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Antivertigo Agents. II.[1] Structure–Activity Relationships of 6-Substituted 5,6,7,8-Tetrahydro-1,6-naphthyridines[2]

AKIRA SHIOZAWA,*,[a] YUH-ICHIRO ICHIKAWA,[a] MICHIO ISHIKAWA,[a] YOSHIYA KOGO,[a] SHUJI KURASHIGE,[a] HIROSHI MIYAZAKI,[a] HIROSHI YAMANAKA,[b] and TAKAO SAKAMOTO[b]

Research Laboratories of Pharmaceutical Division, Nippon Kayaku Co.,[a] Shimo, Kita-ku, Tokyo 115, Japan and Pharmaceutical Institute, Tohoku University,[b] Aobayama, Sendai 980, Japan

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A number of 6-substituted 5,6,7,8-tetrahydro-1,6-naphthyridines designed as cyclic homologues of betahistine, 2-(2-methylaminoethyl)pyridine, were synthesized by the reduction of the corresponding 1,6-naphthyridinium salts. The antivertigo activity of these derivatives was evaluated in terms of their ability to inhibit spontaneous nystagmus in cats. The relationships between the molecular structures of the test compounds and their antivertigo activities were investigated by a regression analysis based on the lipophilicity (π) of the substituents at the 6-position and by a conformational analysis of the compounds of interest using the modified neglect of diatomic overlap molecular orbital method. Among these compounds, the 6-allyl- and 6-cyclopropylmethyl derivatives exhibited extremely potent activity with greatly reduced hypotensive action.

Keywords——1,6-naphthyridine; 5,6,7,8-tetrahydro-1,6-naphthyridine; sodium borohydride reduction; antivertigo activity; nystagmus; structure–activity relationship; molecular orbital calculation; regression analysis; betahistine

Betahistine,[3] 2-(2-methylaminoethyl)pyridine (**1a**), has been clinically used as an antivertigo agent. In order to investigate the structure–activity relationships of betahistine derivatives, we have previously synthesized[1] a number of 2-(2-dialkylaminoethyl)pyridines (**1**) by the Michael-type addition of secondary amines to 2-vinylpyridine and evaluated the pharmacological characters of these compounds. During this investigation, some of these compounds were found to show more potent antivertigo activity than the parent compound (**1a**), although a relatively strong adverse hypotensive action similar to that of **1a** could not be separated from the antivertigo activity.

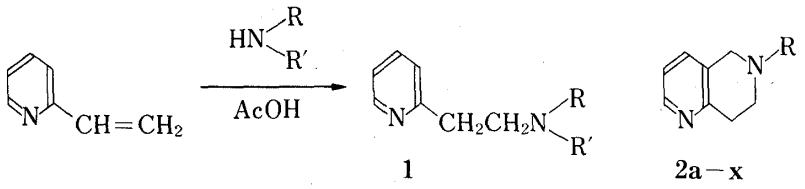


Chart 1

The aim of our subsequent work was therefore to minimize this undesirable side-effect by modifying the structure of the test compounds. By structural analogy, 6-substituted 5,6,7,8-tetrahydro-1,6-naphthyridines (**2**) can be regarded as cyclic homologues of **1**, in which the conformation of the 2-dialkylaminoethyl moiety in **1** is fixed to prevent free rotation of the side chain around a C–C–N linkage. In addition, the pharmacology of 5,6,7,8-tetrahydro-1,6-

naphthyridine derivatives has not been well explored except for some investigations on their antiulcer activity[4] and central nervous system depressing activity.[5] Thus, compounds belonging to the series **2** were employed in our second investigation, instead of 2-(2-dialkylaminoethyl)pyridine derivatives.

Chemistry

Haglid *et al.*[6] synthesized 6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**2a**, R=Me) by the condensation of 3-formyl-1-methyl-4-piperidone with cyanoacetamide, followed by hydrolysis, decarboxylation, chlorination, and reductive dechlorination of the resulting intermediates. However, such a series of reactions to obtain the final compound seems to be circuitous for the introduction of a variety of substituents into the 6-position of **2**. On the other hand, Ikekawa and Armarego reported[7] the catalytic hydrogenation of 1,6-naphthyridine itself (**3**), but the product was 1,2,3,4-tetrahydro-1,6-naphthyridine. Accordingly, no general method was available for the facile construction of our desired structural features, prior to our present work.

The sodium borohydride reduction of quaternary salts of such *N*-heteroaromatics as pyridine, quinoline, and isoquinoline is well known[8] to give the corresponding tetrahydro compounds. Further, Gribble *et al.* and Katayama *et al.* reported[9] that the reduction of quinoline and isoquinoline with sodium borohydride in formic acid or in acetic acid afforded the *N*-methyl- or *N*-ethyl-1,2,3,4-tetrahydro derivatives. Thus, our efforts were firstly directed to the sodium borohydride reduction of 1,6-naphthyridine (**3**) in acidic media.

