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Synthesis and antimicrobial activity of some quinoxaline derivatives

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Abstract

Some new structural motifs containing the quinoxaline nucleus have been synthesized and examined for their pharmacological properties. In this study, 6-chloroquinoxaline-2,3(1H, 4H)-dione and 6 nitroquinoxaline-2,3(1H, 4H)-dione were synthesized as basic nuclei for the preparation of the new quinoxaline-2,3-diones by alkylation reactions under the conditions of phase transfer catalysis. The products were characterized by spectroscopic methods ^{1}H and ^{13}C NMR. Then, the synthesized products were tested for their antibacterial effects against two bacterial strains. The values of minimum inhibitory concentrations (MIC) vary according to the nature of the alkyl bonded to the quinoxaline nucleus.

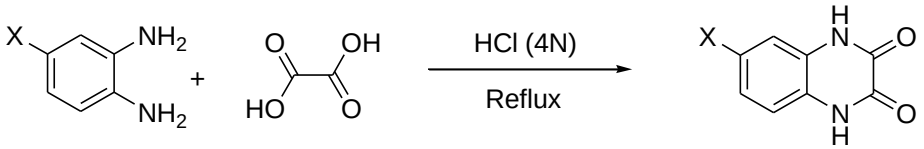
Keywords: *Quinoxaline-2,3-dione, Alkylation, phase transfer catalysis, Antibacterial activity.*

1. Introduction

Heterocyclic compounds occupy a large part of chemical compounds, given their enormous uses. Indeed, they are encountered in several fields such as the pharmaceutical [1] and the environmental field [2]. Benzopyrazines are heterocycles that have a benzene ring bonded to a pyrazine. They can be prepared in several ways, namely, the condensation of *o*-phenylenediamine with derivatives providing units with two carbons [3, 4], from nitroarenes [5], N-Arylenamines [6] or from aniline derivatives [7]. The motifs containing the quinoxaline structure exhibit several biological activities. They are encountered as anticancer [8], antimicrobial [9], antioxidant and antiproliferative [10], antitubercular [11], anti-inflammatory [12, 13], antimalarial agents [14]. As well they are also used in the environmental field, in fact they have anticorrosive effect [15, 16]. This study consists of the synthesis of new quinoxaline-2,3-diones through alkylation reactions under the conditions of phase transfer catalysis, as well as studying their antibacterial effects against two strains of bacteria.

2. Materials and methods

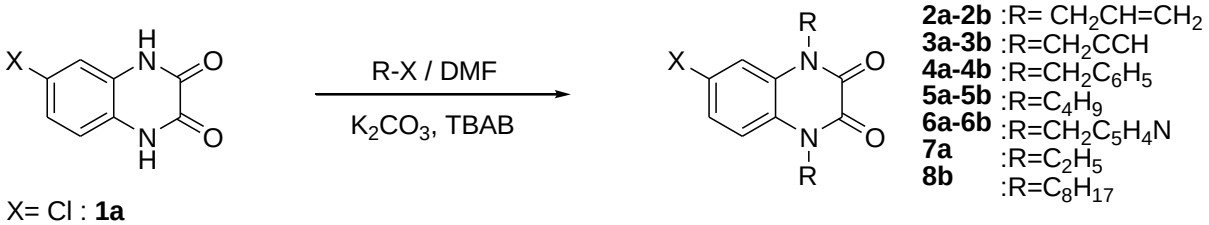
To conduct this study, we synthesized several products derived from 6-chloro and 6-nitroquinoxaline-2,3-dione. To do so, the first step was to prepare the basic nuclei, namely 6-chloroquinoxaline-2,3-dione **1a** and 6-nitroquinoxaline-2,3-dione **1b** (scheme 1).



1a : X= Cl
1b : X= NO_2

Scheme 1

Then, they were reacted under the conditions of phase transfer catalysis with different alkylating agents (scheme 2). It should be noted that the compounds **1a** and **1b** have two sites capable of being alkylated, namely the nitrogen atoms in position 1 and 4. In all cases, the alkylation reactions are carried out at the two nitrogen atoms at the same time so as to obtain dialkylated products with good yields.



