

INVESTIGATIONS IN THE REGION OF 2,3'-BIQUINOLINE.

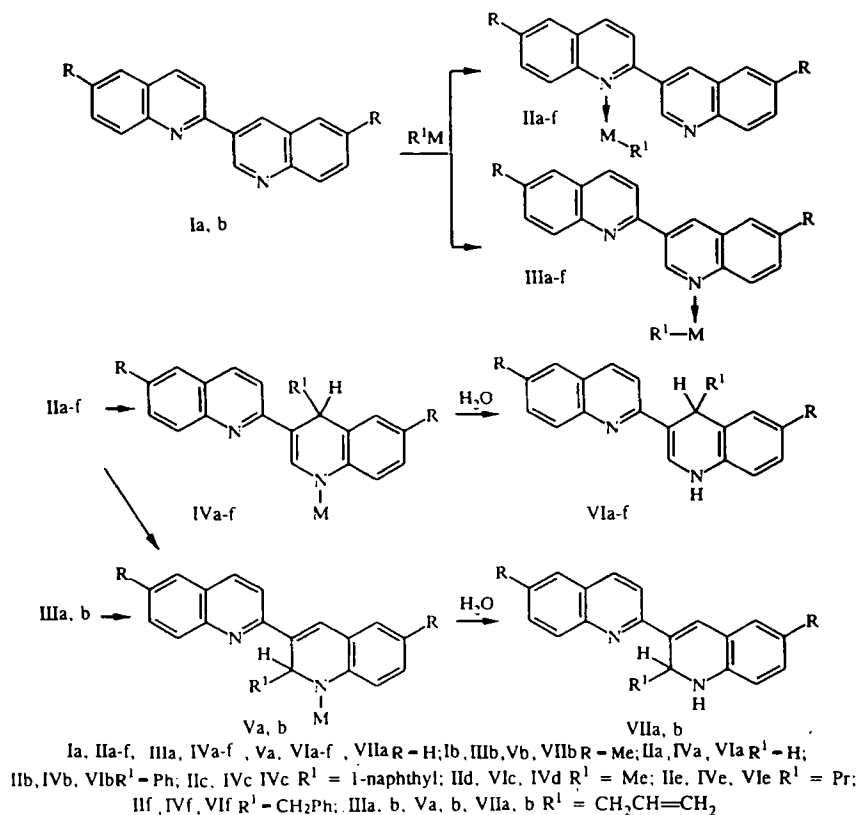
2.* INVESTIGATION OF THE NUCLEOPHILIC ADDITION OF ORGANOMAGNESIUM COMPOUNDS AND SODIUM HYDRIDE TO 2,3'-BIQUINOLINE

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With sodium hydride and alkyl- and arylmagnesium halides, 2,3-biquinoline forms the products from addition at position 4', and with allylmagnesium chloride it forms the products from addition at position 2'. Methods were developed for the synthesis of 4'-R-1',4'-dihydro- and 2'-allyl-1',2'-dihydro-2,3'-biquinolines.

In a continuation of researches into the synthesis and reactivity of 2,3'-biquinolines (Ia, b) [1-4], we studied the reaction of the latter with sodium hydride and Grignard reagents. In spite of the fact that such reactions of azines are well known [5], they have been studied very little in the series of unsymmetrical bisheteroaromatic compounds.

Scheme 1



*For Communication 1, see [1].

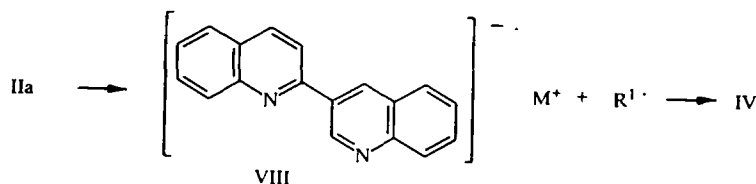
Stavropol' State University, Stavropol 355009, Russia. Russian Chemical Technology University, Moscow 125190. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 2, pp. 232-235, February, 1998. Original article submitted May 16, 1997.

