Synthesis and Characterization of Two New Quinoxaline Derivatives

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Abstract

Two new quinoxaline derivatives, 2-benzamide-3-3-cyanoquinoxaline-4-oxide (**I**) and *N*-(3-cyano-1,4-dioxy-quinoxaline-2-yl)-4-nitro-benzamide **(II**) were synthesized from 2-amino-3-cyano-quinoxaline-1,4-dioxide. The chemical structures of the two compounds were confirmed by IR, ^{1}H and ^{13}C NMR and MS spectroscopic analysis. The *p*-nitrobenzamide group is inserted in position 2 in quinoxaline-1,4-dioxide using benzoyl chloride as a reagent under basic conditions. The structure of both compounds were confirmed by MS spectrometry, $[C_{16}H_{10}N_4O_2]^+$ and $[C_{16}H_{10}N_5O_5]^+$. The quasimolecular ions $[M+H]^+$ of compounds were found equals to *m/z* 290.2 and 351.3, respectively.

***Keywords**: Quinoxaline derivatives, 2-NH_2-3-CN-quinoxaline-1,4-dioxide, nitrogen compounds*

1.Introduction

Quinoxaline are nitrogenous compounds, used in various industries [1-3]. Many quinoxaline derivatives have been used as antibiotic [4], anticancer [5-7], antituberculosis [8], antimalarial [9], antimycobacterial [10,11], anti-intammatory [12], antiviral [13], antiprotozal [14-16] and antibacterial activities [17]. The most striking examples are levomycin and hinomcic, which inhibit the growth of gram positive bacteria and are active against transplantable tumors [18,19]. Quinoxalines also have been used as a pigment in the technology of organic dyes [20].

The diversity of useful synthesis of quinoxaline derivative accounts for the appearance of modifications of the classical synthetic methods. From these methods, the reaction of pyruvates with 1,2-diaminobenzenes (1,2-DABs), first discovered by Hinsberg, is still the most appropriate method for the synthesis of 3-substituted quinoxaline-2(1H)-ones [21,22]. There are many examples of quinoxalines being prepared form α-diketones usually involving the reaction 1,2-DABs in refluxing ethanol or acetic acid [23,25], using various catalysts such as graphite [26], and bismuth(III) triflate [27]. However, as distinct from reactions of dicarbonyl compounds, the reaction of α-halo keton with 1,2-DABs proceeds with the formation of noncyclized products [28,29]. In 2009, Tanimari and coworkers [30] reported a new efficient method for the synthesis of quinoxalin-2-ones in up to 86% yield, based on reactions of substituted 2-bromoanilines with pipecolinic acid. However, benzimidazole, like benzofuroxan, can also serve as an initial reagent in quinoxaline synthesis [31]. Raju *et al*. [32] prepared a new quinoxaline derivatives from the interaction of benzoxepine-4-carboxylates with 1,2-DABs. A series of new quinoxaline derivatives has been prepared in moderate to excellent yields from 2-(indol-1-yl)benzenamines with aromatic aldehydes [33]. A green protocol for the synthesis of quinoxaline derivatives catalyzed by polymer supported sulphanilic acid has also been reported [34]. The aim of the present work is to synthesize some of quinoxaline derivatives that might have some specific properties.

2. Experimental Section

2.1. Chemicals and Instruments.

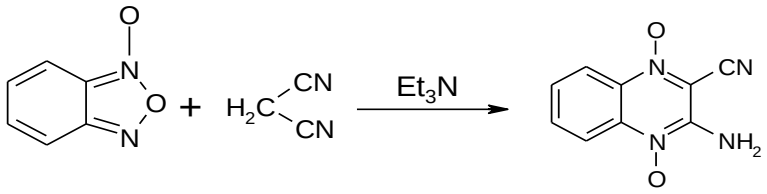
All chemicals and solvents in this study were supplied from Aldrich (France/Spain). Melting points were determined by the open capillary method. The NMR spectra were recorded using a Bruker Advanced 300 WB spectrometer, at 300 MHz in DMSO-d_6. All chemical shifts were

given in δ ppm with reference to trimethylsilane (TMS) as internal standard. Infrared spectra (4000-400 cm^{-1}) were recorded as KBr pellets on a Unicam Mattson 1000 FTIR spectrometer. The mass spectra (ESI-MS) were recorded on Shimadzu-Japan.

