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INVESTIGATIONS IN THE FIELD OF 2,3'-BIQUINOLYL. 13.* REGIOSELECTIVITY IN THE NITRATION OF 2,3'-BIQUINOLYLS AND THEIR 1',4'-DIHYDRO DERIVATIVES

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The nitration of 2,3'-biquinolyls in concentrated sulfuric acid with an equivalent amount of nitric acid at room temperature takes place exclusively at the 2-quinolyl fragment with the formation of the 5- and 8-nitro derivatives or their mixtures. The nitration of the 1',4'-dihydro derivatives under these conditions leads to analogous compounds. Reduction of the nitrobiquinolyls gives the respective amines. Acylation of the latter leads to acylamino-2,3'-biquinolyls.

Keywords: amino-2,3'-biquinolyls, acylamino-2,3'-biquinolyls, 2,3'-biquinolyl, 1',4'-dihydro-2,3'-biquinolyl, nitro-2,3'-biquinolyls, acylation, reduction, nitration.

Investigations of the reactivity of derivatives of 2,3'-biquinolyl have shown that nucleophilic addition and substitution take place exclusively at the 3-quinolyl fragment [2, 3]. Reactions with electrophilic reagents have not been reported.

The aim of the present work was to investigate the nitration of 2,3'-biquinolyls **1** and their 1',4'-dihydro derivatives **2**.

It is known [4] that the mononitration of quinoline leads to a mixture of 5- and 8-nitroquinolines in a ratio of 1:1. Consequently, the formation of four isomeric nitro derivatives should be expected in the case of 2,3'-biquinolyl **1a**, containing two quinoline rings.

We found that the reaction of **1a** with KNO_3 in concentrated sulfuric acid led to the formation of the products of nitration exclusively at the 2-quinolyl fragment, i.e., 5-nitro-2,3'-biquinolyl (**4a**) and 8-nitro-2,3'-biquinolyl (**5a**), in a ratio of 1:4.

The result can be explained by monoprotonation of the 2,3'-biquinolyls **1** (supported by the ^{1}H NMR data) at position 1', which increases the electron deficiency of the 3-quinolyl fragment.

6'-Bromo-2,3'-biquinolyl (**1b**) behaves similarly to compound **1a**. Here the corresponding 5- and 8-nitro derivatives **4b** and **5b** (according to ^{1}H NMR spectroscopy) are formed in a ratio of 2:3. Unfortunately we were unable to isolate the individual substances.

6,6'-Dimethyl-2,3'-biquinolyl (**1c**) and 7,7'-dimethyl-2,3'-biquinolyl (**1d**) each form one mononitration product, i.e., 5-nitro-6,6'-dimethyl-2,3'-biquinolyl (**4c**) and 8-nitro-7,7'-dimethyl-2,3'-biquinolyl (**5d**).

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* For communication 12, see [1].

