The First Example of Dienediamine Utilization in the Nenitzescu Reaction

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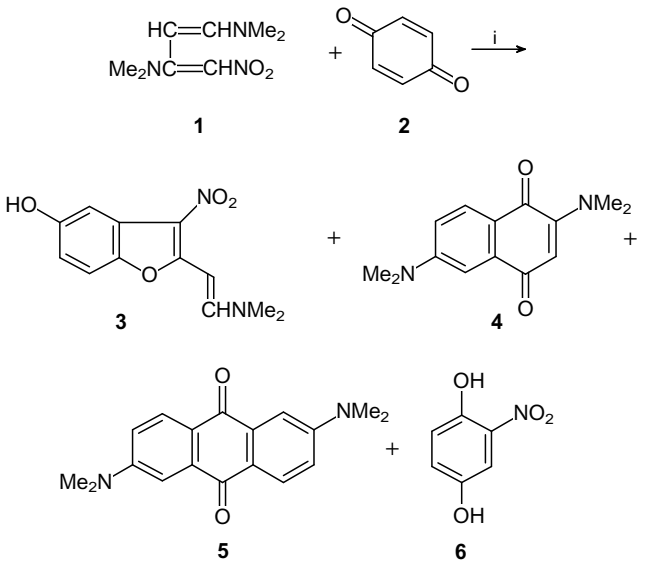
For the first time, a dienediamine – 2,4-bis(dimethylamino)-1-nitrobuta-1,3-diene – has been used in a reaction with benzoquinone to give 'Nenitzescu' product 2-(2-dimethylaminovinyl)-5-hydroxy-3-nitrobenzofuran together with 1,4-cycloaddition products 2,6-bis(dimethylamino)-1,4-naphthoquinone and 2,6-bis(dimethylamino)-5,10-anthraquinone.

Recently we carried out a new synthesis of a number of dienediamines.[1] This type of compound has not previously been used as the enamine component in the Nenitzescu reaction. The aim of the present investigation was to study the reaction of 2,4-bis(dimethylamino)-1-nitrobuta-1,3-diene **1** with benzoquinone **2** under different conditions. It turns out that the essential factor determining the direction of the process in this reaction (as in other examples of the Nenitzescu reaction[2–4]) is the choice of solvent. Interaction of **1** and **2** in acetic acid (in the presence of acetic anhydride or toluenesulfonic acid)[5,6] results in tar formation (as distinct from the reactions of nitroenamines and quinone[5,6]) and according to spectral data (NMR spectroscopy, mass spectrometry) and TLC only quinone from low molecular products is present in the reaction mixture. It can perhaps be assumed that the presence of an additional enamine fragment, removed from the nitro group, leads to the facile protonation of **2** and that the appearance of a positively charged substituent sharply reduces the ability of the dienediamine to be subject to electrophilic action by quinone. On the contrary, the condensation of **1** and **2** takes place in neutral solvents – dichloroethane, acetone, methanol, nitromethane – and the reaction proceeds in two directions (Scheme 1). The first is the common Nenitzescu reaction resulting in formation of 2-(2-dimethylaminovinyl)-5-hydroxy-3-nitrobenzofuran **3**,† yield 10%, m.p. 264 °C (decomp., dioxane), identical to the sample described previously by an alternative method.[7] The second direction is 1,4-cycloaddition‡ which leads to 2,6-bis(dimethylamino)-1,4-naphthoquinone **4**, yield 9%, m.p. 189–191 °C (ethyl acetate). In principle it is impossible to exclude the formation of the 2,7-isomer. However, ^{1}H NMR spectroscopy (and especially ^{13}C NMR spectroscopy) confirm precisely structure **4**: ^{1}H NMR ([$^2H_6$]Me_2SO) δ 3.08 (s, 3H, NMe), 3.16 (s, 3H, NMe), 5.62 (s, 1H, 3-CH), 6.87 (d, 1H, $J_{ortho} \sim 9$ Hz, 8-CH), 7.04 (d, 1H, $J_{meta} \sim 3$ Hz, 5-CH), 7.74 (dd, 1H, $J_{ortho} \sim 9$ Hz, $J_{meta} \sim 3$ Hz, 7-CH); ^{13}C NMR ([$^2H_6$]Me_2SO) δ 39.8, 40.4 Me_2, 105.0, 106.3, 113.6, 128.9 (C_3, C_5, C_7, C_8), 120.0 and 134.3 (C_{4a} and C_{8a}), 180.9 and 181.7 (1-CO and 4-CO). In non-decoupled ^{13}C NMR spectra the signals of C_{4a} and C_{8a} are triplets ($J_1 = J_2$ 6 Hz); MS m/z 244 (M^+). In the case of 2,7-isomer formation the multiplicity of C_{4a} and C_{8a} signals (^{13}C NMR in the same regime) should be different (doublet for C_{4a} and triplet for C_{8a}). Apart from **4**, 2,6-bis(dimethylamino)-5,10-anthraquinone **5** is isolated from the cycloaddition reaction, yield 8%, m.p. 298–300 °C (pyridine) (lit.,[9] 289 °C). NMR spectroscopy confirms the symmetrical structure of 5.§

