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Autoxidation of 4-Hydrazinylquinolin-2(1H)-one; Synthesis of Pyridazino[4,3-c:5,6-c′]diquinoline-6,7(5H,8H)-diones

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Abstract: An efficient synthesis of a series of pyridazino[4,3-c:5,6-c′]diquinolines was achieved via the autoxidation of 4-hydrazinylquinolin-2(1H)-ones. IR, NMR (1H and 13C), mass spectral data, and elemental analysis were used to fit and elucidate the structures of the newly synthesized compounds. X-ray structure analysis and theoretical calculations unequivocally proved the formation of the structure. The possible mechanism for the reaction is also discussed.

Keywords: 4-hydrazinylquinolin-2(1H)-one; pyridazino[4,3-c:5,6-c′]diquinoline-6,7(5H,8H)-dione; autoxidation reaction; X-ray; DFT

1. Introduction

Compounds with quinolin-2(1H)-one (carbostyril) skeletons are present in a large number of biologically active compounds [1–12]. During the twentieth century [13], various research groups dealt with the chemistry and biological applications of quinolines [14].

Pyridazine and its polycyclic structures have still played an interesting role in organic chemistry because of their remarkable properties in forming supramolecular assembly [15–18]. Pyridazine molecules are important heterocycle scaffolds that reveal diverse biological activities in medicine [19–25] and agriculture [26]. For example, Pyridazomycin is an antifungal and antibiotic compound, the first pyridazine derivative isolated from a natural source [27]. In contrast, Pyridaben is widely used as an acaricide with a long residual action, whereas Chloridazon has a long history of use as an herbicide [28]. Minaprine is a psychotropic drug that has effectively treated various depressive states [29] (Figure 1).

Functionalized pyridazines have high electron-deficient properties, encouraging their utilization as electrochromic materials and metal–organic frameworks [30,31].

Hydrazines have shown basic and reducing characteristics that enable their utility in many industrial and medical applications. Accordingly, hydrazines have served as rocket fuel, antioxidants, oxygen scavengers, and as intermediates for the production of explosives, propellants, and pesticides [32].

It has been demonstrated that oxygen makes hydrazine solutions unstable, especially under alkaline or neutral conditions. However, hydrazines are stable under strongly acidic conditions or without oxygen [33].

Wagenerova et al. [34] have reported that cobalt-tetrasulphophthalocyanines enhance the autoxidation process of hydrazines [34]. On the other hand, Ichiro Okura et al. [35] reported that the autoxidation of hydrazine occurred with manganese (III)-hematoporphyrin...
at room temperature, and that has an advantage because of its reactivity for the formation of oxygen coordinated Mn(III)-Hm peroxide adduct [36]. Andrew P. Hong et al. [37] reported that satisfactory autoxidation of hydrazines occurred using cobalt (II) 4,4′,4″,4‴-tetrassulfophthalocyanine (CoIIITSP).

![Chemical structures of biologically active Pyridazomycin, Minaprine, Pyridaben and Chloridazone.](image)

**Figure 1.** Chemical structures of biologically active Pyridazomycin, Minaprine, Pyridaben and Chloridazone.

Previously, it was reported [38] that 1-ethyl-4-hydroxyquinolin-2(1H)-one (I) reacted with hydrazine hydrate, in 1,2-dichlorobenzene (o-DCB), to give a mixture of two compounds. These compounds were separated using fractional recrystallization to give quinoline-1,4-dihydrazine 2a in 19% yield and diquinopyridazine 3a in 41% yield (Scheme 1).

![Scheme 1. Formation of compound 3a from the reaction of 1-ethyl-4-hydroxyquinolin-2(1H)-one (I) with hydrazine in o-DCB.](image)

**Scheme 1.** Formation of compound 3a from the reaction of 1-ethyl-4-hydroxyquinolin-2(1H)-one (I) with hydrazine in o-DCB.

