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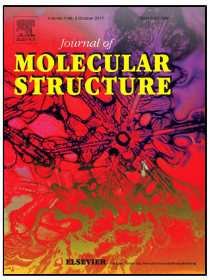

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Synthesis and structural analysis of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinediones

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Abstract

This article presents the unexpected synthesis of 3-phenylethyl-2,4(1H,3H)-quinazolinediones by means of oxidative expansion of the 3-phenylethylimino-2-indolinone ring promoted by sodium borohydride. The ^{1}H-NMR spectroscopic patterns showed the presence of two conformational isomers in equilibrium, the first was a staggered conformation and the second was a gauche structure. The crystal structure of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione revealed a staggered conformation with the quinazoline fragment and the phenyl ring in *anti*-arrangement. The molecules of quinazolinedione are associated in centrosymmetric dimers through two N-H···O hydrogen bonds between the NH moieties and the adjacent carbonyl groups.

Keywords

Ring expansion
Oxidative cleavage
Isatin
Quinazolinedione
Schiff base

1. Introduction

Isatin (1*H*-indole-2,3-dione) **1** is a benzofused cyclic ketone of great interest in organic chemistry because it has a highly electrophilic carbonyl which is useful in the synthesis of nitrogen heterocyclic and spiroheterocyclic systems [1,2]. Isatin-derived Schiff bases are also of interest in organic and medicinal chemistry due to their usefulness as substrates when preparing compounds having biological activity, such as anti-HIV, anticonvulsant, antibacterial, antifungal and antiviral activity and their capability for forming compounds with different metals [3-2].

It has been established recently that some phenylethylamines react with isatin to form the respective Schiff bases (3-phenylethylimino-2-indolinones) **2** as a mixture of *E*/*Z* stereoisomers; *E* is the kinetic product and *Z* is the thermodynamic product. The mixture of isomers is obtained in variable proportions, depending on the experimental conditions used (Scheme 1) [7].

Continuing our studies related to the chemical and structural behaviour of phenylethylamine derivates and carbonyl compounds [8-10], this article describes a study of the behaviour of Schiff bases produced by reaction of isatin **1** with phenylethylamine **2a** and with tyramine **2b** regarding a reducing agent like sodium borohydride. The results showed that (in the reaction conditions used here) no reduction of Schiff bases occurred for the formation of the respective amine **3** and the corresponding 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinediones **4** were obtained as the main product by means of a reaction involving the oxidative expansion of the indolinone ring (scheme 2). This article provides a structural analysis of the 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinediones **4** obtained and proposes a mechanistic explanation for the reaction.

2. Experimental Section

2.1. General

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded at room temperature on a Bruker Avance 400 spectrometer. $CDCl_3$ were used as solvent. IR spectra were registered in a Nicolet iS10 spectrometer (Thermo Fisher Scientific, 4000 - 400 cm^{-1}) using KBr disks. Mass spectra were recorded on a Shimadzu LCMS-IT-TOF liquid chromatograph mass spectrometer using electrospray ionization (ESI). The ESI probe was operated in the positive mode using the following parameters: CDL temperature, 200 °C; heating block, 200 °C; flow gas (N_2), 1.5 L/min; detector voltage, 1.69 kV; and scan range, *m/z* 100-350. All reagents and solvents were purchased and used without further purification. 3-phenylethylimino-2-indolinones were prepared according to the literature procedures [7].

2.2. Crystallization and X-ray diffraction

Purple needles of compound **4** were grown from a toluene/chloroform (1:1) solution by slow evaporation at room temperature. The crystals were removed from the vial and covered with a layer of a viscous perfluoropolyether (FomblinY). A suitable crystal selected with the aid of a microscope was mounted on a cryoloop and placed in the low temperature nitrogen stream of the diffractometer. The intensity data sets were collected at 200 K on a Bruker-Nonius KappaCCD diffractometer equipped with an Oxford Cryostream 700 unit. The molybdenum radiation was used, graphite monochromated, and enhanced with a MIRACOL collimator. Crystallographic data are presented in Table 1.

