Chemistry of Heterocyclic Compounds, Vol. 39, No. 6, 2003

SYNTHESIS AND CRYSTAL STRUCTURE OF 3-CARBAMOYL-6-METHYL-5-PHENYLCARBAMOYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIDINE-4-SPIROCYCLOHEXANE

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3-Carbamoyl-6-methyl-5-phenylcarbamoyl-2-thioxo-1,2,3,4-tetrahydropyridine-4-spirocyclohexane has been synthesized by the condensation of cyclohexylidenecyanothioacetamide with acetoacetanilide and piperidine. The structure of the product was established by X-ray structural analysis.

Keywords: acetoacetanilide, 3-carbamoyl-6-methyl-5-phenylcarbamoyl-2-thioxo-1,2,3,4-tetrahydropyridine-4-spirocyclohexane, piperidine, cyclohexylidenecyanothioacetamide, X-ray structural analysis.

Unlike the 3-cyano-substituted pyridine-2-thiones [1-3], which have been adequately studied, their carbamoyl-substituted analogs are represented in the literature by single examples [4-6]. The carbamoyl group is introduced into the pyridine nucleus with the initial malonic acid monothioamide. The nitrile group may be transformed into carbamoyl on boiling enamines of β-diketones or β-ketoaldehydes with malononitrile in alcohol [7], or benzylideneacetoacetic ester with cyanoacetamide [8]. In both cases 3-carbamoyl-substituted pyridin-2-ones are formed.

The reaction of cyclohexylidenecyanothioacetamide (**1**) with acetoacetanilide (**2**) in absolute alcohol at 20°C catalyzed by N-methylmorpholine leads, according to our data, to the formation of 3-cyano-6-methyl-5-phenylcarbamoyl-2-thioxo-1,2,3,4-tetrahydropyridine-4-spirocyclohexane [9]. In the present work we have shown that when using piperidine as catalyst a different product is formed, *viz*. 3-carbamoyl-6-methyl-5-phenylcarbamoyl-2-thioxo-1,2,3,4-tetrahydropyridine-4-spirocyclohexane (**3**) (see Scheme 1). This conversion is the result of a sequence of reactions probably comprising the formation of an adduct of Michael addition **4**, cyclization of the latter into iminopyran **5**, which undergoes further recyclization through enamine **6** into compound **3**.

The smooth conversion described, the mechanism of which is in agreement with the data of [7], is the first example of the synthesis of a substituted pyridinethione containing transformation of a nitrile group into an amide under mild conditions. This opens a new route to the synthesis of potentially pharmacologically desirable compounds **3**, the carbamoyl-substituted pyridinethiones.

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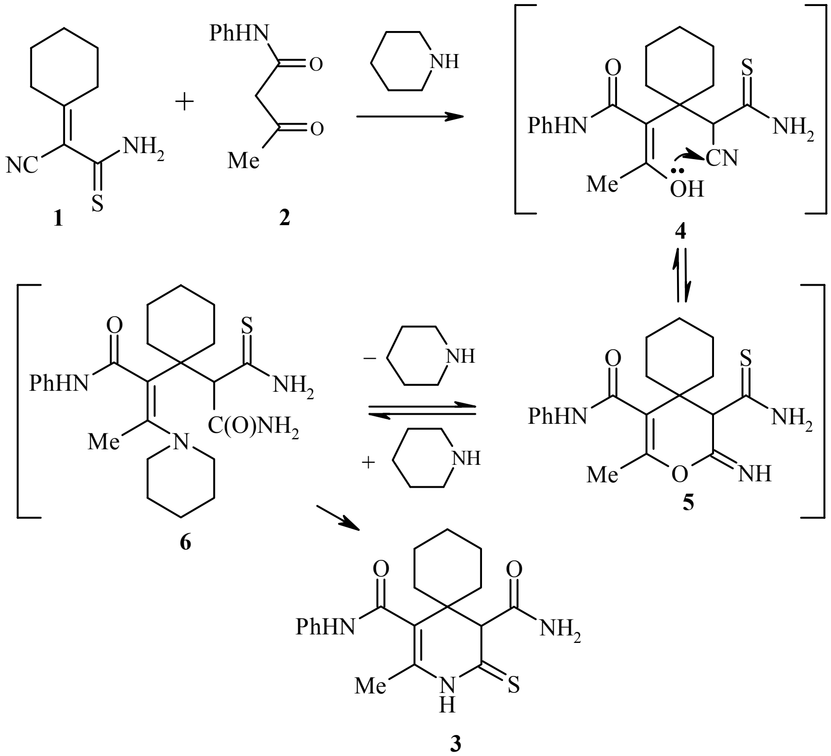
Scheme 1



The structure of compound **3** was demonstrated by X-ray structural analysis (see Fig. 1 and Tables 1 and 2).

