C. R. Chimie 15 (2012) 753–757

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Preliminary communication/Communication

Crystal structure of [2]benzopyrano[3,4-*b*]quinoxalin-5-one through spontaneous air oxidation rearrangement of 6-Chloro-isoindolo[2,1-*a*]quinoxaline☆

Stéphane Moreau [a,b], Vanessa Desplat [a,b], Solène Savrimoutou [a,b], Stéphane Massip [a,b], Gérard Déléris [a,b,†], Jean Guillon [a,*,b]

[a] *Université Bordeaux, CNRS FRE 3396, Pharmacochimie, UFR des Sciences Pharmaceutiques, 146, rue Léo-Saignat, 33076 Bordeaux cedex, France*
[b] *CNRS, Pharmacochimie, FRE 3396, 33000 Bordeaux, France*

ARTICLE INFO

Article history:
Received 13 January 2012
Accepted after revision 12 March 2012
Available online 9 August 2012

Keywords:
Autoxidation
[2]benzopyrano[3,4-*b*]quinoxalin-5-one
Isochromeno[3,4-*b*]quinoxalin-5-one
X-ray crystal structure

ABSTRACT

The complete structure of [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1**, also named isochromeno[3,4-*b*]quinoxalin-5-one, was established unequivocally by a single crystal X-ray analysis. Its process of formation probably included the autoxidation of the isoindole moiety of 6-chloro-isoindolo[2,1-*a*]quinoxaline **2** followed by a deshydratation and oxidation leading to a non isolated acid. Then a subsequent rearrangement of this adduct produces isochromeno[3,4-*b*]quinoxalin-5-one **1** through an intramolecular cyclization. The crystal is triclinic, space group $P\bar{1}$ with $a = 7.173$ (1), $b = 11.668$ (2), $c = 13.430$ (2) Å, $\alpha = 85.56$ (1)°, $\beta = 83.26$ (1)°, $\gamma = 81.32$ (1)°, $V = 1101.4$ (3) Å^3, $Z = 4$, $C_{15}H_8N_2O_2$, $D_c = 1.497$ g/cm^3, μ (MoKα) = 1.5418 Å, $S = 1.017$, F (000) = 512.00, $R = 0.0758$ and $wR = 0.1840$. In the unit cell, there are two independent molecules.

RÉSUMÉ

La structure complète de la [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1**, également nommée isochromeno[3,4-*b*]quinoxalin-5-one, a été établie sans équivoque par une analyse cristallographique aux rayons X. Sa formation passe probablement par une auto-oxydation de l'isoindole de la 6-chloro-isoindolo[2,1-*a*]quinoxaline **2** suivie d'une déshydratation et d'une oxydation menant à un intermédiaire acide non isolé. Finalement, un réarrangement de cet acide conduit à l'isochromeno[3,4-*b*]quinoxalin-5-one **1** via une cyclisation intramoléculaire. Le cristal est triclinique, de groupe spatial $P\bar{1}$ avec $a = 7{,}173$ (1), $b = 11{,}668$ (2), $c = 13{,}430$ (2) Å, $\alpha = 85{,}56$ (1)°, $\beta = 83{,}26$ (1)°, $\gamma = 81{,}32$ (1)°, $V = 1101{,}4$ (3) Å^3, $Z = 4$, $C_{15}H_8N_2O_2$, $D_c = 1{,}497$ g/cm^3, μ (MoKα) = 1,5418 Å, $S = 1{,}017$, F (000) = 512,00, $R = 0{,}0758$ et $wR = 0{,}1840$. Dans l'unité asymétrique, il existe deux molécules indépendantes.

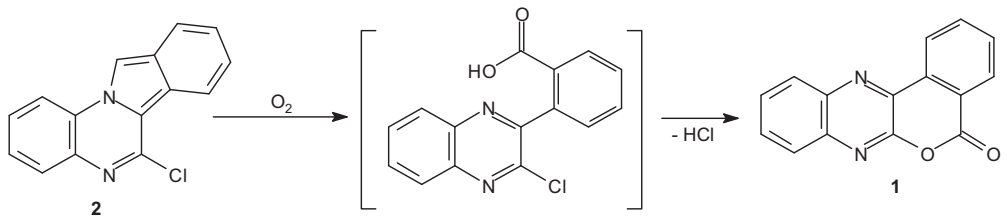
1. Introduction

The coumarin (benzopyranone or chromenone) ring system, present in natural products that display interesting pharmacological properties, has intrigued chemists and medicinal chemists for decades to explore the natural coumarins, semi-synthetic or synthetic analogs for their applicability as drugs. Many molecules based on the

☆ This paper is dedicated to the memory of Gérard Déléris, deceased on January 19th, 2012.

