SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION AND X-RAY ANALYSIS OF 6-NITROQUINAZOLINE-2,4(1*H*,3*H*)-DIONE

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ABSTRACT

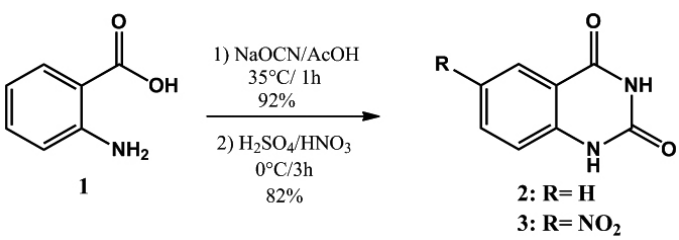
In this work, 6-nitroquinazoline-2,4(1H,3H)-dione was obtained in two step with good yields using a facile synthetic method. Its structure was characterized by X-ray single crystal diffraction technique (XRD), IR, 1D-NMR (^{1}H-NMR and ^{13}C-NMR) and 2D-NMR (H-H COSY and H-C HMBC) spectroscopy. All N and O carbonyl atoms are involved in hydrogen bonding, with an average H···O distance of 1.89(2) Å and N—H···O angles in the range 169.5(2)-177.2(2)°. In the crystal packing the molecules are associated by two strong intermolecular N—H···O hydrogen bonds forming centrosymmetric ring with graph-set motif $R^2_2(8)$, which are linked by N—H···O hydrogen bonds.

INTRODUCTION

The quinazolinone nucleus and its derivatives have been extensively studied because of their wide range of pharmacological activities. As medicines, many of them display antifungal[1], antimicrobial[2], anti-HIV[3] , antitubercular[4] , anticancer[5], antiinflammatory[6], anticonvulsant[7], antidepressant[8], hypolipidemic[9], antiulcer[10], analgesic[11] or immu-notropic activities[12] and are also known to act as thymidyalate synthase[13], poly(ADP-ribose) polymerase (PARP)[14], and protein tyrosine kinase[15] inhibitors. As pesticides, they are used as insecticides[16] and fungicides[17]. In light of the growing number of applications in recent years there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazoline derivatives. Several methods of synthesis quinazolindiones have been reported such as, from 2-aminobenzonitrile with supercritical CO_2[18], or by direct carbonylation of 2-aminobenzamide[19] or starting from anthranilic acid with sodium cyanate, among others[20]. The structure has been confirmed by X-ray crystallography methods.

RESULTS AND DISCUSSION

Synthesis of 2,4-(1*H*, 3*H*)-quinazolindione **3** (Scheme 1), was made it using the Lange y Sheible method[20] modified, obtaining a better yield (92%) respect to reported (87%). The nitration was carried out using the procedure described by Mendenhall and Smith[21] due they uses low temperatures and most favorable conditions for this type of reaction.



Scheme1. Reagents and reaction conditions in synthesis of **3**.

The complete ^{1}H and ^{13}C NMR assignments of compounds **3**, based on one- and two-dimensional NMR experiments (e.g. Figure 1a; gives the atom numbering), is shown in Table 1.

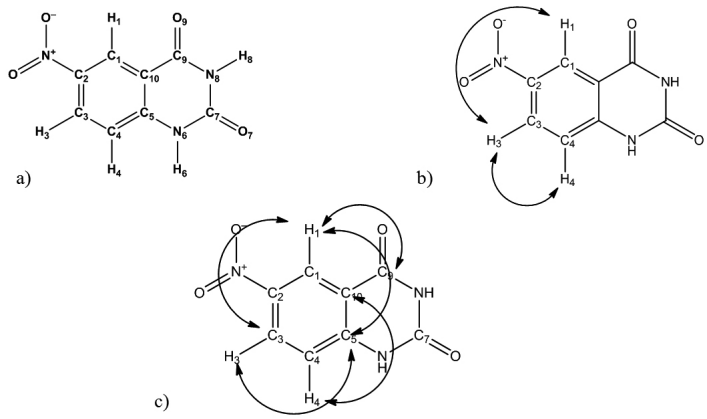


Figure 1: a) Numbering Scheme of 6-Nitro-2,4-(1*H*, 3*H*)-quinazolindione, b) H-H COSY and c) H-C HMBC principal correlations.

COSY experiment (Fig. 1b) of **3**, we can see the interactions between H1/H3 and H3/H4. HMBC spectrum shows correlations between C3/H1, C5/H1, C9/H1, C9/H3 and C10/H4.

The crystal structure was determined by single crystal X-ray diffraction. The title compound is planar (rms deviation 0.074Å), Figure 2. All N and O carbonyl atoms are involved in hydrogen bonding, with an average H···O distance of 1.89(2) Å and N—H···O angles in the range 169.5(2)-177.2(2)°, so in the crystal packing the molecules are associated by two strong intermolecular N—H···O hydrogen bonds forming centrosymmetric ring with graph-set motif[22] $R^2_2(8)$, which are linked by N—H···O hydrogen bonds, Figure 3, Table 2. π-π stacking interactions are not observed. The bond length and angles are normal[23].