2a-2b :R= $CH_2CH=CH_2$
3a-3b :R=CH_2CCH
4a-4b :R=$CH_2C_6H_5$
5a-5b :R=C_4H_9
6a-6b :R=$CH_2C_5H_4N$
7a :R=C_2H_5
8b :R=C_8H_{17}

X= Cl : **1a**
X= NO_2 : **1b**

Scheme 2

The structures of the synthesized compounds have been elucidated from spectroscopic data (^1H and ^{13}C NMR). It should be pointed out that the synthesis and characterization of compounds **1a, 5a** and **7a** have been the subject of a previously published work [17].

Bacterial strains and culture conditions:

In this work, the synthesized compounds were tested for their antibacterial activities, and this on two bacterial strains, Gram+ and Gram- : *Staphylcocus aureus* (ATCC 29213) and *Salmonella typhi*. The

bacterial strains employed were provided by the microbial biotechnology laboratory. Before their use, the bacterial strains were kept on nutrient agar for 24 hours at 37 ° C, in the dark.

Minimum inhibitory concentration determination (MIC) against bacterial strains:

The minimum inhibitory concentration (MIC) can be defined as the minimum concentration of tested product capable of preventing the growth of microorganisms. The measurement of the MIC was carried out by the microdilution protocol described by Chraibi and al [18]. The determination of MIC values done using a 96-well microplate. The tested product was suspended in DMSO and serially diluted. The micro-dilution was done by adding 100 µl of the product to be tested, at a concentration of 5 mg / ml in the first well, then 50 µl of the first well was added in the second well, and so on, in other words a dilution of base 2. Then 50 µl of a standardized microbial suspension prepared in Mueller Hinton broth (MHB) is added to each well. The last well of each line contains 50 µl of MHB and 50 µl of the bacterial suspension, serving as a blank test. Then the microplates are placed in the incubator for 24 hours at a temperature of 37 °C.

The MIC is revealed by adding 10 µl of resazurin to all wells for 2 hours. The well, which contains the lowest concentration of tested product, which does not show a variation in the color of resazurin, is the one, which represents the absence of bacterial growth.

3. Experimental:

The uncorrected melting points were taken in capillary tube on a Buchi apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC-300 instrument. The chemical shifts were expressed in parts per million of the inductor field, and measured with an accuracy of ± 0.1 for ^{13}C and ± 0.05 for ^{1}H. Tetramethylsilane (TMS) served as a reference. Spin multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), q (quadruplet).

Synthesis of 6-Chloroquinoxaline-2,3(1H,4H)-dione: 1a

To 1g (7.01 mmol) of 4-chloro-*o*-phenylenediamine was added 0.63g (7 mmol) of oxalic acid and 20 ml of HCl 4N, the mixture was refluxed for 5 hours and cooled. Thereafter, a black solid was formed, and then was filtered, washed with distilled water, dried and recovered in good yield.

Yield (94%); **Mp** >300 °C; ^{1}H NMR (DMSO-d_6) δ: 7.04-7.17 (m, 3H, CH_{arom}); 11.96 (s,1H, NH) 11.98 (s,1H, NH). ^{13}C NMR (DMSO-d6) δ: 155.47 (C=O); 155.27 (C=O) ; 127.34 (Cq); 127.00 (Cq); 125.22 (Cq); 123.09 (CH_{arom}); 117.02 (CH_{arom}); 114.88 (CH_{arom}).

Synthesis of 6-nitroquinoxaline-2,3(1H,4H)-dione: 1b

To 1g (6.53mmol) of 4-nitro-*o*-phenylenediamine was added 0.71g (7.89mmol) of oxalic acid and 20 ml of HCl 4N; the mixture was refluxed for 5 hours and cooled. Thereafter, a black solid was formed, and then was filtered, washed with distilled water, dried and recovered in good yield.

Yield (90%); **Mp** >300 °C; ^{1}HNMR (DMSO-d_6) δ: 7.21 (d, 1H, CHarom, J=5.7Hz); 7.91-7.96 (m, 2H, CH_{arom}); 12.15 (s, 1H, NH); 12.35 (s, 1H, NH). ^{13}C NMR (DMSO-d6) δ: 155.56 (C=O); 155.16 (C=O); 142.52 (Cq); 132.05 (Cq); 126.50 (Cq); 119.01 (CH_{arom}); 115.92 (CH_{arom}); 110.76 (CH_{arom}).

