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Synthesis and first characterization of *N*-alkyldiaminoresorcinols

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Abstract—We report the synthesis and first characterization of *N*-alkyldiaminoresorcinols (or 4,6-bis-dialkylaminobenzene-1,3-diols $C_6H_2(NHR)_2(OH)_2$) (**10a**, R = CH_2-2-Py; **10b**, R = CH_2-3-Py; **10c**, R = CH_2-4-Py) which result from one-pot stepwise reactions: (i) air–oxidation of diaminoresorcinol **3**, (ii) transamination reaction leading to the corresponding functional 6π+6π quinonemonoimine zwitterions $C_6H_2(\dddot{}NHR)_2(\dddot{}O)_2$ (**9a**, R = CH_2-2-Py; **9b**, R = CH_2-3-Py; **9c**, R = CH_2-4-Py), (iii) reduction and re-aromatization in the presence of the corresponding primary amine bearing a pyridine moiety.
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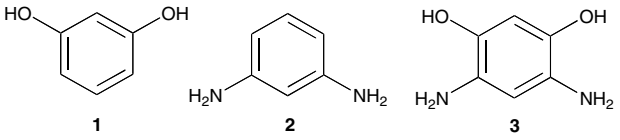
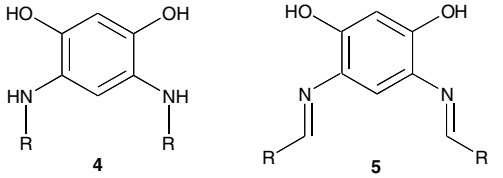
Introduction of substituent(s) on the benzene ring[1,2] has led to hundreds of compounds showing dramatic changes of their properties depending on the nature of the substituent(s).[3] Amino and/or hydroxy benzene derivatives have attracted considerable interest in organic,[3] colour (cosmetic),[4] inorganic[5] and supramolecular chemistry[6,7] owing to the ability of the NH_2 and/or OH groups to act as nucleophiles, coordinating moieties or H-donor sites. Resorcinol **1** and 1,3-diaminobenzene **2** have been the object of 21,416 and 12,999 references (Scifinder source, June 2006), respectively. Therefore, it is surprising that the aromatic system **3**, which combines the structural elements of **1** and **2** and is commercially available, has been much less explored (635 references), although the substitution pattern of its amino and hydroxy groups would allow bis-*ortho*-condensation reactions by analogy with those involving 1,2,4,5-tetraaminobenzene,[8–15] metal complexation (bis-chelation),[16,17] or supramolecular interactions[18,19] by analogy with other N_2O_2 donor systems.

N-substituted diaminoresorcinol derivatives **4** are very few, compared to the diiminoresorcinol analogs **5** which



1 **2** **3**

are much more stable and used as Schiff bases in coordination chemistry.[20,21]



4 **5**

To the best of our knowledge, only seven molecules of type **4** have been described in the literature: compound **6**[22] for which R is a triazine group and six compounds of type **7** for which R^1 = aryl,[23,24] alkyl,[25,26] carbonyl[11] or –NHTs (Ts = tosyl) groups.[27]

Although molecules of type **4** with *N*-alkyl substituent have been proposed as reactive intermediates in different reactions,[19,28] none of them has been isolated and structurally characterized owing to their high instability. A fine-tuning of the N-substituent R could be attractive for applications in organic, organometallic and/or