When **3** was treated with sodium borohydride in 1 N hydrochloric acid and methanol at 10—15 °C, colorless needles were obtained in 68% yield. Based on the spectral data, the 1,2-dihydro-1,6-naphthyridine structure was clearly assignable to the product (**4**). That is, in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum the signal due to the ring proton of the 5-position appears at 7.72 ppm as a singlet (1H). In acetic acid, on the contrary, the reduction proceeded to give 6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**2b**, R=Et) in 22% yield, together with a small amount of **4** (8%). When the reduction was carried out in acetic acid containing 25% acetic anhydride at room temperature, 6-acetyl-5,6-dihydro-1,6-naphthyridine (**5**) was obtained in 32% yield. The catalytic hydrogenation of **5** in methanol in the presence of platinum dioxide gave 6-acetyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**6**) in 78% yield. The ^{1}H-NMR spectra of **5** and **6** clearly supported their 5,6-dihydro and 5,6,7,8-tetrahydro structures, respectively. For example, in the ^{1}H-NMR spectrum of **5** a signal due

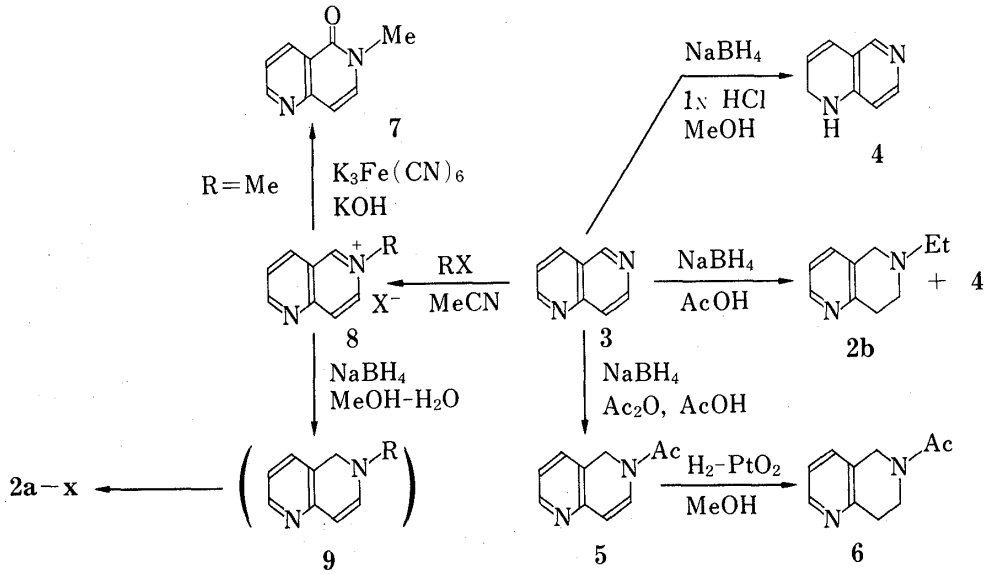
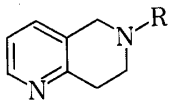


Chart 2

to the ring proton at the 2-position was observed at 8.33 ppm as a double doublet (1H, $J=4.5$ and 1.0 Hz).

Based on the results described above, it is concluded that the direct reduction of **3** with sodium borohydride is impractical for the preparation of 6-alkyl-5,6,7,8-tetrahydro-1,6-naphthyridines, because of the low yields of products. In connection with this, the methiodide formation of **3** with methyl iodide, investigated by Paudler *et al.*,[10] seemed to represent a possible route to our desired compounds (**2**). Namely, the reaction of **3** with an equimolecular amount of methyl iodide was reported to give a monomethiodide as a sole product. The location of the methyl group in the quaternary salt was proved to be the 6-position by converting the methiodide into 6-methyl-1,6-naphthyridin-5-one (**7**). This finding suggested the possibility that the sodium borohydride reduction of a quaternary salt (**8**) derived from the reaction of **3** with an appropriate alkyl halide might give the corresponding 6-alkyl-5,6,7,8-tetrahydro derivative of the compound **3**.

TABLE I. Effects[a] of 6-Substituted 5,6,7,8-Tetrahydro-1,6-naphthyridines on Spontaneous Nystagmus in Cats



Compd. No.	R	ID_{30}[b] (μmol/kg, *i.v.*)
1a	Betahistine	100
2a	CH_3	251
2b	C_2H_5	145
2c	n-C_3H_7	112
2d	n-C_5H_{11}	76.9
2e	iso-C_5H_{11}	87.3
2f	n-C_6H_{13}	83.0
2g	n-C_7H_{15}	98.6
2h	n-C_8H_{17}	141
2i	n-$C_{10}H_{12}$	184
2j	$CH_2CH=CH_2$	23.3
2k	$CH_2C(CH_3)=CH_2$	36.2
2l	$CH_2CH=CHCH_3$	Inact.[c]
2m	$CH_2CH_2CH=CH_2$	Inact.[c]
2n	$CH_2CH=C(CH_3)CH_3$	Inact.[c]
2o	$CH_2CH_2C(CH_3)=CH_2$	Inact.[c]
2p	$CH_2CH_2CH_2CH=CH_2$	Inact.[c]
2q		Inact.[c]
2r	CH_2- 	31.3
2s	CH_2- 	90.8
2t	CH_2- 	Inact.[c]
2u	$CH_2C\equiv CH$	Inact.[c]
2v	$CH_2C_6H_5$	108
2w	$CH_2CH_2C_6H_5$	55.3
2x	$CH_2CH_2CH_2C_6H_5$	59.0

a) Each compound was injected as its hydrochloride (see Table IV).
b) See ref. 1.
c) Inact. indicates that the compound is inactive at dose of 12 mg/kg, *i.v.*