Synthesis of new derivatives of 1a-1b

To a solution of 0.3 g (1.53mmol) of 6-chloroquinoxaline-2,3(1H,4H)-dione **1a** or 0.3g of 6-nitroquinoxaline-2,3-(1H,4H)dione **1b** in 25 ml of DMF was added 1.5 equivalents of potassium carbonate K_2CO_3. The mixture is stirred for 5 minutes, before adding 0.01 equivalents of tetra-n-butylammonium bromide (BTBA) and 2.5 equivalents of the mono-halogenated reagent. Afterward, the mixture was stirred at room temperature for 12 hours. After filtration of salts, the DMF was evaporated under reduced pressure. The obtained residue was dissolved in waiter and extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and then concentrated. The obtained residue was chromatographed on Silica gel column (eluent: hexane/ethyl acetate (3/1)).

1,4-diallyl-6-chloroquinoxaline-2,3(1H,4H)-dione: **2a**

Yield (87%); **Mp** =147°C; ^{1}H NMR (DMSO-d6) δ: 4.79 (m, 4H, C**H**$_2$-CH); 5.22 (m, 4H, C**H**$_2$=CH); 5.92(m, 2H, CH$_2$=C**H**); 7.19-7.36 (m, 3H, CH$_{arom}$). ^{13}C NMR (DMSO-d6) δ: 154.05 (C=O); 153.82 (C=O); 131.75 (CH=CH$_2$); 131.72 (CH=CH$_2$); 128.24 (Cq); 128.14 (Cq); 126.09 (Cq); 123.56 (CH$_{arom}$); 117.73(CH$_{arom}$); 117.54 (CH$_2$); 117.44 (CH$_2$); 115.82 (CH$_{arom}$); 45.34 (N-CH$_2$); 45.21 (N-CH$_2$).

1,4-diallyl-6-nitroquinoxaline-2,3(1H,4H)-dione: **2b**

Yield (86%); **Mp** =98°C; ^{1}H NMR (CDCl$_3$) δ: 4.95 (m, 4H, C**H**$_2$-CH); 5.26-5.43 (m, 4H, C**H**$_2$=CH); 5.88-6.03 (m, 2H, CH$_2$=C**H**); 7.28-7.38 (m, 1H, CH$_{arom}$); 8.11-8.19 (m, 2H, CH$_{arom}$).^{13}C NMR (CDCl$_3$) δ: 153.47 (C=O); 153.16 (C=O); 143.59 (Cq); 131.63 (Cq); 130.15 (CH=CH$_2$); 126,98 (Cq); 119.54 (CH$_2$); 119.40 (CH$_{arom}$); 119.14 (CH$_2$); 115.95(CH$_{arom}$); 111.40 (CH$_{arom}$); 46.15 (N-CH$_2$); 46.04 (N-CH$_2$).

6-chloro-1,4-di(prop-2-yn-1-yl)quinoxaline-2,3(1H,4H)-dione: **3a**

Yield (82%); **Mp** =127°C; ^{1}H NMR (DMSO-d6) δ: 3.38 (m, 2H, C≡CH); 4.97 (d, 2H, CH$_2$, J=2.4Hz); 5,00 (d, 2H, CH$_2$, J=2.4Hz); 7.41-7.58 (m, 3H, CH$_{arom}$). ^{13}C NMR (DMSO-d6) δ: 153.35 (C=O); 153.15 (C=O); 128.67 (Cq); 127.51(Cq); 125.40 (Cq); 124.12 (CH$_{arom}$); 117.75 (CH$_{arom}$); 115.92 (CH$_{arom}$); 78.05 (Cq); 78.03(Cq); 76.12 (C≡CH); 76.06 (C≡CH); 32.91 (N-CH$_2$); 32.82 (N-CH$_2$).