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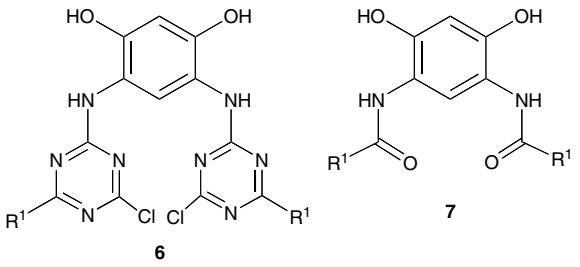
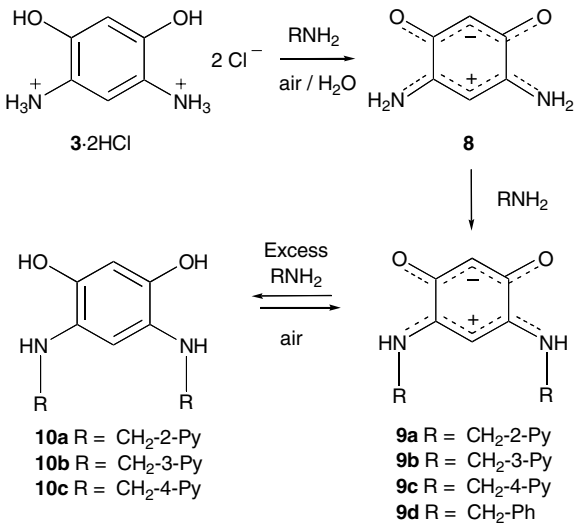


supramolecular chemistry, in particular because the reactivity of the N–H groups (i.e., their basicity and/or nucleophilic character) would be strongly modified by the presence of a more electron-donating moiety.

Herein, we report the high yield synthesis and first isolation of *N*-alkyl diaminoresorcinol derivatives—or 4,6-bisdialkylaminobenzene-1,3-diols $C_6H_2(NHR)_2(OH)_2$ (**10a**, R = CH_2-2-Py; **10b**, R = CH_2-3-Py; **10c**, R = CH_2-4-Py)—from the parent diaminoresorcinol $C_6H_2(NH_2)_2(OH)_2$ (**3**) via 6π+6π zwitterionic intermediates.

The easy access to a family of functional 6π+6π quinonemonoimine zwitterions of the type $C_6H_2(\dddot{=}NHR)_2(\dddot{=}O)_2$ (**9**) has recently become possible by a transamination reaction of the parent molecule $C_6H_2(\dddot{=}NH_2)_2(\dddot{=}O)_2$ (**8**), the oxidized form of **3**, with primary amines.[29,30] In the course of these studies, we realized that primary amines bearing a pyridine moiety behaved differently. When an excess of 2-, 3-, or 4-picolylamine was added in air to an aqueous solution of **3**·2HCl, the formation of purple intermediates was observed, consistent with the expected zwitterions **9a**–**c**, respectively, the amine acting simultaneously as a base (deprotonation of the salt) and a nucleophile (Scheme 1).

However, after a few minutes, we observed the formation of grey green precipitates which were almost insoluble in all solvents. These new compounds were then



Scheme 1. Synthesis of **9a**–**c** and **10a**–**c**.

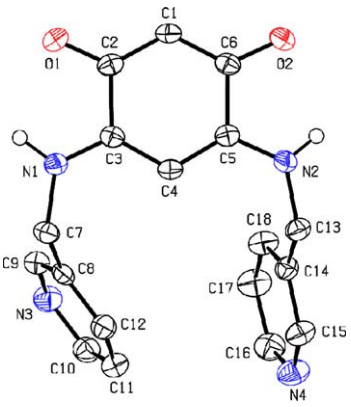


Figure 1. ORTEP view of the crystal structure of the zwitterionic compound **9b** in **9b**·4H_2O. Displacement parameters include 50% of the electron density. Selected bond distances (Å) and angles (°): O(1)–C(2) = 1.259(2), C(2)–C(1) = 1.390(3), C(1)–C(6) = 1.392(2), C(6)–O(2) = 1.257(2), N(1)–C(3) = 1.313(2), C(3)–C(4) = 1.390(2), C(4)–C(5) = 1.384(3), C(5)–N(2) = 1.321(2), C(2)–C(3) = 1.526(2), C(6)–C(5) = 1.521(2); O(1)–C(2)–C(1) = 125.83(15), O(1)–C(2)–C(3) = 116.25(17), N(1)–C(3)–C(4) = 124.25(16), N(1)–C(3)–C(2) = 114.83(15).

identified as **10a**–**c**.[31] The purple intermediates **9a**–**c** could be isolated independently and fully characterized,[32] including by X-ray diffraction analysis of molecule **9b**·4H_2O (Fig. 1).[33] Examination of the bond distances within the N(1)–C(3)–C(4)–C(5)–N(2) and O(1)–C(2)–C(1)–C(6)–O(2) moieties shows an equalization of the C–C, C–O and C–N distances which is consistent with a complete electronic delocalization of the π system.

