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Crystal structures of 3-methyl-2(1H)-quinoxalinone and three substituted derivatives

Denise Mondieig^{a*}, Philippe Negrier^a, Stéphane Massip^b,
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3-Methyl-2(1H)-quinoxalinone and three derivatives (3,7-dimethyl-2(1H)-quinoxalinone, 3-methyl-6,7-dichloro-2(1H)-quinoxalinone and 3-methyl-7-nitro-2(1H)-quinoxalinone) have been synthesised and analysed by ¹H NMR and IR spectral spectroscopies. The crystal structures have been determined at room temperature from X-ray single crystal diffraction data for three of them and from powder diffraction data for the nitro derivative. 3-Methyl-2(1H)-quinoxalinone crystallises in the P2₁/c monoclinic system, 3,7-dimethyl-2(1H)-quinoxalinone in the Pbc_a orthorhombic system and the two others compounds in the P $\bar{1}$ triclinic system. For the nitro derivative, C—H...N short contacts are established between the carbon of the methyl and the double bounded nitrogen of the ring. For the three other compounds N—H...O hydrogen bonds involve the atoms of the heterocyclic ring.

Keywords: 3-methyl-2(1H)-quinoxalinone derivative; intermolecular interaction; powder structure; single crystal structure; synthesis

INTRODUCTION

Quinoxalin-2-ones display interesting biological properties, including the inhibition of the aldose reductase enzyme,^[1] partial agonists for complex receptors γ -aminobutyric acid (GABA)/benzodiazepine^[2–4] and as multiple-drug-resistance antagonists,^[5] amongst others properties. Additionally, the quinoxalin-2-one (Fig. 1) showed antimicrobial,^[6–8] antifungic,^[9] antiviral^[10] and anticancer^[11] activities. Methylquinoxalin-2(1H)-one had recently been identified as corrosion inhibitor for mild steel in 1 M HCl solution.^[12] Hence it is of interest to obtain accurate structural parameters of these molecules. Up today, only few structural data on quinoxalin-2-one derivatives have been published. Two papers^[13,14] reported on the 2-hydroxyquinoxaline structure and another one on a different compound as 3-benzoylmethylene-1-methyl-3,4-dihydroquinoxalin-2(1H)-one^[15] or 2-[N-(2-hydroxyethyl) carboxamide]-3-methylquinoxaline 1,4-dioxide.^[16]

In this article, we focus on the crystal structures of four substituted 3-methyl-2(1H)-quinoxalinones which have been synthesised and analysed by NMR and IR spectroscopies. The structures of 3-methyl-2(1H)-quinoxalinone, 3,7-dimethyl-2(1H)-quinoxalinone and 3-methyl-6,7-dichloro-2(1H)-quinoxalinone were determined from single crystal data while the structure of 3-methyl-7-nitro-2(1H)-quinoxalinone was obtained from powder X-ray diffraction data.

EXPERIMENTAL PART

Synthesis of substituted 3-methyl-2(1H)-quinoxalinones 6–9

Substituted 3-methyl-2(1H)-quinoxalinones **6–9** were prepared by the reaction of the corresponding *o*-phenylenediamines **1–4**

and ethyl pyruvate **5** in aqueous HCl^[17] (Scheme 1). The yields of products **6–9** were in the range of 75–85%. Bakerman *et al.* suggested a mechanism,^[18] in which the two amino groups of **1–4** stepwisely attack the two carbonyl centers of **5** (first to the carbonyl carbon) followed by elimination of water and ethanol.

General methods

All chemicals were purchased from Aldrich or Acros (France). All solvents were distilled before use. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F254 (E. Merck) plates with visualisation by UV light (254 nm). Melting points were evaluated by means of a DSC7 Perkin Elmer. Because of the elevated temperature of melting, we use a relatively high heating rate 10 K min⁻¹ in order to diminish the time of heating and thus to prevent degradation of the material. ¹H NMR spectra were recorded on a Bruker 300 WB spectrometer at 300 MHz, in

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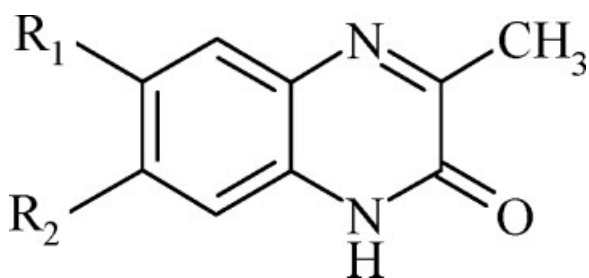


Figure 1. Substituted quinoxalin 2 ones

Me₂SO-*d*₆. Chemical shifts are given as δ values with reference to tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were performed on Bruker tensor 27 FT/IR spectrophotometer.

