Syntheses based on anabasine. Preparation and transformations of *N*-oxides

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The oxidation of *N*-acetyl- and *N*-benzoylanabasine with the *tert*-butyl hydroperoxide (TBHP)—$MoCl_5$ system or MCPBA proceeds selectively at the nitrogen atom of the pyridine ring. The oxidation of *N*-methylanabasine under similar conditions gives a mixture of stereoisomeric *N*-oxides at the piperidine nitrogen atom, their ratio depending on the reagent used. The oxidation of anabasine by TBHP—$MoCl_5$ or MCPBA is accompanied by dehydrogenation and results in anabaseine *N*-oxide. The reactions of anabasine and anabaseine pyridine *N*-oxides with acetic anhydride were investigated. The substituted 1*H*-3-pyridin-2-ones were prepared.

Key words: anabasine, oxidation, anabaseine *N*-oxide, *N*-benzoylanabasine pyridine *N*-oxide, *N*-acetyl anabasine pyridine *N*-oxide, methylanabasine *N*-oxide, *N*-benzoylpiperidyl-2-pyridone, *N*-acetylpiperidyl-2-pyridone, anabasein-3-one.

Anabasine, 3-(2-piperidyl)pyridine (**1**), is the principal alkaloid of the *Anabasis aphylla* L. plant.[1] Anabasine hydrochloride is used as a means for giving up smoking;[2] the mechanism of its action includes binding to nicotine-sensitive receptors. The anabasine base exhibits clear-cut physiological activity. The action of this alkaloid is due to affection of the H-cholinoreactive structures of various parts of the nervous system and violation of the membrane permeability of cells, which results in a faulty course of redox processes in the organism.[3]

Anabasine is an initial base in the synthesis of reversible and irreversible choline esterase inhibitors,[4] in particular, phosphamide,[5] carbamide derivatives,[6] and a number of pharmacologically valuable compounds obtained by reactions at the piperidine-ring nitrogen atom.[7,8] Anabasine derivatives containing bulky acyl and alkyl substituents at the piperidine-ring nitrogen atom exert an antinicotinic action,[9] and its hydrogenated derivatives exhibit analgesic activities.[10]

Thus, targeted synthetic transformations of anabasine may produce effective analogues with other types of physiological activities.

This paper describes a study of the oxidation of anabasine (**1**) and its *N*-acetyl (**2**), *N*-benzoyl (**3**) and *N*-methyl (**4**) derivatives on treatment with *tert*-butyl hydroperoxide (TBHP) and MCPBA and some transformations of the *N*-oxides thus formed.

Results and Discussion

Previously,[11] we demonstrated that anabasine oxidation with hydrogen peroxide in acetic acid is accompanied by cleavage of the piperidine ring. No *N*-oxidation of anabasine or its derivatives **2—4** by other reagents has yet been carried out. We found that refluxing of anabasine (**1**) in the presence of the TBHP—$MoCl_5$ system in benzene with water removal gives crystalline anabaseine *N*-oxide (**5**) in 54% yield (Scheme 1). Thus, the hydroperoxide serves as a dehydrogenating agent. The oxidation of *N*-acetyl- (**2**) or *N*-benzoylanabasine (**3**) under the action of TBHP—$MoCl_5$ affords individual *N*-acetyl- and *N*-benzoylanabasine pyridine *N*-oxides **6** and **7** in 79 and 89% yields, respectively. It should be emphasized that previously, this reagent has been successfully used for *N*-oxidation of diverse pyridine derivatives.[12—14] The use of $VO(acac)_2$ as the catalyst proved inefficient. The attempted *N*-oxidation of anabasine derivatives **2** and **3** with 3 equiv. TBHP in the presence of $VO(acac)_2$ (see Ref. 14) resulted in the recovery of the initial bases.

The oxidation of *N*-methylanabasine (**4**) with the TBHP—$MoCl_5$ system results in a mixture of two stereoisomeric *N*-methylanabasine piperidine-*N*-oxides **8´** and **8″** (yield 51%) in a *N*-Me_{ax} : *N*-Me_{eq} ratio of 1 : 4. The attempts of further oxidation of mono-*N*-oxides **6—8** with an excess of TBHP—$MoCl_5$ did not yield dioxides. In all

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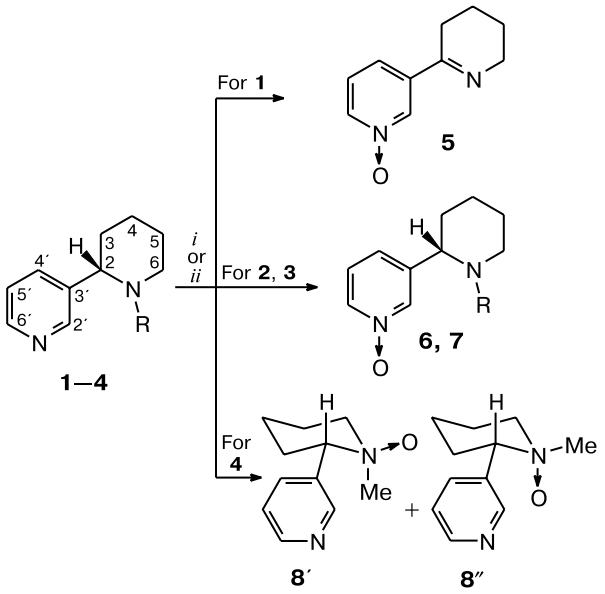
Scheme 1



R = H (**1**), Ac (**2**, **6**), Bz (**3**, **7**), Me (**4**)

Reagents and conditions: *i*. TBHP—$MoCl_5$, benzene, refluxing, 5—8 h. *ii*. MCPBA, $CHCl_3$, 20 °C, 3—5 h.

cases, the starting compounds **6—8** were quantitatively recovered. Thus, hydroperoxide oxidation proceeds selectively at the pyridine nitrogen atom for compounds **1—3** or for the piperidine nitrogen atom for *N*-methylanabasine (**4**).

