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Pyrazolo[2′,3′:3,4][1,3]oxazino[5,6-*b*]quinoxaline, a novel tetracyclic ring system

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Abstract—Reaction of 2-chloro-3-(3-chloro-1*H*-pyrazol-5-yl)quinoxaline and aldehydes does not afford the corresponding *N*-(α-hydroxyalkylated) derivatives but results in a cyclisation reaction to give a derivative bearing the hitherto undescribed pyrazolo[2′,3′:3,4][1,3]oxazino[5,6-*b*]quinoxaline system.

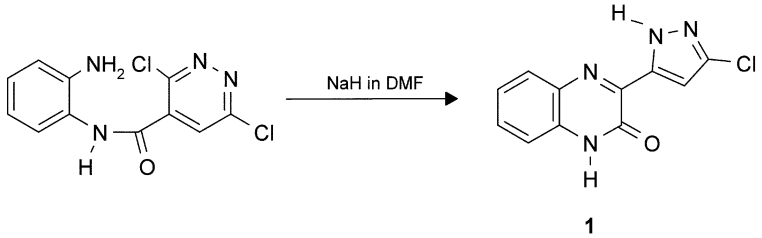
1. Introduction

In the course of our ongoing studies aimed at the synthesis of heterocyclic compounds of potential pharmaceutical relevance,[1–4] we were interested in novel derivatives bearing a 1,2-diazine core. The pyrazolyl-substituted quinoxalinone **1** became conveniently available by an unusual ring transformation reaction, which was found to occur by treatment of *N*-(2-aminophenyl)-3,6-dichloro-4-pyridazinecarboxamide with sodium hydride in dry *N*,*N*-dimethylformamide[2] (Scheme 1)

Starting from this heterocyclic compound **1**, potential antiinfective 2-amino substituted quinoxalines of type **3**[3] as well as [1,2,4]triazolo[4,3-*a*]quinoxalines **4**[4] which exhibit adenosine receptor antagonistic activities were prepared via the 2-chloroquinoxaline **2** (Scheme 2). The latter compound was formed by refluxing the lactam **1** in a mixture of phosphorus oxychloride and pyridine.[3]

Moreover, we have shown that the chloro compound **2** can be converted into the two isomeric *N*-acetyl derivatives **5a** and **5b**.[5]

N-(α-Hydroxyalkylated) pyrazole congeners, especially *N*-hydroxymethyl derivatives became an object of our interest as potential intermediates for the formation of novel bioactive compounds. In order to prepare the target *N*-hydroxymethylated compounds, 2-chloro-3-(3-chloro-1*H*-pyrazol-5-yl)quinoxaline **2** was treated with 37% aqueous formaldehyde in the presence of potassium carbonate (Scheme 3). Whereas *N*-acetylation of **2** led to a mixture of two isomers, the ratio depending on the reaction conditions,[5] employment of formaldehyde only resulted in the formation of one compound. However, spectroscopic data were not consistent with the expected structure of our target compounds. The mass spectrum showed that the reaction product possessed the elemental composition $C_{12}H_7ClN_4O$. Moreover, the ^1H NMR spectrum exhibited only signals of aromatic



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Scheme 1. Synthesis of compound **1**.