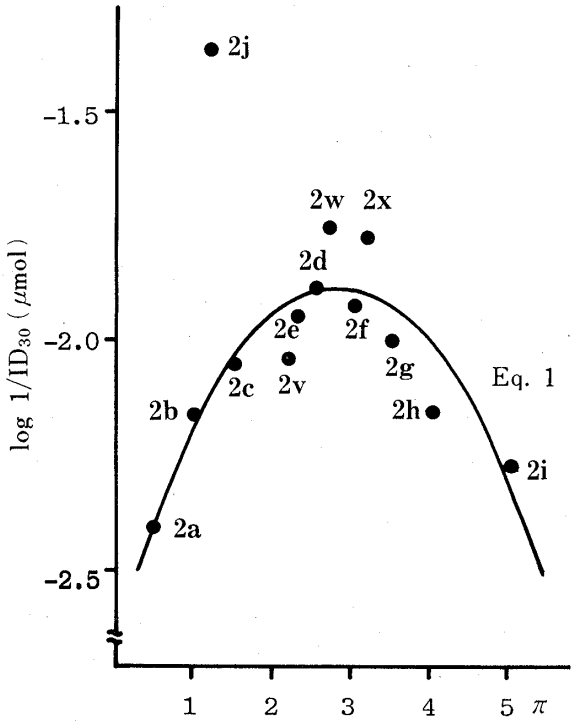


Fig. 1. Relationship between Antivertigo Activity (ID_{30}) and Lipophilicity (π) of Substituents in 6-Substituted 5,6,7,8-Tetrahydro-1,6-naphthyridines

In fact, when **3** was reacted with ethyl bromide in boiling acetonitrile, 6-ethyl-1,6-naphthyridinium bromide (**8b**) was isolated in good yield, and could be readily reduced with sodium borohydride in aqueous methanol (MeOH : H_2O = 3 : 1) at room temperature to give 6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**2b**) in 68% yield, as expected. Thus, more than twenty kinds of **2** were successfully synthesized in the above manner. The yields and physical constants of all the products (**2a**—**x**) are listed in Table IV, together with the results of elemental analyses.

In addition, the catalytic hydrogenation of **8** was unsuccessful. When a methanolic solution of **8b** (R = Et) was shaken in a hydrogen stream over platinum dioxide, the reaction ceased before two equivalent molecular amounts of hydrogen had been absorbed. The poor yield of **2b** in this case suggested spontaneous decomposition of an intermediate, 6-ethyl-5,6-dihydro-1,6-naphthyridine (**9b**), probably owing to its enamine character.

Structure–Activity Relationships

The antivertigo activity of 6-substituted 5,6,7,8-tetrahydro-1,6-naphthyridines (**2a**—**x**) obtained in this study was evaluated in terms of their ability to inhibit spontaneous nystagmus which was induced by unilateral destruction of the labyrinth in cats. The activity was expressed as ID_{30} (μmol/kg, *i.v.*)[1] and compared with that of betahistine (**1a**). These pharmacological data are listed in Table I, in which a major role of the 6-substituent in the activity is clearly apparent. In the case of the 6-alkyl analogues (**2a**—**i**), the antivertigo activity increased with increase in the number of carbon atoms (up to five). As shown in Fig. 1, the order of increase in activity was methyl (**2a**) < ethyl (**2b**) < *n*-propyl (**2c**) < isoamyl (**2e**) < *n*-amyl (**2d**). More than five carbon atoms led to a gradual decrease of the activity; *n*-amyl (**2d**) > *n*-hexyl (**2f**) > *n*-heptyl (**2g**) > *n*-octyl (**2h**) > *n*-decyl (**2i**). Therefore, five carbon atoms in the alkyl substituent seemed to be optimal.

When the aralkyl analogues (**2v**—**x**) were examined, the activity of a benzyl group (**2v**) was similar to that of the heptyl moiety (**2g**) with the same carbon number. Further, the replacement of the benzyl group (**2v**) with a 2-phenylethyl (**2w**) or 3-phenylpropyl (**2x**) group

enhanced the activity, and compound **2w** showed the most potent activity among the alkyl and aralkyl derivatives. The lipophilicities of substituents in the compounds such as **2d—f**, **2w**, and **2x** which gave high potency corresponded to π values[11] of 2.50—3.18, as shown in Fig. 1. The findings indicate that the lipophilicity (π) of the substituent at the 6-position might play an important role in the enhancement of the antivertigo activity.

Thus, regression analysis of the 6-alkyl and 6-aralkyl derivatives was tried based on the π values of the substituents as a physicochemical parameter. Table II shows the π values of the substituents and $\log 1/ID_{30}$ of **2a—i** and **2v—x**. Equation 1 was derived by the regression analysis.

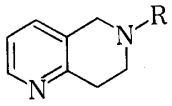
$$\log 1/ID_{30} = -0.091(\pm 0.034)\pi^2 + 0.512(\pm 0.186)\pi - 2.614(\pm 0.240) \quad (1)$$

$$(n=12,\ r=0.901,\ s=0.093,\ F_9^2=19.418)$$

Here, n, r, s, and F_9^2 represent the number of compounds used, the correlation coefficient, the standard deviation, and the figure in the F test, respectively, and the values in parentheses after each term represent the 95% confidence intervals. Equation 1 gave a high correlation coefficient ($r=0.901$) and was statistically significant at the 99% level with the F value of 19.418 ($F_{9\,(\alpha=0.01)}^2=8.022$) in the F test. The expected values of $\log 1/ID_{30}$ calculated from Eq. 1 were in good agreement with those observed for the 6-alkyl and 6-aralkyl analogues, as shown in Table II. Consequently, the potency (ID_{30}) of the alkyl and aralkyl series can be estimated easily by the use of Eq. 1 with the π values of the substituents as a parameter, as shown in Fig. 1. The optimum π value is 2.830 from Eq. 1, and adequate prediction of the potency of these alkyl and aralkyl compounds is possible.