The structures of the synthesized compounds were determined by spectroscopy. The ^{1}H NMR spectra of pyridine *N*-oxides **5—7** show an upfield shift of the signals of the H(2′), H(4′), and H(6′) protons of the pyridine ring. For example, for compounds **2** and **6**, the differences between the chemical shifts (Δδ) of these proton signals are 0.42, 0.20, and 0.42, respectively. The upfield shift was also noted for the ^{13}C NMR signals of the C(2′), C(4′), and C(6′) atoms in compounds **5—7**. The differences between the C(2′), C(4′), and C(6′) chemical shifts for *N*-oxide **7** and anabasine derivative **3** are 10.86, 8.82, and 10.55 ppm, respectively. The formation of the pyridine *N*-oxides is also confirmed by UV spectra. A comparison of the UV absorption spectra of compounds **1—3** with the spectra of *N*-oxides **5—7** shows a pronounced shift of the absorption peaks to longer wavelengths. In addition, the absorption intensity increases (the ε values increase from 2670 to 6375 and from 3594 to 11220 for **5** and **6**, respectively). Similar changes in the UV spectra of pyridine *N*-oxides have been noted previously.[15]

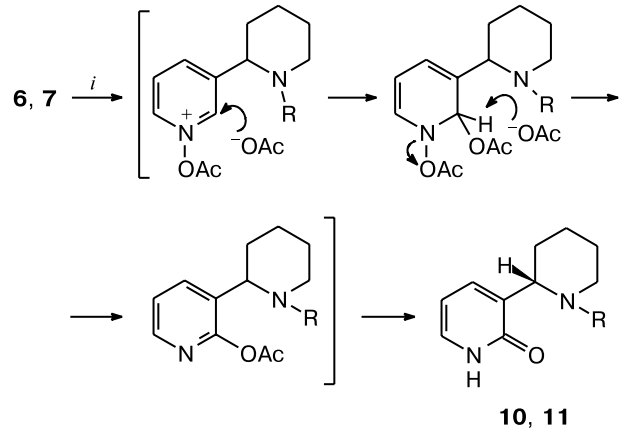
In the ^{1}H NMR spectra of piperidine *N*-oxides **8′** and **8″**, the singlets of the *N*-Me-group protons (δ 2.65 and 2.74) are shifted downfield with respect to their positions in the spectrum of compound **4** (δ 1.95). The configuration of the quaternary nitrogen atom in the *N*-oxide diastereomers was established in the following way. The major differences between the ^{1}H NMR spectra of a mixture of *N*-oxides with an equatorial or axial orientation of the *N*-Me group is in the chemical shifts of the H(2) (δ 3.98 and 3.89) and H(4′) (δ 8.00 and 8.21) signals for isomers **8′** and **8″**, respectively. The isomer ratio was found from the integral intensity ratio of these signals. The configuration analysis of a mixture of *N*-oxide diastereomers shows that in the major reaction product, the *N*-Me group is equatorial (**8″**). With this arrangement of the *N*-Me group, the axial proton in the α-position at C(2) would undergo a smaller downfield shift. Otherwise, the proton at C(2) would shift downfield due to the effect of the *N*-oxide fragment.

We also studied *N*-oxidation of compounds **1—4** with MCPBA. The results were similar to those obtained using the TBHP—$MoCl_5$ system. The oxidation of anabasine (**1**) at the pyridine nitrogen atom is also accompanied by dehydrogenation of the piperidine ring, giving rise to anabaseine *N*-oxide (**5**) (yield 62%). Note that compound **5** is of interest as a potential agonist of muscle and neuronal nicotinacetyl choline receptors,[16] while its derivatives are selective ligands of *p*-acetyl choline receptors of the α7-type.[17] The synthesis of 3-substituted anabaseine derivatives, agents suitable for the therapy of neuronal diseases, has also been described.[18] The oxidation of compounds **2** and **3** with MCPBA gives the corresponding pyridine *N*-oxides **6** and **7** in >90% yield. The oxidation of *N*-methylanabasine (**4**) with MCPBA gives a mixture of configurational isomers of *N*-oxides at the piperidine nitrogen atom **8′** and **8″** (yield 81%, 1 : 2 ratio) with predominance of isomer **8″** with an equatorial configuration of the nitrogen-attached Me group. *N*-Oxide **8″** was isolated in the crystalline state. Treatment of a mixture of *N*-oxides **8′** and **8″** (1 : 2 ratio) with picric acid afforded a single stereoisomer, picrate **9a**, with the axial orientation of the *N*-Me group (for compound **8′**). It should be noted that oxidation of *N*-methylanabasine with H_2O_2 in acetic acid has been reported[11] to give the mono-*N*-oxide at the piperidine ring in which the configuration of the *N*-Me group has not been determined. This compound was characterized as a dipicrate and, according to the melting point, it was identical to the dipicrate **9b**, which we prepared from isomer **8″**. Thus, according to our data, the product formed upon the reported[11] oxidation of compound **4** with hydrogen peroxide is the piperidine *N*-oxide with an equatorial orientation of the *N*-Me-group (**8″**). The oxidation of compound **4** on treatment with MCPBA or TBHP—$MoCl_5$ yields two piperidine *N*-oxides **8**, the oxidation with the TBHP—$MoCl_5$ system being more stereoselective.

The ready availability of *N*-oxides promoted our interest in the study of their transformations, in particular, acylation. We found that treatment of pyridine *N*-oxides **6**

and **7** with acetic anhydride followed by hydrolysis affords pyridin-2-ones **10** and **11** in moderate yields (Scheme 2). Detailed analysis of the reaction mixture shows that no isomeric 6-pyridin-2-ones resulting from oxidation of the *N*-pyridinium salt of anabasine[19] have been formed. The structures of pyridin-2-ones **10**, **11** were confirmed by ^{1}H NMR data. The signals of the protons of the pyridin-2-one ring in the spectrum of compound **10** resonate at δ 6.25 (dd, H(5′), J = 6.5 Hz, J = 6.7 Hz), 7.28 (d, H(4′), J = 6.7 Hz), and 7.33 (d, H(6′), J = 6.5 Hz). With H(5) proton decoupling, the doublets for H(4) and H(6) are transformed into singlets.