A convenient microwave-assisted, one-pot, four-component synthetic approach was developed as a route to functionalized benzo[a]pyridazino[3,4-c]phenazine derivatives starting from 2-hydroxy-1,4-naphthoquinone, aromatic aldehydes, methyl hydrazine, and o-phenylenediamine. Compounds of a similar pentacyclic structure such as bisanthranilate showed an intramolecular electrophilic cyclization and afforded an angular cis-quinacridone compound, which condensed with hydrazine to give a phthalazine derivative [39]. The biological profiles of some of the compounds mentioned above exhibited good cytotoxic activities against KB, HepG2, Lu1, and MCF7 human cancer cell lines. In addition, a compound of the derivatives exhibited promising antimicrobial activities toward *Staphylococcus aureus* and *Bacillus subtilis* bacterial strains with IC₅₀ < 6 μM [40].

Recently, it has been reported that hydrazines can be used as catalysts for removing oxygen in the closing carbonyl–olefin metathesis process [41]. We have also found that prolonged reflux during the formylation process of 2-quinolones via a DMF/Et₃N mixture caused
dimerization to occur, and unexpected 3,3'-methylenabis(4-hydroxyquinolin-2(1H)-ones) were obtained [42].

The above-mentioned findings encouraged us to generalize the method of preparation for heteroannulated pentacyclic compounds with the structure of this interesting molecule.

2. Results and Discussion

The strategy started with the preparation of derivatives of compounds 1, 2, 4, and 5 according to reported methods, and their structures were confirmed by matching their spectral data with those reported [43–45]. The key intermediates, hydrazine quinolones 2a–g, were prepared by refluxing compounds 4a–g with hydrazine hydrate (Scheme 2) [46]. During the heating of 4-hydrazinylquinolin-2(1H)-ones 2a–g in pyridine, we observed the abnormal formation, in good yields, of pyridazino[4,3-c:5,6-c']diquinoline-6,7-(5H,8H)-diones 3a–g. As had been suggested, compounds 2a–g underwent an autoxidation reaction.

![Scheme 2. Synthesis of pyridazino[4,3-c:5,6-c']diquinoline-6,7(5H,8H)-diones 3a–g. Reagents and conditions: (a) POCl₃, reflux, 2 h; (b) AcOH, reflux 12 h; (c) NH₂.NH₂.H₂O, reflux 12 h; (d) pyridine reflux, 6–12 h.](image)

The structures of the products 3a–g were proved from their elemental analyses and IR, ¹H NMR, and ¹³C NMR spectra. For example, the mass spectrum and elemental analysis of 3a established its molecular formula as C₂₂H₁₈N₄O₂. The ¹H NMR spectrum of 3a exhibited the ethyl protons as a triplet at δ_H = 1.22 (J = 7.6 Hz) for CH₃ and a quartet at δ_H = 4.39 ppm (J = 7.6 Hz) for CH₂. The eight aromatic protons appeared as three multiplets at δ_H = 7.36–7.40 for 2H, 7.68–7.78 for 4H, and 8.06–8.08 ppm for 2H. The reported spectroscopic data for the ¹³C NMR spectrum of compound 3a showed the carbonyl-quinolone, 2NCH₂, and CH₃ carbon signals at δ_C = 165.72, 39.11, and 14.11 ppm, respectively. Similar spectroscopic results of compound 3a were also reported [38]. The structure of 3a was unambiguously determined by a single crystal structure (Figure 2).
We carried out the reaction in different conditions using compound 1a as an example with the optimized reaction conditions. In EtONa/EtOH (Method B, Table 1), it was found that the yield of 3a was decreased (74%). Refluxing of 1a in toluene/Et3N (Method C, Table 1) did not increase the yield (60%), and the time taken to obtain 3a was increased (2d). Furthermore, adding a few drops of Et3N to DMF (Method D, Table 1) improved the yield of 3a compared with methods B and C, but it was still lower compared with our method A. Using Na/toluene, the oxidation of 1a occurred satisfactorily; however, it was lower compared with method A. In our trial of an acidic medium using HCl/EtOH mixture, the reaction failed. Thus, the best condition to obtain high yields and a short reaction time of 3a–g is reflux in dry pyridine (Method A, Table 1).

