**2f**). These results suggested that decrease of the lipophilicity of the substituent on the nitrogen atom of the piperazine moiety might lead to a decrease in the activity.

In addition, the replacement of the amine moiety with 4-phenylpiperazine analogs enhanced the activity as shown in compounds **3b—g** and **3i—o** (excluding **3a** and **3h**). As shown in Table I, the kind and position of the substituents on the phenyl ring affected the activity remarkably. In the series of methoxy derivatives, the 2-methoxy compound (**3i**) was more potent than the 3- (**3j**) and 4-isomers (**3k**). Compound **3i** was found to exhibit the most potent activity. Similarly, the 2-chloro (**3b**) and 2-methyl (**3e**) compounds were more potent than the corresponding 3- (**3c** and **3f**) and 4-isomers (**3d** and **3g**). These results suggest that the presence of an *ortho* substituent on the phenyl ring may play an important role in enhancement of the activity. When 4-(disubstituted phenyl)piperazine derivatives with the methyl group at the *ortho* position of the phenyl ring were further examined, compounds **31** (2-CH_3, 4-Cl), **3m** (2-CH_3, 5-Cl), **3n** (2,5-di-CH_3), and **3o** (2,6-di-CH_3) showed lower activity than **3e** (2-CH_3) which has the mono-substituted phenyl ring.

Thus, in order to clarify the effect of the substituent on the phenyl group, the quantitative structure–activity relationships (QSAR) of the 4-phenylpiperazines were investigated by using various physicochemical parameters of the substituents. A regression analysis was carried out by using the values of various parameters of the substituents published by Hansch *et al.*[9] as shown in Table II. Hammett's σ_m and σ_p were used as σ of the *meta* and *para* positions and σ_p was also adopted as σ in the *ortho* position in the conventional manner.[10] Molar refractivity (*MR*) or Taft's steric constant (E_s) was used as a parameter of the steric effect of substituents in the *ortho* position, while the parameter in the case of *ortho*-disubstituted compounds such as 4-(2,6-dimethylphenyl)piperazine (**3o**) was obtained by assuming the mono-substituent values to be applicable. Firstly, Eq. (1)—(4) were derived by regression analysis using π, σ, *MR*, or E_s as a single parameter. In these equations (Table III), *n*, *s*, *r*, and F_0 represent the number of data used for the regression analysis, standard deviation, correlation coefficient, and observed *F* value, respectively. Figures in parentheses after each term represent the 95% confidence interval. Equations (3) and (4) satisfied the *F* test at the 95% level with F_0 values of 5.836 and 32.440 ($F^1_{13\,(\alpha=0.05)}=4.667$), respectively, whereas Eqs. (1) and (2) did not satisfy the

TABLE II. Nystagmus Inhibitory Activity and Physicochemical Parameters of 4-(Substituted phenyl)-1-[2-(2-pyridyl)ethyl]piperazines **3a—o** Used for Regression Analysis



Compd. No.	R_4	$\pi^{a)}$	$\sigma^{a)}$	$E_s^{b)}$	$MR^{c)}$	$\log(1/ID_{30})$		
						Obsd.[d]	Calcd[e]	Δ
3a	H	0	0	0	0	−1.935	−1.473	0.462
3b	2-Cl	0.71	0.23	−0.97	6.03	−0.574	−0.766	0.192
3c	3-Cl	0.71	0.37	0	0	−1.503	−1.768	0.266
3d	4-Cl	0.71	0.23	0	0	−1.534	−1.768	0.229
3e	2-CH_3	0.56	−0.17	−1.24	5.65	−0.869	−0.767	0.103
3f	3-CH_3	0.56	−0.07	0	0	−1.547	−1.706	0.159
3g	4-CH_3	0.56	−0.17	0	0	−1.507	−1.706	0.199
3h	3-CF_3	0.88	0.43	0	0	−1.900	−1.839	0.060
3i	2-OCH_3	−0.22	−0.27	−0.55	7.87	−0.137	−0.156	0.019
3j	3-OCH_3	−0.22	0.12	0	0	−1.588	−1.464	0.124
3k	4-OCH_3	−0.22	−0.27	0	0	−1.543	−1.464	0.079
3l	2-CH_3, 4-Cl	1.27[f]	0.06	−1.24	5.65	−1.041	−1.062	0.021
3m	2-CH_3, 5-Cl	1.27[f]	0.20[g]	−1.24	5.65	−1.117	−1.062	0.055
3n	2,5-$(CH_3)_2$	1.12[f]	−0.24[g]	−1.24	5.65	−1.305	−1.000	0.305
3o	2,6-$(CH_3)_2$	1.12[f]	−0.34[g]	−1.24[h]	5.65[h]	−1.171	−1.000	0.170

