

Unexpected transformations of an azoxyquinoxaline

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DOI: <http://dx.doi.org/10.3998/ark.5550190.0011.a17>

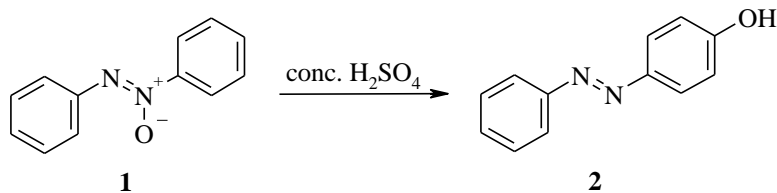
Abstract

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

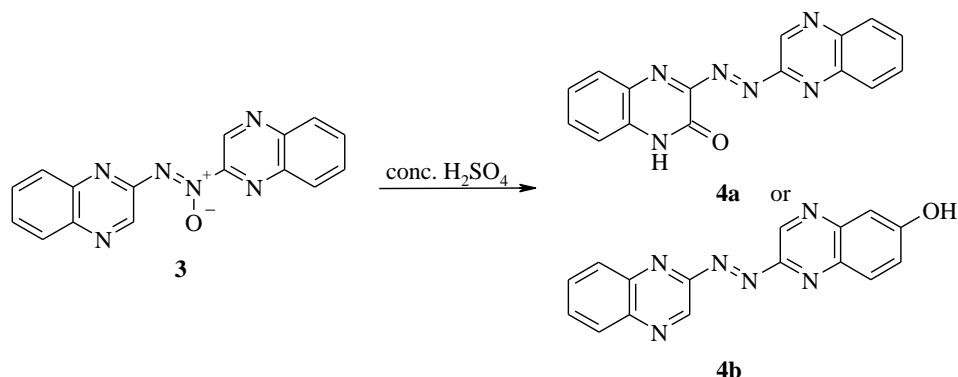
Treatment of azoxybenzene **1** and its derivatives with certain strong acids is known to result in the corresponding hydroxyazobenzene **2** (Scheme 1).¹ This rearrangement, discovered by Wallach, was named after him.² The products of the Wallach transformation have been found to depend on the reaction conditions: the hydroxyl group generally appears in a *para* position, though the application of photochemical³ or Lewis acid-catalysed⁴ reactions or blocking of both *para* positions⁵ leads to the formation of *ortho*-hydroxy derivatives. Kinetic studies have resulted in much mechanistic information being deduced from the structural changes in the azoxybenzene⁶ 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 Buncl 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.



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).

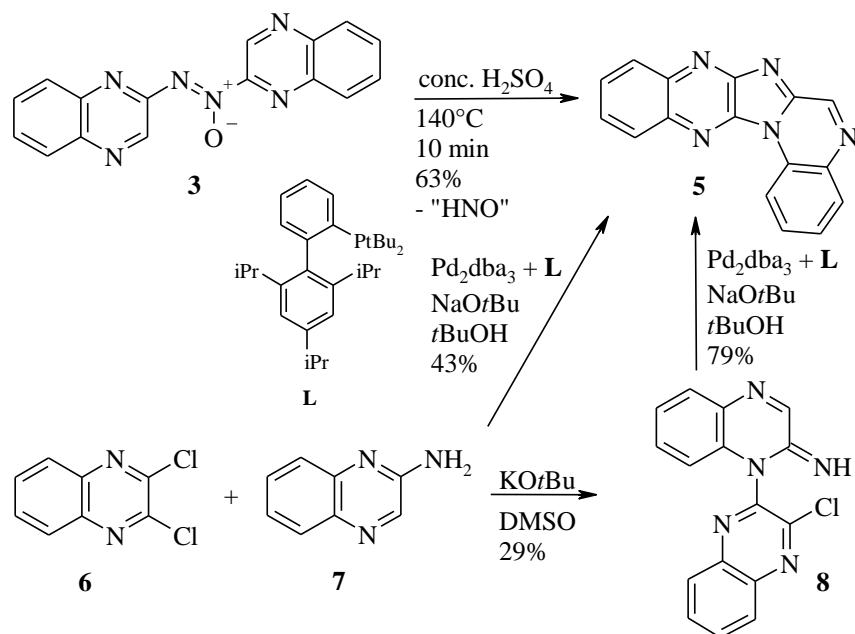


Scheme 2. Expected reaction of **3** in conc. sulfuric acid.

