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SYNTHESIS AND CRYSTAL STRUCTURE OF 5-AMINO-4-CYANO-8-ISOBUTYL-7-ISOPROPYL-6-THIOCARBAMOYL-2-AZABICYCLO-[2.2.2]OCT-5-EN-3-THIONE

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5-Amino-4-cyano-8-isobutyl-7-isopropyl-6-thiocarbamoyl-2-azabicyclo[2.2.2]oct-5-en-3-thione was synthesized by the condensation of isovaleryl aldehyde with cyanothioacetamide. The structure of the product was established by X-ray crystallography.

Keywords: 5-amino-4-cyano-8-isobutyl-7-isopropyl-6-thiocarbamoyl-2-azabicyclo[2.2.2]oct-5-en-3-thione, isovaleryl aldehyde, cyanothioacetamide, condensation, X-ray crystallography.

Arylmethylencyanothioacetamides, prepared by the Knoevenagle reaction [1-4], have been used successfully for several decades by synthetic chemists to prepare sulfur containing heterocyclic compounds, dominated by functionally substituted pyridinethiones [5-7]. However alkylmethylenecyanothioacetamides have not yet been studied [5].

With the objective of preparing and studying the properties of alkylmethylenecyanothioacetamides we have studied the condensation of isovaleryl aldehyde (**1**) with cyanothioacetamide (**2**) in ethanol at 20°C in the presence of morpholine. The product of the reaction was 5-amino-4-cyano-8-isobutyl-7-isopropyl-6-thiocarbamoyl-2-azabicyclo[2.2.2]oct-5-en-3-thione (**3**), isostructural with 5-amino-4,6-dicyano-3-dicyanomethylene-1,8,8-trimethyl-2-azabicyclo[2.2.2]oct-5-ene which we prepared previously by the reaction of mesityl oxide with malonitrile [8].

The probable mechanism for the formation of the tricyclic system of **3** is discussed below.

Initially the alkene **4** is formed *via* the Knoevenagle reaction. It is then dimerized *via* the Michael reaction which includes formation of the carbanion **5** and the corresponding adduct **6**. The latter is cyclized to the substituted piperidinethione **7**, which undergoes further transformations under the influence of the base *via* the anions **8** and **9** into the tricyclic imine **10**, which is stabilized in its turn in the form of the structure **3**. We note that arylmethylenecyanothioacetamides are dimerized *via* a $[2_s + 4_s]$ cycloaddition into 3,4-dihydro-2H-thiopyranes [4].

The structure of compound **3** was established by X-ray crystallography. The basic geometric parameters of the molecule of **3** are given in Table 1 and its general shape is shown in Fig. 1.

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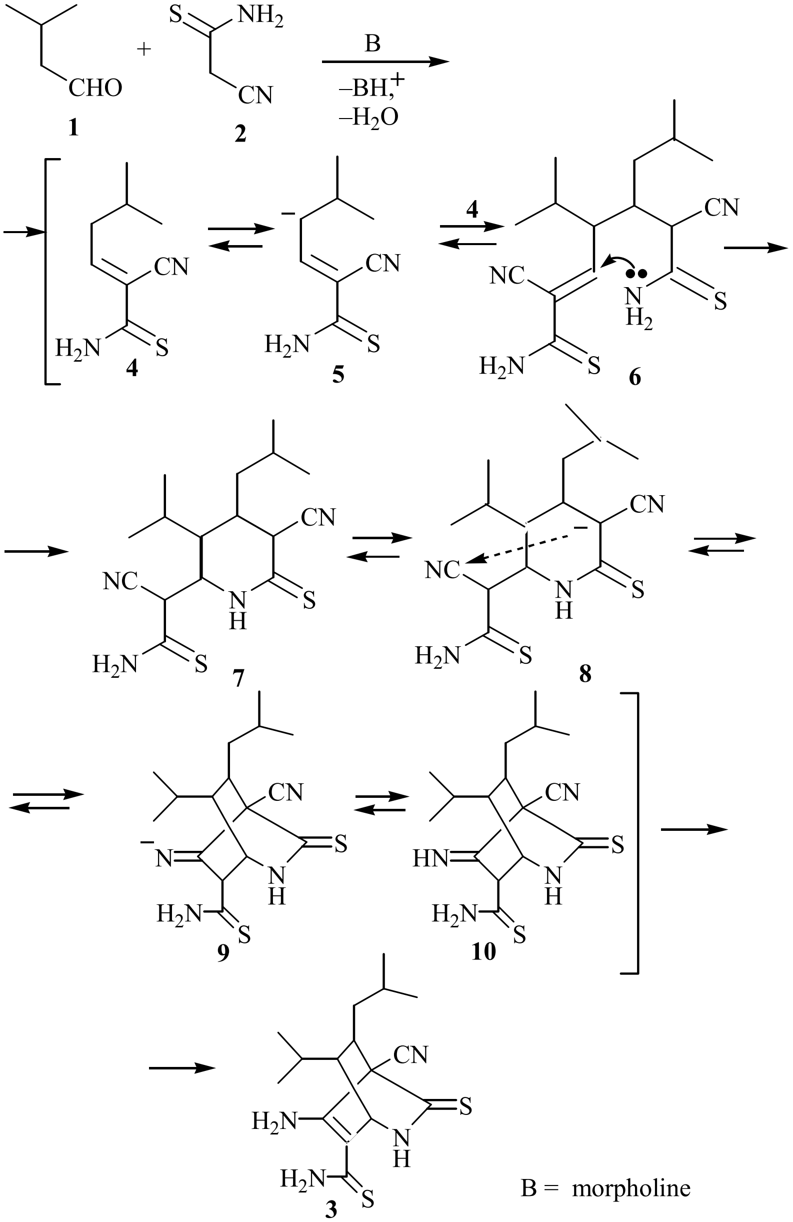