The structure was solved, using the WINGX package [11], by direct methods (SHELXS-2013) and refined by least-squares against F^2 (SHELXL-2014/7) [12,13]. These crystals showed disorder for the carbon atoms C(11)-C(16) of the phenyl ring. This disorder was treated using the PART tool and allowing free refinement of the occupancy factors with the FVAR command. The final values of occupancy were 50.8 and 49.2%. All non-hydrogen atoms were anisotropically refined. In addition the position and the thermal parameters of C(11) and C(11)' were constrained to be identical. All hydrogen atoms were positioned geometrically and refined by using a

riding model, except the hydrogen H(2), linked to N(2), which was located in the difference Fourier map and isotropically refined.

2.3. 3-phenylethylimino-2-indolinone 2a reaction with sodium borohydride in methanol.

Sodium borohydride (80 mg, 2.11 mmol) was added to a solution of 3-phenylethylimino-2-indolinone **2a** (460 mg, 1.84 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 24 hours. Once this time had elapsed, water was added until the precipitate appeared. The precipitate was then filtered, washed with water and dried at room temperature. A purple product was obtained: 402 mg, yield: 82%, mp 114-116°C, ^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ= 3.05 (CH_2-Ph, t, $J_{H,H}$= 8 Hz and dd, $J_{H,H}$= 10 Hz and 6Hz, 2H), 4.36 (CH_2-N, t, $J_{H,H}$= 8Hz and dd, $J_{H,H}$= 10 Hz and 6 Hz, 2H), 7.17 (H-C8, d, $J_{H,H}$= 8 Hz, 1H), 7,67 (H-C6, t, $J_{H,H}$= 8Hz, 1H), 8.17 (H-C5, d, $J_{H,H}$=8Hz, 1H), 7.22-7.40 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.0 (C4), 152.1 (C2), 138.58 (C9), 138.56 (C1'), 135.1(C7), 129.0 (C3',C5'), 128.5 (C2',C6'), 128.4 (C5), 126.5 (C4'), 123.4 (C6), 115.1 (C8), 114.7 (C10), 42.3 (C-N), 34.1 (C-Ph). FT-IR (KBr) cm^{-1}: 3189, 1719, 1654. EI-MS: 266.07(16%), 162.10 (22%), 146.10 (40%), 104.18 (100 %). ESI-HRMS: m/z 267.1424 ($[M+H]^+$, calc. 267.1128).

2.4. 3-phenylethylimino-2-indolinone 2a reaction with sodium borohydride in acetonitrile.

Sodium borohydride (80 mg, 2.11 mmol) was added to a solution of 3-phenylethylimino-2-indolinone **2a** (460 mg, 1.84 mmol) in acetonitrile (10 mL). The mixture was stirred at room temperature for 24 hours. Once this time had elapsed, HCl (5 %) was added until the precipitate appeared. The precipitate was then filtered, washed with water and dried at room temperature. A purple product was obtained (Mixture of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4** and 3-[(2-phenylethyl)amino]-1,3-dihydro-2*H*-indol-2-one **5** (2:0.88), quinazolinedione **4**: yield: 56 %, and amine **3**: yield: 25 %. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.97 (CH_2-Ph, t, $J_{H,H}$= 7 Hz, 2H), 3.77 (CH_2-N, t, $J_{H,H}$= 7Hz, 2H), 4.41 (H-C, s,1H), 6.67 (H-C7, d, $J_{H,H}$= 8

Hz, 1H), 6.92 (H-C5, t, $J_{H,H}$= 8Hz, 1H), 7.62 (H-C6, t, $J_{H,H}$=8Hz, 1H), 7.97 (H-C4, d, $J_{H,H}$= 8 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.2 (C8), 133.1 (C1'), 128.9 (C3',C5'), 128.8 (C2',C6'), 128.7 (C4') , 128.3 (C6), 126.8 (C4), 126.5 (C5), 120.0 (C9), 115.1 (C7), 60.4 (C3), 48.1 (C-N), 34.6 (C-Ph).

2.5. 3-(4-hydroxyphenylethyl)imino-2-indolinone 2b reaction with sodium borohydride in methanol.