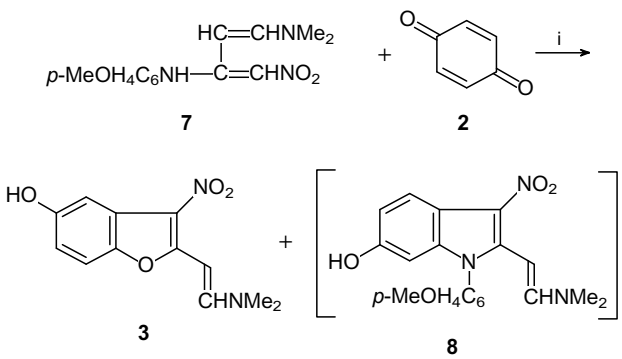
In addition to **4** and **5** the nitrohydroquinone **6** is isolated from the reaction mixture in ⩽1% yield, m.p. 132–133 °C, MS m/z 155 (M^+). The formation of the latter is caused by nitrous acid evolution in the preparation of either **4** or **5**. The



Scheme 1 *Reagents and conditions*: i, addition of a solution of **2** (2.16 g, 20 mmol) in dichloroethane (30 ml) at 80 °C to a solution of **1** (3.7 g, 20 mmol) in dichloroethane (45 ml) with stirring for 0.5 h then cooling to 20 °C.

HNO_2 formed interacts with quinone to form **5** and dimethylamine is able to add to both starting quinone **2** and the product of cycloaddition of one molecule of **1** to **2** yielding **4** as the final product.¶

In addition, reaction of quinone **2** with another dienediamine – 4-dimethylamino-2-(4-methoxyphenylamino)-1-nitrobuta-1,3-diene **7**[1] – has been studied (Scheme 2). The



Scheme 2 *Reagents and conditions:* i, addition of **7** (0.79 g, 3 mmol) to a solution of **2** (0.32 g, 3 mmol) in nitromethane (10 ml) with stirring (20 °C, 24 h).

reaction proceeds optimally in nitromethane (in comparison with the above solvents), the solvent wich promotes the synthesis of indole (not benzofuran) under Nenitzescu reaction conditions.[3,4,10] Nevertheless, interaction of **2** and **7**

† All new compounds gave the expected IR, ^{1}H NMR and mass spectra and satisfactory elemental analyses.

‡ It is known that 1,4-cycloaddition proceeds under the reaction of benzoquinone and dieneamines.[2,8]

§ *Spectroscopic data for* **5**: ^{1}H NMR ([$^2H_6$]Me_2SO) δ 3.12 (s, 12H, two NMe_2), 7.02 (dd, 2H, J_{ortho} 9 Hz, J_{meta} 3 Hz, 3,7-CH), 7.28 (d, 2H, J_{meta} 3 Hz, 1,6-CH), 7.98 (d, 2H, J_{ortho} 9 Hz, 4,9-CH); ^{13}C NMR: 107.5, 115.1, 129.0 (C_1, C_3, C_4, C_6, C_8, C_9), 121.1, 135.1 (C_{4a}, C_{5a}, C_{9a}, C_{10a}), 153.7 (C_2, C_7), 181.2 (CO). Signals due to the NMe_2 groups are masked by the solvent (δ 39.6); MS m/z 294 (M^+).

¶ Similar processes included a number of oxidation-reduction stages, which is typical of quinone and hydroquinone reactions and, in particular, for the Nenitzescu reaction.[2,3]

yields 5-hydroxybenzofuran derivative **3** in a satisfactory yield (48%). The compound with m/z 353 (M^+) can be identified by mass spectrometry, and is probably 2-(2-dimethylamino-vinyl)-6-hydroxy-3-nitroindole **8**. That compound **8** belongs to the 6-hydroxyindole series follows logically from our earlier investigations into the direction of nitroenamine reactions with quinones.[3,6]

The research described in this publication was made possible in part by grant no. M81000 from the International Science Foundation.

References

1 V. M. Lyubchanskaya, T. I. Mukhanova, E. K. Panisheva, L. M. Alekseeva and V. G. Granik, *Mendeleev Commun*., 1995, 24.
2 G. R. Allen, *Organic Reactions*, New York, Wiley Interscience, 1973, vol. 20, p. 337.
3 V. G. Granik, V. M. Lyubchanskaya and T. I. Mukhanova, *Khim.-Farm. Zh*., 1993, **6**, 37 [*Pharm. Chem. J. (Engl. Transl.)*, 1993, **6**, 413].
4 T. I. Mukhanova, L. M. Alekseeva, E. F. Kuleshova, Yu. N. Sheinker and V. G. Granik, *Khim.-Farm. Zh*., 1993, **2**, 60 [*Pharm. Chem. J. (Engl. Transl.)*, 1993, **2**, 136].
5 V. M. Lyubchanskaya and V. G. Granik, *Khim. Geterotsikl. Soedin*., 1990, **5**, 597 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1990, **5**, 503].
6 V. M. Lyubchanskaya, L. M. Alekseeva and V. G. Granik, *Khim. Geterotsikl. Soedin*., 1992, **1**, 40 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1992, **1**, 34].
7 V. M. Lyubchanskaya, G. A. Bogdanova, I. S. Nikolaeva, M. G. Iljina, A. N. Fomina and V. G. Granik, *Khim.-Farm. Zh*., 1990, **3**, 34 [*Pharm. Chem. J. (Engl. Transl.)*, 1990, **3**, 196].
8 W. Langenbeck, O. Goedde, L. Weschky and R. Schaller, *Chem. Ber.,* 1942, **75**, 232.
9 D. C.-R. Jones and F. A. Mason, *J. Chem. Soc*., 1934, 1813.
10 J. B. Patrick and E. K. Saunders, *Tetrahedron Lett*., 1979, **42**, 4009.

Received: Moscow, 24th October 1994
Cambridge, 7th December 1994; Com. 4/06649I