a) From ref. 9*a*. In the case of a *meta* or *para* substituent, σ_m or σ_p is used as Hammett's σ constant, but in the case of an *ortho* substituent, σ_p is also used as Hammett's σ constant.
b) In the case of a *meta* or *para* substituent $E_s=0$; for an *ortho* substituent E_s is taken from ref. 9*b*.
c) In the case of a *meta* or *para* substituent $MR=0$; for an *ortho* substituent MR is taken from ref. 8*a*.
d) See Table I.
e) The calculated values were obtained from Eq. (7).
f) $\pi_{CH_3,Cl}=\pi_{CH_3}+\pi_{Cl}=1.27$, $\pi_{(CH_3)_2}=2\times\pi_{CH_3}=1.12$.
g) $\sigma_{2\text{-}CH_3,4\text{-}Cl}=\sigma_{2\text{-}CH_3}+\sigma_{4\text{-}Cl}=0.06$, $\sigma_{2\text{-}CH_3,5\text{-}Cl}=\sigma_{2\text{-}CH_3}+\sigma_{3\text{-}Cl}=0.20$.
h) The value was assumed to be due to the contribution of 2-CH_3 of 2,6-$(CH_3)_2$.

TABLE III. Correlation Equations between Nystagmus Inhibitory Activity and Physicochemical Parameters of 4-(Substituted phenyl)-1-[2-(2-pyridyl)ethyl]piperazines **3a—o**

Eq. No.	$\log 1/ID_{30}=$	$n^{a)}$	$s^{b)}$	$r^{c)}$	$F_o^{d)}$
(1)	$0.010(\pm0.683)^{e)}\pi-1.273(\pm0.528)$	15	0.554	0.009	$F^1_{13}=0.001$
(2)	$-0.684(\pm1.217)\sigma-1.262(\pm0.293)$	15	0.525	0.319	$F^1_{13}=1.474$
(3)	$-0.499(\pm0.446)E_s-1.524(\pm0.344)$	15	0.460	0.567	$F^1_{13}=5.836$
(4)	$0.143(\pm0.054)MR-1.668(\pm0.225)$	15	0.296	0.845	$F^1_{13}=32.440$
(5)	$-0.648(\pm0.651)\pi-0.820(\pm0.511)E_s-1.282(\pm0.391)$	15	0.406	0.710	$F^2_{12}=6.105$
(6)	$-0.375(\pm1.145)\sigma-0.454(\pm0.479)E_s-1.498(\pm0.363)$	15	0.469	0.581	$F^2_{12}=3.063$
(7)	$-0.417(\pm0.322)\pi+0.166(\pm0.048)MR-1.473(\pm0.237)$	15	0.239	0.910	$F^2_{12}=28.887$
(8)	$-0.063(\pm0.768)\sigma+0.141(\pm0.061)MR-1.670(\pm0.244)$	15	0.308	0.845	$F^2_{12}=15.028$

a) The number of compounds. *b*) Standard deviation. *c*) Correlation coefficient.
d) Observed F value. *e*) Figures in parentheses after each term represent the 95% confidence intervals.