Keywords: pyrazolo[2′,3′:3,4][1,3]oxazino[5,6-*b*]quinoxaline; tetracyclic system; novel ring system.
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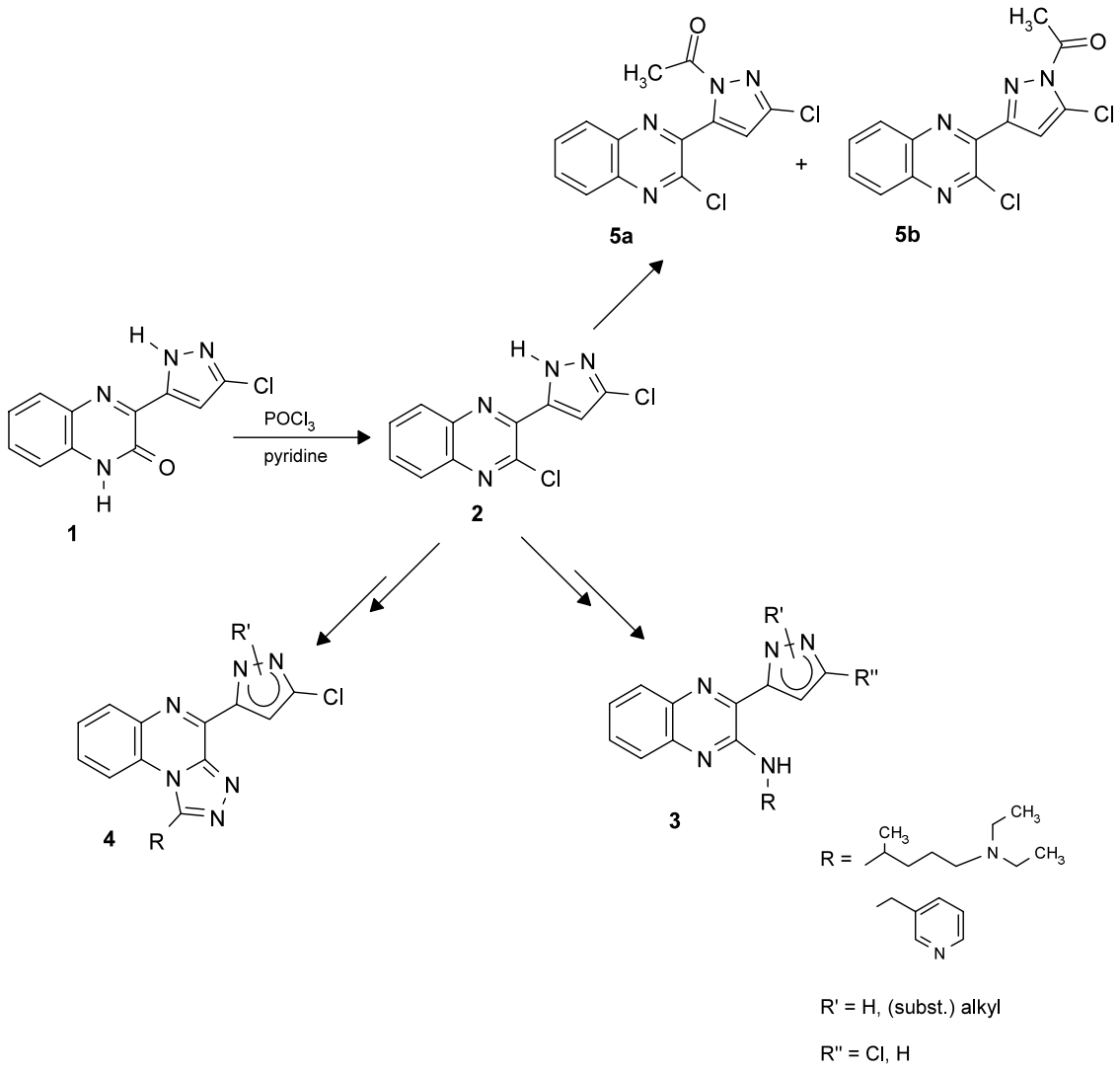
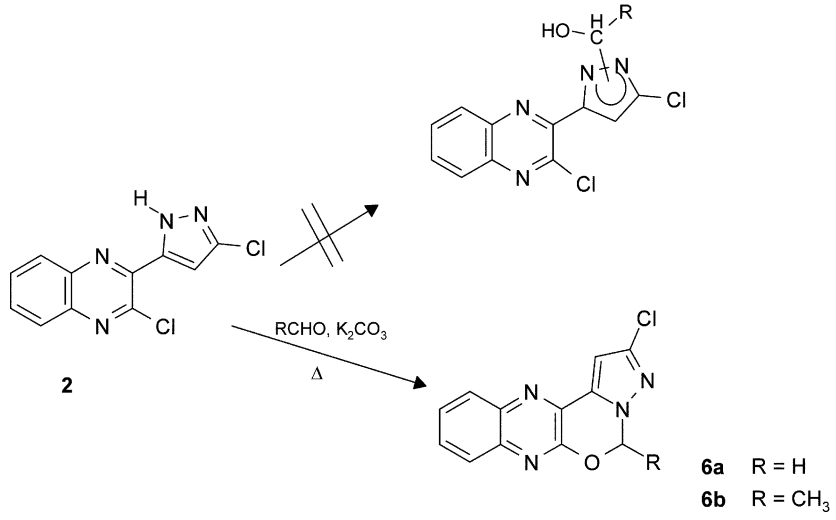


Scheme 2. Synthesis of pyrazolyl substituted quinoxaline derivatives.



