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INVESTIGATIONS IN THE FIELD OF 2,3'-BIQUINOLYL. 14.* REACTION OF DIHYDRO DERIVATIVES OF 2,3'-BIQUINOLYL WITH BROMINE AND IODINE

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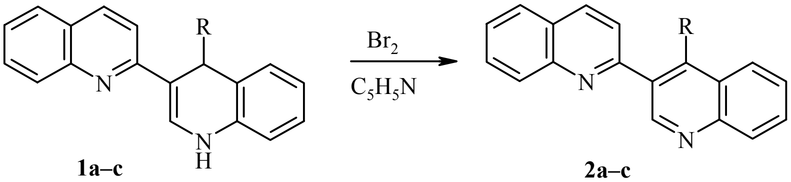
Methods were developed for the synthesis of 6'-bromo- and 6',8'-dibromo-2,3'-biquinolyls and 3',4'-dibromo- and 3',4',6'-tribromo-1'-ethoxycarbonyl-1',2',3',4'-tetrahydro-2,3'-biquinolyls on the basis of the bromination of the dihydro derivatives of 2,3'-biquinolyl. It was shown that the reaction of 1'-alkyl-1',4'-dihydro-2,3'-biquinolyls with bromine and iodine leads to 1'-alkyl-1',2'-dihydro-2,3'-biquinolyl-2'-ones.

Keywords: 1'-alkyl-1',2'-dihydro-2,3'-biquinolyl-2'-ones, 2,3'-biquinolyls, 1',2'-dihydro-2,3'-biquinolyls, 1'-ethoxycarbonyl-1',2',3',4'-tetrahydro-2,3'-biquinolyls, electrophilic substitution.

Earlier [2, 3] we established that the 1',4'-dihydro derivatives **1** not containing substituents at the nitrogen atom form the corresponding 2,3'-biquinolyls **2** in reaction with iodine in pyridine. The reactions of the dihydro derivatives **1** with halogens in an acidic medium and the reactions of 1'-R-1',4'-dihydro derivatives **3** and 1'-R-1',2'-dihydro derivatives **4** with halogens have not been reported before.

We showed that the reaction of compounds **1** with bromine in pyridine takes place similarly to their reaction with iodine in pyridine and leads to the respective 2,3'-biquinolyls **2**.



1, 2 a R = H; **b** R = Ph; **c** R = 2-C_5H_4N

The reaction probably involves addition at the C(2')–C(3') multiple bond with subsequent elimination of two molecules of hydrogen halide.

With iodine in pyridine in the presence of alkali 1'-alkyl-1',4'-dihydro-2,3'-biquinolyls **3** form 1'-alkyl-1',2'-dihydro-2,3'-biquinolyl-2'-ones **5** with yields close to quantitative.

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* For Communication 13, see [1].

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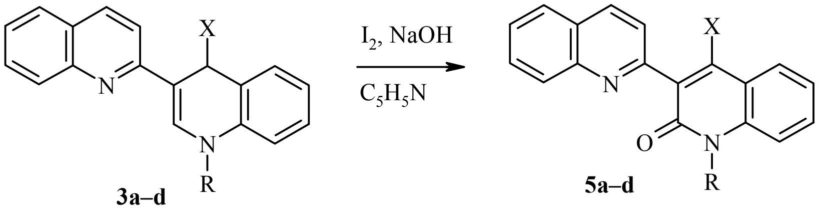