There is no conjugation between these two moieties since the C(2)–C(3) and C(6)–C(5) distances of 1.526(2) and 1.521(2) Å, respectively, correspond to typical single bonds.[19] This bonding situation is similar to that encountered in other, related 6π+6π zwitterions.[19,29,30] Compounds **9a** and **9b** are soluble in MeOH, CH_2Cl_2, DMSO and slightly soluble in acetone and H_2O and give purple solutions whereas **9c** is only soluble in CH_2Cl_2, acetone or DMSO. In contrast, only **10a** could be characterized in solution owing to its slight solubility in DMSO and relative stability compared to **10b** and **10c**. The formation of **10c**, the most unstable in the series, was indicated by the colour and solubility changes. The difference of solubility between **10a**–**c** may be due to the strength of the H-bonding interactions in the solid state depending on the position of the pyridyl nitrogen. The ^{1}H NMR spectrum of **10a** revealed the presence of two –OH ($\delta = 8.30$) and two –NH ($\delta = 8.50$) groups, and of two signals at δ 5.85 and 6.31 that would suggest its aromatic character (compared with $\delta = 5.04$ and 5.62 for the potentially antiaromatic system **9a**).[19b] This was further confirmed by X-ray diffraction on a single crystal obtained from the reaction mixture kept under nitrogen (Fig. 2).[33] The C–C distances within the C_6 ring are in the range 1.383(4)–1.392(4) Å, which reveals their equalization compared to the situation in **8**·H_2O where they range from 1.382(3) to 1.520(3) Å.[29] Together with the presence of a hydrogen atom on each oxygen, this is consistent with a re-aromatization of the system.

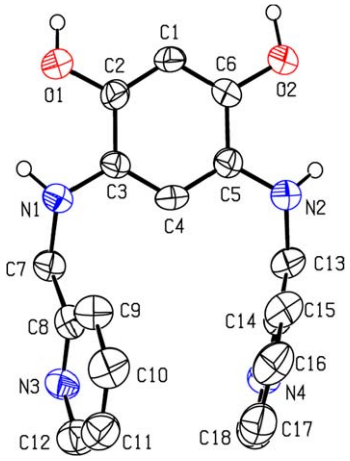
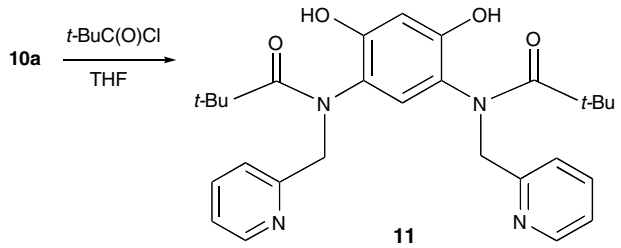


Figure 2. ORTEP view of the crystal structure of the aromatic compound **10a**. Displacement parameters include 50% of the electron density. Selected bond distances (Å) and angles (°): O(1)–C(2) = 1.378(3), C(2)–C(1) = 1.383(4), C(1)–C(6) = 1.384(4), C(6)–O(2) = 1.386(3), N(1)–C(3) = 1.405(4), C(3)–C(4) = 1.392(4), C(4)–C(5) = 1.391(4), C(5)-N(2) = 1.404(4), C(2)–C(3) = 1.386(4), C(6)–C(5) = 1.388(4); O(1)–C(2)–C(1) = 123.4(3), O(1)–C(2)–C(3) = 116.7(3), N(1)–C(3)–C(4) = 123.2(3), N(1)–C(3)–C(2) = 117.9(3).