B = morpholine

In the central tricyclic skeleton all three heterocycles $N_{(1)}C_{(1\text{-}5)}$, $C_{(2\text{-}5,7,8)}$, and $N_{(1)}C_{(1,2,8,7,5)}$ have the conformation of a practically undistorted twist-boot. Modified Cremer–Pople parameters [9] for these heterocycles are S = 0.99, 1.00, and 0.93, θ = 89.49, 86.99, and 88.15°, ψ = 4.90, 3.07, and 2.65° (the ideal twists-boot correspond to the parameters $\theta = 90.0°$ and $\psi = 60\times n$, where $n = 0, 1, 2 \ldots$ [9]). Atoms $N_{(1)}$, $N_{(3)}$, and $N_{(4)}$ have planar trigonal configurations with the sum of the bond angles for each equal to 360° within the limits of experimental error. The grouping $S_{(1)}N_{(3)}C_{(9)}C_{(5)}C_{(7)}C_{(8)}N_{(4)}C_{(2)}$ is planar (maximum divergence of the atoms from the mean squared plane does not exceed 0.022 Å). The amino groups $N_{(3)}H_2$ and $N_{(4)}H_2$ are twisted out of this plane by only 14.4 and 4.2° respectively. The distribution of bond lengths in the group indicates notable delocalisation of electron density, caused by n-π and π-π conjugation. For example the bonds $N_{(3)}$–$C_{(9)}$ 1.328(4) Å and $N_{(4)}$–$C_{(8)}$ 1.327(4) Å are considerably shortened compared with the standard single bond length $C(sp^2)$–$N(sp^2)$ of 1.45 Å [10, 11]. Similarly the bond $C_{(7)}$–$C_{(9)}$ 1.423(4) Å is shorter than the value of 1.476 Å typical for a $C(sp^2)$–$C(sp^2)$bond [12]. On the other hand the length of the $C_{(7)}$=$C_{(8)}$ bond of 1.368(4) Å is much

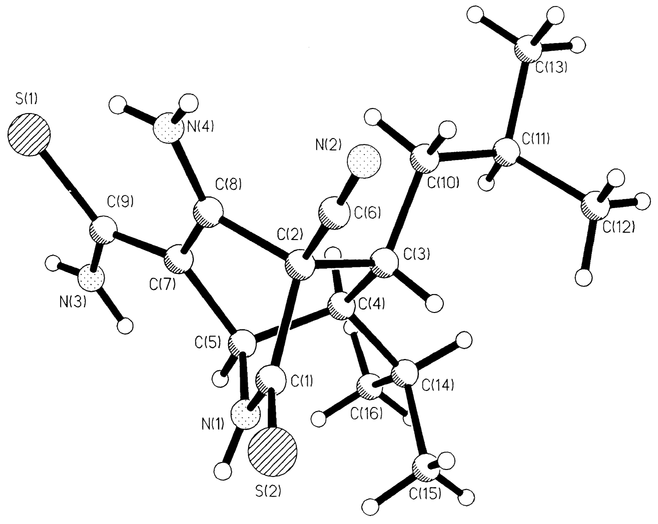

Fig. 1. General view of the molecule of **3** and numbering of the atoms.