Buncel and his coworkers reported that the phenylazoxy pyridines 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 azoxyquinoline **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 C₁₆H₉N₅, 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-dichloroquinoline **6** and 2-aminoquinoline **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'-quinoxaliny)quinoxalin-2(1*H*)-imine **8**, which underwent the Buchwald-Hartwig cyclization¹⁰ 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 ₂ SO ₄	-3.0	140	5	63
2	conc. H ₂ SO ₄	-3.0	r.t.	5	67 ^b
3	CH ₃ SO ₃ H	-2.6	140	5	56
4	CF ₃ COOH	-0.25	72 ^c	5	56
5	HCOOH	3.77	101 ^c	5	67
6	AcOH	4.76	118 ^c	12	85
7	Ac ₂ O	-	140 ^c	12	87
8	glycol	-	140	12	80
9	morpholine	-	129 ^c	16	87

^aReaction time 10 min; yield after isolation and recrystallization.

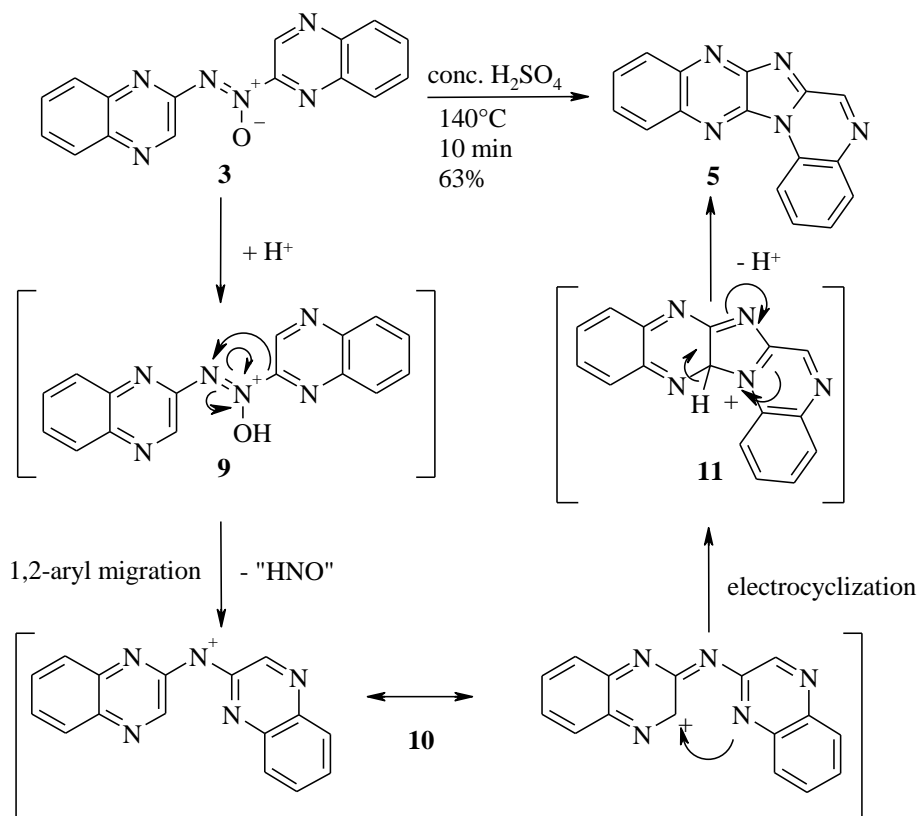
^bReaction time 48 h.

^cAt 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

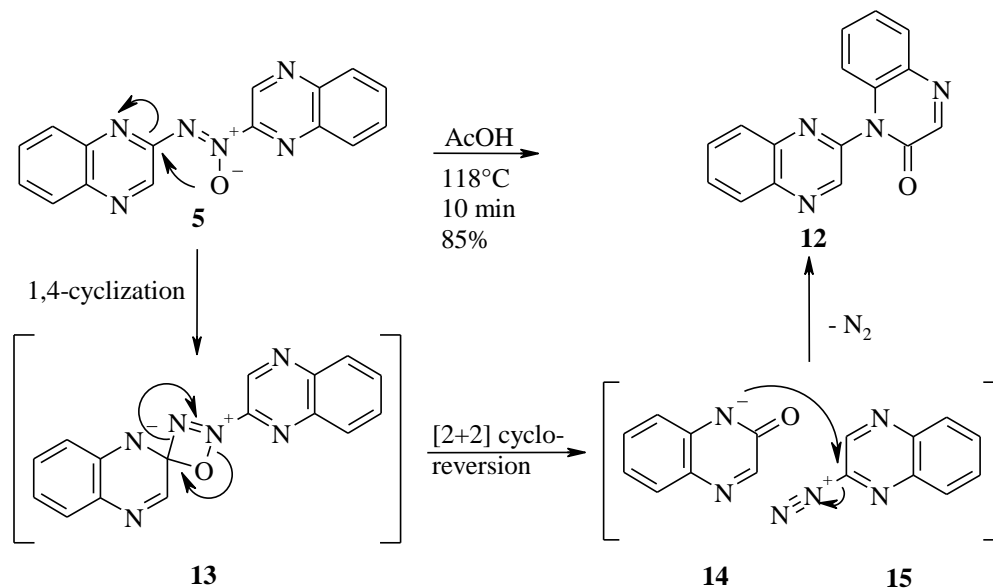
the nature or quantity of the product, but the necessary reaction time increased considerably, from 10 min to 48 h (Entry 2).

