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Molecular and crystal structures of hetero-analogues of bicyclo[3.3.1]nonane with nitrogen and sulfur atoms

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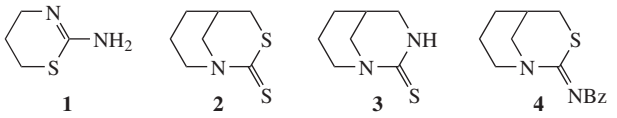
The X-ray molecular structures of bridgehead heterocycles, namely, 3-thia-1-azabicyclo[3.3.1]nonane-2-thione, 1,3-diazabicyclo-[3.3.1]nonane-2-thione, (2*Z*)-2-(*N*-benzoylimino)-3-thia-1-azabicyclo[3.3.1]nonane and (2*Z*)-2-(3,4-dichlorophenylimino)-3-thia-1-azabicyclo[3.3.1]nonane were determined and their molecular packing in the crystals was revealed. The rings distortion in the bridgehead core was evaluated by the calculation of ZP and CP puckering parameters.

In order to design nitric oxide synthase inhibitors with radioprotective activity and oral bioavailability, we studied bicyclo-[3.3.1]nonane analogues of the enzyme inhibitor 2-amino-5,6-dihydro-4*H*-1,3-thiazine **1**.[1] Synthetic routes to these compounds led to different bridgehead heterocycles with nitrogen and sulfur atoms, *e.g.*, compounds **2**–**4**.[1]



A detailed study of the crystal structures of **2**† and **3**‡ revealed the following regularities concerning molecular geometry and conformation: the presence of heteroatoms in the bicyclic fragments leads, as expected, to a change in the most stable double-chair conformation of bicyclo[3.3.1]nonane[4] (Figure 1). To estimate quantitatively the rings distortion from standard conformations, we calculated both Zefirov–Palyulin (ZP)[5] and Cremer–Pople (CP)[6] puckering parameters for these rings in the structures of **2** and **3**. All these data were calculated using the RICON[7] program (Table 1). Note that there are two symmetrically independent molecules of thione **2** in the unit cell, both being disordered over two orientations. The absolute values of torsion angles and puckering parameters of the major disordered independent molecules (referred to as **2A** and **2B**) are close to each other.

Table 1 Zefirov–Palyulin (ZP) and Cremer–Pople (CP) puckering parameters for cyclic frameworks.

Structure/Ring	ZP				CP		
	S	θ	ψ_2	σ	Q	θ	φ_2
2A/C(7)C(3)C(4)C(5)C(6)N(1)	1.150	10.5	11.2	2.1	0.586	18.2	13.1
C(7)N(1)C(1)S(1)C(2)C(3)	0.909	64.2	8.6	2.0	0.757	79.9	9.8
2B/C(7)C(3)C(4)C(5)C(6)N(1)	1.181	8.0	8.2	1.4	0.596	13.0	9.5
C(7)N(1)C(1)S(1)C(2)C(3)	0.894	65.7	4.4	2.2	0.741	81.1	6.0
3 / C(7)C(3)C(4)C(5)C(6)N(2)	1.171	9.0	18.3	1.3	0.593	14.9	21.5
C(7)N(2)C(1)N(1)C(2)C(3)	0.848	62.9	11.9	2.0	0.636	69.6	14.5
4 / C(7)C(3)C(4)C(5)C(6)N(1)	1.177	7.0	21.6	1.2	0.590	11.3	25.8
C(7)N(1)C(1)S(1)C(2)C(3)	0.929	76.3	1.5	2.8	0.838	88.9	359.3
5 / C(7)C(3)C(4)C(5)C(6)N(1)	1.184	5.2	17.8	1.0	0.591	7.6	23.8
C(7)N(1)C(1)S(1)C(2)C(3)	0.927	78.0	1.1	2.9	0.838	89.8	359.5

The data show that piperidine rings in the bridgehead cores of **2A**, **2B** and **3**, *i.e.*, C(7)–C(3)–C(4)–C(5)–C(6)–N(1) and C(7)–C(3)–C(4)–C(5)–C(6)–N(2), respectively, have a conformation close to the chair (with a slight distortion to the half-chair direction in the case of **3**, and to envelope in the case of **2A** and

