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Short Note

3-Phenyl-3*H*-naphtho[1,2-*e*][1,2,3]oxadiazine

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Abstract: In this study, we considered the reaction of (*E*)-1-[(2-phenylhydrazono)methyl]naphthalen-2-ol with iodobenzene diacetate in dichloromethane-produced novel 3-phenyl-3*H*-naphtho[1,2-*e*][1,2,3]oxadiazine in 11% yield. By analogy to previously published work, we suggested that the reaction proceeds via the intermediacy of an *o*-naphthoquinone azomethide that undergoes conjugated 6π-electrocylization to produce the product. 1D, 2D NMR, HRMS, IR, and UV-VIS spectra provided information that supported the structure of the product.

Keywords: heterocycle; oxadiazine; naphtho[1,2-*e*][1,2,3]oxadiazine; *o*-naphthoquinone azomethide; hydrazone

1. Introduction

Natural oxadiazines were considered non-existent until the first 1,2,3-oxadiazine, nocuolin A (NoA) (Figure 1), was isolated in 2017 from strains of three genera of cyanobacteria: Nostoc, Nodularia, and Anabaena [1]. NoA exhibits a potent antiproliferative activity against human p53-mutated cancer cell lines and is considered a novel bioactive secondary metabolite. Although oxadiazines do not appear in the list of U.S. FDA approved drugs, 1,2,4-oxadiazine FRM-024 (Figure 1) is a preclinical candidate for the treatment of familial Alzheimer's disease [2]. Useful pharmaceutical applications by 1,3,4-oxadiazines include uses as antibacterial [3,4], antifungal [3], antitumor [5,6] and antileishmanial [5] agents.

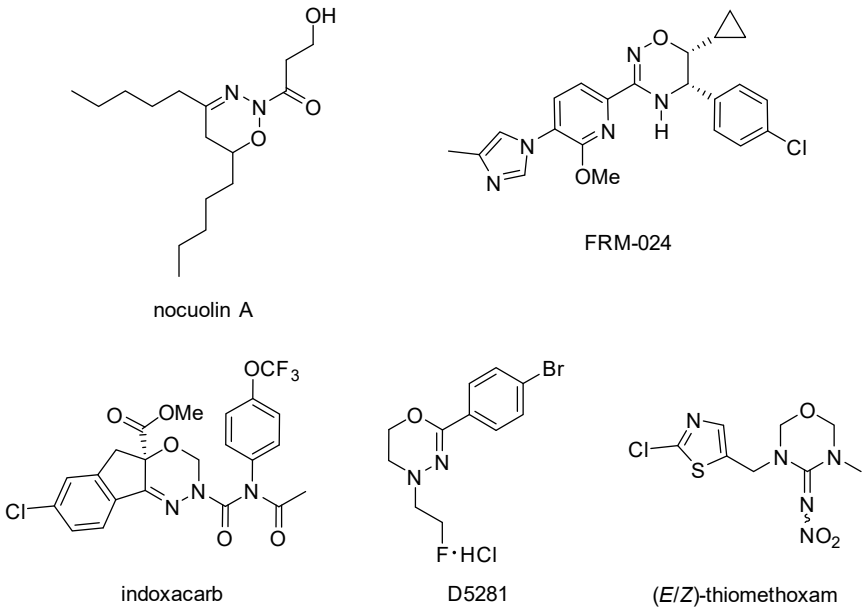

Figure 1. Bioactive oxadiazines.

The 1,3,4- and 1,3,5-oxadiazine skeletons have also been developed as agrochemicals. Important commercialized insecticides are indoxacarb [7], D5281 [8], and (*E*/*Z*)-

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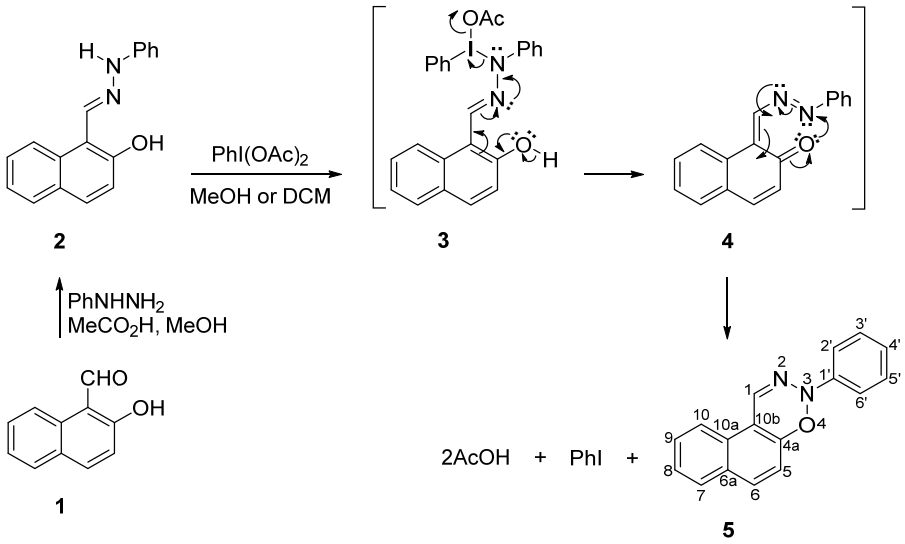
thiamethoxam [9] (Figure 1). The chemistry and certain biological aspects of oxadiazines have recently been reviewed [10].