6-nitro-1,4-di(prop-2-yn-1-yl)quinoxaline-2,3(1H,4H)-dione: **3b**

Yield (85%); **Mp** =132°C; ^{1}H NMR (DMSO-d6) δ: 3.42 (t, H, C≡CH, J=2.4Hz); 3.46 (t, H, C≡CH, J=2.4Hz); 5.03 (d, 2H, CH$_2$); 5.09 (d, 2H, CH$_2$); 7.71 (d, 1H, CH$_{arom}$, J=9.3Hz); 8.22-8.31 (m, 2H, CH$_{arom}$). ^{13}C NMR (DMSO-d6) δ: 153.49 (C=O); 153.23 (C=O); 143.32 (Cq); 131.98(Cq); 126.99 (Cq); 119.73 (CH$_{arom}$); 116.89 (CH$_{arom}$); 111.36 (CH$_{arom}$); 78.72 (Cq); 78.67(Cq); 76.70 (C≡CH); 76.41 (C≡CH); 33.36 (N-CH$_2$); 33.03 (N-CH$_2$).

1,4-dibenzyl-6-chloroquinoxaline-2,3(1H,4H)-dione: **4a**

Yield (87%); **Mp** =202°C; ^{1}H NMR (CDCl$_3$) δ: 5.53 (s, 2H, CH$_2$); 5.55 (s, 2H, CH$_2$); 6,98-7.62 (m, 13H, CH$_{arom}$). ^{13}C NMR (CDCl$_3$) δ: 154.44 (C=O); 154.22 (C=O); 134.41 (Cq); 134.26 (Cq); 129.83 (Cq); 129.18 (CH$_{arom}$); 129.12 (CH$_{arom}$); 128.11 (CH$_{arom}$); 128.01 (CH$_{arom}$); 127.79 (Cq); 126.96 (CH$_{arom}$); 126.79 (CH$_{arom}$); 125.42 (Cq); 124.19 (CH$_{arom}$); 116.99 (CH$_{arom}$); 115.92 (CH$_{arom}$); 47.28 (CH$_2$).

1,4-dibenzyl-6-nitroquinoxaline-2,3(1H,4H)-dione: **4b**

Yield (91%); **Mp** =180°C; ^{1}H NMR ($CDCl_3$) δ: 5.54 (s, 2H, CH_2); 5.55 (s, 2H, (CH_2); 7.28-7.41 (m, 11H, CH_{arom}); 6.97 (dd, 1H, CH_{arom}, J=9Hz). 8.21 (d, 1H, CH_{arom}, J=2.4Hz) ^{13}C NMR ($CDCl_3$) δ: 154.24 (C=O); 153.92 (C=O); 143.54 (Cq); 133.87 (Cq); 133.75 (Cq); 131.70 (Cq); 129.39 (CH_{arom}); 139.31 (CH_{arom}); 128.47 (CH_{arom}); 128.39 (CH_{arom}); 127.38 (CH_{arom}); 127.09 (Cq); 126.75 (CH_{arom}); 119.44(CH_{arom}); 116.20(CH_{arom}); 111.53 (CH_{arom}); 47.70 (CH_2); 47.55 (CH_2).

1,4-dibutyl-6-chloroquinoxaline-2,3(1H,4H)-dione: **5a**

Yield (85%); **Mp** =120°C; ^{1}H NMR ($CDCl_3$) δ: 0.92-1.08 (m, 6H, CH_3); 1.41-1.55 (m, 4H, C**H**$_2$-CH_3); 1.67-1.80 (m, 4H, CH_2); 4.14-4.20 (m, 4H, **CH**$_2$-N); 7.16-7.28 (m, 3H, CH_{arom}). ^{13}C NMR ($CDCl_3$) δ: 153.80 (C=O); 153.54 (C=O); 129.51 (Cq); 127.76 (Cq); 125.41 (Cq); 123.83 (CH_{arom}); 116.14 (CH_{arom}); 115.14 (CH_{arom}); 43.15 (CH_2); 28.80 (CH_2); 28.74 (CH_2); 20.14 (CH_2); 13.76 (CH_3).

