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Intermolecular double Michael reaction to construct 4-benzyl-5-imino-3-phenyl-6-oxa-1-aza-tricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene-4-carbonitrile

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1-azabicyclo[2.2.2]octan-3-one. HCl (**1**) reacts with ylidene nitrile through photo- thermal reaction conditions to give 4-benzyl-5-imino-3-phenyl-6-oxa-1-aza-tricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene-4-carbonitrile. (**3**) via intermolecular double Micheal reaction, whereas, 5-imino-3-phenyl-6-oxa-1-azatricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene-4-carbonitrile (**4**) was achieved via thermal conditions only.

Keywords: 1-azabicyclo[2.2.2]octan-3-one. HCl, benzylidinemalononitrile, 1-azatricyclo-[6.2.2.0^{2,7}]dodec-2(7)-ene derivatives.

Quinuclidine (1-azabicyclo[2.2.2]octane)[1] (**1**) is a part of the structure of a number of natural physiologically active compounds and synthetic drugs.[2,3] Among the natural alkaloids, the quinoline and indol derivatives contain the quinuclidine ring: cinchonine, cinchonamine (alkaloids of cinchina species)[4], sarpagine, ajmaline and makvsine (strychnous alkaloids).[5,6] Phencarol (used as the excipients) and[7] aceclidine (decreased ocular tone of rabbit eye)[8] are two examples of synthetic drugs of quinuclidine derivatives.

In view of the aforementioned information, it seemed of interest to design and synthesize new quinuclidine derivatives which incorporate heterocyclic moieties of biological value, via ylidene nitriles which are versatile tools for the construction of a variety of novel complex hetrocycles.[9,10]

Results and discussion

Pyrans individually or in combination with heterocycles possess significant biological properties[11-14]. It was decided to prepare quinuclidino[3,2-*b*]pyrane derivatives aiming to improve their biological potency. A variety of routes for the synthesis of these compounds have prepared 4-benzyl-5-imino-3-phenyl-6-oxa-1-azatricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene-4-carbonitrile **(3)**, whereas, when the same reaction was repeated as above but in the dark, compound 5- imino-3-phenyl-6-oxa-1-aza-tricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene-4-carbonitrile **(4)** was obtained.

The structure of **3** was based on its analytical and spectroscopic features. The molecular ion peak in mass spectrum of **3** at (*m/z*) 368(6.6), 365(100). A plausible mechanism for the formation of pyran derivatives **3** and **4** probably involves an acyclic Michael adduct as intermediates which cyclise via the addition of enolic OH to the cyano group,[22] Scheme (1). The products suggested to us that the product **3** was obtained through a photothermal reaction conditions, whereas, the product **4** was achieved via thermal condition only.

The negatively charged compound (1) actually has two possible forms, the keto and enol tautomers. Molecular orbital calculations using the PM3 semi-empirical MO method† showed that the enolic form has a lower total electronic energy than the keto form (–1939 and –1897 kcal/mole respectively) which indicates that the enolic form is actually expected to be present in solution of this compound. Inspection of the results of MO calculations, showed that C(2) atom in both forms posses the highest negative centre in the molecules and the highest occupied MO (HOMO) of both forms, has its highest coefficients from the P_z-orbital of this C(2) centres.

On the other hand, results of MO calculations carried out on the benzylidinemalononitrile **(2)** showed that it has a positively charged centres on both carbons C(3') and C(2') (+0.041 and +0.104 Muliken charges respectively). The calculated eigenvector of the lowest unoccupied molecular orbital (LUMO) had its highest atomic orbital coefficients at atoms C (3') and C (2') (–0.524 and +0.469 Muliken charges respectively), see Fig. 1 and Table 1.

A thermal reaction between compound **1** and benzylidinemalononitrile **(2)** is quantum chemically possible since the main quantum requirements are achieved. The electron flow is expected from the HOMO of the electron-rich species (compound **1** through carbon C(2)) to the LUMO of the electron-poor benzylidinemalononitrile (through carbon C(3')). Also, the energies of the HOMO of compound **1** and the LUMO of the benzylidinemalononitrile are of the same order (the differences is about 0.7 eV).