Sodium borohydride (40 mg, 1.05 mmol) was added to a solution of 3-(4-hydroxyphenylethyl)imino-2-indolinone **2b** (204 mg, 0.77 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 24 hours. Once this time had elapsed, water was added until the precipitate appeared. The precipitate was then filtered, washed with water and dried at room temperature. A brown product was obtained: 175 mg, yield: 81 %, mp 244-246 °C, ^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ= 2.86 (CH_2-Ph, t, $J_{H,H}$= 8 Hz and dd, $J_{H,H}$= 8 Hz and 6Hz, 2H), 4.17 (CH_2-N, t, $J_{H,H}$= 8Hz and dd, $J_{H,H}$= 8 Hz and 6 Hz, 2H), 6.73 (H-C3', H-C5', d, $J_{H,H}$= 10 Hz, 2H), 7.04 (H-C2', H-C6', d, $J_{H,H}$= 10 Hz, 2H), 7.18 (H-C8, d, $J_{H,H}$=8Hz, 1H), 7.24 (H-C6, t, $J_{H,H}$=8Hz, 1H), 7.65 (H-C7, t, $J_{H,H}$=8Hz, 1H), 8.04 (H-C5, d, $J_{H,H}$=8Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.6 (C-Ph), 42.0 (C-N), 114.1 (C10), 114.7 (C3', C5'), 114.8 (C8), 122.7 (C6), 127.4 (C5), 129.3 (C2', C6'), 129.4 (C1'), 134.8 (C7), 139.4 (C9), 150.9 (C2), 155.6 (C4'), 162.8 (C4). FT-IR (KBr) cm^{-1}: 3500-2500, 1716, 1639. Found C: 67.65, H: 5.10, N: 9.71, calc. for $C_{16}H_{14}N_2O_3$: C: 68.07, H: 5.00, N: 9.92.

3. Results and Discussion

Our research group has been synthesising phenylethylamine-derived amines by means of indirect reductive amination reactions using sodium borohydride as reducing agent. The respective amine **3** was not formed when isatin- and phenylethylamine-derived Schiff bases **2a** were used in the same experimental conditions (sodium borohydride in methanol for 24 h.). A purple solid ($C_{16}H_{13}N_2O_2$ molecular formula) was obtained whose structure was determined by 1D and 2D NMR spectroscopy. ^{1}H-NMR spectrum revealed characteristic signals for the *ortho*-

disubstituted system from isatin **1** and for the monosubstituted ring from phenylethylamine in the aromatic region; the aliphatic region showed signals corresponding to the two methylenes from phenylethylamine. Different to that expected for amine **3**, no singlet signal corresponding to methine was observed (which should appear around 4 ppm). Different from the starting Schiff base **2a**, no signal corresponding to the methine from the imino group was observed at 8.3 ppm. In addition to the information obtained from the ^{1}H-NMR spectrum, the ^{13}C-NMR spectrum revealed two signals (at 152 and 162 ppm) corresponding to carbonyl groups assigned to two amide groups present in the molecule.

The correlations in HMBC spectrum (Fig.1) between methylene hydrogens and carbonyl carbons and between some aromatic hydrogens and carbonyl carbons led to confirming that the compound obtained was a 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4**. Such compound should have been formed by means of a sodium borohydride-induced oxidative expansion of 3-phenylethylimino-2-indolinone **2a**.

Methylenes in phenylethylamine-derived usually generate two triplets ^{1}H-NMR spectrum, appearing around 3 and 4 ppm. These two signals were observed at 3.05 and 4.37 ppm in 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4** ^{1}H-NMR spectrum; however, multiplicity was different, as shown in Figure 2. Each methylene generated a group of signals having greater complexity. This spectroscopic pattern can be explained by the presence of two conformational isomers in equilibrium, one of the conformers generating a triplet for each methylene and the other a double doublet; both overlapping signals produced the pattern shown in Figure 2.

The Gaussian 03 software package was used for analysing possible 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4** conformers by means of DFT-B3LYP/6-31G(d,p) computational calculations to obtain greater information about the spectroscopic patterns. The results revealed two conformations having similar energy (1.39Kcal/mol difference) (Fig. 3); the first was a staggered conformation having the

aromatic ring and the quinazolinedione in an *anti*-relationship; the hydrogens from each methylene in this structure were magnetically equivalent and appeared in the spectrum as triplets. The second conformation was a gauche structure; the hydrogens from each methylene in this conformation were in different settings, producing double doublets having chemical shift similar to those observed for the *anti*-conformation. Figure 2 shows the overlapping of these signals as a multiplet. The Boltzmann factors were calculated at room temperature for each conformation to predict the relationship between both conformers' populations. The results showed that the anti-conformer was mainly obtained (91%), the gauche conformer much less so (only 9%); the experimental results showed that both conformers were present in similar proportions in solution. However, a single-crystal X-ray diffraction analysis of **4** revealed a staggered conformation with the quinazoline fragment and the phenyl ring in *anti*-arrangement (Fig. 4) with a N(1)-C(9)-C(10)-C(11) torsion angle of 175.5(2)º.