2.2. Ligand Synthesis.

***Synthesis of 2-amino-3-cyanoquinoxaline 1,4-oxide* (ACQO).**

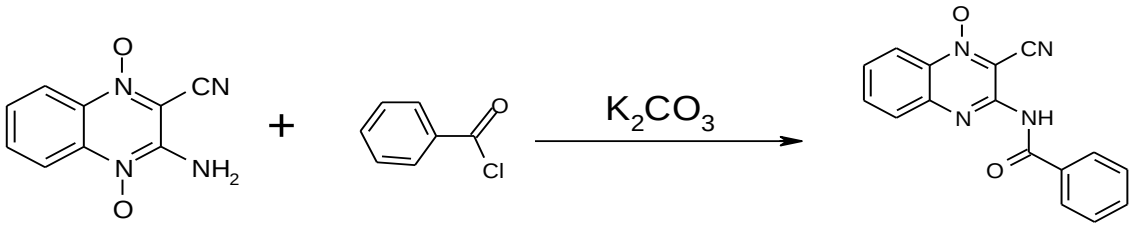
The synthesis of ACQO was carried out following a reported method by Ley *et. al*. [35], by the condensation of corresponding triethylamine with benzofurazanoxide and malononitrile (*Schem* 1).



Scheme 1: The synthesis of 2-amino-3-cyanoquinoxaline 1,4-oxide (ACQO), [35].

***Synthesis of 2-benzamide-3-3-cyanoquinoxaline-4-oxide*, (I).**

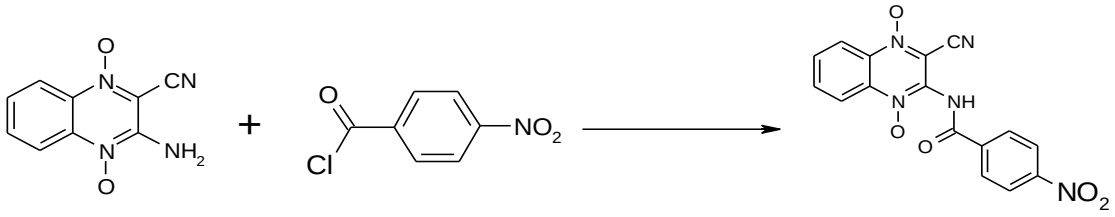
The compound was synthesized by the condensation of ACQO (0.50g, 0.002 mol) and benzoyl chloride (1.70g, 0.01 mol), in the presence of 2.0g of K_2CO_3 and 40 mL dioxane. The mixture was heated at 70^0C under reflux for 24h, with continuous stirring. After cooling, the solid product was filtered and washed with absolute ethanol. Compound I was thus obtained as grey colored crystals. Yield 95%; m.p. 215-217^0C. Elemental analysis for $C_{16}H_{10}N_4O_2$, (290.2 g/mol): C, 66.2; H, 3.4; and N, 19.3. Scheme 2, presents the synthesis route of the compound.



Scheme 2: The synthesis of 2-benzamide-3-3-cyanoquinoxaline-4-oxide, (**I**)

***Synthesis of N-(3-cyano-1,4-dioxy-quinoxaline-2-yl)-4-nitro-benzamide,* (II).**

A mixture of ACQO (0.50g, 0.002 mol), 4-nitrobenzoyl chloride 2.25g (0.01mol) and 40 mL dioxane, were mixed in flask equipped with magnetic stirrer. The mixture was stirred at room temperature for few hours. The resulting precipitate was filtered off, dried and re-crystallized from absolute ethanol to give the pure product (compound II), Yield; 90%, m. p. 206-208^{0}C, Elemental analysis for $C_{16}H_9N_5O_5$, (351.3 g/mol): C, 54.6; H, 2.6; and N, 19.9. (*Scheme* 3).