The expected structure, as represented in Fig. 2, has the probability to be present in more than one conformation as a result of the rotation about the new formed C(2)–C(3') bond

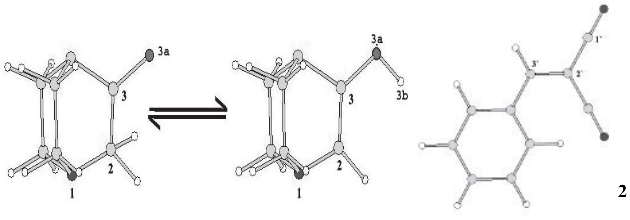

Fig. 1 Molecular representation of **1** and **2**.

Table 1 Indicative quantum chemical parameters of compounds **1** and **2**

Compound **1**			Compound **2**		
	$_{-28}$ HOMO	$_{-29}$ LUMO		$_{-25}$ HOMO	$_{-26}$ LUMO
E (eV)	–2.30	–1.66	*E* (eV)	–9.695	–1.600
MO coefficients:			MO coefficients:		
C(2) S	–0.000	0.000	C(3') S	–0.000	0.000
C(2) P_x	0.0114	–0.005	C(3') P_x	–0.000	0.000
C(2) P_y	0.059	–0.024	C(3') P_y	–0.000	0.000
C(2) P_z	–0.811	0.324	C(3') P_z	0.300	–0.524
Muliken charges on C(2)= –0.656			Muliken charges on C(3')= +0.041		

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† The Hyperchem Pro Release 7.5 (eval) from Hypercube, was used to carry out all calculations mentioned in the present work. (www.hyper.com)

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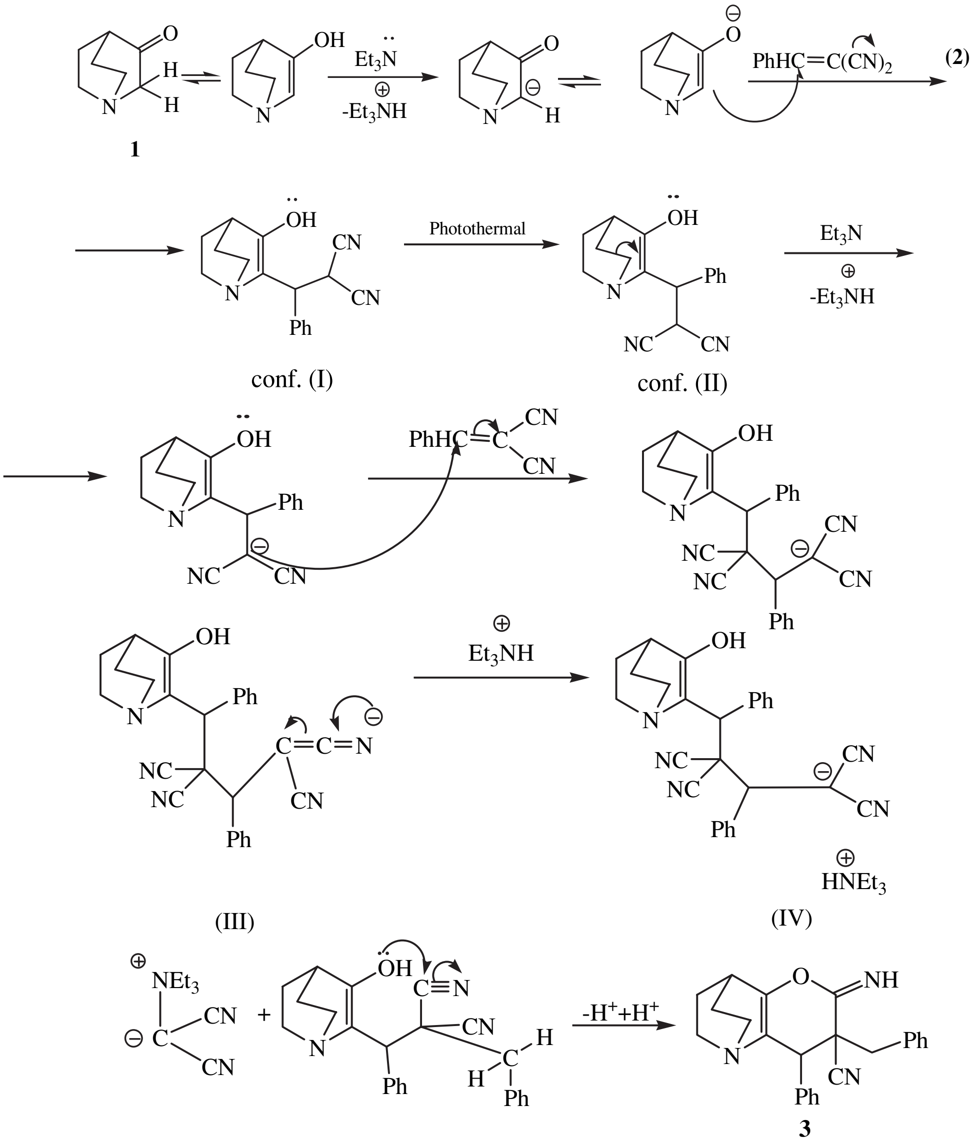