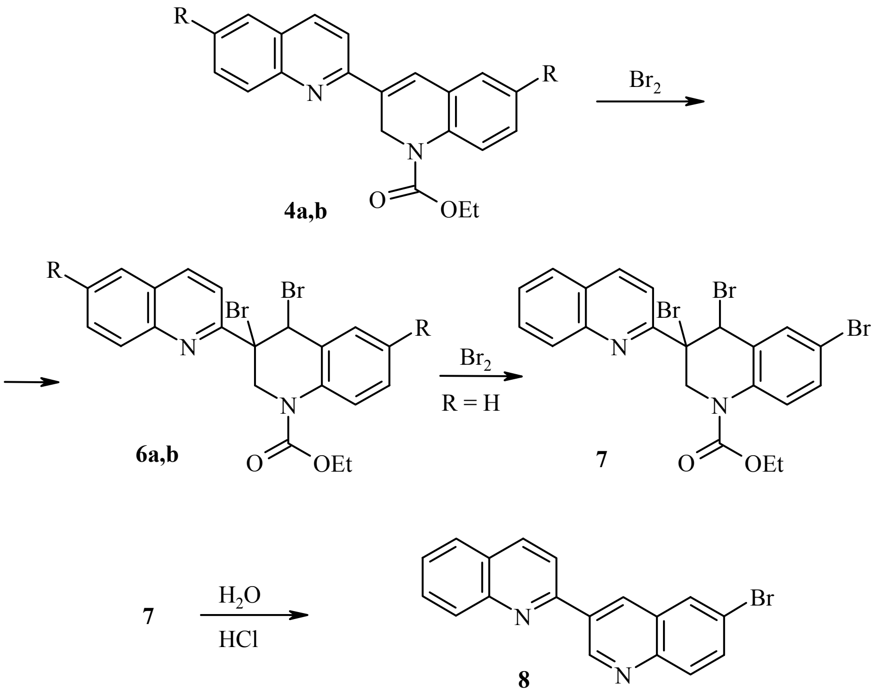
3, 5 a R = Me, X = H; **b** R = Me, X = CN; **c** R = Bu, X = CN; **d** R = CH$_2$Ph, X = CN

The reaction of the dihydro derivatives **3** and **4** with bromine in an acidic medium includes both addition at the multiple bond of the dihydropyridine ring and halogenation in the aromatic ring.

Thus, the reaction of 1'-ethoxycarbonyl-1',2'-dihydro-2,3'-biquinolyl (**4a**) with an excess of bromine in acetic acid leads to the formation of 3',4',6'-tribromo-1'-ethoxycarbonyl-1',2',3',4'-tetrahydro-2,3'-biquinolyl (**7**) (Scheme 1). The reaction of the 6,6'-dimethyldihydro derivative **4b** under the given conditions is limited to the formation of 3',4'-dibromo-1'-ethoxycarbonyl-1',2',3',4'-tetrahydro-2,3'-biquinolyl (**6b**).

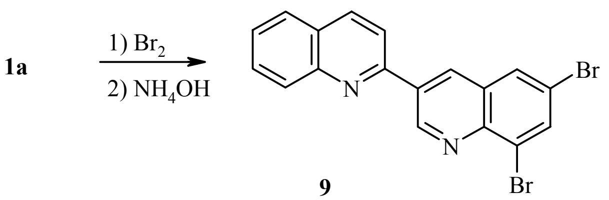
Acid hydrolysis of compound **7** gave a quantitative yield of 6'-bromo-2,3'-biquinolyl (**8**).

Scheme 1



4, 6 a R = H; **b** R = Me

During bromination with an excess of bromine in alcohol followed by treatment of the reaction mixture with a solution of ammonia 1',4'-dihydro-2,3'-biquinolyl (**1a**) forms 6',8'-dibromo-2,3'-biquinolyl (**9**) with a quantitative yield.



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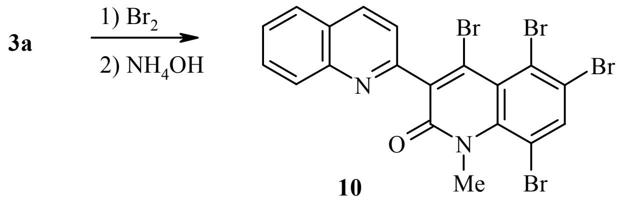
4',5',6',8'-Tetrabromo-1',2'-dihydro-2,3'-biquinolyl-2'-one (**10**) was obtained by the reaction of compound **3a** with an excess of bromine followed by treatment of the reaction mixture with a solution of ammonia.



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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 1:1 ethyl acetate–hexane. Column chromatography was conducted on silica gel L 40/100.

General Procedure for the Synthesis of 2,3'-Biquinolyls 2a-c. A mixture of 1',4'-dihydro-2,3'-biquinolyl **1a-c** (1 mmol) and bromine (0.18 g, 1.1 mmol) in pyridine (10 ml) was boiled for 30 min. The solidified reaction mass was washed with a 20% solution of thiosulfate (20 ml) and diluted with water (50 ml), and the crystals that separated were filtered off.

2,3'-Biquinolyl (2a). Yield 0.24 g (95%); mp 175-176°C (benzene). According to published data [2], mp 175-176°C. A mixed melting test with an authentic sample did not give a melting point depression. The ^{1}H NMR spectrum was identical with that given in [2].

