Unexpected transformations of an azoxyquinoxaline

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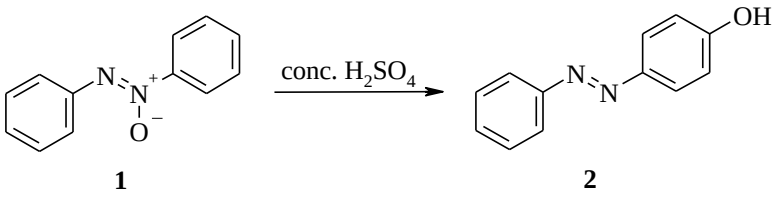
Abstract

Treatment of *N*,*N*'-di(quinoxalin-2-yl)diazene *N*-oxide **3** with strong acids did not give the expected Wallach-type hydroxylated product, but the first representative of the pentacyclic imidazo[1,2-*a*:4,5-*b'*]diquinoxaline system **5**. Heating in a weaker acid or neat furnished 1-(quinoxalin-2-yl)quinoxalin-2(1*H*)-one **12**. The structures of these products were confirmed by independent synthesis and NMR experiments or X-ray crystallography.

Keywords: Nitrogen heterocycles, azoxy compound, thermal transformation, acid catalyzed transformation, rearrangement

Introduction

Treatment of azoxybenzene **1** and its derivatives with certain strong acids is known to result in the corresponding hydroxyazobenzene **2** (Scheme 1).[1] This rearrangement, discovered by Wallach, was named after him.[2] The products of the Wallach transformation have been found to depend on the reaction conditions: the hydroxyl group generally appears in a *para* position, though the application of photochemical[3] or Lewis acid-catalysed[4] reactions or blocking of both *para* positions[5] leads to the formation of *ortho*-hydroxy derivatives. Kinetic studies have resulted in much mechanistic information being deduced from the structural changes in the azoxybenzene[6] and azoxynaphthalene series,[7] but extension of such studies to the heterocyclic azoxy compounds has not been systematically reported. Only the phenylazoxypyridines and their *N*-oxides were investigated by Buncel and his coworkers.[8] We set out to extend the generic Wallach rearrangement to heterobicyclic ring systems, and started our investigations with azoxyquinoxaline **3**;[9] this revealed some interesting and surprising reactions and products, depending on the reaction media. This short paper reports our findings.

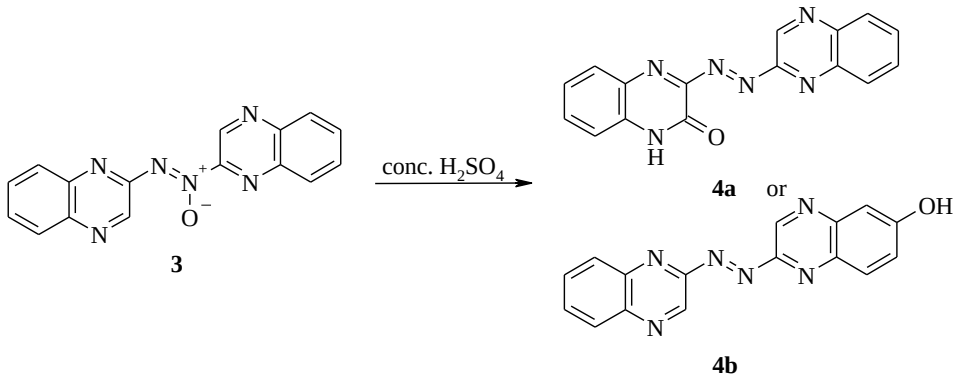


1 **2**

Scheme 1. Wallach rearrangement.

Results and Discussion

We first applied the original Wallach rearrangement conditions, treating azoxy compound **3** with conc. sulfuric acid in the expectation of obtaining the corresponding 3-oxo (*ortho*-like product, **4a**) or 6-hydroxy (*para*-like product, **4b**) azo compound (Scheme 2).



