

Synthesis and Study of Influence of the Methylene Group Quantity on the Structural Behavior of Polymethylene-Quinazolinethiones

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Abstract: 6,7,8,10-Tetrahydropyrrolo[2,1-b]quinazolin-10-thione (**4**), 6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-thione (**5**), and their seven-membered homologue - 6,7,8,9,10,12-hexahydroazepino[2,1-b]quinazolin-12-thione (**6**) have been synthesized by interaction of corresponding quinazolones (**1-3**) with phosphorus pentasulfide. First time the comparable X-ray crystal structure analysis of polymethylenequinazolinethiones (**4-6**) are studied. It was revealed some regularity of the structure of obtained thiones **4-6** by XRD and identified the conformational state cycloalkanoic rings and the reactivity of the methylene protons at C-6.

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INTRODUCTION

It is known that tricyclic quinazolones, which are condensed with pyrrole, piperidine and azepine rings are different from each other, both chemical and biological point of view. Previously it has been proved that the increase of the number of methylene groups adversely affect on reactivity of methylene groups protons in position 6. It was interesting to study the effect of thiocarbonyl group on the reactivity and structural behavior of polymethylenequinazolinethiones.

Earlier the polymethylenequinazolones (**1-3**) and their different substituted derivatives were subjected to various reactions: reduction, acylation, bromination, nitration, formylation and condensation with aldehydes [Shakhidoyatov, 1983; Shakhidoyatov and Kaisarov, 1998; Shakhidoyatov et al., 1976, 1977, 2011; Turdibaev et al., 2011; Elmuradov et al., 2010; Abdurazakov et al., 2009]; wherein was revealed that depending on the structure of the starting reagents and reaction conditions the reaction goes in different directions. It should be emphasized that the penta-, -hexa-, and heptamethylenequinazolones (**1-3**) very hard / or do not react with electrophilic (acid chlorides, formylating agent, aldehydes and etc.) reagents. These results also demonstrated using deuterium H → D exchanges of 6-CH₂ protons in the presence of acid and alkali catalysts in various solvents [Shakhidoyatov et al., 2014].

MATERIALS AND METHODS

¹HNMR spectra was recorded in CD₃COOD and CDCl₃, on Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxane

(HMDSO) was used as internal standard, chemical shift δ of ¹H was recorded in ppm.

Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected. IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer) as KBr pellets.

The reactionary process was monitored by TLC on Whatman UV-254 precoated aluminum plates using C₆H₆/CH₃OH (5:1) solvent system and developed plates were visualized under UV lamp and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na₂SO₄ and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.

Unit cell parameters of the crystal **5** were determined and refined on a CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using Cu Kα-radiation (300 K, graphite monochromator). A three dimensional data set of reflections was obtained on the same diffractometer. Absorption corrections were applied using a semi-empirical method in the SADABS program [Sheldrick, 1996]. X-ray diffraction experiment for crystal **6** was carried out by Stoe STADI-IV diffractometer using Mo Kα-radiation (300 K, graphite monochromator). Absorption correction was not applied.

Synthesis of thiones **4-6** was done by the method of [Shakhidoyatov and Kadyrov, 1977]: 36 mmol of compounds **1-3** and 36 mmol P₂S₅ in m-xylene (or pyridine) was refluxed for 3 hours. The mixture was cooled to room temperature, the precipitate was filtered off. The precipitate was treated with 10% aqueous NaOH solution, left for an hour, then

filtered, washed with water to neutral pH, and dried. Recrystallization from hexane (or cyclohexane) gave reaction products **4-6** in good yields.

6,7,8,10-Tetrahydropyrrolo[2,1-b]quinazolin-10-thione (**4**)

Yield: 83%, $C_{11}H_{10}N_2S$, mp 138°C (hexane), R_f 0.72 (benzene : methanol, 5: 1). 1H NMR (δ , ppm, J/Hz): 8.67 (1H, dd, J=8.3, J=1.7, H-1), 7.69 (1H, td, J=8.3, J=1.7, H-3), 7.59 (1H, dd, J=8.3, J=1.2, H-4), 7.43 (1H, td, J=8.3, J=1.2, H-2), 4.47 (2H, t, J=7.5, 8-CH₂), 3.25 (2H, t, J=7.9, 6-CH₂), 2.28 (2H, m, 7-CH₂). IR (ν , cm⁻¹): 1603 ($\nu_{C=N}$), 1474 (ν_{C-N}), 1293 (ν_{C-S}).

