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Synthesis of Dithiocarbamine Derivatives on the Matrix of Cytisine, Anabasine and *d*-Pseudoephedrine Alkaloids. Crystalline Structure of *N*-Cytisine Dithiocarbamate Ammonium Salt

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Abstract—On the matrix of physiologically active alkaloids such as cytisine, anabasine, and *d*-pseudoephedrine the simplest alkaloid dithiocarbamates ammonium salts were synthesized by reaction with carbon disulfide in solution of ammonia in alcohol. Spatial structure of ammonium *N*-cytisine dithiocarbamate crystal hydrate was proved with X-ray diffraction analysis.

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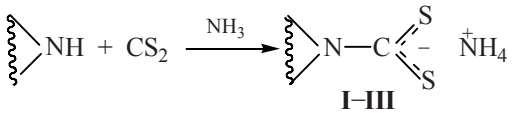
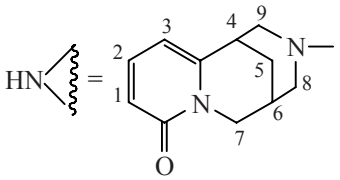
Among the wide class of sulfur-containing compounds an important role belongs to the acids dithiocarbamine derivatives. Interest in these compounds is caused by their great usability [1]. Acids dithiocarbamine derivatives possess antifungal, antibacterial, insecticide, fungicide and other practical important properties [2–5].

Synthesis of dithiocarbamates on the matrix of ephedrine alkaloids was reported earlier [6].

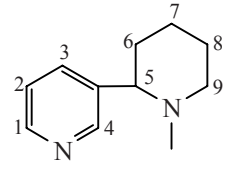
To continue the work on the synthesis of new dithiocarbamine derivatives on the basis of cytisine, anabasine, and *d*-pseudoephdrine alkaloids, we obtained the alkaloid dithiocarbamates simple ammonium salts. Dithiocarbamine derivatives **I–III** were produced by reaction of alkaloids with carbon disulfide in ethanol saturated with ammonia.



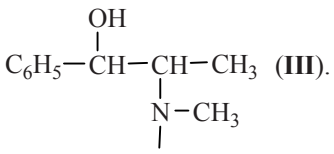
I–III



(**I**),



(**II**),



(**III**).

The target products yields are 60–70%. Compounds **I–III** synthesized are crystalline substances soluble in polar solvents. Composition and structure of **I–III** was proved by elemental analysis and ^{1}H NMR spectroscopy. Compound **I** forms crystal hydrate with three water molecules.

Aiming to confirm spatial structure and also to continue studying cytisine stereochemistry, we performed X-ray diffraction analysis of the obtained salt: ammonium *N*-cytisine dithiocarbamate crystalline hydrate **I**. General view of compound **I** is shown in Fig. 1.

