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# INVESTIGATIONS IN 2,3'-BIQUINOLINE SERIES

# 24*. SYNTHESIS OF 3-HETARYLQUINOLINES AND THEIR 1,4-DIHYDRO DERIVATIVES UNDER CONDITIONS OF THE VILSMEIER REACTION

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*Methods have been developed for the synthesis of 2,3'-biquinolines, their 1',4'-dihydro derivatives, 3-pyrid-2-ylquinolines, and 3-pyrazin-2-ylquinoline based on the interaction of hetarylethylenes and vinyl butyl ether with imidoyl chlorides and Vilsmeier complexes. Using the example of the synthesis of 3-hetarylquinolines and their dihydro derivatives the synthetic possibilities of the Vilsmeier method were shown for creating various bonds in different quinoline nuclei of the bisheterocyclic system.*

**Keywords:** acid amides, 2,3'-biquinolines, 1',4'-dihydro-2,3'-biquinolines, 3-pyrid-2-ylquinolines, 3-pyrazin-2-ylquinoline, Vilsmeier reaction, cyclization.

A series of methods was developed previously for the synthesis of 2,3'-biquinolines **6** based on the coupling of quinolines by the action of various catalysts, for example [2-5], with the closing of bonds N(1')–C(2') and C(3')–C(4') [6-8], N(1)–C(2) and C(3)–C(4) [9, 10]. There are no methods comprising formation of the C(4')–C(4'a) and C(4)–C(4a) bonds. In the present work we report a series of such methods developed by us based on formylation and acylation of substituted ethylenes by compounds related to the Vilsmeier reagent.

We have shown that 2,3'-biquinolines **6a-f** may be obtained by the interaction of acid amides with compounds **3b** in the presence of $POCl_3$. Yields were 27-61%.

Replacement of the dimethylamino group in compound **3b** by hydrogen, alkyl, or aryl enabled the reaction to be stopped at the stage of forming the dihydro derivatives **7a-e**, the yield of which was 56-76%*[2].

The reaction probably includes the formation of salt **2** at the first stage, which adding at the double bond of compounds **3** form cations **4**. Their subsequent cyclization leads to compound **5**, which by losing HCl, is converted into the dihydro derivative **7** or, by losing HCl and dimethylamine, forms biquinolines **6**.

The method may also be used for the synthesis of other 3-hetarylquinolines.

* For Communication 23 see [1].

*[2] For a preliminary report see [11].