* Corresponding author.
E-mail addresses: stephane.moreau@u-bordeaux2.fr (S. Moreau), vanessa.desplat@u-bordeaux2.fr (V. Desplat), solene.savrimoutou@u-bordeaux2.fr (S. Savrimoutou), stephanemassip@u-bordeaux2.fr (S. Massip), jean.guillon@u-bordeaux2.fr (J. Guillon).
† Deceased author.

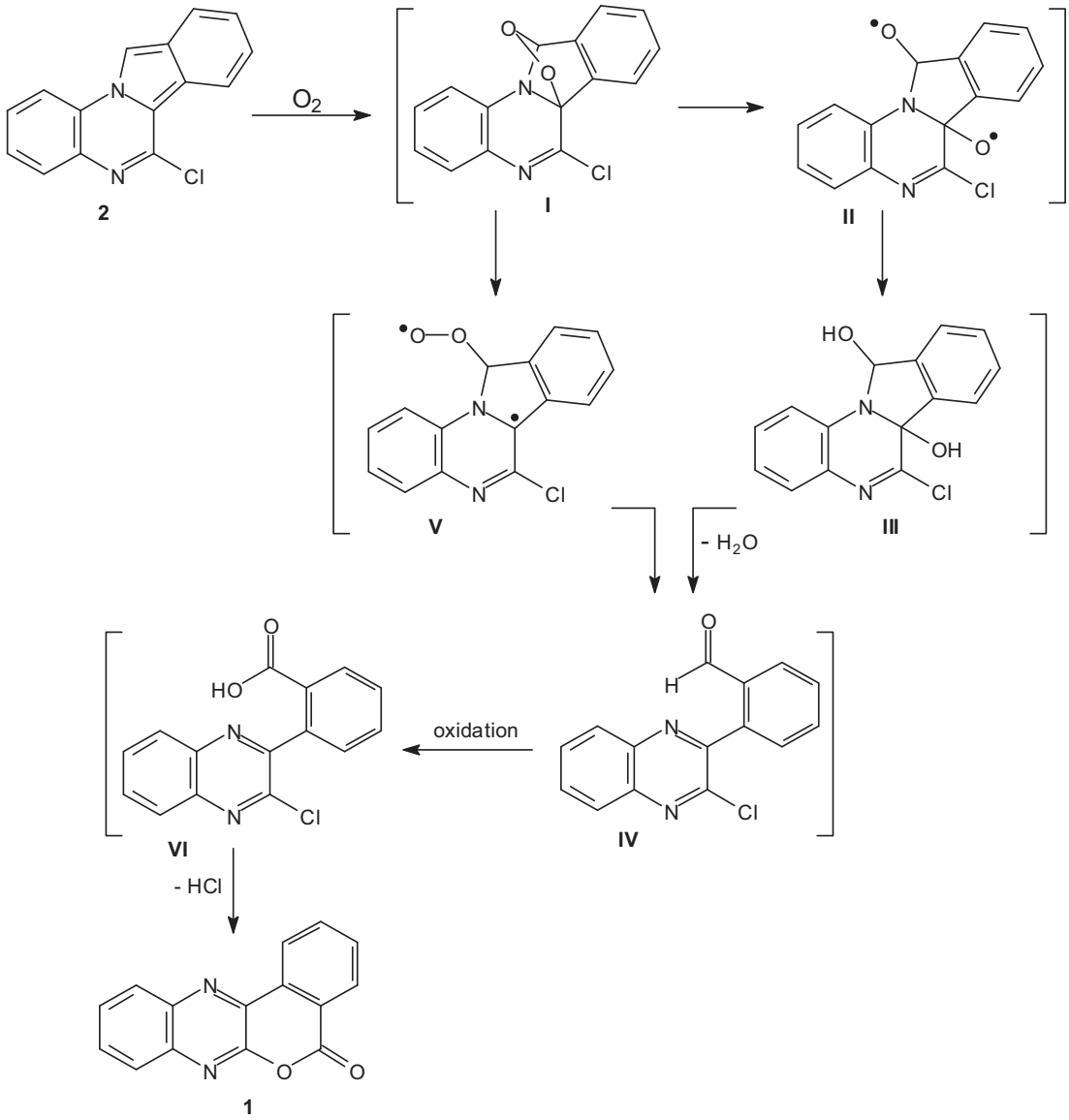
1631-0748/$ – see front matter
http://dx.doi.org/10.1016/j.crci.2012.03.016



Scheme 1. Possible formation of [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1**.

coumarin ring system have been synthesized utilizing innovative synthetic techniques. The diversity oriented synthetic routes have led to interesting coumarins condensed with aromatic, heteroaromatic and alicyclic systems, which have been reported to possess antiallergic, anticoagulant, antidiabetic, antitumor, antibacterial, anti-inflammatory, anti-HIV therapy and analgesic activities [1–4].

