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Synthesis and Conformational Analysis of a Bridged Anabasine and Related Compounds. A Nuclear Magnetic Resonance Spectroscopy and Molecular Modeling Study.

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Abstract: The synthesis and conformational analysis of a "bridged" anabasine, 5,8,9,10,11,11a-hexahydro-6H-pyrido[2,1-f][1,6] naphthyridine (**5**), and related compounds are reported. Conformational assignments were made using NMR data (including coupling constants, homonuclear Overhauser effects, and 2D correlations) and the results of molecular mechanics (MM2) calculations. The tricyclic compounds have trans-quinolizidine ring fusion with a chair-shaped piperidine ring. The center ring shows a half-chair conformation for the title compound, and a half-boat shape for its 6-oxo derivative. Calculated vicinal coupling constants are in good agreement with those obtained experimentally.

INTRODUCTION

Anabasine is a tobacco alkaloid[1,2] with an action similar to that of nicotine in the nervous system. However, it may exist in many stable conformations, making prediction of its preferred geometry when bound to a specific nicotinic receptor difficult.

In recent years a number of studies[3-6] have attempted to examine the pharmacological consequences of constraining the mobility of highly flexible molecules by converting them to derivatives. This type of approach may permit the determination of more precise structure-activity relationships for the interaction of the parent molecules with their receptors. Similar investigations have also been described for nicotine[7,8].

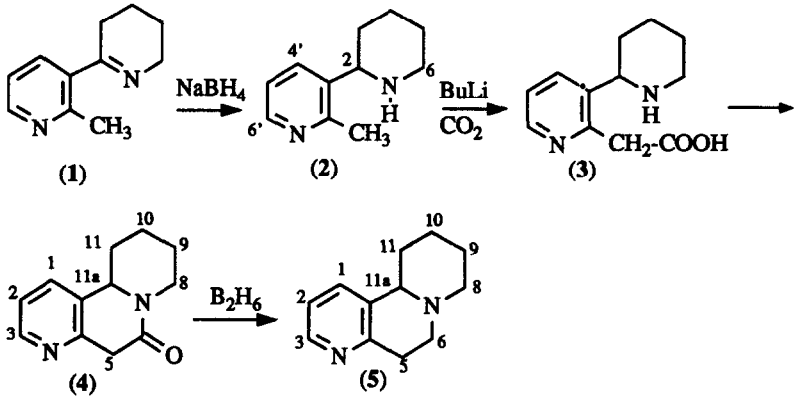
We report an unequivocal synthesis and nuclear magnetic resonance (NMR) analysis of 5,8,9,10,11,11a-hexahydro-6H-pyrido[2,1-f][1,6] naphthyridine (**5**), a "bridged" anabasine, constrained to a cisoid conformation by having a two carbon chain linking the piperidine and pyridine rings. The preparation of **5** had been reported by Sadykov et al. in 1952[9], but later they suggested a different reaction product using the same starting material[10]. Their procedure for the synthesis of **5** was not reproducible by Haglid[11].

Moreover, the structures of the reaction products claimed by Sadykov et al.[9,10] were also proved to be incorrect[11].

In **5** the orientation of the piperidine ring is fixed relative to the pyridine ring. There are, however, numerous possible conformations. Finding the minimum energy conformation by an analysis of NMR data is hampered by overlapping signals and higher-order couplings in the proton spectrum. Therefore, it has been necessary to start with the assignment of the conformations of the less complex synthetic intermediates, and continue with the detailed analysis of increasingly complex structures as they evolve from the underlying synthetic procedure. Computer aided conformational search was also done. Our aim was to match the NMR based conformational assignment to plausible conformers obtained by molecular modeling.

RESULTS AND DISCUSSION

The title compound (**5**), a conformationally restricted cisoid anabasine analog, was prepared by the route[7] illustrated in Scheme 1.



Scheme 1.

2'-Methylanabaseine[12] (**1**) was reduced with $NaBH_4$ to 2'-methylanabasine (**2**), which was lithiated with BuLi. Compound **3** was obtained after carboxylation with CO_2. The acid then was cyclized to tricyclic lactam **4** under neutral conditions. Reduction of **4** with B_2H_6 produced the desired bridged anabasine **5**.