F test at the 95% level with F_0 values of 0.001 and 1.474, respectively. Thus, Eqs. (3) and (4) were adopted as fundamental equations for this QSAR. The introduction of π or σ into Eqs. (3) and (4) gave the corresponding four equations (Eqs. (5)—(8)) as shown in Table III. Thus, the sequential F test[11] was used to statistically evaluate the introduction of the π or σ term

into Eqs. (3) and (4). Comparing Eqs. (5) and (6) with Eq. (3), and Eqs. (7) and (8) with Eq. (4), the sequential F test gave the following F values: $F_{12}^{1}=4.709$ for Eq. (5), $F_{12}^{1}=0.150$ for Eq. (6), $F_{12}^{1}=7.962$ for Eq. (7), and $F_{12}^{1}=1.001$ for Eq. (8) ($F_{12\,(\alpha=0.05)}^{1}=4.747$). Of these F values, only that of Eq. (7) satisfies the sequential F test at the 95% level. Furthermore, as shown in Table III, Eq. (7) has the highest F_0 value and satisfies the F test at the 99% level with the F_0 value of 28.887 ($F_{12\,(\alpha=0.01)}^{2}=6.927$). Thus, Eq. (7) was adopted as the best equation. The log $1/ID_{30}$ values calculated from Eq. (7) were in good agreement with those observed in the 4-phenylpiperazine derivatives as shown in Table II. The coefficient of π in this Eq. (7) is negative, indicating that the introduction of a hydrophobic substituent into the phenyl ring leads to a decrease in the activity. The coefficient of MR is positive, indicating that bulky substituents at the *ortho* position enhance the activity. Equation (7) reveals that the effect of the substituents at the *ortho* position decreases in the order of 2-methoxy > 2-chloro > 2-methyl > hydrogen.

The linkage of a carbonyl or thiocarbonyl group on the nitrogen atom of the piperazine moiety such as **4a**—**d** resulted in no activity. Compounds **5a** and **5b** with a phenyl carbinol group also had no activity. These results suggested that the nature of the nitrogen atom adjacent to the phenyl ring on the piperazine might play an important role in the inhibition of the spontaneous nystagmus. On the other hand, it was suggested that the introduction of an alkyl substituent into the pyridine ring of the molecule **3i** might improve the activity. For example, the 6-methyl (**6a**) and 5-ethyl (**6b**) analogs of **3i** exhibited the same remarkable activity as **3i**. The role of these alkyl groups of the pyridine moiety remains to be determined. The 4-(2-methoxyphenyl)piperazine group may be an essential amine moiety in this series for the appearance of potent activity.

In order to investigate the relationships between inhibitory activities on spontaneous nystagmus and other pharmacological actions, we examined the histamine-like, anti-histaminic, anti-cholinergic, and papaverine-like actions of representative compounds in this

TABLE IV. Pharmacological Actions[a] of 2-(2-Aminoethyl)pyridines

No.	His.[b] (%)	Anti-his.[c] (pA_2)	Anti-ach.[d] (pA_2)	Pap.[e] (pD_2')	MBP[f] Δ (mmHg)
1a	89.7		*[g]	*	−100
1b	96.7		*	*	
1c	51.4		*	*	
2a		4.8	*	*	
2b		5.1	*	*	−10
2c		4.9	*	*	
2d		4.9	*	*	
2e		6.2	*	*	
2f		6.3	*	*	−18
3b		7.0	*	*	−25
3h		7.2	5.4	4.3	−60[h]
3i		6.9	5.3	*	−60
4b		5.5	*	*	

a) Each value represents the mean of two experiments.
b) Percentage contraction relative to that induced by histamine (10^{-7} M) in isolated ileum of guinea pigs.
c) Anti-histaminic action in isolated ileum of guinea pigs.
d) Anti-cholinergic action in isolated ileum of guinea pigs.
e) Papaverine-like action in isolated ileum of guinea pigs.
f) Decrease in mean blood pressure at the dose of 1 mg/kg *i.v.* in dogs.
g) * This symbol represents less than 4.0 in pA_2 or pD_2'.
h) Decrease in mean blood pressure at the dose of 0.3 mg/kg *i.v.* in dogs.