longer than the statistical average value for a carbon-carbon double bond (1.33 Å [11, 12]) and is approximately the same as the bond length in aromatic compounds (1.39 Å). Note that the $C_{(9)}=S_{(1)}$ is longer by 0.055 Å than the $C_{(1)}=S_{(2)}$ bond.

In the crystal molecules of compound **3** appear as centrosymmetric dimers *via* the hydrogen bonds $S_{(1)}\cdots H_{(1)}$–$N_{(1)}$ (S···N 3.279(3), S···H 2.52(3), $N_{(1)}$–$H_{(1)}$ 0.83(3) Å, $S_{(1)}\cdots H_{(1)}$–$N_{(1)}$ 152(2)°). Packing of the molecules in the crystal is shown in Fig. 2

TABLE 1. Basic Bond Lengths (*d*) and Bond Angles (ω) in the Molecule of Compound **3**

Bond	*d*, Å	Angle	ω, deg.
$S_{(1)}$–$C_{(9)}$	1.706(3)	$C_{(1)}$–$N_{(1)}$–$C_{(5)}$	118.2(3)
$S_{(2)}$–$C_{(1)}$	1.651(3)	$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	108.9(2)
$N_{(1)}$–$C_{(1)}$	1.308(4)	$N_{(1)}$–$C_{(1)}$–$S_{(2)}$	126.4(2)
$N_{(1)}$–$C_{(5)}$	1.467(4)	$C_{(2)}$–$C_{(1)}$–$S_{(2)}$	124.6(2)
$N_{(2)}$–$C_{(6)}$	1.140(4)	$C_{(8)}$–$C_{(2)}$–$C_{(1)}$	106.6(2)
$N_{(3)}$–$C_{(9)}$	1.328(4)	$C_{(8)}$–$C_{(2)}$–$C_{(3)}$	108.2(2)
$N_{(4)}$–$C_{(8)}$	1.327(4)	$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	107.0(2)
$C_{(1)}$–$C_{(2)}$	1.537(4)	$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	108.2(2)
$C_{(2)}$–$C_{(3)}$	1.580(4)	$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	107.7(2)
$C_{(2)}$–$C_{(6)}$	1.462(5)	$N_{(1)}$–$C_{(5)}$–$C_{(7)}$	108.0(2)
$C_{(2)}$–$C_{(8)}$	1.535(4)	$N_{(1)}$–$C_{(5)}$–$C_{(4)}$	107.8(2)
$C_{(3)}$–$C_{(4)}$	1.542(4)	$C_{(4)}$–$C_{(5)}$–$C_{(7)}$	108.2(2)
$C_{(4)}$–$C_{(5)}$	1.542(4)	$N_{(2)}$–$C_{(6)}$–$C_{(2)}$	174.6(3)
$C_{(5)}$–$C_{(7)}$	1.513(4)	$C_{(5)}$–$C_{(7)}$–$C_{(8)}$	110.9(2)
$C_{(7)}$–$C_{(8)}$	1.368(4)	$C_{(2)}$–$C_{(8)}$–$C_{(7)}$	113.0(2)
$C_{(7)}$–$C_{(9)}$	1.423(4)	$S_{(1)}$–$C_{(9)}$–$N_{(3)}$	117.1(2)
		$S_{(1)}$–$C_{(9)}$–$C_{(7)}$	124.5(2)
		$N_{(3)}$–$C_{(9)}$–$C_{(7)}$	118.4(3)