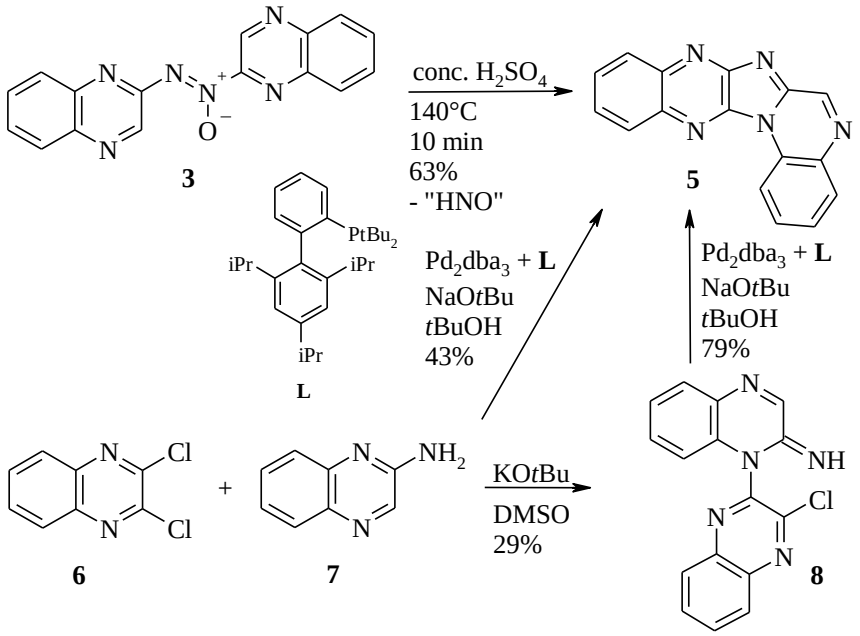
3 **4a** **4b**

Scheme 2. Expected reaction of **3** in conc. sulfuric acid.

Buncel and his coworkers reported that the phenylazoxypyridines and their *N*-oxides react much more slowly than does azoxybenzene itself, presumably because of the extra positive charge present in the substrates.[8] We therefore decided to carry out the transformation of **3** at higher temperature. After azoxyquinoxaline **3** had been stirred in conc. sulfuric acid at 140 °C for 10 min, the isolated product was recrystallized and characterized by HRMS assay. Surprisingly, we observed nitrous gas evolution and, consistently, HRMS assay did not contain any O atom: instead of the Wallach rearrangement, formally "HNO" was eliminated from **3**. Compound **5**, with the molecular formula $C_{16}H_9N_5$, was obtained in 63% yield (Scheme 3). On the basis of 2D NMR measurements, a new pentacyclic system, imidazo[1,2-*a*:4,5-*b'*]diquinoxaline **5**, is proposed for the structure.

This structure was supported by an independent synthesis starting from 2,3-dichloroquinoxaline **6** and 2-aminoquinoxaline **7**, subjected to the Buchwald-Hartwig protocol,[10] yielding compound **5** in 43%. The synthesis was also carried out in a two-step reaction. The

nucleophilic substitution of compound **6** with amine **7** gave 1-(3'-chloro-2'-quinoxalinyl)quinoxalin-2(1*H*)-imine **8**, which underwent the Buchwald-Hartwig cyclization[10] to yield pentacyclic compound **5**.



Scheme 3. Formation of **5**.

Table 1. Influence of the nature of the acid and temperature on the transformation of **3**