series using isolated ileum of guinea pigs. In addition, the mean blood pressure in anesthetized dogs after intravenous administration of each of these compounds was measured. Table IV shows the pharmacological actions of the representative compounds and their effects on mean blood pressure. Among compounds such as **1c** and **2a**, **b** (having activity similar to that of **1a** in the inhibition of spontaneous nystagmus) and **1b** (having activity less than **1a**), compounds **1b** and **1c** exhibited ileum-contracting action equal to that of betahistine (**1a**). The potency of the ileum-contracting action of the three compounds decreased in the order of **1b** > **1a** > **1c**. On the other hand, compounds **2a** and **2b** showed weak anti-histaminic action. However, compounds **2c** and **2d**, which exhibited no activity against spontaneous nystagmus, showed weak anti-histaminic action. Among the 4-phenylpiperazine analogs **3a**—**o**, **3i** (with the most potent antivertigo action) exhibited a relatively potent anti-histaminic action, whereas **3h** (with a weak antivertigo activity) exhibited anti-histaminic action similar to that of **3i**. When the anti-cholinergic and papaverine-like actions were examined, the compounds except for **3h** and **3i** exhibited weak anti-cholinergic action, as shown in Table IV. Consequently, it was difficult to characterize the antivertigo activity of this series in relation to the above pharmacological actions. Further investigations are in progress and the results will be published elsewhere. Compound **3i** had the most potent antivertigo activity among compounds **3a**—**o** and showed a relatively strong hypotensive action, the potency of which was less than that of **1a**.

In conclusion, modification of the amine moiety of betahistine (**1a**) enhanced the antivertigo activity. In particular, it was found that the introduction of the 4-(2-methoxyphenyl)piperazine moiety into **1a** improved the antivertigo activity and provided an entirely different pattern of pharmacological action from that of **1a**.

Experimental

All melting points and boiling points are uncorrected. The structures of all compounds were supported by the infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS). IR spectra were measured on a JASCO IR-G spectrometer. NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer using Me_4Si as an internal standard. MS were determined with a Shimadzu GCMS-7000 spectrometer.

Chemistry

General Procedure for Preparation of 2-(2-Aminoethyl)pyridines (2e, f, 3e, f, h, j, l—o, 5a, b, and 6a, b). A Typical Example: 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-[2-(2-pyridyl)ethyl]piperazine (2f)——A solution of 2-vinylpyridine (1.6 g, 15 mmol), 1-[2-(3,4-dimethoxyphenyl)ethyl]piperazine (3.8 g, 15 mmol),[12] and AcOH (0.9 g, 15 mmol) in EtOH (15 ml) was refluxed for 5 h. The reaction mixture was evaporated *in vacuo*, and the residue was made alkaline with 5 N NaOH. The mixture was extracted with $CHCl_3$. The extract was dried over K_2CO_3, and evaporated *in vacuo* to afford a crude solid, which was recrystallized from iso-Pr_2O to give **2f** (3.9 g, 73%) as colorless prisms, mp 68—70 °C, NMR ($CDCl_3$) δ: 2.30—3.30 (16H, m, aliphatic H), 3.85 (6H, s, $2 \times OCH_3$), 6.76 (3H, s, phenyl H), 6.93—7.80 (3H, m, pyridyl H (3, 4, 5)), 8.52 (1H, dd, J=4.5, 1.5 Hz, pyridyl H (6)), MS m/z (relative intensity): 335 (M^+, 3.8), 204 (100), 186 (13.8), 135 (17.5), 111 (42.3).