A priori attack on 2,3'-biquinoline (Ia) by nucleophilic reagents can take place at one of three possible positions, i.e., at positions 4, 2', and 4'. It is known [5] that an important role in nucleophilic addition (substitution) reactions is played by the formation of complexes with the metal cation. In the case of 2,3'-biquinoline complex formation is basically possible in two directions. This can lead to the appearance of complexes (II) and (III) with the subsequent formation of the products from addition at positions 2' [compound (IV)] and 4' [compound (V)] respectively (Scheme 1). As seen from the presented scheme, it is not possible to reach a conclusion about the regioselectivity of nucleophilic addition to (Ia, b) on the basis of complexation. We suppose that the regioselectivity of nucleophilic addition under the conditions of kinetic control must depend on the relative "hardness" ("softness") of the nucleophilic reagent.

In the case of hard reagents a polar (ionic) mechanism is realized, and the regioselectivity of nucleophilic addition is determined by the magnitude of the overall positive charge. In the molecule of 2,3'-biquinoline, the largest positive charge is concentrated at position 2'. This is confirmed by MNDO calculations (Fig. 1) and by the data from NMR spectroscopy (the chemical shifts of the proton at position 2' — 9.76 ppm — and of the protons at positions 4' and 4 — 8.93 and 8.23 ppm respectively).

With relatively soft reagents there is an SET mechanism, including the formation of charge-transfer complexes and the subsequent transfer of an electron to the substrate with the formation of the radical-anion (VIII) (Scheme 2), in which according to data in [1] the highest spin density is localized at position 4'. Consequently, relatively soft reagents must add at position 4'.

Scheme 2



As shown by our previous investigations [3], the one-electron reduction potential of 2,3'-biquinoline is lower than that of quinoline. An increase in the probability of the SET mechanism must therefore be expected in the case of (Ia, b).

In fact, in the reaction of (Ia) with the relatively soft sodium hydride at 160°C in diethylene glycol diethyl ether we obtained a quantitative yield of 1',4'-dihydro-2,3'-biquinoline (VI_f), whereas a mixture of the 1,2- and 1,4-dihydro derivatives in a ratio of 2:3 was formed in the case of quinoline [6].

The reaction of (Ia) with alkyl- and arylmagnesium halides (in a mixture of absolute ether with THF at room temperature) leads to the products from addition at position 4', i.e., to 4'-alkyl- and 4'-aryl-1',4'-dihydro-2,3'-biquinolines (VI_{a-e}) with yields close to quantitative.

According to data in [7], allylmagnesium is a harder nucleophile than alkyl- and arylmagnesium halides. With (Ia, b) under similar conditions it therefore gives the products from addition at position 2', i.e., 2'-allyl-1',2'-dihydro-2,3'-biquinolines (VII_{a, b}) with yields of 90-94%. In this case, it is convenient to conduct the reaction with the production of allylmagnesium chloride *in situ* from magnesium and allyl chloride in the presence of 2,3'-biquinoline.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WP-200 spectrometer with TMS as internal standard. The THF and diglyme were purified by distillation over lithium aluminum hydride.

1',4'-Dihydro-2,3'-biquinoline (VI_a) (C₁₈H₁₄N₂). A mixture of 1.28 g (5 mmole) of 2,3'-biquinoline and 0.18 g (7.5 mmole) of sodium hydride in 5 ml of dry diglyme was boiled in an atmosphere of argon for 5 h. On cooling we carefully added 50 ml of water; yellow crystals separated. The yield was 1.27 g (98%); mp 209-211°C (from benzene). Published data [3, 4]: mp 209-211°C.

A mixed melting test with an authentic sample did not give a melting depression. The PMR spectra were identical.

4'-Phenyl-1',4'-dihydro-2,3'-biquinoline (VI_b) (C₂₄H₁₈N₂). To 0.18 g (7.5 mmole) of magnesium we carefully added 1.16 g (7.4 mmole) of bromobenzene in 7 ml of absolute ether, after which the reaction mixture was boiled for 1.5 h.

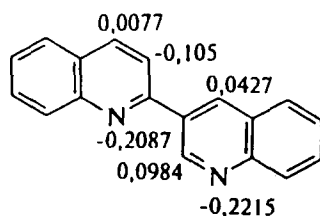


Fig. 1. Distribution of charge in 2,3'-biquinoline (calculated by the MNDO method).

To the obtained solution of phenylmagnesium bromide we carefully added 1.28 g (5 mmole) of 2,3'-biquinoline in 30 ml of tetrahydrofuran. The reaction mixture was stirred for 1 h, 50 ml of water containing 2 ml of acetic acid was added, and the product was extracted with benzene (30 × 3 ml). The benzene extracts were combined, washed with 50 ml of 5% aqueous ammonia, dried over sodium sulfate, and evaporated. Yellow crystals were obtained. The yield was 1.57 g (94%); mp 213-214°C (from benzene). Published data [1]: mp 213-214°C. A mixed melting test with an authentic sample did not give a melting point depression. The PMR spectra were identical.

