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# Synthesis, characterization and photophysical properties of novel 5,7-disubstituted-1,4-diazepine-2,3-dicarbonitriles

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ABSTRACT

Three 5,7-disubstituted-1,4-diazepine-2,3-dicarbonitriles with bulky 2-(3,5-dibromophenyl)ethenyl, 2-(4-*tert*-butylphenyl)ethenyl and 2-(3,5-dibenzyloxyphenyl)ethenyl substituents were synthesized and characterized using UV–Vis, MS ES, elemental analysis and NMR spectroscopy. NMR data indicated that diazepine rings of all obtained compounds adopted 6*H*-tautomeric form. In addition, *trans*-isomerism within styryl substituents was observed. Experimental data for diazepine derivative containing 2-(4-*tert*-butylphenyl)ethenyl substituents were verified by X-ray crystallography. The obtained compounds were subjected to photophysical studies. In the UV–Vis absorption spectra two characteristic bands were found. In the solvatochromic study, the first band maxima were located in the range of 384–418 nm, whereas second band maxima in the range of 313–345 nm. Fluorescence intensity of novel diazepine derivatives was rather low in all solvents used with the values of fluorescence quantum yield $\Phi_F = 10^{-4}$ for 2-(3,5-dibromophenyl)ethenyl, and $10^{-5}$ for 2-(4-*tert*-butylphenyl)ethenyl and 3,5-(dibenzyloxyphenyl)ethenyl 1,4-diazepine-2,3-dicarbonitriles.



## 1. Introduction

There has been growing interest in compounds whose key structural feature is the diazepine ring. Diazepines constitute the basic system of many pharmacologically active substances and the importance of their applications in medicinal chemistry cannot be overestimated [1–3]. Noteworthy, 1,4-diazepine ring annulated with benzene is a part of various drug molecules. 1,4-Benzodiazepine derivatives possess anxiolytic and sedative properties and are used in the treatment of insomnia, epilepsy, and to relieve the symptoms of withdrawal in alcoholism [4]. Moreover, in recent years they have been tested in the direction of anticonvulsant [5], antitumoral [6], antimicrobial, antiviral, antischistosomal and antioxidant activities [7–9].

The chemistry of diaminomaleonitrile and its utilisation in the synthesis of heterocyclic compounds, including azepines was reviewed by Al-Azmi et al. [10]. The research of 1,4-diazepine-2,3-dicarbonitrile derivatives was initiated by Begland et al. [11,12] and Ohtsuka [13]. Further methodology was developed by Horiguchi et al. [14–17]. These studies led to various important insights into the synthesis of new fluorescent dyes by condensation of 1,4-diazepine-2,3-dicarbonitrile derivatives with aromatic aldehydes. It is noteworthy that the final product equipped at its 5,6,7-positions with different substituents exhibited specific absorption and emission properties with the maxima in the ranges of 450–550 nm and 500–600 nm, respectively. Extensive systems of conjugated, unsaturated bonds present in some of 5,7-distyryl substituted 1,4-diazepine-2,3-dicarbonitriles resulted in interesting optical properties [14,16]. Lately presented reactions of 2,3-diaminomaleonitrile with various ketones led to large libraries of 1,4-diazepine-2,3-dicarbonitrile derivatives of potential value as synthetic fragments with unique properties in medicinal chemistry [18,19].

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Broad studies concerning the applications of 1,4-diazepine-2,3-dicarbonitrile derivatives in porphyrazine synthesis were performed by Ercolani and Stuzhin and their coworkers. They reported the synthesis of 5,7-diphenyl- and 5,7-di(4-*tert*-butylphenyl)-2,3-dicyano-6*H*-1,4-diazepines and studied their utility in macrocyclization reactions in the direction of different symmetrical porphyrazines and tribenzoporphyrazines with annulated diazepine rings [20–24]. For the continuation of this study, various 1,4-diazepine-2,3-dicarbonitrile derivatives of potential applications as intermediates in the macrocyclization reactions were developed, including (*i*) tetrahydrodiazepines [25,26], and (*ii*) styryldiazepines [26–29]. Moreover, some of the lately obtained 5,7-bis(2′-arylethenyl)-6*H*-1,4-diazepine-2,3-dicarbonitriles, including derivatives substituted with propyl at C6 position, have demonstrated interesting conformational and physico-chemical properties [30].

Novel 1,4-diazepine derivatives can be considered as both (*i*) compounds of potential value for medicinal and materials chemistry and/or (*ii*) intermediates in azaporphyrin synthesis, thus leading to novel valuable macrocycles for medicine and technology. Herein, we are presenting our research on the synthesis of 1,4-diazepine-2,3-dicarbonitriles with bulky substituents at 5,7-positions and their characterization using UV–Vis, MS ES, elemental analysis and NMR spectroscopy. The discussion of spectroscopic properties evaluating the influence of bulky substitution in 5,7-positions of 1,4-diazepine-2,3-dicarbonitriles with 2-(3,5-dibromophenyl)ethenyl, 2-(4-*tert*-butylphenyl) ethenyl and 2-(3,5-dibenzyloxyphenyl)ethenyl is presented.

