3-(Arylamino)quinolin-2(1*H*)- and -4(1*H*)-ones: Reinvestigation of the Reaction between Ethyl 2-Chloro-3-(phenylamino)but-2-enoate and Arylamines

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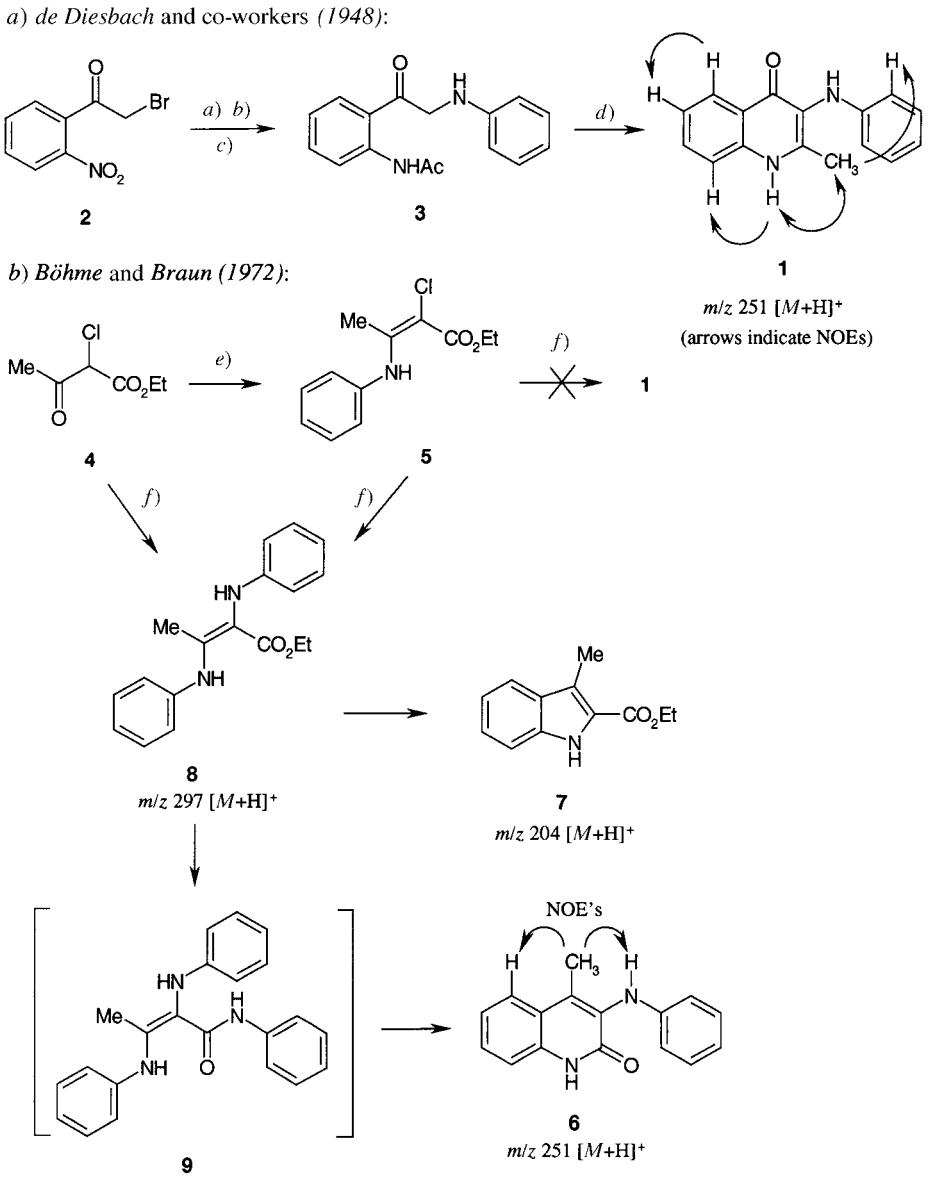
The reaction between ethyl 2-chloro-3-(phenylamino)but-2-enoate (**5**) and aniline gave 4-methyl-3-(phenylamino)quinolin-2(1*H*)-one (**6**) and not, as reported earlier in the literature, the isomeric 2-methyl-3-(phenylamino)quinolin-4(1*H*)-one (**1**). The latter could be prepared by an alternative procedure. The structures of both isomers were established by extensive NMR spectroscopy including 1D-NOE, 2D-HSQC, and HMBC experiments. Consequently, the reinvestigation of the title reaction revealed an unexpected simple access to novel 4-alkyl-substituted 3-(arylamino)quinolin-2(1*H*)-ones.