However, when the alkenyl derivatives (**2j—q**) were examined, an allyl group (**2j**) was unexpectedly found to increase the activity greatly in comparison with a propyl group (**2c**). As shown in Table II and Fig. 1, the expected value of $\log 1/ID_{30}$ calculated from Eq. 1 using

TABLE II. Nystagmus Inhibitory Activity and Lipophilicity (π) of the 6-Substituent of 5,6,7,8-Tetrahydro-1,6-naphthyridines



Compd. No.	π[a]	log(1/ID$_{30}$)		
		Obsd[b]	Calcd[c]	Δ
2a	0.50	−2.400	−2.380	0.020
2b	1.00	−2.161	−2.192	0.031
2c	1.50	−2.049	−2.049	0.000
2d	2.50	−1.886	−1.899	0.014
2e	2.30	−1.941	−1.915	0.026
2f	3.00	−1.919	−1.892	0.027
2g	3.50	−1.994	−1.931	0.063
2h	4.00	−2.149	−2.014	0.135
2i	5.00	−2.265	−2.317	0.053
2j	1.20	−1.367	−2.130	0.763
2v	2.18	−2.103	−1.928	0.106
2w	2.68	−1.743	−1.892	0.149
2x	3.18	−1.771	−1.901	0.130

a) From ref. 11.
b) See ref. 1.
c) The calculated values were obtained from Eq. 1.

the π value ($=1.20$)[11] of an allyl group was entirely different from the actual value for **2j**. The lipophilicity (π) of an allyl group (**2j**) should not much affect the activity in comparison with those of the substituents in the alkyl and aralkyl analogues. The great enhancement of the activity in **2j** may be explained by assuming that the double bond of the alkenyl group interacts with a putative receptor for the antivertigo activity.

Therefore, the effect of substituents having a double bond on the activity was investigated. A 2-methyl-2-propenyl group (**2k**) with a terminal double bond gave high potency, whereas 2-butenyl (**2l**), 3-methyl-2-butenyl (**2n**) and cyclohexenyl (**2q**) groups with a inner double bond led to disappearance of the activity. The inactivity of compounds **2l**, **2n**, and **2q** may be due to steric hindrance on the basis of the bulkiness of the terminal substituent on the double bond. However, compounds with 3-butenyl (**2m**), 3-methyl-3-butenyl (**2o**), and 4-pentenyl (**2p**) groups, in which the number of methylene units is increased relative to the allyl (**2j**) and the 2-methyl-2-propenyl (**2k**) groups, were inactive even though no terminal substituent is present on the double bond. Accordingly, these findings suggested that π-type electrons at the 11 position (see Fig. 2) in **2j** and **2k** might contribute to the enhancement of the activity. In addition, a propargyl group (**2u**) and the cyclopropylmethyl group (**2r**), which is generally known[12] to have similar π-type electrons to an allyl group, were evaluated. Compound **2r** showed extremely potent activity, similar to that of **2j** or **2k**, whereas **2u** exhibited no activity. Furthermore, enlargement of the cyclopropylmethyl group (**2r**) into a cyclobutylmethyl (**2s**) or cyclohexylmethyl (**2t**) group reduced the activity, presumably because of the decrease of π-type electrons.

Molecular Orbital Calculation

In order to clarify the differences in the activities of compounds **2j**, **2k**, **2r**, and **2u**, the conformations of the four compounds were investigated by means of modified neglect of diatomic overlap (MNDO) calculation.[13] All the calculations were carried out by taking 30° increments in the variations of the torsion angles, as shown in Fig. 3 (see Experimental for details). Figure 3 shows that the overall shapes of the heat of formation (ΔH_f) curves as a function of τ_1[C(10)–C(9)–N(6)–C(7)] for these compounds are very similar and that the calculated barriers for rotation around the N(6)–C(9) bond are about 5—8 kcal/mol. If the criterion of $\Delta H_f \leq 3$ kcal/mol for the rotational barrier is taken, the rotation between the substituents and N(6) of the 5,6,7,8-tetrahydro-1,6-naphthyridine ring in the four compounds may be comparatively free in the neighborhood of the calculated energy minimum. However, the three compounds **2j**, **2k**, and **2r** but not **2u** have the additional possibility of rotation around the C(9)–C(10) bond as well as rotation around the N(6)–C(9) bond. Figure 3 shows the curves as a function of τ_2[C(11)–C(10)–C(9)–N(6)]; it can be seen that the calculated barriers for rotation around the C(9)–C(10) bond are 3—5 kcal/mol. These calculated results indicate that the rotation about τ_2 in the substituents of **2j**, **2k**, and **2r** is rather free. Consequently, each substituent in the three compounds (**2j**, **2k**, and **2r**) possesses a wide conformational domain in comparison with that of **2u**. That is, the π-type electrons at the 11-

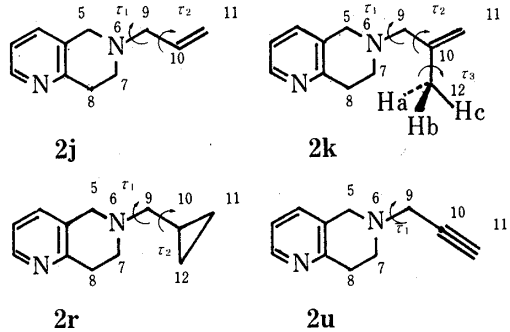


Fig. 2. Numbering of Atoms of 6-Substituted 5,6,7,8-Tetrahydro-1,6-naphthyridines Used in This Work