## 2. Experimental

### 2.1. Materials and instruments

All reactions were conducted in oven dried glassware under argon. Solvents and all reagents were obtained from commercial suppliers and used without further purification. All solvents were removed by rotary evaporation at or below 50 °C. Reaction temperatures reported refer to external bath temperatures. Dry flash column chromatography was carried out on Merck silica gel 60, particle size 40–63 μm. Thin layer chromatography (TLC) was performed on silica gel Merck Kieselgel 60 $F_{254}$ plates and visualized with UV ($\lambda_{max}$ 254 or 365 nm). Melting points were obtained on a "Stuart" Bibby apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were acquired at 298 K on Agilent DD2 800 spectrometer. Chemical shifts ($\delta$) are quoted in parts per million (ppm) and are referred to a DMSO-$d_6$ solvent peak (2.50 ppm for $^1$H, 39.5 ppm for $^{13}$C). Coupling constants ($J$) are quoted in Hertz (Hz). The abbreviations s, d, t, Ar, ax, eq refer to respectively singlet, doublet, triplet, aromatic, axial and equatorial. $^1$H and $^{13}$C signals were unambiguously assigned based on $^1$H–$^1$H COSY, $^1$H–$^{13}$C HSQC and $^1$H–$^{13}$C HMBC experiments. Mass spectra (MS ES, HRMS ES) and combustion analyses were carried out by the Advanced Chemical Equipment and Instrumentation Facility at the Faculty of Chemistry and the Wielkopolska Centre for Advanced Technologies at Adam Mickiewicz University in Poznan, and at the European Centre of Bioinformatics and Genomics in Poznan.

### 2.2. Synthesis

#### 2.2.1. 5,7-Bis[(E)-2-(3,5-dibromophenyl)ethenyl]-6H-1,4-diazepine-2,3-dicarbonitrile (**7**)

Diazepine derivative **3** (0.86 g, 5.0 mmol), 3,5-dibromobenzaldehyde **4** (2.60 g, 10.0 mmol), piperidine (5 drops) and benzene (30 mL) were refluxed for 8 h. After the solvent had been evaporated, the dry residue was chromatographed in dichloromethane to give yellow solid **7** (0.76 g, 23% yield). M.p. 288 °C dec. $R_f$ (dichloromethane) 0.43. UV–Vis (dichloromethane): $\lambda_{max}$, nm (log $\varepsilon$) 322 (5.02), 390 (4.66). $^1$H NMR (799.926 MHz, DMSO-$d_6$): $\delta_H$, ppm 8.05 (d, 4H, $^4J$ = 2 Hz, C2′, C6′, ArH), 7.92 (d, 2H, $^3J$ = 16 Hz, C5(7)–CH=CH), 7.89 (t, 2H, $^4J$ = 2 Hz, C4′, ArH), 7.29 (d, 2H, $^3J$ = 16 Hz, C5(7)–CH=CH), 5.17 (s, 1H, N=C-CH$^{eq}$), 2.08 (s, 1H, N=C-CH$^{ax}$). $^{13}$C NMR (201.162 MHz, DMSO-$d_6$): $\delta_C$, ppm 150.7 (C=N), 141.5 (C5(7)–CH=CH), 138.7 (C1′, ArC), 135.0 (C4′, ArC), 130.0 (C2′, C6′, ArC), 127.2 (C5(7)–CH=CH), 123.2 (C3′, C5′, ArC), 123.0 (C≡N), 115.6 (C–C≡N), 40.0 (C6). MS (ES pos) *m/z* 665 [M+H]$^+$, 687 [M+Na]$^+$, 703 [M+K]$^+$. MS (ES neg) *m/z* 663 [M–H]$^-$, 700 [M+Cl]$^-$. Anal. calcd for $C_{23}H_{12}Br_4N_4$: C, 41.60; H, 1.82; N, 8.44. Found: C, 41.49; H, 1.92; N, 8.05.