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 quinoxalinyloquinolone **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 $63.2(2)^\circ$ (Figure 1).¹¹ Quinoxalinyloquinolone **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**.

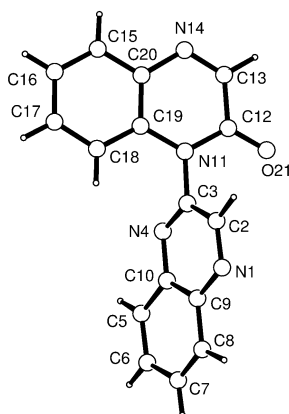


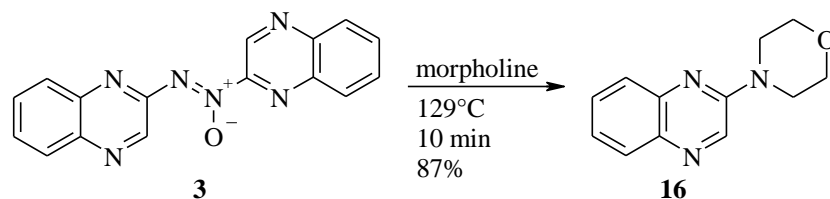
Figure 1. Structure of compound **12** with the crystallographic atomic numbering.

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 ($\mathbf{3} \rightarrow \mathbf{12}$, $\Delta H_{166^\circ\text{C}} = 84.6 \text{ kcal/mol}$) was detected, and the gravimetry demonstrated a relative loss of mass $\Delta m_{172^\circ\text{C}} = 9.3\%$, which is consistent with N_2 elimination (theoretical loss: $\Delta m = 9.3\%$). When the same sample (now containing quinoxalinyloxyquinoxalonyl **12**) was further heated to 220°C , endothermic melting ($\Delta H_{220^\circ\text{C}} = 7.2 \text{ kcal/mol}$) 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 N₂ 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**. N₂ loss occurred during recombination of cation **15** and anion **14** providing quinoxalinyloxyquinoxalinone **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**.



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 quinoxalinyloxyquinoxalinone **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 NaHCO₃ 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 Pd₂dba₃ (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 F₂₅₄, 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 Pd₂dba₃ (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 F₂₅₄, 2 mm, toluene : methanol = 4 : 1). The product was recrystallized from methanol. Yield 117 mg, 43%; orange crystals (from methanol); mp 244-245 °C; ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 27 °C): δ 148.9 (7a-C), 146.1 (6a-C), 146.0 (6-C), 142.9 (8a-C or 12a-C), 140.0 (8a-C or 12a-C), 138.2 (13a-C), 135.2 (4a-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 (13c-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 C₁₆H₁₀N₅⁺ 272.0936.

1-(3'-Chloro-2'-quinoxaliny)quinoxalin-2(1H)-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. ¹H 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); ¹³C NMR (100 MHz, DMSO-*d*₆, 27 °C) δ 148.4 (2-C), 145.4 (2'-C or 4a'-C), 141.3 (br, 3-C), 140.8 (8a-C), 140.3 (3'-C), 139.4 (8a'-C), 138.9 (4a-C), 138.1 (4a'-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 C₁₆H₁₁ClN₅⁺ 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 NaHCO₃ 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); ¹H 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); ¹³C 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 (4a'-C), 141.5 (8a'-C), 132.8 (8a-C), 132.7 (4a-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 C₁₆H₁₁N₄O⁺ 275.0933; IR(KBr) 1667 cm⁻¹ (ν_{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 F₂₅₄, 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); ¹H 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); ¹³C NMR (50 MHz, DMSO-*d*₆, 27 °C) δ 152.6 (2-C), 141.4 (8a-C), 137.2 (3-C), 136.8 (4a-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 C₁₂H₁₄N₃O⁺ 216.1137; IR(KBr) 2926 cm⁻¹, 2858 cm⁻¹.

Acknowledgements

We are grateful David Durham for the linguistic improvement of the manuscript. One of the authors (A.M.) expresses her thanks for support through a Sanofi Aventis Fellowship.

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