Chemistry of Heterocyclic Compounds, Vol. 37, No. 8, 2001

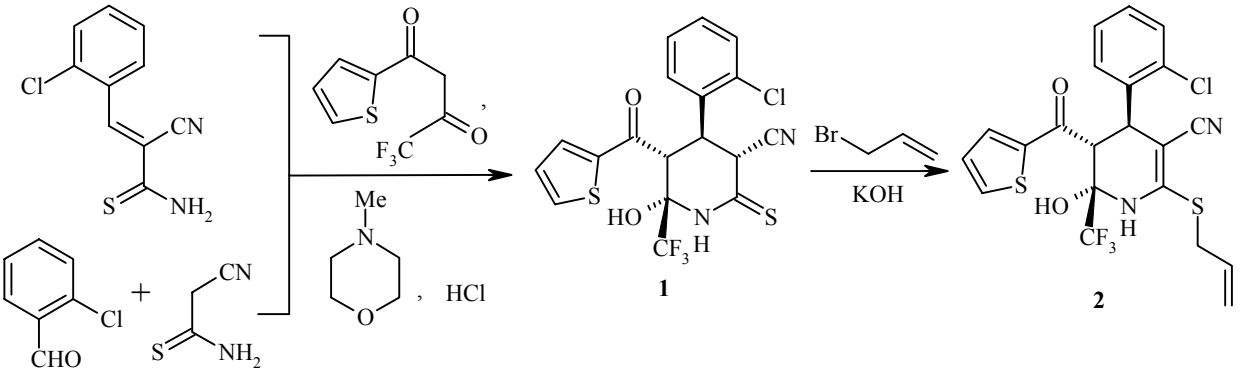
SYNTHESIS AND ALKYLATION OF 4-(2-CHLOROPHENYL)-3-CYANO-6-HYDROXY-5-(2-THIENOYL)-6-TRIFLUOROMETHYLPIPERIDIN-2-THIONE

S. G. Krivokolysko[1], V. D. Dyachenko[1], E. B. Rusanov[2], and V. P. Litvinov[3]

4-(2-Chlorophenyl)-3-cyano-6-hydroxy-5-(2-thienoyl)-6-trifluoromethylpiperidin-2-thione, which was used for the synthesis of 2-allylthio-4-(2-chlorophenyl)-3-cyano-6-hydroxy-5-(2-thienoyl)-6-trifluoromethyl-1,4,5,6-tetrahydropyridine, was obtained by the reaction of 2-thienoyltrifluoroacetone with 2-chlorophenylphenylmethylenecyanothioacetamide or with a mixture of 2-chlorobenzaldehyde and cyanothioacetamide in the presence of N-methylmorpholine. The molecular and crystal structure of the piperidinthione have been established by X-ray crystallography.

Keywords: piperidinthione, tetrahydropyridine, 2-thienoyltrifluoroacetone, 2-chlorobenzaldehyde, 2-chlorophenylmethylenecyanothioacetamide, cyanothioacetamide, alkylation, X-ray crystallography.

In a continuation of our search for suitable methods for the preparation of the poorly studied 3-cyanopiperidin-2-thiones [1], and taking into account the physiological activity of fluorine containing heterocyclic compounds [2], we have carried out a regioselective synthesis of 4-(2-chlorophenyl)-3-cyano-6-hydroxy-5-(2-thienoyl)-6-trifluoromethylpiperidin-2-thione (**1**) in the form of its stable ethanol solvate based on 2-chlorophenylmethylenecyanothioacetamide and 2-thienoyltrifluoroacetone in the presence of N-methylmorpholine. Product (**1**) was also prepared independently by the cascade interaction of 2-chlorobenzaldehyde, cyanothioacetamide, and 2-thienoyltrifluoroacetone.



[1] Taras Shevchenko Lugansk State Pedagogical University, Lugansk 34801. Ukraine; e-mail: kgb@gpi.lugans.ua. [2] Institute of Organic Chemistry, Ukraine National Academy of Sciences, Kiev 253660, Ukraine. [3] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913, Russia. e-mail: vpl@cacr.ioc.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, 1076-1081, August, 2001. Original article submitted May 18, 1999. Revised version submitted January 7, 2000.