Compounds **2e**, **3e**, **f**, **h**, **j**, **l**—**o**, and **5a**, **b** were prepared in the same manner as described above. Compounds **6a** and **6b** were also prepared in the same manner as described above using 6-methyl- and 5-ethyl-2-vinylpyridine, respectively, instead of 2-vinylpyridine. Compound **2e**; colorless oil, bp 167 °C (0.6 mmHg). Compound **3e**; colorless prisms, mp 53—55 °C (petroleum ether–*n*-hexane). Compound **3f**; colorless oil, bp 187—193 °C (0.5 mmHg). Compound **3h**; colorless prisms, mp 64—65 °C (iso-Pr_2O). Compound **3j**; colorless prisms, mp 57 °C (iso-Pr_2O–*n*-hexane). Compound **3l**; colorless prisms, mp 48—49 °C (petroleum ether–iso-Pr_2O). Compound **3m**; colorless oil, bp 178—180 °C (0.2 mmHg). Compound **3n**; colorless oil, bp 181—183 °C (0.4 mmHg). Compound **3o**; colorless oil, bp 167—169 °C (0.4 mmHg). Compound **5a**; colorless needles, mp 103.5—104.5 °C (iso-Pr_2O). Compound **5b**; colorless needles, mp 150—156 °C (iso-Pr_2O). Compound **6a**; colorless needles, mp 59.5 °C (*n*-hexane). Compound **6b**; light yellow oil, bp 207—209 °C (0.8 mmHg).

1-[2-(2-Pyridyl)ethyl]piperazine (2c)[13]——A solution of 2-vinylpyridine (21 g, 0.2 mol) and piperazine dihydrochloride monohydrate (71 g, 0.4 mol) in water (200 ml) was refluxed for 1 h. After the reaction mixture had been cooled to room temperature, the reaction mixture was made alkaline with 40% NaOH, and extracted with toluene. The toluene layer was dried over K_2CO_3 and evaporated *in vacuo* to give the residue. This residue was dissolved in iso-

TABLE V. The Salts of 2-(2-Aminoethyl)pyridines

Compd. No.	Yield[a]	mp (°C)	Recrystn. solvent	Formula[b]	Analysis (%) Calcd (Found)		
					C	H	N
1b[c]	53	171—174	EtOH–iso-PrOH	$C_7H_{10}N_2 \cdot C_4H_4O_4$[d]	55.45 (55.38	5.92 6.11	11.76 11.78)
1c[e]	67	59—62	AcOEt–CH_3COCH_3	$C_9H_{14}N_2 \cdot 1.5C_4H_4O_4$	55.55 (55.29	6.22 6.34	8.64 8.45)
2a[f]	73	68—69	AcOEt–CH_3COCH_3	$C_{11}H_{16}N_2 \cdot 2C_4H_4O_4$	55.87 (55.46	5.92 6.02	6.86 6.72)
2b[g]	61	93—95	THF	$C_{12}H_{18}N_2 \cdot 1.5C_4H_4O_4$[d]	59.33 (59.61	6.64 6.83	7.69 7.74)
2c[h]	34	247—252	MeOH	$C_{11}H_{17}N_3 \cdot C_4H_4O_6$[i]	52.77 (52.97	6.79 6.74	12.31 12.24)
2d[j]	28	176	MeOH–EtOH	$C_{12}H_{19}N_3 \cdot 2C_4H_4O_4$	54.91 (54.66	6.22 6.53	9.61 9.78)
2e	43	185—186	MeOH	$C_{18}H_{23}N_3 \cdot 2C_4H_4O_4$	60.81 (61.12	6.08 6.29	8.18 8.09)
2f	69	166—167	EtOH	$C_{21}H_{29}N_3O_2 \cdot 2C_4H_4O_4$	59.27 (59.36	6.35 6.25	7.15 7.07)
2g[k]	59	157—158	EtOH	$C_{18}H_{24}N_4 \cdot 3C_4H_4O_4$	55.89 (55.73	5.63 5.43	8.69 8.70)
3a[l]	64	102—114	AcOEt–CH_3COCH_3	$C_{17}H_{21}N_3 \cdot C_4H_4O_4$	65.78 (65.30	6.57 6.36	10.96 10.37)
3b[l]	72	113—119	AcOEt–CH_3COCH_3	$C_{17}H_{20}ClN_3 \cdot 2C_4H_4O_4$	56.23 (56.09	5.29 5.14	7.87 7.49)
3c[m]	40	127—130	AcOEt–CH_3COCH_3	$C_{17}H_{20}ClN_3 \cdot 2C_4H_4O_4$	56.23 (56.38	5.29 5.07	7.87 7.65)
3d[n]	49	110—113	AcOEt–CH_3COCH_3	$C_{17}H_{20}ClN_3 \cdot 2C_4H_4O_4$	56.23 (56.15	5.29 5.42	7.87 7.67)
3e	41	115—116	AcOEt–CH_3COCH_3	$C_{18}H_{23}N_3 \cdot 2C_4H_4O_4$	60.81 (60.73	6.08 6.07	8.18 8.21)
3f	49	138—140	CH_3COCH_3	$C_{18}H_{23}N_3 \cdot C_4H_4O_4$[d]	66.48 (66.72	6.85 6.75	10.57 10.86)
3g[m]	40	140—143	MeOH–CH_3COCH_3	$C_{18}H_{23}N_3 \cdot 2C_4H_4O_4$[d]	60.81 (60.90	6.08 6.11	8.18 8.34)
3h	67	117—120	AcOEt–CH_3COCH_3	$C_{18}H_{20}F_3N_3 \cdot 2C_4H_4O_4$	55.02 (55.28	4.97 5.23	7.41 7.08)
3i[l]	61	99—103	AcOEt–CH_3COCH_3	$C_{18}H_{23}N_3O \cdot C_4H_4O_4$	63.90 (63.79	6.58 6.76	10.16 10.23)
3j	55	122—127	AcOEt–CH_3COCH_3	$C_{18}H_{23}N_3O \cdot C_4H_4O_4$[d]	63.90 (63.98	6.58 6.45	10.16 10.44)
3k[n]	62	87—89	AcOEt–CH_3COCH_3	$C_{18}H_{23}N_3O \cdot 2C_4H_4O_4$	58.97 (58.62	5.90 5.86	7.94 7.78)
3l	67	124—125	AcOEt–CH_3COCH_3	$C_{18}H_{22}ClN_3 \cdot 2C_4H_4O_4$[d]	56.98 (57.13	5.52 5.67	7.67 7.49)

