Chemistry of Natural Compounds, Vol. 46, No. 4, 2010

SYNTHESIS AND CRYSTAL STRUCTURE OF 5-METHYL-2-(*N*-ANABASINYL)-5,6-DIHYDRO-1,3-THIAZIN-4-ONE FROM THE ALKALOID ANABASINE

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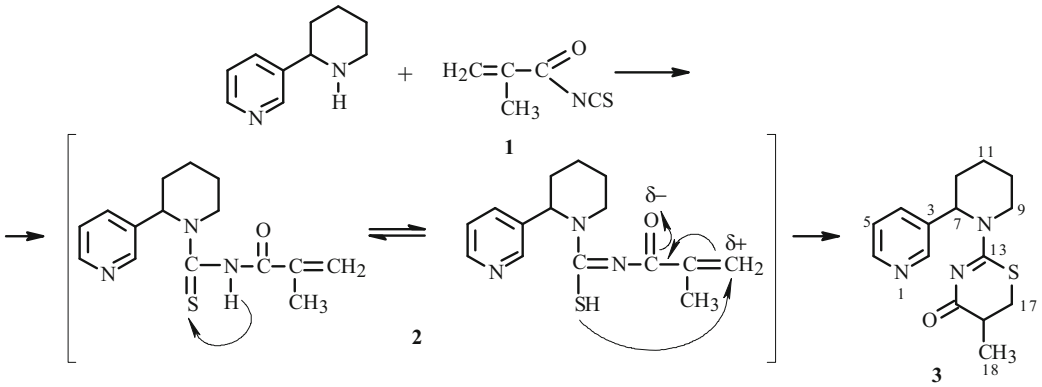
UDC 547.94; 547.298.61

*5-Methyl-2-(*N*-anabasinyl)-5,6-dihydro-1,3-thiazin-4-one was synthesized in one step from the alkaloid anabasine. Its structure was proved by IR and PMR spectroscopy, mass spectrometry, and an x-ray structure analysis.*

Keywords: anabasine alkaloid, methacryloylisothiocyanate, intramolecular heterocyclization, 5,6-dihydro-1,3-thiazin-4-one, x-ray structure analysis.

We have previously synthesized thiourea derivatives of the alkaloids cytisine, anabasine, *d*-pseudoephedrine, and *l*-ephedrine [1–3]. Many thiourea derivatives based on these alkaloids are excellent synthons for synthesizing new heterocyclic derivatives [4, 5]. It was found [6] during preparation of the thiosemicarbazide derivative of isonicotinic acid that reaction of the corresponding hydrazide with methacryloylisothiocyanate produced its intramolecular heterocyclization product, 5,6-dihydro-1,3-thiazin-4-one.

Therefore, we investigated the reaction of anabasine with methacryloylisothiocyanate (**1**), which was prepared *in situ* (without isolation) by heating methacryloylchloride with potassium thiocyanate in acetone. The reaction occurred with intramolecular heterocyclization of the intermediate methacrylamide derivative **2** into the corresponding product **3**. The reaction occurred under rather mild conditions at 25–30°C in acetone.



The yield and purity of the synthesized derivative 5,6-dihydro-1,3-thiazin-4-one (**3**) varied depending on the rate and order of addition of the reagents. The most acceptable (up to 40%) yields of **3** were obtained with slow dropping of a freshly prepared acetone solution of **1** to a vigorously stirred solution of anabasine.

Only trace amounts of heterocyclization product **3** could be detected with the reverse order of addition of reagents to the reaction mixture. Its amount increased with time as a result of gradual spontaneous intramolecular cyclization of **2**. The reaction mixture contained after work up also several unidentified crystalline and oily side products with –NH, –SCN, and C=O groups (IR spectroscopy data). As a result, it was impossible to separate and characterize in a pure state the methacrylamide intermediate **2**.