In the ^{1}H NMR spectrum of compound **1** the signals of protons 3-H, 4-H, and 5-H appear as a multiplet in the 4.8 ppm region which makes it difficult to determine its structure. Consequently the molecular structure of thione **1** was determined by X-ray crystallography.

An overall view of molecule **1** is given in Fig.1, the main geometric parameters cited in Table 1 (the atomic numbering is not according to IUPAC rules, which is used in the cited ^{1}H NMR spectrum). The central piperidine cycle is far from planar: the deviation of atoms from the least squared plane is as much as 0.33 Å. The calculated Cramer-Pople parameters [3] (S =0.91, θ = 19.9, Ψ = 29.7) indicate that this heterocyclic ring has

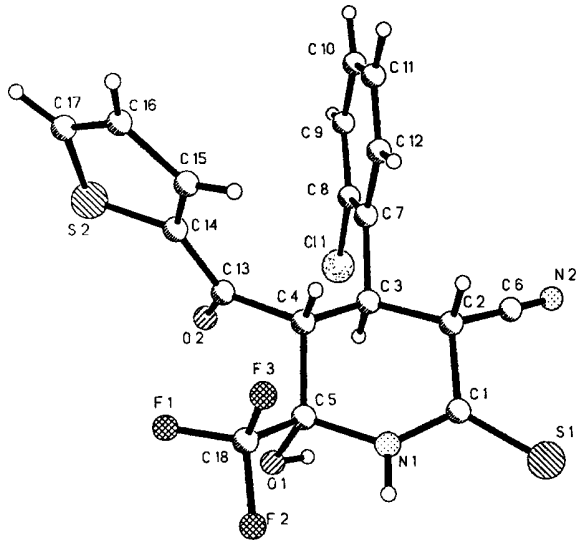


Fig. 1. General view of molecule **1** with numbering of the atoms.

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

Bond	*d*, Å	Angle	ω, deg.
$Cl_{(1)}$–$C_{(8)}$	1.748(7)	$C_{(1)}$–$N_{(1)}$–$C_{(5)}$	128.5(5)
$S_{(1)}$–$C_{(1)}$	1.632(6)	$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	115.5(5)
$O_{(1)}$–$C_{(5)}$	1.381(6)	$N_{(1)}$–$C_{(1)}$–$S_{(1)}$	122.6(4)
$O_{(2)}$–$C_{(13)}$	1.213(6)	$C_{(2)}$–$C_{(1)}$–$S_{(1)}$	121.8(4)
$N_{(1)}$–$C_{(1)}$	1.334(6)	$C_{(6)}$–$C_{(2)}$–$C_{(1)}$	110.4(4)
$N_{(1)}$–$C_{(5)}$	1.459(6)	$C_{(6)}$–$C_{(2)}$–$C_{(3)}$	109.8(4)
$C_{(1)}$–$C_{(2)}$	1.511(7)	$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	114.6(4)
$C_{(2)}$–$C_{(6)}$	1.469(8)	$C_{(7}$ –$C_{(3)}$–$C_{(2)}$	110.9(4)
$C_{(2)}$–$C_{(3)}$	1.552(6)	$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	106.5(4)
$C_{(3)}$–$C_{(7)}$	1.513(8)	$C_{(13)}$–$C_{(4)}$–$C_{(3)}$	108.0(4)
$C_{(3)}$–$C_{(4)}$	1.542(7)	$C_{(13)}$–$C_{(4)}$–$C_{(5)}$	112.5(4)
$C_{(4)}$–$C_{(13)}$	1.538(7)	$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	109.0(4)
$C_{(4)}$–$C_{(5)}$	1.545(7)	$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	109.0(4)
$C_{(5)}$–$C_{(18)}$	1.535(8)	$O_{(1)}$–$C_{(5}$ –$N_{(1)}$	110.4(5)
$C_{(7)}$–$C_{(3)}$–$C_{(4)}$	111.9(4)	$O_{(1)}$–$C_{(5)}$–$C_{(18)}$	104.2(5)
		$N_{(1)}$–$C_{(5)}$–$C_{(18)}$	107.0(5)
		$O_{(1)}$–$C_{(5)}$–$C_{(4)}$	116.1(5)
		$N_{(1)}$–$C_{(5)}$–$C_{(4)}$	109.5(4)
		$C_{(18)}$–$C_{(5)}$–$C_{(4)}$	109.2(5)

