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LETTERS TO THE EDITOR

THE SYNTHESIS OF BENZO[*a*]PHENAZINE-5,6-DIONE 7-OXIDES

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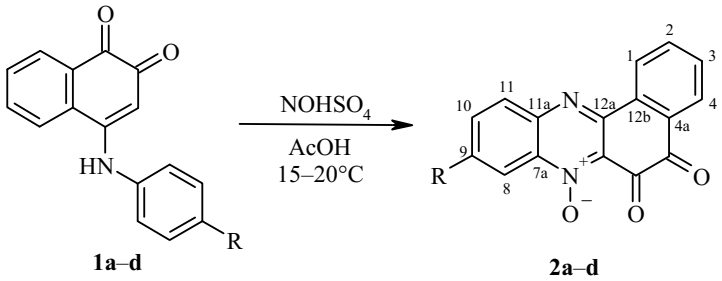
Tetracyclic nitrogen-containing quinone derivatives exhibit various types of biological activity and show promise for practical applications [1, 2]. Linear and angular quinoid derivatives of benzophenazines are of particular interest. Thus, it was recently discovered that benzo[*a*]phenazine-5,6-dione derivatives, diimines in particular, may function as ligands for rhodium and ruthenium, and also possess selective anticancer activity [3].

We found that the 4-arylamino-1,2-naphthoquinones **1a-d** were converted to the benzo[*a*]phenazine-5,6-dione *N*-oxides **2a-d** by treatment with nitrosylsulfuric acid that was prepared *in situ* from sodium nitrite and sulfuric acid [4], and using acetic acid as the solvent.



1a–d **2a–d**

1, **2 a** R = H, **b** R = Me, **c** R = Cl, **d** R = F

The arylaminonaphthoquinones **1a-d** were apparently cyclized to the phenazine *N*-oxides **2a-d** by a radical cation mechanism that could involve the formation of 4-arylamino-3-nitroso-1,2-naphthoquinones [5]. It is known that 2-nitrosodiarylamines cyclized to the corresponding phenazine *N*-oxides by the action of sodium nitrite in hydrochloric acid [6-7].

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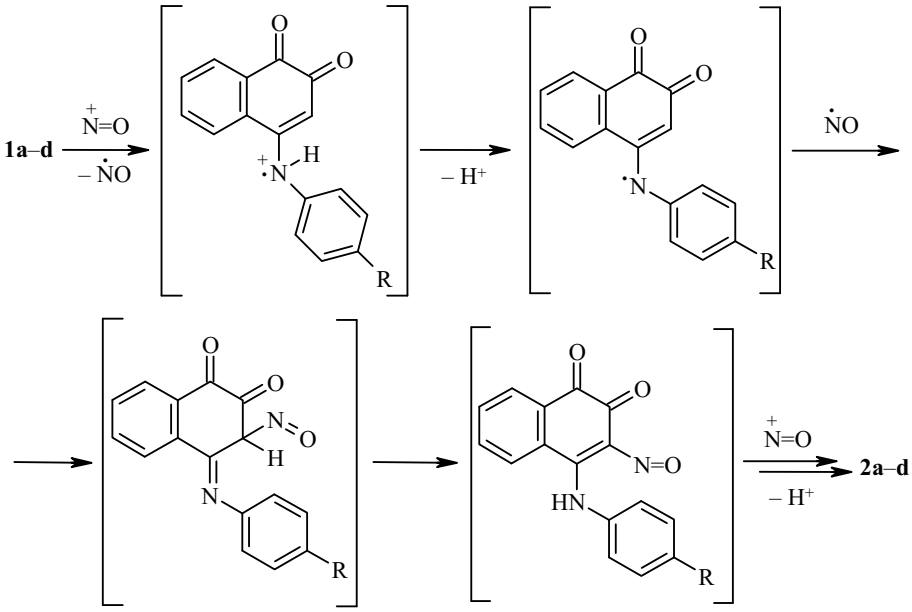
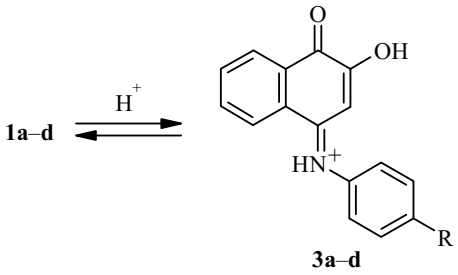
It should be noted that our discovered cyclization reaction gave high yields of the phenazine *N*-oxides **2a-d** only when a large excess of nitrosylsulfuric acid was used. This observation may indicate a multistage mechanism for the cyclization of nitrosonium cation. An additional evidence for a radical mechanism in the heterocyclization of compounds **1a-d** and **2a-d** was found in the approximately equal duration of these reactions.