Scheme 3: The synthesis of *N*-(3-cyano-1,4-dioxy-quinoxaline-2-yl)-4-nitro-benzamide, **(II).**

3. Results and Discussion

In this study, two derivative compounds of quinoxaline (I & II) have been synthesized by the nucleophilic substitution of substituted position 2 in quinoxaline-1,4-dioxide using benzoyl chloride as a reagent under basic conditions. The structures and molecular masses of the new compounds were established by ^{1}H and ^{13}C NMR, FTIR and MS spectrometry.

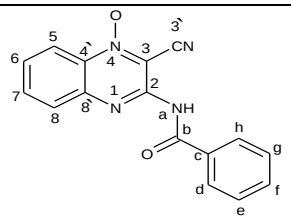
The IR spectrum of the first compound (I) exhibited strong C–H vibration bands at 3421-3074 cm^{-1}. A very strong absorption band at 1766 cm^{-1} was due to the C=O stretch vibrations of the imide group moiety. Furthermore, the IR spectrum of compound II exhibited characteristic absorption bands

around 3236 cm^{-1} and 1692 cm^{-1} corresponding for >NH and C=O str. (*asym*. and *sym*. stretching, respectively) functional groups.

The structures of the studied compounds were also confirmed by ^{1}H and ^{13}C NMR study. ^{1}H NMR (DMSO-d_6) data analysis of compound I shows the presence of a singlet peak at δ12.1 corresponding to >NH proton, and the appearance of a six doublet peak at δ 9.7, 7.6, 8.5, 8.6, 7.9, 8.1 ppm, which could be attributed to the protons of quinoxaline and aromatic ring. A triplet peak at δ 7.7, 7.8 ppm could be assigned to the three proton at benzene ring. The ^{13}C NMR spectrum of compound I shows 14 peaks, in the δ range from 111.6 to 167.2 ppm. The ^{1}H NMR (DMSO-d_6) data analysis of compound II also shows a singlet peak at δ 13.2-14.3ppm corresponding to >NH proton. An eight doublet peak at δ 8.0 to 8.55ppm could be attributed to the all proton in quinoxaline and benzene ring. ^{13}C NMR study confirmed the presence of 15 peaks in the range from 124.3 to 166.2 ppm. Tables 1 and 2 showed some details of the NMR data.

Finally, the structures and molecular weights of both compounds were confirmed by mass spectrometric analysis. The ESIMS spectrum of compound I (**Figure 1**), displayed a peak at *m/z* 290.2, corresponding to the quasimolecular ions $[M+H]^{+}$. The molecular formula of the compound ($C_{16}H_{10}N_4O_2$) was confirmed by its molecular weight in combination with the date from elemental analysis. The ESIMS spectrum of compound II (**Figure 2**), displayed a peak at *m/z* 351.3, corresponding to the quasimolecular ions $[M+H]^{+}$. The molecular formula of the compound is $C_{16}H_9N_5O_5$.

Table 1: Some of ^{1}H and ^{13}C NMR shifts and DEPTH data of ligand (I).

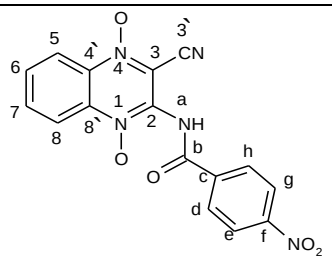


2-Benzamide-3-3-cyanoquinoxaline-4-oxide, (**I**)

^{1}HNMR					
H-a	***H-6,7***	***H-5,8***	***H-f***	***H-e,g***	***H-d,h***
11.70-12.30	7.95-8.15	7.85-7.95	7.65-7.75	7.50-7.65	8.40-8.50

^{13}CNMR						
C-6	***C-5***	***C-4'***	***C-3***	***C-2***	***C-d***	***C-b***
128.8	130.9	111.6	132.7	135.0	135.0	167.2
C-8'	***C-8***	***C-7***	***C-c***	***C-3'***	***C-f***	***C-e***
117.1	129.3	129.0	149.7	143.2	119.0	133.3
DEPTH						
C-f	***C-g,e***	***C-d,h***	***C-8***	***C-7***	***C-6***	***C-5***
119.0	133.3	135.1	129.3	127.0	128.8	130.9

Table 2: Some of ^{1}H and ^{13}C NMR shifts and DEPTH data of ligand (II).