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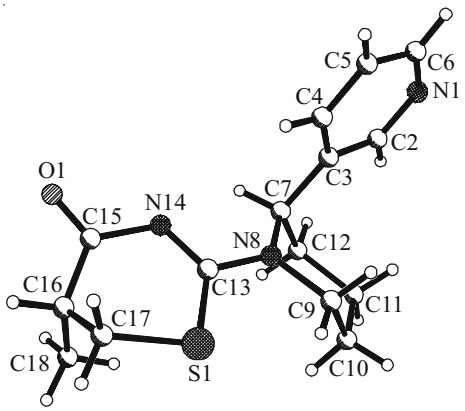

Fig. 1. Molecular structure of **3**.

Purification by column chromatography and double recrystallization of thiazine derivative **3** gave a white crystalline compound that was soluble in most organic solvents except saturated hydrocarbons.

Cyclization of intermediate **2** into 5-methyl-2-(*N*-anabasinyl)-5,6-dihydro-1,3-thiazin-4-one (**3**) occurred apparently via intramolecular nucleophilic attack of the S atom in the thiol form at the electron-deficient C atom of the unsaturated C=C bond of **2**.

The formation of cyclic 5,6-dihydro-1,3-thiazin-4-one (**3**) was proved by the lack in the PMR spectrum of methylene protons (=CH_2), which appear for analogous methacrylic derivatives as two doublets at 5.70 and 6.00 ppm, and a singlet for the amide N–H proton, which was involved in the thione–thiol rearrangement required for cyclization. Furthermore, the CH_3 methyl protons in the PMR spectrum of **3** split into a doublet, indicating that they were coupled to the methine CH-proton of the thiazine ring. Resonances of the methine and methylene protons appeared as a multiplet and two doublets of doublets, which also was consistent with formation of **3** with the aforementioned cyclization pattern.

The rapid formation of 5-methyl-2-(*N*-anabasinyl)-5,6-dihydro-1,3-thiazin-4-one (**3**) upon addition of **1** to anabasine is probably explained by the excess of anabasine in the reaction mixture because it is a rather strong base and increases noticeably the formation of the thiol form of **2**, which plays a decisive role in the intramolecular cyclization.

An x-ray structure analysis of **3** was performed in order to prove finally its structure and to establish the molecular structure of the tricyclic 5-methyl-2-(*N*-anabasinyl)-5,6-dihydro-1,3-thiazin-4-one (**3**). Figure 1 shows a general view of **3**.

The bond lengths and angles in **3** were close to normal [7]. The piperidine ring adopted an ideal chair conformation (ΔC_s^8 = 0.7 Å), like in anabasine *O*,*O*-diethylthiophosphate [8], *N*-anabasino(2-vinyloxyethylamino)methanethione [9], and *N*-(anabasino-1-carbonothioyl)furan-2-carboxamide [2]. The pyridine ring is planar within ±0.007 Å and is oriented axially (C3C7C8C9 torsion angle = –70.6°) relative to the piperidine ring, in contrast with anabasine *O*,*O*-diethylthiophosphate, where it is oriented equatorially. Such an orientation of the pyridine ring has been observed previously in *N*-anabasino(2-vinyloxyethylamino)methanethione [9] and *N*-(anabasino-1-carbonothioyl)furan-2-carboxamide [2]. In our opinion, such an orientation is due to non-bonded repulsion between the bulky substituent and the pyridine ring. The bulky thiazine substituent on N8 is oriented equatorially. The thiazine ring itself has a distorted twist-chair conformation ($\Delta C_2^{17,16}$ = 6.21 Å). The ring is distorted because of the C16 methyl that repels this atom to the α-side. The carbonyl group is oriented equatorially. Atom O1 lies in the plane of N14C13S1C17. In general the ring is stabilized by the anti-orientation of the carbonyl and methyl groups (torsion angle O1C15C16C18 = 97.1°).

Computer prediction of the biological activity of **3** using the on-line [10] PASS program (Prediction of Activity Spectra for Substances), which can predict a large number of probable types of biological activity based on the structural formula [11], showed very high coefficients for manifestation of nootropic activity (probability coefficient for manifestation of such activity P_a = 0.944; probability coefficient for lack of this type of activity P_i = 0.003).