Spectral assignments for compounds **2**, **4**, and **5** were aided by ^1H-^1H (COSY) and ^{13}C -^1H correlations, attached proton test (APT), nuclear Overhauser enhancement (NOE) difference measurements and spin decoupling experiments. Molecular mechanics (MM2)[13] calculation were performed to find possible energy minima using the interactive modeling program MacroModel[14]. Once conformational mapping had been obtained for each molecule, vicinal coupling constants were calculated using a generalized Karplus equation[15] and then compared with experimental values.

The NMR data for 2'-methylanabasine (**2**) are summarized in Table 1. Based on the C2 methine carbon resonance at 56.77 ppm that was easily distinguished by the APT, the H2 resonance with only one large (J>10 Hz) coupling at 3.61 ppm was identified with the help of the carbon-proton 2D correlation map. In agreement with the MM2-calculated conformation (Fig. 1), this proton occupies an axial orientation. The MM2 calculation also shows that the chair conformation of the piperidine ring is energetically favored. The calculated vicinal coupling constants using Altona's[15] equation are 11.4 Hz (H2-H3a) and 2.4 Hz (H2-H3e). They are in good agreement with those obtained experimentally.

Table 1. NMR data of 2'-methylanabasine in $CDCl_3$ obtained at 300 MHz

Carbon	δ_C ppm	Proton	δ_H ppm	Multip.		$J^*_{exp.}$ (Hz)	
C2'	152.26						
C6'	146.04	H6'	8.16	dd		4.8(5')	1.7(4')
C3'	137.96						
C4'	133.01	H4'	7.66	dd		7.7(5')	1.4(6')
C5'	120.78	H5'	6.93	dd		7.8(4')	4.8(6')
C2	56.77	H2	3.61	dd		11.0(3a)	2.2(3e)
C6	47.01	H6e	3.04	ddt	11.5(6a)	4.4(5a)	2.1(5e,4e)
		H6a	2.71	td	11.5(6e)	11.5(5a)	2.9(5e)
C3	32.71	H3e	1.60	dm	10.8(3a)		
		H3a	1.25	qd	10.9(3e)	10.9(4a,2a)	3.3(4e)
C5	24.96	H5e	1.51	bd**	10.8(5a)		
		H5a	1.39	qt	11.1(5e)	11.1(6a,4a)	4.3(6e,4e)
C4	24.62	H4e	1.73	dm	11.1(4a)		
		H4a	1.38-1.25	m			
CH_3	20.96	CH_3	2.51	s			

* The site number of the coupling partner is in parentheses.
** Broad doublet.

The higher field **H6** resonance is assigned to the proton trans to the nitrogen lone pair, the axial **H6a**, because of the trans shielding effect of this lone pair[16,17] and the NOE obtained for this proton upon irradiation of **H2**. We reasoned that irradiation of the **H2** would result in an enhancement of the **H6** proton *syn* to **H2**. An *anti* relationship should not afford an NOE. Indeed, irradiation of **H2** resulted in a 1% enhancement of the **H6** resonance at 2.71 ppm. Since **H2** is axial, the enhancement should arise from the axial proton **H6a**. The **H6** proton *syn* to the lone pair, the equatorial **H6e**, has couplings of 4.4 Hz and 2.1 Hz to the vicinal **H5** protons. These experimental J values are very similar to those calculated: 4.1 Hz for **H6e-H5a** and 2.3 Hz for **H6e-H5e** couplings. The calculated diaxial **H6a-H5a** coupling is 12.2 Hz and the **H6a-H5e** coupling is 3.2 Hz. The assignment of **H6** and **H2** protons is consistent with those previously reported for nicotine and its analogs[18,19].

Identification of the rest of the piperidine protons **H3**, **H4**, and **H5** is not straightforward because spectral overlap at 300 MHz makes it difficult to see how many large couplings are present in each multiplet. The complex overlapping also complicates spin decoupling and NOE experiments. The **H4e** resonance was assigned on the basis that it has only one large coupling (geminal) and a four-bond "W"-coupling[20] with **H6e**. The latter coupling could be detected on the COSY map. Similar long-range coupling has also been found in other molecules[21-23].

The highest-field signal of the piperidine ring was assigned to the axial **H3a**, since this multiplet has more than one large coupling. Irradiation of this multiplet perturbs the **H2** and **H3e** resonances; the geminal pair (**H3e**) simplified to a broad singlet, and **H2** lost the large (axial-axial) coupling. The protons bonded to the **C5** carbon were located on the COSY map and identified through coupling constant evaluation.

