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Synthesis and Structure of 2-Amino-1-benzyl-4-methylthio-6-oxo-*N*-phenyl-5-cyano-1,6-dihydropyridin-3-ylcarboxamide

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Abstract—Reaction of 3,3-bis(methylthio)-2-cyano-*N*-phenylacrylamide with *N*-benzyl-2-cyanoacetamide proceeds regiospecifically to give 2-amino-1-benzyl-4-methylthio-6-oxo-*N*-phenyl-5-cyano-1,6-dihydropyridin-3-ylcarboxamide. The structure of the latter was studied by means of XRD analysis.

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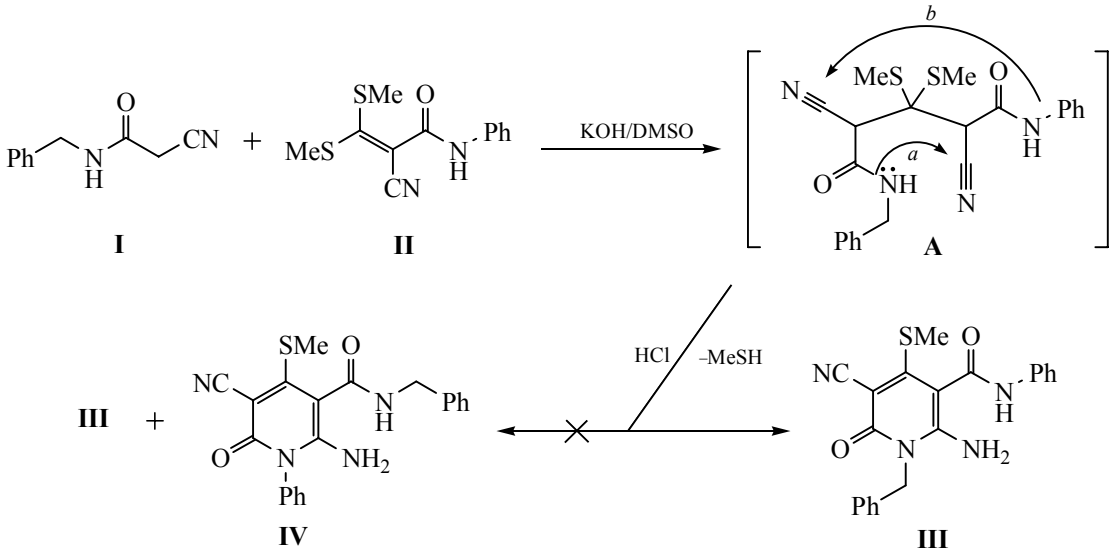
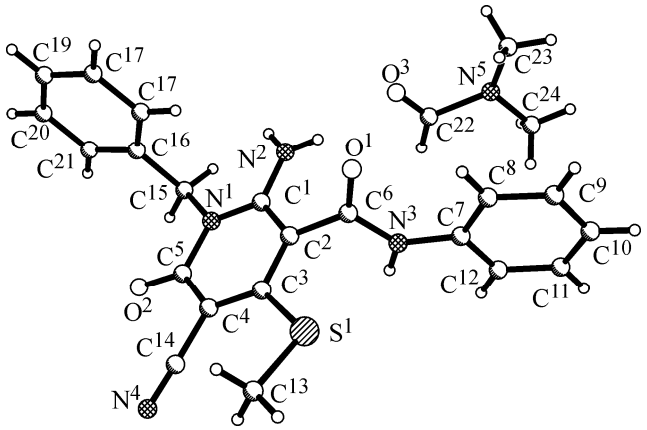
We have previously shown that the reaction of cyanoacetanilides with 3,3-bis(methylthio)-2-cyano-*N*-arylacrylamides proceeds to form isomeric *N*,1-diaryl-1,6-dihydropyridin-3-ylcarboxamides [1], the potential biologically active compounds [2–7].

The present study shows that the reaction of *N*-benzyl-2-cyanoacetamide **I** with 3,3-bis(methylthio)-2-cyano-*N*-phenylacrylamide **II** leads to the formation of a single reaction product, dihydropyridine **III**, rather than a mixture of isomers **III** and **IV**, as we expected.