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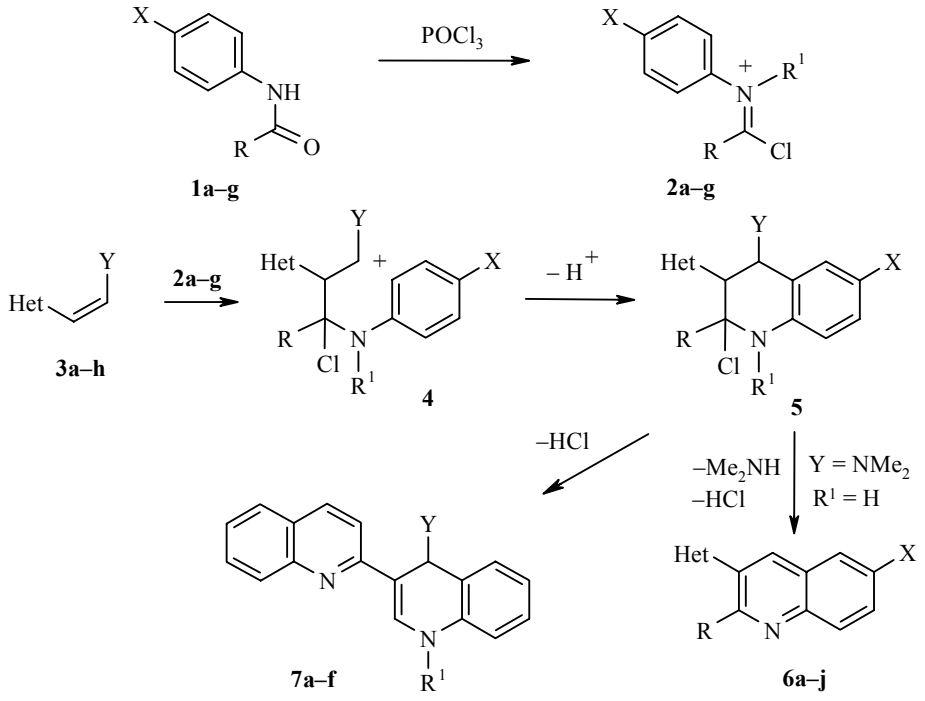
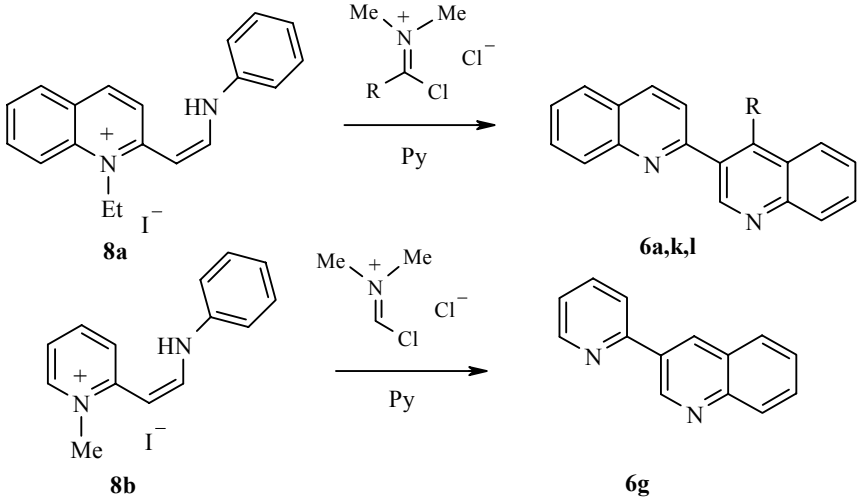
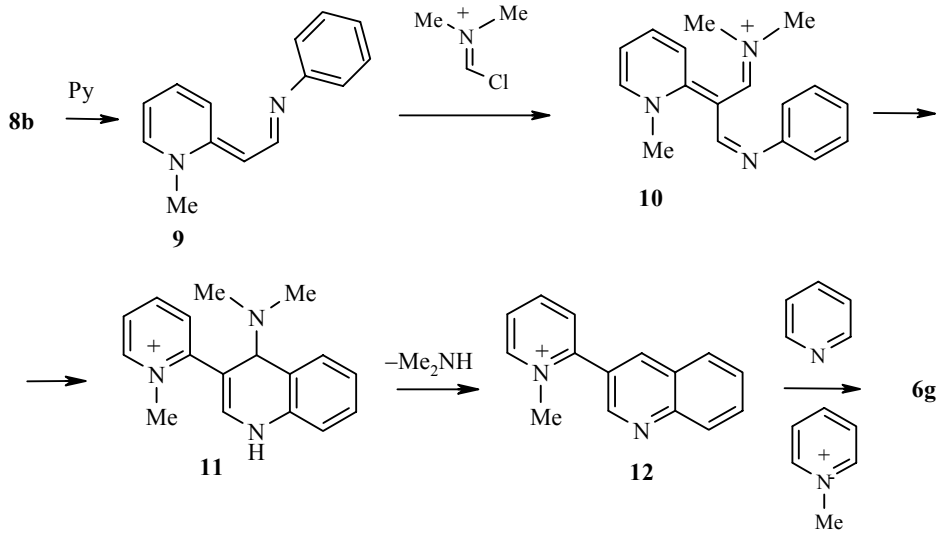



**1, 2 a–e** $R^1$ = X = H, **a** R = H, **b** R = Me, **c** R = Pr, **d** R = Bu, **e** R = Ph, **f** R = $R^1$ = H, X = Br, **g** R = X = H, $R^1$ = Me; **3 a–d** Het = quinol-2-yl, **a** Y = H, **b** Y = $NMe_2$, **c** Y = Me, **d** Y = Ph, **e–h** Y = $NMe_2$, e Het = pyrid-2-yl, **f** Het = 5-methylpyrid-2-yl, **g** Het = 5-bromopyrid-2-yl, **h** Het = pyrazin-2-yl; **6 a–f** Het = quinol-2-yl, **a** R = X = H, **b** R = Me, X = H, **c** R = Pr, X = H, **d** R = Bu, X = H, **e** R = Ph, X = H, **f** R = H, X = Br, **g–j** R = X = H, **g** Het = pyrid-2-yl, **h** Het = 5- methylpyrid-2-yl, **i** Het = 5- methylpyrid-2-yl, **j** Het = pyrazin-2-yl; **7 a** $R^1$ = Y = H, **b** $R^1$ = H, Y = Me, **c** $R^1$ = H, Y = Ph, **d** $R^1$ = Me, Y = H, **e** Y = $R^1$ = Me, **f** $R^1$ = Me, Y = Ph

In the following part of our work we carried out a variant of the Vilsmeier procedure for the synthesis of 3-hetarylquinolines. We showed that 2,3'-biquinolines **6a,k,l** may be obtained in 72-78% yield by the reaction of salt **8a** with chloroimminium salts in pyridine. 3-(2-Pyridyl)quinoline (**6g**) was obtained in 75% yield from salt **8b**.