Scheme 2



R = Ac (**10**), Bz (**11**)

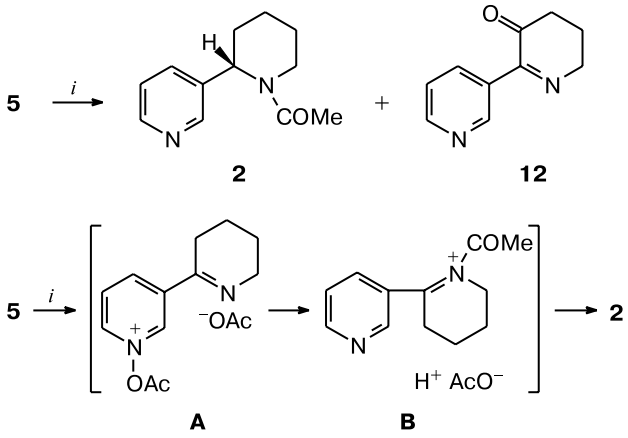
Reagents and conditions: *i*. (1) Ac_2O, refluxing, 6 h; (2) treatment with 10% HCl, 100—110 °C, 2.5—3 h.

Under similar conditions, the reaction of anabaseine *N*-oxide (**5**) with acetic anhydride (Scheme 3) gives rise to a mixture of *N*-acetylanabasine (**2**) and anabasein-3-one (**12**) (yields 22 and 18%, respectively). The structure of compound **12** was determined on the basis of spectroscopy. The ^{1}H NMR spectrum of anabasein-3-one (**12**) exhibits a set of signals for the pyridine-ring protons (two α-protons, one β-proton, and one γ-proton) and for three methylene groups of the piperidine fragment. The ^{13}C NMR signal for the carbonyl carbon occurs at δ 196.86.

The synthesis of anabaseinone **12** from anabaseine *N*-oxide (**5**) probably involves a second molecule of compound **5**, which is an oxidant. As regards *N*-acetylanabasine (**2**), the process starts, most likely, with the formation of the acyloxamine salt **A**, which is converted into salt **B** with the subsequent hydride transfer (see Scheme 3).

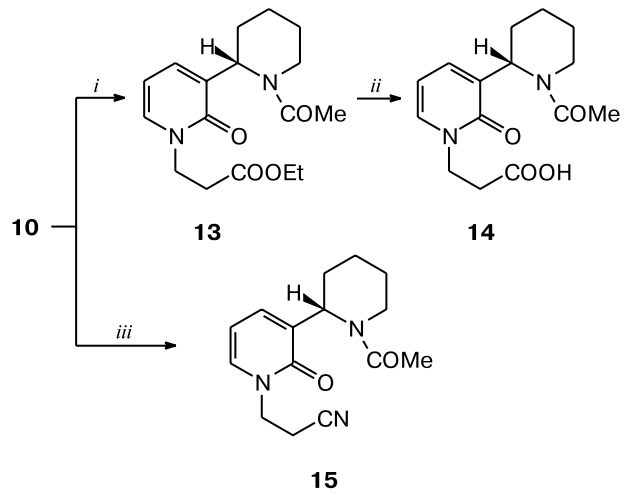
N-Unsubstituted 2-pyridinones are known[20] to enter into the Diels—Alder or substitutive addition reactions. We found that the reaction of ethyl acrylate and acrylonitrile with substituted 2-pyridone **10** occurs as a substitutive addition giving rise to compounds **13** and **15** (Scheme 4). Alkaline hydrolysis of ester **13** yields acid **14**.

Scheme 3



Reagents and conditions: *i*. (1) Ac_2O, refluxing, 6 h; (2) treatment with 10% HCl, 100—110 °C, 2.5—3 h.

Scheme 4



Reagents and conditions: *i*. CH_2=CHCOOEt, toluene, 115—120 °C, 24 h. *ii*. 2% solution of NaOH, 20 °C, 1 h. *iii*. CH_2=CHCN, toluene, 115—120 °C, 22 h.

Thus, we have studied the oxidation of anabasine and its derivatives with the TBHP—$MoCl_5$ system or with MCPBA. *N*-Acetylanabasine and *N*-benzoylanabasine pyridine *N*-oxides and anabaseine *N*-oxide were synthesized. It was shown that *N*-oxidation of *N*-methylanabasine furnishes stereoisomeric *N*-methylanabasine piperidine *N*-oxides, the reaction in the presence of the TBHP—$MOCl_5$ systems having a higher selectivity. Pyridine *N*-oxides react with acetic anhydride to give pyridin-

2-ones. The reaction of anabaseine *N*-oxide with acetic anhydride yields *N*-acetylanabasine and anabasein-3-one. The reaction of *N*-acetylanabasin-2′-one with ethyl acrylate and acrylonitrile occurs according to the substitutive addition pattern.

Experimental

All experiments were carried out in solvents purified by standard procedures. Commercial TBHP (Aldrich) and MCPBA (Fluka) were used. The reactions were monitored by TLC on Silufol UV-254 plates (using $CHCl_3$—EtOH, 1 : 1, as the eluent). The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument in $CDCl_3$ and $(CD_3)_2SO$. The signals in the NMR spectra were assigned using ^1H—^1H 2D (COSY) and ^1H—^{13}C (COLOC) spectra. Mass spectra were recorded on a Finnigan MAT 8200 mass spectrometer (EI, 70 eV). IR spectra were measured on a VECTOR-22 instrument in KBr. UV absorption spectra were recorded on an HP 8453 UV—Vis instrument in ethanol. The optical rotation was measured on a Polamat A polarimeter at 578 nm and 20—23 °C.

Anabasine used in the study was isolated from *Anabasis aphylla* L. according to a published procedure;[1] purity 99.0% (GLC data), $[\alpha]_{578}^{23}$ −72.3 (*c* 5.2, $CHCl_3$).