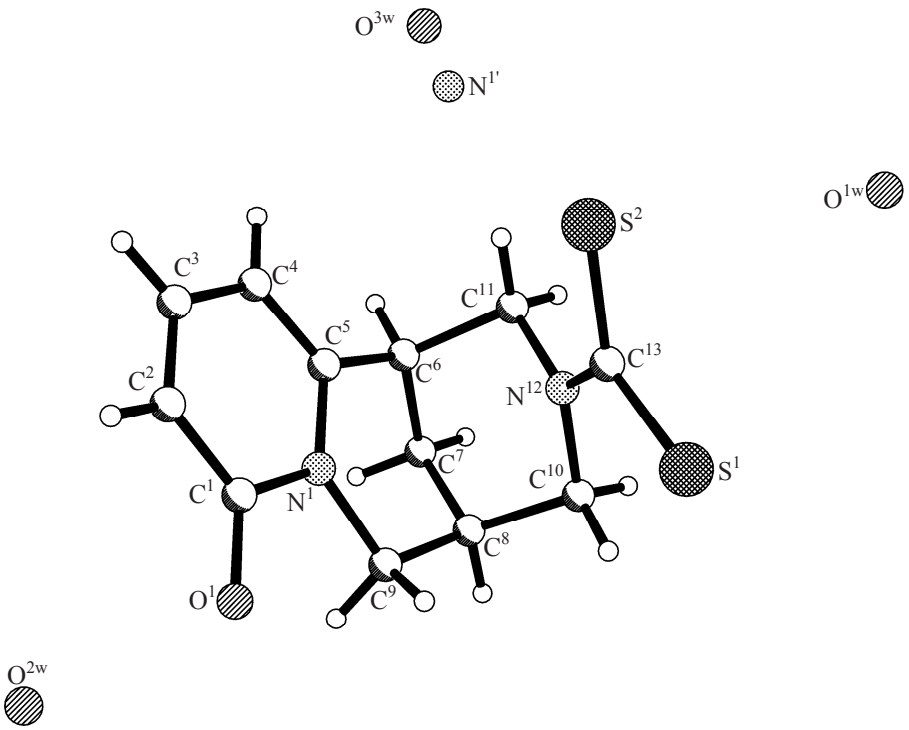


Fig. 1. Structure of ammonium *N*-cytisinodithiocarbamate crystallohydrate molecule **I**.

Bond lengths and bond angles in cytisine frame are close to the standard (Tables 1–3) [7] except for bond angles at N^{12} atom. Thus, in *N*-methylcytisine and *N*-cyanomethylcytisine molecules studied earlier [8, 9] coordination of the atom N^{12} is pyramidal (sum of bond angles is 335.7°, 334.0°), whereas in the molecule **I** coordination is planar-trigonal (sum of bond angles is 359.3°), same as in acrylic acid *N*-cytisinylamide molecule (sum of bond angles is 360°). Distinction in the nitrogen atom coordination in the *N*-methylcytisine and *N*-cyanomethylcytisine on the one hand, and in compound **I** and acrylic acid *N*-

Table 1. Bond lengths (*d*, Å) for molecule **I**

Bond	*d*, Å	Bond	*d*, Å
S^1–C^{14}	1.69(2)	C^6–C^7	1.45(2)
S^2–C^{14}	1.72(18)	C^7–C^8	1.51(2)
O^1–C^2	1.28(2)	C^7–C^{13}	1.58(2)
N^1–C^6	1.39(2)	C^8–C^9	1.51(3)
N^1–C^2	1.41(2)	C^9–C^{11}	1.55(2)
N^1–C^{10}	1.49(2)	C^9–C^{10}	1.56(2)
C^2–C^3	1.38(3)	C^{11}–N^{12}	1.51(2)
C^3–C^4	1.32(3)	N^{12}–C^{14}	1.35(2)
C^4–C^5	1.40(3)	N^{12}–C^{13}	1.46(2)
C^5–C^6	1.35(2)		

Table 2. Bond angles (ω, grad) for structure **I**

Angle	ω, deg	Angle	ω, deg
$C^6N^1C^2$	121.9(14)	$C^8C^7C^{13}$	112.0(15)
$C^6N^1C^{10}$	124.5(13)	$C^9C^8C^7$	103.5(14)
$C^2N^1C^{10}$	113.4(14)	$C^8C^9C^{11}$	114.3(14)
$O^1C^2C^3$	123.5(17)	$C^8C^9C^{10}$	109.6(15)
$O^1C^2N^1$	119.8(16)	$C^{11}C^9C^{10}$	111.0(14)
$C^3C^2N^1$	116.7(19)	$N^1C^{10}C^9$	112.7(13)
$C^4C^3C^2$	121.5(18)	$N^{12}C^{11}C^9$	107.9(13)
$C^3C^4C^5$	121.4(18)	$C^{14}N^{12}C^{13}$	123.1(15)
$C^6C^5C^4$	120.1(18)	$C^{14}N^{12}C^{11}$	122.5(16)
$C^5C^6N^1$	118.2(15)	$C^{13}N^{12}C^{11}$	113.9(14)
$C^5C^6C^7$	126.0(16)	$N^{12}C^{13}C^7$	106.4(13)
$N^1C^6C^7$	115.7(14)	$N^{12}C^{14}S^1$	119.7(14)
$C^6C^7C^8$	115.1(14)	$N^{12}C^{14}S^2$	120.2(15)
$C^6C^7C^{13}$	110.7(14)	$S^1C^{14}S^2$	120.1(10)

