Acylation of a Novel Quinoxalinyl Substituted Pyrazole Derivative. Synthesis, Quantum Chemistry Calculations, and X-ray Structure Analysis

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The preparation of *N*-acetylpyrazolyl-quinoxalines and results of semiempirical MO calculations are presented. The structure determination of the isomers **3a,b** was achieved by X-ray analysis.

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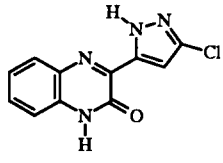
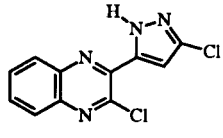
In continuation of studies aimed at the synthesis of potentially bio-active heterocyclic compounds we became interested in derivatives of the quinoxalinyl substituted pyrazole system. Recently, the novel pyrazolyl substituted quinoxalinone **1** became conveniently available by an unusual pyridazine → pyrazole ring contraction reaction [1]. The preparation of **2** as the starting material for our ongoing studies has been reported in a previous paper [2]. The *N*-acetyl derivatives of type **3** were now requested both as potential drug molecules and as educts for the synthesis of further compounds of pharmaceutical interest.



1



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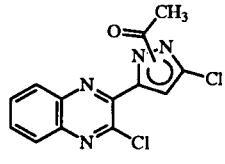


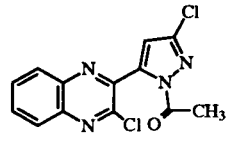
3

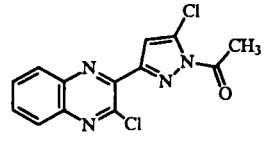
Treating **2** with acetic anhydride was shown to yield a mixture of the expected two isomeric products **3a,b** in a ratio depending strongly on the reaction conditions [3]. When the reaction was conducted under reflux temperature for several minutes, one isomer (δ = 6.66 ppm (pyrazole-H-4), δ = 2.70 ppm (CH_3)) was obtained almost quantitatively, whereas both isomers [4] were isolated when the reaction mixture was heated to 140° shortly followed by stirring at room temperature for several hours. When the temperature was raised for a very short period only up to 80°, the other isomer (δ = 7.17 ppm (pyrazole-H-4), δ = 2.85 ppm (CH_3)) was found predominantely in the resulting mixture, which could be converted into the first one by heating in xylene solution or by melting on a Kofler hot stage microscope [5].

In order to elucidate which structure has to be attributed to the isomeric compounds, semi-empirical molecular orbital calculations were performed with compounds **3a,b**. As can be seen from the results of computations using both the AM1 and the PM3 hamiltonians, isomer **3a** is energetically favored compared to **3b** (Table 1). Therefore structure **3a** has to be attributed to the thermodynamically stable isomer formed when heating the reaction mixture whereas **3b** represents the product obtained under low temperature conditions.

For hypothesis verification, we finally determined the structure of the thermodynamically stable isomer using single crystal X-ray diffraction. The results obtained are given in Figure 1. In fact, our assumptions deduced from quantum chemistry calculations were confirmed by the results of the X-ray analysis, since the structure found was the 3-(1-acetyl-3-chloro-1*H*-pyrazol-5-yl)-2-chloroquinoxaline **3a**. It has to be noted that the geometric features of the MO optimized structure of **3a** are in good agreement with the experimentally determined ones. The torsion angle between both heteroaromatic systems was found to be 63° in the crystal state, compared to 73° in the calculated structure.

