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Synthesis of a Bifunctional 1,1′-Diphenyl-1,2,3,4-tetrahydroquinoline Derivative: 1,1′-Diphenyl-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-biquinolinyl-3,3′-diol

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Summary. Intramolecular cyclization of *N*,*N*′-di(3-chloro-2-hydroxy)propyl-*N*,*N*′-diphenylbenzidine occurs to give bis-1,2,3,4-tetrahydroquinoline derivative 1,1′-diphenyl-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-biquinolinyl-3,3′-diol.

Keywords. 1,2,3,4-Tetrahydroquinoline; Epichlorohydrin; Cyclization; 1,1′-Diphenyl-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-biquinolinyl-3,3′-diol; Oxidative coupling.

Introduction

During recent years rapid developments in the chemistry of 1,2,3,4-tetrahydroquinolines have been observed. The growing interest in them can be explained by their biological activities. Substituted tetrahydroquinolines are the core structures in many important pharmacological agents [1–5], many relatively simple synthetic 1,2,3,4-tetrahydroquinolines are already in use or have been tested as potential drugs [6–8]. Besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides [9], antioxidants [10], corrosion inhibitors [11], and active components of various dyes [12]. In addition, they also have found application in modern recording technologies [13, 14]. Consequently, synthesis methodologies for preparing tetrahydroquinoline derivatives have attracted considerable interest and several methods offering good results have been reported [15]. The nature, number, and relative location of the substituents are the key parameters to consider before choosing a method. Until now, much attention has been paid to the development of synthesis of monofunctional 1,2,3,4-tetrahydroquinolines, but the bifunctional 1,2,3,4-tetrahydroquinoline derivatives have been seldom investigated.

Results and Discussion

During our ongoing research program on the study of interaction products of epichlorohydrin with aromatic amines, we have found recently that 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline (**1**) can be prepared from the *N*-2,3-epoxypropyl derivative of diphenylamine [16]. In previous works **1** has been obtained by heating diphenylamine with an excess epichlorohydrin [17, 18]. The same authors have proved the formation of compound **1** *via* the intermediate *N*-(3-chloro-2-hydroxypropyl)diphenylamine [19]. This prompted us to apply these procedures in developing the synthesis of a compound containing two tetrahydroquinoline rings. We expected electrophilic attack of the aliphatic side chains in **2** and **3** on the *o*-position of the phenyl or biphenyl moieties, thus leading to intramolecular cyclization to two tetrahydroquinoline rings hereby giving compounds **4** or **5** (Scheme 1).

First, the reaction of *N*,*N*′-diphenylbenzidine with epichlorohydrin in the presence of KOH at 30–35°C was carried out and **2** was obtained in 55% yield.

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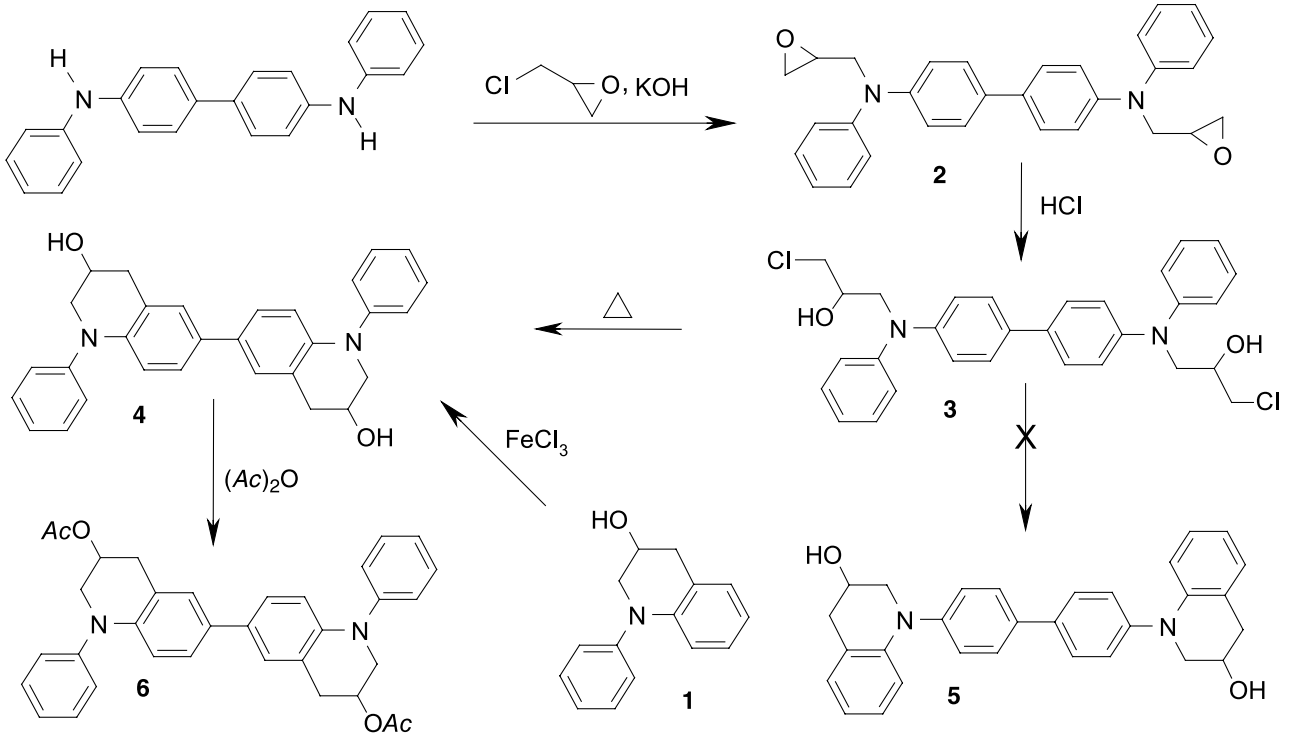

