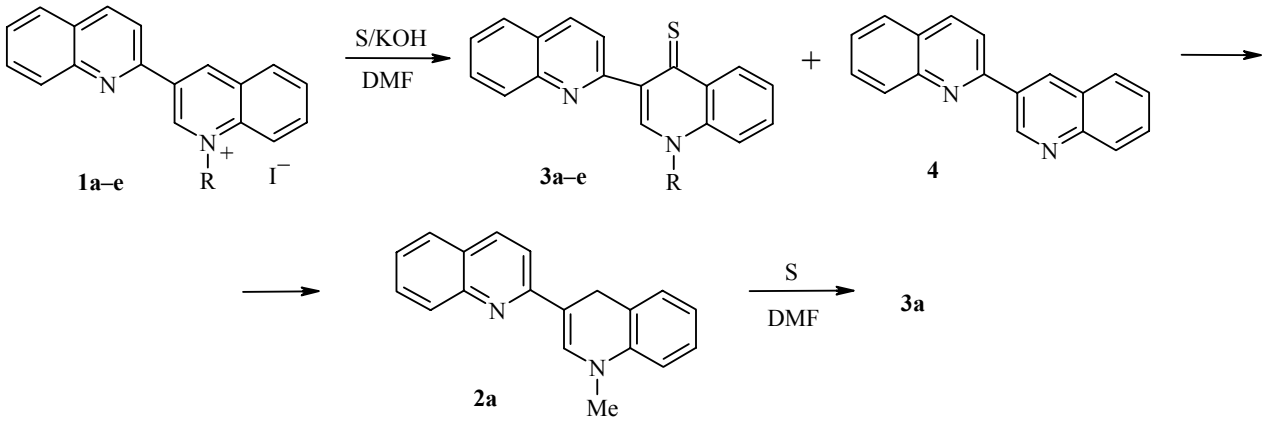
INVESTIGATIONS ON 2,3'-BIQUINOLINES. 18*. NEW CONVENIENT ONE-POT SYNTHESIS OF 1'-ALKYL-1',4'-DIHYDRO-2,3'-BIQUINOLYL-4'-THIONES AND THEIR CONVERSION INTO 1'-ALKYL-1',4'-DIHYDRO-2,3'-BIQUINOLYL-4'-ONES

D. V. Moiseev[1], N. V. Demidova[1], V. I. Goncharov[2], and A. V. Aksenov[1]

A method has been developed for the one pot synthesis of 1'-alkyl-1',4'-dihydro-2.3'-biquinolyl-4'-thiones based on the reduction of 1-alkyl-3-(2-quinolyl)quinolinium halides with sodium borohydride and subsequent thiolation. 1'-Alkyl-1',4'-dihydro-2,3'-biquinolyl-4'-ones were obtained in close to quantitative yield by the oxidation of 1'-alkyl-1',4'-dihydro-2,3'-biquinolyl-4'-thiones.

Keywords: 1'-alkyl-1',4'-dihydro-2,3'-biquinolyl-4'-ones, 1'-alkyl-1',4'-dihydro-2,3'-biquinolyl-4'-thiones, sodium borohydride, 1-alkyl-3-(2-quinolyl)-quinolinium halides, 1',4'-dihydro-2,3'-biquinolines, sulfur, oxidation, thiolation.

The thiocarbonyl group offers broad possibilities for the synthetic chemist. As a result of its ready polarizability it acts as an a^0, a^1, d^0, and even a d^1 synthon [2]. In addition many 4-quinolones possess high biological activity. In view of this the development of methods of synthesizing thioaldehydes and thioketones, and also 4-quinolones is an urgent problem.



1, 3 a R = Me, **b** R = Et, **c** R = Bu, **d** R = $CH_2CH_2CHMe_2$, **e** R = CH_2Ph

* For Part 17 see [1].

[1] Stavropol State University, Stavropol 355009, Russia; e-mail: biochem-org@stavsu.ru. [2] Stavropol State Medical Academy, Stavropol 355017, Russia; e-mail: sgma@stavropol.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 67-70, January, 2006. Original article submitted May 3, 2004.