a chair conformation, somewhat distorted towards the "half-boat". The atoms $C_{(1)}$–$C_{(2)}$–$C_{(4)}$–$C_{(5)}$ are coplanar within 0.08 Å, while the nodes $N_{(1)}$–$C_{(1)}$–$C_{(5)}$ and $C_{(2)}$–$C_{(3)}$–$C_{(4)}$ have dihedral angles with this plane of 156.5 and 127.8°. The torsion angles in the piperidine ring are: $N_{(1)}$–$C_{(1)}$–$C_{(2)}$–$C_{(3)}$ -29.7(7), $C_{(1)}$–$C_{(2)}$–$C_{(3)}$–$C_{(4)}$ 52.5(6), $C_{(2)}$–$C_{(3)}$–$C_{(4)}$–$C_{(5)}$ -63.5, $C_{(3)}$–$C_{(4)}$–$C_{(5)}$–$N_{(1)}$ 51.7(6), $C_{(4)}$–$C_{(5)}$–$N_{(1)}$–$C_{(1)}$ -30.8(8), $C_{(5)}$–$N_{(1)}$–$C_{(1)}$–$C_{(2)}$ 19.3(8)°. The torsion angles $H_{(2)}$–$C_{(2)}$–$C_{(3)}$–$H_{(3)}$ 176.5, $H_{(3)}$–$C_{(3)}$–$C_{(4)}$–$H_{(4)}$ 173.3, $H_{(4)}$–$C_{(4)}$–$C_{(5)}$–$O_{(1)}$ 167.4, $C_{(6)}$–$C_{(2)}$–$C_{(3)}$–$C_{(7)}$ -60.7, and $C_{(7)}$–$C_{(3)}$–$C_{(4)}$–$C_{(13)}$ 52.7° indicate that the protons of the piperidine ring and the OH group are in axial positions, while the CN, 2-chlorophenyl, thienoyl, and CF_3 groups are equatorial. Conjugation between the unshared pair of the $N_{(1)}$ atom and the π-system of the $C_{(1)}$=$S_{(1)}$ double bond leads not only to considerable shortening (to 1.334(6) Å) of the $N_{(1)}$–$C_{(1)}$ bond in comparison with the range 1.43-1.45 Å, which is typical for normal bonds of the N(sp^2)–C(sp^2) type, and also to flattening of the $N_{(1)}$ pyramid (the sum of the bond angles at this atom is 359.8°), but also to an increase of the $C_{(1)}$–$N_{(1)}$–$C_{(5)}$ bond angle to 128.5° and flattening of the heterocycle (in unsubstituted piperidine the C–N–C bond angle and the C–N–C–C torsion angles are 109.8 and 63.6° respectively [6]). As a result of the steric conditions the benzene and thiophene rings are practically orthogonal to the mean squared plane of the piperidine ring: the corresponding dihedral angles are 84.1 and 87.2°.

Molecules of compound **1** exist as centrosymmetric dimers (Fig. 2) in the crystal as a result of hydrogen bonding to the ethanol solvate molecules: $O_{(1)}$–$H_{(1)}$···$O_{(3)}$ ($O_{(1)}$···$O_{(3)}$ 2.954(7) Å) and $O_{(3)}$–$H_{(3)}$···$O_{(1)}$ ($O_{(1)}$···$O_{(3)}$ 2.679(7) Å).