Scheme 3. Formation of compounds of type **6**.

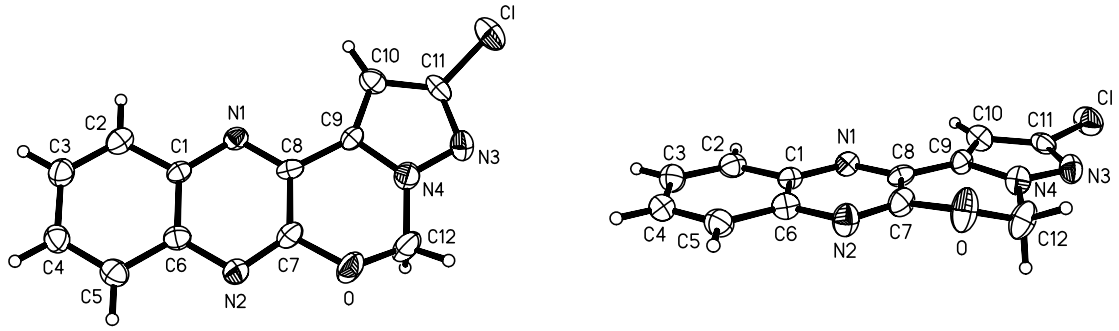


Figure 1. Thermal ellipsoid plots (30% ellipsoids) of **6a**.

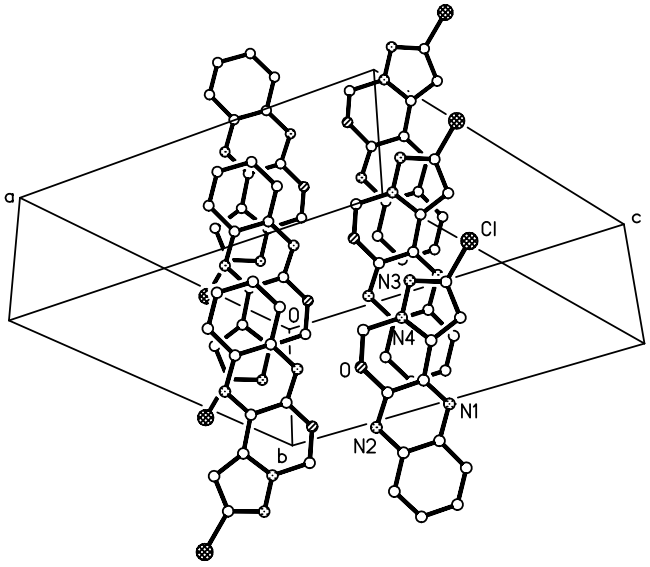


Figure 2. π-Stacking of **6a** in the crystalline state.

protons (multiplets), one pyrazole-CH (singlet, $\delta = 7.01$ ppm), and one methylene group (singlet, $\delta = 6.19$ ppm). Thus, under our experimental conditions, not only hydroxymethylation but also HCl elimination had taken place to yield a tetracyclic compound. Unequivocal proof for the postulated pyrazolo[2′,3′:3,4][1,3]-oxazino[5,6-*b*]quinoxaline structure was achieved by single crystal X-ray analysis of compound **6a** (see Figs. 1 and 2 and Experimental).

Performing the reaction with acetaldehyde instead of formaldehyde led to the analogous methyl substituted tetracyclic compound **6b**.

2. Experimental

2.1. 2-Chloropyrazolo[2′,3′:3,4][1,3]oxazino[5,6-*b*]quinoxaline 6a

A mixture of **2** (0.199 g, 0.75 mmol), potassium carbonate (0.194 g, 1.40 mmol), and 0.6 mL of aqueous formaldehyde (37%) in 5 mL of THF was heated under reflux for 5 h, then stirring was continued at room temperature for 12 h. The solvent was removed in vacuo and the residue was taken up in dichloromethane. This solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated to yield 0.166 g (75%) of pure compound **6a** (pale yellow powder), mp 172-174°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.11$–8.06 (m, 1H, quinoxaline-H), 7.97–7.92 (m, 1H, quinoxaline-H), 7.81–7.67 (m, 2H, quinoxaline-H), 7.01 (s, 1H, pyrazole-H), 6.19 (s, 2H, CH_2). EI MS (70 eV): $m/z = 258$ [M^+].