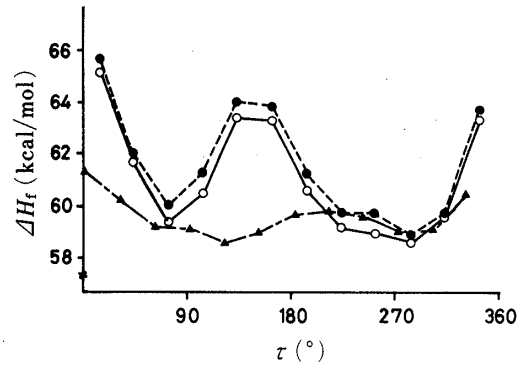


Fig. 3(a). Calculated Heats of Formation (ΔH_f) of **2j** as Functions of Torsion Angles τ_1 and τ_2

○: Function of τ_1 with optimization of τ_2 using 123° as the starting value of τ_2.
●: Function of τ_1 with optimization of τ_2 using 303° as the starting value of τ_2.
▲: Function of τ_2 with optimization of τ_1 using 284° as the starting value of τ_1.

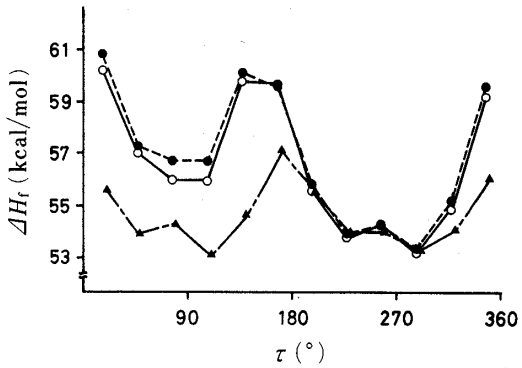


Fig. 3(b). Calculated Heats of Formation (ΔH_f) of **2k** as a Function of Torsion Angles τ_1 and τ_2

○: Function of τ_1 with optimization of τ_2 using 109° and −41° as starting values of τ_2 and τ_3, respectively.
●: Function of τ_1 with optimization of τ_2 using 289° and −41° as starting values of τ_2 and τ_3, respectively.
▲: Function of τ_2 with optimization of τ_1 using 287° and −41° as starting values of τ_1 and τ_3, respectively.

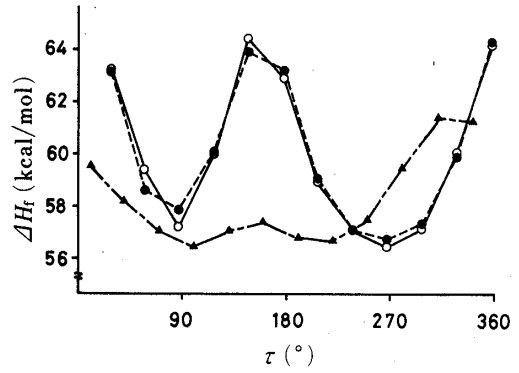


Fig. 3(c). Calculated Heats of Formation (ΔH_f) of **2r** as a Function of Torsion Angles τ_1 and τ_2

○: Function of τ_1 with optimization of τ_2 using 100° as the starting value of τ_2.
●: Function of τ_1 with optimization of τ_2 using 280° as the starting value of τ_2.
▲: Function of τ_2 with optimization of τ_1 using 268° as the starting value of τ_1.

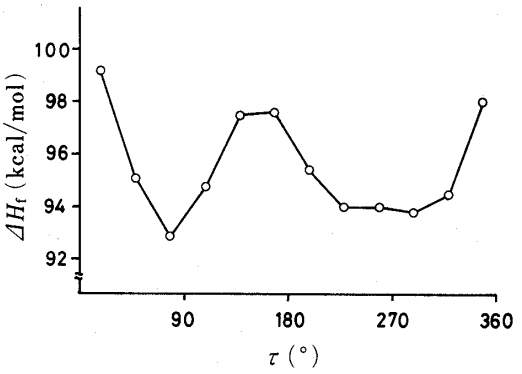


Fig. 3(d). Calculated Heats of Formation (ΔH_f) of **2u** as a Function of Torsion Angle τ_1

position in **2j**, **2k**, and **2r** can enter spatial domains which those in **2u** cannot. Accordingly, the π-type electrons in the more potent compounds (**2j**, **2k**, and **2r**) are concluded to interact with a putative receptor at a location that is forbidden in **2u**.

On the other hand, the pharmacological profile (histamine-like, anti-histaminic, anti-cholinergic, and papaverine-like actions) of the compounds of interest was evaluated using isolated ileum of guinea pigs. These results are shown in Table III. Betahistine (**1a**) had a marked hypotensive action, whereas **2f**, **2r**, and **2x** were found to have very weak hypotensive actions.

In conclusion, some 6-substituted 5,6,7,8-tetrahydro-1,6-naphthyridines with a rigid conformation of betahistine (**1a**) showed antivertigo activity more potent than that of **1a**. The 6-allyl (**2j**) and 6-cyclopropylmethyl (**2r**) analogues, in particular, showed the most potent

Table III. Pharmacological Profile of Representative 6-Substituted 5,6,7,8-Tetrahydro-1,6-naphthyridines

Compd. No.	His.[a] (%)	Anti-his.[b] (pA_2)	Anti-ach.[c] (pA_2)	Pap.[d] (pD_2')	MBP[e] Δ (mmHg)
1a	89.7		*[f]	*	−100
2f		5.0	*	4.2	−18.5
2j		*	*	*	−24.5
2r		*	*	*	0
2x		*	*	*	−18.5

a) Percentage constriction relative to that induced by histamine (10^{-7} M) in isolated ileum of guinea pigs.
b) Anti-histaminic action in isolated ileum of guinea pigs.
c) Anti-cholinergic action in isolated ileum of guinea pigs.
d) Papaverine-like action in isolated ileum of guinea pigs.
e) Decrease in mean blood pressure at the dose of 1 mg/kg, *i.v.* in dogs.
f) Each value is lower than 4.0.

activity with greatly decreased adverse hypotensive action as compared to **1a**.