In the present work, we reported herein the structural characterization of [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1** [5] (Scheme 1), also named isochromeno[3,4-*b*]quinoxalin-5-one, which was serendipity formed by



Scheme 2. Hypothetical mechanism for the formation of [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1**.

recrystallization of 6-chloro-isoindolo[2,1-*a*]quinoxaline **2** [6] through an autoxidation and a rearrangement.

2. Results and discussion

As a part of our program on crystal structure analysis, the crystal structure of [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1** has been studied. Hence, after crystallization in a mixture of dichloromethane and methanol (4/1–v/v) at room temperature, isochromeno[3,4-*b*]quinoxalin-5-one **1** was surprisingly isolated as yellow-green needles having a different melting point in comparison with the starting material 6-chloro-isoindolo[2,1-*a*]quinoxaline **2** (m.p. = 204 °C for **1** versus 183 °C for **2**). The title compound was then subjected to spectroscopic analysis to confirm its structure in comparison with its previously described analytical data [5].

The mechanism of formation of **1** from **2** could be probably explained by the described pathway through an autoxidation followed by a rearrangement (Scheme 2).

Isoindoles are well known to be air sensitive and give autoxidation products [7–12]. Oxidation is demonstrated to be free radical chain process. Thus, 6-chloro-isoindolo[2,1-*a*]quinoxaline **2** reacted with oxygen to give the cyclic peroxide **I** through a [4 + 2] cycloaddition. The mechanistic step involving O–O bond homolysis led to compound **II**, then hydrogen atom abstraction from solvent of this diradical **II** gave the dihydroxy intermediate **III**. Oxidation proceeds readily in solvents, which can be considered hydrogen donors such as methanol. The ensuing deshydratation of **III** gave the imine **IV**. Alternatively a peroxo diradical intermediate **V** arising via the cyclic peroxide **I** could be the precursor of the imino-carboxaldehyde **IV** by peroxide decomposition [10,13,14]. Oxidation of the carboxaldehyde function of **IV** led to the non isolated carboxylic acid **VI**. Such a similar autoxidation and reactivity was previously described in polysubstituted isoindoles [10–12]. Finally, an intramolecular aromatic nucleophilic substitution of the chlorine atom with the carboxylic acid function of this adduct furnished the [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1**.

The title compound **1** crystallized in the triclinic system, space group $P\bar{1}$ with unit cell parameters: $a = 7.173$ (1), $b = 11.668$ (2), $c = 13.430$ (2) Å, $\alpha = 85.56$ (1)°, $\beta = 83.26$ (1)°, $\gamma = 81.32$ (1)°, $V = 1101.4$ (3) Å^3, $Z = 4$, $C_{15}H_8N_2O_2$, $D_c = 1.497$ g/cm^3, μ (MoKα) = 1.5418 Å, $S = 1.017$, F (000) = 512.00, T = 213 (2) K (Table 1). In the unit cell, there are two independent molecules (molecules A and B). The molecular structure of [2]benzopyrano[3,4-*b*]quinoxalin-5-one **1** is depicted in Fig. 1.

The double bonds C7═O19 and C57═O69 are confirmed by their respective lengths of 1.206 (4) and 1.216 (4) Å. The values of the four C–O bonds (C7–O8 = 1.378 (4) Å, C57–O58 = 1.380 (4) Å, C9–O8 = 1.377 (4) Å, and C59–O58 = 1.373 (4) Å) in the pyrone rings were in agreement with the C(sp^2)–O distance [15]. The bond angles O8–C9–N14 and C5–C10–N11, then O58–C59–N64 and C55–C60–N61, at the junction of the pyrone and the quinoxaline rings are, respectively, smaller and greater than 120° (Table 2). This phenomenon has also been observed in some azacoumarins [16–18].