Molecules of **4** are associated in centrosymmetric dimers through two N-H···O hydrogen bonds between the NH moieties and the adjacent carbonyl groups (N(2)···O(1)i and H(2)···O(1)i distances of 2.817(2) and 1.94(2) Å respectively, and N(2)-H(2)···O(1)i angle of 173(2)º, symmetry code: (i) –*x*, 1 – *y*, –*z*) (Figure 5). These dimers are packed maintaining the quinazoline rings in a face-to-face stacking arrangement (Figure 6), due to C-H···O hydrogen bonds (C(9)···O(2)ii length of 3.367(3) Å, symmetry code: (ii) *x*, 1 + *y*, *z*) and weak intermolecular $\pi\cdots\pi$ interactions (centroid-centroid separations of 4.257 and 4.362 Å).

On the other hand, it has been proposed that a secondary alcohol and oxygen are needed for the oxidative cleavage of sodium hydride-induced 2-hydroxyacetones and 1,2-diones. An acid-base reaction between the hydroxyl from alcohol and the hydride has been proposed as the first step; such acid-base reaction would favour the oxidation of alcohol to ketone and the production of a hydride which would react with oxygen to form hydroperoxide [14,15]. Such studies have led to concluding that an equivalent of secondary alcohol reacting with an equivalent of sodium hydride

and equivalent of oxygen would produce an equivalent of hydroperoxide; yield would thus be low when working with atmospheric oxygen.

The synthesis of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4** by Schiff base **2a** reaction with sodium borohydride was done in methanol; it was thus initially thought that a reaction mechanism analogous to that discussed above was involved. The same procedure was carried with acetonitrile as solvent to confirm the participation of alcohol in the oxide-reduction reaction necessary for ring expansion. ^{1}H-NMR analysis of the reaction product in acetonitrile revealed a mixture of two compounds; the majority compound was the product of oxidative expansion (3-phenylethyl-2,4(1*H,*3*H*)-quinazolinedione **4**), whilst the minority product was the product of 3-phenylethylimino-2-indolinone **2** reduction (3-[(2-phenylethyl)amino]-1,3-dihydro-2*H*-indol-2-one **3**); the ratio of the integrals in ^{1}H-NMR spectrum revealed two products (2:1 ratio) (scheme 3). This result led to demonstrating that an alcohol is not necessary for the oxidative expansion of the ring to occur and that the direct interaction between sodium borohydride and atmospheric oxygen produces the hydroperoxide needed for the reaction.

Considering the forgoing observations, 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4** formation can be rationalised by means of the initial formation of hydroperoxide by the interaction, probably via free radicals between sodium borohydride and atmospheric oxygen. Hydroperoxide anion nucleophile attack on imino induces Baeyer-Villiger oxidation, leading to the formation of the respective 4-imino-(1*H*,4*H*)-3,1-benzoxazine-2-one **5**. The acid-base interaction between the nitrogen from benzoxazine-2-one **5** and the reaction medium leads to the opening of the cycle with the formation of the respective intermediary, isocyanate carboxamide **6**, a previously proposed mechanism for the rearrangement of 4-imino-(1*H*,4*H*)-3,1-benzoxazine-2-one to 2,4-quinazolinedione [16]. The intramolecular nucleophilic attack by the nitrogen from carboxamide on isocyanate leads to the formation of the respective quinazolinedione 4 (Scheme 4).

Previous studies have shown that phenolic hydroxyls on the phenylethylamine ring affect both aromatic ring and nitrogen reactivity [17]. Tyramine-derived Schiff base **2b** was put to react with sodium borohydride in methanol for establishing whether the presence of phenolic hydroxyls affected the course of the reaction regarding the oxidative expansion of 3-phenylethylimino-2-indolinones **2** (whether due to the presence of acid hydrogens from phenol or to changes in nucleophilicity of the nitrogen); this reaction led to the formation of the respective quinazolinedione **7** as sole product, having good yield (scheme 5). The reproducibility observed regarding both the course of the reaction and purification enables explaining the oxidative expansion of isatin-derived Schiff bases induced by sodium borohydride as a simple, economic and efficient methodology for quinazolinedione synthesis.