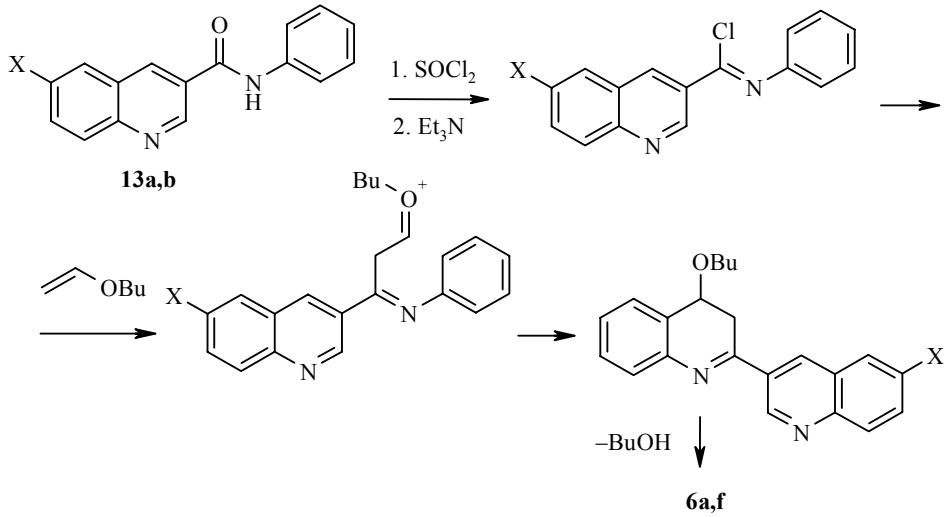

**6 a** R = H, **k** R = Me, **l** R = Ph




This method, unlike the previous, enables 4-substituted 3-hetarylquinolines to be obtained.

The reaction probably proceeds through the following sequence of steps (synthesis of compound **6g** as example). In the first stage deprotonation of salt **8b** occurs. The resulting enamine **9** is converted into salt **10**, which is cyclized with the formation of salt **11**. Subsequently dimethylamine is lost forming salt **12**, demethylation of which with pyridine leads to compound **6g**.

We then showed the use of the Vilsmeier reaction for building the 2-substituted quinoline fragment in 2,3'-biquinolines. The problem is the creation of the C(2)–C(3) and C(4)–C(4') bonds. Anilides of quinoline-3-carboxylic acids **13a,b** were taken as starting materials. We have shown that the sequential reaction of the initial anilide with $SOCl_2$ in chloroform, treatment of the reaction mixture with triethylamine, and then boiling with butyl vinyl ether leads to biquinolines **6a,f** in 58 and 52% yields respectively.




**13 a** X = H, **b** X = Br

The synthetic possibilities of the Vilsmeier procedure has therefore been shown for creating different bonds in various quinolines in bisheterocyclic systems, using the example of the synthesis of 3-hetaryl-quinolines and their dihydro derivatives.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Bruker WP-200 (200 MHz) instrument, internal standard was TMS. A check on the progress of reactions and the homogeneity of the synthesized compounds was carried out on Silufol UV-254 plates, solvent system was ethyl acetate–petroleum ether, 1:1.

**Synthesis of 3-Hetarylquinolines and 1',4'-Dihydro-2,3'-biquinolines by the Reaction of Compounds 3a-h with Acid Anilides in the Presence of $POCl_3$ (M1). (General Method).** A mixture of compound **3a-h** (1 mmol), anilide (1.1 mmol), and $POCl_3$ (2 mmol) in chloroform (5 ml) was boiled for 2.5 h, poured into water (20 ml), neutralized with ammonia solution, and extracted with benzene (3×50 ml). The obtained solution was evaporated and the residue chromatographed. Compounds **6a-j** and **7a-f** were obtained.