† Compound **2** was synthesized as a racemic mixture as described previously[1] and crystallized from toluene. Crystals of **2** ($C_7H_{11}NS_2$, M = 173.29) are monoclinic, space group *Cc*, at 120 K: a = 6.2681(10), b = 18.895(3) and c = 13.957(2) Å, β = 101.164(3)°, V = 1621.7(4) Å^3, Z = 8 (Z' = 2), d_{calc} = 1.419 g cm^{-3}, μ(MoKα) = 5.78 cm^{-1}. Intensities of 7912 reflections were measured on a SMART 1000 CCD diffractometer [λ(MoKα) = 0.71073 Å, $2\theta < 56°$] and 3795 independent reflections (R_{int} = 0.0321) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Two independent molecules in the unit cell of **2** are disordered over two orientations, the ratio for one of them being 82:18. Atomic positions of the minor orientation were refined isotropically. The positions of the CH and CH_2 hydrogen atoms were calculated from geometrical point of view. The refinement converged to wR_2 = 0.1151 and GOF = 1.072 for all independent reflections [R_1 = 0.0456 was calculated against F for 3441 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.1.[2,3]

‡ Compound **3** was synthesized as described previously[1] and crystallized from toluene. Crystals of **3** ($C_7H_{12}N_2S$, M = 156.25) are monoclinic, space group $P2_1/n$, at 100 K: a = 6.5288(7), b = 10.2745(11) and c = 11.7729(13) Å, β = 104.823(2)°, V = 763.45(14) Å^3, Z = 4, d_{calc} = 1.359 g cm^{-3}, μ(MoKα) = = 3.45 cm^{-1}. Intensities of 7357 reflections were measured on a Bruker APEX-II CCD diffractometer [λ(MoKα) = 0.71073 Å, $2\theta < 56°$] and 1842 independent reflections (R_{int} = 0.0306) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The positions of the CH and CH_2 hydrogen atoms were calculated from geometrical point of view. The position of hydrogen atom at nitrogen atom was located from the Fourier density synthesis. The refinement converged to wR_2 = 0.0868 and GOF = 1.069 for all independent reflections [R_1 = 0.0322 was calculated against F for 1605 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.1.[2,3]

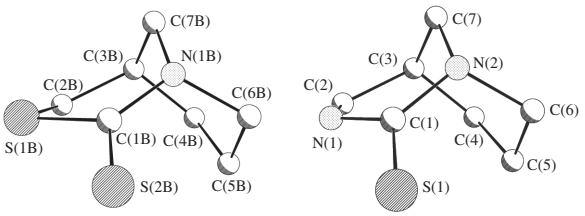


Figure 1 Molecular structures of compounds **2B** and **3**. (Atomic numbering used in RSA data differs from that used in the names of compounds according to IUPAC nomenclature).

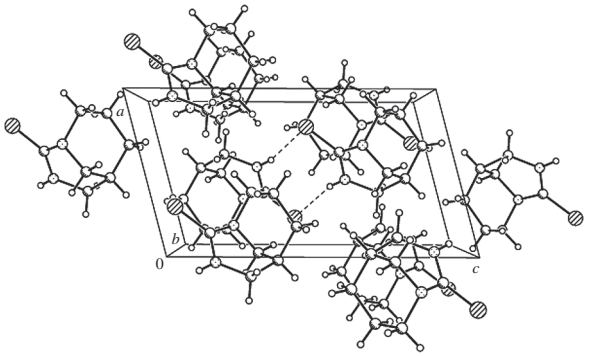


Figure 2 Molecular packing of 1,3-diazabicyclo[3.3.1]nonane-2-thione **3**.

2B). Contrary, the cycles with two heteroatoms, C(7)–N(1)–C(1)–S(1)–C(2)–C(3) (**2A**, **2B**) and C(7)–N(2)–C(1)–N(1)–C(2)–C(3) (**3**), adopt a conformation intermediate between half-chair and boat, the greater distortion of these rings being caused by the presence of both an sp^2 carbon atom and the heteroatom in the position corresponding to the C(3) of bicyclo[3.3.1]nonane.[4]

Considering the molecular packing of bridgehead heterocycles **2** and **3**, it should be mentioned that both compounds crystallize in groups with either the plane (*Cc* for **2**) or the centre ($P2_1/c$ for **3**) of symmetry; consequently, both enantiomers are present in each structure. The difference in the molecular packing of compounds **2** and **3** is caused by the presence of intermolecular contacts N–H···S (2.57 Å) in diazathione **3** (Figure 2).