4. Conclusions

This paper has thus presented a new synthesis of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinediones by the oxidative expansion of the 3-phenylethylimino-2-indolinone. The crystal structure of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione revealed a staggered conformation with the quinazoline fragment and the phenyl ring in *anti*-arrangement. The molecules of quinazolinedione are associated in centrosymmetric dimers through two N-H···O hydrogen bonds between the NH moieties and the adjacent carbonyl groups.

Acknowledgements

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Supplementary data

CCDC-1546873 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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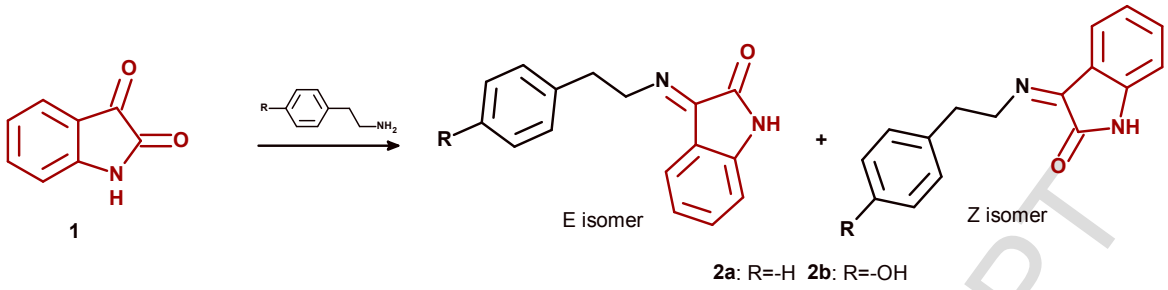
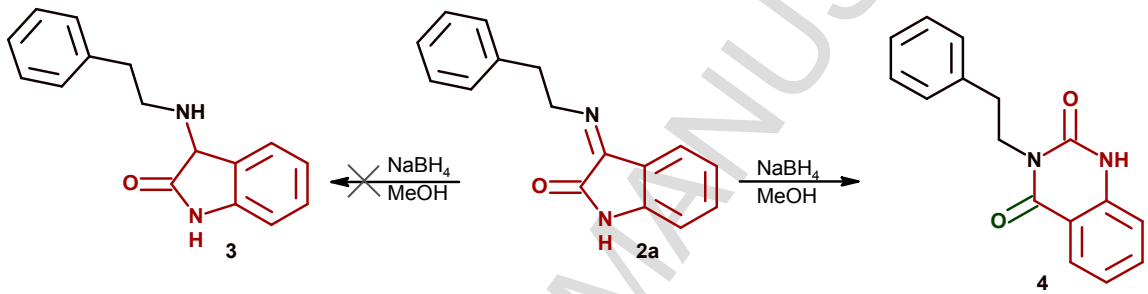


Scheme 1. 3-phenylethylimino-2-indolinone **2** synthesis from isatin **1** and phenylethylamines.



Scheme 2. 3-phenylethylimino-2-indolinones **2** reaction with sodium borohydride in methanol.

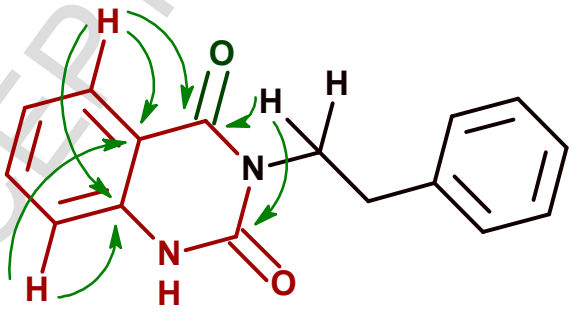


Figure 1. Selected HMBC correlations of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4**.

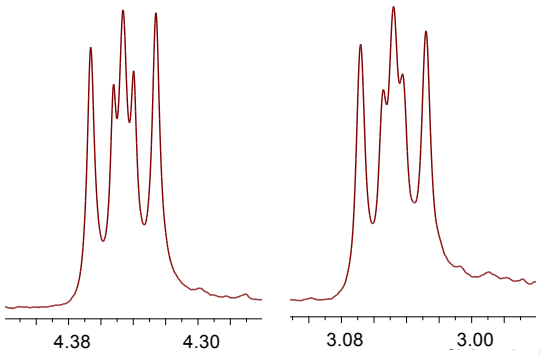


Figure 2. ^{1}H-NMR spectrum for 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione 4, aliphatic region.