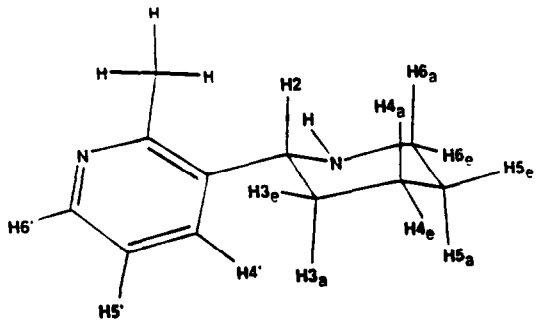


Fig.1. The preferred conformation of 2'-methylanabasine

Using ^{1}H-^{1}H homonuclear and ^{13}C-^{1}H heteronuclear chemical shift correlations, the complete assignment of carbons in $CDCl_3$ was achieved. (The ^{13}C shifts may be solvent dependent as it was shown for nicotine[24]). The very close **C5** and **C4** resonances (24.96 ppm and 24.62 ppm, respectively) were distinguished with the help of the COSY map which allows for locating the **H5** and **H4** resonances unambiguously. The same assignment of the ^{13}C-NMR spectrum of the anabasine was reached by Leete[25].

The methine carbon (**C11aa**) and proton (**H11aa**) of the piperidine moiety in tricyclic lactam 5,8,9,10,11,11a-hexahydro-6H-pyrido[2,1-f][1,6] naphthyridine-6-one (**4**) were also easily identified on the APT and ^{1}H-^{13}C correlation map. Spectral data together with the calculated (vicinal and long-range) J values are summarized in Table 2. Part of the ^{1}H-NMR spectrum can be seen in Fig.2. The one large coupling constant of **H11aa** (identical with that of **H2** for **2**) clearly indicates that this proton occupies an axial orientation. The MM2 calculated conformer, which shows a trans-quinolizidine type of structure (Fig. 3), further supports this conclusion. This resonance at 4.39 ppm is a doublet of quartets at 500 MHz with a

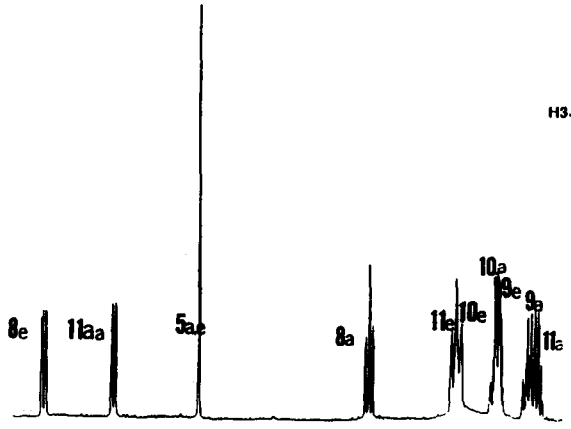


Fig. 2. Partial ^{1}H-NMR spectrum of **4** at 500 MHz.

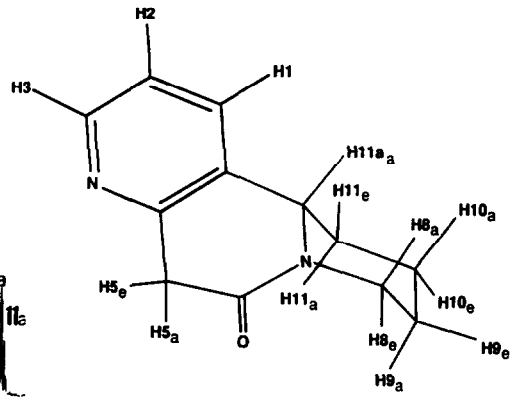


Fig. 3. The preferred conformer of **4**.