Scheme 1

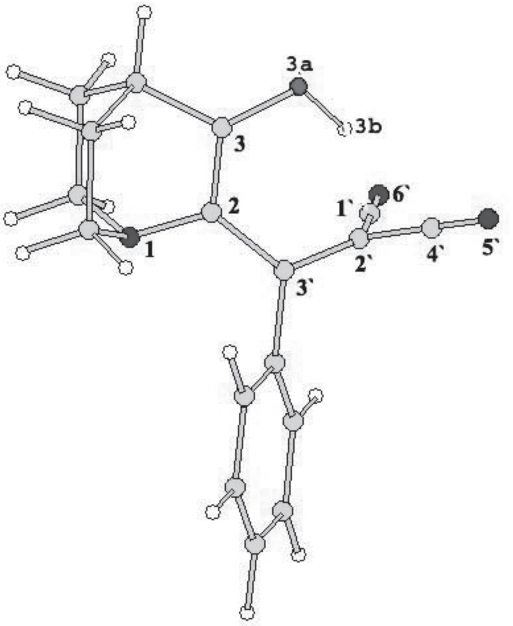

Fig. 2 Conformation I, in which the OH-group directly interact with the C(CN)$_2$ moiety.

and the relative orientation of the OH- group with respect to the C–(CN)$_2$ moiety. Geometry optimisation of the formed structure showed that the lowest energy conformation was that in which the partially positively charged H(3b) atom of the OH- group (charge= +0.114) was present in a position allowed it to directly interact with the electron cloud of the C-(CN)$_2$ moiety through the highest negatively charged C(2') atom making a distance H(3b)–C(2') of 1.82 Å. The effective structural and quantum chemical parameters of the formed new species are given in Table 2. This structural behavior of

Table 2 Calculated charges on effective centers and distances between them and some quantum and structural parameters of conformation I

Atom	Charge	Bond	Distance (Å)
H(3b)	+ 0.284	H(3b)–C(2')	1.82
O(3a)	− 0.300	H(3b)–N(6')	3.27
C(2')	− 0.426	H(3b)–N(5')	3.39
C(3')	+ 0.191	H(3b)–C(1')	2.41
N(5')	− 0.297	H–(3b)–C(4')	2.49
N(6')	− 0.295	O(3a)–H(3b)	0.986

Total energy = –4113.71 kcal/mol
Dipole moment = 11.434 Debye
(2')-(1')-(3')-(4') out of plane angle = 28 degrees
(3)-(2)-(3')-(2') dihedral angle = 11 degrees

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this formed compound will have no capability to add more benzylidinemalononitrile since the active negative centre at C(2') is not more free for further interaction and consequently the thermal reaction stops at this stage.