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Table 1: ^{1}H and ^{13}C chemical shifts and 2D-NMR correlation data of compound **3**.

Atom N°	^{1}H NMR, multiplicity, *J*(H,H) (Hz)[a]	^{13}C-APT NMR[a]	COSY[b]	HMBC[c]
1	8.59 [H-1, d, J(1,3)=2.62]	123.06	1(3)	1(C:2,3,5,9)
2	-	141.84	-	-
3	8.45 [H-3, dd, J=9.01, J=2.66]	129.55	3(1,4)	3(C:1,2,5)
4	7.32 [H-4, d, J(4,3), J=7.60]	116.64	4(3)	4(C:2,10)
5	-	145.61	-	1,3
6	11.69 [H-6, s]	-	-	-
7	-	149.93	-	-
8	11.74 [H-8, s]	-	-	-
9	-	161.57	-	-
10	-	114.51	-	-

[a] In ppm from TMS; [b] H-H COSY and [c] H-C HMBC interactions.

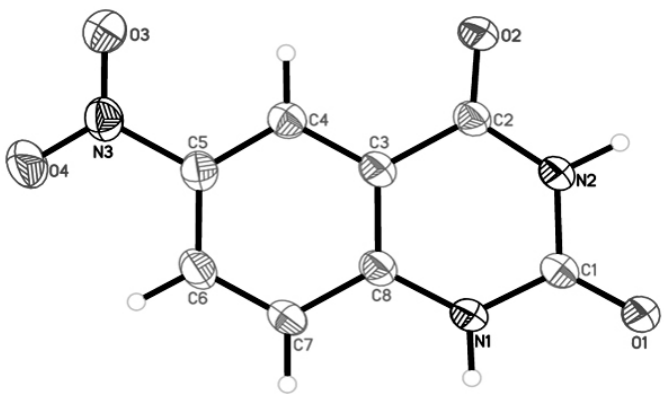

Figure 2. View of the title compound, showing 50% probability displacement ellipsoids and atom-numbering scheme. H atoms are shown as small spheres of arbitrary radii.

Table 2. Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O2^{ii}	0.887(18)	1.974(18)	2.8512 (14)	169.5(2)
N1—H2···O1^{i}	0.95(2)	1.81(2)	2.7627 (13)	177.2(2)

Symmetry codes: (ii) −*x*, −*y*+*2*, −*z*+*1*; (i) *x*, −*y*+3/2, *z*+1/2.

EXPERIMENTAL

Melting points were determined on a Kofler-type apparatus and are uncorrected. The IR were taken on a Perkin-Elmer 200 spectrophotometer with KBr. NMR spectra were collected in DMSO-d6 or $CDCl_3$ on a Varian Unity Inova 500 MHz spectrometer equipped with a microflow probe from Protasis. Mass spectra were recorded on a Micromass-LCT Premier Time-of-Flight electrospray (ESI) spectrometer with interface system Acquity UPLC (Ultra Performance Liquid Chromatography). TLC was performed on Al Si gel Merck 60 F254 and TLC plates were visualized by spraying with phosphomolybdic acid reagent and heating. Commercially available, laboratory grade reagents were used without further purification.

General Procedure

Synthesis of quinazoline-2,4(1H,3H)-dione, **2**

A solution containing 20 g (146 mmol) of anthranilic acid **1** in 0.7 l of water and 11 mL (190 mmol) of acetic acid was heated at 35 °C by 30 minutes. While the mixture is maintained stirring, a solution of 12 g (185 mmol) of sodium cyanate in 100 mL of water is dropwise slowly added and allowed to react for 30 minutes. After this time, the mixture was cooled on ice bath and after, 200 g (5 moles) of NaOH in small pieces were added slowly and stirring continued for 12 hours. The precipitate was washed in 1L of water and neutralized with aqueous sulfuric acid (1:1) until pH 7 and filtered under vacuum. The crude product, 21 g (yield 92%) was crystallized in water giving colorless crystals (m.p. 350-351°C).

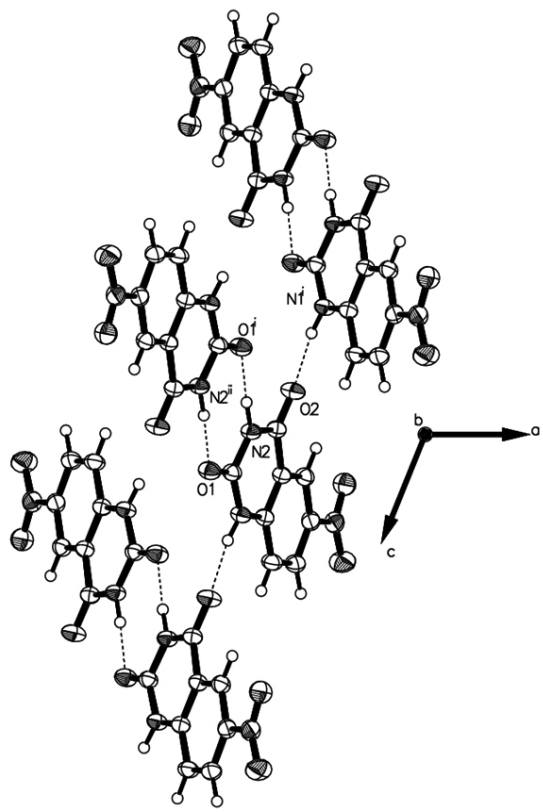

Figure 3. A view of the part of the crystal structure of the title compound showing 50% probability displacement ellipsoids illustrating the N-H···O interactions. Dashed lines indicate hydrogen bonds. Symmetry codes: (ii) −*x*, −*y*+*2*, −*z*+*1*; (i) *x*, −*y*+3/2, *z*+1/2.