The six C–C bond lengths in the phenyl ring of the isochromenone skeleton lie in the range 1.370 (5)–1.406 (4) Å.

The benzopyranoquinoxaline moiety is almost planar; a derivation of the C18 atom (molecule A) was noticed at 0.0790 (3) Å from the plane defined by the tetracyclic system. In molecule B, the derivation of the C67 atom was observed at 0.0790 (3) Å from this latter plane.

The crystal structure cohesion is partially ensured by the formation of π-stacked polymeric units in the crystal packing. Hence, the distances of these intermolecular π-π

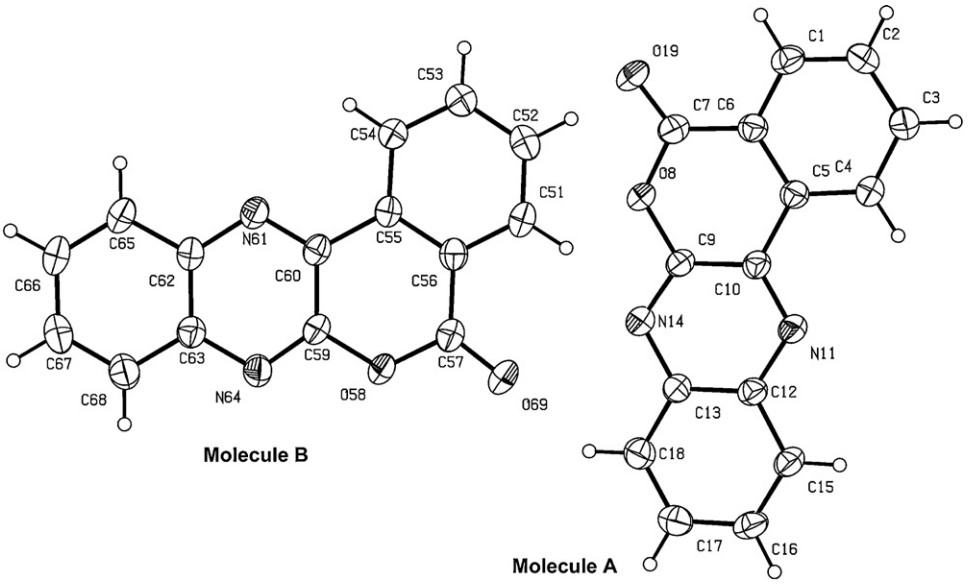


Fig. 1. ORTEP drawing of **1** showing the atom numbering scheme of the asymmetric unit containing two independent molecules. Displacement ellipsoids are drawn at the 30% probability level.

Table 1
Crystallographic data and structure refinement details.

CCDC deposit number	761528
Chemical formula	$C_{15}H_8N_2O_2$
Formula weight	248.23
Temperature (K)	213 (2)
Wavelength (Å)	1.54180
Crystal size (mm)	0.10 × 0.02 × 0.02
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	7.173 (1)
b (Å)	11.668 (2)
c (Å)	13.430 (2)
α (°)	85.56 (1)
β (°)	83.26 (1)
γ (°)	81.32 (1)
V (Å^3)	1101.4 (3)
Z	4
D_c (g/cm^3)	1.497
F (000)	512
Absorption coeff. (mm^{-1})	0.838
θ range (°)	6.78–71.76
Index ranges	$-8 \le h \le 8$; $-14 \le k \le 14$; $-15 \le l \le 16$
Reflection collected	18,226
Independent reflections	4,009 [R_{int} = 0.0673]
Observed reflections	2,075
Data/restraints/parameters	4,009/0/343
Goodness-of-fit on F^2	1.017
R, wR indices [$I > 2\sigma(°)$]	0.0758, 01840
R, wR indices (all data)	0.1018, 0.1921
Largest diff. peak and hole (e Å^{-3})	0.366, −0.347

Table 2
Selected bond lengths (Å) and angles (°).