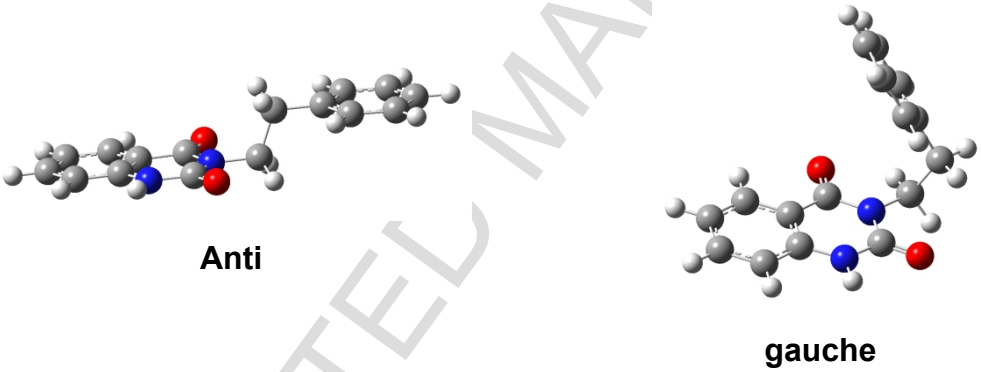


Figure 3. Conformers in solution for 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4**.

Table 1. Experimental data for the X-ray diffraction study on compound **4**

formula	$C_{16}H_{14}N_2O_2$
M_r	266.3
T [K]	200
λ [Å]	0.71073
crystal system	monoclinic
space group	$P2_1/c$
a [Å]	14.004(1)
b [Å]; β [º]	4.955(1); 102.19(1)
c [Å]	19.472(4)
V [Å^3]	1320.7(4)
Z	4
ρ_{calcd} [g cm^{-3}]	1.339
$\mu_{MoK\alpha}$ [mm^{-1}]	0.090
F(000)	560
crystal size [mm^3]	0.40 × 0.18 × 0.12
θ range (deg)	3.28−27.50
index ranges	−17 to 18
	−6 to 6
	–25 to 25
reflns collected	28362
unique data	3034[R(int)= 0.091]
obsd data [$I > 2\sigma(I)$]	1797
GOF on F^2	1.036
Final R[a] indices [$I > 2\sigma(I)$]	R1 = 0.055
	wR2 = 0.123
R[a] indices (all data)	R1 = 0.113
	wR2 = 0.157
largest diff. peak/hole [e Å^{-3}]	0.249 and −0.220

[a] $R1 = \sum||F_0|-|F_c||/[\sum|F_0|]$; $wR2 = \{[\sum w(F_0^2 - F_c^2)^2]/[\sum w(F_0^2)^2]\}^{1/2}$

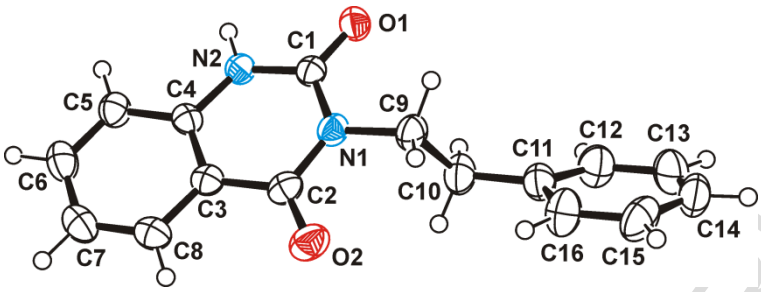


Figure 4. ORTEP diagram of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione **4**. Thermal ellipsoids are drawn at the 50% probability level.