Synthesis of 3-methyl-2(1H)-quinoxalinone 6 and its derivatives 7–9

A solution of **1** (5.4 g, 50 mM) in aq. HCl (20%, 50 mL) was added to a solution of ethyl pyruvate (11.6 g, 100 mM) in aq. HCl (20%, 50 mL). The mixture was stirred at room temperature for 15 min. The dark coloured precipitate of **6** was filtered, washed with water (2 \times 20 mL) and dried on anhydrous sodium sulphate to give light-yellow crystals of 3-methyl-2(1H)-quinoxalinone **6** (6.0 g, yield 75%, mp 251 \pm 5 $^{\circ}$ C).

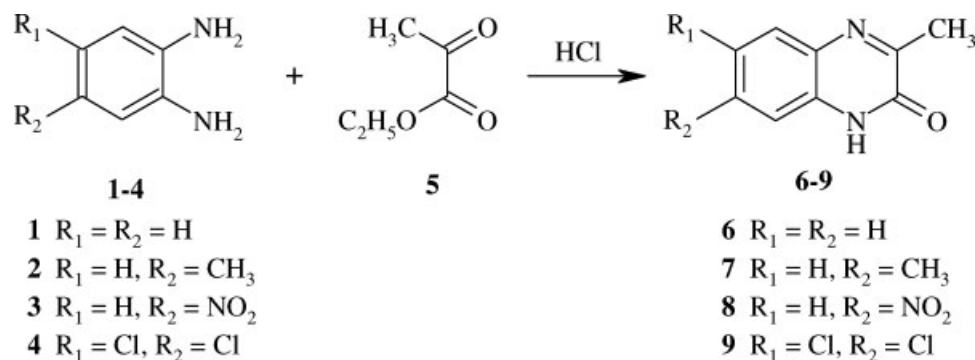
3,7-Dimethyl-2(1H)-quinoxalinone **7** (6.61 g, yield 76%, mp 217 \pm 5 $^{\circ}$ C), 3-methyl-7-nitro-2(1H)-quinoxalinone **8** (10.1 g, yield 88%, mp 250 \pm 5 $^{\circ}$ C), and 3-methyl-6,7-dichloro- 2(1H)- quinoxalinone **9** (8.03 g, yield 85%, mp 336 \pm 5 $^{\circ}$ C) were prepared by the procedure similar to that used in the preparation of **6**. All

compounds were recrystallised from a mixture of DMF-ethanol (v/v, 3:7). The ¹H NMR and IR spectral data of **6–9** are shown in Table 1.

X-ray diffraction measurements

For compounds **6** and **9** X-ray crystal measurements were performed with an Enraf-Nonius CAD4 using the 'Enraf-Nonius SDP' program system. The crystal of **7** has been measured with a R-Axis Rapid diffractometer equipped with a rotating anode and an image plate. The X-ray wavelength was Cu-K α (λ = 1.54180 Å). The structures were solved by direct methods and refined by full-matrix least-squares using SHELXS-97 software. All of the non-hydrogen atoms were refined anisotropically meanwhile the H-atoms were allowed to ride on the parent atoms in the model. Additional details of structure determination are summarised in Table 2.

For **8**, we did not obtain single crystals of quality good enough for single crystal X-ray structure determination. Consequently we performed high-quality powder X-ray diffraction measurements by an INEL CPS-120 diffractometer operating with Debye–Scherrer transmission geometry. Powder diffraction patterns were collected on a 120 $^{\circ}$ curved counter by gas ionisation (Argon + C₂H₆). Powder sample was loaded into 0.5 mm diameter Lindemann glass capillary that is rotated about its axis during data collection in order to minimise the crystallites preferential orientation. The powder pattern was measured in a 2 θ range from 3 $^{\circ}$ to 106 $^{\circ}$ (step size = 0.029 $^{\circ}$) although the information used for structure determination ranges from 3.5 $^{\circ}$ to 65 $^{\circ}$. Pattern was recorded during six hours at room temperature. Monochromatic Cu-K α ₁ radiation (λ = 1.5405 Å) was selected with asymmetric focusing incident-beam curved quartz



Scheme 1.