Table 1
Results from Semiempirical MO Calculations





method [a]	**3a**	**3b**
AM1	ΔHF[b] = 100.75	ΔHF[b] = 105.43
PM3	ΔHf[b] = 56.56	ΔHf[b] = 59.73

[a] Hamiltonian used. [b] Heat of formation (kcal/mol)

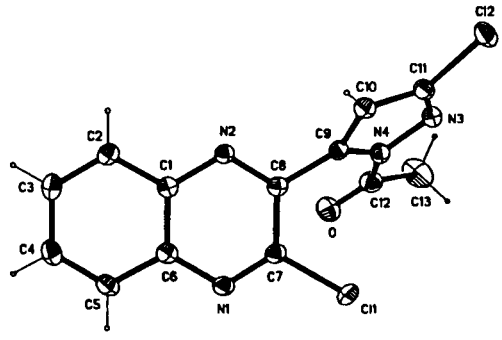


Figure 1. Molecular structure of $C_{13}H_8N_4OCl_2$ (**3a**) in the crystalline state with crystallographic atom designation (20% ellipsoids). The angle between the quinoxaline and the pyrazole moiety is 62.7°.

Table 2

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for $C_{13}H_8N_4OCl_2$ (**3a**). U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor

	x	y	z	U_{eq}
Cl(1) *	0.31686(3)	0.07122(13)	0.54130(5)	60(1)
Cl(2) *	0.06113(3)	-0.33565(13)	0.28150(5)	61(1)
N(1)	0.3844(1)	0.4373(4)	0.4666(1)	47(1)
N(2)	0.2754(1)	0.5066(3)	0.3132(1)	40(1)
N(3)	0.0990(1)	0.0177(4)	0.4171(2)	52(1)
N(4)	0.1538(1)	0.1934(4)	0.4419(1)	48(1)
O	0.1980(1)	0.5287(4)	0.5393(1)	70(1)
C(1)	0.3375(1)	0.6471(4)	0.3177(2)	39(1)
C(2)	0.3468(1)	0.8324(4)	0.2443(2)	47(1)
C(3)	0.4073(1)	0.9795(5)	0.2497(2)	55(1)
C(4)	0.4607(1)	0.9488(5)	0.3274(2)	59(1)
C(5)	0.4537(1)	0.7712(5)	0.3985(2)	54(1)
C(6)	0.3914(1)	0.6163(4)	0.3949(2)	43(1)
C(7)	0.3252(1)	0.3095(4)	0.4600(2)	44(1)
C(8)	0.2684(1)	0.3448(4)	0.3841(2)	40(1)
C(9)	0.2019(1)	0.1876(4)	0.3774(2)	40(1)
C(10)	0.1775(1)	0.0066(4)	0.3095(2)	44(1)
C(11)	0.1151(1)	-0.0907(4)	0.3386(2)	47(1)
C(12)	0.1516(1)	0.3706(6)	0.5204(2)	60(1)
C(13)	0.0900(2)	0.3396(9)	0.5740(3)	110(1)

* site occupancy factors refined to 0.955(3) for Cl(l) and 0.955(3) for Cl(2).

Table 3

Selected Bond Lengths [Å] and Angles [deg] for $C_{13}H_8N_4OCl_2$ (**3a**)

Bond distances		Selected torsion angles		
Cl(1)-C(7)	1.729(2)	0.16	(0.23)	C11-N3-N4-C9
Cl(2)-C(11)	1.714(2)	174.08	(0.20)	C11-N3-N4-C12
N(1)-C(7)	1.289(3)	0.47	(0.29)	C8-N2-C1-C6
N(1)-C(6)	1.365(3)	-177.79	(0.19)	C8-N2-C1-C2
N(2)-C(8)	1.302(3)	177.78	(0.19)	N2-C1-C2-C3
N(2)-C(1)	1.370(3)	-0.52	(0.32)	C6-C1-C2-C3
N(3)-C(11)	1.299(3)	0.10	(0.35)	C1-C2-C3-C4
N(3)-N(4)	1.371(3)	0.47	(0.38)	C2-C3-C4-C5
N(4)-C(9)	1.372(3)	-0.61	(0.37)	C3-C4-C5-C6
N(4)-C(12)	1.418(3)	-2.42	(0.30)	C7-N1-C6-C1
O-C(12)	1.189(3)	177.79	(0.20)	C7-N1-C6-C5
C(1)-C(6)	1.398(3)	2.32	(0.31)	N2-C1-C6-N1