Introduction. – A first report toward the synthesis of 2-methyl-3-(phenylamino)-quinolin-4(1*H*)-one (**1**) appeared in 1948 by *de Diesbach* and co-workers, who described a four-step synthesis starting from 2-bromo-1-(2-nitrophenyl)ethanone (**2**; *Scheme 1,a*) [1]. The melting point (302°) and elemental analyses were the only analytical data given for the characterization of the product. More than twenty years later, *Böhme* and *Braun* [2] described a new method for the synthesis of **1**. Therein, ethyl 2-chloro-3-(phenylamino)but-2-enoate (**5**) was heated under reflux in neat excess aniline (*Scheme 1,b*). ^{1}H-NMR and IR spectra and the melting point (217°) characterized the isolated product. The intense IR bands at 1629 and 1531 cm^{-1} were interpreted as vinyloguous amide bands I and II. From their analytical data, the authors assigned structure **1** to their product, and concluded that the product described earlier in the work of the *de Diesbach* group could be an isomeric form.

Herein, we present the results of a reinvestigation of the title reaction as part of a chemistry program aimed at the synthetic access of 3-(arylamino)-1*H*-quinolinones. The structures of the products obtained with either procedure were established by NMR spectroscopy.

Results and Discussion. – First, we applied the procedure of *Böhme* and *Braun* [2] to synthesize **1** (*Scheme 1,b*). Both steps, condensation of aniline and **4** to the (*E*)-isomer of enamine **5** [3], and subsequent cyclization were performed as reported [2]. Electrospray mass spectrometric analyses of the crude reaction mixture revealed a product with the expected molecular mass *m*/*z* 251 and accompanying products with *m*/*z* 204, 136, and 297. Application of a different workup procedure than the published one yielded a homogeneous product with the expected mass *m*/*z* 251 in 39% yield. At first glance, the ^{1}H-NMR spectrum was in agreement with published data [2] and consistent with structure **1**. However, further NMR-spectroscopic investigations, such

Scheme 1



a) Cu, H_2SO_4. *b*) Ac_2O. *c*) Aniline, EtOH. *d*) NaOH, EtOH. *e*) Aniline (1 equiv.), benzene, reflux. *f*) Aniline (10 equiv.), 180°.

as ^{13}C-NMR, 1D-NOE, 2D heteronuclear single-quantum coherence (HSQC), and 2D-heteronuclear multiple-bond coherence (HMBC) experiments were performed to verify the structure. From these data, we assigned structure **6** and not **1** to the product obtained in the title reaction (*Scheme 1,b*).

The ^{1}H-NMR spectra of **6** indicated two exchangeable NH protons at δ 11.37 and 9.86. A 1D-NOE experiment showed an enhancement at the aromatic H–C(5) and NH signals of the aniline moiety when the Me protons at δ 2.54 were irradiated. Irradiation of the aromatic H–C(5) at δ 7.63 as well as irradiation of the NH proton at δ 9.86 produced an enhancement of the Me signal. Direct ^{1}H,^{13}C correlations were demonstrated by the HSQC, whereas long-range ^{1}H,^{13}C correlations from HMBC experiments provided further connectivity information. The Me protons at δ 2.54 showed long-range correlations to C-atoms resonating at δ 115.1, 127.7, 160.6, and 128.0. The aromatic proton resonating at δ 7.63 showed long-range correlations to the quaternary C-atoms at δ 128.0 and 115.1. Long-range correlations were observed for the proton at δ 11.37 to C-atoms resonating at δ 160.6, 127.7, and 128.0. The exchangeable NH proton at δ 9.86 could be correlated to C-atoms resonating at δ 160.6 and 119.8.

Interestingly, the formation of **6** from **4** *via* **5** is in contrast to the thermal cyclization of β-anilinoacrylates providing quinolin-4(1*H*)-ones, known as the *Conrad-Limpach* reaction [4][5]. However, our findings were supported by the work of *Chilin et al.*, who reported that the reaction between anilines and ethyl acetoacetate or its 2-methyl derivative yielded quinolin-2(1*H*)-ones [6]. So far, the synthesis of only a few specific examples of 3-(phenylamino)quinolin-2(1*H*)-ones from the reaction of 3-amino-quinolin-2(1*H*)-ones with *o*-chloronitrobenzene have been described [7].