N-(3-Cyano-1,4-dioxy-quinoxaline-2-yl)-4-nitro-benzamide, **(II)**

^{1}HNMR	
H-5,6,7,8,h,d,g,e	***H-a***
8.00-8.55	13.20-14.30

^{13}CNMR						
C-6	***C-5***	***C-4'***	***C-3***	***C-2***	***C-d***	***C-b***
124.10	131.10	137.80	138.10	138.90	135.10	166.20
C-8'	***C-8***	***C-7***	***C-c***	***C-3'***	***C-f***	***C-e***
136.80	130.4	124.20	165.40	150.50	132.70	120.10
DEPTH						
C-e	***C-d***	***C-8***	***C-7***	***C-6***	***C-5***	***C-g***
120.20	135.20	130.50	124.20	124.10	131.10	120.7

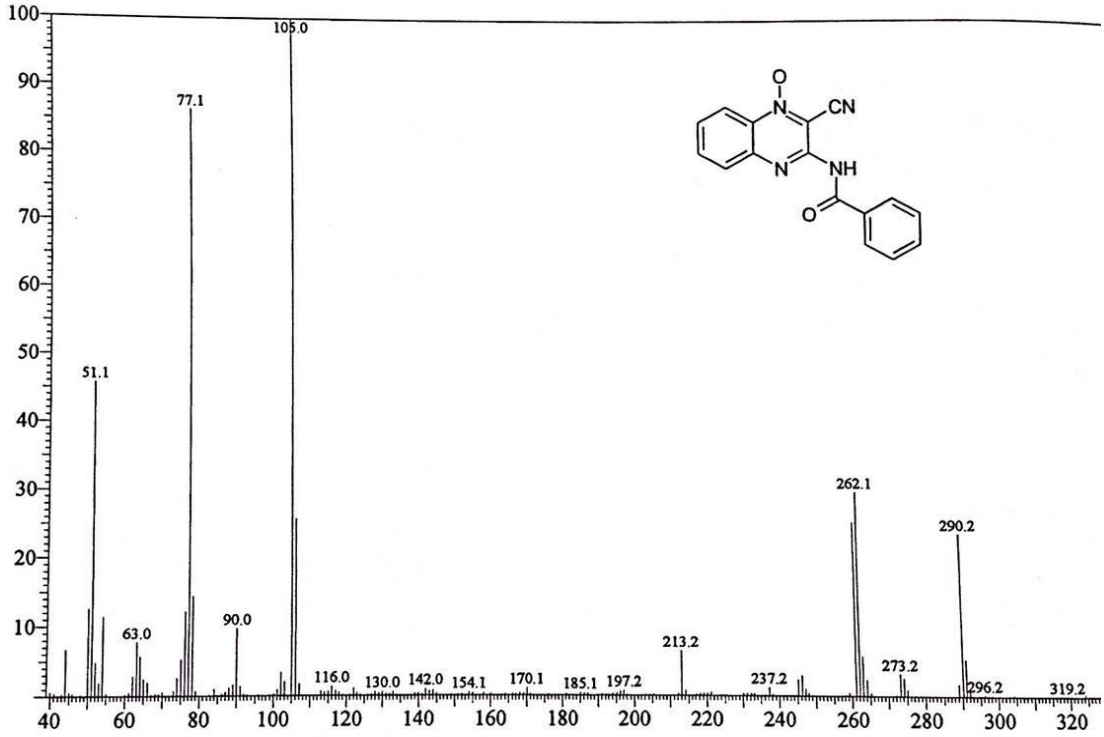