Scheme 1

Unfortunately, all our attempts to isolate the desired tetrahydroquinoline derivative under the reaction conditions described in Ref. [16] were unsuccessful (TLC monitoring showed many substances, the major one remaining at the starting spot, presumably a polymeric product). Next, we focused our attention on compound **3**, which was easily obtained by the action of dilute hydrochloric acid on the diepoxy compound **2**. Initially, **3** was heated at 130°C, *i.e.*, under the conditions at which *N*-(3-chloro-2-hydroxypropyl)diphenylamine would cyclize to **1** [19]. No desired products were observed after 24 h. Only, when the reaction temperature was raised to 155°C (the reaction is carried out at T_b of 1-hexanol), the reaction occurred, and was almost completed within 58 h. TLC monitoring during the course of the reaction showed two products, one of them (presumably monofunctional) gradually blending in favor of the other (bifunctional). The final product with melting point 185–185.5°C was isolated with the help of column chromatography. Since we could expect two possible tetrahydroquinoline products (**4** or **5**), depending on the direction of cyclization, we recorded NMR, IR, and mass spectra.

Thus, the mass spectrum and elemental analysis are consistent with both probable structures **4** or **5**. The ^{1}H NMR spectrum (*DMSO*-d_6) of the isolated product showed the formation of a tetrahydroquinoline ring that can be proved by the clearly defined parts of two ABX systems of the non-equivalent geminal protons of the two NCH_2 and *Ar*CH_2. The resonances of *Ar*CH_2 protons appeared as two doublets of doublets at $\delta = 2.75$ and 3.06 ppm with $J_{AB} = 15.6$, $J_{AX} = 7.9$, and $J_{BX} = 4.5$ Hz, due to the coupling with C*H*, while the protons of NCH_2 respectively gave two dd in the region of $\delta = 3.24$–3.77 ppm ($J_{AB} = 11.1$, $J_{AX} = 7.8$, and $J_{BX} = 2.5$ Hz). The preservation of a secondary hydroxyl is confirmed by a doublet at $\delta = 5.22$ ppm in the ^{1}H NMR spectrum, as by an absorption band at $\bar{\nu} = 3495\ \mathrm{cm}^{-1}$ in the IR spectrum. The direction of intramolecular cyclization can be estimated from the analysis of the aromatic part of the ^{1}H NMR spectrum. The chemical shift of a doublet at $\delta = 5.12$ ppm is closely consistent with that of 8-*H* of 6-substituted 1,2,3,4-tetrahydroquinolines, as reported in Ref. [13]. Moreover, this doublet is assigned to two protons, as is in accordance with structure **4**, but not four protons, as had to be expected in the case of structure **5**. From

all this we can conclude unambiguously, that cyclization occurs at the *o*-position of the phenyl ring to give one of the presumable bifunctional compounds – 1,1′-diphenyl-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-biquinolinyl-3,3′-diol (**4**) in moderate yield. The optimal cyclization temperature was found to be the boiling temperature of 1-heptanol; under such conditions reaction duration is reduced to 20 h, while the increase of the temperature gives a poorer yield of the product **4**. Additionally, the structure of **4** was supported by reacting it with acetic anhydride to give **6**.

