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# NOVEL STEREOSELECTIVE SYNTHESIS AND MOLECULAR AND CRYSTALLINE STRUCTURE OF 3-ALLYL-4-(4-BROMOPHENYL)-3-CYANO-6-OXOPIPERIDINE-2-THIONE

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*The stereoselective synthesis of 3-allyl-4-(4-bromophenyl)- 3-cyano-6-oxopiperidine-2-thione has been carried out by refluxing N-methylmorpholinium 5-[1-(4-bromophenyl)-2-cyano-2-thiocarbamoylethyl]-2,2-dimethyl-1,3-dioxa-6-oxo-4-cyclohexen-4-olate with allyl bromide in ethanol. The structure of the product was confirmed by X-ray investigation.*

**Keywords:** 3-allyl-4-(4-bromophenyl)-3-cyano-6-oxopiperidine-2-thione, X-ray structural investigation.

Functionally substituted 3-cyanopiperidine-2-thiones remain a little studied group of organic compounds [1, 2] and this is principally due to the absence of convenient methods for their synthesis. The synthesis of 3-allyl-4-(4-bromophenyl)-6-oxo-3-cyanopiperidine-2-thione (**1**) from the corresponding sulfide **2** has been brought about [3] by a regioselective [3,3]sigmatropic rearrangement. Bearing in mind the multistage preparation of the sulfide there is an interest in an investigation of simpler, technologically achievable methods for stereoselectively synthesizing the thione **1**.

In our work we have studied the reaction of the substituted N-methylmorpholinium cyclohexen-4-olate **3** (described in [3]) with allyl bromide **4** by means of refluxing in ethanol. In the first stage of the indicated reaction it is likely that a regioselective heterocyclization of compound **3** occurs to give the thiolate **5** which is then converted to the derivative **2** by the alkyl bromide **4**. Subsequent allyl rearrangement leads to the thione **1**.

The structure of compound **1** was studied using X ray structural analysis (Fig. 1, Tables 1 and 2). In this molecule the heterocycle has a half chair conformation, the atoms $C_{(3)}$ and $C_{(4)}$ deviating from the plane defined through atoms $N_{(1)}$, $C_{(2)}$, $C_{(5)}$ and $C_{(6)}$ (deviation of these atoms from the mean plane $\pm 0.006$ Å) by 0.406 and -0.305 Å respectively. The dihedral angle between the pseudoaxial p-bromophenyl substituent and the plane of the heterocyclic fragment was 97.8°.

As shown in Fig. 1, the pseudoaxial allyl substituent is situated in a trans position relative to the aryl fragment (torsional angle $C_{(14)}C_{(3)}$, $C_{(4)}C_{(8)}$ 163.9°). Hence the [3,3]sigmatropic allyl rearrangement of compound **2** to thione **1** occurs as a result of attack of the $C_{(3)}$ atom of the heterocycle by the allyl group from the side opposite to the aryl substituent. The remaining geometric parameters of the investigated molecule have usual values [4].

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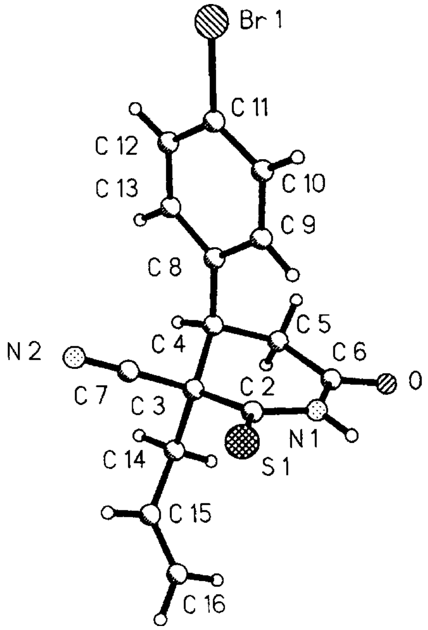
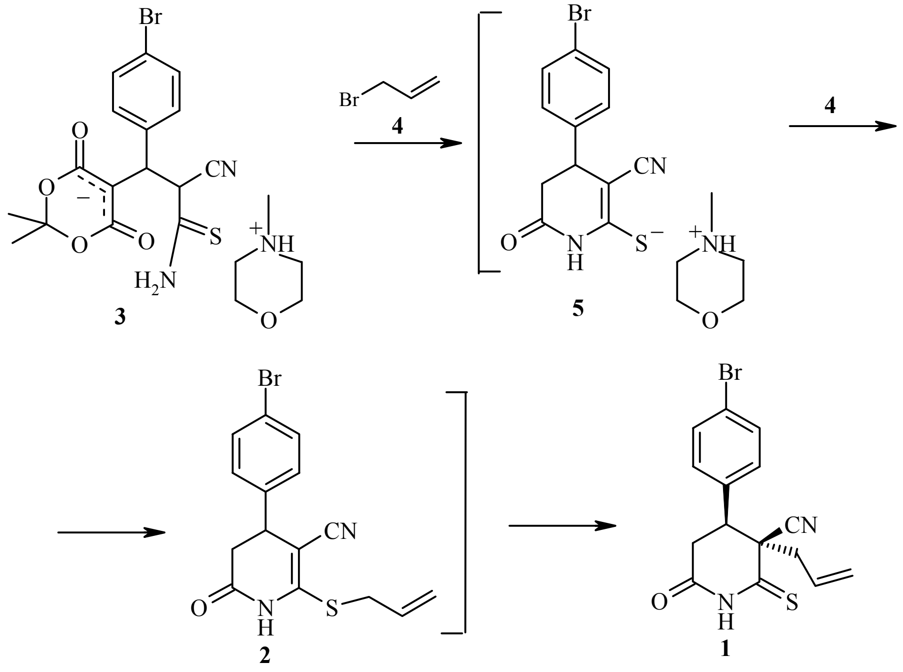