Spectroscopic data:

IR (cm^{-1}) 3254 (N-H), 3055 (Csp2-H), 1702 (C=O), 1506 (CAr-CAr).

^{1}H-NMR (DMSO-d6, 500 MHz) (ppm): 7.16 (1H, m, H4), 7.62 (1H, t, J=7.7, H1), 7.88 (1H, d, J=7.4, H3), 11.09 (1H, s, H6), 11.22 (1H, s, H8).

^{13}C-NMR (DMSO-d6, 125.70 MHz) (ppm): 114.32 (C10), 115.28 (C2), 122.26 (C4), 126.91 (C1), 134.87 (C3), 140.83 (C5), 150.26 (C7), 162.79 (C9).

HRESIMS: m/z 163.0497 for $C_8H_7N_2O_2$ $[M+H]^+$, calculated: m/z 163.0508.

Synthesis of 6-Nitroquinazoline-2,4(1H,3H)-dione. **3**

On an ice bath, 2 g (12,3 mmol) of quinazoline-2,4(*1H,3H*)-dione **2**, were dissolved in 19 mL of sulfuric acid. Maintaining the mixture under agitation, a solution of 0.68 mL of nitric acid (12.3 mmol) and 1.37 mL of sulfuric acid were by dropwise added during 30 minutes and left reacting for 3 hours at 0°C. After this time, the reaction mixture was poured into a beaker containing 70 ml cold water. Subsequently, 70 ml of solution 9.5N of NaOH was dropwise added. The resulting precipitate was filtered at vacuum, dried and purified by chromatographic column using petroleum-ether/ethylacetate (3/7) as eluent. This gave 2.1 g (82% yield) of a yellow product.

Spectroscopic Data:

IR (cm^{-1}) 3338 (N-H), 3018 (Csp2-H), 1683 (C=O), 1533 (CAr-NO_2).

^{1}H-NMR (DMSO-d6, 500 MHz) (ppm): 7.32 (1H, d, J= 9, H4), 8.45 (1H, dd, J= 9, H3), 8.59 (1H, d, J=6.6, H1), 11.69 (1H, s, H6), 11.74 (1H, s, H8).

^{13}C-NMR (DMSO-d6, 125.70 MHz) (ppm): 114.51 (C10), 116.64 (C4), 123.06 (C1), 141.84 (C2), 145.61 (C5), 149.93 (C7), 161.57 (C9).

HRESIMS: m/z 206.0193 for $C_8H_4N_3O_4$ $[M-H]^+$, calculated: m/z 206.0202.

X- Ray Crystallography

Single crystal analysis data were collected on a Stoe IPDS-II two-circle Diffractometer with MoKα radiation. Data collection: X-AREA[24]; cell refinement X-AREA[24]; data reduction: X-AREA[24]. Program used to solve structure program(s) used to refine structure: SHELXL97[25]; molecular graphics: XP in SHELXTL-Plus[25] & OLEX2[26], software used to prepare material for publication: SHELXL97[25]. Crystal dimension of $C_8H_5N_3O_4$, 0.37x 0.35x0.12 mm^3; Mr = 207.15 Dalton; Monoclinic P21/c; a = 10.9071(8) Å; b = 6.5758(6) Å; c = 12.4614(9) Å; α = 90°; β = 112.382(5)°; γ = 90.0°; V = 826.44(11) $Å^3$; Z = 4; m = 0.137 mm^{-1}; T = 173(2) K; absorption correction Semi-empirical from equivalents [27 - 28]; max. and min. transmission 0.9837 and 0.9509. 8995/1898 measured/unique reflection with I>2s(I) [R_{int} = 0.0556]; R[I>2s(I)] 0.0393, wR_2 = 0.1093; S = 1.097; 144 parameters; Dr_{max} = 0.284 e$Å^{-3}$and Dr_{min} = -0.209 e$Å^{-3}$. H1 and H2 atoms were freely refined; all H atoms were located in difference maps and their positions and isotropic displacements parameters of 1.2 times those of the attached atoms. Supplementary information: Crystallographic data (excluding structure factors) for the structural analysis have been deposited in the Cambridge Crystallographic Data Centre, CCDC 927348. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre; Postal Address : CCDC, 12 Union Road , Cambridge CB21EZ, UK, Telephone: (44) 01223 762910, Fax: (44) 01223 336033, e-mail: deposit@ccdc.cam.ac.uk

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