Table 3 (continued)

Bond distances		Selected torsion angles		
C(1)-C(2)	1.412(3)	-179.41	(0.19)	C2-C1-C6-N1
C(2)-C(3)	1.361(3)	-177.88	(0.19)	N2-C1-C6-C5
C(3)-C(4)	1.396(4)	0.38	(0.31)	C2-C1-C6-C5
C(4)-C(5)	1.354(4)	179.97	(0.22)	C4-C5-C6-N1
C(5)-C(6)	1.412(3)	0.18	(0.34)	C4-C5-C6-C1
C(7)-C(8)	1.424(3)	-0.05	(0.32)	C6-N1-C7-C8
C(8)-C(9)	1.483(3)	177.22	(0.16)	C6-N1-C7-C11
C(9)-C(10)	1.350(3)	-2.88	(0.29)	C1-N2-C8-C7
C(10)-C(11)	1.394(3)	-178.28	(0.17)	C1-N2-C8-C9
C(12)-C(13)	1.484(4)	2.86	(0.34)	N1-C7-C8-N2
		-174.35	(0.16)	C11-C7-C8-N2
		177.98	(0.20)	N1-C7-C8-C9
Bond angles		0.77	(0.29)	C11-C7-C8-C9
		0.46	(0.23)	N3-N4-C9-C10
C(7)-N(1)-C(6)	116.3(2)	-172.83	(0.22)	C12-N4-C9-C10
C(8)-N(2)-C(1)	117.3(2)	-177.81	(0.18)	N3-N4-C9-C8
C(11)-N(3)-N(4)	102.9(2)	8.90	(0.34)	C12-N4-C9-C8
N(3)-N(4)-C(9)	111.8(2)	61.25	(0.28)	N2-C8-C9-C10
N(3)-N(4)-C(12)	119.7(2)	-114.02	(0.26)	C7-C8-C9-C10
C(9)-N(4)-C(12)	128.1(2)	-120.85	(0.23)	N2-C8-C9-N4
N(2)-C(1)-C(6)	121.3(2)	63.88	(0.29)	C7-C8-C9-N4
N(2)-C(1)-C(2)	119.6(2)	-0.83	(0.22)	N4-C9-C10-C11
C(6)-C(1)-C(2)	119.1(2)	177.41	(0.20)	C8-C9-C10-C11
C(3)-C(2)-C(1)	120.0(2)	-0.72	(0.25)	N4-N3-C11-C10
C(2)-C(3)-C(4)	120.5(2)	178.03	(0.15)	N4-N3-C11-C12
C(5)-C(4)-C(3)	120.9(2)	1.02	(0.26)	C9-C10-C11-N3
C(4)-C(5)-C(6)	119.8(2)	-177.61	(0.16)	C9-C10-C11-C12
N(1)-C(6)-C(1)	120.6(2)	-177.30	(0.22)	N3-N4-C12-O
N(1)-C(6)-C(5)	119.8(2)	-4.47	(0.38)	C9-N4-C12-O
C(1)-C(6)-C(5)	119.7(2)	3.21	(0.36)	N3-N4-C12-C13
N(1)-C(7)-C(8)	124.3(2)	176.03	(0.27)	C9-N4-C12-C13
N(1)-C(7)-Cl(1)	116.9(2)			
C(8)-C(7)-Cl(1)	118.8(2)			
N(2)-C(8)-C(7)	120.2(2)			
N(2)-C(8)-C(9)	117.0(2)			
C(7)-C(8)-C(9)	122.7(2)			
C(10)-C(9)-N(4)	106.4(2)			
C(10)-C(9)-C(8)	127.6(2)			
N(4)-C(9)-C(8)	126.0(2)			
C(9)-C(10)-C(11)	104.6(2)			
N(3)-C(11)-C(10)	114.3(2)			
N(3)-C(11)-Cl(2)	118.9(2)			
C(10)-C(11)-Cl(2)	126.8(2)			
O-C(12)-N(4)	119.2(2)			
O-C(12)-C(13)	124.9(3)			
N(4)-C(12)-C(13)	115.8(3)			