Figure 3(*a*) shows that the benzoyl group of **4**[§] has *Z*-configuration with respect to the C=N double bond. The calculation of the puckering parameters (Table 1) for the rings in the bridgehead framework of this structure indicates that the piperidine cycle [C(7)–C(3)–C(4)–C(5)–C(6)–N(1)] adopts a conformation close to chair analogously to compounds **2** and **3**. However, the presence of the bulky *N*-benzoyl substituent in **4** leads to a greater distortion of another ring in a boat direction due to the steric repulsions, so that the cycle formed by the C(7), N(1), C(1), S(1), C(2) and C(3) atoms has a conformation intermediate between boat and envelope. Note that this ring represents an example when

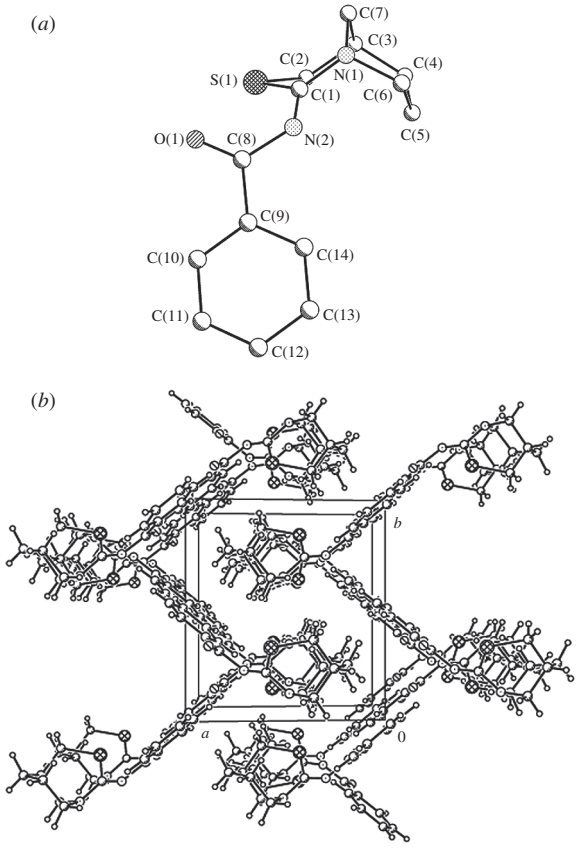


Figure 3 (*a*) Molecular structure and (*b*) crystal packing of (2*Z*)-2-(*N*-benzoylimino)-3-thia-1-azabicyclo[3.3.1]nonane **4**.

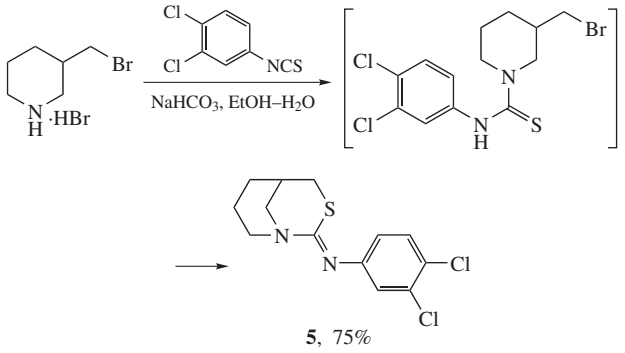
ZP puckering parameters, based on the angular parameters of the cycles, give more precise data than the CP ones (based on the atomic deviation from the average plane).[5] The calculation of the latter for the C(7)–N(1)–C(1)–S(1)–C(2)–C(3) ring in **4** gives an almost ideal boat conformation (Table 1), while the X-ray data [Figure 3(*a*)] indicate a noticeable distortion of the boat in accordance with the ZP parameters, the resultant conformation being intermediate between boat and envelope.

In the crystal structure of **4**, the molecules form dimers by means of symmetric contacts between the carbonyl oxygen at C(8) and the hydrogen atom at C(10) (*ortho*-position) of the benzene ring. There are short intermolecular contacts C(8)···H–C(2) (2.87 Å) and short contacts between hydrogen atoms of aromatic rings in the *meta*- and *para*-positions (2.44 Å), which connect dimers into chains along the *a* and *c* axes, respectively. The chains form folded sheets along the *c* and *b* axes, bridgehead fragments being arranged in the bends (curves) of the adjacent sheets. Thus, a 'macramé knots' structure is formed with the interlayers composed from bridgehead cores and benzene rings [Figure 3(*b*)].

The interesting molecular packing of compound **4** inspired us to synthesize its analogue **5** devoid of the above structure-forming elements and to investigate it by X-ray analysis. Compound **5** was synthesized as indicated in Scheme 1[¶] by the

[§] Compound **4** was synthesized as described previously[1] and crystallized from benzene. Crystals of **4** ($C_{14}H_{16}N_2SO$, M = 260.35) are monoclinic, space group $P2_1/c$, at 120 K: a = 9.4256(7), b = 10.3104 (8) and c = = 13.2200(10) Å, β = 99.497(2)°, V = 1267.13(17) Å^3, Z = 4, d_{calc} = = 1.365 g cm^{-3}, μ(MoKα) = 2.45 cm^{-1}. Intensities of 11694 reflections were measured on a SMART 1000 CCD [λ(MoKα) = 0.71073 Å, $2\theta < 54°$] and 2753 independent reflections (R_{int} = 0.0527) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The positions of the CH and CH_2 hydrogen atoms were located from the Fourier density synthesis. The refinement converged to wR_2 = 0.1432 and GOF = 1.087 for all independent reflections [R_1 = 0.0538 was calculated against F for 2151 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.1.[2,3]

