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Synthesis of Hydrazones of Anabasinylacetic Acid and Structure of Its Isopropylidenehydrazone

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Abstract—Some hydrazones based on *N*-anabasinylacetic acid hydrazide have been synthesized. Structure of *N*'-isopropylidenehydrazone of *N*-anabasinylacetic acid has been studied by X-ray diffraction.

Keywords: alkaloid, anabasine, hydrazone, X-ray diffraction

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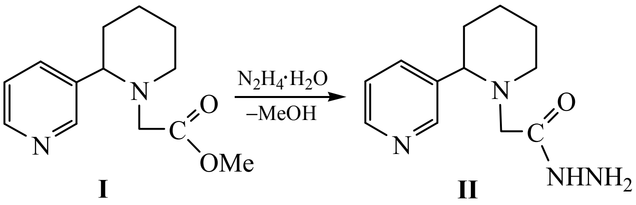
Hydrazides chemistry is of emerging interest due to broad range of physiological activity of these compounds, including pronounced antituberculous activity [1, 2]. For example, we synthesized hydrazides and acylhydrazide of *N*-aminoacetic acids based on physiologically active ephedrine alkaloids [3] and studied their antituberculous activity [4]. Some derivatives of anabasine alkaloid showed biological activity as well [5].

Hydrazide **II** was prepared via hydrazinolysis of the esters (methyl or ethyl) of *N*-anabasinylacetic acid **I** with hydrazine hydrate (yield 57%) [2].



I **II**

Unfortunately, hydrazide **II** was isolated in the form of viscous oil; therefore, its further modification and studies (including structural and biological) were complicated. After a number of attempts to obtain the crystalline hydrazide, we isolated its hydrazone with acetone; the latter was formed in the course of short heating of hydrazide **II** in acetone. Isopropylidenehydrazone **III** isolated after cooling down was white crystallizing solid.

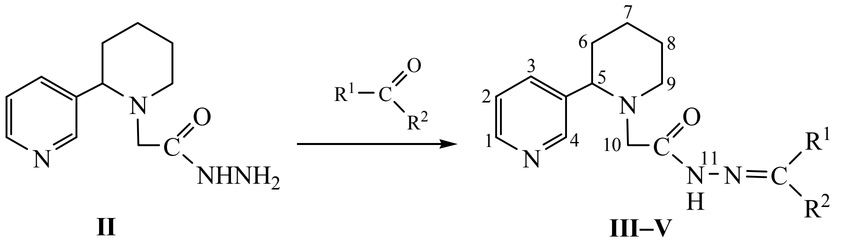
Similarly, condensation of hydrazide of *N*-anabasinylacetic acid **II** with certain aromatic aldehydes (*p*-fluorobenzaldehyde or 5-bromosalicylaldehyde) afforded novel *N*-arylidenehydrazones of anabasinylacetic acid, **IV** and **V**. The synthesized hydrazones **III–V** were white or yellow crystalline powders soluble in polar organic solvents (Scheme 1).

In ^1H NMR spectra of **III–V**, methylene protons of the $NCH_2C(O)$ moiety resonated as two doublets due to their non-equivalence (H^{10a} 2.64 and H^{10b} 2.94 ppm, *J* 16.2 Hz).

Structure of hydrazone **III** was determined by X-ray diffraction and compared with that of hydrazide of *N*-*d*-pseudoephedrinylacetic acid hydrochloride [6]. According to XRD, a unit cell of **III** contained two molecules **IIIa** and **IIIb** in the crystallographically independent positions, connected via the intermolecular hydrogen bond (see figure).

The bond lengths and angles (Tables 1 and 2) in the molecule of **III** were close to typical of common organic molecules [6, 7]. Piperidine ring adopted a conformation of almost ideal *chair* (ΔC_s^{10} = 1.74 Å), similar to the cases of anabasine *O*,*O*-diethyl thiophosphate and anabasine *O*,*O*-diisopropyl thiophosphate molecules [8]. Pyridine ring was planar within ±0.007 Å. Despite the bulky substituent at the N^8 atom, the pyridine ring was equatorially oriented with respect to the piperidine ring (torsion angle $C^3C^7C^8C^9$ =

Scheme 1.