Table 1. Spectral data of 2(1H)-quinoxalinones derivatives

Product	¹ H NMR (DMSO- <i>d</i> ₆), ppm	IR (KBr), cm ⁻¹
6	12.31 (br, 1H, NH), 7.69 (d, <i>J</i> = 8.0 Hz, 1H, Ar–H), 7.47 (t, <i>J</i> = 6.8 Hz, 1H, Ar–H), 7.29 (m, 2H, Ar–H), 2.42 (s, 3H, CH ₃)	3308 (NH), 1669 (C=O)
7	12.23 (br, 1H, NH), 7.58–7.05 (m, 3H, Ar–H), 2.39 (s, 3H, CH ₃), 2.37 (s, 3H, CH ₃)	3312 (NH), 1667 (C=O)
8	12.73 (br, 1H, NH), 8.41–7.37 (m, 3H, Ar–H), 2.44 (s, 3H, CH ₃)	3323 (NH), 1682 (C=O), 1539 (C–NO ₂), 1343 (C–NO ₂)
9	12.23 (br, 1H, NH), 7.25–7.71 (m, 2H, Ar–H), 2.40 (s, 3H, CH ₃)	3152 (NH), 1670 (C=O)

Table 2. Crystal structures refinement information and crystallographic data for compounds **6**, **7** and **9** from X-rays single crystal analysis

Compound	6	7	9
Empirical formula	C ₉ H ₈ N ₂ O	C ₁₀ H ₁₀ N ₂ O	C ₉ H ₆ Cl ₂ N ₂ O
Formula weight	160.17	174.20	229.06
Temperature (K)	293(2)	293(2)	293(2)
Crystal system	Monoclinic	Orthorhombic	Triclinic
Space group	P2 ₁ /c	Pbca	P $\bar{1}$
Z	4	8	2
a (Å)	4.050(2)	5.0654(3)	5.941(4)
b (Å)	11.240(2)	16.0072(7)	8.350(2)
c (Å)	16.975(5)	21.9719(10)	10.160(3)
α (°)	90	90	67.81(2)
β (°)	91.38(3)	90	75.54(3)
γ (°)	90	90	87.45(3)
Volume (Å ³)	772.5(5)	1781.5(2)	451.2(3)
d (g cm ⁻³)	1.377	1.299	1.686
Crystal size mm	0.25 × 0.15 × 0.15	0.20 × 0.10 × 0.10	0.20 × 0.15 × 0.15
R _{all}	0.0527	0.0705	0.0635
μ (Cu-K α) (mm ⁻¹)	0.758	0.699	6.181
2 θ _{max} (°)	129.8	140.1	129.8
No. reflections used	1285	1645	1502
No. of parameters	111	121	129
Goodness of fit on F ²	1.008	1.008	1.035
Final R	R ₁ = 0.0500,	R ₁ = 0.0684,	R ₁ = 0.0530,
indices [<i>I</i> > 2 σ (<i>I</i>)]	wR ₂ = 0.1316	wR ₂ = 0.1831	wR ₂ = 0.1566
Max. and min. transmission	0.8948 and 0.8331	0.9334 and 0.8729	0.4575 and 0.3712
F(000)	336	736	232
(Δ/ρ) max (Å ⁻³)	0.195	0.301	0.313
(Δ/ρ) min (Å ⁻³)	0.223	0.175	0.243
CCDC deposition number	785053	785054	785055

monochromator. The generator power was set to 40 kV and 25 mA. External calibration to convert the measured 4096 channels into 2 θ degrees was carried out with the Na₂Ca₃Al₂F₁₄ cubic phase mixed with silver behenate as external standard. The peak positions were determined after pseudo-Voigt fitting by using DIFFRACTINEL software.