J=11.9 Hz axial-axial coupling. The long-range couplings[20] in the planar arrangement with **H5** and **H1** can be detected on the ^{1}H-^{1}H correlation map. The **H8** protons were identified on the basis of their multiplicity and chemical shift. The triplet of doublets at 2.58 ppm arises from the axial **H8a** because only this proton is expected to show one small (axial-equatorial) and two large (geminal and axial-axial) couplings in a chair conformation of the piperidine ring (Fig. 3). Hence, the lower field **H8** proton at 4.86 ppm with only one large coupling occupies an equatorial orientation. This proton is strongly deshielded due to the presence of the carbonyl group, as observed for similar molecules[26-27]. On the COSY map, the **H8e-H10e** "W-coupling"

Table 2. NMR data for 5,8,9,10,11,11a-hexahydro-6H-pyridol[2,1-f][1,6]naphthyridine-6-one (**4**) obtained at 500 MHz together with calculated vicinal and long-range coupling constants.

Carbon	δ_C ppm	Proton	δ_H ppm	Multip.	$J_{exp.}$ (Hz) gem.	vic.	long-range	$J_{calc.}$ (Hz) vic.	long-range
C4a	149.82								
C3	148.67	**H3**	8.44	dd		4.8 (**2**)	1.6 (**1**)		
C11b	129.07								
C1	133.06	**H1**	7.44	dd		7.8 (**2**)	1.6 (**3**)		
C2	121.74	**H2**	7.14	dd		7.8 (1)	4.8 (**3**)		
C6	165.86								
C11aa	59.81	**H11aa**	4.39	dq		11.9 (**11a**)	2.0 (**11e**) 2.0 (**5a,1**)	12.1 2.2	2.0
C8	43.22	**H8e**	4.86	dtd	12.9	4.0 (**9a**)	4.0 (**9e**) 2.1 (**10e**)	3.8	2.1
		H8a	2.58	td	12.8	12.8 (**9a**)	2.5 (**9e**)	12.4 2.4	
C5	37.38	**H5a,e**	3.79	bd			1.8 (**11aa**)		2.0
C11	35.93	**H11e**	1.99	dq*	11.7	2.3 (**11aa,10a**)	2.3 (**10e**)	2.6	
		H11a	1.42	qd	11.8	11.8 (**11aa,10a**)	3.4 (**10e**)	11.9 3.1	
C10	24.86	**H10e**	1.96	d**	12.5				
		H10a	1.68	qm*	12.6	12.6 (**11a,9a**)		11.9	
C9	24.52	**H9e**	1.74-1.66	m***					
		H9a	1.46	qt	12.5	12.5 (**8a,10a**)	3.9 (**8e,10e**)	12.4 3.8	

The site number of the coupling partner is given in parentheses.

*Determined from NOE exp. (300 MHz); **Unresolved doublet; ***Overlaps with **H10a**.

Table 3. NMR data for the bridged anabasine (**5**) obtained at 500 MHz together with calculated vicinal and long-range coupling constants.

Carbon	δ_C ppm	Proton	δ_H ppm	Multip.	$J_{exp.}$ (Hz) gem.	vic.	long-range	$J_{calc.}$ (Hz) vic.	long-range
C4a	154.86								
C3	147.09	**H3**	8.30	dd		4.6 (**2**)	1.5 (**1**)		
C11b	133.60								
C1	132.47	**H1**	7.40	dd		7.9 (**2**)	1.6 (**3**)		
C2	120.78	**H2**	7.00	dd		7.8 (1)	4.6 (**3**)		
C11aa	62.35	**H11aa**	3.02	d*		12.0 (**11a**)		11.8	
C8	56.31	**H8e**	2.93	dtd	11.5	3.2 (**9a**)	3.2 (**9e**) 1.5 (**10e**)	3.4	2.0
		H8a	2.24	td	11.7	11.7 (**9a**)	3.1 (**9e**)	12.1 2.9	
C6	52.61	**H6e**	2.96	ddd	11.7	6.4 (**5a**)	1.5 (**5e**)	5.4 2.1	
		H6a	2.54	td	11.7	11.7 (**5a**)	3.9 (**5e**)	12.0 4.1	
C5	32.31	**H5a**	3.22	ddd	17.4	11.3 (**6a**)	6.1 (**6e**)	12.0 5.4	
		H5e	2.82	bdd	17.2	3.5 (**6a**)		4.1	
C11	30.49	**H11e**	2.19	dq	11.9	3.0 (**11aa,10a**)	3.0 (**10e**)	3.4	
		H11a	1.32	qd	12.1	12.1 (**11aa,10a**)	3.7 (**10e**)	11.8 3.4	
C9	24.90	**H9a,e**	1.59	nm**					
C10	24.33	**H10e**	1.84	bd	11.9				
		H10a	1.38	qt***	11.5	11.5 (**11a,9a**)	3.1 (**11e,9e**)	11.8 3.4	

The site number of the coupling partner is given in parentheses.