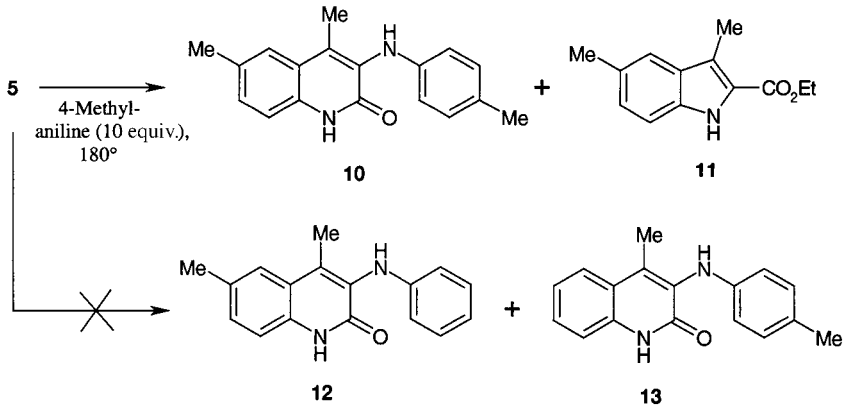
The by-product displaying *m*/*z* 204 was isolated in 25% yield and identified as ethyl 3-methyl-1*H*-indole-2-carboxylate (**7**; *Scheme 1,b*). Its structure was confirmed by NMR spectroscopy, the analytical data obtained being in good agreement with the reported values [8]. In addition, structure **7** was confirmed by a 1D-NOE experiment (NOE for aromatic H–C(4) at δ 7.65 on irradiation of Me at δ 2.60). The by-product with *m*/*z* 136 was isolated by flash chromatography and identified as acetanilide, whereas for the by-product displaying *m*/*z* 297, structure **8** [9] was determined.

The main products **6** and **7** were also obtained, but with much lower yields, by heating a boiling mixture of ethyl 2-chloroacetoacetate (**4**) and excess aniline in a one-pot reaction for 6 h (*Scheme 1,b*), whereas only traces were formed when 3 equiv. of aniline were reacted with **4** in diphenyl ether as solvent.

Compounds **6** and **7** were shown to be stable under prolonged exposure to the harsh reaction conditions such as boiling aniline, and, consequently, could be excluded as precursors of **1**. We rather assume that **8**, which is exclusively formed from **5** in boiling EtOH in the presence of aniline [9], is the common intermediate for both products **6** and **7**, suggesting that **8** is first condensed to anilide **9** [10] (not detectable), which then cyclizes to **6** in a thermal reaction with concurrent elimination of the aniline in the β position. Cyclization of **8**, again with elimination of the β-positioned aniline moiety, would explain the formation of **7**, whereas direct cyclization of **5** with elimination of Cl^- would lead to isomeric 2-methyl-1*H*-indole-3-carboxylate. Further support for the elimination of the aniline moiety at the β position was obtained when the reaction was performed with enamine **5** in the presence of excess 4-methylaniline (*Scheme 2*). Under these conditions, only quinolin-2(1*H*)-one **10** and 1*H*-indolcarboxylate **11** [11] were detectable in the crude product mixture. Both products could be isolated in pure form in 30 and 11% yield, respectively. The structures were unequivocally established by ^{1}H- and ^{13}C-NMR, NOE, HSQC, and HMBC spectroscopy. Neither quinolinones **12** and **13** nor indolecarboxylate **7** were detectable in the crude reaction mixture by means of HPLC and mass-spectrometric analysis.

Eventually, a reference sample of **1** was obtained by the procedure of *de Diesbach* and co-workers (*Scheme 1,a*) [1]. The product was fully characterized by spectroscopic

Scheme 2



means. From these data, we could unequivocally assign structure **1** to this compound, thus confirming the originally published structure.

The ^{1}H-NMR spectra of **1** indicated two exchangeable protons at δ 11.68 and 6.82 for the NH protons. The data of direct ^{1}H,^{13}C correlations were obtained in a HSQC experiment. 1D-NOEs were observed between aromatic H–C(5) and H–C(6), between H–C(8) and the NH proton at δ 11.68, which also was affected when the Me protons at δ 2.30 were irradiated. This latter 1D-NOE experiment showed an additional effect on C_o. The methyl *s* at δ 2.30 showed long-range correlations (HMBC) to the ring C-atoms at δ 146.1 and 120.2. Additional long-range correlations were observed for NH proton at δ 6.82 to the carbonyl C-atom at δ 173.0, to the C-atoms at δ 146.1 and 112.7. The aromatic proton at δ 8.07 was also correlated with the carbonyl C-atom and in addition with C(8a) at δ 138.2.