**Synthesis of 3-Hetarylquinolines from Salts 8 (M2). (General Method).** To the formylating Vilsmeier mixture obtained by adding $POCl_3$ (0.34 ml, 3.5 mmol) dropwise to the dimethylamide (4 mmol) in pyridine (3 ml), was added a solution of salt **8** (2 mmol) in pyridine (2 ml) in small portions with vigorous stirring. The obtained reaction mixture was boiled for 5 h, cooled, poured onto finely ground ice (30 g), and washed with water. The mixture was extracted with benzene (3×50 ml). The obtained solution was evaporated and the residue chromatographed. Compounds **6a,g,k,l** were obtained.

**Synthesis of 2,3'-Biquinolines from Anilides of Quinoline-3-carboxylic Acids (M3). (General Method).** A mixture of quinoline-3-carboxylic acid anilide (1 mmol), thionyl chloride (1.5 mmol) in chloroform (10 ml) was boiled for 10 min. A precipitate of chloroimminium salt formed. The reaction mixture was cooled and triethylamine (2 ml) was carefully added. The mixture was heated to boiling and butyl vinyl ether (2 mmol) in chloroform (3 ml) was added during 1 h. The mixture was boiled for 4 h, poured into water (20 ml), and extracted with benzene (3×50 ml). The obtained solution was evaporated, and the residue chromatographed. Compounds **6a,f** were obtained.

**2,3'-Biquinoline (6a).** Yield 27 (M1), 78 (M2), 58% (M3); mp 175-176°C (benzene). Lit. mp 175-176°C [2]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [3].

**2'-Methyl-2,3'-biquinoline (6b).** Yield 45%; mp 57-58°C (benzene with hexane). Lit. mp 57-58°C [12]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [12].

**2'-Propyl-2,3'-biquinoline (6c).** Yield 41%. White oil. $^1$H NMR spectrum (acetone-$d_6$), δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.2, 2'-$CH_2CH_2C\underline{H}_3$); 1.70 (2H, m, 2'-$CH_2C\underline{H}_2CH_3$); 3.20 (2H, t, *J* = 7.65, 2'-$C\underline{H}_2CH_2CH_3$); 7.60 (1H, dd, $J_{5',6'}$ = 8.4, $J_{6',7'}$ = 7.0, H-6'); 7.67 (1H, dd, $J_{5,6}$ = 8.05, $J_{6,7}$ = 7.0, H-6); 7.79 (1H, dd, $J_{6',7'}$ = 7.0, $J_{7',8}$ = 8.35, H-7'); 7.85 (1H, dd, $J_{6,7}$ = 7.0, $J_{7,8}$ = 8.3, H-7); 7.87 (1H, d, $J_{3,4}$ = 8.5, H-3); 8.02 (1H, d, $J_{5',6'}$ = 8.4, H-5'); 8.07 (1H, d, $J_{8',7'}$ = 8.35, H-8'); 8.06 (1H, d, $J_{5,6}$ = 8.05, H-5); 8.12 (1H, d, $J_{7,8}$ = 8.3, H-8); 8.43 (1H, s, H-4'); 8.52 (1H, d, $J_{3,4}$ = 8.5, H-4). Found, %: C 84.81; H 6.02; N 9.17. $C_{21}H_{18}N_2$. Calculated, %: C 84.52; H 6.08; N 9.39.

**2'-Butyl-2,3'-biquinoline (6d).** Yield 38%. White oil. The $^1$H NMR spectrum was identical to that given in [12].

**2'-Phenyl-2,3'-biquinoline (6e).** Yield 61%; mp 76-77°C (benzene with hexane). Lit. mp 76-77°C [12]. A melting test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [12].

**6'-Bromo-2,3'-biquinoline (6f).** Yield 34 (M1), 52% (M3); mp 238-239°C (ethanol). Lit. mp 238-239°C [13]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [13].

**3-Pyrid-2-ylquinoline (6g).** Yield 22 (M1), 75% (M2); mp 99-101°C Lit. mp 99-100°C [14]. $^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.18 (1H, d, *J* = 7.7, H-3'); 7.31 (1H, dd, $J_{4',5'}$ = 7.5, $J_{5',6'}$ = 4.7, H-5'); 7.52 (2H, m, H-4',6); 7.71 (1H, dd, $J_{6,7}$ = 7.0, $J_{7,8}$ = 8.1, H-7); 7.89 (1H, d, *J* = 8.1, H-5); 8.14 (1H, d,

$J$ =8.1, H-8); 8.68 (1H, d, $J$ = 2.1, H-4); 8.81 (1H, dd, $J_{5',6'}$ = 4.7, H-6'); 9.56 (1H, d, $J$ = 2.1, H-2). Found, %: C 81.28; H 4.71; N 13.53. $C_{14}H_{10}N_2$. Calculated, %: C 81.53; H 4.89; N 13.58.