4'-Phenyl-2,3'-biquinolyl (2b). Yield 0.31 (94%); mp 133-134°C (benzene). According to published data [3], mp 133-134°C. A mixed melting test with an authentic sample did not give a melting point depression. The ^{1}H NMR spectrum was identical with that given in [3].

4'-(2-Pyridyl)-2,3'-biquinolyl (2c). Yield 0.32 g (95%); mp 93-94°C (benzene). According to published data [3], mp 93-94°C. A mixed melting test with an authentic sample did not give a melting point depression. The ^{1}H NMR spectrum was identical with that given in [3].

1'-Ethoxycarbonyl-6,6'-dimethyl-1',2'-dihydro-2,3'-biquinolyl (4b). The compound was obtained similarly to 1'-ethoxycarbonyl-1',2'-dihydro-2,3'-biquinolyl [4] from 6,6'-dimethyl-2,3'-biquinolyl (1.42 g, 5 mmol), ethyl chloroformate (1.09 g, 10 mmol), and sodium borohydride (0.2 g, 5.5 mmol). Yield 1.59 g (89%); mp 152-153°C (alcohol). ^{1}H NMR spectrum (acetone-d$_6$), δ, ppm, *J* (Hz): 1.30 (3H, t, *J* = 6.84, $\underline{CH_3}CH_2$); 2.33 (3H, s, 6'-Me); 2.53 (3H, s, 6-Me); 4.24 (2H, q, *J* = 6.84, $CH_3\underline{CH_2}$); 5.15 (2H, d, $J_{2'4'}$ = 1.28, 2'-H); 7.11 (1H, dd, $J_{5'7'}$ = 1.28, $J_{7'8'}$ = 8.11, 7'-H); 7.18 (1H, s, $J_{5'7'}$ = 1.28, 5'-H), 7.55 (1H, s, $J_{2'4'}$ = 1.28, 4'-H); 7.61 (1H, d, J_{78} = 8.11, 7-H); 7.69 (1H, s, 5-H); 7.95 (1H, d, J_{78} = 8.11, 8-H); 8.01 (1H, d, J_{34} = 8.96, 4-H); 8.22 (1H, d, J_{34} = 8.96, 3-H). Found, %: C 77.14; H 6.12; N 7.73. $C_{23}H_{22}N_2O_2$. Calculated, %: C 77.07; H 6.19; N 7.82.

General Procedure for the Synthesis of 1'-Alkyl-1',2'-dihydro-2,3'-biquinolyl-2'-ones 5a-d. A mixture of 1'-alkyl-1',4'-dihydro-2,3'-biquinolyl **3a-d** (1 mmol) and iodine (0.76 g, 3 mmol) in pyridine (10 ml) was stirred at room temperature for 15 min, sodium hydroxide (0.12 g, 3 mmol) was added, and the mixture was boiled for 1 h. The cooled reaction mixture was washed with a 20% solution of thiosulfate (20 ml) and diluted with water (50 ml), and the crystals that separated were filtered off.

1'-Methyl-1',2'-dihydro-2,3'-biquinolyl-2'-one (5a). Yield 0.55 g (81%); mp 174-175°C (alcohol). According to published data [5], mp 174-175°C. A mixed-melting test with an authentic sample did not give a melting point depression. The ^{1}H NMR spectrum was identical with that given in [5].

1'-Methyl-4'-cyano-1',2'-dihydro-2,3'-biquinolyl-2'-one (5b). Yield 0.27 g (81%); mp 221-222°C (benzene). IR spectrum (thin layer), ν, cm^{-1}: 1612 (C=O). ^{1}H NMR spectrum (acetone-d_6), δ, ppm, *J* (Hz): 3.87 (3H, s, Me); 7.54 (1H, dd, J_{56} = 8.23, J_{67} = 7.88, 6-H); 7.72 (1H, dd, $J_{5'6'}$ = 7.91, $J_{6'7'}$ = 7.88, 6'-H); 7.77 (1H, d, $J_{7'8'}$ = 7.96, 8'-H); 7.86 (1H, dd, $J_{6'7'}$ = 7.88, $J_{7'8'}$ = 7.96, 7'-H); 7.87 (1H, dd, J_{67} = 7.88, J_{78} = 8.41, 7-H); 8.00 (1H, d, J_{34} = 8.54, 3-H); 8.07 (1H, d, $J_{5'6'}$ = 7.91, 5'-H); 8.11 (1H, d, J_{56} = 8.23, 5-H); 8.17 (1H, d, J_{78} = 8.41, 8-H); 8.47 (1H, d, J_{34} = 8.54, 4-H). Mass spectrum, *m/z* (*I*, %): 311 $[M]^+$ (100). Found, %: C 77.34; H 4.16; N 13.45. $C_{20}H_{13}N_3O$. Calculated, %: C 77.16; H 4.21; N 13.50.