Crystal structure determination from powder data methodology

Peak positions were determined manually using the Peak picking option of the PC modelling platform Materials Studio.^[19] Potential solutions of cell parameters and space groups were obtained using the X-Cell^[20] algorithm available in the Powder Indexing module of Materials Studio. The cell parameters and space group that best reproduced the experimental diffraction patterns were chosen and refined using a Pawley profile-fitting procedure^[21] over a 2 θ range from 3.5° to 60°. Pawley refinement was used to provide refined cell parameters, the peak profile parameters (profile function, FWHM and asymmetry), the background and the zero shift. All the parameters used are consigned in Table 3.

Structure solution was attempted afterwards. First, the molecule was drawn in a 3D worksheet and it was minimised in energy by geometry optimisation using the COMPASS force field^[22] to obtain relevant distances, angles and torsions for its various bonds. Structure solution was attempted by direct-space methods following a Monte-Carlo simulated annealing approach and full profile comparison as implemented in Powder Solve.^[23] For **8**, the minimised molecule shape was not correct, the heterocyclic ring was flattened with the two nitrogen atoms closer than those of the three other compounds. Therefore, the molecule was drawn by adding the nitro group at the molecule of compound **6**. Considering the Cambridge Structural Database CSD of the CCDC and literature data,^[24–26] bond lengths and torsion angles of the nitro group were set at 1.466 Å, 1.220 Å, 123.4° and 118.3°, respectively, for C—N, N—O, O—N—O and C—N—O (so, the four atoms are coplanar). The drawn molecule was then set as a rigid body, but with the C2—C1—N13—O14 torsion angle involving the nitro group allowed to adjust freely and it is placed inside the unit cell previously determined, together with its homologues related by the space group symmetry. The total number of degrees of freedom is seven: three translations, three rotations and the dihedral angle of the

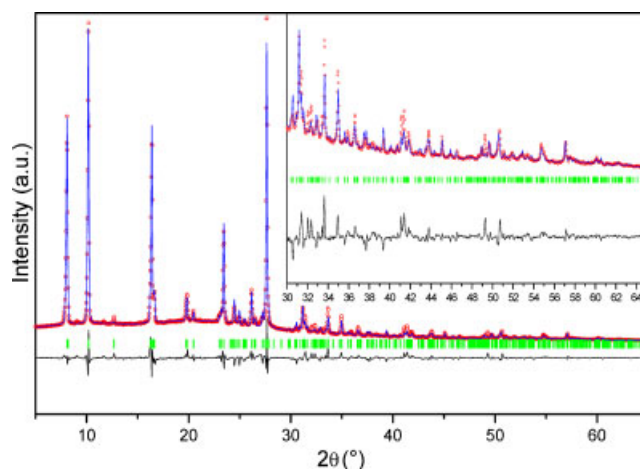
Table 3. Results from the Rietveld refinement for compound **8**

Parameter	Value
Empirical formula	C ₉ H ₇ N ₃ O ₃
Formula weight	205.18
Temperature (K)	293
Crystal system	Triclinic
Space group	P $\bar{1}$
Z	2
Lattice parameters	
<i>a</i> (Å)	11.226 (2)
<i>b</i> (Å)	11.168 (1)
<i>c</i> (Å)	3.931(1)
α (°)	97.64 (1)
β (°)	95.38 (1)
γ (°)	101.56 (1)
Volume (Å ³)	474.9(6)
<i>d</i> (g cm ⁻³)	1.435
2 θ -angular range	5.0–65.0
2 θ -shift (zero correction)	0.01797 ± 0.00098
Asymmetry parameters (Finger–Cox–Jephcoat function)	
2 θ limit	17.000
H/L	0.02015 ± 0.00015
S/L	0.02032 ± 0.00015
Reliability parameters	
<i>R</i> _{wp}	6.44%
<i>R</i> _p	4.46%
Peak shape parameters	
<i>u</i>	0.03012 ± 0.02508
<i>v</i>	0.04822 ± 0.00882
<i>w</i>	0.00314 ± 0.00068
Overall isotropic temperature factor, <i>U</i> /Å ²	0.05932 ± 0.00227
Preferred orientation (Rietveld–Toraya function)	
<i>a</i> [*]	0.05932 ± 0.00227
<i>b</i> [*]	0.20997 ± 0.04292
<i>c</i> [*]	0.46389 ± 0.02376
G1	0.15864 ± 0.05758
G2	0.00000
CCDC deposition number	785056