2.1.1. Crystal structure determination of 6a. The compound crystallized with difficulty in very thin hair-like to fibrous forms from all common solvents like methanol, ethanol, acetone, DMF and pyridine. The crystal used for X-ray diffraction, a pale yellow prism of 0.8×0.06×0.03 mm obtained from ethanol, was the thickest available. Crystal data: $C_{12}H_7ClN_4O$, $M_r = 258.67$, monoclinic, space group $P2_1/n$ (no. 14), $a = 13.875(8)$, $b = 5.814(4)$, $c = 15.120(9)$ Å, $\beta = 111.65(2)°$, $V = 1133.7(12)$ Å^3, $Z = 4$, $D_{calcd} = 1.516$ mg/m^3, $T = 301$ K, $\mu = 0.33$ mm^{-1}, $\lambda = 0.71073$ Å, $F(000) = 528$, X-ray data collection with a Bruker AXS Smart APEX CCD area detector system covered a hemisphere of the reciprocal space (Mo Kα radiation, $\theta \leq 22°$, 1675 ω-scan frames of 0.3° and 40 s); total reflections 3887, unique reflections 1333, $R_{int} = 0.092$. Structure solution with direct methods, structure refinement on F^2 (Bruker AXS Inc., Madison, WI, USA, 2002: programs SMART, version 5.626; SAINT, version 6.36A; XPREP, version 6.12; SHELXTL, version 6.10). Hydrogen atoms after check by a difference Fourier synthesis inserted in calculated positions. Final refinement: data/restraints/parameters = 1333/13/163, $R_1 = 0.044$ (observed data), $wR_2 = 0.086$ (all data). Bond lengths (Å): Cl–C(11) 1.713(5), O–C(7) 1.383(5), O–C(12) 1.401(5), N(1)–C(8) 1.314(5), N(1)–C(1) 1.375(4), N(2)–C(7) 1.299(6), N(2)–C(6) 1.374(4), N(3)–C(11) 1.340(6), N(3)–N(4) 1.359(5), N(4)–C(9) 1.366(5), N(4)–C(12) 1.452(6), C(1)–C(6) 1.406(6), C(1)–C(2) 1.419(5), C(2)–C(3) 1.365(5), C(3)–C(4) 1.401(6), C(4)–C(5) 1.370(5), C(5)–C(6) 1.418(5), C(7)–C(8) 1.419(6), C(8)–C(9) 1.453(6), C(9)–C(10) 1.357(6), C(10)–C(11) 1.389(6). The oxazine ring is notably non-planar with oxygen O and carbon C(12) off by −0.223(5) and +0.258(6) Å from the mean

plane of the molecule. Coherence of the structure and needle-like growth is obviously due to an efficient staircase-like π-stacking of the molecules with formation of infinite rods along the *b* axis of the unit cell. CCDC 218185 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk.

2.2. 2-Chloro-5-methylpyrazolo[2′,3′:3,4][1,3]oxazino[5,6-*b*]quinoxaline 6b

A mixture of **2** (0.199 g, 0.75 mmol), potassium carbonate (0.194 g, 1.40 mmol), and 5.0 mL of acetaldehyde in 3 mL of dichloromethane was heated under reflux for 5 h, then stirring was continued at room temperature for 12 h. The reaction mixture was diluted with dichloromethane and the organic phase was washed with sodium bisulfite (3×), water (3×), and brine, and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the remaining residue was purified by column chromatography (silica gel, dichloromethane/ethyl acetate, 50:1) followed by recrystallization from diisopropyl ether to yield 0.09 g (44%) of pure compound **6b** (pale yellow needles), mp 173–175°C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.11$–8.06 (m, 1H, quinoxaline-H), 7.96–7.91 (m, 1H, quinoxaline-H), 7.79–7.69 (m, 2H, quinoxaline-H), 7.02 (s, 1H, pyrazole-H), 6.31 (q, $J = 5.8$ Hz, 1H, CH), 2.07 (d, $J = 5.8$ Hz, 3H, CH_3).

In conclusion, the 2-chloro-3-(3-chloro-1*H*-pyrazol-5-yl)quinoxaline **2** was shown to represent a suitable precursor for the hitherto unknown pyrazolo-[2′,3′:3,4][1,3]oxazino[5,6-*b*]quinoxalines of type **6**.

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