Table 1. The reaction optimization for the formation of 3a.

| Entry | Method                      | Yields of 3a (%) |
|-------|-----------------------------|-----------------|
| A     | Pyridine, reflux, 8 h       | 88              |
| B     | EtONa/EtOH, reflux 24 h a   | 74              |
| C     | Toluene/Et3N, reflux 2 d b  | 60              |
| D     | DMF/Et3N, reflux 20 h c     | 78              |
| E     | Na/Toluene, reflux 18 h d   | 82              |
| F     | EtOH/HCl, reflux e          | No reaction     |

The formation of pyridazino[4,3-c:5,6-c']diquinoline-6,7(5H,8H)-diones 3a–g can be rationalized as depicted in Scheme 3. It is clear from the suggested mechanism (Scheme 3) that it constitutes several steps of nucleophilic substitution, dimerization, autoxidation, and electrocyclic reactions in a one-pot process leading to the pentacyclic final products 3a–g. The mechanism starts with a proton shift of compound 2 to its isomer 2'. Then, the starting molecule of 2 reacts with its isomer 2' to give 6 (Scheme 3). The elimination of a hydrazine molecule in 6 would give the dimerized hydrazene 7, which undergoes another proton shift to give the intermediate 7'. Because the reaction did not proceed under an inert argon atmosphere (i.e., under argon atmosphere, the starting quinolinyl-hydrazines 2a–g were recovered), we proposed that the intermediate 7' undergo an aerial oxidation NH-NH group to give the intermediate 8. After that, the intermediate 8 would undergo internal electrocyclization to give 9. Finally, another mode of aerial oxidation of 9 would produce compound 3 (Scheme 3).
Then, the starting molecule of 2 reacts with its isomer 2′ to give 6 via the BP and BCP between the two oxygen atoms (O ∙∙∙O). The preceding literature supports the mechanism [47] describing aryl hydrazine chlorides’ aerial oxidation into diazines. Accordingly, it supports the steps of transformations of 7′ into 8 and 9 into 3. Moreover, aerial catalytic oxidation in pyridine transformed hydrazones into diazo compounds [48].

Firstly, the stability of compound 3a (Figure 3), as an example, was described. Therefore, the quantum mechanical calculations were performed for compound 3a. The investigated compound was first optimized using the DFT method (see the Methods section for details). The optimized structure was then subjected to vibrational frequency and single-point energy calculations. The quantum theory of atoms in molecules (QTAIM) was invoked to achieve an in-depth insight into the topological features of compound 3a [49]. In the context of QTAIM, the (3,–1) bond critical points (BCPs) and bond paths (BPs) were generated, and the electron density was computed. Moreover, noncovalent interaction (NCI) index analysis was executed to pictorially elucidate the origin and nature of intramolecular interactions within compound 3a [50]. According to the results, no imaginary frequencies were observed for the investigated structure of compound 3a, confirming that this conformer is a true minimum. Based on the QTAIM results presented in Figure 4a, the occurrence of intramolecular bonds within the inspected compound was revealed by the existence of BPs and BCPs. Chalcogen–chalcogen intramolecular interaction was also noticed in compound 3a via the BP and BCP between the two oxygen atoms (O–O). The BCP at the BP O–O within compound 3a exhibited electron density with a value of 0.0144 au.

The stability of compound 3a might also be interpreted as a consequence of the aromatic planarity, which could be detected from Figure 4a via dihedral angles (Φ) with a value of 1.83°. Notably, the difference between the dihedral angle of the optimized geometry of compound 3a and the X-ray data was nearly 0.36°.