Probably, the first stage of this reaction is the formation of intermediate **A**, in which the rotation around the single bonds followed by the heterocyclization via the *a* and *b* ways is possible. However, the regiospecific intramolecular heterocyclization proceeds regioselectively involving the nitrile group and the nitrogen atom of *N*-benzylcarbamoyl moiety (*a*). This can be attributed to the higher nucleophilicity of the latter, since the lone electron pair of the nitrogen atom in this case is not conjugated with the benzene ring.

A preliminary evaluation of the possible biological activity of the compound obtained was carried out using the PASS Inet program (Prediction of Activity Spectra for Substances) forecasting the possible types of biological activity, using the structural formula of a chemical compound to establish the structure–activity dependence [8]. By the virtual screening, the





General view of the structure **III** by the X-ray diffraction data.

compound **III** has the potential anti-asthma and anti-allergic activities.

The structure of **III** was confirmed by the X-ray diffraction analysis (see the figure, Tables 1, 2).

A crystal of compound **III** is a solvate involving DMF and ethanol. There is one solvent molecule per one molecule of dihydropyridine **III**. The position of the solvent occupies either DMF or ethanol, with a 0.75:0.25 probability.

The presence of six substituents in the dihydropyridine ring leads to a significant steric strain.

Table 1. Bond lengths (Å) in the structure **III**

Bond	Bond lenght, (Å)	Bond	Bond lenght, (Å)
S^1–C^3	1.7568(15)	C^7–C^{12}	1.389(2)
S^1–C^{13}	1.777(2)	C^8–C^9	1.387(2)
O^1–C^6	1.2196(17)	C^9–C^{10}	1.370(3)
O^2–C^5	1.2319(18)	C^{10}–C^{11}	1.370(3)
N^1–C^1	1.3728(18)	C^{11}–C^{12}	1.387(2)
N^1–C^5	1.4080(19)	C^{15}–C^{16}	1.508(2)
N^1–C^{15}	1.4780(18)	C^{16}–C^{17}	1.370(2)
N^2–C^1	1.3293(19)	C^{16}–C^{21}	1.378(2)
N^3–C^6	1.3474(18)	C^{17}–C^{18}	1.382(3)
N^3–C^7	1.4113(18)	C^{18}–C^{19}	1.361(3)
N^4–C^{14}	1.143(2)	C^{19}–C^{20}	1.356(3)
C^1–C^2	1.401(2)	C^{20}–C^{21}	1.388(3)
C^2–C^3	1.398(2)	O^3–C^{22}	1.201(4)
C^2–C^6	1.506(2)	N^5–C^{22}	1.315(3)
C^3–C^4	1.390(2)	N^5–C^{23}	1.453(3)
C^4–C^{14}	1.425(2)	N^5–C^{24}	1.479(3)
C^4–C^5	1.430(2)	O^4–C^{25}	1.432(5)
C^7–C^8	1.382(2)	C^{25}–C^{26}	1.536(5)

This is expressed in almost orthogonal orientation of the N^3–C^6–O^1 amide fragment relative to the heterocycle plane [torsion angle is $C^1C^2C^6O^1$ 75.0(2)°]. This leads to disrupting conjugation between these molecule fragments resulting in a lengthening of the C^2–C^6 bond to 1.506 (2) Å, compared with an average value (1.46 Å) [9]. The methylthio group is deviated out of the heterocycle plane and oriented to the cyano group [torsion angle $C^{13}S^1C^3C^4$ is –18.95(17)°]. Between these groups there are shortened intramolecular contacts $H^{13a}\cdots C^{14}$ 2.56 Å and $H^{13c}\cdots C^{14}$ 2.79 Å (the sum of van der Waals radii is 2.87 Å [10]), which are repulsive, as evidenced by a significant increase in the bond angles $S^1C^3C^4$ to 126.30(11)° and $C^3C^4C^{14}$ to 126.03(14)° compared to with the angles $S^1C^3C^2$ 114.31(11)° and $C^5C^4C^{14}$ 112.67(14)°, respectively. The phenyl substituent $C^{16}\cdots C^{21}$ is oriented perpendicularly to the dihydropyridine ring [torsion angle is $C^1N^1C^{15}C^{16}$ –95.93(16)°], giving rise to much shortened intramolecular contact $H^{2b}\cdots H^{15a}$ 1.88 Å (the sum of van der Waals radii is 2.32 Å [10]). In this case the aromatic ring is somewhat turned relative to the N^1–C^{15} bond [torsion angle $N^1C^{15}C^{16}C^{17}$ is 45.6(2)°].