TABLE V (continued)

Compd. No.	Yield[a]	mp (°C)	Recrystn. solvent	Formula[b]	Analysis (%) Calcd (Found)		
					C	H	N
3m	66	119—120	AcOEt–CH_3COCH_3	$C_{18}H_{22}ClN_3 \cdot 2C_4H_4O_4$[d]	56.98 (57.02	5.52 5.50	7.67 7.69)
3n	68	183—185	MeOH–EtOH	$C_{19}H_{25}N_3 \cdot C_4H_4O_4$[d]	67.13 (66.97	7.10 7.36	10.21 10.18)
3o	65	181—183	EtOH	$C_{19}H_{25}N_3 \cdot C_4H_4O_4$[d]	67.13 (67.40	7.10 6.99	10.21 10.23)
4a	57	112—114	AcOEt–CH_3COCH_3	$C_{16}H_{19}N_3O_2 \cdot 2C_4H_4O_4$[d]	55.70 (55.43	5.26 5.20	8.12 8.34)
4b	75[n]	102—106	CH_3COCH_3	$C_{18}H_{21}N_3O \cdot 2C_4H_4O_4$	59.19 (59.32	5.54 5.63	7.97 7.68)
4c	82[n]	175—177	EtOH	$C_{18}H_{22}N_4O \cdot C_4H_4O_4$	61.96 (61.82	6.15 6.22	13.14 13.85)
4d	80[n]	143—146	EtOH	$C_{18}H_{22}N_4S \cdot C_4H_4O_4$[d]	59.71 (60.14	5.92 5.73	12.66 12.58)
5a	65	148—150	EtOH	$C_{18}H_{22}N_2O \cdot 2C_4H_4O_4$	60.69 (60.67	5.88 5.91	5.45 5.37)
5b	64	143—144	CH_3COCH_3	$C_{18}H_{21}ClN_2O \cdot 2C_4H_4O_4$	56.88 (56.59	5.32 5.41	5.10 5.36)
6a	65	120—122	AcOEt–CH_3COCH_3	$C_{19}H_{25}N_3O \cdot 2C_4H_4O_4$	59.66 (59.81	6.12 6.34	7.73 7.90)
6b	64	146—149	CH_3COCH_3	$C_{20}H_{27}N_3O \cdot 1.5C_4H_4O_4$[d]	62.50 (62.82	6.66 6.75	8.41 8.36)