N-Acetylanabasine (**2**), *N*-benzoylanabasine (**3**), and *N*-methylanabasine (**4**) were prepared by known procedures.[21—23] *N*-Oxidation of compounds **1—4** was carried out by treatment with TBHP—$MoCl_5$ (method *A*) and MCPBA (method *B*).

Anabaseine *N*′-oxide (3,4,5,6-tetrahydro[2,3′]bipyridinyl 1′-oxide) (5). ***A.*** Anabasine (**1**) (1.04 g, 6.4 mmol) was added to a mixture of 70% aq. TBHP (2.32 g, 12.88 mmol) and $MoCl_5$ (0.01 g) in benzene (50 mL). The reaction mixture was refluxed for 5 h with a Dean—Stark trap, cooled, treated with 10% aq. NaOH, and washed with distilled water (3×5 mL). The resulting aqueous layer was extracted with chloroform (7×10 mL). The benzene and chloroform fractions were dried over $MgSO_4$, combined, and concentrated. The residue was recrystallized from diethyl ether to give 0.58 g (54%) of compound **5**, m.p. 103—104 °C (Et_2O), $[\alpha]_{578}^{23}$ −13.3 (*c* 1.5, $CHCl_3$). Found (%): C, 68.12; H, 6.67; N, 15.97. $C_{10}H_{12}N_2O$. Calculated (%): C, 68.18; H, 6.81; N, 15.91. ^1H NMR ($CDCl_3$), δ: 1.82—2.10 (m, 4 H, 2 H(4), 2 H(5)); 2.81 (t, 2 H, 2 H(3), J = 6.2 Hz); 3.99 (t, 2 H, 2 H(6), J = 6.2 Hz); 7.31 (m, 1 H, H(5′)); 8.53 (dt, 1 H, H(4′), $J_1 = J_2$ = 2.0 Hz, J_3 = 5.4 Hz); 8.65 (dt, 1 H, H(6′), $J_1 = J_2$ = 2.0 Hz, J_3 = 8.2 Hz); 9.08 (dd, 1 H, H(2′), $J_1 = J_2$ = 2.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 21.69 (C(4)), 25.71 (C(5)), 31.07 (C(3)), 63.39 (C(6)), 125.37 (C(5′)), 132.58 (C(2)), 138.27 (C(4′)), 141.75 (C(3′)), 151.27 (C(2′)), 152.52 (C(6′)). UV, λ_{max}/nm (ε): 289 (6376).

B. A solution of anabasine (**1**) (1.04 g, 6.4 mmol) in $CHCl_3$ (15 mL) was added with stirring to a solution of 70% aq. MCPBA (3.17 g, 12.88 mmol) in $CHCl_3$ (35 mL). After 3 h, the reaction mixture was alkalized with 10% aq. NaOH (~5 mL) to pH 10—11, and the organic layer was separated and washed with distilled water (2×2 mL). The aqueous layer was extracted with chloroform (5×10 mL). The chloroform extracts were combined and dried with $MgSO_4$. The solvent was evaporated. The resulting oily substance was purified by column chromatography on silica gel (elution with $CHCl_3$—EtOH, 100 : 1) and recrystallized from diethyl ether to give 0.71 g (62%) of compound **5**.

N*-Acetylanabasine *N*′-oxide (3-(*N*-acetylpiperidin-2-yl)pyridine *N*-oxide) (6).** ***A. Molybdenum(v) chloride (0.01 g) and *N*-acetylanabasine (**2**) (1.01 g, 4.93 mmol) were added successively to a 70% aqueous solution in TBHP (0.89 g, 9.86 mmol) in benzene (50 mL). The reaction mixture was refluxed for 7 h with a Dean—Stark trap, cooled, and worked-up as described in method *A*. The oily residue was purified by column chromatography on silica gel ($CHCl_3$—EtOH, 100 : 2) to give 0.85 g (79%) of compound **6**, $[\alpha]_{578}^{23}$ −114.4 (*c* 4.7, $CHCl_3$). Found (%): C, 65.10; H, 7.42; N, 12.61. $C_{12}H_{16}N_2O_2$. Calculated (%): C, 65.45; H, 7.27; N, 12.72. ^1H NMR ($CDCl_3$), δ: 1.34—1.49, 1.55—1.66 (both m, 2 H each, H(4), H(5)); 1.79 (dm, 1 H, H(3), J_{gem} = 13.5 Hz); 2.11 (s, 3 H, Me); 2.15 (dm, 1 H, H(3), J_{gem} = 13.5 Hz); 2.87 (dm, 1 H, H(6), J_{gem} = 13.5); 3.62 (d, 1 H, H(6), J = 13.5 Hz); 5.75 (br.s, 1 H, H(2)); 7.04 (d, 1 H, H(4′), J = 7.0 Hz); 7.18 (t, 1 H, H(5′), J_1 = 7.0 Hz); 8.00 (s, 1 H, H(2′)); 8.01 (d, 1 H, H(6′), J = 7.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 19.01 (C(5)), 21.36 (Me), 25.36 (C(4)), 26.31 (C(3)), 42.75 (C(6)), 48.03 (C(2)), 124.8 (C(5′)), 125.5 (C(4′)), 137.05 (C(2′)), 137.86 (C(6′)), 139.40 (C(3′)), 169.60 (C=O). UV, λ_{max}/nm (ε): 214 (14134), 266 (11220).

B. A solution of *N*-acetylanabasine (**2**) (1.00 g, 4.9 mmol) in $CHCl_3$ (10 mL) was added to a solution of 70% MCPBA (2.42 g, 9.8 mmol) in $CHCl_3$ (40 mL). The reaction mixture was stirred for 5 h at ~20 °C and worked-up as described above in method *B*. The residue was chromatographed on a column with silica gel (elution with $CHCl_3$—EtOH, 100 : 2) to give 0.98 g (91%) of compound **6**.