Alkylation of thione **1** with allyl bromide in ethanol in the presence of KOH occurred regioselectively to give sulfide **2**. In its ^{1}H NMR spectrum the signals of protons 4-H and 5-H occur as broad doublets at 4.84 and 4.30 ppm respectively with ^3J = 12.1 Hz which indicates their *trans*-diaxial position. The signals of these protons appear as a minor broadened peak at 4.42 ppm which is the result of the broadened doublets superposition (the ratio of the major and minor signals is 4:1) and belong to the other conformer of compound **2**. This phenomenon has been explained by X-ray crystallography for isostructural analogs of pyridine **2**.

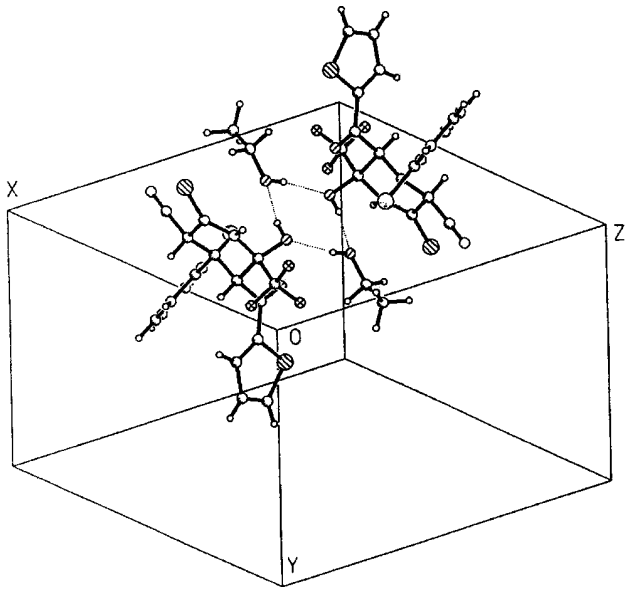


Fig. 2. Crystal packing of compound **1**.

TABLE 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters U_{eq} ($Å^2 \times 10^3$) in Structure **1**

Atom*	*x*	*y*	*z*	$U_{экв}$
$Cl_{(1)}$	4353(1)	-865(2)	2141(2)	111(1)
$S_{(1)}$	8748(1)	322(2)	4324(1)	76(1)
$S_{(2)}$	3081(1)	3814(2)	2671(2)	100(1)
$F_{(1)}$	5492(3)	3614(3)	5079(3)	89(1)
$F_{(2)}$	6917(3)	3169(4)	5898(3)	95(1)
$F_{(3)}$	6749(3)	4133(3)	4616(3)	83(1)
$O_{(1)}$	5851(3)	1269(4)	5003(3)	66(1)
$O_{(2)}$	4188(3)	1661(4)	3481(3)	74(1)
$N_{(1)}$	7320(3)	1632(4)	4610(3)	57(1)
$N_{(2)}$	7359(4)	-1069(5)	2188(4)	73(2)
$C_{(1)}$	7677(4)	966(5)	4017(4)	50(2)
$C_{(2)}$	7055(3)	922(5)	3018(4)	43(1)
$C_{(3)}$	5942(3)	1053(5)	2918(4)	43(1)
$C_{(4)}$	5807(3)	2211(5)	3460(4)	42(1)
$C_{(5)}$	6317(4)	2031(5)	4511(4)	46(1)
$C_{(6)}$	7248(4)	-198(6)	2554(4)	51(2)
$C_{(7)}$	5389(4)	1123(5)	1895(4)	51(2)
$C_{(8)}$	4643(4)	352(6)	1499(5)	71(2)
$C_{(9)}$	4104(5)	489(8)	564(6)	94(3)
$C_{(10)}$	4341(7)	1416(9)	42(6)	105(3)
$C_{(11)}$	5094(5)	2177(7)	424(5)	82(2)
$C_{(12)}$	5605(4)	2052(6)	1321(4)	63(2)
$C_{(13)}$	4706(4)	2446(6)	3288(4)	52(2)
$C_{(14)}$	4307(4)	3578(6)	2850(4)	57(2)
$C_{(15)}$	4746(5)	4543(6)	2535(5)	73(2)
$C_{(16)}$	4057(7)	5457(8)	2141(5)	103(3)
$C_{(17)}$	3159(6)	5172(8)	2175(5)	102(3)
$C_{(18)}$	6367(5)	3255(7)	5019(5)	65(2)
$O_{(3)}$	3910(4)	1072(5)	5386(5)	122(2)
$C_{(19)}$	3281(8)	1974(11)	5340(8)	167(5)
$C_{(20)}$	3326(9)	2920(10)	5855(10)	226(8)