2. Results

As shown in Scheme 1, (*E*)-1-[(2-Phenylhydrazono)methyl]naphthalen-2-ol (**2**) [11,12] was produced, in 74% yield, by heating commercially available 2-hydroxy-1-naphthaldehyde (**1**) with just over one equivalent of freshly distilled phenylhydrazine in methanol, containing a few drops of glacial acetic acid, at 60 °C for 2 h. The crude material was purified by dry column vacuum chromatography (Scheme 1). 3-Phenyl-3*H*-naphtho[1,2-*e*][1,2,3]oxadiazine (**5**) was synthesized via the oxidative cyclisation of hydrazine (**2**) using iodobenzene diacetate either in methanol or in DCM, as solvents. The workup, after the consumption of (**2**) that was realized by TLC, involved evaporation of solvents and purification of the oily residue by dry column vacuum chromatography. The dry column contained dark polar material that moved as a streak when eluted with methanol. The yield of product (**5**) from the reaction in methanol was 10%, while the yield of product (**5**) from the reaction in DCM was 11%. It is postulated that the secondary amino group of hydrazone (**2**) displaces acetate anion from iodobenzene diacetate and forms the organoiodo complex (**3**), having eliminated acetic acid. From complex (**3**), iodobenzene and acetic acid are eliminated to provide the *o*-naphthoquinone azomethide intermediate (**4**). The latter undergoes 6π-electrocyclization to afford naphthooxadiazine (**5**).

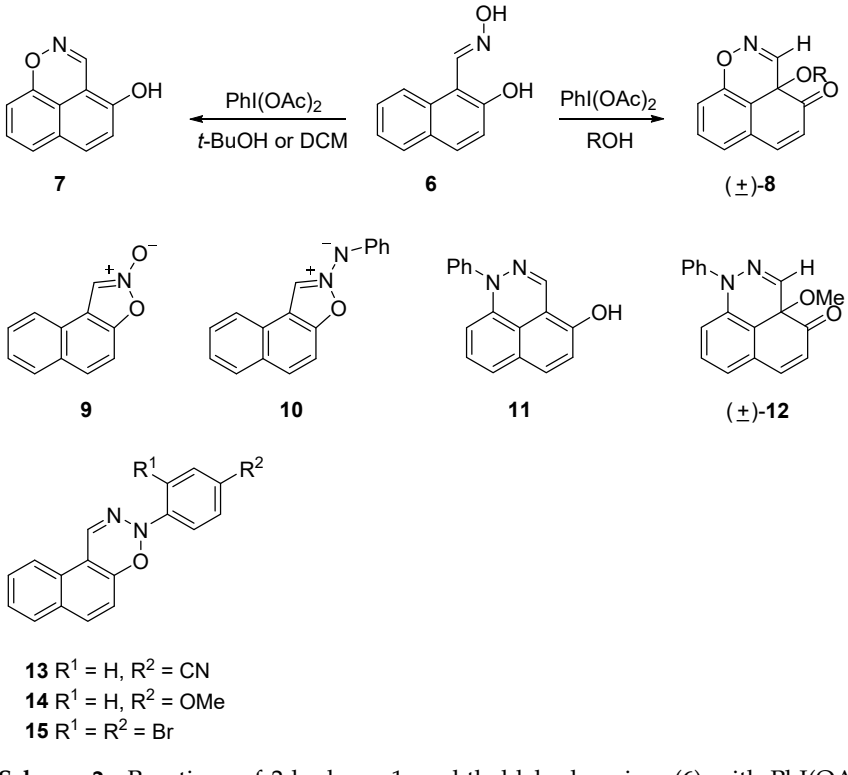


Scheme 1. Proposed mechanism for the oxidation of hydrazone (**2**) to naphthooxadiazine (**5**). Synthesis of hydrazine (**2**). Synthesis and oxidation by $PhI(OAc)_2$ of hydrazone (**2**).