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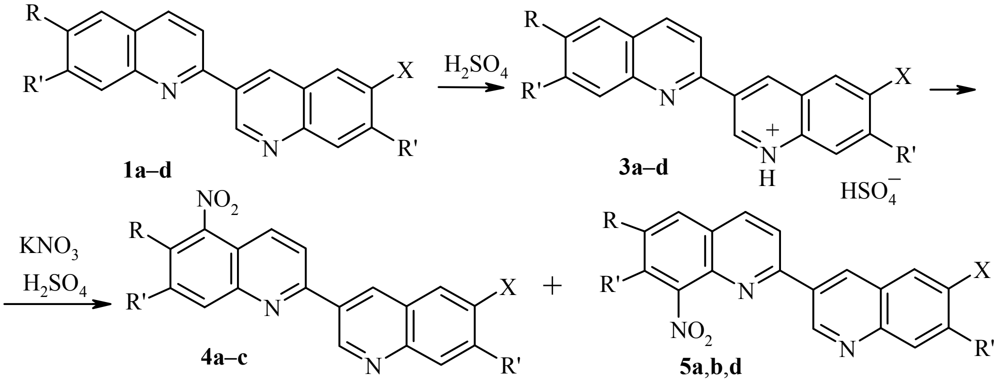
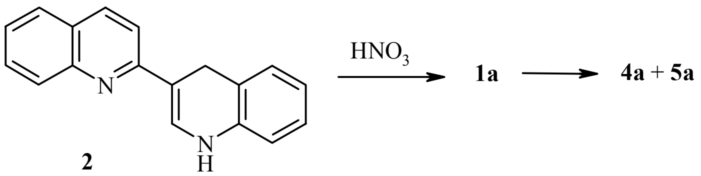
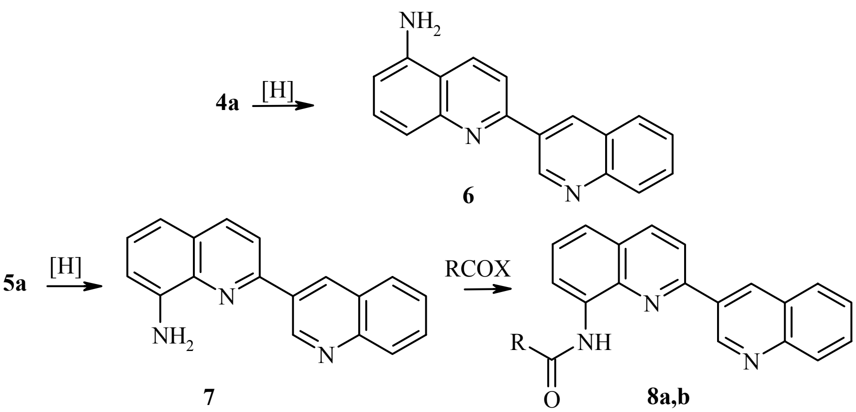


1, 3-5 a R = R' = X = H; **b** R = R' = H, X = Br; **1**, **3**, **4 c** R = X = Me, R'=H;
1, **3**, **5 d** R = X = H, R' = Me

The nitration of 1',4'-dihydro-2,3'-biquinolyl (**2**) leads to a mixture of 5- and 8-nitrobiquinolyls **4a** and **5a** in a ratio similar to compound **1a**, which is explained by the ease of oxidation of the dihydro derivative **2**. The latter is confirmed by the fact that the nitration of compound **2** under milder conditions leads to a quantitative yield of 2,3'-biquinolyl **1a**.



Reduction of the nitro derivative with iron in an acidic medium or with hydrazine on Raney nickel gave the respective amines **6** and **7** with yields of 43-89%. Acylation of these amines led to the amides **8a**,**b**.



8 a R = Me; **b** R = Ph

EXPERIMENTAL

The NMR spectra were recorded on a Bruker WP-200 instrument at 200 MHz with TMS as internal standard. The IR spectra were obtained on a Hitachi 215 instrument. The mass spectra were recorded on a Varian CH 7 instrument (ionizing electrons 70 eV). The reactions and the individuality of the compounds were monitored on Silufol UV-254 plates in ethyl acetate. Flash chromatography was conducted on silica gel L 5/40.

5-Nitro-2,3'-biquinolyl (4a) and 8-Nitro-2,3'-biquinolyl (5a). To a solution of 2,3'-biquinolyl (1.28 g, 5 mmol) or compound **2** (1.29 g, 5 mmol) in concentrated sulfuric acid (10 ml) we added in one portion potassium nitrate (0.56 g, 5.5 mmol) (in the case of compound **2** – 1.1 g (11 mmol)), and we kept the mixture at room temperature for 30 min. To the obtained solution we added water dropwise with stirring (here the solution boiled) until the mixture was cloudy. The mixture was stirred for a further 15-20 min. The precipitate was filtered off and washed first with cold water and then with a solution of ammonia. Compound **5a** was obtained. The filtrate was neutralized with ammonia solution, and a mixture of 5- and 8-nitrobiquinolyls separated. It was separated by flash chromatography.