a) The yield is based on the corresponding 2-vinylpyridine derivatives unless otherwise noted.
b) Maleate unless otherwise noted. *c*) Dipicrate was reported.[5]
d) Fumarate. *e*) Dipicrate was reported.[14] *f*) Picrate was reported.[14]
g) Dipicrate was reported.[15] *h*) Free base was reported.[13] *i*) DL-Tartrate.
j) Free base was reported.[16] *k*) Free base was reported.[6] *l*) Free base was reported.[4]
m) Dihydrochloride was reported.[17] *n*) Trihydrobromide was reported.[2b]

Pr_2O and insoluble material was removed by filtration. The filtrate was evaporated *in vacuo* to give a residual oil. This oil was distilled to give **2c** (19 g, 49%) as an oil, bp 112 °C (0.6 mmHg), NMR ($CDCl_3$) δ: 1.62 (1H, s, NH, exchangeable by adding D_2O), 2.33—3.07 (12H, m, aliphatic H), 6.93—7.80 (3H, m, pyridyl H (3, 4, 5)), 8.53 (1H, dd, J=5.0, 2.0 Hz, pyridyl H (6)), MS *m/z* (relative intensity): 191 (M^+, 0.7), 161 (18.2), 149 (29.5), 106 (74.6), 99 (100), 70 (36.7), 56 (65.4).

1-(2-Furoyl-4-[2-(2-pyridyl)ethyl]piperazine (4a)——A solution of 2-furoyl chloride (3.3 g, 25 mmol) in $CHCl_3$ (16 mmol) was added dropwise to a solution of 1-[2-(2-pyridyl)ethyl]piperazine (**2c**) (3.8 g, 20 mmol) in $CHCl_3$ (38 ml) under ice cooling, and the mixture was allowed to stand overnight at room temperature. The reaction mixture was washed with saturated aq. Na_2CO_3, dried over K_2CO_3, and evaporated *in vacuo*. The residue was distilled to give **4a** (4.3 g, 75%) as an oil, bp 196—198 °C (0.4 mmHg), IR (neat) ν: 1630 cm^{-1} (CO), NMR ($CDCl_3$) δ: 2.57 (4H, t, J= 5.0 Hz, piperazinyl H (3, 5)), 2.70—3.30 (4H, m, 2-pyridyl-$\underline{CH_2CH_2}$–), 3.83 (4H, t, J=5.0 Hz, piperazinyl H (2, 6), 6.47 (1H, dd, J=3.5, 2.0 Hz, fury H (5)), 6.80—7.90 (5H, m, pyridyl H (3, 4, 5) and furyl H (3, 4)), 8.55 (1H, dd, J= 5.0, 2.0 Hz, pyridyl H (6), MS *m/z* (relative intensity): 285 (M^+, 2.1), 193 (68.9), 161 (34.6), 148 (28.0), 106 (47.6), 95 (100).

Compound **4b** was prepared in the same manner as described above using benzoyl chloride. Compound **4b**; light yellow viscous oil, bp 200 °C (0.3 mmHg).

1-(*N*-Phenylcarbamoyl)-4-[2-(2-pyridyl)ethyl]piperazine (4c)——Phenyl isocyanate (2.9 g, 25 mmol) was added dropwise to a solution of 1-[2-(2-pyridyl)ethyl]piperazine (**2c**) (3.8 g, 20 mmol) in CH_3CN (40 ml) under ice cooling,

and then the mixture was stirred overnight at room temperature. The precipitated crystals were filtered off and washed with Et_2O to afford **4c** (6.0 g, 98%) as colorless needles, mp 204—206 °C, IR (KBr) ν: 3260 (NH), 1625 cm^{-1} (CO), NMR ($CDCl_3$–CD_3OD) δ: 2.27—2.67 (4H, m, aliphatic H), 2.67—3.20 (4H, m, aliphatic H), 3.20—3.73 (4H, m, aliphatic H), 6.70—7.83 (8H, m, aromatic H), 8.46 (1H, dd, J=4.5, 1.5 Hz, pyridyl H (6)), MS m/z (relative intensity): 310 (M^+,4.4), 218 (32.2), 174 (28.9), 161 (49.8), 149 (52.0), 119 (100), 106 (32.0), 99 (92.9), 91 (28.1).