Fig. 1. General view of molecule **1**.



Analysis of the packing of the molecule in the crystal showed the presence of only an intermolecular non valence contact for $\mathrm{Br_{(1)}\cdots S_{(1)}}$ (1 + *x*, *y*, *z*) of 3.64(1) Å, comparable with the sum of their van der Waal radii (3.65 Å, [5]).

In the crystal, the intermolecular hydrogen bonds $\mathrm{N_{(1)}–H_{(1)}\cdots O_{(1)}}$ (-*x*, 2-*y*, -*z*) [$\mathrm{N_{(1)}\cdots O_{(1)}}$ 2.88 (1), $\mathrm{N_{(1)}–H_{(1)}}$ 0.90, $\mathrm{H_{(1)}\cdots O_{(1)}}$ 1.99(1) Å, angle $\mathrm{N_{(1)}–H_{(1)}\cdots O_{(1)}}$ 168(2)°] assemble molecule **1** as centrosymmetric dimers (Fig. 2).

TABLE 1. Bond Lengths (*d*) in Molecule **1**

| Bond | *d*, Å | Bond | *d*, Å | Bond | *d*, Å |
|---|---|---|---|---|---|
| $\mathrm{Br_{(1)}{-}C_{(11)}}$ | 1.88(1) | $\mathrm{C_{(3)}{-}C_{(4)}}$ | 1.58(1) | $\mathrm{C_{(8)}{-}C_{(13)}}$ | 1.40(1) |
| $\mathrm{S_{(1)}{-}C_{(2)}}$ | 1.62(1) | $\mathrm{C_{(3)}{-}C_{(7)}}$ | 1.51(2) | $\mathrm{C_{(9)}{-}C_{(10)}}$ | 1.36(2) |
| $\mathrm{O_{(1)}{-}C_{(6)}}$ | 1.23(1) | $\mathrm{C_{(3)}{-}C_{(14)}}$ | 1.55(1) | $\mathrm{C_{(10)}{-}C_{(11)}}$ | 1.37(1) |
| $\mathrm{N_{(1)}{-}C_{(2)}}$ | 1.37(1) | $\mathrm{C_{(4)}{-}C_{(5)}}$ | 1.52(2) | $\mathrm{C_{(11)}{-}C_{(12)}}$ | 1.41(1) |
| $\mathrm{N_{(1)}{-}C_{(6)}}$ | 1.36(1) | $\mathrm{C_{(4)}{-}C_{(8)}}$ | 1.48(1) | $\mathrm{C_{(12)}{-}C_{(13)}}$ | 1.34(2) |
| $\mathrm{N_{(2)}{-}C_{(7)}}$ | 1.12(2) | $\mathrm{C_{(5)}{-}C_{(6)}}$ | 1.50(1) | $\mathrm{C_{(14)}{-}C_{(15)}}$ | 1.44(2) |
| $\mathrm{C_{(2)}{-}C_{(3)}}$ | 1.52(1) | $\mathrm{C_{(8)}{-}C_{(9)}}$ | 1.41(1) | $\mathrm{C_{(15)}{-}C_{(16)}}$ | 1.28(2) |