5-Nitro-2,3'-biquinolyl (4a). Yield 0.26 g (17%); mp 223-225°C (alcohol); R_f 0.9 (ethyl acetate). IR spectrum (thin layer), ν, cm^{-1}: 1330, 1518 (NO_2). ^{1}H NMR spectrum (acetonitrile-d$_3$), δ, ppm, *J* (Hz): 7.69 (1H, dd, $J_{5'6'}$ = 8.11, $J_{6'7'}$ = 8.14, 6'-H); 7.85 (1H, dd, $J_{6'7'}$ = 8.14, $J_{7'8'}$ = 8.54, 7'-H); 7.94 (1H, dd, J_{67} = 8.11, J_{78} = 8.54, 7-H); 8.11 (1H, d, $J_{5'6'}$ = 8.11, 5'-H); 8.14 (1H, d, $J_{7'8'}$ = 8.54, 8'-H); 8.41 (1H, d, J_{78} = 8.54, 8-H); 8.45 (1H, d, J_{34} = 8.97, 3-H); 8.53 (1H, d, J_{67} = 8.11, 6-H); 9.08 (1H, d, J_{34} = 8.97, 4-H); 9.11 (1H, d, $J_{2'4'}$ = 2.56, 4'-H); 9.84 (1H, d, $J_{2'4'}$ = 2.56, 2'-H). Mass spectrum, *m/z* (*I*, %): 301 $[M]^+$ (37), 255 (100). Found, %: C 72.04; H 3.56; N 13.85. $C_{18}H_{11}N_3O_2$. Calculated, %: C 71.75; H 3.68; N 13.95.

8-Nitro-2,3'-biquinolyl (5a). Yield 1.02 g (68%); mp 227-229°C (alcohol); R_f 0.77 (ethyl acetate). IR spectrum (thin layer), ν, cm^{-1}: 1522 (NO_2). ^{1}H NMR spectrum (acetonitrile-d$_3$), δ, ppm, *J* (Hz): 7.67 (1H, dd, $J_{5'6'}$ = 8.14, $J_{6'7'}$ = 8.11, 6'-H); 7.71 (1H, dd, J_{56} = 8.46, J_{67} = 8.15, 6-H); 7.83 (1H, dd, $J_{6'7'}$ = 8.11, $J_{7'8'}$ = 8.53, 7'-H); 8.09 (1H, d, $J_{5'6'}$ = 8.14, 5'-H); 8.12 (1H, d, $J_{7'8'}$ = 8.53, 8'-H); 8.15 (1H, dd, J_{56} = 8.46, J_{57} = 1.28, 5-H); 8.22 (1H, dd, J_{67} = 8.15, J_{57} = 1.28, 7-H); 8.36 (1H, d, J_{34} = 8.97, 3-H); 8.58 (1H, d, J_{34} = 8.97, 4-H); 9.03 (1H, d, $J_{2'4'}$ = 2.13, 4'-H); 9.72 (1H, d, $J_{2'4'}$ = 2.13, 2'-H). Mass spectrum, *m/z* (*I*, %): 301 $[M]^+$ (100), 255 (34), 254 (64). Found, %: C 71.94; H 3.58; N 13.87. $C_{18}H_{11}N_3O_2$. Calculated, %: C 71.75; H 3.68; N 13.95.

6'-Bromo-5-nitro-2,3'-biquinolyl (4b) and 6'-Bromo-8-nitro-2,3'-biquinolyl (5b). To a solution of 2,3'-biquinolyl (1.69 g, 5 mmol) in concentrated sulfuric acid (10 ml) we added in one portion potassium nitrate (0.56 g, 5.5 mmol). The mixture was kept at room temperature for 30 min. It was then carefully poured into water (20 ml) and neutralized with a 22% solution of ammonia. The precipitate was filtered off. We obtained 1.62 g (85%) of a mixture of compounds **4b** and **5b** in a ratio of 2:3.