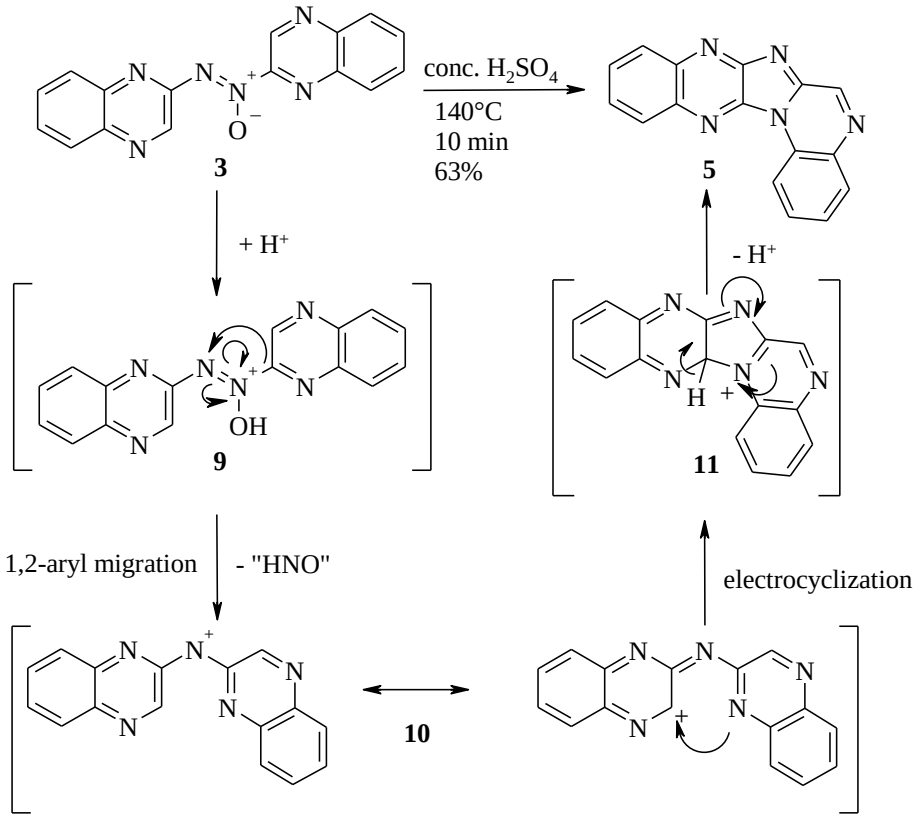
Entry	Medium	pK_a	T [°C]	Product	Yield [%][a]
1	conc. H_2SO_4	-3.0	140	**5**	63
2	conc. H_2SO_4	-3.0	r.t.	**5**	67[b]
3	CH_3SO_3H	-2.6	140	**5**	56
4	CF_3COOH	-0.25	72[c]	**5**	56
5	HCOOH	3.77	101[c]	**5**	67
6	AcOH	4.76	118[c]	**12**	85
7	Ac_2O	-	140[c]	**12**	87
8	glycol	-	140	**12**	80
9	morpholine	-	129[c]	**16**	87

[a]Reaction time 10 min; yield after isolation and recrystallization.
[b]Reaction time 48 h.
[c]At boiling temperature.

Various strong mineral and organic acids uniformly furnished **5** (Table 1, Entries 1-5). In the presence of sulfuric acid, a reduction of the temperature did not have a significant influence on

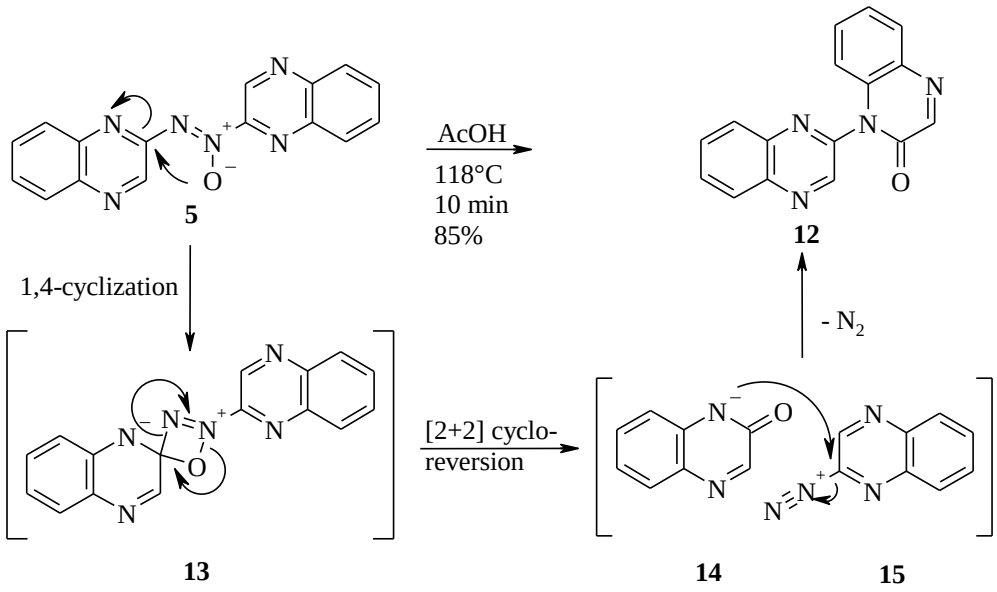
the nature or quantity of the product, but the necessary reaction time increased considerably, from 10 min to 48 h (Entry 2).

