Chemistry of Heterocyclic Compounds, Vol. 45, No. 6, 2009

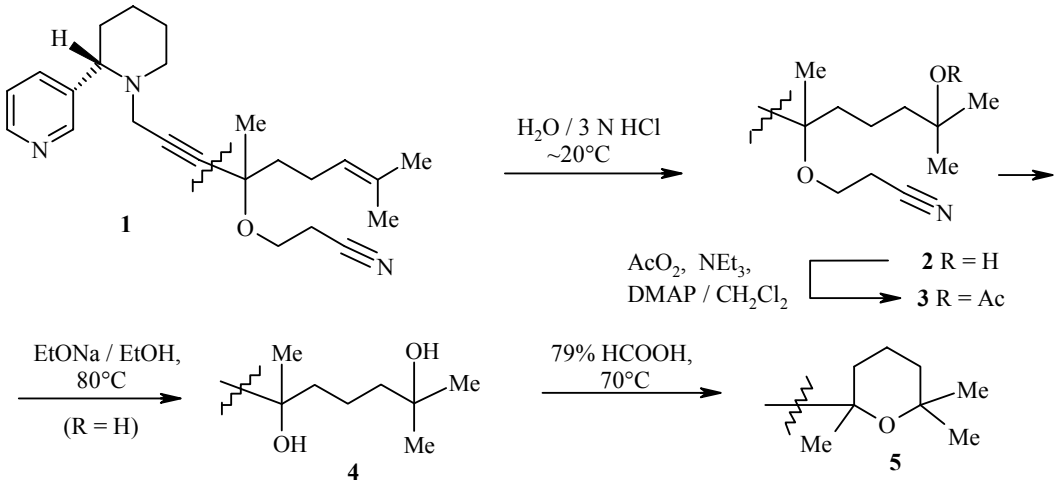
ISOPRENOID DERIVATIVES OF N-PROPARGYLANABASINE: MILD HYDRATION OF A TRISUBSTITUTED DOUBLE BOND

M. V. Mavrov[1] and S. G. Zlotin[1]*

(2S,4'RS)-N-[4-(2-Cyanoethoxy)-4,8-dimethylnon-7-en-2-yn-1-yl]-2-(3-pyridyl)piperidine has been synthesized by the three-component condensation of (S)-anabasine with (2-cyanoethoxy)dehydrolinalool and formaldehyde. A series of previously unreported N-propargylanabasine derivatives has been synthesized from this compound.

Keywords: anabasine, homoterpenoids, propargylamines, hydration.

It has been established that (2*S*,4'*RS*)-N-[4-(2-Cyanoethoxy)-4,8-dimethylnon-7-en-2-yn-1-yl]-2-(3-pyridyl)piperidine (**1**), obtained by three-component condensation of (*S*)-anabasine with (2-cyanoethoxy)dehydrolinalool and formaldehyde according to [1], is unexpectedly readily converted into tertiary



DMAP – 4-(dimethylamino)pyridine

* To whom correspondence should be addressed, e-mail: zlotin@ioc.ac.ru.

[1]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 119991, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 853-857, June, 2009. Original article submitted March 12, 2008.

alcohol **2** by the action of aqueous HCl (3 N) at room temperature. The initial dehydrolinalool, containing no heterocyclic fragment, does not react with aqueous HCl even on boiling [2, 3].