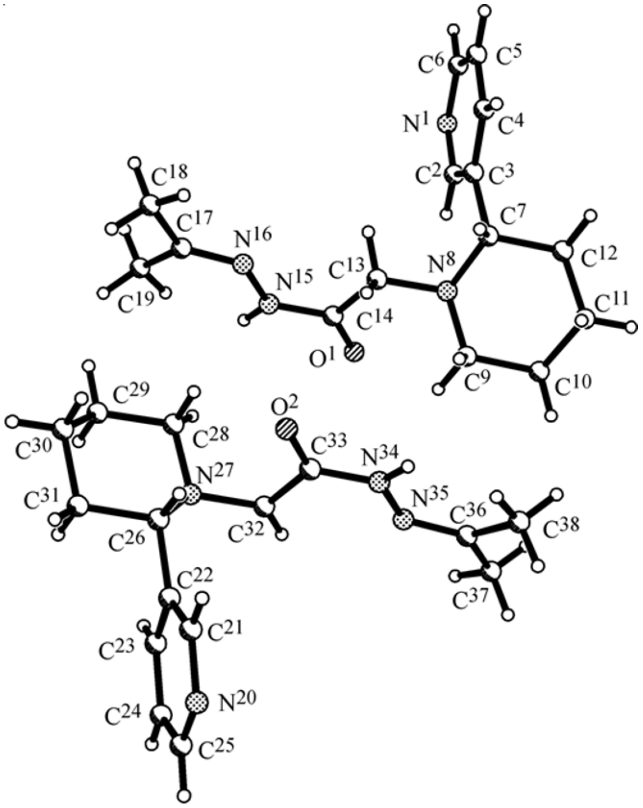


$R^1 = CH_3$, $R^2 = CH_3$ (**III**); R^1 = *n*-F–C_6H_4, R^2 = H (**IV**); R^1 = 2-OH-5-BrC_6H_3, R^2 = H (**V**).

–171.1°). The presence of methylene bridge with a hydrazide moiety did not create additional steric hindrance for axial orientation of the pyridine ring with respect to the piperidine moiety, as it was found by X-ray diffraction for other anabasine derivatives [9–11].

EXPERIMENTAL

IR spectra (KBr) were recorded with the Fourier transformed Nicolet AVATAR-320 spectrometer. ^{1}H NMR spectra (DMSO-d_6) were registered with the Bruker DRX500 spectrometer (500 MHz) relative to internal TMS reference. Mass spectra were obtained with the FINNIGAN MAT.INCOS 50 instrument (70 eV). Melting points were determined with the Boetius apparatus. The reaction progress was monitored with TLC (Silufol UV-254 plate, propan-2-ol–benzene–ammonia 10 : 5 : 2, developing with iodine vapor).



General view of *N*'-isopropylidenehydrazone of *N*-anabasinylacetic acid **III** molecule.

X-Ray diffraction studies were performed at 173 K with the Bruker P4 automatic diffractometer (MoK_α irradiation, graphitic monochromator, θ/2θ-scanning, $2\theta \le 56°$). The crystals were monoclinic (0.6 × 0.4 × 0.3 mm), the unit cell parameters were as follows: *a* 6.086(1), *b* 28.161(1), *c* 8.949(1) Å, β 97.10°, *V* 1522.0(1) Å^3, space group $P2_1$, d_{calc} 1.197 g cm^{-3}, $C_{30}H_{44}N_8O_2$, *Z* 2. Intensity of 7100 independent reflections was measured. The structure was solved by direct method and refined in anisotropic approximation (non-hydrogen atoms) by full-matrix least square method. Positions of H atoms were geometrically calculated using the *rider* model. Final refinement parameters: *R* 0.1063, wR_2 0.2667. The structure was solved and refined using SIR-2002 and SHELXL-97 [12] software, respectively.

***N*'-Isopropylidenehydrazone of *N*-anabasinylacetic acid (III).** A mixture of 2.34 g (10 mmol) of hydrazide *N*-anabasinylacetic acid **I** and 50 mL of acetone was refluxed during 3 h. After cooling, the formed crystals were filtered off and washed with cold acetone. Yield 2.52 g (92%), mp 125–126°C. IR spectrum (KBr), ν, cm^{-1}: 3185 (NH), 1676 (C=O), 1577 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32–1.80 m (6H, H$^{6-8}$), 1.86 s (3H, CH$_3$), 1.94 s (3H, CH$_3$), 2.34 t (1H, H^5, $J_{5,6}$ 11.9), 2.64 d (1H, NCH^a, J_{ab} 16.8), 2.94 d (1H, NCH^b, J_{ba} 16.2), 2.99 br.d (1H, H^9_a, *J* 11.48), 3.41 br.d (1H, H^9_e, *J* 11.12), 7.36 d.d (1H, H^2, $J_{2,1}$ 4.76, $J_{2,3}$ 7.78), 7.77 d (1H, H^3, $J_{3,2}$ 7.84), 8.47 d (1H, H^1, $J_{1,2}$ 4.76), 8.55 s (1H, H^4), 9.80 s (1H, NH). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 234 (1.3) $[M]^+$, 175 (100), 176 (13), 161 (69), 132 (36), 92 (17), 44 (55), 42 (27), 41 (21).