1,4-dibutyl-6-nitroquinoxaline-2,3(1H,4H)-dione: **5b**

Yield (82%); **Mp** =102°C; ^{1}H NMR (DMSO-d6) δ: 0,97-1,04 (m, 6H, CH_3); 1,42-1,56 (m, 4H, CH_2); 1.68-1.79 (m, 4H, CH_2); 4,15-4,41 (m, 4H, CH_2-N); 7.38 (m, 1H, CH_{arom}); 8.11-8.19 (m, 2H, CH_{arom}). ^{13}C NMR (DMSO-d6) δ: 153.56 (C=O); 153.26 (C=O); 143.47 (Cq); 131.80 (Cq); 127.11 (Cq); 119.29 (CH_{arom}); 115.30 (CH_{arom}); 110.75 (CH_{arom}); 45.83 (CH_2); 43.68 (CH_2); 43.47 (CH_2); 28.80 (CH_2); 28.76 (CH_2); 20.12 (CH_2); 20.10 (CH_2); 13.70 (CH_3).

6-chloro-1,4-bis(pyridin-2-ylmethyl)quinoxaline-2,3(1H,4H)-dione: **6a**

Yield (91%); **Mp** =228°C; 1H NMR (CDCl3) δ: 5.55 (s, 2H, CH_2); 5.57 (s, 2H, CH_2); 7.09-7.12 (m, 1H, CH_{arom}); 7.22-7.71 (m, 8H, CH_{arom}); 8.56-8.57(m, 2H, H_{arom}). 13C NMR (CDCl3) δ: 154.78 (C=O); 154.49 (C=O); 154.40 (Cq); 154.18 (Cq); 149.54 (CH_{arom}); 149.41 (CH_{arom}); 137.31 (CH_{arom}); 137.27 (CH_{arom}); 130.06 (Cq); 127.96(Cq); 125.59 (Cq); 124.33 (CH_{arom}); 123.13 (CH_{arom}); 123.13 (CH_{arom}); 122.61 (CH_{arom}); 122.53 (CH_{arom}); 117.40 (CH_{arom}); 116.36 (CH_{arom}); 49.27 (CH_2); 49.20 (CH_2).

6-nitro-1,4-bis(pyridin-2-ylmethyl)quinoxaline-2,3(1H,4H)-dione: **6b**

Yield (87%); **Mp** =194°C; 1H NMR (CDCl3) δ: 5.61 (s, 2H, CH_2); 5.63 (s, 2H, CH_2); 7.23-8.04 (m, 8H, CH_{arom}); 7.52-7.57 (m, 3H, CH_{arom}). 13C NMR (CDCl3) δ: 154.24 (C=O); 154.04 (C=O); 153.89 (Cq); 153.82 (Cq); 149.69 (CH_{arom}); 149.52 (CH_{arom}); 143.73 (Cq); 137.45 (CH_{arom}); 137.36 (CH_{arom}); 131.89(Cq); 127.44 (Cq); 123.38 (CH_{arom}); 123.33 (CH_{arom}); 122.85 (CH_{arom}); 119.55 (CH_{arom}); 116.79 (CH_{arom}); 112.19 (CH_{arom}); 49.43 (CH_2); 49.18 (CH_2).

6-chloro-1,4-diethylquinoxaline-2,3(1H,4H)-dione: **7a**

Yield (89%); **Mp** =201°C; 1H NMR (CDCl3) δ: 1.30-1.47 (m, 6H, CH_3); 4.15-4.34 (m, 4H, CH_2); 7.15-7.33 (m, 3H, CH_{arom}). 13C NMR (CDCl3) δ: 153.61 (C=O); 153.37 (C=O); 129.66 (Cq); 127.52 (Cq); 125.18 (Cq); 123.96 (CH_{arom}); 116.04 (CH_{arom}); 115.04 (CH_{arom}); 38.47 (CH_2); 38.46 (CH_2); 12.06 (CH_3); 12.02 (CH_3).

6-nitro-1,4-dioctylquinoxaline-2,3(1H,4H)-dione: **8b**

Yield (80%); **Mp** =92°C; ^{1}H NMR ($CDCl_3$) δ: 0.89 (m, 6H, CH_3); 1.29-1.54 (m, 20H, CH_2); 1.72-1.85 (m, 4H, CH_2- CH_2-N); 4.22-4.29 (m, 4H, CH_2-N); 7.36 (d, 1H, CH_{arom}); 8.17 (m,2H, CH_{arom}). ^{13}C NMR ($CDCl_3$) δ: 153.56 (C=O); 153.25 (C=O); 143.43 (Cq); 131.80 (Cq); 127.08 (Cq); 119.31 (CH_{arom}); 115.33 (CH_{arom}); 110.76 (CH_{arom}); 43.93 (CH_2); 43.71 (CH_2); 31.72 (CH_2); 29.20 (CH_2); 29.14 (CH_2); 29.11 (CH_2); 29.10 (CH_2); 26.84 (CH_2); 26.79 (CH_2); 26.70 (CH_2); 22.61 (CH_2); 14.08 (CH_3).