1'-Butyl-4'-cyano-1',2'-dihydro-2,3'-biquinolyl (5c). Yield 0.29 (82%); mp 208-209°C (benzene). IR spectrum (thin layer, ν, cm^{-1}: 1618 (C=O). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 1.18 (3H, t, *J* = 7.68, 1'-$CH_2CH_2CH_2\underline{CH_3}$); 1.53 (2H, m, 1'-$CH_2CH_2\underline{CH_2}CH_3$); 1.79 (2H, m, 1'-$CH_2\underline{CH_2}CH_2CH_3$); 4.39 (2H, t, *J* = 7.69, 1'-$\underline{CH_2}CH_2CH_2CH_3$); 7.42 (1H, dd, $J_{5'6'}$ = 7.91, $J_{6'7'}$ = 7.88, 6'-H); 7.48 (1H, d, $J_{7'8'}$ = 7.96, 8'-H), 7.62 (1H, dd, J_{56} = 8.23, J_{67} = 7.88, 6-H); 7.73 (1H, dd, $J_{6'7'}$ = 7.88, $J_{7'8'}$ = 7.96, 7'-H); 7.78 (1H, dd, J_{67} = 7.88, J_{78} = 8.41, 7-H); 7.90 (1H, d, $J_{5'6'}$ = 7.91, 5'-H); 7.94 (1H, d, J_{34} = 8.54, 3-H); 8.19 (1H, d, J_{56} = 8.23, 5-H); 8.23 (1H, d, J_{78} = 8.41, 8-H); 8.30 (1H, d, J_{34} = 8.54, 4-H). Mass spectrum, *m/z* (*I*, %): 353 $[M]^+$ (88). Found, %: C 78.34; H 5.32; N 11.69. $C_{23}H_{19}N_3O$. Calculated, %: C 78.16; H 5.42; N 11.89.

1'-Benzyl-4'-cyano-1',2'-dihydro-2,3'-biquinolyl-2'-one (5d). Yield 0.33 g (85%); mp 192-193°C (alcohol). IR spectrum (thin layer), ν, cm^{-1}: 1608 (C=O). ^{1}H NMR spectrum (acetone-d_6), δ, ppm, *J* (Hz): 5.76 (2H, s, CH_2); 7.30 (1H, t, *J* = 6.91, 4-H_{Ph}); 7.35 (2H, d, *J* = 6.91, 2-H_{Ph}, 6-H_{Ph}); 7.41 (2H, t, *J* = 6.91, 3-H_{Ph}, 5-H_{Ph}); 7.50 (1H, dd, $J_{5'6'}$ = 7.98, $J_{6'7'}$ = 7.86, 6'-H); 7.63 (1H, d, $J_{7'8'}$ = 8.12, 8'-H); 7.71 (1H, dd, J_{56} = 8.23, J_{67} = 7.88, 6-H); 7.73 (1H, dd, $J_{6'7'}$ = 7.86, $J_{7'8'}$ = 8.12, 7'-H); 7.86 (1H, dd, J_{67} = 7.88, J_{78} = 8.41, 7-H); 8.07 (1H, d, J_{34} = 8.54, 3-H); 8.07 (1H, d, J_{56} = 8.23, 5-H); 8.13 (1H, d, $J_{5'6'}$ = 7.98, 5'-H); 8.19 (1H, d, J_{78} = 8.41, 8-H); 8.48 (1H, d, J_{34} = 8.54, 4-H). Mass spectrum, *m/z* (*I*, %): 387 $[M]^+$ (92). Found, %: C 80.74; H 4.36; N 10.65. $C_{26}H_{17}N_3O$. Calculated, %: C 80.60; H 4.42; N 10.85.