3. Discussion

Varvounis et al. described the one-step synthesis of 3a-alkoxynaphtho[1,8-*de*][1,2]oxazin-4(3a*H*)-ones (Scheme 2, **8**) via oxidative ring closure and alkoxylation of 2-hydroxy-1-naphthaldehyde oxime (**6**), by reaction with two equivalents of iodobenzene diacetate [13] in primary or secondary alcohols as the solvent and the nucleophile, respectively. The reactions were performed at room temperature for 1 h. When the reaction of (**6**) with iodobenzene diacetate was repeated, using either *tert*-butanol or DCM [14] as solvent, the product formed was naphtho[1,8-*de*][1,2]oxazin-4-ol (**7**), in 80% and 75% yield, respectively (Scheme 2). It was therefore of interest to investigate whether the reaction of hydrazone (**2**) with iodobenzene diacetate, in either DCM or methanol as solvent (Scheme 1), would produce, by analogy, 1-phenyl-1*H*-benzo[*de*]cinnolin-4-ol (**11**) and racemic 3a-methoxy-1-phenyl-1,3a-dihydro-4*H*-benzo[*de*]cinnolin-4-one (**12**), respectively (Scheme 2). On the contrary, naphthooxadiazine (**5**) was the only isolable product, albeit in a low 10–11% yield (Scheme 1). An explanation of the low yield of (**5**) is the formation of a dark reaction

mixture and the polar material observed by TLC, after 10 min. of reaction time. The polar material moved on TLC as a streak when eluted with methanol, while attempts to form observable/separable spots on TLC, using less polar solvents, failed. It seemed that product (**5**) and, even more, the other possible products (**10**–**12**) were not stable under the prevailing oxidative reaction conditions. The formation of compound (**11**) would require that the Ph-N=N group in intermediate (**4**) (Scheme 2) adopt a peri conformation, so that the nitrogen atom attached to the phenyl ring may nucleophilically attack position 8 of the (*E*)-1-{[(*E*)-phenyldiazenyl]methylene}naphthalen-2(1*H*)-one ring. The conjugation of the lone pair of electrons of the nitrogen atom into the phenyl ring could significantly reduce the nucleophilicity of this atom and thus discourage peri cyclization toward compound (**11**).



Scheme 2. Reactions of 2-hydroxy-1-naphthaldehyde oxime (**6**) with $PhI(OAc)_2$. Analogously, products (**10**–**12**) could be expected for reaction of (**2**).

The conceivable structures for the isolated compound could be in principle isomers (**10**), (**11**) and (**12**), the latter being formed when methanol was used as solvent. Compound (**5**) was characterized mainly with 1D and 2D NMR spectroscopy. The UV-VIS spectrum showed two strong absorptions at 214 nm and 249 nm, which are within the range of the absorptions found in unsubstituted naphthalene. In the IR spectrum, the absorption band at 3052 (w) cm^{-1} was assigned to aromatic C-H str. Vibrations, while the absorption bands at 1592 (m) and 1489 (m) cm^{-1} were assigned to aromatic C=C str. vibrations. In the ^1H NMR spectrum of product (**5**) in DMSO-d_6, the single peak at 8.94 ppm represented the proton of the imine group. In the aromatic region, the most downfield proton, at 8.37 ppm, was assigned to H-10 of the naphthalene ring. The remaining five protons of the naphthalene ring were determined to be a doublet of doublets at 7.86 ppm of H-7, a doublet at 7.82 ppm of H-6, a doublet of doublets of doublets at 7.57 ppm of H-9, a triplet at 7.44 ppm of H-8, and a doublet at 7.21 ppm of H-5. The connectivity of these six protons was supported by the ^1H-^1H TOCSY and ^1H-^1H NOESY spectra, while a cross-peak between the imine hydrogen H-1 and the aromatic hydrogen H-10 in the ^1H-^1H NOESY spectrum confirmed the position of these atoms. A triplet at 7.30 ppm and a doublet at 6.99 ppm, each integrating for two protons, were assigned to the protons H-3′, H-5′, and H-2′ and H-6′, respectively. The most upfield proton was determined to be the triplet at 6.82 ppm of H-4′. The ^{13}C NMR spectrum showed 15 signals. Signals at 129.45 ppm and 111.62 ppm contained two