*Unresolved doublet; **Narrow multiplet; ***Determined from NOE exp. (300 MHz).

can also be recognized. An NOE experiment (irradiation of **H11a**) further supported our assignment and is based on the same stereochemical argument as for **2**.

The ^{1}H-^{1}H and ^{13}C-^{1}H correlation spectra allowed us to locate all the remaining geminal pairs of protons **H9, H10, H11** of the piperidine moiety, but were of limited use in recognizing how many large (J>10 Hz) couplings were present in each multiplet due to complex overlapping even at 500 MHz. However, NOE and spin decoupling experiments enabled the recognition of further connectivities.

Irradiation of **H11aa** also caused NOEs (1%) in the higher field region. The increase at 1.99 ppm is expected to come from the equatorial neighbor **H11e** (only one large coupling) and the other at 1.68 ppm from the axial **H10a**, due to a 1,3-diaxial interaction. The rest of the protons of the piperidine ring are located (MM2) too far away from **H11aa** to give any NOEs. The geminal partner of **H11e** is located in the highest field multiplet, as also found for compound **2**. This assignment was confirmed by spin decoupling experiments.

Irradiation of **H11e** does not affect the large (axial-axial) coupling of **H11aa**. However, decoupling of the **H11a** multiplet perturbs the **H11aa** resonance. Therefore, **H11a** and **H11e** can be assigned with confidence. The equatorial neighbor **H10e** was identified on the basis of its single large (geminal) coupling and the long-range coupling[20] with **H8e**.

The remaining unassigned resonances arise from protons bonded to **C9**. The highest field (1.46 ppm) resonance exhibits more than one large coupling and therefore arises from the axial proton **H9a** of the chair conformation. Consequently, the other **H9** signal overlapping with **H10a** arises from the equatorial **H9e**.

In the center ring, which shows a half-boat conformation (Fig.3), the geminal coupling constants of **H5** protons are not detectable, but the five bond 1.8 Hz long-range coupling with **H11aa** in a planar arrangement can be recognized on the ^{1}H-^{1}H correlation map. The calculated[15] J=2.0 Hz coupling agrees well with that obtained.

For the "bridged" anabasine **5**, the methine proton **H11aa** occupies an axial orientation, since it has only one large coupling. Hence, the axial orientation of **H11aa**, as also found for **2** and **4**, is confirmed. Spectral data together with the calculated vicinal coupling constants are provided in Table 3. The preferred conformation (MM2) of this molecule is illustrated in Fig. 4. Since the carbonyl group has been removed

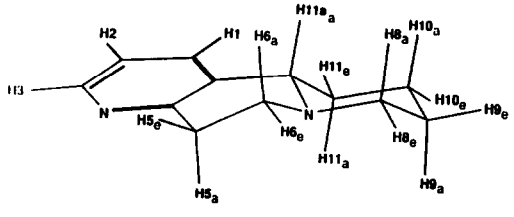


Fig. 4. The preferred conformation of **5**.

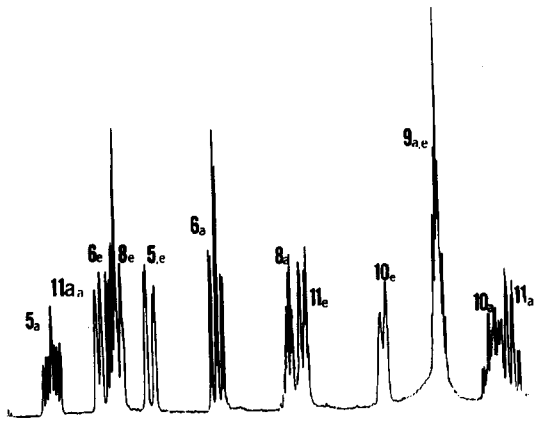


Fig.5. Partial ^{1}H-NMR spetcrum of **5** at 500 MHz.

and the piperidine ring shows a chair conformation (MM2), chemical shifts similar to those of compound **2** are expected (Table 3). Part of the ^{1}H-NMR spectrum and COSY map are presented in Fig. 5 and Fig. 6, respectively.