***N*'-(4-Fluorobenzylidene)hydrazone of *N*-anabasinylacetic acid (IV).** 0.52 mL (0.62 g, 5 mmol) of

Table 1. Bond lengths and bond angles in the molecule of **III**

Bond	*d*, Å	Angle	ω, deg	Bond	*d*, Å	Angle	ω, deg
O^1–C^{14}	1.238(6)	$C^2N^1C^6$	117.3(5)	C^4–C^5	1.384(7)	$O^1C^{14}N^{15}$	120.4(4)
O^2–C^{33}	1.248(6)	$C^9N^8C^{13}$	109.0(4)	C^5–C^6	1.376(8)	$O^1C^{14}C^{13}$	122.9(5)
N^1–C^2	1.337(7)	$C^9N^8C^7$	112.9(4)	C^7–C^{12}	1.543(7)	$N^{15}C^{14}C^{13}$	116.6(4)
N^1–C^6	1.345(8)	$C^{13}N^8C^7$	110.1(4)	C^9–C^{10}	1.528(8)	$N^{16}C^{17}C^{19}$	124.8(5)
N^8–C^9	1.453(6)	$C^{14}N^{15}N^{16}$	120.1(4)	C^{10}–C^{11}	1.521(9)	$N^{16}C^{17}C^{18}$	116.8(5)
N^8–C^{13}	1.457(6)	$C^{17}N^{16}N^{15}$	117.8(4)	C^{11}–C^{12}	1.520(7)	$C^{19}C^{17}C^{18}$	118.4(4)
N^8–C^7	1.479(6)	$C^{25}N^{20}C^{21}$	118.0(4)	C^{13}–C^{14}	1.520(6)	$N^{20}C^{21}C^{22}$	124.1(5)
N^{15}–C^{14}	1.348(6)	$C^{32}N^{27}C^{28}$	111.1(4)	C^{17}–C^{19}	1.502(7)	$C^{21}C^{22}C^{23}$	117.6(4)
N^{15}–N^{16}	1.389(5)	$C^{32}N^{27}C^{26}$	114.0(4)	C^{17}–C^{18}	1.511(7)	$C^{21}C^{22}C^{26}$	121.3(4)
N^{16}–C^{17}	1.280(6)	$C^{28}N^{27}C^{26}$	114.8(4)	C^{21}–C^{22}	1.376(7)	$C^{23}C^{22}C^{26}$	120.9(4)
N^{20}–C^{25}	1.346(8)	$C^{33}N^{34}N^{35}$	119.7(4)	C^{22}–C^{23}	1.413(7)	$C^{24}C^{23}C^{22}$	118.4(5)
N^{20}–C^{21}	1.354(7)	$C^{36}N^{35}N^{34}$	117.2(4)	C^{22}–C^{26}	1.519(6)	$C^{23}C^{24}C^{25}$	120.6(5)
N^{27}–C^{32}	1.461(6)	$N^1C^2C^3$	124.6(5)	C^{23}–C^{24}	1.373(7)	$N^{20}C^{25}C^{24}$	121.2(5)
N^{27}–C^{28}	1.472(6)	$C^4C^3C^2$	116.5(4)	C^{24}–C^{25}	1.397(8)	$N^{27}C^{26}C^{22}$	111.3(4)
N^{27}–C^{26}	1.474(6)	$C^4C^3C^7$	121.3(4)	C^{26}–C^{31}	1.533(7)	$N^{27}C^{26}C^{31}$	110.4(4)
N^{34}–C^{33}	1.343(6)	$C^2C^3C^7$	122.0(4)	C^{28}–C^{29}	1.520(7)	$C^{22}C^{26}C^{31}$	107.7(4)
N^{34}–N^{35}	1.393(5)	$C^5C^4C^3$	119.8(5)	C^{29}–C^{30}	1.532(8)	$N^{27}C^{28}C^{29}$	112.0(4)
N^{35}–C^{36}	1.281(6)	$C^6C^5C^4$	119.1(5)	C^{30}–C^{31}	1.531(7)	$C^{28}C^{29}C^{30}$	109.3(5)
C^2–C^3	1.393(7)	$N^1C^6C^5$	122.7(5)	C^{32}–C^{33}	1.522(6)	$C^{31}C^{30}C^{29}$	108.5(4)
C^3–C^4	1.391(7)	$N^8C^7C^3$	111.0(4)	C^{36}–C^{37}	1.481(7)	$C^{30}C^{31}C^{26}$	111.0(4)
C^3–C^7	1.513(6)	$N^8C^7C^{12}$	110.4(4)	C^{36}–C^{38}	1.533(7)	$N^{27}C^{32}C^{33}$	116.4(4)
		$C^3C^7C^{12}$	106.8(4)			$O^2C^{33}N^{34}$	119.8(4)
		$N^8C^9C^{10}$	111.8(5)			$O^2C^{33}C^{32}$	122.0(4)
		$C^{11}C^{10}C^9$	109.6(5)			$N^{34}C^{33}C^{32}$	118.2(4)
		$C^{12}C^{11}C^{10}$	108.2(5)			$N^{35}C^{36}C^{37}$	117.4(5)
		$C^{11}C^{12}C^7$	113.0(4)			$N^{35}C^{36}C^{38}$	124.7(5)
		$N^8C^{13}C^{14}$	112.9(4)			$C^{37}C^{36}C^{38}$	117.9(5)