$$R_{wp} = \left[\frac{\sum_i w_i |cY^{sim}(2\theta_i) - I^{exp}(2\theta_i) + Y^{back}(2\theta_i)|^2}{\sum_i w_i |I^{exp}(2\theta_i)|^2} \right]^{1/2}$$
$$R_p = \left[\frac{\sum_i |cY^{sim}(2\theta_i) - I^{exp}(2\theta_i) + Y^{back}(2\theta_i)|}{\sum_i |I^{exp}(2\theta_i)|} \right]$$

nitro group. Following the global optimisation algorithm, trial structures are continuously generated by modifying the seven degrees of freedom to find the trial structure that yields the best agreement between calculated and experimental powder patterns.

The following Rietveld procedure included refinement of the translation, rotation and dihedral angle of the molecule, the isotropic temperature factors, and the preferred orientations, also with the parameters previously refined in the Pawley procedure. Preferred-orientation corrections of the powder sample were

**Figure 2.** Experimental (red circles) and calculated (blue line) diffraction patterns along with the difference profile (black line) of 3-methyl-7-nitro-2(1H)-quinoxalinone (compound **8**) at 295K. Inset corresponds to the scale for the data with 2 θ > 35°

initially searched within the Powder Solve module by the March–Dollase function^[27] and the Rietveld–Toraya function^[28,29] for the final Rietveld refinement.

The experimental collected and the final calculated profiles for **8** are shown in Fig. 2 together with the difference plot between them. Calculated and experimental profiles are in a good agreement as shown by the difference plot (black curve) and the reliability parameters (Table 3).

RESULTS AND DISCUSSION

The crystallographic data and structural parameters of refinement at room temperature for **6**, **7** and **9** are given in Table 2 and in Table 3 for **8**. They crystallise in three different systems. Compound **6** is monoclinic, **7** orthorhombic as compound **1**^[13,14] but with different space group. Compounds **8** and **9** are triclinic.

The ORTEP representations (with the ellipsoids drawn at the 50% probability level and including the atomic numbering) of these structures are shown in Fig. 3a, b, c, d for **6**, **7**, **9** and **8**, respectively. The molecules of these compounds are very similar and intra-molecular bonds are comparable to those of.^[13] Relevant bond distances are summarised in Table 4. The carbon ring is aromatic (mean C–C bond distance is 1.39 Å). The heterocyclic and benzene rings are planar, the dihedral angle between the planes are small, 1.4°, 0.5°, 2.0° and 1.6°^[13] for **6**, **7**, **9** and **1**, respectively. The C8=O11 double bonds vary between 1.228 and 1.239 Å. For **8**, the refined values of torsion angles involving the nitro group are given in Table 5, they indicate that the nitro group is slightly out of the heterocyclic ring plane.

Projections of the structures are shown in Figs. 4, 5, 6 and 7 for **6**, **7**, **8** and **9**, respectively. The shortest donor–H···acceptor distances are represented with blue dashed lines. Despite the similarities of the molecule shapes, their packing in the crystal is diverse as they crystallise in three distinct space groups. In the orthorhombic structure of **7** (Fig. 5), molecules form a zigzag along *b* direction with an angle of 83° between the molecules. Though in the monoclinic structure of **6** (Fig. 4), the angles between molecules are smaller, 17° and 25°, respectively, for the