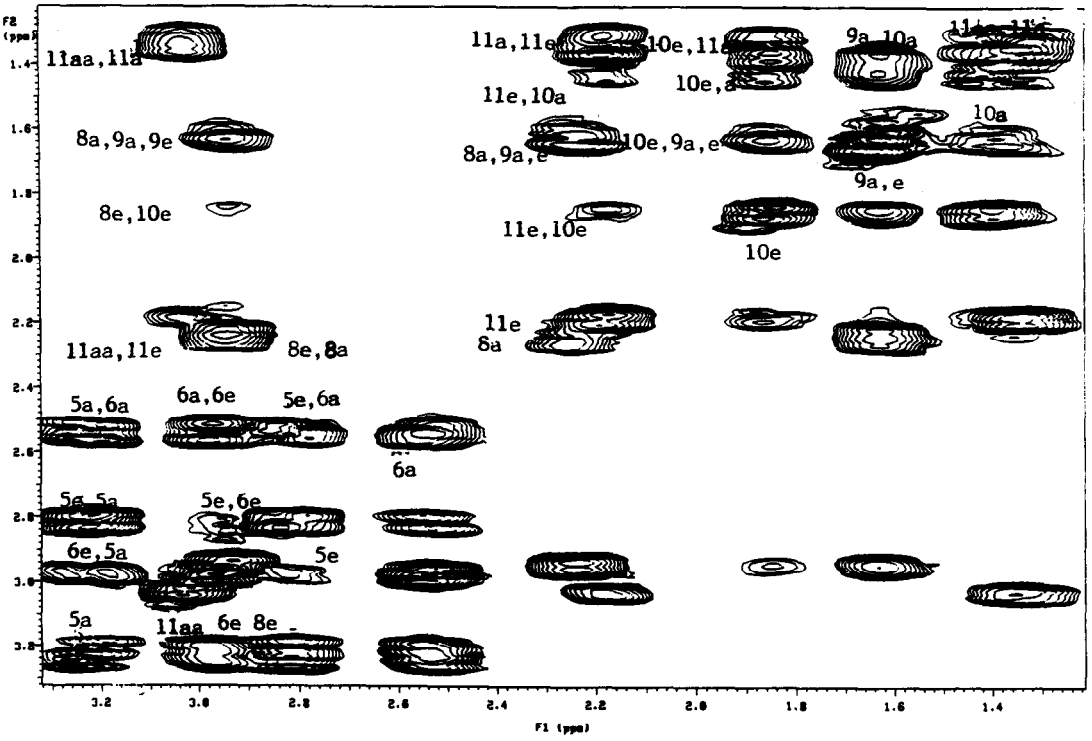


Fig. 6. Contour plot of the ^{1}H-COSY spectrum of **5** in the range of 1.30-3.30 ppm.

The presence of the newly saturated carbon also required the investigation of the carbon spectrum. The two pairs of carbon resonances around 55 ppm arise from **C6** and **C8**, and those around 30 ppm come from **C11** and **C5**. The lower field carbons were assigned with the help of two- dimensional correlation maps, since the couplings of **H8** protons can easily be separated from those of **H6** on the COSY map.

For the unambiguous assignment of **C11** and **C5**, NOE difference measurements were applied. The calculated conformer of **5** (Fig.3), which shows a trans-quinolizidine type of structure, indicates that irradiation of the **H1** pyridine proton should enhance the signal of the equatorial **H11** proton (calculated distance is 2.09 Å). Indeed, irradiation of **H1** pyridine proton enhanced (6.7 %) the doublet of quintets at 2.19 ppm, now identified as **H11e**. Consequently, the **C11** resonance at 30.49 ppm and the geminal partner **H11a** at 1.32 ppm can also be identified on the ^{13}C-^{1}H correlation map. Therefore, the carbon similar in shift to **C11** is assigned to **C5**. The assignment of the highest field signals to **C9** and **C10** is consistent with those found for trans quinolizidine[28-30] and 2'-methylanabasine (**2**).