Compound **4d** was prepared in the same manner as described above using phenyl isothiocyanate. Compound **4d**; colorless needles (CH_2Cl_2–iso-Pr_2O), mp 114.5—116.0 °C.

Compounds **1b**,[5] **1c**,[14] **2a**,[14] **2b**,[15] **2d**,[16] **2g**,[6] **3a**,[4] **3b**,[4] **3c**,[17], **3d**,[2b] **3g**,[17] **3i**,[4] **3k**[2b] were prepared according to the reported methods (see Table V).

Preparations of Salts——The free bases obtained above were converted into maleates (in AcOEt) or fumarates (in CH_3COCH_3) and the resulting salts were recrystallized from an appropriate solvent. Yields of salts except for **4a—d** were calculated on the basis of 2-vinylpyridine, 6-methyl-2-vinylpyridine, or 5-ethyl-2-vinylpyridine. Yields of the salts of **4a—d** were calculated on the basis of 1-[2-(2-pyridyl)ethyl]piperazine (**2c**). The yields and elemental analysis data of the salts are listed in Table V.

Pharmacological Methods

Spontaneous Nystagmus[8]——The cervical cord of the cat was transected at the C_2 level under ether anesthesia with artificial respiration. Unilateral destruction of the labyrynth was carried out by the ventral approach. The animal's head was fixed with the mouthpiece. Wound edges were infiltrated with 4% xylocaine. About 3 h after discontinuation of ether, spontaneous nystagmus appeared with its quick component directed towards the intact side, and was stable for more than 12 h. The nystagmus was recorded with Ag–AgCl cup electrodes placed laterally to the orbits through an amplifier with a time constant of 3 s. Beat number of nystagmus was counted with a pulse counter during successive 10 s intervals and displayed in histogram form on a chart recorder. All compounds dissolved in saline were injected through a cannula which had been inserted into the radial vein.

The effect of each compound was expressed as inhibition percent, $I(\%)$, from the following formula: $I(\%) = (A-B) \times 100/A(\%)$, where A and B are the values of total beat number of nystagmus for 40 min before and after the administration of the compounds, respectively. Mean $I(\%)$ at not less than 3 screening dose levels was obtained from at least three different preparations, and ID_{30} of each compound was determined graphically from the dose-response curves plotted on semilogarithmic paper.

Mean Blood Pressure——Adult mongrel dogs of either sex (8—18 kg) were anesthetized with sodium pentobarbital (30 mg/kg, *i.v.*).

Carotid arterial pressure was measured with a polyethylene cannula and a pressure transducer. The change in mean arterial blood pressure was calculated by the use of an electric integrator with a time constant of 2 s. Solutions of the compounds dissolved in saline were injected through a cannula into the femoral vein. Each value represents the mean of two experiments.

Isolated Guinea Pig Ileum——Guinea pigs were stunned and bled. The abdomen was opened and the ileum was excised. The isolated ileum was then suspended in an organ bath, into which air was continuously bubbled, at 25±1 °C. Solutions of compounds dissolved in distilled water were added to the bath. The ileum-contracting activities of these compounds were compared with that of histamine and expressed as percentage contraction relative to that induced by histamine (10^{-7} M). In addition, 2 min before the addition of spasmogens such as methacholine and histamine, the test compounds were added to the bath. Their anti-histaminic and anti-cholinergic actions were expressed as pA_2 values. When the antagonistic actions of the compounds were non-competitive, the actions were defined as papaverine-like ones and expressed as pD_2'. Each value represents the mean of two experiments.

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