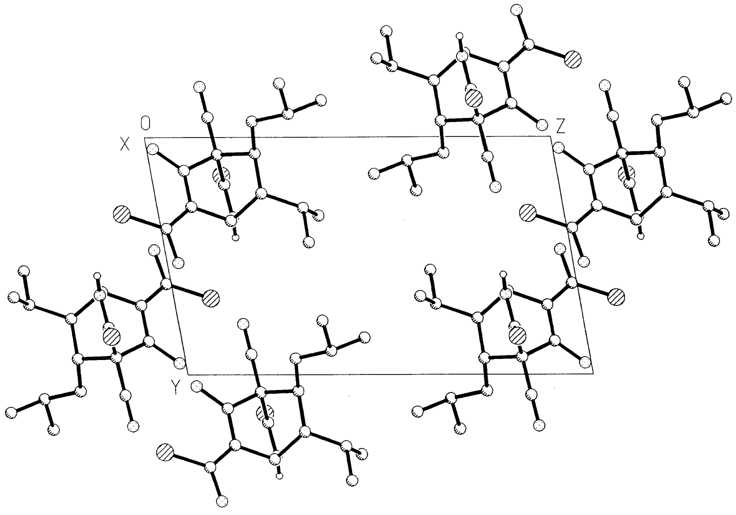

Fig. 2. Crystal packing (projection *bc*) of compound **3**.
Hydrogen bonds are shown by broken lines.

TABLE 2. Atom Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters U_{eq} ($\times 10^3$) in the Structure of **3**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
1	2	3	4	5
$S_{(1)}$	1214(1)	6785(1)	906(1)	46(1)
$S_{(2)}$	7944(1)	8398(1)	-1717(1)	54(1)
$N_{(1)}$	5798(3)	6629(3)	-1811(2)	35(1)
$N_{(2)}$	4200(4)	12125(3)	-1582(2)	54(1)
$N_{(3)}$	2220(4)	4727(3)	-267(2)	44(1)
$N_{(4)}$	2470(4)	9516(4)	-155(2)	43(1)
$C_{(1)}$	5999(4)	8016(3)	-1748(2)	35(1)
$C_{(2)}$	4112(4)	9262(3)	-1700(2)	32(1)
$C_{(3)}$	3072(4)	9322(3)	-2633(2)	34(1)
$C_{(4)}$	2887(4)	7638(3)	-2616(2)	34(1)
$C_{(5)}$	3951(4)	6497(4)	-1747(2)	32(1)
$C_{(6)}$	4243(4)	10850(4)	-1640(2)	39(1)
$C_{(7)}$	3053(4)	7083(3)	-840(2)	30(1)
$C_{(8)}$	3118(4)	8601(3)	-821(2)	32(1)
$C_{(9)}$	2221(4)	6166(3)	-127(2)	33(1)
$C_{(11)}$	231(4)	10998(4)	-3632(2)	50(1)
$C_{(10)}$	1265(4)	10675(4)	-2712(2)	39(1)
$C_{(12)}$	1282(7)	11548(7)	-4511(3)	76(1)
$C_{(13)}$	-1617(6)	12255(6)	-3546(4)	79(1)
$C_{(14)}$	3306(5)	7032(4)	-3580(2)	48(1)
$C_{(15)}$	5274(7)	6706(7)	-3927(3)	84(2)
$C_{(16)}$	2650(9)	5594(6)	-3565(3)	83(2)
$H_{(1)}$	6688(40)	5802(36)	-1788(20)	37(9)
$H_{(3.1)}$	2774(40)	4343(35)	-788(23)	48(10)
$H_{(3.2)}$	1787(37)	4222(34)	124(21)	27(9)
$H_{(4.1)}$	2636(41)	10378(41)	-176(22)	45(11)

TABLE 2 (continued)

1	2	3	4	5
$H_{(4.2)}$	1936(50)	9068(46)	320(28)	77(14)
$H_{(3)}$	3808(35)	9556(30)	-3139(20)	33(8)
$H_{(4)}$	1652(37)	7725(30)	-2477(18)	30(7)
$H_{(5)}$	4071(30)	5408(31)	-1753(16)	18(6)
$H_{(10.1)}$	1473(36)	11656(37)	-2662(19)	42(9)
$H_{(10.2)}$	471(36)	10446(31)	-2168(21)	38(8)
$H_{(11)}$	33(38)	9964(37)	-3736(20)	49(9)
$H_{(12.1)}$	599(58)	11702(51)	-5091(34)	108(15)
$H_{(12.2)}$	2473(62)	10717(55)	-4604(30)	109(16)
$H_{(12.3)}$	1557(56)	12502(54)	-4373(29)	97(16)
$H_{(13.1)}$	-1302(56)	13358(55)	-3470(30)	106(15)
$H_{(13.2)}$	-2303(58)	12492(51)	-4124(33)	103(15)
$H_{(13.3)}$	-2285(57)	11987(50)	-2981(32)	100(16)
$H_{(14)}$	2560(36)	7922(33)	-4063(20)	39(8)
$H_{(15.1)}$	5339(53)	6408(47)	-4524(31)	94(14)
$H_{(15.2)}$	5753(77)	7648(72)	-3862(40)	165(26)
$H_{(15.3)}$	6020(61)	5720(56)	-3533(32)	108(17)
$H_{(16.1)}$	2734(52)	5287(46)	-4201(31)	93(13)
$H_{(16.2)}$	3367(53)	4717(49)	-3148(30)	89(14)
$H_{(16.3)}$	1360(64)	5779(54)	-3266(35)	113(19)