In the proton spectrum the lowest field (3.22 ppm) aliphatic proton is bonded to **C5**. Since its signal has two large couplings, this proton occupies an axial orientation and may be expected to show long-range coupling with **H11aa**. We calculated[15] 2.0 Hz for the **H11aa-H5a** long-range coupling. Identification of **H6** and **H8** protons through coupling constants and chemical shift evaluation followed the same stereochemical argument as already described for compounds **2** and **4**. However, NOE experiments on **H8a**, **H8e** and **H6e** are limited in use, because of complex overlapping. The **H8e** equatorial proton, compared with that in **4**, is much less deshielded, since no carbonyl group is present. The chemical shifts and coupling constants of **H6e** and **H8e** are characteristic of trans-fused quinolizidines[16-17, 30-31]. In this conformation the axial protons next to the nitrogen and the lone pair of the nitrogen are antiperiplanar and hence shielded. The calculated vicinal

coupling constants for the **H5** and **H6** protons in the center ring agree well with those obtained. Similar J values have also been found for the related portion of other trans-fused structures[26].

Irradiation of the broad doublet of **H10e** enhanced (18%) the geminal partner **H10a**, confirming its multiplicity (three large couplings). Equatorial proton **H10e** forms a W configuration with **H8e**; the long-range[20] coupling can be recognized on the COSY map.

The chemical shifts of the remaining piperidine protons **H11a**, **H9a** and **H9e** are very similar to those found for **2**. The assignment of axial **H11** was also confirmed by spin decoupling experiments.

In the MM2 generated conformer of **5** (Fig. 4) the piperidine ring shows a chair conformation, and the center ring is half-chair. **C6** and **N7** are out of the approximate plane established by the pyridine ring, and **C5** and **C11aa**; **C6** is above, and **N7** is below this plane.

The nitrogen-nitrogen distance may have an important pharmacological consequence[32]. In the "bridged" anabasine (**5**) they are 4.18 Å apart. For the 2'-methylanabasine (**2**) this distance is 4.32 Å in the conformation illustrated.

In conclusion, we have unequivocally synthesized and characterized by NMR spectroscopy a cisoid "bridged" anabasine (**5**) and related compounds **2** and **4**. The title compound has a trans-quinolizidine type of structure; the piperidine ring shows a chair conformation and the center ring has a half-chair shape. Conformational search for each molecule was aided by molecular modeling (MM2) and the theoretical vicinal coupling constants were computed. The excellent agreement between the experimental and the calculated J values also support the assignment of the predominant conformers of **2**, **4** and **5**. The synthetic route[7] and conformational search presented in this paper is expected also to be suitable for obtaining and characterizing the isomeric *transoid* "bridged" anabasine, using 4'-methylanabaseine[12] as a starting material.

The pharmacology of 2'-methylanabasine (**2**) and 5,8,9,10,11,11a-hexahydro-6H-pyrido[2,1-f][1,6] naphthyridine (**5**) will be reported elsewhere.

EXPERIMENTAL

Instruments and Methods

Melting points are uncorrected. Elemental analyses were supplied by Atlantic Microlabs, Inc. (Norcross, GA). Chemicals and solvents were obtained from Aldrich Chemical Co.

The 300 MHz ^{1}H- and ^{13}C-NMR spectra of compounds in $CDCl_3$ (TMS) were recorded on a Varian VXR 300 instrument. Homonuclear proton NOEs were determined by means of an NOE difference technique using 8 s low-power presaturation (multi-irradiation technique) at each peak of a multiplet. Samples were degassed by bubbling argon through the sample and the temperature was set at 22° C.

The heteronuclear 2D (^{1}H-^{13}C- COSY) experiment was performed at 300 MHz with sweep widths of 5500.6 Hz in F2, and 793.2 Hz in F1 dimensions, respectively. The 90° pulses for ^{1}H and ^{13}C were 10 μs and 11.2 μs, respectively. Each FID was acquired with 256 scans and a relaxation delay of 1.0 s. Experiments were acquired using standard Varian software.

The 500 MHz spectra (^{1}H) were recorded on Varian Unity 500. COSY spectra were recorded with a sweep width of 5499.8 Hz in the F2 dimension. The 90° pulse was 10 μs, the relaxation delay was 1.0 s and each FID was acquired with 8 scans and 2 dummy scans.

Fast atom bombardment (FAB) mass spectra were recorded on a Kratos MS80RFA instrument (Kratos Analyticals, Manchester, U.K.). FAB analyses[33] (xenon beam, 8 keV energy) were performed by dissolving the sample in 3-nitrobenzyl alcohol as a matrix. High resolution (>10,000, 10 % valley definition) mass spectrum was recorded using electron ionization (EI) at 75 eV, direct introduction, and perfluorokerosene as an internal standard that provided reference ions for accurate mass determination.