Conclusion. – We could demonstrate that the reaction between ethyl 2-chloro-3-(phenylamino)but-2-enoate and aniline produced 4-methyl-3-(phenylamino)quinolin-2(1*H*)-one (**6**) and not, as reported in [2], the expected isomeric 2-methyl-3-(phenylamino)quinolin-4(1*H*)-one (**1**). The latter was obtained by an alternative procedure [1]. The structures of both quinolinone isomers were established unequivocally by 1D-NOE, HSQC, and HMBC NMR spectroscopy. Consequently, the reinvestigation of the title reaction revealed a simple access to novel 4-alkyl-substituted 3-(arylamino)quinolin-2(1*H*)-ones.

Experimental Part

1. *General.* All reagents were commercially available and used without further purification. The reactions were monitored and the products analyzed by reversed-phase HPLC: *Merck-Hitachi* system, *AS-2000* autosampler, *L-6200A* intelligent pump, *L-4500* diode array detector, and *D-6000* interface; *Nucleosil* C_{18} column (250 × 4.6 mm, 3 µm, 100 Å; from *Macherey-Nagel*, Düren, FRG); linear gradient of MeCN/0.09% CF_3COOH (*A*) and H_2O/0.1% CF_3COOH (*B*) from 2 to 100% *B* within 20 min, flow rate 1 ml/min; detection at 215 nm. IR Spectra: KBr plates or in soln.; *Bruker-IFS-88*-FT-IR spectrophotometer; in cm^{-1}. NMR Spectra (^{1}H, ^{13}C, NOE, HMBC, HSQC): *Bruker-Avance-500* or *Varian-Gemini-300* spectrometer; at 300 K, $CDCl_3$ or (D_6)DMSO soln.; δ in ppm downfield from $SiMe_4$ using the residual solvent signal (δ(H) 7.24 and δ(C) 77 for $CDCl_3$, δ(H) 2.49 and δ(C) 39.5 for (D_6)DMSO) as an internal standard; coupling constants *J* in Hz. Electrospray mass spectra (ESI-MS): *Fisons Instruments VG Platform II*; *m*/*z*.

2. *Ethyl 2-Chloro-3-(phenylamino)but-2-enoate* (**5**) was obtained in 78% yield [3]. B.p. 104–105°/0.06 mbar ([3]: 87–90°/10^{-2} Torr). ^{1}H-NMR (500 MHz, $CDCl_3$): 10.71 (*s*, 1 NH, exchangeable with D_2O); 7.32 (*t*, 2 H_m); 7.17 (*t*, H_p); 7.04 (*d*, 2 H_o); 4.24 (*q*, Me*C*H_2O); 2.18 (*t*, *Me*CH_2O). ^{13}C-NMR (125.75 MHz, $CDCl_3$): 167.2; 156.8; 139.0; 92.6; 60.5; 18.2; 14.4. ESI-MS (pos. mode): 240 (242, $[M+1]^+$). Anal. calc. for $C_{12}H_{14}ClNO_2$: C 60.13, H 5.89, Cl 14.79, N 5.84; found: C 60.1, H 6.0, Cl 14.6, N 5.8.

3. *Reaction of Ethyl 2-Chloro-3-(phenylamino)but-2-enoate with Arylamines. Method I.* A mixture of **5** (1.2 g, 5 mmol) and aniline (4.7 g, 50 mmol) was heated under reflux for 4 h. After cooling to r.t., diisopropyl ether was added, and the precipitate was filtered off and distributed between AcOEt and 2N HCl. The AcOEt layer was washed with H_2O, sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated. Diisopropyl ether was added to the remaining residue, affording **6** as pale yellow crystals (0.39 g). The filtrate was evaporated and the residue chromatographed (silica gel, toluene) to give additional crystalline **6** (0.10 g; total yield 39%) and **7** (0.30 g, 29%) as a pale yellow solid.

Method II. A mixture of ethyl 2-chloro-3-oxobutanoate (**4**; 30 mmol) and aniline (300 mmol) was heated under reflux for 6 h. Workup was performed as described above to give **6** and **7** in 17 and 11% isolated yield, resp.