**3-(5-Bromopyrid-2-yl)quinoline (6h).** Yield 36%; mp 148-149°C. Lit. mp 150°C [14]. $^1$H NMR spectrum ($CDCl_3$), δ, ppm ($J$, Hz): 7.46 (1H, dd, $J_{6,7}$ = 7.0, $J_{7,8}$ = 8.1, H-6); 7.75 (2H, m, H-5,7); 7.79 (2H, m, H-4',8); 8.03 (1H, d, $J$ = 8.3, H-3'); 8.58 (1H, d, $J$ = 2.2, H-4); 8.68 (1H, d, $J$ = 3.2, H-6'); 9.34 (1H, d, $J$ = 2.2, H-2). Found, %: C 58.83; H 3.16; N 9.54. $C_{14}H_9BrN_2$. Calculated, %: C 58.97; H 3.18; N 9.82.

**3-(5-Methylpyrid-2-yl)quinoline (6i).** Yield 32%; mp 103-104°C. Lit. mp 105°C [15]. $^1$H NMR spectrum ($CDCl_3$), δ, ppm ($J$, Hz): 2.36 (3H, s, $CH_3$); 7.55 (2H, m, H-6,3'); 7.72 (2H, m, H-7,4'); 7.87 (1H, d, $J$ = 8.1, H-5); 8.13 (1H, d, $J$ = 8.1, H-8); 8.56 (1H, s, H-6'); 8.69 (1H, d, $J$ = 2.1, H-4); 9.51 (1H, d, $J$ = 2.1, H-2). Found, %: C 81.93; H 5.38; N 12.96. $C_{15}H_{12}N_2$. Calculated, %: C 81.82; H 5.45; N 12.72.

**3-Pyrazin-2-ylquinoline (6j).** Yield 56%; mp 145-146°C. Lit. mp 146°C [14]. $^1$H NMR spectrum ($CDCl_3$), δ, ppm ($J$, Hz): 7.18 (1H, d, $J$ = 7.7, H-3'); 7.31 (1H, dd, $J_{4',5'}$ = 7.5, $J_{5',6'}$ = 4.7, H-5'); 7.52 (2H, m, H-4',6); 7.71 (1H, dd, $J_{6,7}$ = 7.0, $J_{7,8}$ = 8.1, H-7); 7.89 (1H, d, $J$ = 8.1, H-5); 8.14 (1H, d, $J$ = 8.1, H-8); 8.68 (1H, d, $J$ = 2.1, H-4); 8.81 (1H, dd, $J_{5',6'}$ = 4.7, H-6'); 9.56 (1H, d, $J$ = 2.1, H-2). Found, %: C 75.15; H 4.52; N 19.99. $C_{13}H_9N_3$. Calculated, %: C 75.35; H 4.38; N 20.28.

**4'-Methyl-2,3'-biquinoline (6k).** Yield 72%; mp 137-138°C (benzene with hexane). Lit. mp 137-138°C [16]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [16].

**4'-Phenyl-2,3'-biquinoline (6l).** Yield 76%; mp 133-134°C (benzene with hexane). Lit. mp 133-134°C [17]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [17].

**1',4'-Dihydro-2,3'-biquinoline (7a).** Yield 56%; mp 209-211°C (benzene). Lit. mp 209-211°C [4]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [4].

**4'-Methyl-1',4'-dihydro-2,3'-biquinoline (7b).** Yield 59%; mp 148-149°C (benzene). Lit. mp 148-149°C [18]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [18].

**4'-Phenyl-1',4'-dihydro-2,3'-biquinoline (7c).** Yield 76%; mp 213-214°C (benzene). Lit. mp 213-214°C [17]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [17].

**1'-Methyl-1',4'-dihydro-2,3'-biquinoline (7d).** Yield 61%; mp 146-147°C (ethanol). Lit. mp 213-214°C [19]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [19].

**1',4'-Dimethyl-1',4'-dihydro-2,3'-biquinoline (7e).** Yield 61%; mp 126-127°C (benzene with hexane). Lit. mp 126-127°C [20]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [20].

**1'-Methyl-4'-phenyl-1',4'-dihydro-2,3'-biquinoline (7f).** Yield 76%; mp 173-174°C (ethanol). Lit. mp 173-174°C [17]. A mixing test with an authentic sample gave no depression of melting point. The $^1$H NMR spectrum was identical to that given in [17].

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