4'-(1-Naphthyl)-1',4'-dihydro-2,3'-biquinoline (VIc) (C₂₈H₂₀N₂). The compound was obtained similarly to 4'-phenyl-1',4'-dihydro-2,3'-biquinoline from 1.28 g (5 mmole) of 2,3'-biquinoline, 1.12 g (5.4 mmole) of 1-bromonaphthalene and 0.132 g (5.5 mmole) of magnesium. The product formed yellow crystals. The yield was 1.75 g (91%); mp 196-197°C (from benzene). Published data [1]: mp 196-197°C.

A mixed melting test with an authentic sample did not give a melting point depression. The PMR spectra were identical.

4'-Methyl-1',4'-dihydro-2,3'-biquinoline (VIId) (C₁₉H₁₆N₂). The compound was obtained similarly to 4'-phenyl-1',4'-dihydro-2,3'-biquinoline from 1.28 g (5 mmole) of 2,3'-biquinoline, 1.05 g (7.4 mmole) of methyl iodide, and 0.18 g (7.5 mmole) of magnesium. The yield was 1.18 g (87%); mp 148-149°C (from benzene). PMR spectrum (deuteriochloroform): 1.36 (3H, d, $J = 7.02$ Hz, Me); 4.61 (1H, q, $J = 7.02$ Hz, 4'-H); 6.07 (1H, d, $J_{\text{NH-2'H}} = 5.97$ Hz, NH); 6.68 (1H, dd, $J_{6'8'} = 1.28$, $J_{7'8'} = 7.68$ Hz, 8'-H); 6.97 (1H, dt, $J_{5'6'} = 7.67$, $J_{6'7'} = 7.26$, $J_{6'8'} = 1.28$ Hz, 6'-H); 7.09 (1H, dt, $J_{6'7'} = 7.26$, $J_{7'8'} = 7.68$, $J_{5'7'} = 1.72$ Hz, 7'-H); 7.27 (1H, dd, $J_{5'6'} = 7.67$, $J_{5'7'} = 1.72$ Hz, 5'-H); 7.38 (1H, dt, $J_{56} = 8.11$, $J_{67} = 6.83$, $J_{68} = 1.28$ Hz, 6-H); 7.44 (1H, d, $J_{\text{NH-2'H}} = 5.97$ Hz, 2'-H); 7.52 (1H, d, $J_{34} = 8.96$ Hz, 3-H); 7.62 (1H, dt, $J_{67} = 6.83$, $J_{78} = 8.53$, $J_{57} = 1.71$ Hz, 7-H); 7.70 (1H, dd, $J_{56} = 8.11$, $J_{57} = 1.71$ Hz, 5-H); 7.97 (1H, d, $J_{34} = 8.96$ Hz, 4-H); 7.98 (1H, dd, $J_{78} = 8.53$, $J_{68} = 1.28$ Hz, 8-H). Found %: C 84.13; H 5.81; N 10.06. C₁₉H₁₆N₂. Calculated %: C 83.78; H 5.93; N 10.29.