Since quinonoid compounds form a long-known class of redox-active molecules owing to their strong electron acceptor ability,[34] one could envisage that formation of **10a–c** resulted from the reduction of **9a–c** by the excess of *n*-picolylamine ($n = 2$, 3 or 4) needed to achieve initial transamination. Although the synthesis of molecules **10** was performed in water, electrochemical studies could not be carried out in this medium owing to the insolubility of the zwitterionic precursors **9** and of the final aromatic products. The electrochemical properties of **9b** and 3-picolylamine have therefore been studied by cyclic voltammetry in anhydrous CH_2Cl_2 containing $N(n\text{-}Bu)_4PF_6$ as supporting electrolyte (scan rate of 250 mV s^{-1}). The cyclic voltammogram (CV) of **9b** showed two monoelectronic reversible waves at very low reduction potential (i.e., −1.234 V and −1.833 V vs Fc^+/Fc) indicating that **9b** is also difficult to reduce. The CV of pure 3-picolylamine shows only an irreversible wave at 1.081 V versus Fc^+/Fc indicating its high oxidation potential. These values obtained in CH_2Cl_2 suggest that formation of **10b** cannot result from a redox reaction between **9b** and 3-picolylamine. Interestingly, the use of benzylamine instead of picolylamines only led to the formation of zwitterion **9d**[29] (i.e., no re-aromatization was observed), which indicates the key role played by the pyridine moiety, probably as a base. Water is likely to have a significant effect on the redox potential of the compounds involved (presence of Lewis basic function) so that the formation of molecules **10** in aqueous solution may thus involve other intermediate species which would form only in the presence of picolylamines.

When the grey/green precipitates of **10a–c** are dried in air, their colour turns to purple. This indicates their easy oxidation in the solid state to form compounds **9a–c**, as observed in solution for the parent diaminoresorcinol **3**.[30,35,36] In order to demonstrate the potential of the *N*-alkyl diaminoresorcinols in organic chemistry, we have used **10a** as precursor for the preparation of a new N_4O_4-type ligand, molecule **11**, which was obtained as a white powder by reaction of a suspension of **10a** in dry THF with 2 equiv of *t*-BuC(O)Cl (Scheme 2).[37]



Scheme 2. Synthesis of **11**.

In conclusion, we have described the synthesis and first characterization of *N*-alkyl diaminoresorcinols, **10a–c**, by using a one-pot stepwise preparation: (i) oxidation of diaminoresorcinol **3**, (ii) transamination reaction leading to the corresponding functional quinonemonoimine zwitterions **9a–c**, (iii) reduction and re-aromatization in the presence of primary amines bearing a pyridine moiety. Molecules **9b** and **10a** have been fully characterized, including by X-ray diffraction analysis. The use of compounds **10** (N_4O_2 donor set) as well as that of the acylated derivative **11** (N_4O_4 donor set) in coordination chemistry is under investigation.