Experimental

All melting points and boiling points are uncorrected. The structures of all compounds were consistent with the infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), and mass spectra. IR spectra were measured with a JASCO IR-G spectrometer, ^{1}H-NMR spectra with a JEOL JNM-PMX 60 spectrometer (using tetramethylsilane as an internal reference), and mass spectra (MS) with a Shimadzu GCMS-7000 spectrometer.

Chemistry

Reduction of 1,6-Naphthyridine (3) with $NaBH_4$—— i) Reduction in 1 N HCl–MeOH: Sodium borohydride (11.3 g, 300 mmol) was added to a solution of **3** (3.9 g, 30 mmol) in 1 N HCl (150 ml) and MeOH (75 ml) under an N_2 atmosphere with ice-cooling, and the mixture was stirred below 15 °C for 1 h, then evaporated *in vacuo* to give an aqueous solution (*ca.* 100 ml). This solution was made alkaline with saturated Na_2CO_3 and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated *in vacuo* to give a residue, which was recrystallized from C_6H_6 to give 1,2-dihydro-1,6-naphthyridine (**4**) (2.7 g, 68%) as colorless needles, mp 126—128 °C. IR ν_{max}^{KBr} cm^{-1}: 2980, 1648, 1582, 1330. ^{1}H-NMR ($CDCl_3$) δ: 4.25—4.50 (2H, m; C_2–H), 4.80 (1H, br s; NH, exchangeable with D_2O), 5.58 (1H, dt, $J_{34}=10$ Hz, $J_{32}=3.3$ Hz; C_3–H), 6.03—6.47 (2H, m; C_4–H and C_8–H), 7.72 (1H, s; C_5–H), 7.85 (1H, d, $J_{78}=6.0$ Hz; C_7–H). MS *m/z* (relative intensity): 132 (M^+, 50.3), 131 (100). *Anal.* Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.85; H, 6.28; N, 20.92.

ii) Reduction in AcOH: Sodium borohydride (3.8 g, 100 mmol) was gradually added to a solution of **3** (1.3 g, 10 mmol) in AcOH (75 ml) under ice-cooling and the mixture was stirred for 1 h at room temperature. The reaction mixture was made alkaline with 20% NaOH, and then extracted with $CHCl_3$. The extract was dried over K_2CO_3 and evaporated *in vacuo* to give a residue, which was triturated with a small amount of Et_2O and filtered. The crude crystals were recrystallized from iso-Pr_2O–CH_2Cl_2 to give **4** (0.54 g, 41%) as colorless prisms, mp 126—128 °C. The filtrates were combined and then evaporated *in vacuo* to give a residue, which was purified on a silica gel column ($CHCl_3$: MeOH = 10 : 1 v/v) to give **3** (0.1 g, 8%) and 6-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine **2b** (0.36 g, 22%) (see Table IV).

iii) Reduction in AcOH and Ac_2O: Sodium borohydride (1.5 g, 40 mmol) was added portionwise to a solution of **3** (1.3 g, 10 mmol) in AcOH (20 ml) and Ac_2O (7 ml) under ice-cooling and the mixture was stirred for 1 h at room temperature. The reaction mixture was evaporated *in vacuo* to give a residue, which was made alkaline with saturated Na_2CO_3 and then extracted with CH_2Cl_2. The extract was dried over K_2CO_3 and evaporated *in vacuo* to give a residue, which was purified on a silica gel column (AcOEt) to give crude crystals, which were recrystallized from Et_2O–petr. ether to give 6-acetyl-5,6-dihydro-1,6-naphthyridine (**5**) (0.57 g, 32%) as colorless prisms, mp 55—58 °C. IR ν_{max}^{KBr} cm^{-1}: 1655, 1630, 1580, 1565. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s; $COCH_3$), 4.98 (2H, s; C_5–H), 5.93 (1H, d, $J_{78}=8.0$ Hz; C_7–H), 6.92 (1H, d, $J_{87}=8.0$ Hz; C_8–H), 7.00 (1H, dd, $J_{32}=4.5$ Hz, $J_{34}=7.5$ Hz; C_3–H), 7.32 (1H, dd, $J_{42}=1.0$ Hz, $J_{43}=7.5$ Hz; C_4–H), 8.33 (1H, dd, $J_{23}=4.5$ Hz, $J_{24}=1.0$ Hz; C_2–H). MS *m/z* (relative intensity): 174 (M^+, 64.1), 146 (9.5), 132 (83.5), 131 (100), 43 (6.9). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.12; H, 6.02; N, 16.26.