3',4',6'-Tribromo-1'-ethoxycarbonyl-1',2',3',4'-tetrahydro-2,3'-biquinolyl (7). To a solution of 1'-ethoxycarbonyl-1',2'-dihydro-2,3'-biquinolyl (0.66 g, 2 mmol) in glacial acetic acid at 0°C while stirring we added dropwise bromine (0.32 g, 2.4 mmol). The mixture was kept for 10-15 min and was then kept at room temperature for 15-20 min. The reaction mass was poured into water, neutralized with a solution of ammonia, and extracted with benzene (3 × 50 ml). The benzene was evaporated. The residue was chromatographed, and the first fraction was collected; R_f 0.84 (1:1 ethyl acetate–petroleum ether). Yield 0.85 g (73%); mp 252-253°C (alcohol). ^{1}H NMR spectrum (acetonitrile-d_3), δ, ppm, *J* (Hz): 1.36 (3H, s, *J* = 7.25, Me); 4.13 (1H, d, J_{gem} = 14.85, 2'-H); 4.35 (1H, q, *J* = 7.25, CH_2); 5.61 (1H, dd, J_{gem} = 14.85, $J_{2'4'}$ = 1.1, 2'-H); 6.88 (1H, d, $J_{2'4'}$ = 1.1, 4'-H); 7.56 (1H, dd, $J_{7'8'}$ = 8.50, $J_{5'7'}$ = 1.20, 7'-H); 7.64 (1H, d, $J_{5'7'}$ = 2.20, 5'-H); 7.69 (1H, dt, J_{56} = 8.13, J_{67} = 8.56, J_{68} = 1.32, 6-H); 7.80 (1H, d, J_{34} = 8.80, 3-H); 7.85 (1H, d, $J_{7'8'}$ = 8.50, 8'-H); 7.95 (1H, dt, J_{67} = 8.56, J_{78} = 8.09, J_{57} = 1.30, 7-H); 7.98 (1H, dd, J_{56} = 8.13, J_{57} = 1.30, 5-H); 8.10 (1H, dd, J_{78} = 8.09, J_{68} = 1.32, 8-H); 8.40 (1H, d, J_{34} = 8.80, 4-H). Found, %: C 44.45; H 2.93; N 4.96. $C_{21}H_{17}Br_3N_2O_2$. Calculated, %: C 44.32; H 3.01; N 4.92.

3',4'-Dibromo-1'-ethoxycarbonyl-6,6'-dimethyl-1',2',3',4'-tetrahydro-2,3'-biquinolyl (6b). The compound was obtained similarly to compound **7** from compound **4b** (0.66 g, 2 mmol) and bromine (0.32 g, 2.4 mmol); R_f 0.84 (1:1 ethyl acetate–petroleum ether). Yield 0.46 g (47%); mp 145-146°C (alcohol). ^{1}H NMR spectrum (acetone-d$_6$), δ, ppm, J (Hz): 1.35 (3H, t, J = 6.83, Me); 2.31 (3H, s, 6'-Me); 2.55 (3H, s, 6-Me); 4.06 (1H, d, J_{gem} = 14.94, 2'-H); 4.32 (2H, q, J = 6.84, CH$_2$); 5.67 (1H, d, $J_{2'4'}$ = 1.70, J_{gem} = 14.94, 2'-H); 6.86 (1H, s, $J_{2'4'}$ = 1.70, 4'-H); 7.23 (1H, dd, $J_{5'7'}$ = 1.29, $J_{7'8'}$ = 8.54, 7'-H); 7.27 (1H, s, $J_{5'7'}$ = 1.29, 5'-H); 7.68 (1H, d, J_{78} = 14.94, J_{57} = 1.70, 7-H); 7.78 (1H, d, J_{34} = 8.54, 3-H); 7.8 (1H, s, J_{57} = 1.70, 5-H); 7.99 (1H, d, J_{78} = 14.94, 8-H); 8.34 (1H, d, J_{34} = 8.54, 4-H). Found, %: C 53.39; H 4.21; N 5.36. $C_{23}H_{22}Br_2N_2O_2$. Calculated, %: C 53.31; H 4.28; N 5.41.