Finally, we had a strong presumption, that the same bifunctional product **4** could be formed by an alternative way, *i.e*. oxidative coupling of 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline using ferric chloride [20]. As is noted [21], the carbon–carbon bond forming step involves the dimerization of a radical cation, to what is attributed the fact, that in the case of benzene derivatives containing an amino substituent, coupling usually occurs *para* to the substituent [21, 22]. Thus, we predicted the carbon–carbon bond formation at 6-C position of the tetrahydroquinoline ring, not excluding the possibility of further coupling at 4-C of the phenyl ring. Our efforts here to develop an alternative synthesis for compound **4** were successful, as oxidative coupling of monofunctional 1,2,3,4-tetrahydroquinoline derivative gave dimer **4** in a good yield.

In conclusion, the synthesis of 1,1′-diphenyl-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-biquinolinyl-3,3′-diol was performed both by cyclization of *N*,*N*′-di(3-chloro-2-hydroxypropyl)-*N*,*N*′-diphenylbenzidine and oxidative dimerization of 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline.

Experimental

The ^{1}H NMR spectra were taken on a Varian Unity Inova (300 MHz) spectrometer in $CDCl_3$. The IR spectra were taken for samples in KBr pellets on a Perkin Elmer Spectrum BX II FT-IR System spectrometer. Mass spectra were recorded on Waters (Micromass) 2Q 200. Melting points were determined in capillary tubes on capillary melting point apparatus MEL-TEMP. The course of the reactions was monitored by TLC on Silufol UV-254 plates (eluent: acetone/*n*-hexane = 7/18) and development with I_2 or UV light. Silica gel (grade 62, 60–200 mesh, 150 Å, Aldrich) was used for column chromatography. Elemental analyses were performed with an Exeter Analytical CE-440 Elemental Analyzer; their results agreed satisfactorily with the calculated values. Compound **1** was made according to Ref. [19].

N,N′-Di(2,3-epoxypropyl)-N,N′-diphenylbenzidine (**2**, $C_{30}H_{28}N_2O_2$)

A mixture of 20.5 g *N*,*N*-diphenylbenzidine (0.06 mol) and 95 cm^3 epichlorohydrin (0.87 mol) was stirred vigorously for 4.5 h at 30–35°C. Then 100 g (1.53 mol) of 85% powdered KOH and 35 g anhydrous Na_2SO_4 (0.25 mol) were added in 10 equal portions every 30 min with prior cooling of the reaction mixture to 30°C. After termination of the reaction (TLC) the reaction mixture was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and filtered. Ethyl acetate and excess of epichlorohydrin were removed under vacuum and the residue was purified by column chromatography (eluent: acetone/*n*-hexane = 1/4). The obtained product was crystallized from a mixture of acetone and methanol (2:1). The crystals were filtered off and washed with diethyl ether. Yield 15 g (55%); mp: 90–92°C; IR (KBr): $\bar{\nu}$ = 3054, 3037, 2990, 2920, 1611, 1592, 1493, 1454, 1365, 1250, 1228, 908, 862, 827, 760, 748, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–6.94 (m, 18H), 3.99 (dd, J = 15.8, 3.7 Hz, 2H), 3.87 (dd, J = 15.8, 4.8 Hz, 2H), 3.28–3.20 (m, 2H), 2.78 (dd, J = 4.5, 4.1 Hz, 2H); 2.57 (dd, J = 4.5, 3.1 Hz, 2H) ppm; ESI-MS: m/z = 450 $[M+H]^+$.

N,N′-Di(3-chloro-2-hydroxy)propyl-N,N′-diphenylbenzidine (**3**, $C_{30}H_{30}CI_2N_2O_2$)

To a solution of 4.6 g **2** (0.01 mol) in 10 cm^3 dioxane 2 cm^3 concentrated HCl were added dropwise. The reaction mixture was stirred at room temperature until the starting material disappeared (2.5 h). After termination of the reaction (TLC), the reaction mixture was treated with ethyl acetate and washed with distilled water until the wash water was neutral. The organic layer was dried ($MgSO_4$), filtered, and the solvents were removed. The residue was dissolved in ethyl acetate. The crystals formed upon standing at room temperature were filtered off, washed with 2-propanol and recrystallized from ethyl acetate. Yield: 4.5 g (84%); mp: 129–130.5°C; IR (KBr): $\bar{\nu}$ = 3344, 3060, 3033, 2953, 2918, 2864, 1592, 1495, 1425, 1250, 1096, 834, 824, 753, 697 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 7.58–6.89 (m, 18H), 5.52 (d, J = 4.9 Hz, 2H), 4.06–3.81 (m, 4H), 3.80–3.48 (m, 6H) ppm; ESI-MS: m/z = 521 $[M+H]^+$.