It should be noted that only traces of compounds **2a-d** were found by TLC after maintaining the starting arylaminonaphthoquinones **1a-d** for many hours in 95% sulfuric acid with an excess of nitrosylsulfuric acid. Obviously, the arylaminonaphthoquinones **1a-d** were completely protonated under these conditions. Compounds



1a-d are known to be protonated at the carbonyl group [8], forming the immonium cations **3a-d**, which are incapable of reacting with nitrosonium cation by the radical mechanism.



The obtained benzo[*a*]phenazine-5,6-dione *N*-oxides **2a-d** were structurally characterized by physicochemical methods. There were intense IR absorption bands at 1356-1404 cm^{-1}, corresponding to the stretching vibrations of the *N*-oxide group, and the absorption bands were shifted to higher frequencies by the presence of electron-withdrawing groups in the molecule [9]. Characteristically, compounds **2a-d** showed intense mass spectral peaks at $[M-44]^+$. Apparently, these peaks could be explained by the elimination of nitrous oxide from the molecular ions. The ^1H and ^{13}C NMR spectral data for compounds **2a-d** (given in Experimental) were similar to the spectral data of polycyclic *o*-quinoid heterocycles [10].

Thus, we have developed a new, convenient synthetic approach to a new type of tetracyclic azine heterocycles incorporating quinoid structures. Presumably, the obtained series of benzo[*a*]phenazine-5,6-dione 7-oxides may be used for further chemical modification.

IR spectra were recorded on a Shimadzu IRAffinity-1 instrument in KBr pellets. UV spectra were recorded on a Thermo Scientific Evolution 300 instrument (10 mm cuvettes) in DMSO. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX spectrometer (500 and 125 MHz) in DMSO-d_6, with TMS as internal standard. Mass spectra were obtained on a Finnigan MAT 8200 instrument (EI, 70 eV). Elemental analysis was performed on a EURO EA 3000 instrument. Melting points were determined on a Boetius micro hot stage. The reaction progress and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates (eluent 10:1 toluene–acetone).

The starting 4-arylamino-1,2-naphthoquinones **1a-d** were obtained by a published method [11].

Benzo[*a*]phenazine-5,6-dione 7-Oxide (2a). Nitrosylsulfuric acid was prepared from sodium nitrite (1.25 g, 18 mmol) and concentrated sulfuric acid (8 ml) and added over the course of 5 min to a solution of 4-phenylamino-1,2-naphthoquinone (**1a**) (1.25 g, 5 mmol) in glacial acetic acid (30 ml). The reaction mixture was stirred for 1 h at 15-20°C, then poured with stirring into ice–water mixture (200 ml). The precipitate was filtered off, washed with water until neutral pH, and dried. Yield 1.16 g (84%). Orange crystals. Mp 284-285°C (*o*-dichlorobenzene). IR spectrum, ν, cm^{-1}: 1363 (N–O), 1676 (C=O). UV spectrum, λ_{max}, nm (log ε): 324 (4.55). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.78 (1H, t, *J* =7.6, H-3); 7.90 (1H, t, *J* = 7.0, H-10); 7.96 (1H, t, *J* = 7.6, H-2); 8.05 (1H, t, *J* = 7.0, H-9); 8.12 (1H, dd, *J* = 7.0, *J* = 1.0, H-11); 8.24 (1H, dd, *J* = 7.6, *J* = 1.3, H-1); 8.50 (1H, dd, *J* = 7.6, *J* = 1.3, H-4) 8.82 (1H, dd, *J* = 7.0, *J* = 0.9, H-8). ^{13}C NMR spectrum, δ, ppm: 119.8 (C-10); 126.9 (C-8); 128.6 (C-3); 130.7 (C-2); 131.8 (C-9); 132.3 (C-11a); 132.5 (C-11); 134.2 (C-12b); 134.6 (C-1); 134.9 (C-4a); 135.7 (C-4); 138.1 (C-7a); 143.8 (C-12a); 150.9 (C-6a); 171.6 (C-5); 177.8 (C-6). Mass spectrum, *m*/*z* (I_{rel},%): 276 [M]$^{+}$ (5), 262 (99), 232 (65), 76 (100). Found, %: C 69.72; H 2.83; N 10.06. $C_{16}H_8N_2O_3$. Calculated, %: C 69.57; H 2.92; N 10.14.