equivalent carbon atoms, each bringing the total number of carbon atoms to 17, as expected. A DEPT-90 experiment supported these findings. Furthermore, complete ^{1}H and ^{13}C NMR chemical shift assignments of compound (**5**) were determined from ^{1}H-^{13}C-HSQC and ^{1}H-^{13}C-HMBC experiments. The molecular formula that identifies each of the two isomeric structures (**10**) and (**11**) is $C_{17}H_{12}N_2O$. High-resolution mass spectrometry analysis confirmed the expected molecular ion at m/z = 261.1018 $[M+H]^+$ (ESI) that took up a proton and was calculated for $C_{17}H_{13}N_2O$ m/z = 261.1022. Isomeric compound (**11**) was excluded from being the product because in the ^{1}H NMR spectrum, apart from the imine proton, there were only 11 aromatic protons of the naphthalene and benzene rings and the signal for the hydroxyl proton was absent. The hydroxyl proton was also absent in the IR spectrum. Compound (**12**) was excluded on the grounds that it did not fit with any of the spectral data (see Supplementary Materials for the mentioned spectra). Isomeric compound **10** was also excluded from being the product because of possible inherent structural instability, because the analogous naphtho[1,2-*d*]isoxazole 2-oxide (**9**) was synthesized only once [15] and thereafter proved to be unstable [16].

Despite the interest in synthesizing a series of 3-alkyl or aryl-substituted naphthooxadiazine derivatives (**5**) for the purpose of investigating their biological activities, the low yield of compound (**5**) and the low yields of 8% to 13% of several other synthesized 3-substituted derivatives (**13**–**15**), nullified the interest in this project.

4. Materials and Methods

All reactions were carried out under an N_2 atmosphere. Solvents and reagents were used as received from the manufacturers (Aldrich, Acros, and Alfa Aesar), except for THF, DCM, MeOH, EtOAc, hexane, and toluene, which were purified and dried according to recommended procedures. Organic solutions were concentrated by rotary evaporation at 23 °C to 40 °C under 15 Torr. Melting points were taken on a Büchi 510 apparatus (Büchi Labortechnik AG, Switzerland). The IR spectrum was acquired on an Agilent Cary 630 FTIR spectrophotometer (Agilent Technologies) as a solid and reported in wave numbers (cm^{-1}). The UV spectrum was recorded using a Jasco V-630 UV-Vis spectrophotometer (Jasco Europe s.r.l., Italy). The sample was measured in a 1 cm quartz cell at room temperature with a 1.84×10^{-5} mol/L concentration in MeCN. Samples for NMR experiments were dissolved in dry DMSO-d_6. ^{1}H, ^{13}C NMR, DEPT-90, ^{1}H-^{1}H TOCSY and ^{1}H-^{1}H NOESY spectra were recorded on a Brüker Avance 400 MHz spectrometer (Brüker BioSpin GmbH, Rheinstetten, Germany), while ^{1}H-^{13}C-HSQC and ^{1}H-^{13}C-HMBC spectra, as well as the ^{1}H spectrum, were recorded on a Brüker Avance 500 MHz spectrometer (Brüker BioSpin GmbH, Rheinstetten, Germany). Chemical shifts (δ) were reported in ppm and coupling constants (*J*) were provided in Hz from residual DMSO (2.50 ppm) as the internal standard. The high-resolution ESI mass spectrum was measured on a ThermoFisher Scientific Orbitrap XL system (Thermo Fisher Scientific, Waltham, MA, USA), while the low-resolution ESI spectrum was measured with an Agilent 1100 LC-MS/MS spectrometer (Agilent Technologies). Analytical thin layer chromatography was performed with Merck 70–230 mesh silica gel precoated TLC plates. Purification of the product was performed by dry column vacuum chromatography, using Merck silica gel 60.

*4.1. (E)-1-[(2-Phenylhydrazono)methyl]naphthalen-2-ol (**2**)*

2-Hydroxy-1-naphthaldehyde (**1**) (0.5 g, 2.90 mmol) was dissolved in methanol (10 mL), then freshly distilled phenylhydrazine (0.31 g, 2.92 mmol) was added, followed by a few drops of glacial acetic acid. The reaction mixture was heated at 60 °C for 2 h. TLC examination revealed the absence of the starting material spot and the presence of a new spot (visualized under a UV lamp). The solvent was evaporated in vacuo and the remaining solid was crystallized from IPA to provide the title compound (0.44 g, 74%) as yellow needles, m.p. = 190–191 °C (lit. [11], m.p. = 191–192 °C); R_f = 0.28 (25% ethyl acetate in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.83 (t, 1H, J = 7.8 Hz), 7.00–7.03 (d, 2H), 7.23 (d, 1H, J = 8.8 Hz), 7.29–7.33 (t, 2H), 7.39 (t, 1H, J = 7.2 Hz), 7.58 (t, 1H, J = 7.9 Hz), 7.82

(d, 1H, J = 8.8 Hz), 7.87 (d, 1H, J = 7.2 Hz), 8.38 (d, 1H, J = 8.5 Hz), 8.95 (s, 1H) 10.54 (s, 1H), 11.1 (s, 1H) (in accordance with the NMR data that were previously reported for this compound [12]); LRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$: 261.10; Found: 260.90.