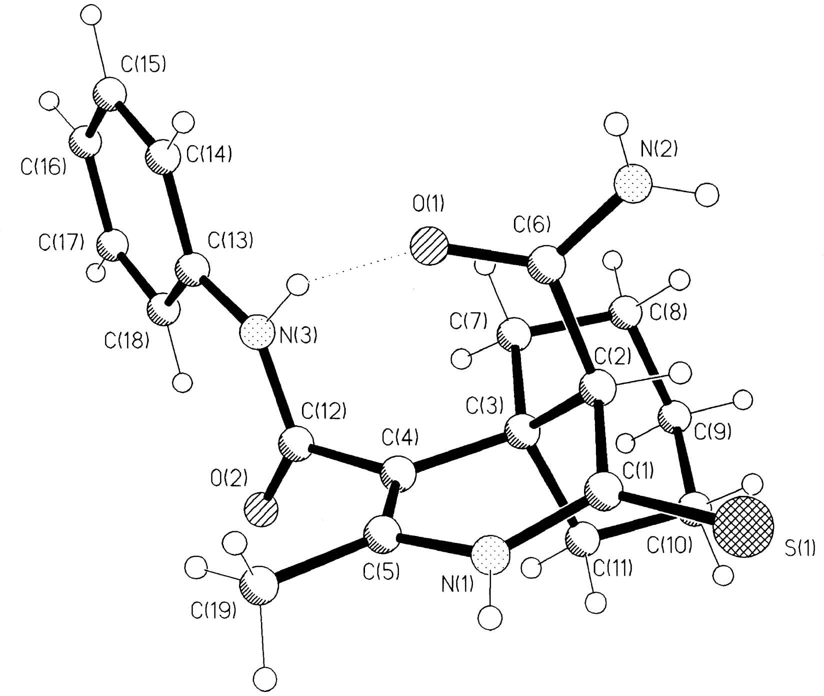


Fig. 1. General form of the compound **3** molecule.

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

Bond	*d*, Å	Angle	ω, deg.
N(1)–C(1)	1.342(5)	C(1)–N(1)–C(5)	125.0(4)
N(1)–C(5)	1.406(5)	N(1)–C(1)–C(2)	114.8(4)
C(1)–C(2)	1.510(6)	C(4)–C(5)–N(1)	119.3(4)
C(2)–C(3)	1.552(5)	C(1)–C(2)–C(3)	111.2(3)
C(3)–C(4)	1.533(6)	C(4)–C(3)–C(2)	106.6(3)
C(4)–C(5)	1.322(6)	C(5)–C(4)–C(3)	120.9(4)
S(1)–C(1)	1.643(4)	C(12)–N(3)–C(13)	128.1(4)
O(1)–C(6)	1.237(5)	N(1)–C(1)–S(1)	123.0(3)
N(2)–C(6)	1.293(6)	C(2)–C(1)–S(1)	122.2(3)
N(3)–C(12)	1.349(6)	C(4)–C(5)–C(19)	126.4(4)
N(3)–C(13)	1.399(6)	N(1)–C(5)–C(19)	114.2(4)
		O(2)–C(12)–N(3)	124.8(4)

