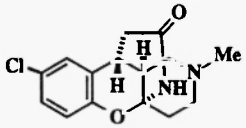
STEREOSELECTIVE SYNTHESIS AND STRUCTURE DETERMINATION OF A NEW 2-METHYL-4-OXO-2,6-METHANO-3,4,5,6-TETRAHYDRO-2H-1,3-BENZOXAZOCINE-5-THIOCARBOXAMIDE

Yaroslav V. Bilokin (Belokon),*[1] Sergey N. Kovalenko, and Valentin P. Chernykh

Department of Organic Chemistry, Ukrainian Academy of Pharmacy, Kharkov 310002, Ukraine

Abstract: Stereoselective one-step synthesis of a new 2-methyl-4-oxo-2,6-methano-3,4,5,6-tetrahydro-2H-1,3-benzoxazocine-5-thiocarboxamide **3** from readily available 2-oxo-2H-1-benzopyran-3-thio-carboxamide **2** has been described. The structure of **3** has been elucidated by X-ray crystallography and NMR spectroscopy. Using the thioamide group of **3** as a synthon, compound **5** with 1,3-benzoxazocine, thiazole and coumarin moieties has been synthesized.

The interest in the chemistry of 1,3-benzoxazocines and their analogs has been reflected in a number of publications devoted to the synthesis of heterocycles related to benzoxazocine, xanthene and benzopyranopyridines.[2,6a] Our program is directed towards the synthesis of novel 5-substituted 2H-1,3-benzoxazocine derivatives. These compounds have an attractive synthetic target because of their relationship to antidepressant *Lortalamine* (LM1404) **1**.[3] However, there are no examples for synthesis of 4-oxo-2,6-methano-3,4,5,6-tetrahydro-2H-1,3-benzoxazocines with a thioamide function or a heterocyclic moiety at position 5.



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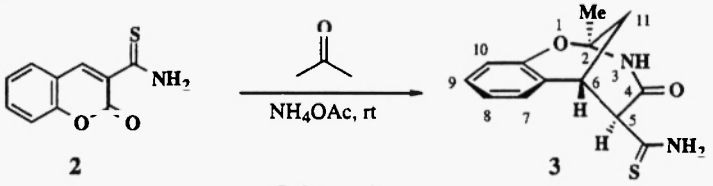
In this communication we wish to report a stereoselective one-step preparation of 2-methyl-4-oxo-2,6-methano-3,4,5,6-tetrahydro-2H-1,3-benzoxazocine-5-thiocarboxamide **3**[4] from readily available 2-oxo-2H-1-benzopyran-3-thiocarboxamide **2**.[5] One of the major obstacles to be overcome in the synthesis of 1,3-benzoxazocine derivatives is the lack of chemoselectivity with preferential formation of benzopyranopyridines and other polyheterocyclic compounds.[6] For example, it was reported[6c] that compound **2** reacted with various ketones in the presence of ammonium acetate in refluxing ethanol to afford only 5-oxo-5H-[1]benzopyrano[3,4-c]pyridine-4(3H)-thione derivatives. Our approach to the synthesis of 2H-1,3-benzoxazocine **3** was based on coumarin ring transformation - Michael condensation of coumarin **2** with acetone in the presence of excess of NH_4OAc under mild conditions. The synthesis of **3** was accomplished as shown in Scheme 1.[7] On treatment with 3 equivalents of ammonium acetate in acetone at rt, thiocarboxamide **2** produced chemo- and stereoselectively compound **3** in 61% isolated yield. A possible mechanism for formation of 1,3-benzoxazocine moiety was discussed in the literature.[2c,d]



2 **3**

Scheme 1

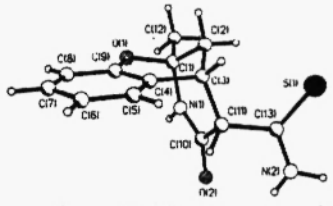
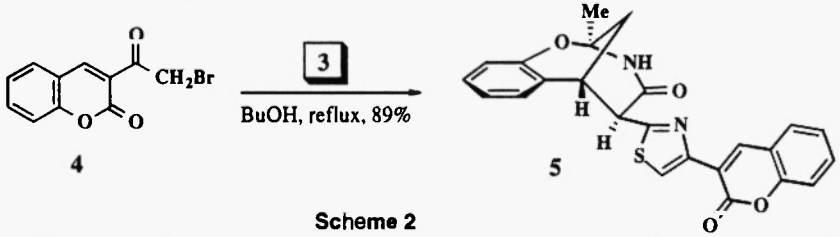


Figure 1: X-Ray structure of **3**[9]

The structure of compound **3** was determined through a complete NMR analysis,[8] which included 1- and 2D experiments. On their basis complete carbon and proton chemical shift assignments were done. The relative stereochemistry of **3** was assigned by X-ray diffraction analysis.[9]



4 **5**

Scheme 2

Thioamides may serve as versatile intermediates in heterocyclic synthesis[10] and the presence of the thioamide group in compound **3** opens possibilities for further structure modifications. In view of the ubiquity of thiazole[10b,11] and coumarin[12] fragments in a variety of biologically active compounds and utilizing the thioamide group of **3** as a synthon,

we synthesized compound **5**[13] (Scheme 2) with 1,3-benzoxazocine, thiazole and coumarin moieties[14] which can be considered as valuable pharmacophores.

