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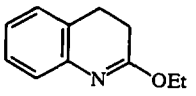
# 2-ETHOXY-3,4-DIHYDROQUINOLINE IN THE SYNTHESIS OF 4,5-DIHYDROIMIDAZO[1,2-*a*]QUINOLINES

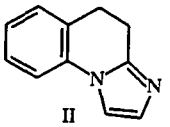
**K. G. Nazarenko, A. M. Demchenko, and V. A. Kovtunenko**

*The amination of 2-ethoxy-3,4-dihydroquinoline by phenacylammonium salts has been studied. The products of this reaction are 2-phenacylamino-3,4-dihydroquinoline hydrochlorides and these are converted to 1-aryl-4,5-dihydroimidazo[1,2-a]quinolines by refluxing in aqueous solution with a catalytic amount of HCl.*

Continuing our investigation of heterocyclization based on lactam ethers [1, 2], we propose a method of obtaining 4,5-dihydroimidazo[1,2-*a*]quinolines (II) from 2-ethoxy-3,4-dihydroquinoline (I).




I




II

Derivatives of the heterocyclic system 4,5-dihydroimidazo[1,2-*a*]quinoline have been little studied. There is a single report in the literature [3] of the preparation of 1-amino-2-carbamoyl-3,4-dihydroimidazo[1,2-*a*]quinoline by condensation of I with α-amino-α-cyanoacetamide. Several 2-substituted 3,4-dihydroimidazo[1,2-*a*]quinolines have been synthesized using the Kröhnke reaction [4, 5].

We have studied the amination of ether I using arylamines (p-bromoaniline, p-anisidine) and the phenacylammonium salts IVa-c. In the first case, refluxing a mixture of the arylamines with dihydroquinoline I in toluene gave the previously unknown 2-arylamino-3,4-dihydroquinolines IIIa, b in high yield. The structures of the quinolines IIIa, b were unambiguously proved by their IR and PMR spectra.

Condensation of ether I with salts IVa-c with a small excess of the former takes place readily in alcohol solvent over 0.5 h to give crystalline salt-like products. Elemental analytical data for these salts shows that the reagent and substrate had reacted in an equimolar ratio. It is known [2] that, in an analogous reaction of salts IVa-c with O-methylvalerolactam, for the majority of examples substitution of the methoxy group for the aminoketone residue is accompanied by subsequent intramolecular addition of the NH group at the C=O bond to give 5-hydroxyimidazolines. Hence, in our case, the question arises as to the structure of the salts as Va-c (the product of nucleophilic substitution) or VI (via substitution and subsequent cyclization).

Structural analysis of the synthesized materials was based on a combined analysis of the IR, UV and $^1H$ and $^{13}C$ NMR spectra. Hence, the IR spectra of the solid salts show two bands: at 1680 $cm^{-1}$ a band corresponding to $\nu_{CO}$ and near 1660 $cm^{-1}$ to $\nu_{C=N}$. The presence of a C=O group in the structure of the obtained salts (in DMSO-$D_6$ solution) is confirmed by the appearance in the $^{13}C$ NMR spectrum of a signal at 192 ppm assigned to the carbonyl carbon atom. The methylene group protons in the phenacyl residue give a $^1H$ NMR signal at 5.3 ppm. The methylene groups of the dihydroquinoline are seen as one broadened singlet at 3.17 ppm in the $^1H$ NMR spectrum. On the basis of the above data, the compounds were assigned as the 2-phenylacylamino-3,4-dihydroquinoline hydrochlorides Va-c. For the alternative structure VI, the methylene group protons in the phenacyl residue would have to be an AB system of diastereotopic protons with a spin-spin coupling not less

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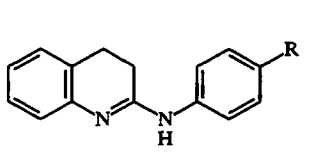
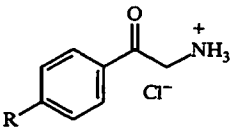
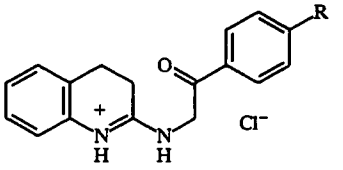


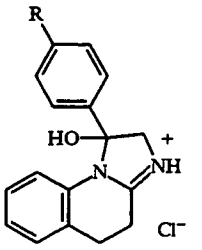
IIIa, b



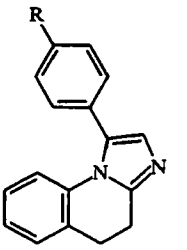
IVa-c



Va-c



VI



VIIb, c

III-V, VII a R = Br b R = $OCH_3$; c R = H

than 12 Hz [2] and in the $^{13}C$ NMR spectrum there would be a characteristic quaternary carbon signal at 92 ppm [6]. The UV spectra of salts Va-c also support their open structure as evidenced by the presence of intense bands at 264-282 nm (log $\varepsilon$ = 4.4) which we assign to the absorption of the benzoyl chromophore [7].