A coplanarity of the amide N^3–C^6–O^1 fragment and phenyl ring $C^7\cdots C^{12}$ [torsion angle $C^6N^3C^7C^8$ is 6.3(3)°] causes the formation of an intramolecular hydrogen bond C^8–$H^8\cdots O^1$ (H···O 2.34 Å, CHO 120°).

In the crystal, the molecules form centrosymmetric dimers connected by the intermolecular hydrogen bond N^3–$H^3\cdots O^{2'}$ [2 – *x*, –*y*, –*z*] (H···O 2.16 Å, NHO 157°) and stacking interactions between the dihydropyridine fragments (the ring center is located at a distance of 3.49 Å from the C^4 atom of the neighboring molecules in the crystal). These dimers are linked into the chains along the crystallographic direction (100) by the hydrogen bonds N^2–$H^{2b}\cdots O^{1'}$ [*x*, 0.5 – *y*, –0.5 + *z*] (H···O 2.16 Å, NHO 159°). Also, a solvent molecule is bound with compound **III** molecule via the hydrogen bond N^2–$H^{2a}\cdots O(^{3'})$ [*x*, 0.5 –*y*, –0.5 + *z*] (H···O 1.97 Å, NHO 158°) (DMF molecule), N^2–$H^{2a}\cdots O^{4'}$ [*x*, 0.5 – *y*, –0.5 + *z*] (H···O 2.05 Å, NHO 146°) (ethanol molecule).

EXPERIMENTAL

The melting point of compound **III** was determined on a Koeffler block. The ^{1}H NMR spectrum was recorded on a Varian Mercury-500 instrument (499.9601 MHz) in DMSO-d_6 solution (internal reference TMS). The mass spectrum was registered on

Table 2. Bond angles (deg) in the structure **III**

Bond angle	ω	Bond angle	ω
$C^3S^1C^{13}$	109.67(9)	$C^8C^7C^{12}$	119.53(14)
$C^1N^1C^5$	122.30(12)	$C^8C^7N^3$	124.44(14)
$C^1N^1C^{15}$	122.29(12)	$C^{12}C^7N^3$	116.03(14)
$C^5N^1C^{15}$	115.40(12)	$C^7C^8C^9$	119.17(16)
$C^6N^3C^7$	129.50(13)	$C^{10}C^9C^8$	121.34(17)
$N^2C^1N^1$	118.60(13)	$C^{11}C^{10}C^9$	119.52(16)
$N^2C^1C^2$	121.79(13)	$C^{10}C^{11}C^{12}$	120.24(17)
$N^1C^1C^2$	119.61(13)	$C^{11}C^{12}C^7$	120.18(16)
$C^3C^2C^1$	120.53(13)	$N^4C^{14}C^4$	175.3(2)
$C^3C^2C^6$	120.74(13)	$N^1C^{15}C^{16}$	113.12(12)
$C^1C^2C^6$	118.68(12)	$C^{17}C^{16}C^{21}$	118.15(16)
$C^4C^3C^2$	119.37(13)	$C^{17}C^{16}C^{15}$	122.46(14)
$C^4C^3S^1$	126.30(11)	$C^{21}C^{16}C^{15}$	119.37(15)
$C^2C^3S^1$	114.31(11)	$C^{16}C^{17}C^{18}$	121.18(18)
$C^3C^4C^{14}$	126.03(14)	$C^{19}C^{18}C^{17}$	120.1(2)
$C^3C^4C^5$	121.24(13)	$C^{20}C^{19}C^{18}$	119.71(18)
$C^{14}C^4C^5$	112.67(14)	$C^{19}C^{20}C^{21}$	120.5(2)
$O^2C^5N^1$	118.72(14)	$C^{16}C^{21}C^{20}$	120.3(2)
$O^2C^5C^4$	124.37(14)	$C^{22}N^5C^{23}$	126.7(3)
$N^1C^5C^4$	116.91(13)	$C^{22}N^5C^{24}$	116.2(3)
$O^1C^6N^3$	124.37(14)	$C^{23}N^5C^{24}$	116.5(3)
$O^1C^6C^2$	122.34(13)	$O^3C^{22}N^5$	123.6(4)
$N^3C^6C^2$	113.27(12)	$O^4C^{25}C^{26}$	109.9(5)