The structure of compounds **1-5** was confirmed by elemental analysis, and also by IR, ^{1}H and ^{13}C NMR and mass spectra. In the mass spectrum of compound **2** there was an intense peak for a fragment ion of *m/z* 59 [Me_2COH] (*I* 100%) together with fragment ions [M-C_5H_4N]$^+$, 199, and 161 characteristic of anabasine derivatives. The obtained compounds **1-5** have large values of the angle of optical rotation, which indirectly shows the retention of the chiral center in the course of reaction.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AU-300 instrument (300 and 75 MHz respectively) in $CDCl_3$, internal standard was TMS. The IR spectra were recorded on a Specord M-80, mass spectra (electron impact) on a MAT-3 instrument (70 eV, direct insertion). Optical rotation was determined in $CHCl_3$ on a PU-7 polarimeter. Compounds **1-5** were isolated by column chromatography on SiO_2 (Merck), eluting with a mixture of MeOH (0-10%), EtOAc, saturated NH_4OH (0-10%) in CH_2Cl_2; for TLC Silufol UV-254 plates were used, eluent was the system MeOH–EtOAc–NH_4OH, 1:1:9, by volume, visualization in iodine vapor. Anabasine hydrochloride of mp 220-222°C was used; base R_f 0.17, [α]$_D$ -81.9° (*c* 0.83).

(2*S*,4'*RS*)-N-[4-(2-Cyanoethoxy)-4,8-dimethylnon-7-en-2-yn-1-yl]-2-(3-pyridyl)piperidine (1). Anabasine hydrochloride (0.56 g, 2.5 mmol) was added in one portion to a mixture of paraformaldehyde (0.24 g, 8.0 mmol), 3-(2-cyanoethoxy)-3,7-dimethyloct-6-en-1-yne (0.82 g, 4.0 mmol), Cu_2Cl_2 (0.30 g), AcONa (0.52 g), and dioxane (20 ml) and vigorously stirred for 6 h at 65-70°C (check by TLC). The dioxane was evaporated on a rotary evaporator, aqueous ammonia was added to the residue (to pH ~8), the mixture was extracted with benzene (3×20 ml), the combined organic layer was washed with saturated NaCl solution, dried over $MgSO_4$, and the product isolated by chromatography on SiO_2. Compound **1** (0.95 g, 58%) was obtained as an oil, R_f 0.79, [α]$_D$ -181.2° (*c* 0.93). IR spectrum, ν, cm^{-1}: 2256, 1656, 1600, 1580, 1436, 1100, 708. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25-1.82 (8H, m, CH_2); 1.42, 1.64, 1.73 (all 3H, s, CH_3); 2.19 (2H, m, CH_2CH=); 2.58 (3H, m, CH_2CH, H-6*a*); 2.93 (1H, br. d, *J* = 11.4, H-6*e*); 3.12, 3.19 (both 1H, d, *J* = 17.0, NCH_2C≡); 3.32 (1H, br. d, *J* = 10.4, H-2); 3.74 (2H, m, OCH_2); 5.12 (1H, t, *J* = 6.4, CH=); 7.38 (1H, br. s, H-5'); 7.69 (1H, br. d, *J* = 7.6, H-4'); 8.2-9.2 (2H, degenerate br. s, H-2',6'). Mass spectrum, *m/z* (I_{rel}, %): 379 [M]$^+$ (4), 309 (26), 301 [M-C_5H_4N]$^+$ (47), 199 (29), 162 (78), 161 (100), 160 (48), 131 (81), 119 (80), 105 (89), 92 (70), 82 (42), 79 (65), 69 (83), 59 (76), 55 (72). Found, %: N 10.58. $C_{24}H_{33}N_3O$. Calculated, %: N 11.07.