Molecular mechanics optimizations were performed using a Silicon Graphics computer system running MacroModel ver. 3.5X. The Monte Carlo method[34] was used for conformational searching from an energy minimized (MM2) starting conformation by using the automatic set-up from the MacroModel program. For three-dimensional viewing, the MM2 files of the geometry-optimized conformers were transferred to a

Tektronix Computer Aided Chemistry (CAChe™) Worksystem (Beaverton, Oregon, U.S.A.) run on an Apple Macintosh™ II computer.

Synthesis

2'-Methylanabasine (2): 2'-Methylanabaseine (1, 2.00 g, 11.5 mmol)[12] dissolved in 30 ml of methanol was reduced with 0.46 g (12 mmol) $NaBH_4$. After adding the hydride under ice cooling, the solution was stirred at room temperature for 4 h. The solvent was removed by evaporation and the residue was dissolved in 20 ml of 2N HCl, then made basic with Na_2CO_3 and extracted with $CHCl_3$ several times. The combined extract was dried over Na_2SO_4 and evaporated to a pale yellow, semisolid (1.80 g, 89%). MS(FAB) $(M+H)^+$ 177. Anal. Calc. for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.89, Found: C, 74.84; H, 9.17; N, 15.82.

3-(2-Piperidino)-2-pyridylacetic acid (3): Under a nitrogen atmosphere 1.2 g (6.8 mmol) of 2'-Methylanabasine (2) dissolved in 40 ml of dry THF was added very slowly (ca. within 1 h) to the dry ice/acetone cooled solution of 7.5 ml (15 mmol) of BuLi (2M solution) in 40 ml of dry THF. The reaction mixture containing a lemon colored precipitate was stirred for 3.5 h and then poured into dry ice covered with ether. After warming to room temperature, the off-white solid was filtered off. The crude reaction mixture was dissolved in 30 ml of ca. 2N HCl and extracted with ethyl acetate to remove the valeric acid. The acidic solution of 3 was used without further purification for the cyclization.

5,8,9,10,11,11a-Hexahydro-6H-pyrido[2,1-f][1,6]naphthyridine-6-one (4): The acidic, aqueous solution of 3 was concentrated to ca. 10 ml and $NaHCO_3$ was added until the pH was about 7. The solution was exhaustively extracted with chloroform. The combined extracts were dried over Na_2SO_4 and evaporated to a yellow oil, which was solidified on adding hexane. The lactam was recrystallized twice from ether-hexane resulting in a pale yellow, hygroscopic solid with 45% (0.61 g) yield (based on 2'-methylanabasine). m.p.= 72-74°C. MS(FAB) $(M+H)^+$ 203. Anal. Calc. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.22; H, 7.03; N, 13.93.

5,8,9,10,11,11a-Hexahydro-6H-pyrido[2,1-f][1,6]naphthyridine (5): Borane-tetrahydrofuran (7.5 ml, 15 mmol, 2M solution) was added through a syringe with ice cooling to a solution of lactam 4 (0.30 g, 1.5 mmol) in 20 ml of dry THF in a nitrogen atmosphere. The bath was removed and the yellow solution was refluxed overnight. After cooling, water (ca. 5 ml) was added slowly until no more gas evolved. The solution was evaporated to dryness and the residue was dissolved in 30 ml of ca. 2N HCl and refluxed for 2-3 h. The solution was made basic with NaOH solution and extracted with ethyl acetate several times. Evaporation of the combined extracts dried over Na_2SO_4, resulted in a pale yellow oil with 81% (0.23 g) yield. MS (EI) m/z 188.1324 (calc. 188.1313).

The oil was dissolved in diluted HCl (pH = ca. 6) and evaporated to dryness. The residue was dissolved in ethanol and precipitated with ethyl acetate. The off-white, very hygroscopic precipitate was recrystallized from 2-propanol-ethyl acetate. m.p.= 215-217 °C. Anal. Calc. for $C_{12}H_{16}N_2$ x HCl x 1.75 H_2O: C, 56.24; H, 8.06; N, 10.93 Found: C, 56.05; H, 8.00; N, 10.90.

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