TABLE 2. Valence Angles (ω) in Molecule **1**

| Angle | ω, deg. | Angle | ω, deg. | Angle | ω, deg. |
|---|---|---|---|---|---|
| $\mathrm{C_{(2)}{-}N_{(1)}{-}C_{(6)}}$ | 127.8(8) | $\mathrm{C_{(3)}{-}C_{(4)}{-}C_{(5)}}$ | 107.8(8) | $\mathrm{C_{(9)}{-}C_{(8)}{-}C_{(13)}}$ | 114.6(9) |
| $\mathrm{S_{(1)}{-}C_{(2)}{-}N_{(1)}}$ | 121.9(7) | $\mathrm{C_{(3)}{-}C_{(4)}{-}C_{(8)}}$ | 115.0(9) | $\mathrm{C_{(8)}{-}C_{(9)}{-}C_{(10)}}$ | 123.3(9) |
| $\mathrm{S_{(1)}{-}C_{(2)}{-}C_{(3)}}$ | 124.9(7) | $\mathrm{C_{(5)}{-}C_{(4)}{-}C_{(8)}}$ | 113.6(8) | $\mathrm{C_{(9)}{-}C_{(10)}{-}C_{(11)}}$ | 119.1(9) |
| $\mathrm{N_{(1)}{-}C_{(2)}{-}C_{(3)}}$ | 113.1(8) | $\mathrm{C_{(4)}{-}C_{(5)}{-}C_{(6)}}$ | 116.3(8) | $\mathrm{Br_{(1)}{-}C_{(11)}{-}C_{(10)}}$ | 120.2(8) |
| $\mathrm{C_{(2)}{-}C_{(3)}{-}C_{(4)}}$ | 112.4(7) | $\mathrm{O_{(1)}{-}C_{(6)}{-}N_{(1)}}$ | 120.5(9) | $\mathrm{Br_{(1)}{-}C_{(11)}{-}C_{(12)}}$ | 120.0(7) |
| $\mathrm{C_{(2)}{-}C_{(3)}{-}C_{(7)}}$ | 109.3(8) | $\mathrm{O_{(1)}{-}C_{(6)}{-}C_{(5)}}$ | 120.3(9) | $\mathrm{C_{(10)}{-}C_{(11)}{-}C_{(12)}}$ | 119.8(10) |
| $\mathrm{C_{(4)}{-}C_{(3)}{-}C_{(7)}}$ | 107.1(8) | $\mathrm{N_{(1)}{-}C_{(6)}{-}C_{(5)}}$ | 119.2(9) | $\mathrm{C_{(11)}{-}C_{(12)}{-}C_{(13)}}$ | 119.6(9) |
| $\mathrm{C_{(2)}{-}C_{(3)}{-}C_{(14)}}$ | 109.7(8) | $\mathrm{N_{(2)}{-}C_{(7)}{-}C_{(3)}}$ | 173.8(11) | $\mathrm{C_{(8)}{-}C_{(13)}{-}C_{(12)}}$ | 123.5(9) |
| $\mathrm{C_{(4)}{-}C_{(3)}{-}C_{(14)}}$ | 111.2(8) | $\mathrm{C_{(4)}{-}C_{(8)}{-}C_{(9)}}$ | 125.0(8) | $\mathrm{C_{(3)}{-}C_{(14)}{-}C_{(15)}}$ | 116.1(9) |
| $\mathrm{C_{(7)}{-}C_{(3)}{-}C_{(14)}}$ | 106.9(8) | $\mathrm{C_{(4)}{-}C_{(8)}{-}C_{(13)}}$ | 120.3(8) | $\mathrm{C_{(14)}{-}C_{(15)}{-}C_{(16)}}$ | 126.4(13) |

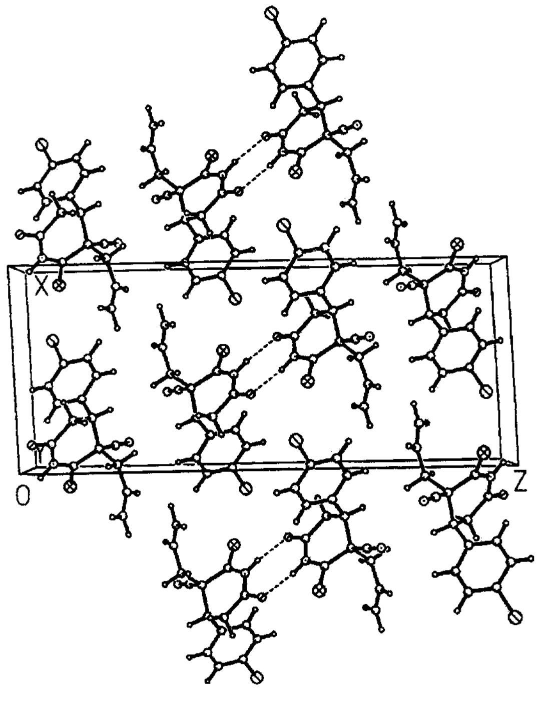


Fig. 2. *ac* Projection of the crystal structure of **1**
(the dotted lines indicate the intermolecular NH···O hydrogen bonds).