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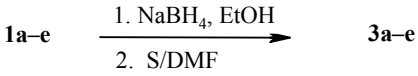
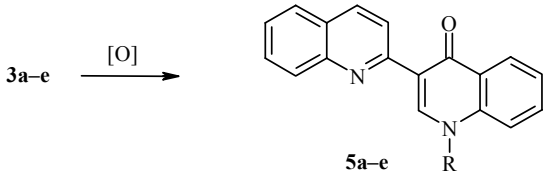
Previously we developed two methods of synthesizing 1'-alkyl-1',4'-dihydro-2,3'-biquinolyl-4'-thiones from quaternized 2,3'-biquinolines **1a-c** [3] and from 1'-alkyl-1',4'-dihydro derivatives **2** [4]. In the first case the synthetic value of the method is reduced due to the low yield of thiones **3** for salts **1a,b,e** which is linked with competing dealkylation (with the formation of biquinolyl **4**) and thiolation. In the second, in spite of the close to quantitative yield of thiones **1**, limitations exist linked with the stability, and consequently the accessibility, of dihydro derivatives **2**.

We improved the method of thiolating of salts **1**, using the following sequence of steps: protection of the 1'-alkyl group in salts **1** by reducing them with $NaBH_4$ into dihydro derivatives **2** and then thiolation of the latter with elementary sulfur as a one pot conversion.



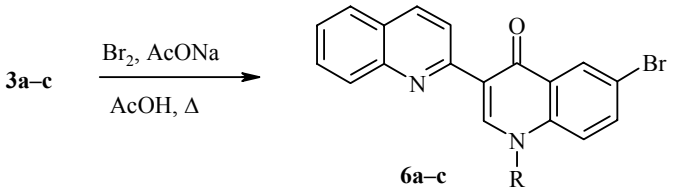
Such a method permitted thiones **3** to be obtained from salts **1** almost quantitatively (90-96% after recrystallization), including some which were impossible to obtain by the direct thiolation of salts **1**, such as 1'-benzyl-1',4'-dihydro-2,3'-biquinolyl-4'-thione (**3e**) [2].

In view of the biological activity of 4-quinolones we developed an efficient method of synthesizing the poorly accessible quinolones **5a-e** by the oxidation of thiones **3a-e**. The acetates of lead and mercury or elementary bromine were used as oxidizing agent. In all cases compounds **5a-e** were formed in yields close to quantitative.



5 a R = Me; **b** R = Et; **c** R = Bu; **d** R = $CH_2CH_2CHMe_2$; **e** R = CH_2Ph

Further, we succeeded in combining the process of oxidizing thiones **3** with bromine and the bromination of quinolones **5**. Treatment of compounds **3** with an excess of bromine in the presence of sodium acetate in boiling glacial acetic acid led to the 6'-bromo derivative **6** in 65-74% yield.



6 a R = Me; **b** R = Et, **c** R = Bu

EXPERIMENTAL

The NMR spectra were recorded on a Bruker WP 200 (200 MHz) instrument, internal standard was TMS. The IR spectra were recorded in KBr disks on a Hitachi 215 spectrometer. A check on the progress of reactions and the homogeneity of the compounds synthesized was effected on Silufol UV 254 plates in the system ethyl acetate–hexane, 1:1.

1'-Alkyl-1',4'-dihydro-2,3'-biquinolyl-4'-thiones 3a-e (General Procedure). 1-Alkyl-3-(2-quinolyl)quinolinium iodide [4] **1a-e** (2 mmol) and $NaBH_4$ (0.152 g, 4 mmol) in a mixture of ethanol (5 ml) and DMF (10 ml) (reduction goes slowly in pure DMF) were boiled with an air condenser for 1 h (to remove ethanol after reduction: thiolation proceeds in boiling DMF). Sulfur (6 mmol) was added to the reaction mixture, which was then boiled for a further 3 h, and poured into 1% KOH solution (100 ml). The orange solid was filtered off, dried, and recrystallized from alcohol.