N*-Benzoylanabasine *N*′-oxide (3-(*N*-benzoylpiperidin-2-yl)pyridine *N*-oxide) (7).** ***A. Molybdenum(v) chloride (0.01 g) and *N*-benzoylanabasine (**3**) (0.63 g, 2.35 mmol) were added successively to a mixture of 70% aq. TBHP (0.61 g, 4.70 mmol) in benzene (50 mL). The reaction mixture was refluxed for 7 h with a Dean—Stark trap, cooled, and worked-up as described in method *A* to give 0.59 g (89%) of compound **7**, $[\alpha]_{578}^{23}$ −125.3 (*c* 4.1, $CHCl_3$). Found (%): C, 72.58; H, 6.58; N, 9.17. $C_{17}H_{18}N_2O_2$. Calculated (%): C, 72.34; H, 6.38; N, 9.92. ^1H NMR ($CDCl_3$), δ: 1.39—1.52 (m, 3 H, H(4), 2 H(5)); 1.67 (dm, 1 H, H(4), J_{gem} = 13.2 Hz); 1.91 (dm, 1 H, H(3), J_{gem} = 13.2 Hz); 2.19 (d, 1 H, H(3), J = 13.2 Hz); 2.77, 3.75 (both m, 1 H each, H(6)); 5.71 (br.s, 1 H, H(2)); 7.15 (d, 1 H, H(5′), J = 8.0 Hz); 7.21 (dd, 1 H, H(4′), J_1 = 6.4 Hz, J_2 = 8.0 Hz); 7.29—7.36 (m, 5 H, Ph); 8.04 (d, 1 H, H(6′), J = 6.4 Hz); 8.12 (s, 1 H, H(2′)). ^{13}C NMR ($CDCl_3$), δ: 19.3 (C(5)); 25.6 (C(4)); 26.99 (C(3)); 43.10 (C(6)); 50.52 (C(2)); 124.5 (C(5′)); 125.3 (C(4′)); 125.14, 125.64, 128.35, 129.40, 129.64, 132.35 (Ph); 137.2 (C(6′)); 137.9 (C(2′)); 139.2 (C(3′)); 171.1 (C=O). UV, λ_{max}/nm (ε): 216 (1598), 266 (857).

B. A solution of *N*-benzoylanabasine (**3**) (1.0 g, 3.75 mmol) in $CHCl_3$ (10 mL) was added to a solution of 70% aq. MCPBA (1.85 g, 7.50 mmol) in $CHCl_3$ (40 mL). The reaction mixture was stirred for 5 h at ~20 °C and worked-up as described in method *B* to give 0.98 g (92%) of compound **7**.

N*-Methylanabasine *N*-oxide (1-methyl-3,4,5,6-tetrahydro-2*H*-[2,3′]bipyridinyl 1-oxide) (isomer mixture 8′ and 8″).** ***A. Molybdenum(v) chloride (0.02 g) and *N*-methylanabasine (**4**) (0.41 g, 2.3 mmol) were added to a mixture of 70% aq. TBHP (0.83 g, 9.2 mmol) in C_6H_6 (50 mL). The reaction mixture was refluxed for 5 h with a Dean—Stark trap, cooled, and alkalized with 10% aq. NaOH до pH 10—11. The organic layer was separated, and the aqueous layer was extracted with chloroform

(6×15 mL). The benzene and chloroform extracts were dried with $MgSO_4$ and concentrated. The benzene extract contained unreacted *N*-methylanabasine (0.18 g). The chloroform extract contained 0.23 g (51%) of a stereoisomer mixture **8′** and **8″** in 1 : 4 ratio.

B. A solution of *N*-methylanabasine (**4**) (0.61 g, 3.4 mmol) in $CHCl_3$ (20 mL) was added to a solution of 70% aq. MCPBA (0.85 g, 3.4 mmol) in $CHCl_3$ (30 mL). The reaction mixture was stirred for 5 h and treated with 10% aq. NaOH (~5 mL) to pH 10—11. The organic layer was separated, dried with $MgSO_4$, and concentrated, and the aqueous layer was extracted with chloroform (6×15 mL). The chloroform extract was dried with $MgSO_4$ and concentrated to give a mixture of compounds **8′** and **8″** in 1 : 2 ratio in an overall yield of 0.54 g (81%). Recrystallization from ether gave isomer **8″**, m.p. 171—174 °C. ^{1}H NMR for isomer **8″** ($CDCl_3$), δ: 1.36—1.46 (dd, 1 H, $H_{eq}(4)$, J_1 = 4.0 Hz, J_2 = 13.5 Hz); 1.51—1.62 (m, 2 H, $H_{ax}(4)$, $H_{eq}(5)$); 1.84 (dm, 1 H, $H_{ax}(5)$, J_{gem} = 13.5 Hz); 2.41—2.57 (dd, 1 H, $H_{ax}(3)$, J_1 = 5.0 Hz, J_2 = 13.5 Hz); 2.57—2.67 (dd, 1 H, $H_{eq}(3)$, J_1 = 4.0 Hz, J_2 = 13.5 Hz); 2.74 (s, 3 H, Me_{eq}); 3.25 (td, 1 H, $H_{ax}(6)$, J_1 = 2.0 Hz, J_2 = 12.0 Hz); 3.36 (dt, 1 H, $H_{eq}(6)$, J_1 = 2.0 Hz, J_2 = 12.0 Hz); 3.89 (dd, 1 H, $H_{ax}(2)$, J_1 = 2.0 Hz, J_2 = 12.0 Hz); 7.24 (dd, 1 H, H(5′), J_1 = 5.0 Hz, J_2 = 7.8 Hz); 8.19 (t, 1 H, H(4′), J = 7.8 Hz); 8.51 (dd, 2 H, H(2′), H(6′), J_1 = 1.5 Hz, J_2 = 5.0 Hz). ^{13}C NMR for isomer **8″** ($CDCl_3$), δ: 20.41 (C(5)), 23.05 (C(4)), 27.67 (C(3)), 58.47 (Me), 68.99 (C(6)), 74.87 (C(2)), 123.33 (C(5′)), 131.51 (C(3′)), 137.78 (C(4′)), 150.30 (C(6′)), 150.60 (C(2′)). UV, λ_{max}/nm (ε): 261 (3584), 266 (3525). ^{1}H NMR for isomer **8′** ($CDCl_3$), δ: 1.27—1.73 (m, 4 H, 2 H(4), 2 H(5)); 2.65 (s, 3 H, Me); 2.12—2.88 (m, 2 H, 2 H(3)); 3.18—3.36 (m, 2 H, 2 H(6)); 3.98 (d, 1 H, H(2), J = 11.2 Hz); 7.00—7.12 (m, 1 H, H(5′)); 8.02 (d, 1 H, H(4′), J = 5.8 Hz); 8.28 (dd, 1 H, H(6′), J_1 = 5.8 Hz, J_2 = 8.6 Hz); 8.34 (d, 1 H, H(2′), J = 5.2 Hz). ^{13}C NMR for isomer **8′** ($CDCl_3$), δ: 22.39 (C(5)), 23.24 (C(4)), 26.81 (C(3)), 58.06 (Me), 71.06 (C(6)), 77.13 (C(2)), 122.09 (C(5′)), 129.02 (C(3′)), 139.93 (C(4′)), 149.34 (C(6′)), 150.99 (C(2′)).