The change in molecular potential energy arised as a result of the change of the C(3)–C(2)–C(3')–C(2') dihedral angle (torsion about C(2)–C(3') bond, see Fig. 1 was calculated and represented in Fig. 3, the curve showed that in addition to the described above lowest energy conformation Conf I, another possible stable conformation Conf II is expected when the torsion angle reaches 78° (the dihedral angle C(3)–C(2)–C(3')–C(2') is –67°). This Conf II has a total energy of –4109.7 kcal/mol which indicates that it is with comparable stability with conf I (higher by about 4 kcal/mol than Conf I). In Conf II the active negative centre at C(2') has no more interactions and becomes completely free and available for further interaction with additional malononitrile molecule in the same behaviour as the first addition process (see Fig. 4). More important is that there is an energy barrier of about 67 kcal/mol (when rotated clockwise) and about 24 kcal/mol (when rotated anticlockwise) for the inter-conversion between Conf. I and Conf. II (see Fig. 3). These values are large to be overcome by acquisition of a certain amount of heat actually available for the reaction environment. Starting from Conf I, the acquisition of a certain daylight photon wavelength in the range of 240–1200 nm boosted the possibility of rotation about C(2)–C(3') and the generation of Conf II.

The quantum chemical behaviour of Conf I enhances the possible migration of the H(3b) atom to one of the N-atoms of the CN-groups and a cyclisation process between O(3a) and C(1') or C(4') atoms to occur. The cyclic structure has a total energy (–4108.7 kcal/mole) is of the same order as the open structure, and a resonance between the cyclic- and the open-structures is expected leading to more stabilisation.

The electronic structure of III was quantum mechanically calculated using the PM3 semi-empirical molecular orbital method. The results indicated that the negative charge on the molecule is not localised on a certain position within the species, but it was distributed overall the molecule. The highest negative charge was detected on the C(2''). The calculated charge densities on the functionally significant atoms and bond orders between them are summarised as follows in Table 3.

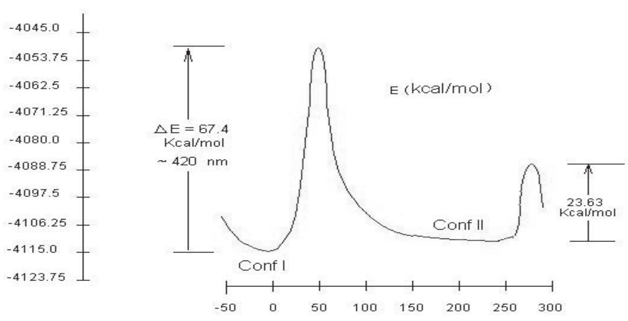
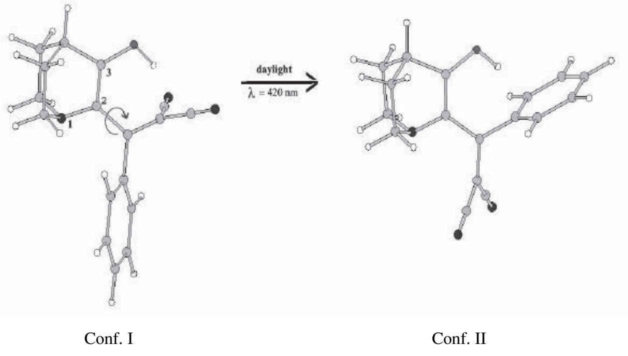


Fig. 3 Potential energy curve of rotation about the C(2)–C(3') single bond.



Conf. I Conf. II

Fig. 4 The effect of photothermal on conf. I.

On the other hand, the electronic structure of the $HNEt_3$ species (which actually present in the medium) was also calculated using the same quantum mechanical method. Results showed that the charge density on the N(4'') was +0.596 and on H(5″) was +0.065 respectively.

When we take into consideration the electronic properties of the two species III and Et_3N^+H which are present at the same time and in the same medium, the generation of a new species formed due to the attraction of the negatively charged C(2'') atom of III, with the positively charged N(4'') atom of the Et_3N^+H species is expected. This is in turn followed by the approach of the positively charged H(6'') atom (of Et_3N^+H) with the C(1'') atom of III. Geometry optimisation were carried out to determine the optimum structure when the two species were allowed to approach one another. The molecular parameters and the electronic structure of the resulted optimum structure was determined. The obtained quantum parameters for the effective centers are summarised in Table 5.

The calculated total energy of IV was found to be –8384.4 kcal/mol which is lower than the sum of energies of III and Et_3N^+H species –8099.6 kcal/mol. This indicates that it is electronically more stable than the two separate species and its formation is expected. The calculated bond orders and bond lengths of the bonds indicated that C(2'')–C(1'') has a weaker strength than C(2'')–C(2'). The H(5'')–C(1'') bond, on the other hand is very weak (bond order of 0.253 and of 1.22 Å length).