As shown in Figure 4b, the NCI results (green isosurfaces) occurred at the interatomic space between the interacting atoms, asserting the occurrence of the intramolecular interactions towards the investigated compound. Large, green, round domains within the
intramolecular forces N_{13}⋯HC_{12} and N_{14}⋯HC_{1} of compound 3a were crucially denoted, reflecting the favorable contribution of such intramolecular forces to the further stability of compound 3a.

Figure 3. The assigned structure of compound 3a.

> Figure 3. The assigned structure of compound 3a.

3. Conclusions

The unprecedented dimerization and oxidation cascade of 4-hydrazinylquinolin-2(1H)-ones delivered pyridazino[4,3-c:5,6-c′]diquinoline-6,7(5H,8H)-diones in good yields. The synthesis of the obtained pyridazino-diquinolones was achieved in different conditions. Heating 4-hydrazinylquinolin-2(1H)-ones in pyridine was the best condition in which to obtain the corresponding products. Quantum mechanical calculations were also performed using the DFT method to prove the stability of the formed products. The method above can be used as a general method for the preparation of various classes of pentacyclic heterocycles from compounds with structural features similar to 4-hydroxy-2-quinolones. Importantly, the biological activity of the obtained products could assist in the development of new drugs.

4. Experimental Section

4.1. Chemistry

The IR spectra were recorded using the ATR technique (ATR = Attenuated Total Reflection) with an FT device (FT-IR Bruker IFS 88), Institute of Organic Chemistry, Karlsruhe University, Karlsruhe, Germany. The NMR spectra were measured in DMSO-d_6 on a Bruker AV-400 spectrometer, 400 MHz for ^1^H, and 100 MHz for ^1^C; the chemical shifts are expressed in δ (ppm), versus internal tetramethylsilane (TMS) = 0 for ^1^H and ^13^C, and external liquid ammonia = 0. The description of signals includes: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, and m = multiplet. Mass spectra were recorded on a FAB (fast atom bombardment) Thermo Finnigan Mat 95 (70 eV). Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt.
4.1.1. Starting Materials

4-Chloro-quinolin-2(1H)-ones 4a–g were prepared according to the literature [43–45], whereas 4-hydrazinylquinolin-2(1H)-ones 2a–g were synthesized according to the literature [46].

4.1.2. General Procedure

4-Hydrazinylquinolin-2(1H)-ones 2a–g (1 mmol) were heated in pyridine for 6–12 h until the reactants had disappeared, as mentioned in Scheme 1. The reaction was monitored using TLC (using toluene: EtOAc; 10:1). Then, the mixture was cooled and poured into iced water; the formed precipitate was filtered, washed with water, and recrystallized from the stated solvents to give pure crystals 3a–g.

5,8-Diethylpyrazidino[4,3-c:5,6-c’]diquinoline-6,7(5H,8H)-dione (3a)

Orange crystals (DMF/H2O), yield: 0.31 g (86%); mp 330–332 °C. IR (KBr): v = 3013 (Ar-CH), 2927 (Ali-CH), 1653 (C=O), 1640 (Ar-C=C) cm−1; 1H NMR (400 MHz, DMSO-d6) δH = 7.05–7.09 (m, 2H, Ar-H), 7.18–7.23 (m, 2H, Ar-H), 7.33–7.38 (m, 2H, Ar-H), 7.68 (dd, 2H, J = 7.8, 1.2 Hz, Ar-H); 13C NMR (100 MHz, DMSO-d6): δC = 39.91 (2 CH3), 115.87, 115.78, 119.12, 122.14, 122.25, 131.66, 136.80, 156.61, 165.81 ppm (C-6 and C-7); MS (Fab, 70 eV, %): m/z = 342 (M+), 289 (6), 197 (13), 171 (23), 169 (36), 157 (100), 134 (48), 105 (15). Anal. Calcd. for C20H14N4O2 (342.35): C, 68.71; H, 4.12; N, 16.37. Found: C, 68.68; H, 4.23; N, 16.44.