EXPERIMENTAL

IR spectra were recorded in KBr pellets on an Avatar-320 spectrometer; PMR spectra, in DMSO-d_6 on a Bruker DRX 500 spectrometer at 500 MHz relative to TMS internal standard. Mass spectra were taken in a Finnigan MAT.INCOS 50 instrument with direct insertion at ionization energy 70 eV. TLC was performed on Sorbfil plates using 2-PrOH:benzene:NH_4OH (10:5:2) with detection by iodine vapor.

X-ray Structure Analysis. Cell constants and intensities of 2235 independent reflections were measured on a Bruker Apex-II CCD automated diffractometer at –50° using MoK_α-radiation, graphite monochromator, θ/2θ-scanning, and 2θ ≤ 52°. The crystals were monoclinic and transparent (0.01 × 0.08 × 0.40), a = 6.829(1), b = 7.168(1), c = 14.632(1) Å, β = 97.29°, V = 710.4(1) Å^3, d_{calcd} = 1.353 g/cm^3, Z = 2 ($C_{15}H_{19}N_3OS$), space group $P2_1$. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms. H atoms were calculated geometrically and placed using a rider model. The calculations used 1600 reflections with $I > 2\sigma(I)$. The final agreement factors were R = 0.0450 and wR_2 = 0.0973. The structure was solved using the SIR-2002 program [12] and refined using the SHELXL-97 program [13]. The geometric parameters were deposited in the CCDC (CCDC 736689).

5-Methyl-2-(*N*-anabasinyl)-5,6-dihydro-1,3-thiazin-4-one (3). A solution of anabasine (3.24 g, 0.02 mol) in acetone (5 mL) at 30°C was stirred vigorously, treated dropwise over 1 h with an acetone solution of methacryloylisothiocyanate that was prepared by refluxing for 2 h methacryloylchloride (2.20 g, 0.021 mol) and potassium thiocyanate (2.04 g, 0.021 mol) in acetone (30 mL), and stirred at 30–40°C for another approximately 4 h. The solvent was distilled off. The brown oily residue was dissolved in benzene (30 mL) and passed over a column packed with silica gel (eluent benzene:2-PrOH, 2:1). The eluent was evaporated. The product was extracted from the resulting oily residue by boiling hexane:benzene (1:2, 3 × 20 mL). The resulting filtrate was poured into a beaker, cooled to 25°C, diluted with three times the amount of hexane, and cooled to 0°C. The solvent was decanted from the viscous light-yellow oil deposited on the bottom of the beaker. The oil was recrystallized from hexane:acetone (2:1). Small pieces of a white crystalline precipitate formed upon cooling to –10°C and were filtered off to afford **3** (2.37 g, 41%) as a white crystalline compound, mp 121–123°C. Crystals for the x-ray structure analysis were grown by slow natural evaporation of solvents after recrystallization from hexane:benzene (2:1). Elemental analysis of **3** agreed with that calculated. $C_{15}H_{19}N_3OS$. IR spectrum (KBr, ν, cm^{-1}): 1653 (–C=O), 1487 (C=N), 1309 (C–N). Mass spectrum (EI, 70 eV, m/z, I_{rel}, %): 289 (10) $[M]^+$, 247 (26), 214 (82), 161 (100), 86 (25), 41 (54). PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.13 (3H, d, J = 6.8, CHC$\underline{H}_3$), 1.36-1.92 (6H, m, H-10, H-11, H-12), 2.46 (2H, m, H-9), 2.93 (1H, br.s, C$\underline{H}$CH$_3$), 3.02 (1H, t, $J_{7,12}$ = 10.7, H-7), 3.05, 3.31 (2H, ddd, J = 4.52, 11.01, S–C$\underline{H}_a\underline{H}_b$), 7.42 (1H, dd, $J_{5,6}$ = 5.02, $J_{5,4}$ = 4.71, H-5), 7.61 (1H, d, H-4), 8.43 (1H, d, H-6), 8.50 (1H, s, H-2).

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