ISSN 1070-4280 Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 5, pp. 739–741. © Pleiades Publishing, Inc. 2006.
Original Russian Text © A.A. Avetisyan, I.L. Aleksanyan, A.A. Pivazyan, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 5, pp. 755–757.

Synthesis and Modification of 4-Hydroxy-2-methyl-3-(2-chloro-2-propenyl)quinoline

A.A. Avetisyan, I.L. Aleksanyan, and A.A. Pivazyan

Yerevan State University, Yerevan, 375025 Armenia
e-mail: organkim@sun.ysu.am

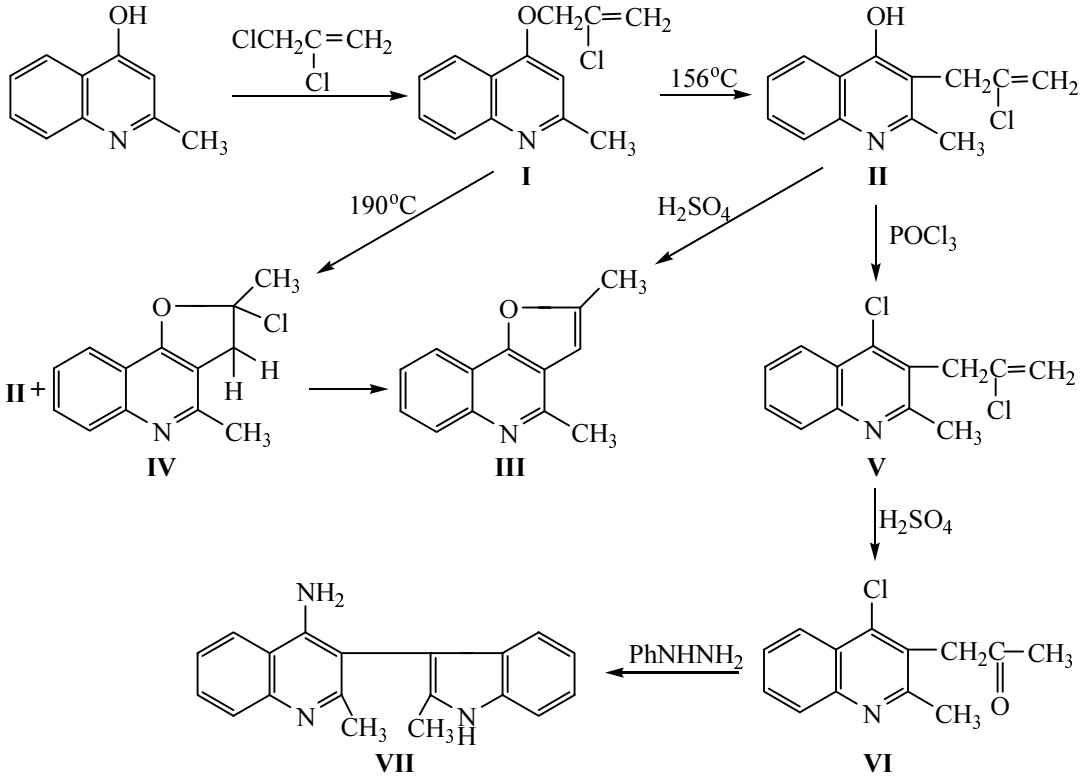
Received June 29, 2004

Abstract—4-Hydroxy-2-methyl-3-(2-chloro-2-propenyl)quinoline was prepared by O-allylation of 4-hydroxy-2-methylquinoline followed by the Claisen rearrangement of the 2-methyl-4-(2-chloro-2-propenyloxy)quinoline obtained. Chemical modifications of 4-hydroxy-2-methyl-3-(2-chloro-2-propenyl)quinoline resulted in the synthesis of 4-amino-2-methyl-3-(2-methyl-3-indolyl)quinoline.