*Data of 4-Methyl-3-(phenylamino)quinolin-2(1*H*)-one* (**6**): M.p. 207–208° (from AcOEt; [2]: 217°). R_f 0.44 (hexane/AcOEt 2:1). t_R 15.96 min (single peak). IR (KBr): 3336, 3052, 2925, 2867, 1884, 1625, 1596, 1533, 1500, 1445, 1431, 1330, 1249, 1181, 769, 740, 737, 688. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.37 (*s*, 1 NH(1), exchangeable with D_2O); 9.86 (*s*, NH–C(3), exchangeable); 7.73 (*d*, $J=7.5$, 2 H_o); 7.63 (*d*, $J=7.5$, H–C(5)); 7.42 (*d*, $J=7.5$, H–C(8)); 7.36 (*t*, $J=7.5$, 2 H_m); 7.24 (*t*, $J=7.5$, H–C(7)); 7.07 (*t*, $J=7.5$, H–C(6)); 7.09 (*t*, $J=7.5$, H_p); 2.54 (*s*, Me–C(4)). 1D-NOE (500 MHz, (D_6)DMSO): irrad. at 2.54 → NOE at 9.86 (1.1%) and 7.63 (2.7%). ^{13}C-NMR (125.75 MHz, (D_6)DMSO): 160.6 (C(2)); 139.0 (C_{ipso}); 135.5 (C(4a)); 128.7 (C_m); 128.0 (C(8a)); 127.7 (C(3)); 124.0 (C(7)); 123.5 (C_p); 119.9 (C(5)); 119.8 (C_o); 119.2 (C(6)); 115.1 (C(4)); 111.9 (C(8)); 9.7 (Me). HMBC Correlation (H/C): NH(1)/C(2), NH(1)/C(3), NH(1)/C(4a), CH(5)/C(4a), CH(5)/C(4), CH(5)/C(7), CH(6)/C(4a), CH(6)/C(8), CH(7)/C(5), CH(7)/C(8), CH(7)/C(8a), CH(8)/C(4a), CH(8)/C(5), Me/C(2), Me/C(3), Me/C(4), Me/C(4a), NH–C(3)/C(2), NH–C(3)/C_o, H_o/C_{ipso}, H_o/C_p, H_m/C_{ipso}, H_p/C_o. ESI-MS (pos. mode): 251 ($[M+H]^+$). Anal. calc. for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.12; found: C 76.91, H 5.58, N 10.96.

*Data of Ethyl 3-Methyl-1*H*-indole-2-carboxylate* (**7**): Anal. data in good agreement with [8]. M.p. 136–138°. R_f 0.50 (hexane/AcOEt 2:1). ^{1}H-NMR (500 MHz, $CDCl_3$): 8.64 (br. *s*, NH(1)); 7.65 (*d*, H–C(4)); 7.35 (*d*, H–C(7)); 7.30 (*t*, H–C(6)); 7.12 (*t*, H–C(5)); 4.40 (*q*, Me*C*H_2O); 2.60 (*s*, Me–C(3)); 1.41 (*t*, *Me*CH_2O). 1D-NOE (500 MHz, $CDCl_3$): irrad. at 2.60 → 1 NOE at 7.65 (1.4%). ESI-MS (pos. mode): 204 ($[M+H]^+$). Anal. calc. for $C_{12}H_{13}NO_2$: C 70.92, H 6.45, N 6.89; found: C 70.90, H 6.40, N 6.90.