Acknowledgments: The authors wish to thank Dr. Daniel Makula (Rhône-Poulenc Agrochimie, Lyon, France) for technical assistance, Dr. Vladimir N. Baumer (Institute for Chemistry at Kharkov State University) for X-ray analysis, and Dr. Alexander V. Turov (Kiev State University) for helpful discussions.

References and Notes

1. Present address: Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

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4. All chiral compounds in this work are racemic; only one enantiomer of each pair is addressed to in the text and displayed in the structural formulas.

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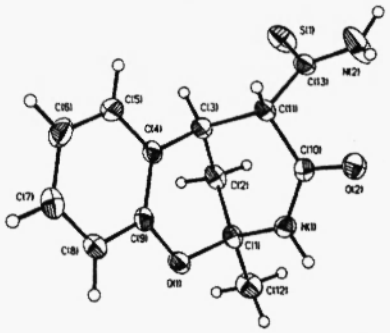
7. The preparation of **3**: A mixture of **2** (503mg, 2.45mmol) with anhydrous NH_4OAc (564mg, 7.32mmol) in 20mL of dry acetone was stirred for 48 hours at room temperature. After completion of the reaction, a white precipitate was filtered, washed with acetone/water (1/1, 2x20mL) and dried at room temperature in air. Recrystallization from BuOH afforded 643mg (61%yield) of the title product **3** with mp 227-229°C. IR (KBr), cm^{-1}: ν 3409m, 3293m (NH_2), 3211m (NH), 1653vs (C=O), 1592vs, 1492s, 1255m, 1175m, 1154m, 1070s, 755s. MS (EI, 70eV) *m/z* (r.i.): 262 (M^+, 8), 202 (M^+ - $CSNH_2$, 100), 184 (13), 110 (14). Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C 59.52; H 5.38; N 10.68; S 12.23. Found: C 59.81; H 5.21; N 10.79; S 12.09.

8. ^1H NMR (400MHz, $CDCl_3$/DMSO-d_6): δ 1.67 (s, 3H, CH_3); 1.93 (dd, 1H, J =13.4; 4.1 Hz; **H-11**); 2.88 (dd, 1H, J = 13.4; 2.0 Hz; **H-11'**); 3.53 (s, 1H, **H-5**); 3.69 (br t, 1H, H-6); 6.74 (dd, 1H, J = 7.4; 1.1 Hz; **H-10**, ArH); 6.90 (dt, 1H, J = 7.2; 1.1 Hz; **H-8**, ArH); 7.13 (dt, 1H, J = 7.7; 1.6 Hz; **H-9**, ArH); 7.30 (dd, 1H, J = 6.8; 1.5 Hz; **H-7**, ArH); 8.49 (s, 1H, NH); 9.14 (s, 1H, NH_2); 9.53 (s, 1H, NH_2).
^{13}C NMR (62MHz, $CDCl_3$/DMSO-d_6): δ26.5 (**C**CH_3); 28.4 (**C-11**); 34.0 (**C-6**); 59.9 (**C-5**); 82.1 (**C-2**); 116.6 (**C-10**, Ar); 120.5 (**C-8**, Ar); 124.0 (**C-6a**, Ar); 128.0 (**C-9**, Ar); 129.0 (**C-7**, Ar); 151.2 (**C-10a**, Ar); 167.9 (**C**=O); 201.2 (**C**SNH_2).

9. X-Ray analysis of **3**: yellowish needles were obtained from acetonitrile, $C_{13}H_{14}N_2O_2S$, FW = 262.3, triclinic, *a* = 5.5445(14), *b* = 9.090(3), *c* = 12.817(4) Å, V = 603.8(3) $Å^3$, soace group P1, Z = 2, D_c = 1.443 Mg m^{-3}, F(000) = 276, μ = 0.263 mm^{-1}. Data were measured using a Siemens P3/PC diffractometer, Mo-Kα radiation (λ = 0.71073 Å, graphite monochromator), and 2θ/θ-scans, with 5° < 2θ ≤ 55°. Reflections collected: 1667, independent reflections: 1578 (R_{int} = 1.53%), and observed reflections with I › 3σ(I): 1483. Lorentz and polarization corrections were applied to the data-set. The structure was solved by direct method and was refined by full-matrix least squares. The weighting scheme was ω = $[\sigma^2 (F) + 0.0000F^2]^{-1}$. Final R indices (obs. data): R = 0. 028, ωR = 0.0289 and R indices (all data): R = 0.0297, ωR = 0.0294. Non-H atoms refined with anisotropic displacement parameters, H-atoms - with isotropic displacement parameters. ORTEP drawing of **3** is shown beside.



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13. ^1H NMR, ^{13}C NMR, IR, and MS (EI) data for *2-methyl-4-oxo-2,6-methano-5-(4-(coumann-3-yl)thiazol-2-yl)-3,4,5,6-tetrahydro-2H-1,3-benzoxazocine* **5** are according to the structure.

14. On syntheses of 2-substituted 4-(coumarin-3-yl)thiazoles starting from 3-(ω-bromo)acetylcoumarin **4** and thioamides, see: Belokon, Y. V.; Kovalenko, S. N.; Silin, A. V.; Nikitchenko, V. M. *Khim. Geterotsikl. Soedin.* 1345 (1997).

Received on January 28, 1998