***N*-Methylanabasine *N*-oxide picrate (9a).** A solution of picric acid (1 equiv.) in EtOH (5 mL) was added to an isomer mixture **8′**, **8″** (0.15 g, 1 : 4 ratio) in EtOH (5 mL). After 24 h, the solvent was evaporated and the material was crystallized from ethanol. Picrate **9a** was filtered off and dried. Yield 0.06 g (93%), m.p. 144—147 °C (EtOH). Found (%): C, 48.58; H, 4.15; N, 16.62. $C_{17}H_{19}N_5O_8$. Calculated (%): C, 48.45; H, 4.51; N, 16.62. ^{1}H NMR ($CDCl_3$), δ: 1.57—2.12 (m, 4 H, 2 H(4), 2 H(5)); 2.38—2.84 (m, 2 H, 2 H(3)); 3.29 (s, 3 H, Me); 3.50 (td, 1 H, H(6), J_1 = 2.8 Hz, J_2 = 12.4 Hz); 4.21 (dd, 1 H, H(6), J_1 = 2.8 Hz, J_2 = 12.4 Hz); 4.51 (d, 1 H, H(2), J = 12.4 Hz); 7.42 (dd, 1 H, H(5′), J_1 = 4.6 Hz, J_2 = 7.8 Hz); 8.06 (d, 1 H, H(4′), J = 7.8 Hz); 8.65 (s, 1 H, H(2′)); 8.67 (d, 1 H, H(6′), J = 7.8 Hz); 8.69 (d, 1 H, H(6′), J = 4.6 Hz); 8.71 (s, 1 H, H(2′)); 8.86 (s, 2 H, C_6H_2). ^{13}C NMR ($CDCl_3$) δ: 20.19 (C(5)); 22.49 (C(4)); 27.74 (C(3)); 55.19 (Me); 68.22 (C(6)); 77.10 (C(2)); 124.16 (C(5′)); 126.31, 126.32, 128.42, 129.00, 161.03, 179.91 (C_6H_2); 137.67 (C(4′)); 141.49 (C(3′)); 150.86 (C(6′)); 152.02 (C(2′)).

***N*-Methylanabasine *N*-oxide dipicrate (9b).** A solution of picric acid (1 equiv.) in EtOH (5 mL) was added to a mixture of isomers **8′**, **8″** (0.29 g, 1 : 2 ratio) in EtOH (5 mL). After 10 min, the crystals of dipicrate **9b** were filtered off. Yield 0.29 g (87%), m.p. 174—174.5 °C (EtOH). Found (%): C, 42.53; H, 3.48; N, 17.12. $C_{23}H_{22}N_8O_{15}$. Calculated (%): C, 42.46; H, 3.38; N, 17.23. ^{1}H NMR ($(CD_3)_2CO$), δ: 1.82—2.91 (m, 6 H, 2 H(3), 2 H(4), 2 H(5)); 3.59 (s, 3 H, Me); 4.07, 4.31 (both td, 1 H each, H(6), J_1 = 3.6 Hz, J_2 = 12.8 Hz); 5.41 (d, 1 H, H(2), J = 12.2 Hz); 8.12—8.23 (m, 1 H, H(5′)); 8.79 (s, 4 H, 2 C_6H_2); 8.89 (t, 1 H, H(4′), J = 6.8 Hz); 9.05 (d, 1 H, H(6′), J = 6.8 Hz); 9.22 (br.s, 1 H, H(6′)).

1-Acetyl-1,2,3,4,5,6-hexahydro-1′*H*-[2,3′]bipyridinyl-2′-one (10). A solution of *N*-acetylanabasine *N*′-oxide (**6**) (0.85 g, 3.86 mmol) in acetic anhydride (9.74 g, 95.38 mmol) was refluxed for 5 h. Then excess Ac_2O was evaporated *in vacuo*, the resulting mass was diluted with 10% aq. HCl (5 mL) and heated for 2.5 h at a bath temperature of 110 °C. The mixture was cooled, alkalized with 10% NaOH to pH 10—11, and extracted with chloroform (5×10 mL). The aqueous layer was completely dried in air, and the product was extracted with chloroform (4×10 mL). The combined chloroform extracts were dried with $MgSO_4$ and concentrated. Recrystallization from acetone gave compound **10**. Yield 0.24 g (28%), m.p. 189—190 °C (from acetone), $[\alpha]_{578}^{23}$ −13.1 (*c* 3.1, $CHCl_3$). Found (%): C, 65.20; H, 7.24; N, 12.26. $C_{12}H_{16}N_2O_2$. Calculated (%): C, 65.45; H, 7.27; N, 12.72. ^{1}H ($CDCl_3$), δ: 1.27—1.36 (m, 1 H, H(5)); 1.43—1.62 (m, 2 H, H(4), H(5)); 1.67—1.75 (m, 1 H, H(4)); 1.79—1.92 (m, 1 H, H(3)); 2.00 (s, 3 H, Me); 2.36 (br.d, 1 H, H(3), J_{gem} = 12.2 Hz); 2.88 (t, 1 H, H(6), J = 12.2 Hz); 4.61 (d, 1 H, H(6), J = 12.2 Hz); 5.11 (br.s, 1 H, H(2)); 6.25 (dd, 1 H, H(5′), J_1 = 6.5 Hz, J_2 = 6.7 Hz); 7.28 (d, 1 H, H(4′), J = 6.7 Hz); 7.33 (d, 1 H, H(6′), J = 6.5 Hz); 12.93 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 171.30, 163.43 (C=O); 137.20 (C(6′)); 133.13 (C(4′)); 131.63 (C(3′)); 106.26 (C(5′)); 53.19 (C(2)); 39.02 (C(6)); 27.16 (C(3)); 24.45 (C(4)); 21.42 (Me); 19.08 (C(5)). IR, ν/cm^{-1}: 3431 (NH), 1631 (N—(C=O)). UV, λ_{max}/nm (ε): 229 (6382), 302 (5194).