p-fluorobenzaldehyde was added dropwise to a stirred solution of 1.17 g (5 mmol) of *N*-anabasinylacetic acid in 20 mL of ethanol. The mixture was stirred at 50–60°C during 60 min. After cooling, yellow precipitate was filtered off and recrystallized from ethanol. Yield 0.85 g (50%), mp 70–71°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32–1.80 m (6H, $H^{6–8}$), 2.37 t (1H, H^5, $J_{5,6}$ 11.7), 2.69 d (1H, NCH^a, J_{ab} 16.5), 2.99 d (1H, NCH^b, J_{ba} 16.4), 3.08 br.d (1H, H^9_a, *J* 11.08), 3.42 br.d (1H, H^9_e, *J* 11.0), 7.17 m (2H, Ar), 7.28 m (2H, Ar), 7.36 d.d (1H, H^2, $J_{2,1}$ 4.8, $J_{2,3}$ 7.9), 7.82 d (1H, H^3, $J_{3,2}$ 7.9), 8.48 d (1H, H^1, $J_{1,2}$ 4.78), 8.55 s (1H, N=CH), 8.59 s (1H, H^4), 10.90 s (1H, NH).

***N*'-(5-Bromo-2-hydroxybenzylidene)hydrazone of *N*-anabasinylacetic acid (V)** was obtained similarly from 1.17 g (5 mmol) of hydrazide of *N*-anabasinylacetic acid, 20 mL of ethanol and 1.0 g (5 mmol) of 5-bromosalicylaldehyde. Yield 1.79 g (86%), mp 97–98°C (propan-2-ol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33–1.80 m (6H, $H^{6–8}$), 2.35 t (1H, H^5, $J_{5,6}$ 11.5), 2.72 d (1H, NCH^a, J_{ab} 15.92), 3.05 d (1H,