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. The ir spectra were taken on a Mattson Galaxy Series FT-IR 3000 spectrophotometer (potassium bromide pellets). The nmr spectra were recorded from deuteriochloroform solutions on a Varian Gemini 200 spectrometer (199.98 MHz for ^1H, 50.29 MHz for ^{13}C). The centre of the solvent multiplet was used as an internal standard, which was related to TMS with δ 7.26 ppm (^1H) and δ 77.0 ppm (^{13}C) respectively. Reactions were monitored by tlc using Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm

layer thickness) and visualized using an uv lamp. Elemental analyses were carried out at the Institute of Physical Chemistry (Mag. J. Theiner), University of Vienna, Austria.

All molecule structures were built within the Sybyl [6] molecular modelling software package installed on a *SGI Indigo2 4400 Solid Impact* workstation starting from geometrically optimized standard fragments of the Tripos library. The potential energies of each structure were fully refined using the MM3 force field [7]. MO calculations were performed within the MOPAC [8] module using both the AM1 and the PM3 hamiltonian, geometries were fully optimized, and the keyword PRECISE was used.

Starting Materials.

2-Chloro-3-(3-chloro-1*H*-pyrazol-5-yl)quinoxaline (**2**) was prepared by refluxing 3-(3-chloro-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (**1**) in a mixture of phosphorus oxychloride and pyridine [2]. Compound **1** became accessible by reaction of *N*-(2-aminophenyl)-3,6-dichloro-4-pyridazinecarboxamide with sodium hydride in dry dimethylformamide [1].

3-(1-Acetyl-3-chloro-1*H*-pyrazol-5-yl)-2-chloroquinoxaline (**3a**).

A mixture of **2** (0.175 g, 0.66 mmole) and 4 ml of acetic anhydride was refluxed for 5 minutes then cooled to room temperature and refluxed for further 2 minutes. After stirring at room temperature (30 minutes) the mixture was poured into ice-water (50 ml) and extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate and evaporated to afford colourless needles (the ^{1}H nmr spectrum of this crude product indicates an isomeric mixture of 1:0.1 = **3a**:**3b**). Recrystallisation from diisopropyl ether gave 0.175 g (86%) of the pure compound **3a** as colourless needles, mp 156-161°; ir: 1742 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.14-8.06 (m, 2H), 7.91-7.78 (m, 2H) (quinoxaline-H-5, -H-6, -H-7, -H-8), 6.66 (s, 1H, pyrazole-H-4), 2.70 (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform): δ 169.1 (s) (C=O), 146.5 (s), 144.6 (s), 144.3 (s), 141.6 (s), 141.3 (s), 140.1 (s) (pyrazole-C-3, -C-5, quinoxaline-C2, -C-3, -C-4a, -C-8a), 131.9 (d), 130.7 (d), 129.3 (d), 128.5 (d) (quinoxaline-C-5, -C-6, -C-7, -C-8), 112.7 (d) (pyrazole-C-4), 22.2 (q) (CH_3).

Anal. Calcd. for $C_{13}H_8N_4OCl_2$ (307.14): C, 50.84; H, 2.63; N, 18.24. Found: C, 50.77; H, 2.55; N 18.37.

Crystal Structure Determination of $C_{13}H_8N_4OCl_2$ (**3a**).