1,1′-Diphenyl-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-biquinolinyl-3,3′-diol (**4**, $C_{30}H_{28}N_2O_2$)

Method A. Compound **3** (4.5 g, 9 mmol) was refluxed under Ar in 25 cm^3 1-heptanol for 20 h. After the reaction was completed (TLC), the solvent was removed by distillation, the obtained residue was dissolved in a mixture of *THF* and ethyl acetate, and the solution was worked up with 15% $NaHCO_3$. The organic layer was washed with water until neutral, dried ($MgSO_4$), and filtered. Then the solvents were removed and the residue was purified by column chromatography (eluent: acetone/*n*-hexane = 1/7). Fractions containing the product were collected and the eluent was evaporated to yield 1.8 g (47%) **4**; mp: 185–186.5°C (*THF*:*Me*OH, 2:1). IR (KBr): $\bar{\nu}$ = 3295, 3056, 3028, 2962, 2921, 2887, 2838, 1613, 1593, 1561, 1490, 1456, 1066, 973, 860, 766, 699 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): δ = 7.41–6.99 (m, 14H), 6.70 (d,

$J = 8.6$ Hz, 2H), 5.12 (d, $J = 4.0$ Hz, 2H), 4.18–4.04 (m, 2H), 3.67 (dd, $J = 11.1$, 2.5 Hz, 2H), 3.37 (dd, $J = 11.1$, 7.8 Hz, 2H), 3.06 (dd, $J = 15.6$, 4.5 Hz, 2H), 2.75 (dd, $J = 15.6$, 7.9 Hz, 2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 147.6$, 141.8, 130.5, 129.5, 127.2, 123.8, 123.7, 123.3, 123.2, 115.2 ppm; (ESI) MS: $m/z = 449$ $[M + 1]^+$.

Method B. To a solution of 6.8 g **1** (0.03 mol) in 125 cm^3 chloroform 19.4 g $FeCl_3$ (0.12 mol) were added. The mixture was stirred vigorously at room temperature for 0.5 h under argon atmosphere. After termination of the reaction, the mixture was decanted, the residue was dissolved in acetone, and both were extracted with ethyl acetate and 3% HCl water solution. Then the organic layer was washed until neutral. The organic layer was dried ($MgSO_4$), filtered, and the organic solvents were removed. The crystalline product was filtered off, washed with 2-propanol, and recrystallized from *THF*:*Me*OH = 2:1. Yield: 5 g (74%). The IR, NMR, and mass spectra were identical to the corresponding spectra of the product synthesized by method A; a sample mixed with the product obtained according to procedure A did not give a depressed melting point.

3,3′-Diacetyl-1,1′-diphenyl-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-biquinolinyl (**6**, $C_{34}H_{32}N_2O_4$)

Compound **4** (1.8 g, 4 mmol) was dissolved in 15 cm^3 acetic anhydride and the mixture was heated at 100°C for 2 h. After termination of the reaction (TCL), the reaction mixture was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed by distillation. The residue was purified by column chromatography (acetone/*n*-hexane = 1/7). The obtained product was dissolved in the mixture of acetone and *THF* (1:1). The crystals formed upon standing at room temperature over night were filtered off and washed with diethyl ether. Yield: 1.5 g (70%); mp: 191–192.5°C; IR (KBr): $\bar{\nu} = 3052$, 3024, 2946, 2913, 2861, 1731, 1614, 1594, 1573, 1492, 1450, 1373, 1042, 1224, 819, 772, 760, 702 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 7.74$–7.37 (m, 14H), 7.18 (d, $J = 8.5$ Hz, 2H), 5.72–5.62 (m, 2H), 4.22–4.00 (m, 4H), 3.57 (dd, $J = 16.5$, 4.8 Hz, 2H), 3.33 (dd, $J = 16.5$, 5.1 Hz, 2H); 2.30 (s, 6H) ppm; ESI-MS: $m/z = 533$ $[M + H]^+$.

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