

Full Paper

Unexpected Reduction of Ethyl 3-Phenylquinoxaline-2-carboxylate 1,4-Di-*N*-oxide Derivatives by Amines[†]

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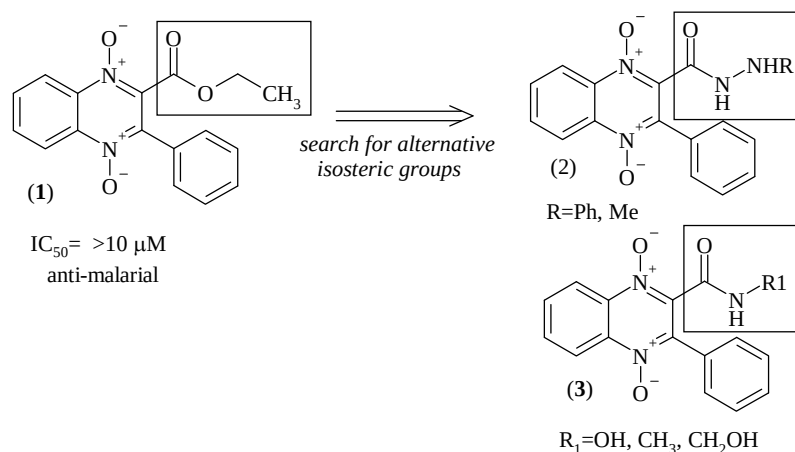
Abstract: The unexpected tendency of amines and functionalized hydrazines to reduce ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-*N*-oxide (**1**) to afford a quinoxaline **1c** and mono-oxide quinoxalines **1a** and **1b** is described. The experimental conditions were standardized to the use of two equivalents of amine in ethanol under reflux for two hours, with the aim of studying the distinct reductive profiles of the amines and the chemoselectivity of the process. With the exception of hydrazine hydrate, which reduced compound **1** to a 3-phenyl-2-quinoxalinecarbohydrazide derivative, the amines only acted as reducing agents.

Keywords: Quinoxaline *N*-oxides, reduction, carboxylate, amines.

Introduction

Quinoxaline and quinoxaline 1,4-di-*N*-oxide are heterocycles that are often used in the synthesis of biologically active compounds [1–31]. The former is described as a bioisoster of the quinoline, naphthyl, benzothienyl and other aromatic rings [32], and it can be found in the structure of anti-bacterial [1], anti-tuberculosis [5–7, 9–11, 13, 14, 16, 22], anti-cancer [8, 18, 20, 28], anti-malarial [12, 24, 26, 29–31], anti-Chagas [15, 25] and anti-inflammatory [19, 27] drug candidates. The widespread activity of quinoxaline 1,4-di-*N*-oxides can be associated with the generation of free radicals [33]. In our continuing efforts to find quinoxaline-1,4-di-*N*-oxide derivatives with anti-malarial activity [12, 23, 24, 26, 29–31], the conversion of compound **1** into hydrazides **2** and amide derivatives **3** was carried out by means of hydrazinolysis and aminolysis reactions, in which unexpected results were obtained. In this work we describe the reducing profiles of amine derivatives when they act upon the ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-*N*-oxide derivative **1**.

Scheme 1. Design of new quinoxaline 1,4-di-*N*-oxide derivatives.