DOI: 10.1134/S1070428006050150

Quinoline derivatives are highly promising and available compounds for preparation of versatile polyheterocyclic systems with a potential pharmacological activity [1, 2].

In extension of former studies on the preparation and modification of 3-substituted allylquinolines [3–5] we developed a method of synthesis for 4-hydroxy-2-methyl-3-(2-chloro-2-propenyl)quinoline (**II**) and for some its derivatives. Compound **II** was previously shown to be impossible to obtain from 2-[1-(arylamino)ethylidene]-4-chloro-4-propenoic acids under conditions of Conrad–Limpach condensation since the arising products under heating immediately suffered cyclization into the corresponding 2,4-dimethylfuro-[3,2-*c*]quinolines (**III**) [6].



We developed the optimum reaction conditions and performed the synthesis of 3-(chloropropenyl)quinoline **II** by the Claisen rearrangement of 2-methyl-4-(2-chloro-2-propenyloxy)quinoline (**I**) which in its turn was prepared by O-allylation of 4-hydroxy-2-methylquinoline with 2,3-dichloropropene in anhydrous ethanol solution in the presence of sodium metal. The rearrngement was achieved by boiling ether **I** for 6–7 h in bromobenzene.

The rearrangement failed to occur in the chlorobenzene. At higher temperature (~180–190°C) alongside the main reaction product **II** formed a small amount of 2,4-dimethyl-2-chloro-2,3-dihyrofuro[3,2-*c*]quinoline (**IV**). The latter at heating with an alcoholic solution of NaOH suffered HCl elimination giving compound **III** that also was obtained by an independent synthesis consisting in keeping compound **II** in sulfuric acid at 25°C for 5–6 h. Most likely the protonation of the carbonyl group generated by the acid hydrolysis of the chlorovinyl fragment facilitated the nucleophilic attack of 4-OH group on the carbonyl carbon that led to cyclization, and under these conditions (by the action of the acid) dehydration and aromatization of the dihydrofuran ring also occurred.

The samples of compound **III** obtained by both reactions are identical, and their physicochemical characteristics are consistent with those previously published [6, 8].

Treatment of compound **II** with phosphorus oxychloride afforded 2-methyl-4-chloro-3-(2-chloro-2-propenyl)quinoline (**V**) that at acid hydrolysis furnished in a high yield 2-methyl-3-(2-oxopropyl)-4-chloroquinoline (**VI**).

To prepare new quinoline derivatives containing also an indole moiety we reacted ketone **VI** with phenylhydrazine hydrochloride. The reaction was carried out in alcohol in the presence of concn H_2SO_4 at the reagents ratio 1:2. We previously reported on the new pathway of the reaction between 2-methyl-3-(3-oxobutyl)-4-chloroquinolines and phenylhydrazine hydrochloride resulting in 4-amino-2-methyl-3-(2-methyl-3-indolyl)methylquinolines [9]. In this case the reaction proceeded analogously through the benzidine rearrangement and aniline elimination to give 4-amino-2-methyl-3-(2-methyl-3-indolyl)-quinoline (**VII**).

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian Mercury-300 from solutions in DMSO-d_6. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates (eluent toluene–ethanol, 3 : 2, development in iodine vapor).

2-Methyl-4-(2-chloro-2-propenyloxy)quinoline (I). To a solution of sodium ethylate prepared from 100 ml of anhydrous ethanol and 2.3 g (0.1 mol) sodium metal was added 15.9 g (0.1 mol) of 4-hydroxy-2-methylquinoline. The mixture was heated for 30 min on a water bath, then 11.2 g (0.1 mol) of 2,3-dichloropropene was slowly dropwise introduced through a dropping funnel within 1 h to the stirred mixture heated at 35–40°C. Then the reaction mixture was boiled on the water bath for 8–9 h. The ethanol was distilled off, and the residue was diluted with 100 ml of water. The separated precipitate was filtered off and recrystallized from an ethanol–water mixture, 1:1. Yield 18.06 g (77%), mp 59–60°C, R_f 0.68. Found, %: C 66.65; H 5.05; Cl 15.35; N 5.78. $C_{13}H_{12}ClNO$. Calculated, %: C 66.81; H 5.18; Cl 15.20; N 5.99.