A possible formation of pentacyclic derivative **5** is depicted in Scheme 4. In the protonated form **9**, 1,2-aryl migration occurred on the diazo moiety, followed by "HNO" loss to give a di(quinoxalin-2-yl)amino cation **10**. Then the pentacyclic skeleton **11** was formed by electrocyclization of **10**, and after deprotonation pentacycle **5** was obtained.



Scheme 4. Proposed mechanism of the acid catalyzed reaction of **3**.

When the value of pK_a was systematically increased, dramatic changes were observed above pK_a 3.77. Reaction in boiling acetic acid provided **12** instead of **5** (Entry 6, Scheme 5). The HRMS assay indicated the elimination of N_2 from **3** to yield quinoxalinylquinoxalinone **12**. Its structure was proved by X-ray crystallography: the relative positions of the two planar quinoxaline rings are characterized by a C12-N11-C3-C2 of a torsion angle of 63.2(2)° (Figure 1).[11] Quinoxalinylquinoxalinone **12** was earlier isolated by Iijima: heating of quinoxaline *N*-oxide with acetic anhydride resulted in formation **12** (4%) among others.[12]



Scheme 5. Proposed mechanism of the thermal reaction of **3**.

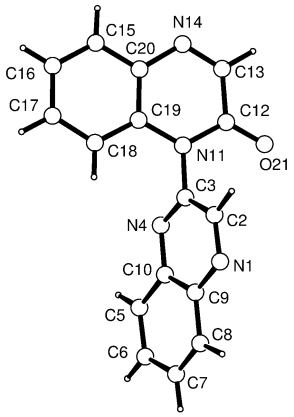


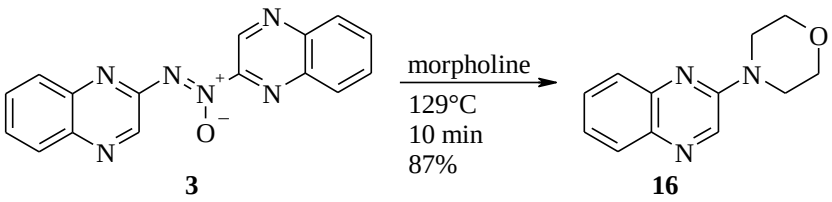
Figure 1. Structure of compound **12** with the crystallographic atomic numbering.

The question arose of the possibility of thermal reaction; the same product was obtained from neutral organic solvents (Entries 7 and 8) and even neat from **3**. Accordingly, we carried out thermoanalytical studies (DSC, TG and DTG). At the melting point of **3**, an intense exothermic reaction (**3** → **12**, $\Delta H_{166°C}$ = 84.6 kcal/mol) was detected, and the gravimetry demonstrated a relative loss of mass $\Delta m_{172°C}$ = 9.3%, which is consistent with N_2 elimination (theoretical loss: Δm = 9.3%). When the same sample (now containing quinoxalinylquinoxalinone **12**) was further heated to 220 °C, endothermic melting ($\Delta H_{220°C}$ = 7.2 kcal/mol) ensued. In solvents, the N_2 elimination proceeded even at lower temperatures, indicating a very strong solvent effect (Entries 6-8). This type of thermal transformation does not appear to have been widely described

in the literature: only one example of the thermolytic loss of N_2 from azoxy compounds is known.[13]

On the evidence of these studies and the literature data, we propose the mechanistic pathway depicted in Scheme 5. The first step involves *ipso*-attack by the oxygen of the azoxy moiety of **3** on the positively charged C2 of the more distant quinoxaline ring to furnish *spiro* derivative **13**. This is followed by a [2+2]-cycloreversion of intermediate **13** to give quinoxalinone anion **14** and quinoxaline-3-diazonium ion **15**. N_2 loss occurred during recombination of cation **15** and anion **14** providing quinoxalinylquinoxalinone **12**.

To find support for the proposed mechanism we attempted to trap cationic species by a nucleophile. In view of the scope and limitations of the trapping reaction, we set out to catch cation **15** in morpholine. When **3** was heated in boiling morpholine, 2-(morpholin-4-yl)quinoxaline **16** was obtained in good yield (Entry 9, Scheme 6).[14] Similar treatment of **12** for 10 min resulted in the formation of < 1% of **16**.



3 **16**

Scheme 6. Formation of **16**.