9-Methylbenzo[*a*]phenazine-5,6-dione 7-Oxide (2b). Nitrosylsulfuric acid was prepared from sodium nitrite (2.50 g, 36 mmol) and concentrated sulfuric acid (15 ml) and added over the course of 5 min to a solution of 4-*p*-tolylamino-1,2-naphthoquinone (**1b**) (2.63 g, 10 mmol) in glacial acetic acid (60 ml). The reaction mixture was stirred for 1 h at 15-20°C, then poured with stirring into ice–water mixture (200 ml). The precipitate was filtered off, washed with water until neutral pH, and dried. Yield 2.65 g (91%). Red crystals. Mp 248-250°C (*o*-dichlorobenzene). IR spectrum, ν, cm^{-1}: 1356 (N–O), 1672 (C=O). UV spectrum, λ_{max}, nm (log ε): 316 (4.62). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.62 (3H, s, CH_3); 7.75 (1H, t, *J* = 7.6, H-3); 7.87 (1H, dd, *J* = 8.5, *J* = 2.0, H-10); 7.93 (1H, t, *J* = 7.6, H-2); 8.10 (1H, dd, *J* = 7.6, *J* = 1.0, H-1); 8.11 (1H, d, *J* = 8.5, H-11); 8.28 (1H, s, H-8); 8.78 (1H, dd, *J* = 7.6, *J* = 1.0, H-4). ^{13}C NMR spectrum, δ, ppm: 22.1 (CH_3); 118.6 (C-10); 126.7 (C-8); 128.6 (C-3); 130.4 (C-2); 132.1 (C-11a); 132.2 (C-11); 133.9 (C-12b); 135.0 (C-4a); 135.7 (C-1); 136.5 (C-4); 137.9 (C-7a); 142.3 (C-12a); 142.8 (C-9); 150.1 (C-6a); 171.1 (C-5); 177.8 (C-6). Mass spectrum, *m*/*z* (I_{rel},%): 290 [M]$^{+}$ (16), 246 (100), 89 (56), 76 (37). Found, %: C 69.85; H 3.35; N 9.54. $C_{17}H_{10}N_2O_3$. Calculated, %: C 70.34; H 3.45; N 9.66.

9-Chlorobenzo[*a*]phenazine-5,6-dione 7-Oxide (2c). Nitrosylsulfuric acid was prepared from sodium nitrite (2.50 g, 36 mmol) and concentrated sulfuric acid (16 ml), and added over the course of 5 min to a solution of 4-(*p*-chlorophenylamino)-1,2-naphthoquinone (**1c**) (2.83 g, 10 mmol) in glacial acetic acid (60 ml). The reaction mixture was stirred for 6 h at 15-20°C, then poured with stirring into ice–water mixture (200 ml). The precipitate was filtered off, washed with water until neutral pH, and dried. Yield 2.65 g (95%). Orange crystals. Mp 305-307°C (*o*-dichlorobenzene). IR spectrum, ν, cm^{-1}: 1396 (N–O), 1674 (C=O). UV spectrum, λ_{max}, nm (log ε): 314 (4.63). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.79 (1H, t, *J* = 7.7, H-3); 7.96 (1H, t, *J* = 7.7, H-2); 8.09 (1H, dd, *J* = 8.9, *J* = 2.4, H-10); 8.13 (1H, dd, *J* = 7.7, *J* = 1.2, H-1); 8.27 (1H, d, *J* = 8.9, H-11); 8.50 (1H, d, *J* = 2.4, H-8); 8.81 (1H, d, *J* = 7.7, H-4). ^{13}C NMR spectrum, δ, ppm: 119.1 (C-10); 126.9 (C-8); 128.7 (C-3); 132.3 (C-11a); 132.6 (C-11); 132.7 (C-2); 134.5 (C-9); 134.6 (C-4a); 135.0 (C-1); 135.8 (C-4); 136.4 (C-12b); 138.4 (C-7a); 142.6 (C-12a); 151.3 (C-6a); 171.4 (C-5); 177.5 (C-6). Mass spectrum, *m*/*z* (I_{rel},%): 310

$[M]^+$ (3), 266 (67), 238 (55), 76 (51), 75 (100), 50 (61), 32 (64). Found, %: C 61.71; H 2.22; N 8.98. $C_{16}H_7ClN_2O_3$. Calculated, %: C 61.84; H 2.25; N 9.02.