It has previously been noted [2, 8] that salts analogous to Va-c, prepared from O-methylbutyrolactim and O-methylvalerolactim, spontaneously cyclize to give hydroxyimidazolines when attempting to form the free bases. In our case, the same work up of salts Va-c with alkali gives oily products not yielding to purification and to identification. Their structure can only be judged by those changes which are observed in the UV spectra of Va-c upon addition of a drop of alcoholic alkali to the examined solution in the cuvet. The absorption band for the benzoyl chromophore, indeed, undergoes almost no change. Overall, the data shown lead us to propose that the condensation products of I with IVa-c, both in the crystalline state and in solution, exist exclusively as the amidine salts Va-c. Within the limits of sensitivity of the methods used, the solution equilibrium of the corresponding free bases is also shifted completely to the acyclic amidine structure.

Prolonged refluxing of salts IIIb, c in water in the presence of catalytic amounts of HCl causes heterocyclization to give 1-substituted 4,5-dihydroimidazo[1,2-*a*]quinolines VIIb, c, presumably via a structure of type VI. The composition of the products obtained was confirmed by their PMR spectra in which there are present two blocks of proton containing groups: two close together triplets from the hydrogenated quinoline part of the tricycle at 3.30-3.45 ppm and a complex multiplet for the aromatic protons (7.15-7.80) with a separated 9-H signal at 6.96 ppm due to shielding by the aryl substituent at $C_{(1)}$. The IR spectra of VIIb, c contained a set of absorptions for the ring system, part of which (according to literature data) can be assigned to the imidazole part of the molecule.

## EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument for KBr tablets. PMR spectra were measured on a Bruker WR-100 instrument working at 100.13 MHz and $^{13}C$ NMR spectra on a Gemini-200 instrument at 50.4 MHz. TMS was used as internal standard. UV spectra were taken on a Specord UV-vis instrument for $5 \cdot 10^{-5}$ M solutions in methanol.

**2-(4′-Bromophenylamino)-3,4-dihydroquinoline (IIIa).** A solution of I (10.5 g, 60 mmole) and p-bromoaniline (50 mmole) in xylene (75 ml) was refluxed for 12 h, cooled, and the precipitated crystals filtered and purified by recrystallization from benzene–hexane to give product (10.5 g, 70%) with mp 166-167°C. $^1H$ NMR spectrum ($CDCl_3$): 8.40 (1H, s, NH); 7.43-6.58 (8H, m, arom.); 2.96-2.52 ppm (4H, m, 3- and 4-$CH_2$). IR spectrum: 3180 (NH); 3080, 2980, 2920 (CH); 1650 $cm^{-1}$ (N=C–NH). Found, %: N 9.21. $C_{15}H_{13}BrN_2$. Calculated, % N 9.30.

**2-(4′-Methoxyphenylamino)-3,4-dihydroquinoline (IIIb)** was prepared similarly to IIIa in 73% yield with mp 183-184°C (from benzene). PMR spectrum ($CDCl_3$): 6.97 (1H, s, NH); 7.1-6.52 (8H, m, arom.); 3.81 (3H, s, $OCH_3$); 2.95-2.54 ppm (4H, m, 3- and 4-$CH_2$). IR spectrum: 3200 (NH); 3080, 3000, 2920 (CH); 1640 $cm^{-1}$ (N=C–N). Found, %: N 11.3. $C_{16}H_{16}N_2O$. Calculated, %: N 11.1.