Figure 1: The ESI-MS spectrum of compound I, $C_{16}H_{10}N_4O_2$

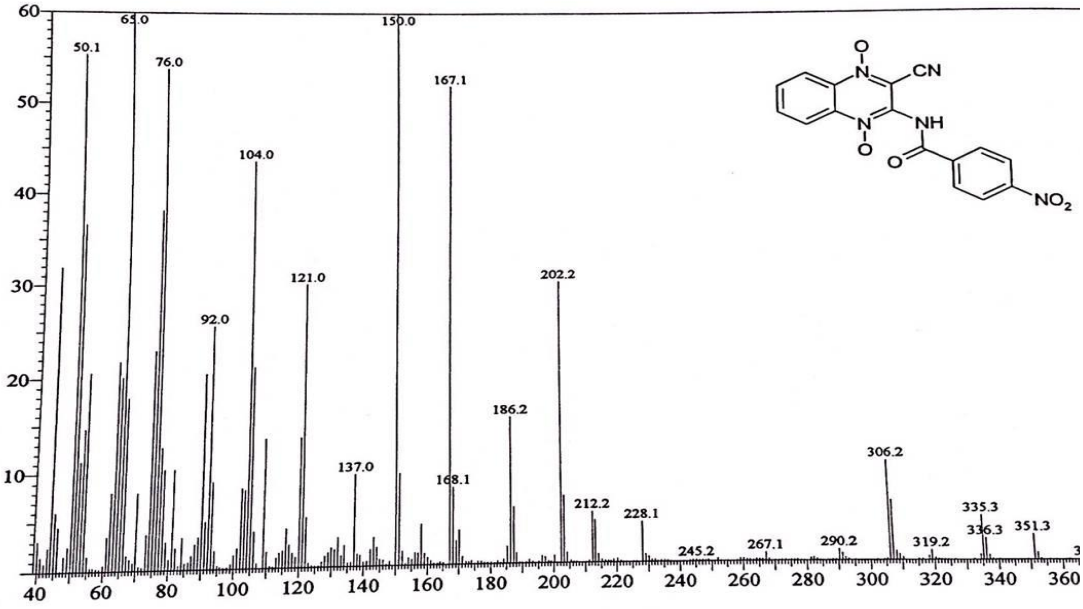


Figure 2: The ESI-MS spectrum of compound II, $C_{16}H_9N_5O_5$

Conclusion

In summary, we have described the preparation and characterization of two new derivative compounds of 2-amino-3-cyanoquinoxaline 1,4-oxide. The compounds ($[C_{16}H_{10}N_4O_2]^+$ and $[C_{16}H_{10}N_5O_5]^+$), were obtained according to the simple operating procedures in satisfactory yields. The new compounds could find a promised biological and medicinal application in future.