The central six-membered heterocycle N(1)C(1-5) is nonplanar. The grouping N(1)C(1)C(3)C(4)C(5) is planar within the limits 0.108 Å, and the C(2) atom emerges from this plane by 0.620 Å. The "corner" C(1)C(2)C(3) forms a dihedral angle of 44.9(3)° with the N(1)C(1)C(3)C(4)C(5) plane. According to the modified Cremer–Pople criterion [10] the conformation of this heterocycle may be characterized as a half-boat ($S = 0.65$, $\theta = 49.32$, $\psi = 25.78°$). The grouping C(12)=O(2)N(3) is folded by 81.8° relative to the latter plane. The valence angle C(4)C(5)C(19) at 126.4(4)° is strongly increased compared with the standard value of 120°, and the angle N(1)C(5)C(19) is reduced to 114.2(4)°. This is probably linked with steric reasons connected with the close spatial disposition of the Me and CONHPh substituents. An extremely short intramolecular contact C(12)–C(19) of 2.978(4) Å is observed in the crystal (the sum of the van der Waals radii of the carbon atoms is 3.42 Å) [11]. The distribution of bond lengths in the heterocycle N(1)C(1-5) (Table 1) indicates significant conjugation of the unshared electron pair of the N(1) atom with the π-systems of the C(4)=C(5) and C(1)=S(1) double bonds. Indeed both the N(1)–C(1) bond at 1.342(5) and N(1)–C(5) bond at 1.406(5) Å are shortened compared with the standard values for a single N(sp^2)–C(sp^2) bond with a range of 1.43-1.45 Å [12,13]. In the substituent C(6)=O(1)N(2)H_2 the C(6)–N(2) bond is also highly shortened at 1.293(6) Å, which is usual for such

TABLE 2. Coordinates of Atoms (×10^4) and Their Equivalent Anisotropic (Isotropic for Hydrogen Atoms) Thermal Parameters U_{eq} (Å^2×10^3) in Structure **3**

Atom	*x*	*y*	*z*	U_{eq}, Å^2
S(1)	917(1)	501(1)	4376(1)	56(1)
O(1)	2571(2)	-1707(2)	5870(2)	58(1)
O(2)	3039(2)	-150(3)	8491(2)	77(1)
N(1)	1147(2)	-135(3)	5916(2)	50(1)
N(2)	2612(3)	-1255(4)	4597(3)	58(1)
N(3)	3311(2)	-1420(3)	7771(3)	53(1)
C(1)	1476(3)	108(3)	5302(3)	42(1)
C(2)	2402(2)	-21(3)	5522(2)	40(1)
C(3)	2840(3)	298(3)	6441(3)	46(1)
C(4)	2410(3)	-229(3)	7003(3)	46(1)
C(5)	1605(3)	-403(3)	6738(3)	46(1)
C(6)	2551(3)	-1080(3)	5340(3)	41(1)
C(7)	3779(3)	117(3)	6680(3)	57(1)
C(8)	4217(3)	767(4)	6220(3)	70(2)
C(9)	4053(4)	1812(4)	6340(4)	89(2)
C(10)	3142(4)	2009(4)	6066(4)	74(2)
C(11)	2690(3)	1375(3)	6532(3)	61(1)
C(12)	2938(3)	-587(4)	7841(3)	50(1)
C(13)	3998(3)	-1838(4)	8351(3)	56(1)
C(14)	4265(4)	-2697(4)	8129(5)	90(2)
C(15)	4966(5)	-3119(5)	8645(6)	116(3)
C(16)	5380(5)	-2715(7)	9379(6)	114(3)
C(17)	5129(4)	-1868(7)	9609(5)	115(3)
C(18)	4426(4)	-1440(5)	9093(4)	89(2)
C(19)	1115(3)	-903(4)	7213(3)	74(2)

a grouping. For example, in the formamide molecule investigated previously by the X-ray method [14] the C–N bond length at 1.319(2) is close to the value obtained in the present work. The orientation of the amino group is extremely favorable for conjugation of its unshared electron pair (UEP) with the π-system of the C(6)=O(1) double bond. The sum of the valence angles at the N(1) atom is 360° but the H(12N) and H(22N) hydrogen atoms lie in the plane of the N(1), C(6), O(1), and C(2) atoms. The C(3)C(7-11) atoms belong to the cyclohexane ring, which is in the chair conformation usual for it. The C(1)=S(1) bond length at 1.643(4) is in the usual range for a C=S double bond.

The formation of an intramolecular hydrogen bond N–H···O [5] was observed in the crystal. Its parameters are N(3)···O(1) 3.058(5), N(3)–H(3N) 0.91(2) Å, N(3)–H(3N)···O(1) 154(3)°. Additionally, the molecules of the compound are linked in centrosymmetric dimers (0.5-*x*, -0.5-*y*, 1-*z*) through a N(2)–H(22N)···O(1) hydrogen bond (N(2)···O(1) 2.953(5), N(2)–H(22N) 0.74(2) Å, N(2)–H(22N)···O(1) 168(3)°). Furthermore, due to a N(2)–H(12N)···O(2) hydrogen bond, the molecules of compound **3** are linked in chains directed along the *z* crystal axis. The parameters of this bond are N(2)···O(2) 2.926(5), N(2)–H(12N) 0.77(2) Å, N(2)–H(12N)···O(2) 158(3)°. The parameters N(1)···S(1) 3.415(3) Å, N(1)–H(1N)···S(1) 162(3)° indicate the possibility of the formation of a further N–H···S intermolecular hydrogen bond (-*x*, -*y*, 1-*z*) [16].