Acknowledgements

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31. *Typical procedure for the synthesis of compounds* **10**: An excess of picolylamine (2.033 g, 18.8 mmol) was added to an aqueous solution of **3**·2HCl (0.500 g, 2.35 mmol) and the mixture allowed to stand for 2–3 h. The green precipitate was isolated by filtration, washed with cold water, then with acetone and dried in vacuo.
Compound **10a**: Yield: 86%. MS (MALDI-TOF$^+$): *m*/*z* 323.1 $[M+1]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 4.21$ (d, $^3J = 6.0$ Hz, 4H, NHCH_2), 4.81 (t, $^3J = 6.0$ Hz, 2H, N*H*CH$_2$), 5.85 (s, 1H, NHCC*H*), 6.31 (s, 1H, OCCH), 7.24 (m. 4H, NCHC*H* and NCC*H*), 7.68 (td, $^3J = 7.7$ Hz, $^4J = 1.8$ Hz, 2H, NCHCHC*H*), 8.30 (br s, 2H, OH), 8.50 (br d, $^3J = 4.8$ Hz, 2H, NCH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 50.07$ (s, CH_2), 98.12 (s, NHCC*H*), 104.34 (s, HOC*C*H), 121.86 (s, NCH*C*H), 122.30 (s, NC*C*H), 130.21 (s, NCHCH*C*H), 135.34 (s, NCH), 136.87 (s, NC), 149.16 (s, NHC), 172.38 (s, HOC). Despite several attempts, no satisfactory elemental analysis could be obtained owing to the sensitivity of **10a**.
Compound **10b**: Yield: ≈78% (calculated immediately after its isolation because of its high unstability). MS (MALDI-TOF$^+$): *m*/*z*: 323.2 $[M+1]^+$. Despite several attempts, no satisfactory elemental analysis could be obtained owing to the sensitivity of **10b**.
32. *Typical procedure for the synthesis of zwitterions* **9**: An excess of picolylamine (1.730 g, 16.0 mmol) was added to an aqueous solution of **3**·2HCl (0.426 g, 2.00 mmol) and the mixture was allowed to stand for 2–3 h. The green precipitate was isolated by filtration, washed with cold water and slowly dried in air to afford a purple powder.
Compound **9a**: Yield: 70%. MS (MALDI-TOF$^-$): *m*/*z*: 319.1 $[M-1]^-$, 228.1 $[M-1-CH_2Py]^-$; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 4.73$ (s, 4H, CH_2), 5.04 (s, 1H, N⋯C⋯CH), 5.62 (s, 1H, O⋯C⋯CH), 7.30 (m, 4H, NCHC*H* and NCC*H*), 7.78 (td, $^3J = 7.7$ Hz, $^4J = 1.8$ Hz, 2H, NCHCHC*H*), 8.51 (ddd, $^3J = 4.8$ Hz, $^4J = 1.8$ Hz, $^5J = 0.9$ Hz, 2H, NCH), 9.53 (br s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 47.72$ (s, CH_2), 83.71 (s, N⋯C⋯*C*), 98.00 (s, O⋯C⋯*C*), 122.16 (s, NCH*C*H), 123.22 (s, NC*C*H), 137.58 (s, NCHCH*C*H), 149.53 (s, NCH), 155.48 (s, NC), 157.17 (s, N⋯C), 172.38 (s, O⋯C). Anal. Calcd for $C_{18}H_{16}N_4O_2{\cdot}4H_2O$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.43; H, 5.61; N, 15.23.
Compound **9b**: Yield: 73%. MS (MALDI-TOF$^-$): *m*/*z*: 319.1 $[M-1]^-$, 228.1 $[M-1-CH_2Py]^-$; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 4.69$ (s, 4H, CH_2), 5.00 (s, 1H, N⋯C⋯CH), 5.72 (s, 1H, O⋯C⋯CH), 7.31 (ddd, $^3J = 7.8$ Hz, $^3J = 4.8$ Hz, $^5J = 0.66$ Hz, 2H, NCHC*H*), 7.64 (dt, $^3J = 7.8$ Hz, $^4J = 1.8$ Hz, 2H, NCHCHC*H*), 8.49 (dd, $^3J = 4.8$ Hz, $^4J = 1.8$ Hz, 2H, NC*H*CH), 8.54 (d, $^4J = 1.8$ Hz, 2H, NC*H*C), 9.63 (br, 2H, NH); ^{13}C NMR(75 MHz, DMSO-d_6) $\delta = 43.75$ (s, CH_2), 82.95 (s, N⋯C⋯*C*), 98.19 (s, O⋯C⋯*C*), 124.09 (s, NCH*C*H), 132.76 (s, NCH*C*), 135.71 (s, NCHCH*C*H), 149.19 (s, N*C*HCH), 149.48 (s, N*C*HC), 157.12 (s, N⋯C), 172.32 (s, O⋯C). Anal. Calcd for $C_{18}H_{16}N_4O_2{\cdot}4H_2O$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.73; H, 6.05; N, 14.61.