4'-Propyl-1',4'-dihydro-2,3'-biquinoline (VIe) (C₂₁H₂₀N₂). The compound was obtained similarly to 4'-phenyl-1',4'-dihydro-2,3'-biquinoline from 1.28 g (5 mmole) of 2,3'-biquinoline, 1.26 g (7.4 mmole) of 1-iodopropane, and 0.18 g (7.5 mmole) of magnesium. The product formed yellow crystals. The yield was 1.28 g (85%); mp 127-129°C (from benzene with hexane). PMR spectrum (deuteriochloroform): 0.8 (3H, t, $J = 7.03$ Hz, Me); 1.28 (2H, m, β-CH₂); 1.65 (2H, m, α-CH₂); 4.58 (1H, dd, $J_{\text{cis}} = 4.88$, $J_{\text{trans}} = 6.41$ Hz, 4'-H); 6.04 (1H, d, $J_{\text{NH-2'H}} = 5.5$ Hz, NH); 6.70 (1H, dd, $J_{7'8'} = 7.89$, $J_{6'8'} = 1.22$ Hz, 8'-H); 6.97 (1H, dt, $J_{5'6'} = 7.63$, $J_{6'7'} = 7.32$, $J_{6'8'} = 1.22$ Hz, 6'-H); 7.11 (1H, dt, $J_{6'7'} = 7.32$, $J_{7'8'} = 7.89$, $J_{5'7'} = 1.52$ Hz, 7'-H); 7.22 (1H, dd, $J_{5'6'} = 7.63$, $J_{5'7'} = 1.52$ Hz, 5'-H); 7.38 (1H, dt, $J_{56} = 7.93$, $J_{67} = 7.02$, $J_{68} = 1.22$ Hz, 6-H); 7.52 (1H, d, $J_{\text{NH-2'H}} = 5.5$ Hz, 2'-H); 7.53 (1H, d, $J_{34} = 8.85$ Hz, 3-H); 7.62 (1H, dt, $J_{67} = 7.02$, $J_{78} = 8.55$, $J_{57} = 1.52$ Hz, 7-H); 7.70 (1H, dd, $J_{56} = 7.93$, $J_{57} = 1.52$ Hz, 5-H); 7.97 (1H, dd, $J_{78} = 8.55$, $J_{68} = 1.22$ Hz, 8-H); 7.98 (1H, d, $J_{34} = 8.85$ Hz, 4-H). Found %: C 84.32; H 6.58; N 9.1. C₂₁H₂₀N₂. Calculated %: C 83.95; H 6.72; N 9.33.

4'-Benzyl-1,4'-dihydro-2,3'-biquinoline (VIIf) (C₂₅H₂₀N₂). The compound was obtained similarly to 4'-phenyl-1',4'-dihydro-2,3'-biquinoline from 1.28 g (5 mmole) of 2,3'-biquinoline, 0.94 g (7.4 mmole) of benzyl chloride, and 0.18 g (7.5 mmole) of magnesium. The yield was 1.6 g (92%); mp 161-163°C (from benzene). PMR spectrum (deuteriochloroform): 2.87 (1H, dd, $J_{\text{gem}} = 12.79$, $J_{\text{trans}} = 8.04$ Hz, CH₂); 3.06 (1H, dd, $J_{\text{gem}} = 12.79$, $J_{\text{cis}} = 3.65$ Hz, CH₂); 4.88 (1H, dd, $J_{\text{trans}} = 8.04$, $J_{\text{cis}} = 3.65$ Hz, 4'-H); 5.93 (1H, d, $J_{\text{NH-2'H}} = 5.84$ Hz, NH); 6.61 (1H, dd, $J_{7'8'} = 7.94$, $J_{6'8'} = 1.21$ Hz, 8'-H); 6.75 (1H, dd, $J_{5'6'} = 7.68$, $J_{5'7'} = 1.83$ Hz, 5'-H); 6.81 (1H, dt, $J_{5'6'} = 7.68$, $J_{6'7'} = 7.31$, $J_{6'8'} = 1.21$ Hz, 6'-H); 6.92 (2H, m, 2''-H, 6''-H); 7.06 (1H, dt, $J_{6'7'} = 7.31$, $J_{7'8'} = 7.94$, $J_{5'7'} = 1.83$ Hz, 7'-H); 7.13

(3H, m, 3''-H, 4''-H, 5''-H); 7.35 (1H, d, $J_{\text{NH}-2'-\text{H}} = 5.84$ Hz, 2'-H); 7.4 (1H, dt, $J_{56} = 7.87$, $J_{67} = 6.81$, $J_{68} = 1.24$ Hz, 6-H); 7.53 (1H, d, $J_{34} = 9.13$ Hz, 3-H); 7.66 (1H, dt, $J_{67} = 6.81$, $J_{78} = 8.41$, $J_{57} = 1.59$ Hz, 7-H); 7.71 (1H, dd, $J_{56} = 7.87$, $J_{68} = 1.59$ Hz, 5-H); 7.96 (1H, d, $J_{34} = 9.13$ Hz, 4-H); 8.06 (1H, dd, $J_{78} = 8.41$, $J_{68} = 1.24$ Hz, 8-H). Found %: C 86.38; H 5.63; N 7.99. $\text{C}_{25}\text{H}_{20}\text{N}_2$. Calculated %: C 86.17; H 5.79; N 8.04.