Pyridazino[4,3-c:5,6-c’]diquinoline-6,7(5H,8H)-dione (3b)

Orange crystals (DMF/CH3OH), yield: 0.30 g (88%); mp 320–322 °C. IR (KBr): v = 3052 (Ar-CH), 1643 (C=O), 1606, 1587 (Ar-C=C) cm−1; 1H NMR (400 MHz, DMSO-d6) δH = 7.05–7.09 (m, 2H, Ar-H), 7.18–7.23 (m, 2H, Ar-H), 7.33–7.38 (m, 2H, Ar-H), 7.68 (dd, 2H, J = 7.8, 1.2 Hz, Ar-H); 13C NMR (100 MHz, DMSO-d6): δC = 39.91 (2 CH3), 115.87, 115.78, 119.12, 122.14, 122.25, 131.66, 136.80, 156.61, 165.81 ppm (C-6 and C-7); MS (Fab, 70 eV, %): m/z = 342 (M+), 289 (6), 197 (13), 171 (23), 169 (36), 157 (100), 134 (48), 105 (15). Anal. Calcd. for C20H14N4O2 (342.35): C, 68.71; H, 4.12; N, 16.37. Found: C, 68.68; H, 4.23; N, 16.44.

2,11-Dichloropyrazidino[4,3-c:5,6-c’]diquinoline-6,7(5H,8H)-dione (3e)

Orange crystals (DMF/H2O), yield: 0.325 g (85%); mp 358–360 °C. IR (KBr): v = 3177 (NH), 3023 (Ar-CH), 1640 (C=O), 1605, 1560 (Ar-C=C) cm−1; 1H NMR (400 MHz, DMSO-d6) δH = 7.34–7.35 (m, 2H, Ar-H), 7.36–7.37 (m, 2H, Ar-H), 7.68–7.70 (m, 2H, Ar-H), 12.19 (s, 2H, NH); 13C NMR (100 MHz, DMSO-d6): δC = 115.78, 115.92, 119.12, 122.10, 128.78, 132.87, 136.80, 157.52, 165.12 ppm (C-6 and C-7); MS (Fab, 70 eV, %): m/z = 383 (M+), 348 (9), 310 (8), 289 (6), 257 (13), 236 (23), 208 (23), 171 (12), 157 (84). Anal. Calcd. for C20H14N4O2 (383.34): C, 68.73; H, 4.12; N, 16.37. Found: C, 68.68; H, 3.99; N, 16.41.

TLC was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with PF254 indicator; TLCs were viewed at λmax = 254 nm.
3,10-Dichloropyridazino[4,3-c:5,6-c']diquinoline-6,7(5H,8H)-dione (3f)

Orange crystals (DMF/EtOH), yield: 0.325 g (87%); mp 354–356 °C. IR (KBr) ν = 3186 (NH), 3039 (Ar-CH), 1648 (C=O), 1607, 1577 (Ar-C=C) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δH = 7.20–7.23 (m, 2H, Ar-H), 7.32–7.33 (m, 2H, Ar-H), 7.34–7.37 (m, 2H, Ar-H), 12.13 (s, 2H, NH); ¹³C NMR (100 MHz, DMSO-d₆): δC = 115.77, 115.89, 112.19, 122.14, 131.12, 132.15, 136.82, 157.62, 164.71 ppm (C-6 and C-7); MS (Fab, 70 eV , %): m/z = 383 (M⁺, 70), 313 (31) 227 (14), 191 (100), 153 (89), 137 (31), 110 (18). Anal. Calcd. for C₁₈H₁₈N₄O₄: C, 64.17; H, 3.77; N, 14.97. Found: C, 64.23; H, 3.60; N, 15.09.