1-Benzoyl-1,2,3,4,5,6-hexahydro-1′*H*-[2,3′]bipyridinyl-2′-one (11). A solution of *N*-benzoylanabasine *N*′-oxide (**7**) (0.6522 g, 2.312 mmol) in acetic anhydride (7.57 g, 74.2 mmol) was refluxed for 5 h, then excess Ac_2O was evaporated *in vacuo*, and the remainder was diluted with 10% aq. HCl (5 mL) and heated for 3 h at 110 °C. The reaction mixture was cooled, treated with 10% NaOH to pH 10—11, and extracted with chloroform (6×10 mL). The aqueous phase was dried in air to dryness and the remaining product was extracted with chloroform (5×10 mL). The chloroform extracts were dried with $MgSO_4$, combined, and concentrated. Crystallization from diethyl ether gave compound **11** as yellow crystals. Yield 0.24 g (37%), m.p. 78—81 °C (hygroscopic), $[\alpha]_{578}^{23}$ +18.4 (*c* 2.1, $CHCl_3$). Found (%): C, 72.11; H, 6.66; N, 9.08. $C_{17}H_{18}N_2O_2$. Calculated (%): C, 72.34; H, 6.38; N, 9.92. ^{1}H NMR ($CDCl_3$), δ: 1.45—2.22 (m, 7 H, 2 H(3), 2 H(4), 2 H(5), H(6)); 2.92 (t, 1 H, H(6), J = 12.5 Hz); 4.05 (d, 1 H, H(2), J = 12.5 Hz); 6.16 (dd, 1 H, H(5′), J_1 = 6.4 Hz, J_2 = 7.0 Hz); 7.11—7.39 (m, 5 H, Ph); 7.53 (t, 2 H, H(4′), H(6′), J = 6.4 Hz); 7.92 (d, 1 H, NH, J = 7.0 Hz); 9.40 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 23.43, 23.10 (C(4), C(5)); 27.75 (C(3)); 45.40 (C(6)); 54.90 (C(2)); 107.00 (C(5′)); 127.40, 127.41, 129.25, 130.06, 130.10, 134.40 (Ph); 134.90 (C(3′)); 137.10 (C(4′)); 139.30 (C(6′)); 163.2, 173.10 (C=O). IR, ν/cm^{-1}: 3415 (NH), 3075 (CH arom.), 1648 (N—(C=O)). UV, λ_{max}/nm (ε): 226 (10386), 302 (5027).

Anabasein-3-one (5,6-dihydro-4*H*-[2,3′]bipyridinyl-3-one) (12). Anabaseine *N*′-oxide (**5**) (0.86 g, 4.88 mmol) and Ac_2O (12.01 g, 0.176 mol) were heated for 3 h at 100 °C, and excess

Ac_2O was evaporated *in vacuo*. The reaction mixture was diluted with 10% HCl (5 mL), heated for 1 h, cooled, and alkalized with 10% NaOH to pH 10—11 (~5 mL), and the product was extracted with chloroform (5×10 mL). The solvent was evaporated, and the extract was chromatographed on a column with silica gel to give successively 0.15 g (18%) of a colorless oil identified as anabasein-3-one (**12**) (elution with $CHCl_3$—EtOH, 100 : 0.5) and 0.21 g (22%) of *N*-acetylanabasine (**2**) (elution with $CHCl_3$—EtOH, 100 : 2). Compound **12**. Found (%): C, 69.06; H, 5.98; N, 16.21. $C_{10}H_{10}N_2O$. Calculated (%): C, 68.96; H, 5.74; N, 16.09. ^{1}H NMR ($CDCl_3$) δ: 2.09 (t, 2 H, H(5), J = 6.8 Hz); 2.50 (t, 2 H, H(4), J = 6.9 Hz); 3.16 (t, 2 H, H(6), J = 6.8 Hz); 7.39 (qd, 1 H, H(5′), J_1 = 1.6 Hz, J_2 = 4.8 Hz); 8.19 (dt, 1 H, H(4′), J_1 = 1.6 Hz, J_2 = 8.0 Hz); 8.73 (dd, 1 H, H(6′), J_1 = 1.6 Hz, J_2 = 4.8 Hz); 9.12 (d, 1 H, H(2′), J = 1.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 16.39 (C(5)), 19.24 (C(4)), 36.48 (C(6)), 118.96 (C(2)), 123.55 (C(5′)), 131.53 (C(3′)), 135.08 (C(4′)), 149.32 (C(2′)), 153.68 (C(6′)), 196.84 (C=O). UV, λ_{max}/nm (ε): 229 (8385), 267 (3057), 310 (974). MS, m/z (I_{rel} (%)): 174.1 $[M]^+$ (5.26), 121.0 (7.52), 106.0 (100.0), 78.0 (56.22), 51.0 (30.43).