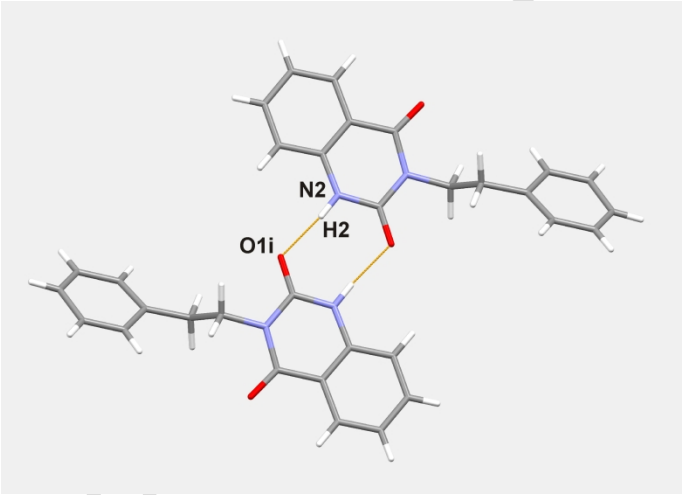


Figure 5. Molecules of **4** connected in dimers by N-H···O hydrogen bonds (in orange). Symmetry code: (i) –*x*, 1 – *y*, –*z*.

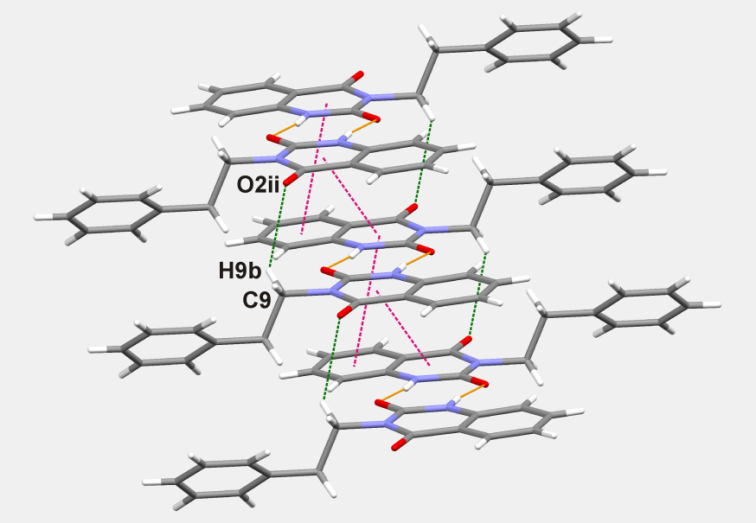
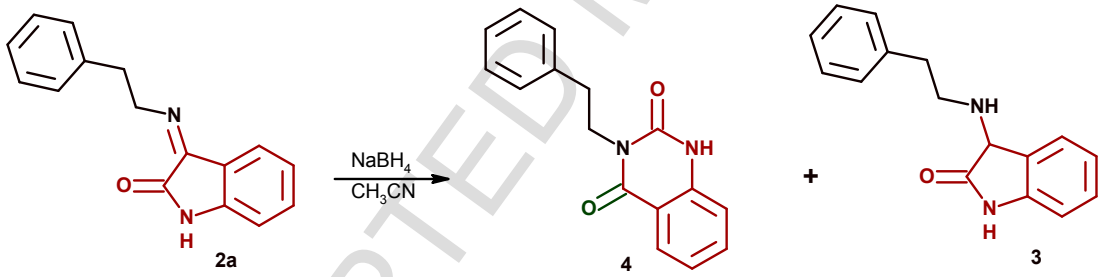
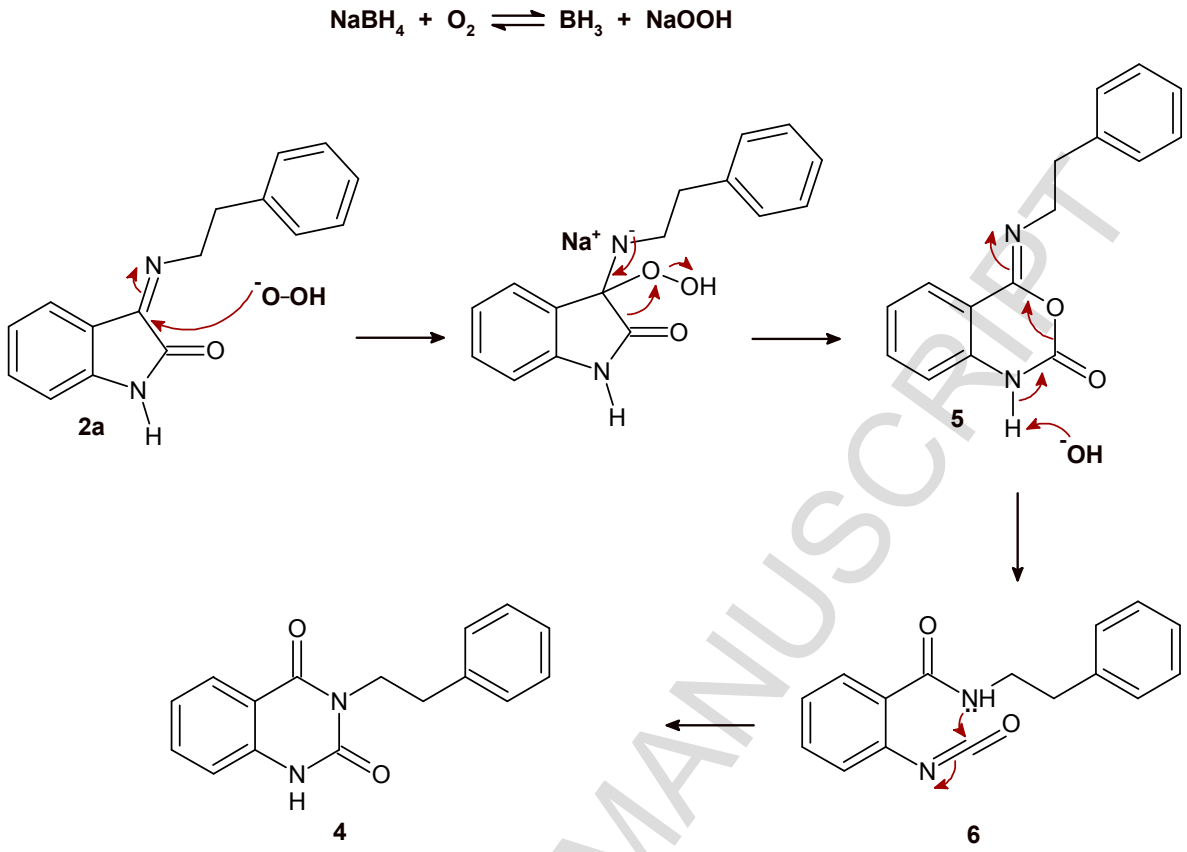