**2-(4′-Bromophenylamino)-3,4-dihydroquinoline Hydrochloride (Va).** Ether Ia (3.85 g, 22 mmole) and IVa (5.01 g, 20 mmole) were refluxed in methanol (100 ml) for 0.5 h. The product solution was cooled and the precipitated crystals filtered and purified by recrystallization from methanol to give Va (5.69 g, 75%) with mp 249°C. PMR spectrum ($CF_3COOD$): 10.0 (1H, s, NH); 8.57 (1H, t, NH); 8.04 and 7.92 (4H, d.d, 4-$C_6H_4Br$); 7.33 (4H, s, quinoline); 5.42 (2H, d, $CH_2CO$); 3.17 ppm (4H, br.s, $CH_2CH_2$). IR spectrum: 3050 (NH); 1690 (C=O); 1660 $cm^{-1}$ (C=N). UV spectrum (log ε): 205.6 (4.47); 264.3 nm (4.44). Found, %: N 7.56. $C_{17}H_{16}BrClN_2O$. Calculated, %: N 7.37.

**2-(4′-Methoxyphenacylamino)-3,4-dihydroquinoline hydrochloride (Vb)** was prepared similarly to Va in 97% yield with mp 216°C (methanol). PMR Spectrum ($CF_3COOD$): 8.14 and 7.12 (4H, d.d, 4-$C_6H_4OMe$); 7.31 (4H, s, quinoline); 5.33 (2H, d, $CH_2CO$); 3.16 ppm (4H, br.s, $CH_2CH_2$). IR Spectrum: 3330 (NH); 1680 (C=O); 1665 $cm^{-1}$. UV Spectrum (log ε): 204.6 (4.34); 282.2 nm (4.44). Found, %: N 8.74. $C_{18}H_{19}ClN_2O_2$. Calculated, % N 8.47.

**2-Phenacylamino-3,4-dihydroquinoline hydrochloride (Vc)** was obtained similarly to Va, b in 65% yield with mp 225°C (methanol). PMR spectrum ($CF_3COOD$): 9.90 (1H, s, NH); 8.61 (1H, t, NH); 7.32-8.14 (9H, m, arom.); 5.41 (2H, s, $CH_2CO$); 3.17 ppm (4H, br.s, $CH_2CH_2$). $^{13}C$ NMR spectrum (DMSO-$D_6$): 191.74 (C=O); 162.99 (2-C); 50.13 ($CH_2C$=O); 25.82 (3-C); 22.27 (4-C); 117.83; 124.98; 125.29; 127.60; 128.24; 128.31; 128.91; 134.16; 134.55 ppm. UV spectrum (log ε): 205 (4.53); 255.6 nm (4.34). Found, %: N 9.54. $C_{17}H_{17}ClN_2O$. Calculated, %: N 9.32.

**1-(4′-Methoxyphenyl)-4,5-dihydroimidazo[1,2-*a*]quinoline (VIIb).** Vb (1.9 g) was refluxed in water (100 ml) in the presence of conc. HCl (2 ml) for 4 h. The solution was cooled and $K_2CO_3$ solution (50%, 10 ml) added. The precipitate was separated, dried *in vacuo*, and the residue recrystallized from hexane-ethyl acetate to give product (1.38 g, 87%) with mp 149°C. PMR Spectrum ($CF_3COOD$): 7.58-7.00 (9H, m, arom.); 4.09 (3H, s, $OCH_3$); 3.33 ppm (4H, m, $CH_2CH_2$). IR spectrum: 1460, 1555 $cm^{-1}$ (imidazole). UV spectrum (log ε): 209.4 (4.61); 249.9 nm (4.22). Found, %: N 10.1. $C_{18}H_{16}N_2O$. Calculated, %: N 10.2.

**1-Phenyl-4,5-dihydroimidazo[1,2-*a*]quinoline Hydrochloride (VIIc).** Water (100 ml) and conc. HCl (5 ml) were added to Vc (3.2 g, 10.6 mmole). The mixture was refluxed until a colorless solution was obtained (4 h). The solution was evaporated *in vacuo* and the residue recrystallized from 2-propanol to give VIIc (2.65 g, 88%) with mp 198°C. PMR spectrum ($CF_3COOD$): 7.70-6.96 (10H, m, arom.); 3.46 (2H, t, 5-$CH_2$); 3.29 ppm. $^{13}C$ NMR spectrum ($CF_3COOD$): 23.35 (5-C); 26.21 (4-C); 133.89 (9a-C); 148.5 (3a-C): 135.67; 133.66; 132.89; 131.34; 131.22; 130.69; 129.84; 129.83; 122.69; 122.20; 118.88; 118.44; 110.93 ppm. IR spectrum: 1480, 1600 $cm^{-1}$ (imidazole). UV spectrum (log ε): 207.1 (4.53); 254.4 nm (4.06). Found, %: N 10.1. $C_{17}H_{15}ClN_2O$. Calculated, %: N 9.91.

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