6-Acetyl-5,6,7,8-tetrahydro-1,6-naphthyridine (6)——A solution of **5** (3.0 g, 17.1 mmol) in MeOH (90 ml) was hydrogenated over PtO_2 (300 mg) at atmospheric pressure and room temperature. The reaction was discontinued

TABLE IV. 6-Substituted 5,6,7,8-Tetrahydro-1,6-naphthyridines

Compd. No.	Free base		HCl salt					
	Yield (%)	bp (mmHg) or mp (°C)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
2a	68	58—62 (2.5)	258—263 (dec.)	MeOH–AcOEt	$C_9H_{12}N_2 \cdot 2HCl$	48.89 (48.70	6.38 6.41	12.67 12.83)
2b	68	97—98 (1.2)	228—230	MeOH–AcOEt	$C_{10}H_{14}N_2 \cdot 2HCl$	51.08 (51.31	6.86 6.59	11.91 11.84)
2c	80	85—86 (0.6)	202—206	MeOH–AcOEt	$C_{11}H_{16}N_2 \cdot 2HCl$	53.02 (53.33	7.28 7.04	11.24 11.56)
2d	68	119—121 (0.9)	190—193	iso-PrOH	$C_{13}H_{20}N_2 \cdot 2HCl \cdot 0.5H_2O$	54.55 (54.72	8.10 7.97	9.79 9.79)
2e	60	112—114 (0.7)	201—207	MeOH–AcOEt	$C_{13}H_{20}N_2 \cdot 2HCl \cdot 0.5H_2O$	54.55 (54.44	8.10 7.90	9.79 9.70)
2f	80	115—117 (0.5)	184—190	MeOH–AcOEt	$C_{14}H_{22}N_2 \cdot 2HCl \cdot 0.5H_2O$	56.01 (55.89	8.39 8.69	9.33 9.38)
2g	80	126—128 (0.5)	192—197	MeOH–AcOEt	$C_{15}H_{24}N_2 \cdot 2HCl \cdot 0.5H_2O$	57.32 (56.95	8.66 8.66	8.91 8.21)
2h	73	144—145 (0.7)	188—192	MeOH–AcOEt	$C_{16}H_{26}N_2 \cdot 2HCl \cdot H_2O$	56.98 (56.54	8.96 8.24	8.30 8.29)
2i	69	156—160 (0.4)	187—193	MeOH–AcOEt	$C_{18}H_{30}N_2 \cdot 2HCl \cdot H_2O$	59.16 (58.87	9.38 9.33	7.67 7.60)
2j	70	98—99 (1.0)	192—197	MeOH–AcOEt	$C_{11}H_{14}N_2 \cdot 2HCl$	53.46 (53.14	6.52 6.87	11.33 11.01)
2k	70	91—92 (0.7)	191—196	MeOH–AcOEt	$C_{12}H_{16}N_2 \cdot 2HCl \cdot 0.5H_2O$	53.34 (53.58	7.09 7.34	10.37 10.43)
2l	68	105—107 (0.7)	204—207	MeOH–AcOEt	$C_{12}H_{16}N_2 \cdot 2HCl$	55.17 (55.02	6.95 6.92	10.73 10.90)
2m	28	100—103	187—190	MeOH–AcOEt	$C_{12}H_{16}N_2 \cdot 2HCl$	55.17 (54.85	6.95 7.19	10.73 11.08)
2n	57	118—120 (0.9)	178—185	MeOH–AcOEt	$C_{13}H_{18}N_2 \cdot 2HCl \cdot 0.25H_2O$	55.82 (55.47	7.39 7.67	10.01 10.14)
2o	27	110—113 (0.6)	176—180	MeOH–AcOEt	$C_{13}H_{18}N_2 \cdot 2HCl$	56.74 (56.54	7.32 7.59	10.18 10.27)
2p	69	110—112 (0.4)	—[a]					
2q	59	134—136 (0.5)	—[a]					
2r	71	106—107 (0.6)	180—186	MeOH–AcOEt	$C_{12}H_{16}N_2 \cdot 2HCl$	55.17 (55.14	6.95 6.84	10.73 10.60)
2s	71	122—123 (0.8)	201—203	MeOH–AcOEt	$C_{13}H_{18}N_2 \cdot 2HCl$	56.74 (56.81	7.32 7.41	10.18 10.18)
2t	44	139—140 (0.4)	214—222 (dec.)	MeOH–AcOEt	$C_{15}H_{22}N_2 \cdot 2HCl \cdot 0.25H_2O$	58.54 (58.62	8.02 7.97	9.10 9.13)
2u	42	105—106 (0.7)	215—217 (dec.)	MeOH–AcOEt	$C_{11}H_{12}N_2 \cdot 2HCl$	53.89 (53.64	5.76 6.03	11.43 11.40)
2v	80	80—81	210—212 (dec.)	MeOH–AcOEt	$C_{15}H_{16}N_2 \cdot 2HCl$	60.62 (60.97	6.10 6.07	9.42 9.30)
2w	58	174—178 (1.3)	218—223	MeOH–AcOEt	$C_{16}H_{18}N_2 \cdot 2HCl$	61.74 (61.46	6.48 6.32	9.00 8.75)
2x	60	166—168 (0.4)	179—180	MeOH–AcOEt	$C_{17}H_{20}N_2 \cdot 2HCl$	62.77 (62.81	6.82 6.90	8.61 8.73)

a) The HCl salt is hygroscopic.

after 1 eq of H_2 had been absorbed, and the reaction mixture was filtered. The filtrate was evaporated *in vacuo* to give a residue, which was recrystallized from Et_2O–petr. ether to give **6** (2.5 g, 78%) colorless prisms, mp 60—63 °C. IR ν_{max}^{KBr} cm^{-1}: 1635, 1440. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s; $COCH_3$), 3.06 (2H, complex t; C_8–H), 3.83 (2H, complex t; C_7–H), 4.67 and 4.75 (2H, each s; C_5–H), 7.13 (1H, dd, $J_{32}=5.0$ Hz, $J_{34}=8.0$ Hz; C_3–H), 7.46 (1H, dd, $J_{42}=1.5$ Hz, $J_{43}=8.0$ Hz; C_4–H), 8.42 (1H, dd, $J_{23}=5.0$ Hz, $J_{24}=1.5$ Hz; C_2–H). MS *m/z* (relative intensity): 176 (M^+, 100), 133 (54.8), 119 (16.1), 118 (44.0), 117 (20.2), 107 (10.7), 106 (10.4), 105 (13.9), 43 (8.4). *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.91; H, 6.72; N, 16.17.