2,11-Dimethoxypyridazino[4,3-c:5,6-c']diquinoline-6,7(5H,8H)-dione (3g)

Orange crystals (DMF/EtOH), yield: 0.325 g (87%); mp 354–356 °C. IR (KBr) ν = 3186 (NH), 3039 (Ar-CH), 1648 (C=O), 1607, 1577 (Ar-C=C) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δH = 3.82 (s, 6H, OCH₃), 7.20–7.23 (m, 2H, Ar-H), 7.32–7.33 (m, 2H, Ar-H), 7.34–7.37 (m, 2H, Ar-H), 12.13 (s, 2H, NH); ¹³C NMR (100 MHz, DMSO-d₆): δC = 55.37 (2 OCH₃), 116.53, 117.54, 120.53, 122.52, 131.30, 132.80, 134.47, 157.77, 165.73 ppm (C-6 and C-7); MS (Fab, 70 eV , %): m/z = 374 (M⁺, 100), 313 (36), 284 (55), 268 (46), 187 (50), 106 (18). Anal. Calcd. for C₂₀H₁₈N₄O₄ (374.35): C, 64.17; H, 3.77; N, 14.97. Found: C, 64.23; H, 3.60; N, 15.09.

4.1.3. Crystal Structure Determination

Single crystals were obtained via recrystallization from DMF/Water. The single-crystal X-ray diffraction study of 3a was carried out on a Bruker D8 VENTURE diffractometer with a PhotonII CPAD detector at 298 K using Cu-Kα radiation (λ = 1.54178 Å). Dual space methods (SHELXT) [51] were used for structure solution, and refinement was carried out using SHELXL [51] (full-matrix least-squares on F²). Hydrogen atoms were localized using difference electron density determination and refined using a riding model (H(N) free). A semi-empirical absorption correction was applied. The absolute structure was determined via the refinement of Parsons’ x-parameters [52].

3a: Orange crystals: C₂₂H₁₈N₄O₂, M_r = 370.40 g mol⁻¹, size 0.20 × 0.12 × 0.04 mm, Orthorhombic, Pca₂₁ (no.29), α = 21.1937 (4) Å, β = 9.2208 (2) Å, γ = 17.9646 (3) Å, V = 3510.69 (12) Å³, Z = 8, D_c calc = 1.402 Mg m⁻³, F(000) = 1552, μ (Cu-Kα) = 0.75 mm⁻¹, T = 298 K, 36,156 measured reflection (2θ max = 144.40), 6865 independent (R_int = 0.057), 506 parameters, 1 restraint, R₁ (for 6684 I > 2σ(I)) = 0.042, wR² (for all data) = 0.115, S = 1.02, largest diff. peak and hole = 0.34 eÅ⁻³/−0.22 eÅ⁻³, x = −0.05(11).

CCDC 2,128,843 (3a) contains the supplementary crystallographic data for this paper (see the Supplementary Materials). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (accessed on 10 February 2022).

4.1.4. Theoretical Calculations

Geometrical optimization and vibrational frequency calculations were carried out at the B3LYP/6-31G* level of theory [53,54] for the compounds under consideration. Upon the optimized structures, the energetic features were then evaluated at MP2/6-311 + G** [55]/B3LYP/6-31G* levels of theory. QTAIM and NCI calculations were performed with the help of Multiwfn 3.7 package [56] and were plotted using Visual Molecular Dynamics (VMD) software [57]. All quantum mechanical calculations were carried out at the B3LYP/6-31G* level of theory using Gaussian 09 software (Gaussian, Inc.: Wallingford, CT, USA) [58].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27072125/s1. Figure S1: ORTEP diagram of compound 3a; Tables S1–S7: Crystal data of 3a; S14–S22: ¹H, ¹³C NMR and Mass spectra of compounds 3a–g; S23–S24: Cartesian coordinates of the compound 3a used in DFT calculation.
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