6,7,8,9-Tetrahydro-11H-pyrido[2,1-b]quinazolin-11-thione (**5**)

Yield: 70%, $C_{12}H_{12}N_2S$, mp 118-120°C (hexane), R_f 0.88 (benzene: methanol, 5: 1). 1H NMR (δ , ppm, J/Hz): 8.73 (1H, dd, J=8.2, J=1.6, H-1), 7.7 (1H, t, J=8.2, J=1.6, H-2), 7.5 (1H, d, J=8.2, H-3), 7.4 (1H, t, J=8.2, H-4), 4.55 (2H, t, J=6.2, 9-CH₂), 3.0 (2H, t, J=6.9, 6-CH₂), 2.0 (2H, m, 8-CH₂), 1.92 (2H, m, 7-CH₂). IR (ν , cm⁻¹): 1584 ($\nu_{C=N}$), 1471 (ν_{C-N}), 1270 (ν_{C-S}).

6,7,8,9,10,12-Hexahydroazepino[2,1-b]quinazolin-12-thione (**6**)

Yield: 81%, $C_{13}H_{14}N_2S$, mp 104-106°C (cyclohexane), R_f 0.83 (benzene: methanol, 5: 1). 1H NMR (δ , ppm, J/Hz): 8.69 (1H, dd, J=8.3, J=1.5, H-1), 7.77 (1H, dd, J=8.2, J=1.3, H-4), 7.58 (1H, td, J=8.2, J=1.5, H-3), 7.44 (1H, td, J=8.3,

J=1.3, H-2), 5.0 (2H, t, J=5.2, 10-CH₂), 3.10 (2H, t, J=6.4, 6-CH₂), 1.77-1.87 (6H, m, 7,8,9-(CH₂)₃). IR (ν , cm⁻¹): 1589 ($\nu_{C=N}$), 1472 (ν_{C-N}), 1267 (ν_{C-S}).

RESULTS AND ITS DISCUSSION

6,7,8,10-Tetrahydropyrrolo[2,1-b]quinazolin-10-one (alkaloid deoxyvasicinone, **1**) 6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (alkaloid mackinazolinone, **2**) was first isolated from the plants *Peganum Harmala* [Tulyaganov and Nazarov, 2000], *Mackinlaya Subulata Philipson* [Fitzgerald et al., 1966] and seven membered homologue - 6,7,8,9,10,12-hexahydroazepino[2,1-b]quinazolin-12-one (**3**) was synthesized by cyclization of anthranilic acid (or its esters) with lactams in the presence of condensing agents (phosphorus oxychloride, thionyl chloride and etc.) [Shakhidoyatov et al., 1974; Lee et al., 2003].

First thio-analogues of tricyclic quinazolinone - 6,7,8,10-tetrahydropyrrolo[2,1-b]quinazolin-10-thione (**4**) synthesized by reaction of deoxyvasicinone with phosphorus pentasulfide in *m*-xylene [Shakhidoyatov and Kadyrov, 1977]. In the present work we have carried out the synthesis of polymethylenequinazolinethiones (**4-6**) according to the modified method [Shakhidoyatov and Kadyrov, 1977]. Condensation of anthranilic acid with lactams in the presence of phosphorous oxychloride to give compound **1-3**, which under the action of phosphorus pentasulfide in pyridine are converted into the corresponding thiones (**4-6**):