Table 3. Torsion angles (τ, grad) for molecule **I**

Angle	τ, deg	Angle	τ, deg
$C^6N^1C^2O^1$	179.7(1)	$C^{13}C^7C^8C^9$	62.6(2)
$C^{10}N^1C^2O^1$	3(2)	$C^7C^8C^9C^{11}$	–60.0(2)
$C^6N^1C^2C^3$	–2(3)	$C^7C^8C^9C^{10}$	65.3(2)
$C^{10}N^1C^2C^3$	–179.5(2)	$C^6N^1C^{10}C^9$	8(2)
$O^1C^2C^3C^4$	–178.2(2)	$C^2N^1C^{10}C^9$	–175.1(1)
$N^1C^2C^3C^4$	4(3)	$C^8C^9C^{10}N^1$	–39.8(2)
$C^2C^3C^4C^5$	–3(4)	$C^{11}C^9C^{10}N^1$	87.5(2)
$C^3C^4C^5C^6$	1(3)	$C^8C^9C^{11}N^{12}$	56.7(2)
$C^4C^5C^6N^1$	1(3)	$C^{10}C^9C^{11}N^{12}$	–67.9(2)
$C^4C^5C^6C^7$	–177.6(2)	$C^9C^{11}N^{12}C^{14}$	133.0(1)
$C^2N^1C^6C^5$	0(2)	$C^9C^{11}N^{12}C^{13}$	–55.6(2)
$C^{10}N^1C^6C^5$	176.7(2)	$C^{14}N^{12}C^{13}C^7$	–130.2(1)
$C^2N^1C^6C^7$	178.7(1)	$C^{11}N^{12}C^{13}C^7$	58.4(2)
$C^{10}N^1C^6C^7$	–4(2)	$C^6C^7C^{13}N^{12}$	66.4(2)
$C^5C^6C^7C^8$	–147.0(2)	$C^8C^7C^{13}N^{12}$	–63.5(2)
$N^1C^6C^7C^8$	34(2)	$C^{13}N^{12}C^{14}S^1$	–172.7(1)
$C^5C^6C^7C^{13}$	85(2)	$C^{11}N^{12}C^{14}S^1$	–2(2)
$N^1C^6C^7C^{13}$	–93.9(2)	$C^{13}N^{12}C^{14}S^2$	8(2)
$C^6C^7C^8C^9$	–65.0(2)	$C^{11}N^{12}C^{14}S^2$	178.2(1)

cytisinylamide on the other hand, is caused by mesomeric effect, i.e. electron density delocalization of S^1 and N^{12} atoms occurs. The latter leads to the increase of bond angles at the nitrogen atom, to lengthening of S=O (C=O) bond and to shortening of C–N bond relative to the standard values.

The presence of ammonium ion in the structure **I** out the field of electronegative charge of dithiocarbamate fragment is explained by the overall charge distribution between molecules in the crystal arrangement (Fig. 2).

Dihydropyridine ring in the structure **I** is planar within ±0.005Å accuracy, carbonyl atom O^1 lies practically in this plane (divergence from this plane is 0.06Å). Tetrahydropyridine ring $N^1C^5C^6C^7C^8C^9$ takes the conformation of distorted sofa with the bridgehead C^7 atom withdrawn from the mean plane of the other ring atoms by 0.76 Å. Piperidine ring takes the distorted chair conformation.

Thus, by reaction of cytisine, anabasine and *d*-pseudoephedrine with carbon disulfide the new alkaloid ammonium salts were first synthesized and characterized. Structure and composition of the thiocarbamate derivatives were confirmed with elemental analysis, X-ray diffraction and ^{1}H NMR spectroscopy data**.**

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Bruker DRX500 device (500 MHz) in DMSO–d_6 relative to internal TMS. Melting points were determined on a Boetius device. Reaction progress and purity of compounds obtained were monitored by TLC on Sorbfil plates, eluent benzene-acetone, 1:1, detecting agent was iodine vapor.

Single crystal X-ray diffraction analysis. The unit cell parameters and intensities of 2564 reflections were measured on a Bruker P4 automatic four-circle diffractometer (λMoK_α radiation, graphite monochromator). The crystals are monoclinic, *a* 24.20(3), *b* 9.047(1), *c* 7.454(1) Å, β 102.26(9)°, *V* 1595(4)Å^3, *Z* 4 ($C_{15}H_{20}N_2OS$), d_{calc}1.401 g cm^{-3}, space group C_2.