6'-Bromo-2,3'-biquinolyl (8). A solution of compound **7** (1.16 g, 2 mmol) in concentrated hydrochloric acid (20 ml) was boiled for 15 min, after which it was poured into water and neutralized with ammonia solution. The precipitate was filtered off. Yield 0.63 g (94%); mp 138-139°C (alcohol). ^{1}H NMR spectrum (DMF-d$_7$), δ, ppm, J (Hz): 7.69 (1H, t, J_{56} = 8.11, J_{67} = 6.94, 6-H); 7.85 (1H, d, J_{56} = 8.11, 5-H); 7.89 (1H, t, J_{67} = 6.98, J_{78} = 8.47, 7-H); 8.01 (1H, dd, $J_{7'8'}$ = 8.97, $J_{5'7'}$ = 2.14, 7'-H); 8.10 (1H, d, $J_{7'8'}$ = 8.97, 8'-H); 8.21 (1H, d, J_{78} = 8.47, 8-H); 8.41 (1H, d, J_{34} = 8.64, 3-H); 8.47 (1H, s, $J_{5'7'}$ = 2.14, 5'-H); 8.62 (1H, d, J_{34} = 8.64, 4-H); 9.25 (1H, s, $J_{2'4'}$ = 2.13, 4'-H); 9.94 (1H, s, $J_{2'4'}$ = 2.13, 2'-H). Mass spectrum, *m/z* (*I*, %): 335 [M]$^+$ (100), 255 [M$^+$–Br] (29). Found, %: C 64.58; H 3.26; N 8.26. $C_{18}H_{11}BrN_2$. Calculated, %: C 64.50; H 3.31; N 8.36.

6',8'-Dibromo-2,3'-biquinolyl (9). To a solution of 1',4'-dihydro-2,3'-biquinolyl (0.51 g, 2 mmol) in alcohol while cooling and stirring we added dropwise bromine (9.92 g, 6.5 mmol). The mixture was left for 15-20 min, poured into water, and neutralized with ammonia solution. The precipitate was filtered off. Yield 0.75 g (91%); mp 220-222°C (alcohol). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, J (Hz): 7.61 (1H, dt, J_{56} = 8.25, J_{67} = 7.15, J_{68} = 1.1, 6-H); 7.81 (1H, dt, J_{67} = 7.15, J_{78} = 8.35, J_{57} = 1.65, 7-H); 7.91 (1H, dd, J_{56} = 8.25, J_{57} = 1.65, 5-H); 8.02 (1H, d, J_{34} = 8.50, 3-H); 8.14 (1H, d, $J_{5'7'}$ = 1.65, 7'-H); 8.20 (1H, d, $J_{5'7'}$ = 1.65, 5'-H); 8.22 (1H, dd, J_{78} = 8.35, J_{68} = 1.1, 8-H); 8.35 (1H, d, J_{34} = 8.50, 4-H); 8.89 (1H, d, $J_{2'4'}$ = 2.20, 4'-H); 9.83 (1H, d, $J_{2'4'}$ = 2.20, 2'-H). Mass spectrum, *m/z* (*I*, %): 414 [M]$^+$ (82.7), 335 [M$^+$–Br] (6.9), 253 (17.2). Found, %: C 52.38; H 2.37; N 6.71. $C_{18}H_{10}Br_2N_2$. Calculated, %: C 52.21; H 2.43; N 6.76.

4',5',6',8'-Tetrabromo-1',2'-dihydro-2,3'-biquinolyl-2'-one (10). To a solution of 1'-methyl-1',2'-dihydro-2,3'-biquinolyl (0.54 g, 2 mmol) in glacial acetic acid (10 ml) at 0°C with stirring we added dropwise bromine (1.6 g, 10 mmol). The mixture was kept at the same temperature for 10-15 min and then at room temperature for 15-20 min. It was then poured into water, neutralized with ammonia solution, and extracted with benzene (3 × 50 ml). The benzene was evaporated, and light-yellow crystals were obtained. Yield 1.01 g (84%); mp 215-217°C (alcohol). IR spectrum (thin layer), ν, cm^{-1}: 800 (C–Br), 1600 (C=O). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm, J (Hz): 4.09 (3H, s, Me); 7.72 (1H, s, 7'-H); 7.73 (1H, dt, J_{56} = 8.11, J_{67} = 8.54, J_{68} = 1.28, 6-H); 7.87 (1H, dt, J_{67} = 8.54, J_{78} = 8.11, J_{57} = 1.28, 7-H); 7.93 (1H, d, J_{34} = 8.54, 4-H); 8.11 (1H, dd, J_{56} = 8.11, J_{57} = 1.28, 5-H); 8.14 (1H, dd, J_{78} = 8.11, J_{68} = 1.28, 8-H); 8.61 (1H, d, J_{34} = 8.54, 3-H). Mass spectrum, *m/z* (*I*, %): 574 [M$^+$–CO] (5.6), 495 (64.2), 415 (33.2), 336 (9.7), 253 (100). Found, %: C 37.98; H 1.59, N 4.56. $C_{19}H_{10}Br_4N_2O$. Calculated, %: C 37.91; H 1.67; N 4.65.

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