6'-Bromo-5-nitro-2,3'-biquinolyl (4b). ^{1}H NMR spectrum (acetonitrile-d$_3$), δ, ppm, *J* (Hz): 7.85 (1H, dd, $J_{6'7'}$ = 8.14, $J_{7'8'}$ = 8.54, 7'-H); 7.93 (1H, dd, J_{67} = 8.11, J_{78} = 8.54, 7-H); 8.24 (1H, d, $J_{5'6'}$ = 8.11, 5'-H); 8.34 (1H, d, $J_{7'8'}$ = 8.54, 8'-H); 8.41 (1H, d, J_{78} = 8.52, 8-H); 8.49 (1H, d, J_{34} = 8.87, 3-H); 8.58 (1H, d, J_{67} = 8.11, 6-H); 8.95 (1H, d, $J_{2'4'}$ = 2.20, 4'-H); 9.06 (1H, d, J_{34} = 8.87, 4-H); 9.81 (1H, d, $J_{2'4'}$ = 2.20, 2'-H).

6'-Bromo-8-nitro-2,3'-biquinolyl (5b). ^{1}H NMR spectrum (acetonitrile-d$_3$), δ, ppm, *J* (Hz): 7.72 (1H, dd, J_{56} = 8.25, J_{67} = 8.15, 6-H); 7.80 (1H, dd, $J_{5'7'}$ = 2.20, $J_{7'8'}$ = 8.53, 7'-H); 8.02 (1H, d, $J_{7'8'}$ = 8.53, 8'-H); 8.20 (1H, d, J_{56} = 8.25, 5-H); 8.21 (1H, d, J_{67} = 7.70, 7-H); 8.26 (1H, d, $J_{5'7'}$ = 2.20, 5'-H); 8.32 (1H, d, J_{34} = 8.80, 3-H); 8.57 (1H, d, J_{34} = 8.80, 4-H); 8.92 (1H, d, $J_{2'4'}$ = 2.20, 4'-H); 9.71 (1H, d, $J_{2'4'}$ = 2.20, 2'-H).

6,6'-Dimethyl-5-nitro-2,3'-biquinolyl (4c). To a solution of compound **1c** (0.28 g, 1 mmol) in concentrated sulfuric acid (5 ml) we added in one portion potassium nitrate (0.11 g, 1.1 mmol). The mixture was kept at room temperature for 30 min. The solution was then poured carefully into water (10 ml) and neutralized with a 22% solution of ammonia. The precipitate was filtered off. Yield 0.274 g (83%); mp 233-235°C (alcohol). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 2.59 (3H, s, 6'-CH_3); 2.60 (3H, s, 6-CH_3); 7.63 (1H, dd, $J_{7'8'}$ = 8.54, $J_{5'7'}$= 1.70, 7'-H); 7.67 (1H, d, J_{78} = 8.97, 7-H); 7.74 (1H, d, $J_{5'7'}$ = 1.70, 5'-H); 8.08 (1H, d, $J_{7'8'}$ = 8.54, 8'-H); 8.15 (1H, d, J_{34} = 8.97, 3-H); 8.26 (1H, d, J_{34} = 8.97, 4-H); 8.29 (1H, d, J_{78} = 8.97, 8-H); 8.81 (1H, d, $J_{2'4'}$ = 2.14, 4'-H); 9.68 (1H, d, $J_{2'4'}$ = 2.14, 2'-H). Found, %: C 73.01; H 4.52; N 12.81. $C_{20}H_{15}N_3O_2$. Calculated, %: C 72.94; H 4.59; N 12.76.