a MX-1321 instrument (70 eV) with the direct injection of the sample into the ion source. The reaction progress and the compound individuality were monitored by TLC using Silufol UV-254 plates, eluting with an acetone–hexane mixture (3:5) and detecting with iodine vapors and UV irradiation.

The crystals of compound **III** are monoclinic, $C_{21}H_{18}N_4O_2S \cdot 0.75C_3H_7NO \cdot 0.25C_2H_5OH$, at 298 K: *a* 12.8036(3), *b* 16.9563(4), *c* 10.5658(3) Å; β 101.387(3)°, *V* 2248.70(10) Å^3, *M* 456.54, *Z* 4, space group $P2_1/c$, d_{calc} 1.349 g cm^{-3}, μ(MoK_α) 0.18 mm^{-1}, *F*(000) 962. The unit cell parameters and intensities of 14186 reflections (7367 independent, R_{int} 0.019) were measured on a Xcalibur 3 automatic four-circle diffractometer (MoK_α, graphite monochromator, CCD detector, ω-scanning, $2\theta_{max}$ 65.06°).

The structure was solved by the direct method using a SHELX-97 software package [11]. The positions of the hydrogen atoms were calculated geometrically and refined in a *rider* model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for the CH_3- and OH-groups and n = 1.2 for the other hydrogen atoms). The structure was refined with respect to F^2 by a full-matrix least-square method using anisotropic approximation for non-hydrogen atoms to wR_2 0.137 for 7367 reflections [R_1 0.053 for 4083 reflections with $F > 4\sigma(F)$, S 0.97]. In refining, on the bond lengths and 1,3-distances in the disordered solvent molecules the limits were imposed in accordance with the average values [10] with an accuracy of 0.005 Å. The bond lengths and angles are given in Tables 1 and 2, respectively.

2-Amino-1-benzyl-4-methylthio-6-oxo-*N*-phenyl-5-cyano-1,6-dihydropyridin-3-ylcarboxamide (III). To a suspension of 0.56 g (10 mmol) of KOH in 10 ml of DMSO was added 10 mmol of *N*-benzyl-2-cyanoacetamide **I**. The mixture was stirred for 15 min. After adding 10 mmol of 3,3-bis(methylthio)-2-cyano-*N*-phenylacrylamide **II**, the mixture was stirred for 1 h, heated at 80°C for 15 min, left standing for 2 h, poured into cold water, and acidified with an equimolar amount of 30% aqueous HCl. The resulting precipitate was filtered off and washed with water. The crystals of compound **III** were grown from a DMF–EtOH mixture. Yield 2.88 g (74%), mp 235–240°C. IR spectrum, ν, cm^{-1}: 3343, 3450 (NH_2), 2209 (CN), 1650, 1673 (CO). ^{1}H NMR spectrum, δ, ppm: 2.55 s (3H, SCH_3), 5.53 s (2H, CH_2), 7.11 t (1H, H_{Ar}, J 7.2 Hz), 7.23 d (2H, H_{Ar}, J 8.0 Hz), 7.31–7.39 m (5H, H_{Ar}), 7.67 br.s (2H, NH_2), 7.69 d (2H, H_{Ar}, J 8.5 Hz), 10.45 br.s (1H, NH). Mass spectrum (EI, 70 eV), m/z (I_{rel}, %): 390 (0.6) $[M]^+$, 298 (0.9) $[M - PhNH_2]^+$, 271 (18.5) $[M - PhNHCO]^+$, 167 (1.7), 119 (20.2) $[PhN{=}C{=}O]^+$, 91 (100) $[PhCH_2]^+$. Found, %: C 64.81; H 4.77; N 14.15. $C_{21}H_{18}N_4O_2S$. Calculated, %: C 64.60; H 4.65; N 14.35.

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