EXPERIMENTAL

Melting points were determined on a Kofler block. The IR spectrum was taken on a IKS-29 instrument in nujol. The ^{1}H NMR spectrum was recorded on a Bruker AM-300 (300 MHz) instrument A check on the progress of reactions was effected by TLC on Silufol UV 254 plates in acetone–hexane, 3:5, visualization was with iodine vapor.

The X-ray Structural Investigation of a Monocrystal of Compound 3 was carried out at room temperature on an automatic four-circle Enraf-Nonius CAD-4 diffractometer (λMo$K\alpha$-radiation, graphite monochromator, $\omega/2\theta$ scanning, θ_{max} 24°, segment of sphere $0 \leq h \leq 19$, $0 \leq k \leq 16$, $-18 \leq l \leq 18$). For the determination of the unit cell parameters and the orientation matrix a crystal of compound **3** with linear dimensions 0.45×0.40×0.11 mm was used with 22 reflections with $11.01 < \theta < 11.95°$. In all 3052 reflections were taken, of which 2941 are independent (*R* factor averaging 0.0396). The crystals of compound **3** were monoclinic, a = 16.899(3), b = 14.020(3), c = 16.609(3) Å; β = 107.26(3)°; V = 3757(1) Å^3; Z = 8, d_{calc} = 1.264 g/cm^3; μ = 0.189 mm^{-1}; $F(000)$ = 1520; space group *C*2/*c* (No. 15). The structure was solved by the direct method and refined by least squares in a full-matrix anisotropic approach using SHELXS and SHELXL-93 programs [17,18]. In the refinement 1646 reflections were used with $I > 2\sigma(I)$ (242 parameters being refined, number of reflections per parameter 6.80, the weighting scheme used was $w = 1/[\sigma^2(Fo^2) + (0.899P)^2]$, where $P = (Fo^2 + 2Fc^2)/3$, the ratio of the maximum (mean) displacement to the error in the final cycle was 0.125(0.011)). Corrections for anomalous dispersion were included, corrections for absorption were not introduced. All hydrogen atoms were made apparent objectively, however they were refined by the "rider" method (with the exception of the hydrogen atoms on nitrogen which were refined isotropically) with a fixed U_{iso} = 0.08 Å. The final values for the divergence factors were $R1(F)$ 0.0638 and $R_w(F^2)$ 0.1436, *GOOF* 0.962. The residual electron density from the Fourier difference series after the last refinement cycle was 0.22 and -0.20 e/Å^3. All structural calculations were carried out on a computer. The coordinates of atoms are given in Table 2.

3-Carbamoyl-6-methyl-5-phenylcarbamoyl-2-thioxo-1,2,3,4-tetrahydropyridine-4-spirocyclohexane (3). Piperidine (1.5 ml, 15 mmol) was added to a suspension of cyclohexylidenecyanothioacetamide **1** (1.80 g, 10 mmol) and compound **2** (1.77 g, 10 mmol) in absolute alcohol (20 ml) at 20°C. The reaction mixture was stirred for 4 h and maintained at the same temperature for 12 h. The resulting yellow crystalline product was filtered off, and washed with absolute alcohol. Yield 2.3 g (64%); mp 268-270°C (alcohol). IR spectrum (thin film), ν, cm^{-1}: 3000, 3370 (NH, NH$_2$), 1690 (C=O), 1660 (δ NH$_2$). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm (*J*, Hz): 11.3 (1H, br. s, 5-CONH); 9.2 (1H, br. s, NH); 7.6 (2H, d, *J* = 9.3, H arom.); 7.5 (1H, br. s, CONH); 7.3 (2H, t, *J* = 8.1, H arom.); 7.1 (2H, m, CONH and H arom.); 4.0 (1H, s, 3-H); 1.9 (3H, s, CH$_3$); 1.2-1.8 (10H, m, 5 CH$_2$). Found, %: C 64.02; H 6.32; N 11.58; S 9.19. $C_{19}H_{23}N_3O_2S$. Calculated, %: C 63.84; H 6.49; N 11.75; S 8.97.

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