References

1. Husain, T., and Abnder, F., (2010), *Orient J. Chem.*, 26(2), 421.
2. Mishra, M., (2011). *Orient J. Chem*. 27(1), 227.
3. Montazari, N., Pourshamsion, K., Fauladi, M., and Bayazi, M., (2012). *Orient J. Chem*. 82(1), 399.
4. Eswaran, S., Adhikari, A., and Shetty, N., (2009). *Eur. J. Med. Chem*., 44(11), 4637.
5. Blunden, S., Patel, B., Smith, P., and Sugavanam, B., (1987). *Appl. Organomet. Chem*. 1(3), 241.
6. Denny, W., Wilson W., Ware, D., Atwell, G., Milbank, J., and Stevenson, R., (2006). US Patent, 70, 55.
7. Lilienkampf, A., Mao, J., Wan, B., Wang, Y., Franzblau, S., and Kozikowah, A., (2009). *J. Med. Chem*., 52(7), 305.
8. Sharma, A., and Mishra, M., (1999). *Orient J. Chem*., 36(5), 299.
9. Torres, E., Moreno, E., Ancizu, S., Barea, C., Galiano, S., Aldana, I., Monge, A., and Perez, S., (2011). *Bioorg Med. Chem. Let*., 21, 3699.
10. Moreno, E., Ancizu, S., Perez, S., Torres, E., Aldana, I., and Moge, A., (2010). *Eur. J. Med. Chem*., 45, 4481.
11. Burguete, A., Pontiki, E., Hadjipavlou, L., Ancizu, S., Villar, R., Solano, B., Moreno, E., Torres, E., Perez, S., and Aldana, I., (2012). *J. Chem. Biol. Drug*., 77, 255.
12. Patel, M., Hugh, R., Cordava, B., Klabe, R., Erickson, V., and Trainor, G., (2003). *J. D. Med. Chem. Lett*., 10. 1729.
13. Vicente, E., Lima, L. M., Bongard, E., Villar, R., Burguete, A., Solano, B., Ancizu, S., Perez, S., Aldana, I.; and Monge, A., (2008). *J. Chem. Biol. Drug*., 13, 69.
14. Villar, R., Solano, B., Burguete A., Perez, S., Aldana, I.; and Vivas, L., (2008). *Eur. J. Med. Chem*. 43, 1903.
15. Burguete, A., Estevez, Y., Castillo, D., Gonzale, G., Villar, R., Solano, B., Vicente, E., Perez, S., Aldana, I.; and Monge, A., (2008). *Memorias do Instituto Oswalde Cruz*, 103, 778.
16. Urquiola, C., Vieites, M., Aguirre, G., Marin, A., Solano, B., Arrambide, G., Nablia, P., Lavaggi, M. L., Torre, M. H., and Gonzales, M., (2006). *Bio. Org. Med. Chem.*, 14, 5503.

17. Lariga, M., Nuvole, A., Paglietti, G., Fadda, G., and Zanetti, S., (1990). *Eur. J. Med. Chem*., 25, 527.
18. Dell, A., Williams, D. H., Morris H. R., Smith G. A., Feeney J., and Roberts G., (1975). *J. Am. Chem. Soc*., 97, 2497.
19. Bailly C., Echepare S., Gago F., and Waring M., (1999*). Anti-Cancer Drug*., 14, 291.
20. Broch E., Lewis D., Yousaf T., and Havper H., (1999). USASWO, 99, 16.
21. Yuan H., Li X., Sun L., Xu W., and Tang W., (2009). *Med. Chem. Res*., 18(9), 671.
22. Singh D., Deivedi S., Hashim S., and Singh R., (2010). *Pharmaceuticals*, 3(8), 2416.
23. Wang F., Chen J., Liu X., Shen S., He X., Jiang H., and Bai D., (2006). *J. Chem. Pharm. Bull*., 54(3), 372.
24. Tingoli M., Mazzella M., Panunzi B., and Tuzi A., (2001). *Eur. J. Org. Chem*., 2, 399.
25. You L., Cho E., Leavitt J., Ma L., and Mantelione G. T., (2011). *Med. Chem. Lett*. 21(10), 3007.
26. Kadam H. Khan S., Kunkalkar R., and Tilve S., (2013). *Tetraheron Lett*., 54, 1003.
27. Yadav J. S., Reddy B., Premalatha K., and Shankar K., (2008). *Synthesis*, 23, 3787.
28. Kumar A., and Pawar S., (2004). *J. Org. Chem*., 69(14), 1419.
29. Gu D., Ji S., and Jiango Z., (2005). *Syn. Lett*., 6, 959.
30. Tanimori S., Nishimnra T., and Kirihata M., (2009). *Bioorg. Med. Chem. Lett*. 19(15), 4119.
31. Reddy G., M., Prasunamba R. L. and Reddy P. S., (1996). *Tetrahedron Lett*. 37(19), 3355.
32. Raju B., C., Prasad K., Saidachary G., and Sridhar B., (2014). *Org. Lett*. 16(2), 420.
33. Xu H., and Fan L., (2011). *Eu. J. Med. Chem*. 46(5), 1919.
34. Umesh P., Bhautik B., and Dipak K., (2017). *Arabian J. Chem*., 10, 2902.
35. Ley, K., Seng, F., Eholzer, U., Nast, R., and Schubart, R., Angew. (1969). *Chem. Internat. Edit*., 8, 596.