* Atoms $O_{(3)}$, $C_{(19)}$, and $C_{(20)}$ belonging to the ethanol solvate molecule.

EXPERIMENTAL

IR spectra of nujol mulls were recorded with an IRS-29 spectrophotometer. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with Bruker WM-250 (250 MHz) (compound **1**) and Bruker WP-100Y (100 MHz) (compound **2**) machines. The course of reactions and the purity of individual substances were monitored by TLC on Silufol UV-254 strips with 3:5 acetone–hexane as eluent.

4-(2-Chlorophenyl)-3-cyano-6-hydroxy-5-(2-thienoyl)-6-trifluoromethylpiperidin-2-thione (1). A. 2-Thienoyltrifluoroacetone (2.22 g, 10 mmol) and N-methylmorpholine (1 ml, 8 mmol) were added with stirring at 20°C to a suspension of 2-chlorophenylmethylenecyanoacetamide (2.23 g, 10 mmol) in ethanol (25 ml). After 20 min 10% HCl was added to the reaction mixture to pH 5 and the mixture was kept at room temperature for 12 h. The crystalline product was filtered off and washed with ethanol and hexane.

B. Cyanothioacetamide (2 g, 20 mmol), then over 5 min 2-thienoyltrifluoroacetone (4.44 g, 20 mmol), and finally N-methylmorpholine (2.52 ml, 25 mmol) were added with stirring at 20°C to a mixture of 2-chlorobenzaldehyde (2.25 g, 20 mmol) and N-methylmorpholine (3 drops) in ethanol (30 ml). After 30 min the reaction mixture was treated as in method A. The ethanol solvate of thione **1** was obtained (3.49 g, 71%, A; 6.38 g, 65%, B); mp 125-127°C. IR spectrum, ν, cm^{-1}: 3330-3480 (NH, OH), 2250 (CN), 1680 (CO). ^{1}H NMR spectrum, δ, ppm: 1.08 t and 3.45 q (5H, EtOH); 4.80 (3H, m, 3-, 4-, 5-H); 7.11 m, 7.34 d, 7.84 m (7H, Ar and Het); 8.15 (1H, br. s, OH); 11.12 (1H, br. s, NH). Found, %: C 48.71; H 3.84; N 5.53; S 13.19. $C_{18}H_{12}ClF_3N_2O_2S_2 \cdot C_2H_5OH$. Calculated, %: C 48.93; H 3.70; N 5.71; S 13.06.

2-Allylthio-4-(2-chlorophenyl)-3-cyano-6-hydroxy-5-(2-thienoyl)-6-trifluoromethyl-1,4,5,6-tetrahydropyridine (2). Aqueous KOH (2.8 ml, 10%, 5 mmol) was added to a suspension of the solvate of thione **1** (2.46 g, 5 mmol) in ethanol (30 ml, 80%), followed by the addition of allyl bromide (0.42 ml, 5 mmol) over 5 min. The precipitate which formed over 1 h was filtered off, washed with ethanol and hexane to give compound **2** (1.87 g, 77%); mp 155-157°C. IR spectrum, ν, cm^{-1}: 3210-3300 (NH, OH), 2195 (CN), 1620, 1650 (CO). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 3.72 (d, ^3J = 7.5, SCH_2); 4.3 (d, ^3J = 12.1, 5-H_A); 4.42 (br. s, 4-H_B and 5-H_B); 4.84 (d, ^3J = 12.1, 4-H_A); 5.22 (m, CH_2=); 5.92 (m, CH=); 7.15, 7.30, 7.70, 7.89 (four m, Ar and Het); 7.43 (br. s, OH); 8.28 (br. s, NH). Found, %: C 52.26; H 3.12; N 5.93; S 13.37. $C_{21}H_{16}ClF_3N_2O_2S_2$. Calculated, %: C 52.10; H 3.33; N 5.78; S 13.22.