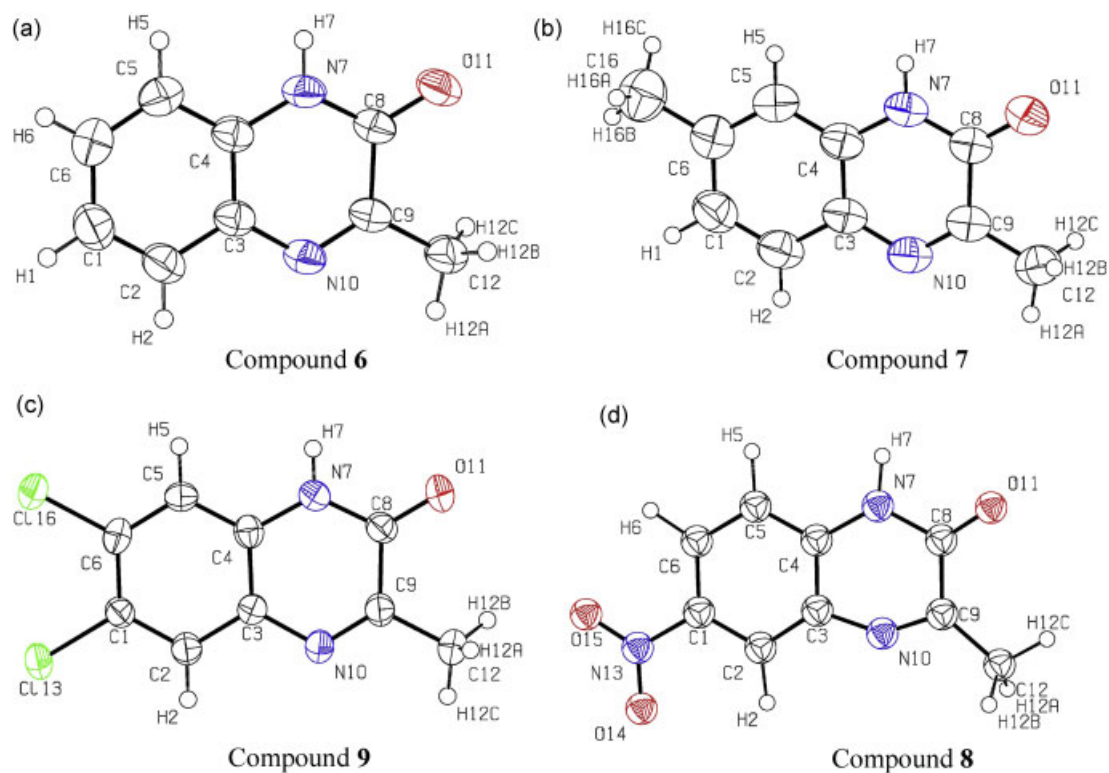


Figure 3. ORTEP plots (with the ellipsoids drawn at the 50% probability level): (a) 3-methyl-2(1H)-quinoxalinone (compound **6**), (b) 3,7-dimethyl-2(1H)-quinoxalinone (compound **7**), (c) 3-methyl-6,7-dichloro-2(1H)-quinoxalinone (compound **9**) and (d) 3-methyl-7-nitro-2(1H)-quinoxalinone (compound **8**)

Table 4. Intramolecular bond distances in Å: (a) Common bonds (common distances in compound **8** have been considered as identical to those of compound **6**), (b) Other bonds

Bonds	Compounds		
	6	7	9
(a)			
N7—C4	1.380	1.377	1.362
N7—C8	1.345	1.354	1.346
N10—C3	1.387	1.384	1.391
N10—C9	1.291	1.288	1.286
C1—C2	1.365	1.375	1.378
C1—C6	1.401	1.402	1.402
C2—C3	1.398	1.396	1.398
C3—C4	1.400	1.401	1.424
C4—C5	1.393	1.395	1.379
C5—C6	1.368	1.373	1.369
C8—C9	1.482	1.490	1.497
C9—C12	1.485	1.453	1.486
O11—C8	1.239	1.232	1.228
(b)			
Compounds	Bond	Distance	
7	C6—C16	1.492	
9	Cl13—C1	1.736	
	Cl16—C6	1.728	

Table 5. Torsion angles involving the nitro group in compound **8**

Torsion	Angle (°)
C6—C1—N13—O14	174.51
C6—C1—N13—O15	5.30
C2—C1—N13—O14	4.23
C2—C1—N13—O15	175.96

2-fold screw axis and by the glide plane symmetry related molecules. Compounds **8** and **9** have the same triclinic space group but molecules are stacked differently. For **8** (Fig. 6), short contact bonds involve the C12...H12_A atoms of the methyl substituent and the double bonded nitrogen N10 of the ring. There are edge-to-edge overlaps of the benzene rings between adjacent neighbouring molecules related by $x, y, z + 1$ and $x, y, z + 1$ symmetry transformations. The C3...C5 and C2...C6 inter-molecular distance is 3.37 Å. For **9** (Fig. 7), the molecules are stacked by two hydrogen bonds involving N7—H7 and O11. Compounds **7** and **8** exhibit the same type of hydrogen bonds as **9**. The characteristic distances and angles relative to the hydrogen bonds and short contacts are summarised in Table 6. Compound **6** exhibits long hydrogen bonds which can be related to the smallest size of R1 and R2 substituents.