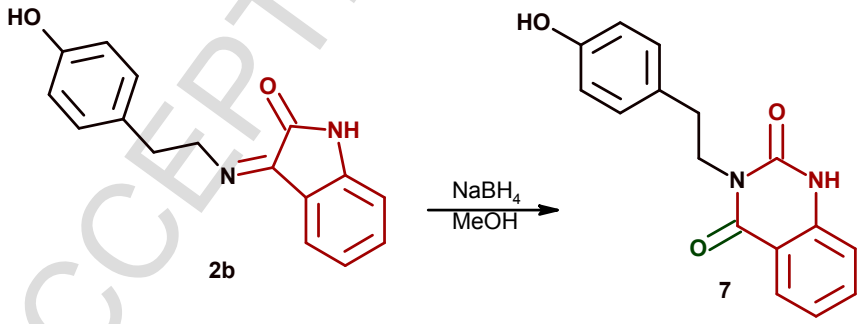
Figure 6. π-stacking arrangement of **4** with C-H···O hydrogen bonds in green and π···π interactions in pink. Symmetry code: (ii) *x*, 1 + *y*, *z*.



Scheme 3. 3-phenylethylimino-2-indolinones **2** reaction with sodium borohydride in acetonitrile.



Scheme 4. The mechanism proposed for 3-phenylethylimino-2-indolinones 2 reaction with sodium borohydride.



Scheme 5. 3-phenylethylimino-2-indolinone **7** reaction with sodium borohydride.

Highlights

-A new synthesis of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinediones is presented.

-The X-ray structure of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione was reported for the first Time. The structural analysis revealed a staggered conformation with the quinazoline fragment and the phenyl ring in *anti*-arrangement.

-Molecules of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinedione are associated in centrosymmetric dimers through two N-H···O hydrogen bonds between the NH moieties and the adjacent carbonyl groups.

Graphical abstract

Synthesis and structural analysis of 3-phenylethyl-2,4(1*H*,3*H*)-quinazolinediones