General Procedure for Preparation of 6-Substituted 5,6,7,8-Tetrahydro-1,6-naphthyridines (2a—x). A Typical Example: 6-Ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (2b)——A solution of **3** (3.9 g, 30 mmol) and ethyl bromide (6.4 g, 60 mmol) in CH_3CN (30 ml) was refluxed overnight, then evaporated *in vacuo* to give a residue. This residue was washed with a small amount of Et_2O and dried *in vacuo* to give a crude quaternary salt. This salt was dissolved in MeOH (180 ml)–H_2O (60 ml), and $NaBH_4$ (6.81 g, 180 mmol) was added portionwise to the solution below 20 °C. After being stirred overnight at room temperature, the mixture was evaporated *in vacuo* to give a residue. The residue was taken up in H_2O and extracted with C_6H_6. The extract was dried over K_2CO_3 and evaporated *in vacuo* to give a residue, which was purified on an alumina column (Et_2O). The resulting oil was distilled to yield **2b** (3.3 g, 68%) as a colorless liquid, bp 97 °C (1.2 mmHg). IR ν_{max}^{neat} cm^{-1}: 2680, 2620, 1575, 1450. ^{1}H-NMR δ ($CDCl_3$): 1.20 (3H, t, J= 7.2 Hz; $CH_2\underline{CH_3}$), 2.65 (2H, q, J=7.2 Hz; $\underline{CH_2}CH_3$), 2.70—3.25 (4H, m; C_7–H and C_8–H), 3.60 (2H, s; C_5–H), 7.15 (1H, dd, $J_{32}=4.4$ Hz, $J_{34}=8.4$ Hz; C_3-H), 7.66 (1H, dd, $J_{42}=1.8$ Hz, $J_{43}=8.4$ Hz, C_4–H), 8.64 (1H, dd, $J_{23}=4.4$ Hz, $J_{24}=1.8$ Hz), MS *m/z* (relative intensity): 162 (M^+, 72.8), 161 (100). The free base was converted into the hydrochloride and recrystallized from MeOH–AcOEt (see Table IV).

All other compounds were prepared in essentially the same manner as described above. Data for these compounds are summarized in Table IV.

Pharmacological Methods

All pharmacological procedures described in this report were carried out in the manner reported[1] previously.

Molecular Orbital Calculation

The molecular orbital calculations were carried out by using the MNDO program[13] with geometry optimization. The initial starting values of all geometrical parameters were taken from the standard values given by Pople and Gordon[14] unless otherwise noted. In all calculations, the C–H bond lengths were held constant without any optimization.

Preliminarily, in order to obtain the basic input geometry of the 5,6,7,8-tetrahydro-1,6-naphthyridine moiety, the geometry of the parent 5,6,7,8-tetrahydro-1,6-naphthyridine was optimized by using the MNDO program on the assumption that the pyridine ring is a regular hexagon with C–C and C–N bond lengths of 1.4 Å.

For the four 6-substituted 5,6,7,8-tetrahydro-1,6-naphthyridines, the geometry of the 5,6,7,8-tetrahydro-1,6-naphthyridine moiety obtained in this manner was always taken as fixed. The N(6)–C(9) bond lengths and the other geometrical parameters for the substituent groups were optimized (except for C–H bond lengths). The initial values of torsion angles τ_1, τ_2, and τ_3 were assumed to be as follows: $\tau_1=270°$ in all compounds (**2j**, **2k**, **2r**, and **2u**); $\tau_2=180°$ in **2j** and **2k**, and $\tau_2=150°$ in **2r**; $\tau_3=-60°$ in **2k**. The torsion angles τ_1, τ_2, and τ_3 denote τ[C(10)–C(9)–N(6)–C(7)], τ[C(11)–C(10)–C(9)–N(6)], and τ[Ha–C(12)–C(10)–C(9)] respectively, where a torsion angle τ(ABCD) is defined as negative for a clockwise rotation of A toward D when viewing along the line B to C. The optimized values of τ_1, τ_2, and τ_3 were as follows: $\tau_1=284°$, $\tau_2=123°$ in **2j**; $\tau_1=287°$, $\tau_2=109°$, and $\tau_3=-41°$ in **2k**; $\tau_1=268°$, $\tau_2=100°$ in **2r**; $\tau_1=288°$ in **2u**. In the calculations of the various rotamers of these four compounds, the optimized values given above were used as the starting ones. Taking into account the conformational flexibility of the substituents of the three compounds (**2j**, **2k**, and **2r**) other than **2u**, the following values were also used as starting ones of τ_2: 303° (=123+180, in **2j**); 289° (=109+180, in **2k**); 280° (100+180°, in **2r**). All the geometrical parameters other than τ_1 and τ_2 (and τ_3) were held constant. In **2j** and **2r**, the torsion angle τ_1 (or τ_2) was systematically varied by steps of 30° with optimization of τ_2 (or τ_1). In the case of **2k**, not only τ_2 (or τ_1) but also τ_3 was optimized for various τ_1 (or τ_2).

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References and Notes

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