7,7'-Dimethyl-8-nitro-2,3'-biquinolyl (5d). The compound was obtained similarly to compound **4c** from compound **1d** (0.28 g, 1 mmol) and potassium nitrate (0.56 g, 5.5 mmol). Yield 0.287 g (87%); mp 225-226°C (alcohol). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 2.58 (3H, s, 7'-CH_3); 2.61

(3H, s, 7-CH_3); 7.44 (1H, dd, $J_{5'6'}$ = 8.11, $J_{6'8'}$ = 2.13, 6'-H); 7.45 (1H, d, J_{56} = 8.11, 6-H); 7.87 (1H, d, $J_{5'6'}$ = 8.11, 5'-H); 7.88 (1H, dd, J_{56} = 8.11, 5-H); 7.93 (1H, d, $J_{6'8'}$ = 2.13, 8'-H); 8.12 (1H, d, J_{34} = 8.74, 3-H); 8.31 (1H, d, J_{34} = 8.74, 4-H); 8.90 (1H, d, $J_{2'4'}$ = 2.13, 4'-H); 9.64 (1H, d, $J_{2'4'}$ = 2.13, 2'-H). Found, %: C 73.02; H 4.51; N 12.72. $C_{20}H_{15}N_3O_2$. Calculated, %: C 72.94; H 4.59; N 12.76.

Reduction of Nitrobiquinolyls 4 and 5. General Procedure. A. To a solution of nitro-2,3'-biquinolyl (1 mmol) in concentrated hydrochloric acid (10 ml) we added alcohol (10 ml), and while boiling we added iron (0.17 g, 3 mmol) in four portions at intervals of 5 min. The mixture was then boiled for 2 h. After this it was neutralized with a solution of ammonia and extracted with benzene (3 × 20 ml). The benzene solution was evaporated.

B. To a mixture of nitro-2,3'-biquinolyl (1 mmol) and Raney nickel in alcohol (10 ml) with stirring we added 85% hydrazine hydrate (0.4 ml). The reaction mixture was stirred at 50°C for 3 h, the Raney nickel was filtered off, water (20 ml) was added to the filtrate, and the product was extracted with benzene (3 × 20 ml). The benzene solution was evaporated.

5-Amino-2,3'-biquinolyl (6). Yield 0.11 g (40%) in method A and 0.23 g (85%) in method B; mp 218-220°C (alcohol). ^{1}H NMR spectrum (acetonitrile-d_3), δ, ppm, *J* (Hz): 4.91 (2H, br. s, NH_2); 6.85 (1H, dd, J_{67} = 7.68, J_{68} = 1.38, 6-H); 7.51 (1H, dd, J_{78} = 8.25, J_{68} = 1.38, 8-H); 7.57 (1H, dd, J_{67} = 7.68, J_{78} = 8.25, 7-H); 7.69 (1H, dd, $J_{5'6'}$ = 8.12, $J_{6'7'}$ = 8.09, 6'-H); 7.84 (1H, dd, $J_{6'7'}$ = 8.09, $J_{7'8'}$ = 8.52, 7'-H); 8.06 (1H, d, $J_{5'6'}$ = 8.12, 5'-H); 8.12 (1H, d, J_{34} = 8.81, 3-H); 8.14 (1H, d, $J_{7'8'}$ = 8.52, 8'-H); 8.51 (1H, d, J_{34} = 8.81, 4-H); 9.04 (1H, d, $J_{2'4'}$ = 2.19, 4'-H), 9.82 (1H, d, $J_{2'4'}$ = 2.19, 2'-H). Found, %: C 79.76; H 4.86; N 15.38. $C_{18}H_{13}N_3$. Calculated, %: C 79.68; H 4.83; N 15.49.