4-Hydroxy-2-methyl-3-(2-chloro-2-propenyl)-quinoline (II). *a*. In 10 ml of bromobenzene was dissolved 2.335 g (0.01 mol) of compound **I**, and the solution was boiled at reflux for 6–7 h. The reaction mixture was cooled, the separated precipitate was filtered off and recrystallized from ethanol. Yield 2.15 g (92%), mp 272°C, R_f 0.56. ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 3.6 s (2H, CH_2), 5.0 d (2H, CH_2), 7.1–8.1 m ($4H_{arom}$), 11.25 s (1H, OH). Found, %: C 66.73; H 4.96; Cl 15.30; N 6.05. $C_{13}H_{12}ClNO$. Calculated, %: C 66.81; H 5.18; Cl 15.20; N 5.99.

b. To 1.17 g (0.005 mol) of compound **I** was added 5 ml of mineral oil, and the mixture was heated for 10 min at 180–190°C. On cooling the substance obtained was filtered off, treated with 5% HCl, the precipitate of compound **II** was filtered off and recrystallized from ethanol. Yield 0.84 g (72%), mp 272°C. The solvent was treated with activated carbon, filtered, and alkalinized with NaOH to pH 8–8.5. The precipitated crystals of **2,4-dimethyl-2-chloro-2,3-dihydrofuro[3,2-*c*]quinoline (IV)** were filtered off and recrystallized from hexane (or from the ethanol–water mixture, 1 : 1). Yield 0.23 g (20%), mp 88°C, R_f 0.72 (ethanol–hexane, 1:2). ^{1}H NMR spectrum, δ, ppm: 1.4 s (3H, 2-CH_3), 2.45 s (3H, 4-CH_3), 7.0–7.70 m ($4H_{arom}$). Found, %: Cl 15.31; N 6.09. $C_{13}H_{12}ClNO$. Calculated, %: Cl 15.20; N 5.99.

2,4-Dimethylfuro[3,2-*c*]quinoline (III) *a.* To 1.17 g (0.005 mol) of 4-hydroxy-2-methyl-3-(2-chloro-2-propenyl)quinoline was added 5 ml of concn H_2SO_4, and the mixture was left standing at 25°C for 5–6 h. Then the mixture was poured on 50 g of crushed ice,

filtered, and alkalinized to pH 8. The precipitate formed was filtered off and recrystallized from hexane (or from the ethanol–water mixture, 1:1). Yield 0.82 g (83%), mp 63°C, R_f 0.62 (chloroform–hexane, 1:2). ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 2.52 s (3H, $NCCH_3$), 6.65 s (1H, 3-CH), 7.37–7.78 m ($4H_{arom}$). Found, %: C 79.12; H 5.62; N 7.15. $C_{13}H_{11}NO$. Calculated, %: C 79.19; H 5.58; N 7.10.

b. To a solution of 0.585 g (0.0025 mol) of compound **IV** in 15 ml of ethanol was added 0.2 g (0.005 mol) of sodium hydroxide in 2 ml of water. The reaction mixture was boiled on a water bath for 2 h, then ethanol was distilled off, the residue was treated with 30 ml of water βОды. The precipitate formed was filtered off and recrystallized from hexane (or from the ethanol–water mixture, 1:1). Yield 0.48 g (98%), mp 63°C. The mixed samples of compound **III** obtained by procedures *a* and *b* melted with no depression of the melting point that is identical to that published [8].