(2*S*,4'*RS*)-N-[4-(2-Cyanoethoxy)-8-hydroxy-4,8-dimethylnon-2-yn-1-yl]-2-(3-pyridyl)piperidine (2). A mixture of compound **1** (0.40 g,1.0 mmol) and 3 N HCl (25 ml) was stirred for 5 h at 20°C, neutralized with NH_4OH and after treatment and chromatography on SiO_2, alcohol **2** (0.34 g, 68%) was isolated. Oil, R_f 0.63, [α]$_D$ -183.4° (*c* 0.91). IR spectrum, ν, cm^{-1}: 3400, 2256, 1592, 1580, 1432, 1172, 1100, 716. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18-1.92 (12H, m, CH_2); 1.21, 1.25, 1.26, 1.39, 1.48 (total 9H, all s, CH_3); 2.51-2.70 (3H, m, CH_2CN, H-6*a*); 2.91 (1H, br. d, *J* = 10.8, H-6*e*); 3.08, 3.16 (both 1H, double set dd, *J* = 17.0, *J* = 2.4, ≡CCH_2N); 3.21 (1H, td, *J* = 12.8, *J* = 1.7, H-2); 3.76 (2H, m, CH_2O); 7.26 (1H, m, H-5'); 7.81 (1H, d, *J* = 7.8, H-4'); 8.49 (1H, d, *J* = 4.6, H-6'); 8.58 (1H, br. s, H-2'). ^{13}C NMR spectrum, δ, ppm: 19.2, 24.4, 25.6, 26.2, 28.9, 29.3, 35.0, 42.0, 43.7, 44.0, 52.9, 58.7, 62.7, 65.6, 69.9, 74.0, and 79.6 (C≡C); 86.1, 117.8 (C≡N); 123.6, 134.9, 138.6, 148.4, 149.0. Mass spectrum, *m/z* (I_{rel}, %): 397 [M]$^+$ (1.0), 301 (7), 199 (13), 161 (59), 136 (29), 131 (74), 122 (61), 124 (62), 106 (31), 69 (57), 59 [Me_2COH]$^+$ (100), 54 (78). Found, %: N 10.29. $C_{24}H_{35}N_3O_2$. Calculated, %: N 10.57.

(2*S*,4'*RS*)-N-[8-Acetoxy-4-(2-cyanoethoxy)-4,8-dimethylnon-2-yn-1-yl]-2-(3-pyridyl)piperidine (3). A mixture of Ac_2O (1.2 ml), NEt_3 (1.3 ml), and dimethylaminopyridine (7 mg) was added to a solution of alcohol **2** (0.20 g, 0.5 mmol) in CH_2Cl_2 (10 ml) with stirring at 0°C. The reaction mixture was stirred for 48 h at 18-20°C, a

mixture of MeOH (1.5 ml) and CH_2Cl_2 (15 ml) was added and after treatment and chromatography on SiO_2 acetate **3** (0.17 g, 78%) was isolated as an oil containing ~2% olefin **1**, R_f 0.72, $[\alpha]_D$ –201.7° (*c* 0.71). IR spectrum, ν, cm^{-1}: 2256, 1728, 1592, 1576, 1428, 1112, 1100, 720. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.02-1.79 (12H, m, CH_2); 1.34 (9H, br. s, CH_3); 1.82 (3H, s, CH_3CO); 2.38-2.57 (3H, m, CH_2CN, H-6*a*); 2.82 (1H, br. d, *J* = 11.0, H-6*e*); 3.01, 3.12 (both 1H, d, *J* = 17.0, ≡CCH_2N); 3.18 (1H, br. d, *J* = 12.0, H-2); 3.64 (2H, sext, *J* = 6.4, CH_2O); 7.14 (1H, dd, *J* = 7.4, *J* = 4.6, H-5'); 7.57 (1H, br. d, *J* = 7.4, H-4'); 8.38 and 8.46 (both 1H, br. s, H-2',6'). Mass spectrum, *m/z* (I_{rel}, %): 439 $[M]^+$ (1.1), 301 (34), 199 (19), 161 (100), 119 (64), 105 (65), 92 (68), 84 (79), 69 (72), 55 (74). Found, %: N 9.69. $C_{26}H_{37}N_3O_3$. Calculated, %: N 9.56.