8-Amino-3,2'-biquinolyl (7). Yield 0.116 g (43%) in method A and 0.24 g (89%) in method B; mp 153-155°C (alcohol). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 5.14 (2H, br. s, NH_2); 6.98 (1H, dd, J_{67} = 7.59, J_{57} = 0.99, 7-H); 7.19 (1H, dd, J_{56} = 7.92, J_{57} = 0.99, 5-H); 7.36 (1H, dd, J_{56} = 7.92, J_{67} = 7.59, 6-H); 7.60 (1H, dt, $J_{5'6'}$ = 8.41, $J_{6'7'}$ = 8.24, $J_{6'8'}$ = 1.02, 6'-H); 7.76 (1H, dt, $J_{6'7'}$ = 8.24, $J_{7'8'}$ = 8.58, $J_{5'7'}$ = 1.32, 7'-H); 7.96 (1H, dd, $J_{5'6'}$ = 8.41, $J_{5'7'}$ = 1.32, 5'-H); 8.00 (1H, d, J_{34} = 8.58, 3-H); 8.19 (1H, dd, $J_{7'8'}$ = 8.58, $J_{6'8'}$ = 1.02, 8'-H); 8.21 (1H, d, J_{34} = 8.58, 4-H); 8.83 (1H, d, $J_{2'4'}$ = 2.15, 4'-H); 9.79 (1H, d, $J_{2'4'}$ = 2.15, 2'-H). Found, %: C 79.94; H 4.78; N 15.28. $C_{18}H_{13}N_3$. Calculated, %: C 79.68; H 4.83; N 15.49.

8-Acetylamino-2,3'-biquinolyl (8a). To a solution of 8-amino-2,3'-biquinolyl (0.27 g, 1 mmol) in benzene (10 ml) we added acetic anhydride (0.12 g, 1.2 mmol). The reaction mixture was boiled for 20 min and cooled, water (10 ml) and a 20% solution of ammonia (10 ml) were added, and the mixture was stirred. The precipitate was filtered off. Yield 0.268 g (86%); mp 190-192°C (alcohol). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 2.42 (3H, s, CH_3); 7.58 (2H, m, 5-, 6-H); 7.66 (1H, dt, $J_{5'6'}$ = 8.09, $J_{6'7'}$ = 8.26, $J_{6'8'}$ = 1.29, 6'-H); 7.82 (1H, dt, $J_{6'7'}$ = 8.26, $J_{7'8'}$ = 8.53, $J_{5'7'}$ = 1.28, 7'-H); 8.00 (1H, dd, $J_{5'6'}$ = 8.09, $J_{5'7'}$ = 1.28, 5'-H); 8.09 (1H, d, J_{34} = 8.54, 3-H); 8.21 (1H, dd, $J_{7'8'}$ = 8.53, $J_{6'8'}$ = 1.29, 8'-H); 8.33 (1H, d, J_{34} = 8.54, 4-H); 8.79 (1H, d, $J_{2'4'}$ = 2.13, 4'-H); 8.84 (1H, dd, J_{67} = 8.09, J_{57} = 1.99, 7-H); 9.85 (1H, d, $J_{2'4'}$ = 2.13, 2'-H); 9.90 (1H, br. s, NH). Found, %: C 76.84; H 4.76; N 13.33. $C_{20}H_{15}N_3O$. Calculated, %: C 76.66; H 4.82; N 13.41.

8-Benzoylamino-2,3'-biquinolyl (8b). The compound was obtained similarly to compound **8a** from compound **7** (0.27 g, 1 mmol) and benzoyl chloride (0.17 g, 1.2 mmol). Yield 0.3 g (81%); mp 209-210°C (alcohol). ^{1}H NMR spectrum (acetonitrile-d_3), δ, ppm, *J* (Hz): 7.69 (6H, m, 6'-H, 5-, 6-H, 3,4,5-Ph); 7.86 (1H, dd, $J_{6'7'}$ = 8.24, $J_{7'8'}$ = 8.51, 7'-H); 8.09 (1H, d, $J_{5'6'}$ = 8.07, 5'-H); 8.17 (3H, m, 8'-H, 2,6-Ph); 8.29 (1H, d, J_{34} = 8.79, 3-H); 8.50 (1H, d, J_{34} = 8.79, 4-H); 8.91 (1H, d, J_{67} = 7.89, 7-H); 9.08 (1H, d, $J_{2'4'}$ = 2.20, 4'-H); 9.85 (1H, d, $J_{2'4'}$ = 2.20, 2'-H); 10.86 (1H, br. s, NH). Found, %: C 80.09; H 4.48; N 11.27. $C_{25}H_{17}N_3O$. Calculated, %: C 79.98; H 4.56; N 11.19.

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