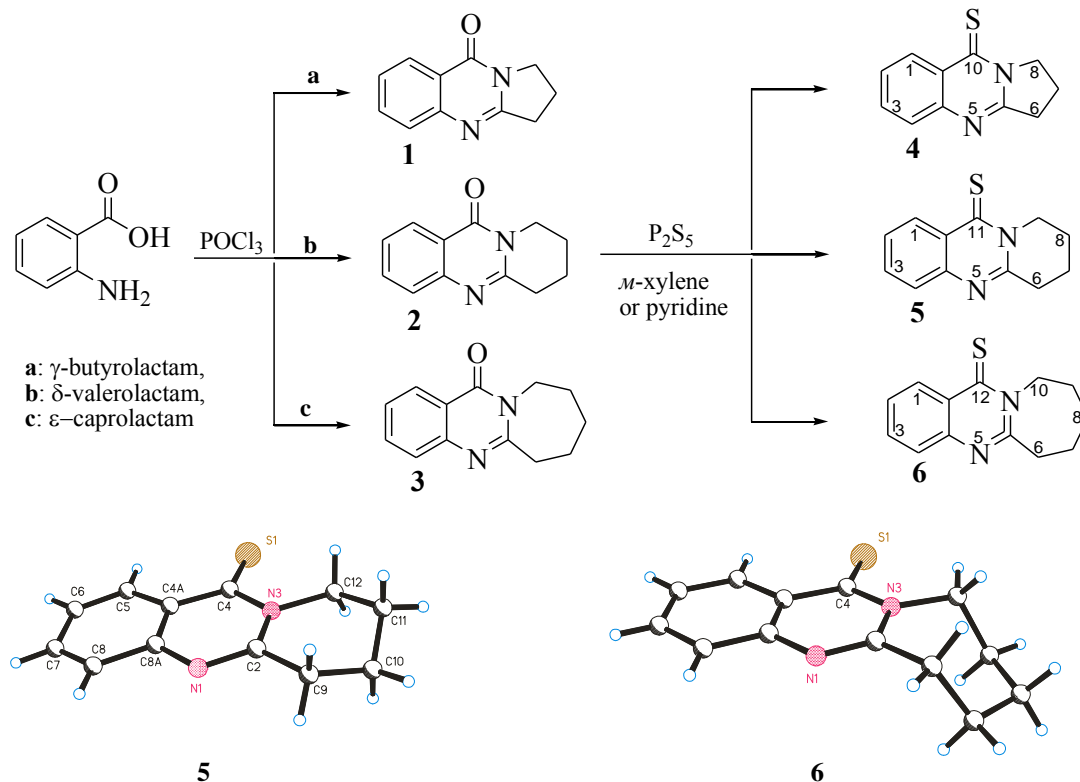


Fig.1. Structures of **5** and **6** molecules by XRD.Table 1: Basic crystallographic parameters and characteristics of the X-ray diffraction experiments for **5** and **6**.

Parameters	5	6
Molecular formula	C ₁₂ H ₁₂ N ₂ S	C ₁₃ H ₁₄ N ₂ S
The molecular weight, g mol ⁻¹	216.30	230.32
space group	P2 ₁ 2 ₁ 2 ₁	P-1
Z	4	2
a, Å	5.039(1)	8.213(3)
b, Å	7.717(3)	8.726(4)
c, Å	26.643(8)	8.906(3)
α, °	90	90.31(3)
β, °	90	95.44(3)
γ, °	90	114.47(3)
V, Å ³	1036.0(5)	577.6(4)
ρ, r/cm ³	1.387	1.324
Crystal size (mm)	0.65 x 0.10 x 0.08	0.75 x 0.55 x 0.20
Scan area	3.3 < θ < 66.0°	1.7 < θ < 26.0°
μ _{exp} (mm ⁻¹)	2.47	0.25
The number of reflections	959	2270
The number of reflections with I > 2σ(I)	559	1802
R ₁ (I > 2σ(I) and general)	0.087(0.140)	0.050(0.068)
wR ₂	0.287	0.123
GOOF	1.01	1.14
Difference peaks of electron density (eÅ ⁻³)	0.22 and -0.49	0.15 and -0.23
CCDC	1482606	1482607

The structures were solved using the SHELXS-2014 program and refined by SHELXL-2014 [Sheldrick, 2015]. All non-hydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F²). Positions of H atoms were found geometrically and refined as riding with fixed Uiso (1.2 of the parent atoms). Results from the X-ray diffraction experiments were deposited in the Cambridge Crystallographic Data Centre (CCDC). Table 1 presents the principal crystallographic parameters and the characteristics of the XRD experiments and crystal structure refinement calculations.

The X-ray structure of the molecules **5** and **6** shown in Figure 1. In the molecules quinazoline moiety is flat with accuracy 0.018 Å and 0.011 Å, respectively. The six-membered tetramethylene ring (**5**) has a half-chair conformation with the deviation of C10 and C11 atoms -0.41 Å and 0.26 Å from the plane of the remaining four atoms of the cycle. Seven-membered pentamethylene ring of **6** has the chair conformation.

In the crystals of the compounds **5** and **6** molecules are located at distances of van-der-Waals interactions, and shortened intermolecular contacts are not observed. In the crystal of **5** is observed π-π stacking interaction between the pyrimidine and benzene rings of the molecules related by translational axis *a*, the distance between the centroids of the rings is equal to 3.812 (8) Å. Such interaction is observed in the crystal of **6** between pyrimidine rings of molecules related by center of symmetry, the distance between the centroids of the rings is equal to 3.823 (2) Å.

It is noteworthy that by increasing number of the methylene groups in the polymethylene ring of the molecules compounds crystallizes with lower

symmetry, since trimethylenequinazolinethione (**4**) crystallizes with space group of R3c [Nasrullaev et al., 2012], the crystals of **5** and **6** have a space groups P2₁2₁2₁ and P-1, respectively (Table 1). In the crystal structures of oxygen analogues (**1-3**) such changes of the symmetry is not observed [Tashkhodzhaev et al., 1995; Tashkhodzhaev et al., 1995].

CONCLUSION

Synthesis and X-ray crystal structure analysis of polymethylenequinazolinethiones (**4-6**) have been carried out. Structure of the obtained thiones **4-6** was studied by XRD and it was revealed some regularity of conformational state of cycloalkanoic rings and the reactivity of the methylene protons at C-6.

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