Compound **9c**: Yield: 76%. Ms (MALDI-TOF$^+$): *m*/*z*: 321.1 $[M+1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 4.64$ (s, 4H, CH_2), 5.02 (s, 1H, N⋯C⋯CH), 5.50 (s, 1H, O⋯C⋯CH), 7.18 (d, $^3J = 5.6$ Hz, 4H, NCHC*H*), 8.45 (d, $^3J = 5.6$ Hz, 4H, NCH), 9.78 (br s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 45.08$ (s, CH_2), 83.51 (s, N⋯C⋯*C*), 98.21 (s, O⋯C⋯*C*), 122.72 (s, NCH*C*H), 145.73 (s, NCHCH*C*H), 150.20 (s, NCH), 157.56 (s, N⋯C), 172.26 (s, O⋯C). Anal. Calcd for $C_{18}H_{16}N_4O_2{\cdot}H_2O$: C, 63.89; H, 5.36; N, 16.56. Found: C, 64.05; H, 5.18; N, 16.87.
33. *Crystal data* for **9b**·4H$_2$O: triclinic, space group $P\bar{1}$ with $a = 9.577(5)$, $b = 10.207(5)$, $c = 10.644(5)$, $\alpha = 96.663(5)$, $\beta = 97.473(5)$, $\gamma = 109.794(5)$ at 173(2) K with $Z = 2$. Refinement of 12,090 reflections (2964 reflections with $I > 2\sigma(I)$), $R = 0.0577$, $Rw = 0.1418$, GOF = 0.948.
For **10a**: orthorhombic, space group *Pbcn* with $a = 13.4520(10)$, $b = 15.3120(10)$, $c = 15.3470(10)$, $\alpha = \beta = \gamma = 90.00$ at 293(2) K with $Z = 8$. Refinement of 6804 reflections (3636 reflections with $I > 2\sigma(I)$), $R = 0.0676$, $Rw = 0.620$, GOF = 0.913. Crystallographic data for the structures **9b**·4H$_2$O and **10a** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 283397 and 283398, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +40 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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37. *Synthesis of* **11**: To a suspension of **10a** (0.466 g, 1.45 mmol) in dry THF (80 mL) was added an excess of NEt_3 (1.0 mL) and then 2 equiv $CH_3C(O)Cl$ (0.349 g, 2.90 mmol). The mixture was stirred at room temperature for 24 h. After removal of $HNEt_3Cl$ by filtration and evaporation of the filtrate to 5 mL, pentane was added to precipitate **11** which was isolated by filtration. Yield: 0.433 g, 61%. MS (MALDI-TOF$^+$): *m*/*z* 491.3 $[M+1]^+$. ^{1}H

NMR (300 MHz, $CDCl_3$) $\delta = 1.04$ (s, 18H, CH_3), 3.97 (d, $^2J = 15.0$ Hz, 2H, CH_aH_b), 5.37 (d, $^2J = 15.0$ Hz, 2H, CH_aH_b), 6.65 (s, 1H, NHCC*H*), 6.99 (s, 1H, OCC*H*), 7.27 (s, overlap with solvent peak, 2H, NCHC*H*), 7.40 (d, $^3J = 7.8$ Hz, 2H, NCCH), 7.77 (td, $^3J = 7.7$ Hz, $^4J = 1.7$ Hz, 2H, NCHCHC*H*), 8.50 (br d, $^3J = 4.7$ Hz, 2H, NCH); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 28.67$ (s, CH_3), 40.55 (s, $C(CH_3)_3$), 59.60 (s, CH_2), 107.00 (s, NC*C*H), 122.68 (s), 122.98 (s), 123.66 (s), 138.28 (s), 147.16 (s), 156.87 (s), 157.43 (s), 178.47 (s, C=O). Anal. Calcd for $C_{28}H_{34}N_4O_4$: C, 68.55; H, 6.99; N, 11.42. Found: C, 68.47; H, 6.93; N, 11.59.