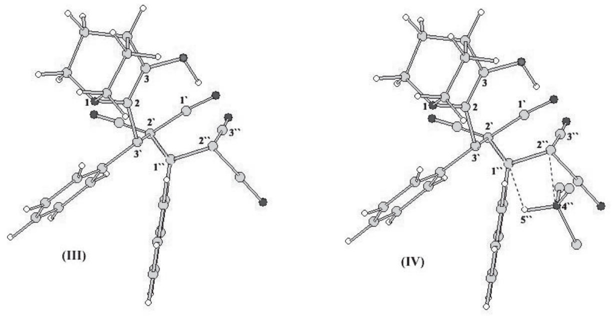


Fig. 5 (III) The resulted species after the addition of the second molecule of bezylidinemalononitrile on (conf. II). (IV) The expected transition state between (III) and Et

Table 3 Important structural parameters of (III) as resulted from MP3-MO calculations

Atom	Atomic Charge	Bond	Bond order
C(2'')	– 0.434	C(2'')-C(1'')	0.998
C(1'')	– 0.121	C(1'')-C(2')	0.885
C(2')	+ 0.242		
Total energy = –6254.224 kcal/mol			

Table 4 Atomic charges of Et_3N^+H as obtained from MP3-MO calculations

Atom	Charge
N-atom (4'')	+0.596
C-atom (of CH_2)	–0.215
C-atom (of CH_3)	–0.410
H-atoms (of CH_3)	+0.066
	+0.072
	+0.099
H (5'')	+0.065
Total energy = –1845.38 kcal/mol	

Table 5 The important quantum chemical parameters for the effective atoms and bonds in IV

Bond	Bond order	Bond length	Atomic charge
C(2'')–C(1'')	0.7118	1.768	C(2'') : –0.105
C(1'')–C(2')	0.9083	1709	C(1'') : +0.056
C(2'')–N(4'')	0.498	1.669	C(2') : +0.274
H(5'')–N(4'')	0.605	1.155	N(4'') : +0.814
H(5'')–C(1'')	0.253	1.218	H(5'') : –0.004
H(5'')–C(2')	—	2.54	
The calculated total energy = –8384.414 kcal/mol			

The atomic orbital coefficients of the effective atoms for the HOMO and LUMO orbitals of IV are summarised in Table 6.

In the case that IV has gained a specific amount of external energy from the reaction environment (heat or day-light), excitation of one electron from the HOMO to the LUMO molecular orbital will take place and the molecule becomes in a new excited state. This new excited state is characterised by the anti-bonding character of C(2")–C(1") than C(1")–C(2'), by higher binding character of N(4")–C(2"), and by weaker bonding character of the N(4")–H(5") bond. This is revealed from inspection of the calculated atomic orbital coefficients of the calculated molecular orbitals.

Results showed that the atomic orbitals of C(2") and C(1") have a strong negative overlapping (or anti-bonding) character, in the LUMO orbital (raised from the opposite signs of their coefficients) when compared with the corresponding coefficients for atoms C(1") and C(2′), where they showed a relatively positive overlapping for the HOMO and negative overlapping for the LUMO. On the other hand, the atomic orbital of the N(4") and C(2") atoms have a negative overlap (anti-bonding) in the HOMO orbital and a positive overlap in case of the LUMO orbital (see Table 6). Also a weaker bonding character was observed due this electronic transition for the N(4")–H(5") bond for the LUMO than HOMO (see Table 6). This can simply interpret the rupture of the C(1")–C(2") bond.

Experimental

General remarks

All melting points (uncorrected) were determined on Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra were measured using KBr disc on a Mattson 5000 FTIR spectrometer.^{1}H-NMR data were obtained in $CDCl_3$ or DMSO on Varian XL 200 MHz instrument using TMS as internal standard. Chemical shifts were reported in ppm (δ) downfield from internal TMS and coupling constants were expressed in hertz. Mass spectra were recorded on GC-MS QP-1000 EX. Shimadzu Instrument. Reactions were monitored by thin layer chromatography (TLC) using EM science silica gel coated plates with visualisation by irradiation with ultraviolet lamp. The new compounds were named according to ChemOffice 2002 (ChemDraw Ultra 7.0) program.