4. Results and Discussion:

The base nuclei were recovered with yields of 94% and 90% respectively for 6-chloroquinoxaline-2,3(1H,4H)-dione and 6-nitroquinoxaline-2,3(1H,4H)-dione. Using the method described by Tanaka and al. [19]. N-alkylation reactions under phase transfer catalysis conditions, employing BTBA as catalyst and K2CO3 in DMF reflux, yielded the desired products in yields ranging from 82% to 91%. The structures of the synthesized compounds have been elucidated on the basis of spectroscopic data (1H and 13C NMR).

Result of antibacterial activity screening: The synthesized compounds showed an antibacterial effect against Gram-positive and Gram-negative bacteria. The results obtained are shown in the table 1.

Table 1: Minimal inhibitory concentrations of the synthesized compounds against a Gram positive and a Gram negative bacterial strain.

Tested products	*Staphylcocus aureus*	*Salmonella typhi*
2a	1.25 mg/ml	2.5 mg/ml
2b	5 mg/ml	10 mg/ml
3a	5 mg/ml	5 mg/ml
3b	5 mg/ml	2.5 mg/ml
4a	10 mg/ml	10 mg/ml
4b	10 mg/ml	5 mg/ml
5a	10 mg/ml	10 mg/ml
5b	10 mg/ml	10 mg/ml
6a	-	-
6b	5 mg/ml	2.5 mg/ml
7a	10 mg/ml	10 mg/ml
8b	-	-

The products resulting from the alkylation reactions were tested for their antibacterial effects. Results showed that most products had an antibacterial effect against both strains except compounds **6a** and **8b**.

Compound **2a** was found to be the most effective against the Gram-positive strain *Staphylococcus aureus*, with a MIC value of 1.25 mg / ml. Compounds **2a**, **3b** and **6b** are found to be the most effective against

Gram-negative strain S*almonella typhi*, with a value of 2.5 mg / ml. The increase in the length of the carbon chain has no influence on the antibacterial activity. In the case of products alkylated with allylbromide **2a**, the mesomeric donor effect (+ M) exerted by the chlorine makes the molecules more effective against the two strains used.On the other hand, in the case of the triple bond, the presence of an attractant group (-M) makes the product more inhibitory against the two tested strains. Moreover, results showed that the studied Gram positive strain was generally more sensitive than the Gram negative one, to most of the tested alkylation derivates of quinoxaline. This could be linked to their cell walls structure, which is more simple for Gram positive bacteria characterized by a cell wall rich in peptidoglycan. While Gram negative bacteria have a more complex cell wall, characterized by a thin peptidoglycan layer and an outer membrane containing a lipoprotein and a lipopolysaccharide layers. In fact, the outer membrane of Gram negative bacteria rich in lipopolysaccharides molecules, form a hydrophilic barrier which confers a protective effect to hydrophobic compounds [20].

5. Conclusion

In conclusion, the 6-chloroquinoxaline-2,3(1H,4H)-dione and the 6-nitroquinoxaline-2,3(1H, 4H)-dione were synthesized and used as basic nuclei for the development of novel heterocycles derivatives of quinoxaline-2,3-dione. This work was done under the conditions of phase transfer catalysis. The synthesized products were characterized by ^{1}H and ^{13}C NMR spectroscopic methods.

The products resulting from the alkylation reactions were tested for their antibacterial effects against two bacterial strains. Compound **2a** was found to be most effective against the Gram-positive strain *Staphylococcus aureus*, with a MIC value of 1.25 mg / ml. As for as Compounds **2a**, **3b** and **6b** are concerned, it is found that they are the most effective against Gram-negative strain *Salmonella typhi*, with a MIC value of 2.5 mg / ml.

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