Bond lengths			
C(7)–O(19)	1.206 (4)	C(57)–O(69)	1.216 (4)
C(7)–O(8)	1.378 (4)	C(57)–O(58)	1.380 (4)
C(9)–N(14)	1.303 (4)	C(59)–N(64)	1.298 (4)
C(9)–O(8)	1.377 (4)	C(59)–O(58)	1.373 (4)
C(10)–N(11)	1.308 (4)	C(60)–N(61)	1.303 (4)
Bond angles			
O(19)–C(7)–C(6)	125.6 (3)	O(69)–C(57)–C(56)	125.7 (4)
N(14)–C(9)–O(8)	113.7 (3)	N(64)–C(59)–O(58)	113.9 (3)
N(11)–C(10)–C(5)	121.0 (3)	N(61)–C(60)–C(55)	121.3 (3)
C(9)–O(8)–C(7)	122.6 (3)	C(59)–O(58)–C(57)	122.6 (3)

interactions (rind A_1 ... ring D_2, ring D_2 ... ring A_3, and ring A_3 ... ring D_4; then rind D_1 ... ring A_2, ring A_2 ... ring D_3, and ring D_3 ... ring A_4) were observed with values ranging from 3.35 to 3.73 Å (Fig. 2).

For the depicted interactions, rings A_1–D_1 belong to the molecule at x, y, z, rings A_2–D_2 to the molecule at $x+1$, $y+1$, z, rings A_3–D_3 to the molecule at $x+1$, y, z, and rings A_4–D_4 to the one at $x+2$, $y+1$, z. Moreover, the inter-isochromeno[3,4-*b*]quinoxalinone contacts are of the van der Waals variety.

3. Experimental

3.1. Preparation

The single crystals of compound **1** suitable for determination were obtained by very slow evaporation (12 days) of the solution of 6-chloro-isoindolo[2,1-*a*]quinoxaline **2** in a mixture dichloromethane: methanol = 4:1 at room temperature.

3.2. X-ray crystallography

A single crystal of the title compound with dimensions 0.10 × 0.02 × 0.02 mm was chosen for X-ray diffraction study. The data were collected on a Rigaku R-axis rapid diffractometer equipped with micro-focus rotating anode Cu-Kα radiation (λ = 1.5418 Å) mode at 213(2) K. In the range of $6.78° < \theta < 71.76°$, a total of 18,226 reflections were collected, of which 4009 were independent (R_{int} = 0.0673) and 2075 were observed with $I > 2\sigma(I)$. The structure was solved by direct

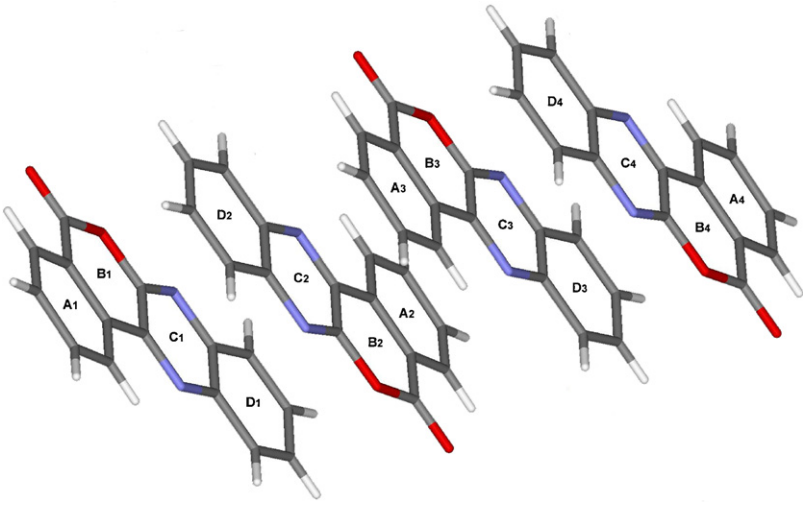


Fig. 2. Ring-stacking interactions in the crystal of isochromeno[3,4-*b*]quinoxalin-5-one **1**.

methods with SHELXS-97 [19]. Non-hydrogen atoms were refined by full-matrix least-squares techniques on F^2 with anisotropic thermal parameters, using SHELXL-97 [20]. All H atoms were located in a difference Fourier map and allowed to ride on their parent atoms at distances of 0.93 Å (C–H aromatic) and 0.96 Å (C–H methyl), with U_{iso}(H) values of 1.2–1.5 times U_{eq} of the parent atoms. The final full-matrix least-squares refinement gave $R = 0.0758$, $wR = 0.1840$ for 2,075 reflections with $I > 2\sigma(I)$. The maximum and minimum difference peaks and holes are 0.366 and −0.347 e Å^{-3}, respectively. $S = 1.017$ and $(\Delta/\sigma)_{max} = 0.000$. The crystal data and refinement details are listed in Table 1. The selected bond lengths and bond angles are listed in Table 2.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.crci.2012.03.016.

Crystallographic data for the structure reported in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-761528. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e mail: deposit@ccdc.cam.ac.uk).

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