9-Fluorobenzo[*a*]phenazine-5,6-dione 7-Oxide (2d). Nitrosylsulfuric acid was prepared from sodium nitrite (1.25 g, 18 mmol) and concentrated sulfuric acid (8 ml) and added over the course of 5 min to a solution of 4-*p*-fluorophenylamino-1,2-naphthoquinone (**1d**) (1.35 g, 5 mmol) in glacial acetic acid (15 ml). The reaction mixture was stirred for 1 h at 15-20°C, then poured with stirring into ice–water mixture (200 ml). The precipitate was filtered off, washed with water until neutral pH, and dried. Yield 0.93 g (63%). Brick-colored crystals. Mp 276-277°C (*o*-dichlorobenzene). IR spectrum, ν, cm^{-1}: 1404 (N–O), 1676 (C=O). UV spectrum, λ_{max}, nm (log ε): 316 (4.61). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.77 (1H, t, *J* = 7.6, H-3); 7.96 (1H, t, *J* = 7.6, H-2); 8.00 (1H, m, H-10); 8.13 (1H, d, *J* = 7.6, H-1); 8.25 (1H, dd, *J* = 9.1, *J* = 2.4, H-11); 8.34 (1H, dd, *J* = 9.1, *J* = 2.4, H-8); 8.80 (1H, d, *J* = 7.6, H-4). ^{13}C NMR spectrum, δ, ppm: 105.0 (C-10); 105.2 (C-8); 126.8 (C-3); 128.7 (C-2); 132.3 (C-11a); 132.5 (C-11); 133.7 (C-1); 134.3 (C-12b); 134.7 (C-4a); 135.8 (C-4); 138.8 (C-7a); 141.1 (C-12a); 150.5 (C-6a); 162.5 (C-9); 171.5 (C-5); 177.6 (C-6). Mass spectrum, *m*/*z* (I_{rel},%): 294 $[M]^+$ (5), 250 (85), 222 (100), 94 (54), 75 (48). Found, %: C 65.48; H 2.41; N 9.49. $C_{16}H_7FN_2O_3$. Calculated, %: C 65.31; H 2.38; N 9.52.

REFERENCES

1. K. Venkataraman (editor), *Chemistry of synthetic dyes* [in Russian], Vol. 5, Khimiya, Leningrad (1977), p. 35.
2. S.-T. Zhuo, C.-Y. Li, M.-H. Hu, S.-B. Chen, P.-F. Yao, S.-L. Huang, T.-M. Ou, J.-H. Tan, L.-K. An, D. Li, L.-Q. Gu, and Z.-S. Huang, *Org. Biomol. Chem.*, **11**, 3989 (2013).
3. A. C. Komor, C. J. Schneider, A. G. Weidmann, and J. K. Barton, *J. Am. Chem. Soc.*, **134**, 19223 (2012).
4. A. V. Yeltsov (editor), *Laboratory synthesis of intermediates and dyes* [in Russian], Khimiya, Leningrad (1985), p. 159.
5. V. G. Koshechko, A. N. Inozemtsev, and V. D. Pokhodenko, *Zh. Org. Khim.*, **12**, 2608 (1981).
6. S. P. Titova, A. K. Arinich, and M. V. Gorelik, *Zh. Org. Khim.*, **22**, 1562 (1986).
7. E. A. Bocharova, L. M. Gornostaev, and N. V. Geets, *Butlerov Comm.*, **26**, No. 11, 61 (2011).
8. I. D. Biggs and J. M. Tedder, *Tetrahedron*, **34**, 1377 (1978).
9. L. Bellami, *New IR spectral data for complex molecules* [Russian translation], Mir, Moscow (1971), p. 216.
10. St. Berger and A. Rieker, in: S. Patai (editor), *The Chemistry of the Quinonoid Compounds*, Vol. 1, J. Wiley & Sons, New York (1974), p. 176.
11. R. E. Harmon, L. M. Phipps, J. A. Howell, and S. K. Gupta, *Tetrahedron*, **25**, 5807 (1969).