X-ray Crystallographic Study of a Monocrystal of Compound 1 was carried out at room temperature with an automatic four-circle Enraf-Nonius CAD-4 diffractometer (λMo*K*α radiation, graphite monochromator, relative rate of scanning ω/θ = 1.2, θ_{max} = 24°, segment of the sphere $0 \le h \le 16$, $0 \le k \le 12$, $-16 \le l \le 16$). 22 Reflexions with $12 < \theta < 13°$ were used to determine the unit cell parameters and the orientation matrices of a crystal with the linear dimensions 0.12 × 0.24 × 0.47 mm. A total of 3754 reflexions were collected of which 3470 were symmetrically independent (*R* factor averaged 0.11). Crystals were monoclinic, a = 14.171(2), b = 11.004(3), c = 14.729(3) Å; β = 104.76(2)°; V = 2221.0(8) $Å^3$; Z = 4; d_{calc} = 1.486 g/cm^3; μ = 0.410 mm^{-1}; $F(000)$ = 1008, space group $P2_1/n$. The structure was solved by direct methods and refined by mean squares method in the full matrix anisotropic approximation by use OF SHELXS and SHELXL-93 programs [8, 9]. 1639 Reflexions were used in the refinement (280 parameters refined) for a ratio of reflexions to parameters of 5.85, the weighting scheme $\omega = 1/[\sigma^2 (F\sigma^2) + (AP)^2]$ was used, where $P = (F\sigma^2 + 2Fc^2)/3$ and the coefficient of the weighting scheme A = 0.0572; a correction for anomalous absorption was included, but no correction for absorption was used. Most of the hydrogen atoms (75%) were revealed objectively, the remainder were found using geometric constraints. However all were refined with fixed thermal and geometric parameters. The final residual factors were $R_1(F)$ = 0.0677 and R_w = 0.1305, Go 1.038. The residual electron densities on a difference Fairer map were 0.23 and -0.32 e/$Å^3$. The atomic coordinates are cited in Table 2.

This work was carried out with financial assistance from the Russian fund for fundamental research (project No. 99-03-32965).

REFERENCES

1. S. G. Krivokolysko, V. D. Dyachenko, V. N. Nesterov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.,* 929 (2001).
2. L. M. Yagupol'skii, *Aromatic and Heterocyclic Compounds with Fluorine Containing Substituents* [in Russian]. Naukova Dumka, Kiev (1988), 320.
3. N. S. Zefirov and V. A. Palyulin, *Dokl. Akad. Nauk SSSR,* **252**, 111 (1980).
4. R. W. Alder, N. C. Goode, T. J. King, J. M. Mellor, and B. W. Miller, *J. Chem. Soc., Chem. Commun.,* **32B**, 173 (1976).

5. M. Burke-Laing and M. Laing, *Acta Crystallogr. (B),* **32**, 3216 (1976).
6. G. Gundersen and D. W. H. Rankin, *Acta Chem. Scand. (A),* **37**, 865 (1983).
7. S. G. Krivokolysko. V. D. Dyachenko, A. N. Chernega, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.,* 790 (2001).
8. G. M. Sheldrick, *SHELXS-86, Program for the Solution of Crystal Structures*, University of Göttingen, Göttingen, Germany 1986.
9. G. M. Sheldrick, *SHELXL-93, Program for the Refinement of Crystal Structures*, University of Göttingen, Göttingen, Germany 1993.