[¶] *Synthesis of compound* **5**. A solution of sodium bicarbonate (1.85 g, 22 mmol) in a minimal amount of water was added dropwise to a stirred solution of 3,4-dichlorophenylisothiocyanate (2.04 g, 10 mmol) and (3-bromomethyl)piperidine hydrobromide (2.56 g, 10 mmol) in 30 ml of methanol. When the formation of the precipitate was over, it was filtered off and recrystallized from dioxane to yield 2.1 g (70%) of compound **5** as a white solid, mp 97–99 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.38 (d, 1H), 6.99 (d, 1H), 6.73 (dd, 1H), 4.19 (dd, 1H), 3.64 (dd, 1H), 3.25 (d, 1H), 3.15 (d, 1H), 3.11 (d, 1H), 2.84 (dd, 1H), 2.51 (d, 1H), 2.10–1.40 (m, 4H). MS (ESI), m/z: 302 [$C_{13}H_{14}Cl_2N_2S$]$^+$, 301. Found (%): C, 51.58, H, 4.84; N, 9.24. Calc. for $C_{13}H_{14}Cl_2N_2S$ (%): C, 51.83; H, 4.68; N, 9.30.



Scheme 1

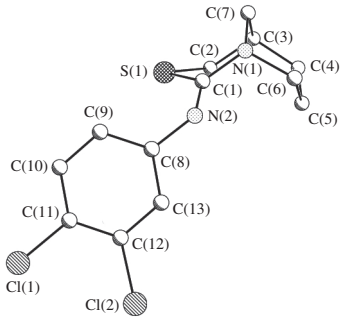


Figure 4 Molecular structure of (2*Z*)-2-(3,4-dichlorophenylimino)-3-thia-1-azabicyclo[3.3.1]nonane **5**.

reaction of 3-(bromomethyl)piperidine hydrobromide with corresponding dichlorobenzoylisothiocyanate. In this reaction, the intermediate thiourea underwent cyclization to give the desired bicyclic product in a good yield. It is noteworthy that this synthetic procedure is much more convenient and affords an essentially higher yield than that in a similar synthesis of compound **4**.[1]

The X-ray study of compound **5**[††] (Figure 4) showed that its configuration (*Z*, in respect to the C=N double bond) and rings conformations (chair-intermediate between boat and envelope) are analogous to that of compound **4** (Table 1). The molecular packing of **5** (though being different from that of **4**) retains the zigzag motifs, namely, the chains along the axis *b* with bicycles located in the chain angles. Short contacts N···Cl (3.056 Å) are present in the crystal structure of **5**.

Zigzag chains in **5** are positioned at distance *a* in respect to each other and form the layers parallel to the *ab* plane; the distance between the layers is *c*/4. That leads to changes in the molecular packing of **5** in comparison with **4**, namely, to the absence of interlayers composed from bridgehead bicycles and aromatic rings.

Thus, the investigation of the molecular and crystal structures of four bicyclo[3.3.1]nonane hetero-analogues with nitrogen and sulfur atoms allowed us to determine ring conformations in the bridgehead cores and reveal an interesting molecular packing of (2*Z*)-2-(*N*-benzoylimino)-3-thia-1-azabicyclo[3.3.1]nonane **4**.

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[††] Compound **5** was crystallized from benzene. Crystals of **5** ($C_{13}H_{14}Cl_2N_2S$, M = 301.22) are orthorhombic, space group *Pbca*, at 120 K: a = 9.2114(7), b = 14.1034(10) and c = 20.7673(15) Å, V = 2697.9(3) Å^3, Z = 8, d_{calc} = = 1.483 g cm^{-3}, μ(MoKα) = 6.18 cm^{-1}. Intensities of 29853 reflections were measured on a SMART 1000 CCD diffractometer [λ(MoKα) = = 0.71073 Å, $2\theta < 60°$] and 3922 independent reflections (R_{int} = 0.0336) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The positions of the CH and CH_2 hydrogen atoms were located from the Fourier density synthesis. The refinement converged to wR_2 = 0.1456 and GOF = 1.090 for all independent reflections [R_1 = 0.0564 was calculated against F for 3216 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.1.[2,3]

CCDC 843178–843181 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2011.

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