#### 2.2.2. 5,7-Bis[(E)-2-(4-tert-butylphenyl)ethenyl]-6H-1,4-diazepine-2,3-dicarbonitrile (**8**)

Diazepine derivative **3** (0.86 g, 5.0 mmol), 4-*tert*-butylbenzaldehyde **5** (1.7 mL, 10.0 mmol), piperidine (5 drops) and benzene (30 mL) were refluxed for 15 h. After the solvent had been evaporated, the dry residue was chromatographed (dichloromethane:methanol, 100:1 to 20:1) to give yellow solid **8** (1.40 g, 59% yield). M.p. 258 °C dec. $R_f$ (dichloromethane) 0.43. UV–Vis (dichloromethane): $\lambda_{max}$, nm (log $\varepsilon$) 339 (4.89), 413 (4.46). $^1$H NMR (799.926 MHz, DMSO-$d_6$): $\delta_H$, ppm 8.09 (d, 2H, $^3J$ = 16 Hz, C5(7)–CH=CH), 7.69 (d, 4H, $^3J$ = 8 Hz, C2′, C6′, ArH), 7.43 (d, 4H, $^3J$ = 8 Hz, C3′, C5′, ArH), 7.08 (d, 2H, $^3J$ = 16 Hz, C5(7)–CH=CH), 5.42 (s, 1H, N=C-CH$^{eq}$), 2.06 (s, 1H, N=C-CH$^{ax}$), 1.24 (s, 18H, 2 × C(CH$_3$)). $^{13}$C NMR (201.162 MHz, DMSO-$d_6$): $\delta_C$, ppm 154.0 (C4′, ArC), 152.0 (C=N), 144.7 (C5(7)–CH=CH), 132.1 (C1′, ArC), 128.3 (C2′, C6′, ArC), 125.9 (C3′, C5′, ArC), 123.7 (C5(7)–CH=CH), 122.6 (C≡N), 115.9 (C–C≡N), 37.9 (C6), 34.6 (C(CH$_3$)$_3$), 30.8 (CH$_3$). MS (ES pos) *m/z* 461 [M+H]$^+$, 483 [M+Na]$^+$. MS (ES neg) *m/z* 459 [M–H]$^-$, 496 [M+Cl]$^-$. HRMS (ES) *m/z* [M+H]$^+$ 461.2714, calcd for $C_{31}H_{33}N_4$ 461.2705. Anal. calcd for $C_{31}H_{32}N_4$: C, 80.83; H, 7.00; N, 12.16. Found: C, 80.24; H, 6.92; N, 12.39.

#### 2.2.3. 5,7-Bis[(E)-2-(3,5-dibenzyloxyphenyl)ethenyl]-6H-1,4-diazepine-2,3-dicarbonitrile (**9**)

Diazepine derivative **3** (0.054 g, 0.31 mmol), 3,5-dibenzyloxybenzaldehyde **6** (0.25 g, 0.78 mmol), piperidine (4 drops) and benzene (10 mL) were refluxed for 24 h. After the solvent had been evaporated, the dry residue was chromatographed (dichloromethane:*n*-hexane, 1:1 to 5:1). Crystallization from *n*-hexane – dichloromethane (1:1) led to a yellow solid **9** (0.059 g, 24% yield). M.p. 140 °C dec. $R_f$ (dichloromethane) 0.65. UV–Vis (dichloromethane): $\lambda_{max}$, nm (log $\varepsilon$) 319 (4.82), 396 (4.63). $^1$H NMR (799.926 MHz, DMSO-$d_6$); $\delta_H$, ppm 8.02 (d, 2H, $^3J$ = 16 Hz, C5(7)–CH=CH), 7.38 (d, 8H, $^3J$ = 7 Hz, C2″, C6″, ArH), 7.34 (t, 8H, $^3J$ = 7 Hz, C3″, C5″, ArH), 7.30 (t, 4H, $^3J$ = 7 Hz, C4″, ArH), 7.20 (d, 2H, $^3J$ = 16 Hz, C5(7)–CH=CH), 7.12 (d, 4H, $^4J$ = 2 Hz, C2′, C6′, ArH), 6.74 (t, 2H, $^4J$ = 2 Hz, C4′, ArH), 5.34 (s, 1H, N=C–CH$^{eq}$), 5.09 (s, 8H, OCH$_2$), 2.07 (s, 1H, N=C–CH$^{ax}$). $^{13}$C NMR (201.162 MHz, DMSO-$d_6$): $\delta_C$, ppm 159.8 (C3′, C5′, ArC), 151.5 (C=N), 144.7 (C5(7)–CH=CH), 136.6 (C1″, ArC), 136.7 (C1′, ArC), 128.4 (C3″, C5″, ArC), 127.8 (C4″, ArC), 127.6 (C2″, C6″, ArC), 125.0 (C5(7)–CH=CH), 122.6 (C≡N), 115.8 (C–C≡N), 107.4 (C2′, C6′, ArC), 104.9 (C4′, ArC), 69.4 (OCH$_2$), 38.1 (C6). MS (ES pos) *m/z* 773 [M+H]$^+$, 795 [M+Na]$^+$. HRMS (ES) *m/z* [M+H]$^+$ 773.3101, calcd for $C_{51}H_{41}N_4O_4$ 773.3128. Anal. calcd for $C_{51}H_{40}N_4O_4$: C, 79.25; H, 5.22; N, 7.25. Found: C, 78.79; H, 5.16; N, 7.43.

### 2.3. Crystallography

Single crystals of **8** were grown from *n*-hexane - dichloromethane (1:1) solution. Diffraction data were collected at 130 K with a SuperNova diffractometer (Cu$K_\alpha$) and processed using the