1'-Methyl-1',4'-dihydro-2,3'-biquinolyl-4'-thione (3a). Yield 0.57 g (95%); mp 180-182°C (alcohol) (Lit. mp 179-180°C [2]). The ^{1}H NMR spectrum was identical with that described in [2].

1'-Ethyl-1',4'-dihydro-2,3'-biquinolyl-4'-thione (3b). Yield 0.58 g (91%); mp 118-119°C (alcohol) (Lit. mp 115-116°C [2]). The ^{1}H NMR spectrum was identical with that described in [2].

1'-Butyl-1',4'-dihydro-2,3'-biquinolyl-4'-thione (3c). Yield 0.66 g (96%); mp 122-124°C (alcohol) (Lit. mp 122-123°C [2]. The ^{1}H NMR spectrum was identical to that described in [2].

1'-Isopentyl-1',4'-dihydro-2,3'-biquinolyl-4'-thione (3d). Yield 0.68 g (95%); mp 131-134°C (alcohol). ^{1}H NMR spectrum (CD_3CN), δ, ppm (*J*, Hz): 1.01 (6H, d, J = 7.4, Me_2); 1.82 (2H, m, $CH_2CH_2C\underline{H}Me_2$, $CH_2C\underline{H}_2CHMe_2$); 4.41 (2H, t, J = 7.1, $C\underline{H}_2CH_2CHMe_2$); 7.57 (1H, m, H-6'); 7.59 (1H, m, H-6); 7.74 (1H, dd, J_{67} = 7.1, J_{78} = 8.5, H-7); 7.83 (2H, m, H-7', 8'); 7.93 (1H, d, J_{56} = 7.7, H-5); 8.05 (1H, d, J_{78} = 8.5, H-8); 8.20 (1H, d, J_{34} = 8.5, H-4); 8.27 (1H, s, H-2'); 8.32 (1H, d, J_{34} = 8.5, H-3); 9.15 (1H, d, $J_{5'6'}$ = 8.5, H-5'). Found, %: C 77.58; H 5.51; N 7.74. $C_{23}H_{22}N_2S$. Calculated, %: C 77.09; H 5.59; N 7.82.

1'-Benzyl-1',4'-dihydro-2,3'-biquinolyl-4'-thione (3e). Yield 0.68 g (90%); mp 219-221°C (alcohol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 5.84 (2H, s, CH_2); 7.3-7.4 (5H, m, C_6H_5); 7.56 (1H, d d, $J_{5'6'}$ = 8.0, $J_{6'7'}$ = 6.9, H-6'); 7.60 (1H, dd, J_{56} = 8.41, J_{67} = 7.0, H-6); 7.75 (2H, m, H-7, 7'); 7.86 (1H, d, $J_{7'8'}$ = 8.4, H-8'); 7.99 (1H, d, J_{56} = 8.4, H-5); 8.05 (1H, d, J_{78} = 8.4, H-8); 8.28 (1H, d, J_{34} = 8.8, H-4); 8.30 (1H, d, J_{34} = 8.8, H-3); 8.68 (1H, s, H-2'); 9.03 (1H, d, $J_{5'6'}$ = 8.0, H-5'). Found, %: C 79.87; H 4.69; N 7.33. $C_{25}H_{18}N_2S$. Calculated, %: C 79.37; H 4.76; N 7.41.

1'-R-1',4'-Dihydro-2,3'-biquinolyl-4'-ones 5a-e (General Procedure). A. A mixture of 1'-R-1',4'-dihydro-2,3'-biquinolyl-4'-thione **3** (1 mmol) and Pb_3O_4 or HgO (2 mmol) was dissolved in glacial acetic acid and stirred for 3 h at ~20°C. The reaction mixture was poured into water (50 ml), neutralized with KOH solution, extracted with benzene (3 × 30 ml), and the extract evaporated.

B. A mixture of compound **3** (1 mmol) and bromine (0.32 g, 2 mmol) was dissolved in glacial acetic acid (10 ml) and stirred for 10 min at ~20°C. The reaction mixture was poured into water (50 ml), neutralized with 25% ammonia solution, extracted with benzene (3 × 30 ml), and the extract evaporated.