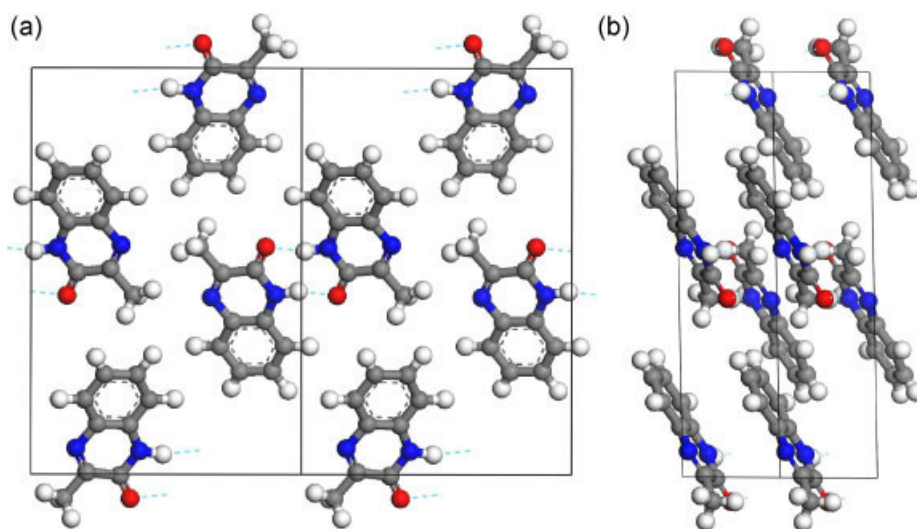


Figure 4. Monoclinic structure of 3-methyl-2(1H)-quinoxalinone (compound **6**). Blue dotted lines indicate the hydrogen bonds. (a) (b, c) plane and (b) (a, c) plane

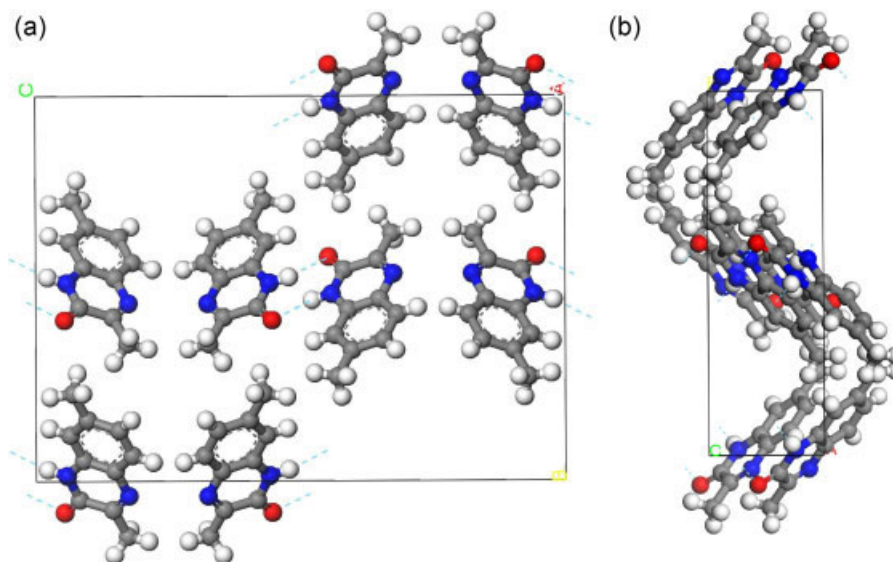


Figure 5. Orthorhombic crystal structure of 3,7-dimethyl-2(1H)-quinoxalinone (compound **7**). (a) (b, c) plane and (b) (a, b) plane