*4.2. 3-Phenyl-3H-naphtho[1,2-e][1,2,3]oxadiazine (**5**)*

To a solution (*E*)-1-[(2-phenylhydrazono)methyl]naphthalen-2-ol (**2**), (0.1 g, 0.38 mmol) in methanol (10 mL) or DCM (10 mL), at room temperature, was added iodobenzene diacetate (0.1 g, 0.38 mmol) over a period of 5 min. Stirring was continued for 10 min, after which TLC examination (visualized under a UV lamp) confirmed the disappearance of the starting material. The reaction mixture was concentrated under reduced pressure and the remaining oily residue was subjected to dry column vacuum chromatography on silica gel, with 25% EtOAC in hexane, to provide in the first fraction, after trituration with diethyl ether, the *title compound* (10 mg, 10%) or (12 mg, 11%) as orange microcrystals, m.p. = 193–195 °C; R_f = 0.43 (25% ethyl acetate in hexane); UV-VIS (MeCN) λ_{max}/nm: 214 (log ε 4.35), 249 (4.07), 334 (3.7), 375 (3.93); FTIR (solid) cm^{-1}: 3312 (w), 3052 (w), 2963 (w), 2122 (m), 1592 (m), 1489 (m), 1366 (w), 1249 (m), 1039 (m), 741 (m); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.94 (s, 1H, H-1), 8.37 (d, J = 8.7 Hz, 1H, H-10), 7.86 (dd, J = 8.1, 1.3 Hz, 1H, H-7), 7.82 (d, J = 8.9 Hz, 1H, H-6), 7.57 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H, H-9), 7.38 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H, H-8), 7.30 (dd, J = 8.5, 7.3 Hz, 2H, H-3′, H-5′), 7.21 (d, J = 8.9 Hz, 1H, H-5), 6.99 (dd, J = 8.7, 1.2 Hz, 2H, H-2′, H-6′), 6.82 (t, J = 7.3 Hz, 1H, H-4′); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 155.6 (C-4a), 144.4 (C-1′), 137.2 (C-1), 130.9 (C-10a), 130.4 (C-6), 129.4 (C3′, C-5′), 128.8 (C-7), 128.1 (C-6a), 127.3 (C-9), 123.3 (C-8), 121.4 (C-10), 119.2 (C-4′), 118.4 (C-5), 111.6 (C-2′, C-6′), 110.1 (C-10b). ^{13}C NMR DEPT-90 (100.6 MHz, DMSO-d_6) δ: 137.2 (C-1), 130.4 (C-6), 129.4 (C3′, C-5′), 128.8 (C-7), 127.3 (C-9), 123.3 (C-8), 121.4 (C-10), 119.2 (C-4′), 118.4 (C-5), 111.6 (C-2′, C-6′); HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$: 261.1022. Found: 261.1018. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$: 261.1022. Found: 261.1018.

Supplementary Materials: The following supporting information can be downloaded at: Figure S1: ^{1}H NMR spectrum of compound (**2**); Figure S2: LRMS (ESI) spectrum of compound (**2**); Figure S3: ^{1}H NMR spectrum of compound (**5**); Figure S4: ^{13}C NMR spectrum of compound (**5**), expanded; Figure S5: ^{13}C NMR spectrum of compound (**5**); Figure S6: DEPT-90 ^{13}C NMR spectrum of compound (**5**); Figure S7: ^{1}H-^{1}H TOCSY NMR spectrum of compound (**5**); Figure S8: ^{1}H-^{1}H NOESY NMR spectrum of compound (**5**); Figure S9: ^{1}H-^{13}C HSQC NMR spectrum of compound (**5**); Figure S10: ^{1}H-^{13}C HMBC NMR spectrum of compound (**5**); Figure S11: ^{1}H and ^{13}C NMR chemical shift assignments of compound (**5**); Figure S12: UV spectrum of compound (**5**); Figure S13: IR spectrum of compound (**5**); Figure S14: HRMS (ESI) spectrum of compound (**5**).

Author Contributions: Conceptualization, G.V.; methodology, A.D.A. and G.V.; investigation, A.D.A. and G.V.; writing—original draft preparation, G.V.; writing—review and editing, A.D.A. and G.V. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds (**2**) and (**5**) are available from the authors.

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