1'-Methyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (5a). A, yield 0.17 g (58%). B, yield 0.27 g (94%); mp 193-195°C (benzene). Lit. mp 193-194°C [6]. The ^{1}H NMR spectrum was identical to that described in [6].

1'-Ethyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (5b). A, yield 0.21 g (71%). B, yield 0.26 g (88%); mp 139-140°C (benzene). Lit. mp 139-140°C [6]. The ^{1}H NMR spectrum was identical to that described in [6].

1'-Butyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (5c). A, yield 0.14 g (42%). B, yield 0.3 g (92%); mp 124-126°C (benzene). Lit. mp 125-126°C [6]. The ^{1}H NMR spectrum was identical to that described in [6].

1'-Isopentyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (5d). A, yield 0.16 g (46%). B, yield 0.31 g (91%); mp 105-107°C (benzene). ^{1}H NMR spectrum, ($CDCl_3$), δ, ppm (*J,* Hz): 1.06 (6H, d, J = 6.7, CH_3); 1.87 (3H, m, 1'-$CH_2CH_2C\underline{H}Me_2$, 1'-$CH_2C\underline{H}_2CHMe_2$); 4.39 (2H, t, J = 7.7, 1'-$C\underline{H}_2CH_2CH_2CH_3$); 7.47 (1H, dd, $J_{5'6'}$ = 7.9, $J_{6'7'}$ = 7.3, H-6'); 7.53 (1H, dd, J_{56} = 7.5, J_{67} = 7.2, H-6); 7.56 (1H, d, $J_{7'8'}$ = 8.2, H-8'); 7.69 (1H, dd, $J_{6'7'}$ = 7.3, $J_{7'8'}$ = 8.2, H-7'); 7.71 (1H, dd, J_{67} = 7.2, J_{78} = 8.3, H-7); 7.84 (1H, d, J_{56} = 7.5, H-5); 8.10 (1H, dd, J_{78} = 8.3, J_{48} = 0.6, H-8); 8.25 (1H, dd, J_{34} = 8.8, J_{48} = 0.6, H-4); 8.65 (1H, d, $J_{5'6'}$ = 7.9, H-5'); 8.94 (1H, d, J_{34} = 8.8, H-3); 9.09 (1H, s, H-2'). IR spectrum, ν, cm^{-1}: 1619 (C=O). Found, %: C 80.75; H 6.41; N 8.13. $C_{23}H_{22}N_2O$. Calculated, %: C 80.67; H 6.48; N 8.18.

1'-Benzyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (5e). A, yield 0.24 g (67%). B, yield 0.34 g (93%); mp 170-172°C (benzene). Lit. mp 171-172°C [6]. The ^{1}H NMR spectrum was identical to that described in [6].

1'-Alkyl-6'-bromo-1',4'-dihydro-2,3'-biquinolyl-4'-ones 6a-c (General Procedure). A mixture of compound **3a-c** (1 mmol), anhydrous sodium acetate (0.2 g, 2.5 mmol), and bromine (0.8 g, 5 mmol) in glacial acetic acid (15 ml) was boiled for 5 h. The reaction mixture was poured into water (50 ml), and neutralized with 25% ammonia solution to a weakly alkaline reaction. The mixture was then extracted with benzene (3 × 30 ml). The organic layer was separated, dried over Na_2SO_4, and evaporated. Beige crystals were obtained.

6'-Bromo-1'-methyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (6a). Yield was 0.26 g (71%); mp 230-231°C (alcohol). Lit. 230-231°C [1]. The ^{1}H NMR spectrum was identical to that described in [1].

6'-Bromo-1'-ethyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (6b). Yield 0.25 g (65%); mp 206-207°C (alcohol). Lit. mp 206-207°C [1]. The ^{1}H NMR spectrum was identical to that described in [1].

6'-Bromo-1'-butyl-1',4'-dihydro-2,3'-biquinolyl-4'-one (6c). Yield 0.3 g (74%); mp 186-188°C (alcohol). Lit. mp 186-187°C [1]. The ^{1}H NMR spectrum was identical to that described in [1].

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