2-Methyl-4-chloro-3-(2-chloro-2-propenyl)-quinoline (V). A mixture of 1.17 g (0.005 mol) of compound **II** and 10 ml of phosphorus oxychloride was heated for 3 h on a water bath. Then excess phosphorus oxychloride was distilled off under reduced pressure, 50 g of crushed ice was added to the residue, and the mixture was left overnight. On neutralization the product obtained was filtered off and recrystallized from the ethanol–water mixture, 1 : 1 . Yield 1.22 g (97%), mp 42–43°C, R_f 0.63. ^{1}H NMR spectrum, δ, ppm: 2.75 s (3H, CH_3), 4.05 s (2H, CH_2), 4.84 s and 5.25 s ($C{=}CH_2$), 7.60–8.20 m ($4H_{arom}$). Found, %: C 61.45; H 4.45; Cl 28.20; N 5.35. $C_{13}H_{11}C_{l2}N$. Calculated, %: C 61.93; H 4.40; Cl 28.17; N 5.56.

2-Methyl-3-(2-oxopropyl)-4-chloroquinoline (VI). To 1.26 g (0.005 mol) of compound **V** was added 5 ml of 85% sulfuric acid, and the mixture was heated on a water bath at 50–60°C till the end of hydrogen chloride evolution, then it was poured on 20 g of crushed ice, filtered, and the solution was alkalinized. The precipitate was filtered off and recrystallized from 50% ethanol. Yield 1.0 g (87%), mp 124°C, R_f 0.41. The compound showed a positive test with chloroform characteristic of methyl ketones. IR spectrum, ν, cm^{-1}: 1720 (C=O). Found, %: C 66.62; H 5.27; Cl 15.30; N 5.90. $C_{13}H_{12}ClNO$. Calculated, %: C 66.81; H 5.18; Cl 15.17; N 5.99.

4-Amino-2-methyl-3-(2-methyl-3-indolyl)-quinoline (VII). A mixture of 1.16 g (0.005 mol) of compound **VI**, 1.44 g (0.01 mol) of phenylhydrazine hydrochloride, 2.5 ml of ethanol, and 0.6 ml of concn H_2SO_4 was heated on a water bath for 12 h, then cooled and diluted with water, the acidic solution was filtered and alkalinized. The separated precipitate was filtered off and recrystallized from the ethanol–water mixture, 1 : 1 . Yield 1.1 g (76%), mp 151°C, R_f 0.76. ^{1}H NMR spectrum, ν, ppm: 2.25 s (3H, $NHCC\underline{H}_3$), 2.60 s (3H, $NCCH_3$), 5.65 s (2H, NH_2), 76.8–8.0 m ($8H_{arom}$), 10.75 s (1H, NH). Found, %: C 79.31; H 6.07; N 14.78. $C_{19}H_{17}N_3$. Calculated, %: C 79.44; H 5.92; N 14.63.

REFERENCES

1. Mohamed, E.A., Ismail, M.M., Gabr, Y., Abass, M., and Farrag, H.A., *Indian J. Chem. B,* 1995, 34, 21.
2. Makosza, M. and Wojciechowski, K., *Heterocycles,* 2001, vol. 51, p. 445.
3. Gyul'budagyan, L. V. and Sagatelyan, Sh.A., *Khim. Geterotsikl. Soedin*., 1973, p. 84.
4. Gyul'budagyan, L. V. and Aleksanyan, I.L., *Arm. Khim. Zh.,* 1983, vol. 36, p. 376.
5. Gyul'budagyan, L. V. and Aleksanyan, I.L., *Arm. Khim. Zh.,* 1989, vol. 42, p. 407.
6. Avetisyan, A.A., Aleksyanyan, I.L., and Pivazyan, A.A., *Zh. Org. Khim*., 2004, vol. 40, p. 1397.
7. Bartlett, P.A., *Tetrahedron*, 1980, vol. 36, p. 28.
8. Aleksanyan, I.L., *Cand. Sci. (Chem.) Dissertation*, Erevan, 1985.
9. Avetisyan, A.A., Aleksyanyan, I.L., and Pivazyan, A.A., *Khim. Geterotsikl. Soedin*., 2005, p. 554.