(2*S*,4'*RS*)-N-(4,8-Dihydroxy-4,8-dimethylnon-2-yn-1-yl)-2-(3-pyridyl)piperidine (4). A mixture of cyano derivative **2** (0.40 g, 1.0 mmol) and 2% EtONa in EtOH solution (10 ml) was maintained at 80°C for 7 h, neutralized with KU-2 cation exchange resin (H^+ form), the solvent was distilled, and the residue chromatographed on SiO_2. Diol **4** (0.16 g, 47%) was obtained containing an unidentified contaminant (~4%). Viscous oil, R_f 0.45, $[\alpha]_D$ –176.4° (*c* 1.0). IR spectrum, ν, cm^{-1}: 3390, 1590, 1584, 1432, 1172, 1116, 1100, 756, 716. ^1H NMR spectrum (DMSO-d_6–CCl_4, 2 : 1), δ, ppm (*J*, Hz): 1.11, 1.36 (6H and 3H, both br. s, CH_3); 1.08-1.92 (12H, m, CH_2); 2.52 (1H, t, *J* = 12.2, H-6*a*); 2.88 (1H, overlap, H-6*e*); 2.92, 3.09 (both 1H, both d, *J* = 17.1, ≡CCH_2N); 3.31 (1H, overlap, H-2); 4.08, 5.09 (both 1H, br. s, OH); 7.38, 7.70, 8.46, 8.52 (all 1H, br. s, HPy). ^{13}C NMR spectrum, δ, ppm: 19.7, 24.4, 25.6, 28.9, 29,3, 30.2, 34.9, 42.9, 43.8, 44.2, 52.9, 62.8, 67.5, 70.3, 76.2, 90.5, 123.6, 135.3, 138.9, 148.1, 149.0. Mass spectrum, *m/z* (I_{rel}, %): 344 $[M]^+$ (13), 328 (26), 312 (59), 268 (53), 250 (90), 245 (58), 226 (50), 200 (66), 162 (100), 161 (31), 123 (96), 85 (86), 77 (60), 69 (50), 55 (52). Found, %: N 8.47. $C_{21}H_{32}N_2O_2$. Calculated, %: N 8.13.

(2*S*)-N-[3-(2,6,6-Trimethyltetrahydropyran-2-yl)prop-2-yn-1-yl]-2-(3-pyridyl)piperidine (5). A mixture of diol **4** (0.34 g, 1.0 mmol) and 70% HCOOH (2 ml) was stirred for 4 h at 70°C (check by TLC), neutralized with aqueous ammonia to pH ~8, and extracted with Et_2O (3×20 ml). Product **5** 0.15 g (47%) was isolated by chromatography on SiO_2, oil, R_f 0.82, $[\alpha]_D$ -194.2° (*c* 0.5). IR spectrum, ν, cm^{-1}: 1592, 1576, 1428, 1220, 1076, 988, 716. ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm (*J*, Hz): 1.13, 1.40 (3H and 6H, both s, CH_3); 1.25-1.96 (12H, m, CH_2); 2.55 (1H, t, *J* = 13.6, H-6*a*); 2.91 (1H, br. d, *J* = 10.2, H-6*e*); 3.01, 3.10 (both 1H, d, *J* = 17.2, ≡CCH_2N); 3.30 (1H, d, *J* = 11.0, H-2); 7.25 (1H, dd, *J* = 7.3, *J* = 4.7, H-5'); 7.64 (1H, d, *J* = 7.3, H-4'); 8.42, 8.46 (both 1H, br. s, H-6',2'). Mass spectrum, *m/z* (I_{rel}, %): 326 $[M]^+$ (30), 248 $[M\text{-}C_5H_4N]^+$ (100), 199 (14), 161 (32), 43 (26). Found, %: N 8.41. $C_{21}H_{30}N_2O$. Calculated, %: N 8.58.

REFERENCES

1. M. V. Mavrov and S. G. Zlotin, *Izv. Akad. Nauk, Ser. Khim.*, 1576 (2007).
2. M. B. Erman, E. V. Golovacheva, S. E. Gulyi, D. L. Zasetskii, L. A. Shutikova, V. G. Cherkaev, and I. S. Aul'chenko, *Zh. Org. Khim.*, **26**, 262 (1990).
3. H. Pakdel, S. Sarron, and C. Roy, *J. Agric. Food Chem.*, **49**, 4337 (2001).