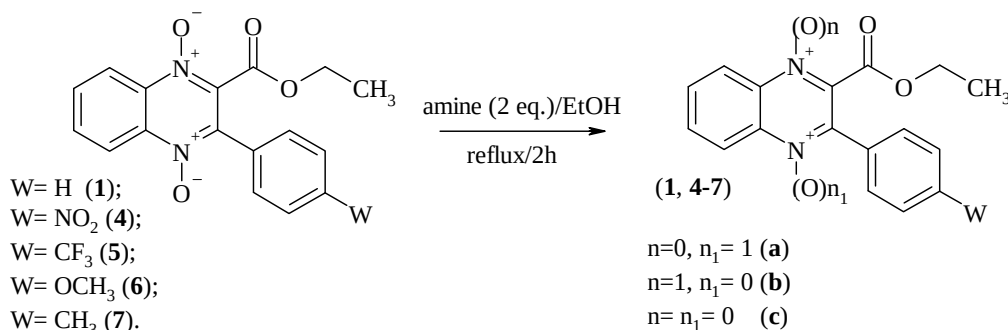


Results and Discussion

In a continuing effort to synthesize new anti-malarial drug candidates, we wished to substitute the carboethoxy moiety present in lead-compound **1**, with a functionalized hydrazide subunit **2** (Scheme 1). For this purpose compound **1** was first treated with phenylhydrazine in the presence of ethanol under reflux for two hours. After workup, the crude oil was analyzed by 1H -NMR, which revealed the presence of four different carboethoxy group signals. This crude oil was purified by silica gel column chromatography and the separated products analyzed by 1H -NMR, IR, mass spectra and elemental analyses. From these analyses, it was observed that the reaction with phenylhydrazine had failed to produce the functionalized hydrazide derivative **2**, but rather this reaction surprisingly gave a mixture of quinoxaline **1c**, quinoxalines *N*-4 monoxide **1a**, *N*-1 monoxide **1b** and 1,4-di-*N*-oxide **1** (Table 1). While the reducing activity of hydrazine hydrate [34, 35] is well known, the aforementioned information was not as clear for phenylhydrazine. In an attempt to determine if the reduction of **1** by phenylhydrazine could be influenced by the electronic profile of quinoxaline-ester **1**, the derivatives **4–7**, attached to electron-withdrawing and electron-donating groups, were treated with phenylhydrazine in ethanol under reflux for two hours; the results are given in Table 1 (entries 2, 3, 4 and 5). These results showed no selective reduction for substrates **5–7**, with the exception of compound **4** (4'-nitro,

$\sigma_p = 0.81$) that could be selectively reduced to quinoxaline **4c** (entry 2). In this particular case, different reducing profiles were observed for phenylhydrazine and hydrazine hydrate because, with the latter no chemoselectivity was observed, and consequently, the nitro group was also reduced and the hydrazinolysis product was formed (data not shown). Intrigued by these results, the possibility that other amines could act as reducing agents towards the quinoxaline 1,4-di-*N*-oxide system was then studied. Derivative **1**, used as template, was treated with different amines (two equivalents) in the presence of ethanol under reflux for two hours (Table 1). The results clearly demonstrated the ability of hydroxylamine (entry 9), methylamine (entry 10), ethanolamine (entry 11), methyl hydrazine (entry 6), and 2,4-dinitrophenylhydrazine (entry 7) to reduce compound **1** to the mono-oxide derivatives **1a** and **1b** and to quinoxaline **1c**, while amines such as triethylamine (entry 12) and aniline (entry 13), were unable to reduce compound **1**, as no significant difference was noted when compared to the experiment carried out in the absence of amine (entry 14).

Table 1: Reduction of ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-*N*-oxide (**1**).



Entry	Reducing Agent	W	n=n ₁ =1 (1 , 4-7)	n=0, n ₁ =1 (1b , 4-7a)	n=1, n ₁ =0 (1c , 4-7b)	n=n ₁ =0 (1a , 4-7c)
1	PhNHNH ₂	H	18.1%	30.1%	28.4%	23.4%
2	PhNHNH ₂	NO ₂	16.7%	0%	0%	83.3%
3	PhNHNH ₂	CF ₃	22.6%	30.0%	23.7%	23.7%
4	PhNHNH ₂	OCH ₃	25.7%	28.6%	17.6%	28.1%
5	PhNHNH ₂	CH ₃	15.1%	31.8%	21.9%	31.2%
6	H ₃ CNHNH ₂	H	43.8%	21.8%	22.5%	11.9%
7	2,4-diNO ₂ PhNHNH ₂	H	57.4%	8.9%	24.1%	9.6%
8	N ₂ H ₄ ·H ₂ O	H	0%	0%	0%	100%*
9	NH ₂ OH·H ₂ O	H	22.6%	8.1%	33.8%	35.5%
10	NH ₂ CH ₃ ·H ₂ O	H	33.8%	8.0%	49.7%	8.5%
11	NH ₂ (CH ₂) ₂ OH	H	0%	34.2%	36.0%	29.8%
12	Et ₃ N	H	80.8%	0%	19.2%	0%
13	PhNH ₂	H	81.2%	0%	18.8%	0%
14	EtOH	H	85.5%	0%	14.5%	0%
15	P(OCH ₃) ₃	H	0%	100%	0%	0%
16	Na ₂ S ₂ O ₄	H	0%	0%	0%	100%

*formation of 3-phenyl-2-quinoxalinecarbohydrazide; absence of chemoselectivity.