2'-Allyl-1',2'-dihydro-2,3'-biquinoline (VIIa) ($\text{C}_{21}\text{H}_{18}\text{N}_2$). A mixture of 0.64 g (2.5 mmole) of 2,3'-biquinoline, 72 mg (3 mmole) of magnesium, and 0.23 g (3 mmole) of allyl chloride in 5 ml of THF was stirred for 2 h in an atmosphere of argon at room temperature. We added 50 ml of water containing 2 ml of acetic acid and extracted the product with benzene (30 × 3 ml). The benzene extracts were combined, washed with 50 ml of 5% ammonia solution, dried with sodium sulfate, and evaporated. Yellow crystals were obtained. The yield was 0.68 g (91%); mp 104-105°C (from alcohol). PMR spectrum (deuteriochloroform): 2.46 (2H, m, $\alpha\text{-CH}_2$); 4.57 (1H, bs, NH); 5.08 (1H, dd, $J_{\text{gem}} = 2.13$, $J_{\text{trans}} = 17.09$ Hz, $\gamma\text{-CH}_2$); 5.18 (2H, m, 2'-H and $\gamma\text{-CH}_2$); 5.94 (1H, m, CH); 6.56 (1H, d, $J_{7'8'} = 8.12$ Hz, 8'-H); 6.68 (1H, dd, $J_{5'6'} = 7.22$, $J_{6'7'} = 7.34$ Hz, 6'-H); 7.07 (1H, dd, $J_{6'7'} = 7.34$, $J_{7'8'} = 8.12$, $J_{5'7'} = 1.52$ Hz, 7'-H); 7.11 (1H, d, $J_{5'6'} = 7.22$ Hz, 5'-H); 7.33 (1H, s, 4'-H); 7.48 (1H, dd, $J_{56} = 8.13$, $J_{67} = 7.37$ Hz, 6-H); 7.68 (1H, dd, $J_{67} = 7.37$, $J_{78} = 8.24$ Hz, 7-H); 7.71 (1H, d, $J_{56} = 8.13$ Hz, 5-H); 7.83 (1H, d, $J_{34} = 8.55$ Hz, 3-H); 8.03 (1H, d, $J_{78} = 8.24$ Hz, 8-H); 8.09 (1H, d, $J_{34} = 8.55$ Hz, 4-H). Found %: C 84.79; H 5.94; N 9.27. $\text{C}_{21}\text{H}_{18}\text{N}_2$. Calculated %: C 84.53; H 6.08; N 9.39.

6,6'-Dimethyl-2'-allyl-1',2'-dihydro-2,3'-biquinoline (VIIb) ($\text{C}_{23}\text{H}_{22}\text{N}_2$). The compound was obtained similarly to 2'-allyl-1',2'-dihydro-2,3'-biquinoline from 0.71 g (2.5 mmole) of 6,6'-dimethyl-2,3'-biquinoline, 72 mg (3 mmole) of magnesium, and 0.23 g (3 mmole) of allyl chloride. The product formed yellow crystals. The yield was 0.76 g (93%); mp 163-164°C (from benzene or alcohol). PMR spectrum (deuteriochloroform): 2.25 (3H, s, 6'-Me); 2.43 (2H, m, $\alpha\text{-CH}_2$); 2.52 (3H, s, 6-Me); 4.48 (1H, bs, NH); 5.05 (1H, dd, $J_{\text{gem}} = 2.13$, $J_{\text{trans}} = 17.09$ Hz, $\gamma\text{-CH}_2$); 5.15 (2H, m, 2'-H and $\gamma\text{-CH}_2$); 5.92 (1H, m, CH); 6.49 (1H, d, $J_{7'8'} = 8.24$ Hz, 8'-H); 6.88 (1H, d, $J_{7'8'} = 8.24$ Hz, 7'-H); 6.92 (1H, s, 5'-H); 7.28 (1H, s, 4'-H); 7.48 (1H, d, $J_{78} = 8.24$ Hz, 7-H); 7.52 (1H, s, 5-H); 7.77 (1H, d, $J_{34} = 8.55$ Hz, 3-H); 7.92 (1H, d, $J_{78} = 8.24$ Hz, 8-H); 8.00 (1H, d, $J_{34} = 8.55$ Hz, 4-H). Found %: C 84.92; H 6.61; N 8.47. $\text{C}_{23}\text{H}_{22}\text{N}_2$. Calculated %: C 84.63; H 6.79; N 8.58.

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