*Data of 4,6-Dimethyl-3-[(4-methylphenyl)amino]quinolin-2(1*H*)-one* (**10**): According to *Method I*, with **5** and 4-methylaniline: yellowish crystalline **10** (0.42 g, 30%). The filtrate was evaporated, and crystalline **11** (0.12 g, 11%) was isolated from an EtOH soln. of the residue. **10**: M.p. 212–214°. t_R 17.87 min (single peak). IR (CH_2Cl_2): 3450, 3300, 3031, 2924, 2867, 1659, 1595, 1543, 1520, 1405, 1327, 1295, 1246, 1222. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.00 (*s*, NH(1), exchangeable); 7.70 (*s*, NH–C(3), exchangeable with D_2O); 7.53 (*d*, $J=8.2$, 2 H_o); 7.43 (*s*, $J=8.2$, H–C(5)); 7.29 (*d*, $J=8.8$, H–C(8)); 7.19 (*d*, $J=8.2$, 2 H_m); 7.14 (*d*, $J=8.8$, H–C(7)); 2.68 (*s*, Me–C(4)); 2.48 (*s*, Me–C(6)); 2.36 (*s*, Me–C_p). 1D-NOE (500 MHz, $CDCl_3$): irrad. at 2.36 → NOE at 7.19 (2.2%); irrad. at 2.48 → NOE at 7.43 (2.2%) and 7.14 (1.3%); irrad. at 2.68 → NOE at 7.43 (2.1%) and 7.70 (2.8%); irrad. at 7.70 → NOE at 2.68 (9.9%) and 7.53 (3.9%); irrad. at 9.00 → NOE at 7.29 (3.2%). ^{1}H-NMR (300 MHz, (D_6)DMSO): 11.2 (*s*, NH(1), exchangeable with D_2O); 9.73 (*s*, NH–C(3), exchangeable). ^{13}C-NMR (125.75 MHz, $CDCl_3$): 160.5 (C(2)); 135.0 (C_{ipso}); 134.3 (C_p); 133.8 (C(8a)); 129.7 (C_m); 129.4 (C(6)); 127.6 (C(4a)); 126.9 (C(7)); 120.3 (C_o); 119.5 (C(5)); 111.3 (C(4)); 21.5 (*Me*–C(6)); 20.9 (*Me*–C_p); 10.4 (*Me*–C(4)). ESI-MS (pos. mode): 279 ($[M+H]^+$).

*Data of Ethyl 3,5-Dimethyl-1*H*-indole-2-carboxylate* (**11**). Data consistent with [11]. M.p. 134–36°. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.57 (br. *s*, NH, exchangeable with D_2O); 7.43 (*s*, H–C(4)); 7.26 (*d*, $J=8.2$, H–C(6)); 7.15 (*d*, $J=8.2$, H–C(7)); 4.41 (*q*, $J=7.0$, Me*C*H_2O); 2.59 (*s*, Me); 2.46 (*s*, Me); 1.43 (*t*, $J=7.0$, *Me*CH_2O). ^{13}C-NMR (100.7 MHz, $CDCl_3$): 162.9; 134.4; 129.4; 129.0; 127.7; 123.7; 120.3; 111.5; 110.0; 60.9; 21.8; 14.8; 10.2. ESI-MS (pos. mode): 218 ($[M+H]^+$).

4. *2-Methyl-3-(phenylamino)quinolin-4(1*H*)-one* (**1**) was prepared according to [1]: M.p. >280° ([1]: 302°). R_f 0.35 (AcOEt). t_R 10.47 min. IR (KBr): 3382, 3049, 3015, 2781, 1641, 1604, 1589, 1557, 1498, 1476, 1406, 1352, 1315, 1301, 1284, 1248, 1178, 1155, 948, 874, 764, 754. 700. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.68 (br. *s*, NH(1), exchangeable with D_2O); 6.82 (br. *s*, NH–C(3), exchangeable); 8.07 (*d*, $J=7.3$, H–C(5)); 7.61 (*dd*, $J=6.9$, H–C(7)); 7.54 (*d*, $J=7.9$, H–C(8)); 7.26 (*t*, $J=7.4$, H–C(6)); 7.04 (*t*, $J=7.5$, 2 H_m); 6.58 (*t*, $J=7.2$, H_p); 6.53

(d, $J = 7.6$, 2 H_o); 2.30 (s, Me–C(2). 1D-NOE (500 MHz, (D_6)DMSO): irrad. at 8.07 → NOE at 7.26 (8.2%); irrad. at 2.30 → NOE at 6.53 (2.2%) and 11.68 (0.7%); irrad. at 7.54 → NOE at 11.68 (0.7%). ^{13}C-NMR (125.75 MHz, (D_6)DMSO): 173.0 (C(4)); 147.2 (C_{ipso}); 146.1 (C(2)); 138.2 (C(8a)); 130.7 (C(7)); 128.1 (C_m); 120.2 (C(3)); 124.6 (C(5)); 123.6 (C(4a)); 121.9 (C(6)); 117.2 (C(8)); 116.3 (C_p); 112.7 (C_o); 15.8 (Me–C(2)). HMBC Correlation (H/C): NH–C(3)/C(2), NH–C(3)/C(4), NH–C(3)/C_o, CH(5)/C(4), CH(5)/C(8a), CH(6)/C(4a), CH(7)/C(8a), CH(8)/C(4a), Me/C(2), Me/C(3). ESI-MS (pos. mode): 251 ($[M+H]^+$). Anal. calc. for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.12; found: C 76.03, H 5.59, N 10.94.

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