The yields were determined by ¹H-NMR analysis of total crude product mixtures obtained after the work-up of each reaction. The methyl (OCH₂CH₃) resonances for the four compounds **1**, **1a**, **1b** and **1c**, were observed at different chemical shifts, and thus, integration of the methyl region (OCH₂CH₃)

allowed relative molar percentages to be readily ascertained. The unequivocal structural assignments of the *N*-4 oxide **1a**, *N*-1 oxide **1b** and quinoxaline **1c** derivatives were accomplished by ¹H-NMR, IR, mass spectra and elemental analyses. In an attempt to specifically identify mono-oxide quinoxaline derivatives (**1a** versus **1b**), a selective mono-deoxygenation of compound **1** was performed (entry 14) using trimethylphosphite (entry 15), as previously described by Kluge and coworkers [36]. By this methodology, it was only possible to obtain the *N*-4 oxide derivative **1a**, which was characterized by ¹H-NMR; the data was used for direct comparison with the *N*-oxides obtained from the reaction with the amines. In a similar way, the quinoxaline di-*N*-oxide **1** was totally reduced to quinoxaline **1c**, using Na₂S₂O₄ (entry 16) in a mixture of methanol and water [37, 24]; the chemical shift of compound **1c** was measured by ¹H-NMR and compared with the products obtained from amine reductions. Compounds **1a**, **1b** and **1c** were evaluated for their ability to inhibit *P. falciparum* (chloroquine sensitive), and were shown to be inactive as anti-malarial agents (data not shown).

Conclusions

In summary, this work clearly demonstrates a tendency of amines and functionalized hydrazines to reduce ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-*N*-oxide (**1**) to a quinoxaline **1c** and mono-oxides quinoxalines **1a** and **1b**. Although the starting material **1** was recovered in most of the reactions (entries 1-7, 9-10, 12-14), suggesting that a longer time reaction could be necessary, the experimental conditions were standardized in two hours, using two equivalents of amine, with the aim of studying the distinct reductive profile of the amine used and the chemoselectivity of the process. With the exception of hydrazine hydrate, a well-known reducing agent, which reduced compound **1** to a 3-phenyl-2-quinoxalinecarbohydrazide derivative, the amines were unable to act as nucleophiles and acted exclusively as reducing agents. Compounds **1a**, **1b** and **1c** were inactive as antimalarial agents.

Experimental

General

All of the synthesized compounds were chemically characterized by thin layer chromatography (TLC), infrared (IR), nuclear magnetic resonance (¹H-NMR), mass spectra (MS) and elemental microanalysis (CHN). Alugram SIL G/UV254 (0.2 mm layer, Macherey-Nagel GmbH & Co. KG, Düren, Germany) was used for TLC and Silica gel 60 (0.040-0.063 mm, Merck) for Flash Column Chromatography. ¹H-NMR spectra were recorded on a Bruker 400 Ultrashield instrument (400 MHz), using TMS as the internal standard with CDCl₃ as the solvent; the chemical shifts are reported in ppm (δ) and coupling constants (*J*) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), q (quadruplet), dd (double doublet) and m (multiplet). IR spectra were recorded on a Nicolet Nexus FTIR (Thermo, Madison, USA) in KBr pellets. Mass spectra were measured on a MSD/DS 5973N G2577A mass spectrometer (Agilent Technologies, Waldbronn, Germany) with a direct insertion probe (DIP). The ionization method was electron impact (EI, 70 eV). Elemental microanalyses were obtained on a Leco CHN-900 Elemental Analyzer (Leco, Tres Cantos, Spain) from vacuum-dried samples. The analytical results for C, H, and N, were within ± 0.4 of the

theoretical values. Chemicals were purchased from Panreac Química S.A. (Barcelona, Spain), Sigma-Aldrich Química, S.A. (Alcobendas, Spain), Acros Organics (Janssen Pharmaceuticaaan, Geel, Belgium) and Lancaster (Bischheim-Strasbourg, France).

General procedure for the reduction of ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-N-oxide (1)

Ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-N-oxide (**1**, 1 mmol) was added to ethanol (10 mL) and the amine derivative (1 mmol). The mixture was refluxed for two hours, then the reactions were worked-up by adding CH₂Cl₂ (50 mL), followed by extraction with 10% aqueous HCl (4 x 15 mL). The organic layer was dried (Na₂SO₄), filtered, and evaporated to dryness. The yields were determined by ¹H-NMR analysis of the total crude product mixture. The residue was later purified by silica gel column chromatography (*n*-hexane-ethyl acetate).

Ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-N-oxide (1). ¹H-NMR: δ 1.08 (t, *J*= 7.2 Hz, 3H, OCH₂CH₃); 4.25 (t, *J*= 7.2 Hz, 2H, OCH₂CH₃); 7.53 (m, 3H, H3'-H5'); 7.61 (m, 2H, H2' and H6'); 7.91 (m, 2H, H6 and H7); 8.65 (m, 2H, H5 and H8) ppm; ¹³C-NMR: δ 13.98 (OCH₂CH₃), 63.65 (OCH₂CH₃), 120.89 (C5), 121.08 (C8), 127.84 (C1'), 129.16 (C3' and C5'), 130.15 (C2' and C6'), 131.26 (C4'), 132.51 (C6), 132.53 (C7), 136.53 (C2), 137.73 (C10), 138.81 (C3), 140.08 (C9), 159.66 (CO₂Et) ppm; IR: 2978 (ArC-H), 1746 (C=O), 1352 (N-oxide), 701 and 666 (monosubstituted phenyl) cm⁻¹; MS: 310 (m/z, 100%), 294 (M⁺, 6%), 249 (M⁺, 51%), 221 (M⁺, 46%), 77 (M⁺, 46%); Anal. calcd. for C₁₇H₁₄N₂O₄: C, 65.80; H, 4.52; N, 9.03. Found: C, 65.65; H, 4.57; N, 8.98.

Ethyl 3-phenylquinoxaline-2-carboxylate 4-N-oxide (1a). ¹H-NMR: δ 1.04 (t, *J*=7.2 Hz; 3H, OCH₂CH₃); 4.20 (q, *J*=7.2 Hz; 2H, OCH₂CH₃); 7.56 (m, 3H, H3'-H5'); 7.61 (m, 2H, H2'and H6'); 7.88 (m, 2H, H6 and H7); 8.26 (dd, *J*= 1.2, 8.2 Hz; 1H, H5); 8.65 (dd, *J*= 1.2, 7.6 Hz; 1H, H8); IR: 2981 (ArC-H), 1742 (C=O), 1359 (N-oxide), 701 and 666 (monosubstituted phenyl) cm⁻¹; MS: 294 (m/z, 65%), 265 (M⁺, 13%), 249 (M⁺, 26%), 221 (M⁺, 100%), 77 (M⁺, 18%); Anal. calcd. for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.37; H, 4.77; N, 9.51.

Ethyl 3-phenylquinoxaline-2-carboxylate 1-N-oxide (1b). ¹H-NMR: δ 1.25 (t, *J*=7.2 Hz; 3H, OCH₂CH₃); 4.42 (q, *J*=7.2 Hz; 2H, OCH₂CH₃); 7.54 (m, 3H, H3'-H5'); 7.80 (m, 3H, H2'and H6' and H7); 7.89 (dt, *J*= 8.4, 7.6 Hz; 1H, H6); 8.20 (d, *J*= 8.4 Hz; 1H, H5); 8.61 (d, *J*= 8.0 Hz; 1H, H8); IR (KBr): 2979 (ArC-H), 1735 (C=O), 1363 (N-oxide), 701 and 671 (monosubstituted phenyl) cm⁻¹; MS: 294 (m/z, 60%), 265 (M⁺, 9%), 249 (M⁺, 31%), 221 (M⁺, 100%), 77 (M⁺, 26%); Anal. calcd. for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.39; H, 4.80; N, 9.51.

Ethyl 3-phenylquinoxaline-2-carboxylate (1c). ¹H-NMR: δ 1.19 (t, *J*=7.2 Hz; 3H, OCH₂CH₃); 4.34 (q, *J*=7.2 Hz; 2H, OCH₂CH₃); 7.53 (m, 3H, H3'-H5'); 7.76 (m, 2H, H2'and H6'); 7.85 (m, 2H, H6 and H7); 8.20 (d, *J*= 8.0 Hz; 1H, H5); 8.24 (d, *J*= 7.6 Hz; 1H, H8); IR: 2990 (ArC-H), 1730 (C=O), 711 and 669 (monosubstituted phenyl) cm⁻¹; MS: 278 (m/z, 33%), 249 (M⁺, 26%), 234 (M⁺, 15%), 206 (M⁺, 100%), 77 (M⁺, 33%); Anal. calcd. for C₁₇H₁₄N₂O₂: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.35; H, 5.08; N, 10.05.

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