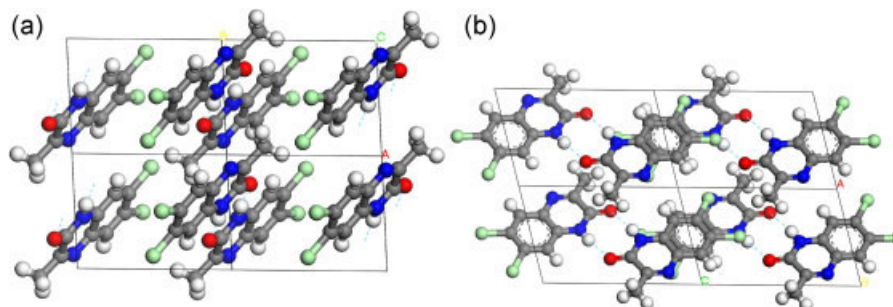


Figure 6. Triclinic structure of 3-methyl-6,7-dichloro-2(1H)-quinoxalinone (compound **9**). (a) (b, c) plane and (b) (a, c) plane

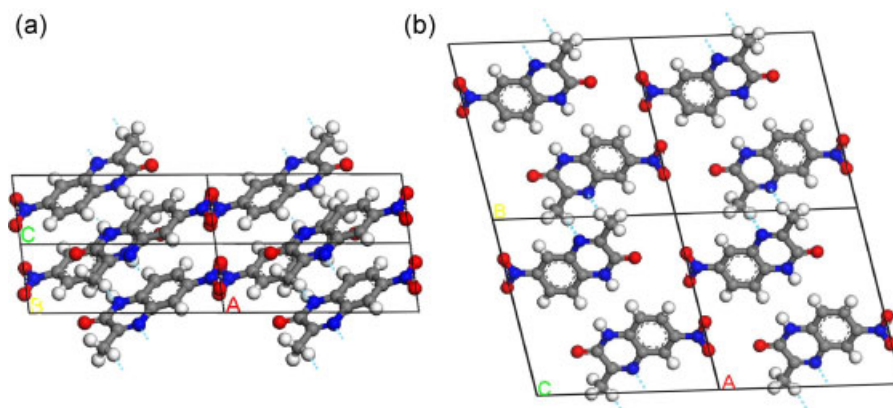


Figure 7. Triclinic structure of 3-methyl-7-nitro-2(1H)-quinoxalinone (compound **8**). (a) (a, b) plane and (b) (a, c) plane

Table 6. Shortest donor–H···acceptor distances

Compound	D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)	(A) Symmetry code
6	N7 H7 O11	0.860	1.949	2.801	170.8	$x + 1, 1, y, z$
7	N7 H7 O11	0.859	1.992	2.836	166.9	$x + 1, y, z + 1$
8	C12 H12 _A N10	0.960	1.680	2.622	166.0	$x + 1, y + 2, z + 3$
9	N7 H7 O11	0.860	1.987	2.839	170.4	$x + 1, y + 2, z 1$

CONCLUSION

3-Methyl-2 (1H)-quinoxalinone and three derivatives (3,7-dimethyl-2 (1H)-quinoxalinone, 3-methyl-6,7-dichloro-2 (1H)-quinoxalinone and 3-methyl-7-nitro-2(1H)-quinoxalinone) have been synthesised and analysed by ¹H NMR and IR spectral spectroscopies.

The crystal structures have been determined at room temperature from X-ray single crystal diffraction for three of them and from powder diffraction for the nitro derivative. This last structure was determined by the combination of direct space Monte-Carlo simulated annealing methods and Rietveld refinement combined with force-field-energy minimisation.

The shape of the molecules only differ by the presence of different R1 and R2 substituents, the common intermolecular distances are very similar. The benzene and the heterocyclic rings are planar and the inter-ring dihedral angles are small ($\leq 2^\circ$).

Crystal structures in terms of crystal packing are very different. 3-Methyl-2(1H)-quinoxalinone crystallises in the monoclinic system, 3,7-dimethyl-2(1H)-quinoxalinone in the orthorhombic system and the two others compounds in the triclinic system. For compounds **6**, **7** and **9**, the molecules are united into centro-symmetric dimers via N—H···O hydrogen bonds involving the atoms of the heterocyclic ring. For the nitro derivative C—H···N short contact bonds are established between the double bonded nitrogen of the ring and the carbons of the methyl.

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