3-(1-Acetyl-2′-oxo-1,2,3,4,5,6-hexahydro-2′*H*-[2,3′]bipyridinyl-1′-yl)propionic acid (14). Ethyl acrylate (0.21 g, 3.99 mmol) was added to a solution of pyridin-2-one **10** (0.18 g, 0.80 mmol) in toluene (5 mL) and the reaction mixture was heated for 24 h at 115—120 °C (TLC monitoring). The solvent was evaporated. Column chromatography gave successively 0.18 g (67%) of **ethyl 3-(1-acetyl-2′-oxo-1,2,3,4,5,6-hexahydro-2′*H*-[2,3′]bipyridinyl-1′-yl)propionate (13)** (elution with $CHCl_3$—EtOH, 100 : 2) and 0.09 g of *N*-acetylanabasin-2′-one (elution with $CHCl_3$—EtOH, 100 : 9). A suspension of compound **13** (0.18 g, 0.56 mmol) in 2% aq. NaOH (~5 mL) was stirred for 1 h, and the mixture was neutralized with 5% HCl (~4 mL) and extracted with chloroform (5×10 mL) to give acid **14**. Yield 0.11 g (69%). Compound **13**. ^{1}H ($CDCl_3$), δ: 1.09 (t, 3 H, Me, J = 6.4 Hz); 1.24—2.00 (m, 5 H, H(3), 2 H(4), 2 H(5)); 1.89 (s, 3 H, Me); 2.22 (d, 1 H, H(3), J = 12.0 Hz); 2.73 (t, 2 H, CH_2, J = 6.4 Hz); 2.77 (m, 1 H, H(6)); 4.05 (m, 4 H, CH_2CH_2); 4.48 (d, 1 H, H(6), J = 10.0 Hz); 5.00 (br.s, 1 H, H(2)); 6.02 (dd, 1 H, H(5′), J_1 = 6.0 Hz, J_2 = 6.2 Hz); 7.03 (d, 1 H, H(4′), J = 6.2 Hz); 7.28 (d, 1 H, H(6′), J = 6.0 Hz). Compound **14**. Found (%): C, 61.78; H, 6.52; N, 9.82. $C_{15}H_{20}N_2O_4$. Calculated (%): C, 61.64; H, 6.85; N, 9.59. ^{1}H NMR ($CDCl_3$), δ: 1.21—1.79 (m, 5 H, H(3), H(4), H(5)); 1.91 (s, 3 H, Me); 2.17 (d, 1 H, H(3), J = 12.8 Hz); 2.73 (m, 3 H, H(6), CH_2); 4.12 (m, 2 H, CH_2); 4.45 (d, 1 H, H(6), J = 12.8 Hz); 5.09 (br.s, 1 H, H(2)); 6.09 (dd, 1 H, H(5′), J_1 = 6.0 Hz, J_2 = 6.2 Hz); 7.11 (d, 1 H, H(4′), J = 6.2 Hz); 7.39 (d, 1 H, H(6′), J = 6.0 Hz); 8.58 (br.s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 18.79 (C(5)); 20.97 (Me); 24.12 (C(4)); 26.89 (C(3)); 32.71 (CH_2); 39.00 (C(6)); 46.25 (CH_2); 53.33 (C(2)); 105.26 (C(5′)); 131.14 (C(3′)); 135.63 (C(4′)); 137.44 (C(6′)); 160.73 (C(2′)); 172.03, 173.08 (C=O). MS, m/z (I_{rel} (%)): 292.2 $[M]^+$ (5.09), 277.2 (69.19), 249.1 (100), 177.2 (77.14). Found: m/z 292.14193 $[M]^+$. $C_{15}H_{20}N_2O_4$. Calculated: M = 292.14230.

3-(1-Acetyl-2′-oxo-1,2,3,4,5,6-hexahydro-2′*H*-[2,3′]bipyridinyl-1′-yl)propionitrile (15). Acrylonitrile (0.18 g, 3.38 mmol) was added to a solution of acetylanabasinone **10** (0.15 g, 0.68 mmol) in toluene (5 mL), and the reaction mixture was heated for 24 h at 115—120 °C (TLC monitoring). The solvent was evaporated. Column chromatography gave 0.09 g (48%) of nitrile **15**. Found (%): C, 66.13; H, 6.77; N, 15.22. $C_{15}H_{19}N_3O_2$. Calculated (%): C, 65.93; H, 6.96; N, 15.38. ^{1}H NMR ($CDCl_3$), δ: 1.25—1.85 (m, 5 H, H(3), 2 H(4), 2 H(5)); 1.98 (s, 3 H, Me); 2.24 (d, 1 H, H(3), J = 10.8 Hz); 2.89 (t, 3 H, H(6), CH_2, J = 6.2 Hz); 4.14 (t, 2 H, CH_2, J = 6.2 Hz); 4.59 (d, 1 H, H(6), J = 12.8 Hz); 5.08 (d, 1 H, H(2), J = 2.0 Hz); 6.21 (dd, 1 H, H(5′), J_1 = 6.0 Hz, J_2 = 6.2 Hz); 7.21 (d, 1 H, H(4′), J = 6.2 Hz); 7.31 (d, 1 H, H(6′), J = 6.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 17.13 (CH_2), 19.16 (C(5)), 21.45 (Me), 24.45 (C(4)), 27.07 (C(3)), 38.93 (C(6)), 46.39 (CH_2), 53.41 (C(2)), 105.86 (C(5′)), 116.93 (CN), 132.29 (C(3′)), 135.58 (C(4′)), 136.19 (C(6′)), 160.66 (C(2′)), 171.23 (C=O). IR, ν/cm^{-1}: 2862, 1416 (CH_2), 2249 (C=N), 1720 (C=O), 1650 (N—(C=O)). UV, λ_{max}/nm (ε): 231 (5663), 305 (5546). MS, m/z (I_{rel} (%)): 273.3 $[M]^+$ (1.27), 230.0 (100), 177.1 (29.74), 149.0 (72.16). Found: m/z 273.14764 $[M]^+$. $C_{15}H_{19}N_3O_2$. Calculated: M = 273.14772.

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