Crystal data are: $C_{13}H_8N_4OCl_2$, M_r = 307.13, monoclinic, space group $P2_1/c$ (No. 14), a = 19.060 (4) Å, b = 4.990 (1) Å, c = 14.026 (3) Å, β = 97.69 (3)°, V = 1322.0 (5) Å^3, Z = 4, D_x = 1.543 g cm^{-3}, λ = 0.71073 Å, μ = 0.491 mm^{-1}, T = 302(2) K. A colourless plate was used for data collection with a Siemens Smart area detector platform type diffractometer and MoKα radiation. Intensity data were harvested over more than one hemisphere of the reciprocal space using 0.3° ω-scan frames. Data were corrected for Lp, decay, absorption and related effects with the empirical method using program SADABS. The structure was solved with the SHELXTL package of programs and was refined with SHELXL93 [9]. Hydrogen atoms were refined riding with the atoms to which they were bonded. The final refinement varied 185 parameters and used 2310 independent reflections weighted by $w = 1/[\sigma^2(F_o^2)+(0.0588P)^2+0.0P]$ where $P = (F_o^2+2F_c^2)/3$. Final R1 = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$ = 0.059, wR2 = $[\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2}$ = 0.106 and S = 1.029 for all data; $R1$ = 0.039 for the 1709 reflections with $F_o^2>2\sigma(F_o^2)$. Atomic coordinates are presented in Table 2 and selected bond lengths and bond angles are recorded in Table 3 [10].

3-(1-Acetyl-5-chloro-1*H*-pyrazol-3-yl)-2-chloroquinoxaline (**3b**).

A mixture of **2** (0.200 g, 0.75 mmole) and 5 ml of acetic anhydride was shortly heated to 80°, cooled to room temperature and stirred at room temperature over night. Then the mixture was poured into ice-water (50 ml) and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and evaporated to afford a colourless solid (the ^{1}H nmr spectrum of this crude product indicates an isomeric mixture of 5:1 = **3b**:**3a**). Recrystallisation from diisopropyl ether gave 0.162 g (70%) of the pure compound **3b** as colourless needles, mp 169-173°; ir: 1752 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.20-8.04 (m, 2H), 7.89-7.79 (m, 2H) (quinoxaline-H-5, -H-6, -H-7, -H-8), 7.17 (s, 1H, pyrazole-H-4), 2.85 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 169.8 (s) (C=O), 150.6 (s), 145.1 (s), 143.7 (s), 141.4 (s), 140.5 (s) (pyrazole-C-3, quinoxaline-C2, -C-3, -C-4a, -C-8a), 131.9 (d), 130.8 (d), 129.4 (d), 128.3 (d) (quinoxaline-C-5, -C-6, -C-7, -C-8), 130.4 (s) (pyrazole-C-5), 111.9 (d) (pyrazole-C-4), 23.6 (q) (CH_3).

Anal. Calcd. for $C_{13}H_8N_4OCl_2$ (307.14): C, 50.84; H, 2.63; N, 18.24. Found: C, 51.07; H, 2.93; N 18.41.

REFERENCES AND NOTES

[1] G. Heinisch, B. Matuszczak and K. Mereiter, *Heterocycles*, **38**, 2081 (1994).

[2] B. Matuszczak and K. Mereiter, *Heterocycles*, in press.

[3] The assignment of the ratios of the isomers was performed by proton nmr spectroscopy after work up.

[4] The isomers were formed in the ratio 0.4:1 [3] with the thermodynamically less stable isomer predominating.

[5] *N,N*-acyl migration reactions in pyrazole chemistry have been described in reference [11].

[6] Sybyl 6.2, Tripos Ass., St. Louis, MO 63144, USA, 1995.

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[9a] G. M. Sheldrick, SADABS. *Program for empirical absorption correction*, University of Göttingen, 1996. [b] SHELXTL, Version 5. *Integrated system of computer programs for crystal structure determination*, Siemens X-ray Analytical, 1994. [c] G. M. Sheldrick, SHELXL93. *Program for crystal structure refinement*. University of Göttingen, 1993.

[10] Further details of the crystal structure investigation are available from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the depository number CSD-407519.

[11] J. Elguero in: Comprehensive Heterocyclic Chemistry II, Vol 5, Part 4A, K. T. Potts, ed., Pergamon Press, Oxford 1996, pp 167-303, and literature cited therein.