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker WP-100 SY (100 MHz) machine. IR spectra of nujol mulls were recorded on an IRS-29 machine. Melting points were determined on a Kofler block. The course of the reaction was monitored by TLC on Silufol UV-254 plates with 3:5 acetone–hexane eluent. Iodine vapor was used to reveal the spots.

X-ray Crystallographic Analysis of a Monocrystal of Compound 3 with linear dimensions 0.30 × 0.34 × 0. 44 mm was carried out at room temperature on an automatic four-circle Enraf-Nonius CAD-4 diffractometer (λMo$K\alpha$ radiation, graphite monochromator, ratio of scanning rates $\omega/2\theta$ 1.2, θ_{max} 24°, segment of sphere $0 \leq h \leq 7$, $-9 \leq k \leq 9$, $-16 \leq l \leq 16$). To determine the unit cell parameters and the orientation matrix 22 reflexions with $12 < \theta < 13°$ were used. In all 2322 reflexions were measured of which 2081 were independent (average *R*-factor 0.022). Crystals of compound **3** are triclinic, $a = 7.749(1)$, $b = 8.873(9)$, $c = 14.148(3)$ Å, $\alpha = 79.28(5)$, $\beta = 85.80(2)$, $\gamma = 71.65(5)°$; $V = 907.1(9)$ Å^3; $Z = 2$; $d_{calc} = 1.232$ g/cm^3; $\mu = 0.296$ mm^{-1}; $F(000) = 360$; space group *P*-1 (No. 2). The structure was solved by the direct method and refined by least squares in the full matrix anisotropic approximation using the SHELXS and SHELXL93 programs [13, 14]. In the refinement 1688 reflexions were used (295 parameters refined, number of reflexions per parameter 5.72, weighting scheme $\omega = 1/[\sigma^2(F_0^2) + (0.044P)^2 + 0.262]$, where $P = (F_0^2 + 2F_c^2)/3$. The ratio of the maximum (average) shift in error in the last cycle 0.001(0). Correction for anomalous dispersion was included but absorption by the crystal was not calculated. All hydrogen atoms were found from electron density difference syntheses and were refined isotropically. The final residual factors were $R1(F)$ 0.0356 and $R_w(F^2)$ 0.0836, *GOOF* 1.080. The residual electron densities in the Fourier difference series were 0.20 and -0.14 *e*/Å^3. Atomic coordinates are shown in Table 2.

5-Amino-4-cyano-8-isobutyl-7-isopropyl-6-thiocarbamoyl-2-azabicyclo[2.2.2]oct-5-en-3-thione (3). A mixture of cyanothioacetamide (**2**) (1 g, 10 mmol), isovaleryl aldehyde (**1**) (1.1 ml, 10 mmol), and morpholine (0.9 ml, 10 mmol) in ethanol (15 ml) was stirred at 20°C for 1 h and then kept under the same conditions for

48 h. The precipitate of yellow cubes of product **3** was filtered off and washed with ethanol and hexane. Yield 1.2 g (71%); mp 228-230°C. IR spectrum (thin layer), ν, cm^{-1}: 3400, 3512 (NH, NH_2), 1635 (δNH_2), 2250 (C≡N). ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 11.6 (1H, d, *J* = 5.3, NH), 9.0 (2H, br. s, NH_2), 8.2 (2H, br. s, NH_2), 4.9 (1H, d, *J* = 5.3, $C_{(1)}H$), 0.9-1.8 (18H, m, H_{aliph}). Found, %: C 56.85; H 7.03; N 15.12. $C_{16}H_{24}N_4S_2$. Calculated, %: C 57.11; H 7.19; N 15.29.

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