In the calculation we used 1499 independent reflections with $I > 2\sigma$. The structure was solved by the

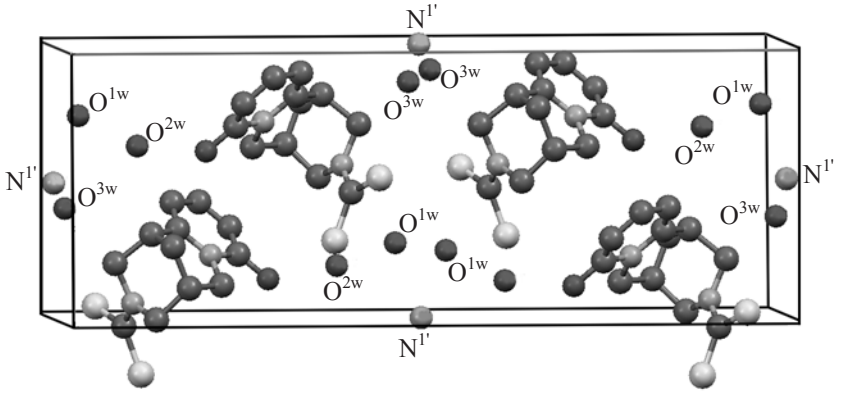


Fig. 2. Molecule **I** crystal arrangement.

direct method and refined by the least-squares method in the full-matrix anisotropic approximation for non-hydrogen atoms. All the H atoms are geometrically placed by the *rider* type, except the hydroxyl hydrogen atoms at the O^1 and O^2 atoms, which were refined in the anisotropic approximation. The final values of the divergence factors are R 0.1316 and wR_2 0.3364. All the calculations were performed using the SHELX-97 program package.

***N*-Cytisinodithiocarbamate ammonium salt crystalline hydrate (I).** 95% ethanol was saturated with ammonia for 3 h. To this solution was added 1 g (0.005 mol) of cytisine and then 0.4 g (0.005 mol) of carbon disulfide was added at gentle cooling (10°C). Further the reaction mixture was stirred at room temperature for 7 h. Then the solvent was removed and the residue was recrystallized from ethanol. Yield 1.03 g (73.6%), mp 169–170°C. ^{1}H NMR spectrum, δ , ppm: 2.00 m (2H, H^5), 2.54 br.s (1H, H^6), 3.35 br.s (1H, H^4), 3.50 m (2H, H^8), 3.60 m (2H, H^7), 4.20 m (2H, H^9), 6.15 d [1H, H^3, $J(H^3H^2)$ 6.85 Hz], 6.25 d [1H, H^1, $J(H^1H^2)$ 9.0 Hz], 7.35 d.d [1H, H^2, $J(H2H^3)$ 6.85 Hz]. Found, %: C 50.29; H 5.87; N 14.25; S 22.91. $C_{12}H_{17}N_3OS_2$ (anhydrous salt). Calculated, %: C 50.85; H 6.05; N 14.83; S 22.63.

***N*-Anabasinodithiocarbamate ammonium salt (II)** was prepared similarly from 1 g (0.006 mol) of anabasine and 0.45 g (0.006 mol) of carbon disulfide. Yield 0.95 g (62.1%), 175–176°C. ^{1}H NMR spectrum, δ, ppm: 1.37–2.05 m (6H, H^6, H^7, H^8), 2.60 m (2H, H^9), 3.04 t (1H, H^5), 7.47 d.d (1H, H^2), 8.0 d (1H, H^3), 8.50 s (1H, H^4), 8.71 d [1H, H^1, $J(H^1H^2)$ 5.0 Hz]. Found, %: C 52.14; H 6.94; N 16.81; S 25.50. $C_{11}H_{17}N_3S_2$. Calculated, %: C 51.73; H 6.71; N 16.45; S 25.11.

***N*-D-Pseudoephedrinodithiocarbamate ammonium salt (III)** was prepared similarly from 0.66 g (0.004 mol) of *d*-pseudoephedrine and 0.3 g (0.004 mol) of carbon disulfide. Yield 0.71 g (69.3%), mp 167–168°C. ^{1}H NMR spectrum, δ, ppm: 0.98 d (3H, CH_3–CH, J 5.1 Hz), 2.85 s (3H, N–CH_3), 3.55 m (1H, C*H*N), 4.75 d (1H, C*H*O, J 3.5 Hz), 7.28 m (5H, H_{Ar}). Found, %: C 50.68; H 6.54; N 10.31; S 25.13. $C_{11}H_{18}N_2OS_2$. Calculated, %: C 51.13; H 7.02; N 10.84; S 24.82.

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