4-Benzyl-5-imino-3-phenyl-6-oxa-1-azatricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene-4-carbonitrile (**3**): A mixture of **1** (0.5g, 3 mmol) and triethylamine (0.5 ml) were refluxed for 2 h. in absolute ethanol then benzylidinemalononitrile **(2)** (0.46g, 3 mmol) was added. The reaction mixture was further refluxed for 5 h., in the prescence of day light, poured onto ice water and extracted with ethyl acetate (3 × 10 ml). The solvent was evaporated under vacuum to give 0.27g of **3**, which was purified using preparative chromatography on Al_2O_3 using pet. ether 40–60 °C/ethyl acetate (1:3) as eluent to give **3**.

Yield 24.5%; m.p. 235 °C; R_f = 0.59 [Pet. ether 40–60 °C/ethyl acetate (1:3)]; IR (KBr) cm^{-1} 2215 (CN), 2950 (C-H stretching); ^{1}H NMR ($CDCl_3$) δ 1.9 [m, 4H, ($C\underline{H}_2)_2C$], 2.5 [q, 1H, bridgehead], 3.06 [m, 4H, ($C\underline{H}_2)_3N$], 3.44 [s, 2H, C$\underline{H}_2$Ph], 3.56 [s, 1H, C$\underline{H}$-Ph], 7.2–7.7 [m, 10H, aromatic], 8.1 [s, 1H, =N$\underline{H}$]; MS 368(M$^+$-1, 6.60), 365(M$^+$-4, 100, base peak), 340 (9.80), 292 (2.80), 278 (5.50), 250 (3.60), 237 (3.60), 215 (2.40), 208 (3.50), 197 (2.80), 139 (3.50), 125 (1.90), 108 (1.60), 82(5.00), 67(15.60), 53(3.60); Analysis calculated for Mol. formula $C_{24}H_{23}N_3O$ (369.66): C, 77.98; H, 6.27; N, 11.42. Found: C, 78.01; H, 6.31; N, 11.38.

Table 6 The atomic orbital coefficients and energies of the HOMO and LUMO of IV

HOMO : *E*= –7.78 eV					
	N(4')	C(3")	C(1")	C(2")	H(5")
S	–0.152	–0.002	+0.010	+0.435	–0.451
Px	–0.053	–0.002	+0.014	+0.004	
Py	+0.154	+0.004	–0.003	+0.314	
Pz	+0.041	+0.009	–0.083	–0.301	
LUMO : *E* = –0.28 eV					
S	–0.274	+ 0.101	+ 0.261	–0.128	+ 0.115
P_x	–0.030	+ 0.102	+ 0.057	–0.087	
P_y	+ 0.117	–0.003	–0.217	+ 0.398	
P_z	+ 0.024	–0.024	–0.158	+ 0.252	

5-Imino-3-phenyl-6-oxa-1-azatricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene-4-carbonitrile (**4**): Compound **4** was prepared according to the above procedure used for the preparation of **3** but it was carried out in the absence of light.

Yield 16%; m.p. 155 °C; R_f = 0.45 [Pet. ether 40–60 °C/ethyl acetate (1:3)]; IR (KBr) cm^{-1} 2217 (CN), 3227 (NH); ^{1}H NMR ($CDCl_3$) δ 1.9 [m, 4H, ($C\underline{H}_2)_2C$], 2.5 [q, 1H, bridgehead], 3.06 [m, 4H, ($C\underline{H}_2)_3N$], 2.9 [d, 1H, C$\underline{H}$–CN], 3.56 [d, 1H, C$\underline{H}$-Ph], 7.2–7.5 [m, 5H, aromatic], 8.1 [s, 1H, =N$\underline{H}$]; MS 264 (M$^+$-NH; 75.76), 253 (69.70), 238 (63.64), 203 (69.70), 177 (79.79), 162 (69.70), 138 (72.73), 125 (60), 108 (69.67), 80 (69.97), 66 (72.73), 51 (100, base peak); Analysis calculated for Mol. formula $C_{17}H_{17}N_3O$ (279.53): C, 73.05; H, 6.13; N, 15.10. Found: C, 73.08; H, 6.12; N, 15.07.

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