TABLE 3. Atomic Coordinates ($\times10^4$; $\times10^3$ for H) in Structure **1**

| Atom | *x* | *y* | *z* | *U* | Atom | *x* | *y* | *z* | *U* |
|---|---|---|---|---|---|---|---|---|---|
| $Br_{(1)}$ | 6476(1) | 1105(2) | 545(1) | 69(1) | $C_{(7)}$ | 1181(10) | 4797(18) | 1848(4) | 45(4) |
| $S_{(1)}$ | -810(3) | 4773(5) | 857(1) | 66(1) | $C_{(8)}$ | 3497(9) | 6008(16) | 1227(4) | 40(3) |
| $O_{(1)}$ | 1424(7) | 10977(11) | 312(3) | 55(3) | $C_{(9)}$ | 3300(10) | 5106(17) | 688(4) | 48(4) |
| $N_{(1)}$ | 422(8) | 8186(13) | 640(3) | 43(3) | $C_{(10)}$ | 4166(10) | 3697(17) | 482(4) | 47(4) |
| $N_{(2)}$ | 1282(11) | 3380(16) | 2110(4) | 70(4) | $C_{(11)}$ | 5286(10) | 3093(17) | 810(4) | 48(4) |
| $C_{(2)}$ | 254(9) | 6600(16) | 1003(4) | 45(4) | $C_{(12)}$ | 5533(10) | 3947(20) | 1347(4) | 58(4) |
| $C_{(3)}$ | 1086(10) | 6826(15) | 1554(4) | 43(3) | $C_{(13)}$ | 4666(10) | 5341(18) | 1537(4) | 54(4) |
| $C_{(4)}$ | 2594(9) | 7552(17) | 1463(4) | 44(4) | $C_{(14)}$ | 345(11) | 8285(15) | 1951(4) | 49(4) |
| $C_{(5)}$ | 2515(10) | 9511(16) | 1123(4) | 48(4) | $C_{(15)}$ | -1018(14) | 7700(21) | 2096(5) | 75(5) |
| $C_{(6)}$ | 1415(10) | 9620(16) | 664(4) | 45(4) | $C_{(16)}$ | -2115(12) | 8719(27) | 2001(6) | 93(8) |

## EXPERIMENTAL

**3-Allyl-4-(4-bromophenyl)- 3-cyano-6-oxopiperidine-2-thione (1).** A mixture of the cyclohexen-4-olate **3** [3] (2.56 g, 5 mmol) and allyl bromide **4** (0.42 ml, 5 mmol) in 80% ethanol (30 ml) was refluxed for 10 min and was then filtered through a pleated filter paper. The crystals formed in the filtrate after 24 h were separated and washed with ethanol and hexane to give thione **1** (1.45 g, 83%). The product was identical in melting point, $^1H$ NMR data (Bruker WP-100 SY (100 MHz) instrument using DMSO solvent and TMS as internal standard), and IR spectrum (IRS-29 spectrometer using vaseline oil) with the compound reported in the study [3].

**X-ray Structural Investigation of Compound 1.** Crystals of the compound are monoclinic, at 24°: $a = 9.781$ (3), $b = 6.599$ (2), $c = 23.738$ (8) Å; $\beta = 92.61$ (2)°; $V = 1531$ (1) Å$^3$; $d_{\text{calc}} = 1.516$ g/cm$^3$; $Z = 4$; space group $P2_1/n$. The unit cell parameters and intensities of 2969 independent reflections were measured on a Syntex P21 automatic four circle diffractometer ($\lambda$MoK$\alpha$, graphite monochromator, $\theta/2\theta$ scanning to $\theta_{\max} = 28°$). The structure was solved by a direct method, revealing all non hydrogen atoms and refined by a full matrix least squares method in the anisotropic approximation for non hydrogen atoms for 1208 reflections with $I > 3\sigma(I)$. All of the hydrogen atoms were directly revealed by difference Fourier synthesis, but due to the large thermal vibrations they were included in the refinement with fixed positions and thermal parameters $U = 0.08$ Å$^2$. The final difference factors were $R = 0.056$ and $R_w = 0.056$. All of the calculations were performed using the SHELXTL PLUS program [6] (PC version). The coordinates and equivalent isotropic thermal parameters for the non hydrogen atoms are given in Table 3.

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