Conclusions

In summary, the treatment of azoxy compound **3** with strong acids or thermally led to two different reaction pathways, furnishing pentacyclic system **5** and quinoxalinylquinoxalinone **12**. The structures of the products were supported by detailed NMR analysis, and confirmed by independent synthesis (for **5**) and X-ray crystallography (for **12**). A possible interpretation of the formations of products **5** and **12** is proposed.

Experimental Section

General. Melting points were determined in open capillary tubes with a Büchi 535 apparatus and are uncorrected. NMR spectra were measured with a Bruker Avance 500, Avance 400 or Avance 200 instrument, mass spectra (GC-MS) with a Shimadzu GCMS-QP2010S instrument, high-resolution mass spectra with a Waters LCT Premier XE instrument, and IR spectra with a VERTEX 70 instrument (KBr).

***N,N'*-Di(quinoxalin-2-yl)diazene *N*-oxide (3).** Compound **3** was prepared as described in method b) in ref. 9. The product was found to be identical.

Imidazo[1,2-*a*:4,5-*b*']diquinoxaline (5)

Method A. A suspension of **3** (300 mg, 1 mmol) in conc. sulfuric acid (1 mL) was stirred at 140 °C for 10 min. The reaction mixture was then cooled to room temperature and poured into $NaHCO_3$ solution, after which the precipitate was filtered off. The crude product was recrystallized from methanol. Yield 171 mg, 63%; orange crystals (from methanol); mp 243-245 °C.

Method B. A solution of **8** (308 mg, 1 mmol), sodium *tert*-butoxide (198 mg, 2 mmol), phosphine ligand **L** (22 mg, 0.05 mmol) and Pd_2dba_3 (46 mg, 0.05 mmol) in *tert*-butanol (2 mL) was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature and was purified by prep. TLC (Kieselgel 60 F_{254}, 2 mm, toluene : methanol = 4 : 1). The product was recrystallized from methanol. Yield 214 mg, 79%; orange crystals (from methanol); mp 244-245 °C.

Method C. A solution of **6** (207 mg, 1 mmol), **7** (160 mg, 1.1 mmol), sodium *tert*-butoxide (218 mg, 2.2 mmol), phosphine ligand **L** (22 mg, 0.05 mmol) and Pd_2dba_3 (46 mg, 0.05 mmol) in *tert*-butanol (2 mL) was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature and was purified by prep. TLC (Kieselgel 60 F_{254}, 2 mm, toluene : methanol = 4 : 1). The product was recrystallized from methanol. Yield 117 mg, 43%; orange crystals (from methanol); mp 244-245 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C) δ 9.57 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 1-H), 9.37 (s, 1 H, 6-H), 8.37 and 8.34 (m, 2 H, 12-H and 9-H), 8.18 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 4-H), 7.88 and 7.86 (m, 3 H, H-10, H-11 and 2-H), 7.66 (dd, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 7.4 Hz, 1 H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C): δ 148.9 (7*a*-C), 146.1 (6*a*-C), 146.0 (6-C), 142.9 (8*a*-C or 12*a*-C), 140.0 (8*a*-C or 12*a*-C), 138.2 (13*a*-C), 135.2 (4*a*-C), 131.5 (2-C), 130.9 (4-C), 129.8 (9-C or 12-C), 129.4 (10-C or 11-C), 129.3 (10-C or 11-C), 128.8 (9-C or 12-C), 128.1 (13*c*-C), 126.7 (3-C), 116.9 (1-C); MS(EI+) *m/z* = 271 [M^+], 244, 143, 129; HRMS(ES+) *m/z* = 272.0919 [MH^+], calcd. for $C_{16}H_{10}N_5^+$ 272.0936.