Table 2. Torsion angles in the molecules of **III**

Angle	τ, deg	Angle	τ, deg	Angle	τ, deg	Angle	τ, deg
$C^{14}N^{15}N^{16}C^{17}$	172.7(4)	$C^{4}C^{3}C^{7}C^{12}$	–85.4(6)	$N^{15}N^{16}C^{17}C^{18}$	177.3(4)	$C^{23}C^{22}C^{26}C^{31}$	71.7(6)
$C^{33}N^{34}N^{35}C^{36}$	–173.2(4)	$C^{2}C^{3}C^{7}C^{12}$	89.2(6)	$C^{25}N^{20}C^{21}C^{22}$	0.3(8)	$C^{32}N^{27}C^{28}C^{29}$	175.2(4)
$C^{6}N^{1}C^{2}C^{3}$	–0.9(10)	$C^{13}N^{8}C^{9}C^{10}$	179.7(4)	$N^{20}C^{21}C^{22}C^{23}$	–1.4(8)	$C^{26}N^{27}C^{28}C^{29}$	–53.6(6)
$N^{1}C^{2}C^{3}C^{4}$	1.6(9)	$C^{7}N^{8}C^{9}C^{10}$	–57.6(6)	$N^{20}C^{21}C^{22}C^{26}$	174.3(5)	$N^{27}C^{28}C^{29}C^{30}$	56.3(6)
$N^{1}C^{2}C^{3}C^{7}$	–173.3(6)	$N^{8}C^{9}C^{10}C^{11}$	59.8(6)	$C^{21}C^{22}C^{23}C^{24}$	0.9(7)	$C^{28}C^{29}C^{30}C^{31}$	–59.1(7)
$C^{2}C^{3}C^{4}C^{5}$	–1.4(8)	$C^{9}C^{10}C^{11}C^{12}$	–57.4(6)	$C^{26}C^{22}C^{23}C^{24}$	–174.8(5)	$C^{29}C^{30}C^{31}C^{26}$	59.2(7)
$C^{7}C^{3}C^{4}C^{5}$	173.5(5)	$C^{10}C^{11}C^{12}C^{7}$	55.5(7)	$C^{22}C^{23}C^{24}C^{25}$	0.6(8)	$N^{27}C^{26}C^{31}C^{30}$	–54.8(6)
$C^{3}C^{4}C^{5}C^{6}$	0.6(8)	$N^{8}C^{7}C^{12}C^{11}$	–52.8(6)	$C^{21}N^{20}C^{25}C^{24}$	1.3(9)	$C^{22}C^{26}C^{31}C^{30}$	–176.4(5)
$C^{2}N^{1}C^{6}C^{5}$	–0.1(10)	$C^{3}C^{7}C^{12}C^{11}$	–173.6(5)	$C^{23}C^{24}C^{25}N^{20}$	–1.8(9)	$C^{28}N^{27}C^{32}C^{33}$	69.0(5)
$C^{4}C^{5}C^{6}N^{1}$	0.2(10)	$C^{9}N^{8}C^{13}C^{14}$	–78.4(5)	$C^{32}N^{27}C^{26}C^{22}$	–58.7(5)	$C^{26}N^{27}C^{32}C^{33}$	–62.6(5)
$C^{9}N^{8}C^{7}C^{3}$	171.1(4)	$C^{7}N^{8}C^{13}C^{14}$	157.3(4)	$C^{28}N^{27}C^{26}C^{22}$	171.5(4)	$N^{35}N^{34}C^{33}O^{2}$	–174.7(5)
$C^{13}N^{8}C^{7}C^{3}$	–66.8(5)	$N^{16}N^{15}C^{14}O^{1}$	176.0(5)	$C^{32}N^{27}C^{26}C^{31}$	–178.3(4)	$N^{35}N^{34}C^{33}C^{32}$	8.0(7)
$C^{9}N^{8}C^{7}C^{12}$	52.9(5)	$N^{16}N^{15}C^{14}C^{13}$	–5.7(7)	$C^{28}N^{27}C^{26}C^{31}$	52.0(5)	$N^{27}C^{32}C^{33}O^{2}$	–0.6(7)
$C^{13}N^{8}C^{7}C^{12}$	175.0(4)	$N^{8}C^{13}C^{14}O^{1}$	3.9(7)	$C^{21}C^{22}C^{26}N^{27}$	134.9(5)	$N^{27}C^{32}C^{33}N^{34}$	176.7(4)
$C^{4}C^{3}C^{7}N^{8}$	154.2(4)	$N^{8}C^{13}C^{14}N^{15}$	–174.3(4)	$C^{23}C^{22}C^{26}N^{27}$	–49.4(6)	$N^{34}N^{35}C^{36}C^{37}$	–176.8(4)
$C^{2}C^{3}C^{7}N^{8}$	–31.2(7)	$N^{15}N^{16}C^{17}C^{19}$	–2.9(7)	$C^{21}C^{22}C^{26}C^{31}$	–103.9(5)	$N^{34}N^{35}C^{36}C^{38}$	4.9(7)

NCH^b, J_{ba} 15.99), 3.11 br.d (1H, H^9_a, J 11.0), 3.40 br.d (1H, H^9_e, J 11.09), 6.88 d (1H, Ar, J 8.74), 7.35 d.d (1H, H^2, $J_{2,1}$ 5.03, $J_{2,3}$ 8.06), 7.41 d (1H, Ar, J 8.75), 7.71 s (1H, Ar), 7.86 d (1H, H^3, $J_{3,2}$ 7.85), 8.46 d (1H, H^1, $J_{1,2}$ 4.65), 8.53 s (1H, N=CH), 8.61 s (1H, H^4), 11.17 s (1H, OH), 11.31 s (1H, NH).

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