1-(3'-Chloro-2'-quinoxalinyl)quinoxalin-2(1*H*)-imine (8). A solution of **6** (218 mg, 1.05 mmol), **7** (145 mg, 1 mmol) and potassium *tert*-butoxide (118 mg, 1 mmol) in DMSO (1.5 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into water (7.5 mL), the precipitate was filtered off. The crude product was recrystallized from acetonitrile. Yield 103 mg, 33%; purity: 83% (HPLC); yellow crystals (from acetonitrile); mp 196 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 27 °C) δ 10,17 (br, 1 H, NH), 9.57 (br, 1 H, 3-H), 8.06 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-H), 7.96 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 5'-H), 7.90 and 7.88 (m, 2 H, 8-H and 8'-H), 7.80 and 7.79 (m, 2 H, 7-H and 7'-H), 7.71 and 7.69 (m, 2 H, 6-H and 6'-H); ^{13}C NMR (100 MHz, DMSO-d_6, 27 °C) δ 148.4 (2-C), 145.4 (2'-C or 4*a*'-C), 141.3 (br, 3-C), 140.8 (8*a*-C), 140.3 (3'-C), 139.4 (8*a*'-C), 138.9 (4*a*-C), 138.1 (4*a*'-C or 2'-C), 131.0 (7'-C), 130.7 (7-C), 128.9 (5-C), 128.0 (6'-C), 127.8 (6-C), 127.75 (5'-C), 127.1 (br, 8-C), 126.8 (8'-C); MS(EI+) *m/z* = 271 [M-HCl]$^+$, 143, 129, 102; HRMS(ES+) *m/z* = 308.0707 [MH^+], calcd. for $C_{16}H_{11}ClN_5^+$ 308.0703.

1-(Quinoxalin-2-yl)quinoxalin-2(1H)-one (12). A suspension of **3** (300 mg, 1 mmol) in acetic anhydride (1 mL) was stirred at the boiling point for 10 min. The reaction mixture was then cooled to room temperature and poured into $NaHCO_3$ solution, after which the precipitate was filtered off. The crude product was recrystallized from methanol. Yield 238 mg, 87%; yellow crystals; mp 222-223 °C (lit.[12] mp 218 °C); ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 27 °C) δ 9.20 (s, 1 H, 3'-H), 8.44 (s, 1 H, 3-H), 8.30 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, 5'-H), 8.20 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 8'-H), 8.06 and 8.02 (m, 2 H, 6'-H and 7'-H), 7.96 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 5-H), 7.48 and 7.44 (m, 2 H, 7-H and 6-H), 6.92 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, 8-H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 27 °C) δ 154.7 (2-C), 151.3 (3-C), 146.1 (3'-C), 145.0 (2'-C), 142.2 (4*a*'-C), 141.5 (8*a*'-C), 132.8 (8*a*-C), 132.7 (4*a*-C), 132.2 (6'-C), 131.8 (7'-C), 131.6 (7-C), 130.1 (5-C), 129.5 (2 C, 5'-C and 8'-C), 124.8 (6-C), 115.8 (8-C); MS(EI+) *m/z* = 274 [M^+], 273, 245, 219; HRMS(ES+) *m/z* = 275.0927 [MH^+], calcd. for $C_{16}H_{11}N_4O^+$ 275.0933; IR(KBr) 1667cm^{-1} ($\nu_{amide\ C=O}$).

2-(Morpholin-4-yl)quinoxaline (**16).** A solution of **3** (300 mg, 1 mmol) in morpholine (1 mL) was stirred at the boiling point for 10 min. The reaction mixture was then cooled to room temperature and purified by prep. TLC (Kieselgel 60 F_{254}, 2 mm, hexane : EtOAc = 1 : 1). The product was recrystallized from methanol. Yield 187 mg, 87%; red crystals; mp 85-87 °C (lit.[14] mp 88-89 °C); ^{1}H NMR (200 MHz, DMSO-*d*$_6$, 27°C) δ 8.81 (s, 1 H, 3-H), 7.84 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 5-H), 7.64-7.54 (m, 2 H, 8-H and 7-H), 7.47-7.43 (m, 1 H, 6-H), 3.73 (br, 8 H, 2'-H and 3'-H); ^{13}C NMR (50 MHz, DMSO-*d*$_6$, 27 °C) δ 152.6 (2-C), 141.4 (8*a*-C), 137.2 (3-C), 136.8 (4*a*-C), 130.4 (7-C), 128.8 (5-C), 126.5 (8-C), 125.0 (6-C), 66.3 (2 C, 2'-C), 44.9 (2 C, 3'-C); MS(EI+) *m/z* = 215 [M^+], 184, 158, 130, 102; HRMS(ES+) *m/z* = 216.1120 [MH^+], calcd. for $C_{12}H_{14}N_3O^+$ 216.1137; IR(KBr) 2926 cm^{-1}, 2858 cm^{-1}.

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