

4-Functionally Substituted 3-Heterylpyrazoles: XVIII.* Intramolecular Cyclization of *N*-[3-(2-Chlorophenyl)-4-pyrazolyl]methylamine and Its *N*-Alkyl Derivatives into 4,5-Dihydro-2*H*-pyrazolo[4,3-*c*]quinolines

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Abstract—*N*-[3-(2-Chlorophenyl)-4-pyrazolyl]methylamine and its *N*-alkyl- derivatives at heating in DMF in the presence of K₂CO₃ undergo an intramolecular cyclocondensation yielding 4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolines.

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We formerly discovered in a series of 4-functionally substituted 3-arylpyrazoles intramolecular electrophilic cyclizations involving the aromatic substituent, carboxy [2] and isocyanate [3] groups. The possibility of formation of pyrazole-containing fused heterocyclic systems through a reaction of a nucleophilic functional group in position 4 with an aromatic substituent in position 3 of pyrazole ring is not yet understood.

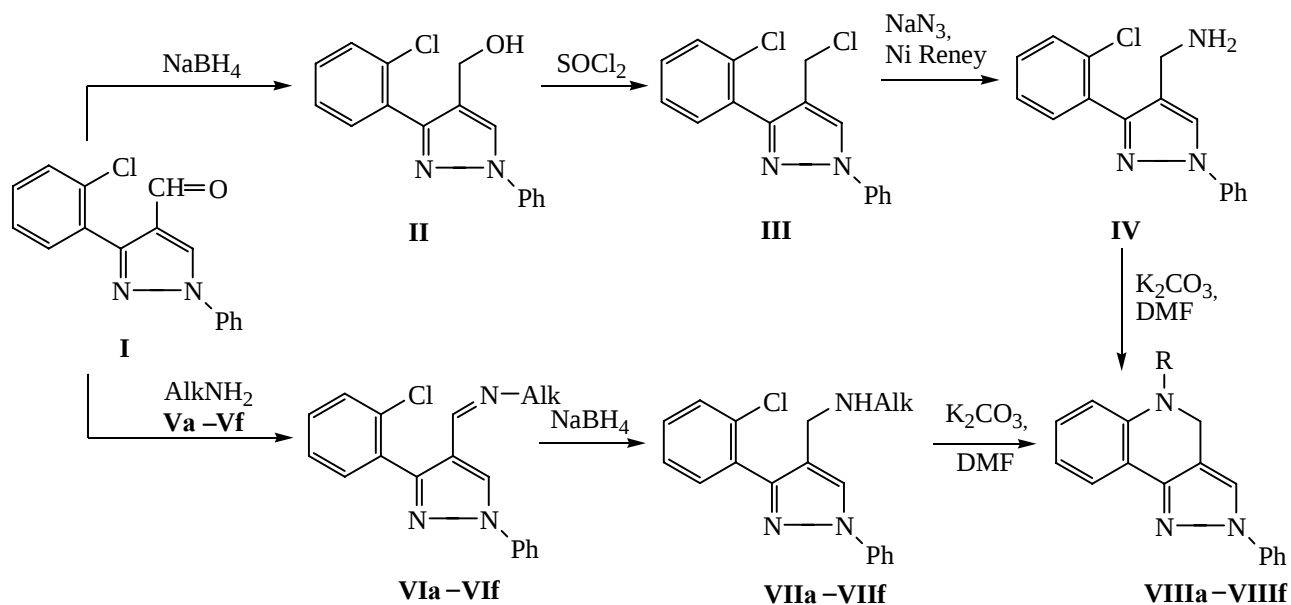
We recently reported on preparation of *N*-[3-aryl(heteryl)-4-pyrazolyl]methylamines [4] and *N*-benzyl-*N*-[3-aryl(heteryl)-4-pyrazolyl]methylamines [5] which proved to be convenient reagents for the synthesis of a series of their important *N*-acyclic derivatives. These type compounds underlie the development in this study of a new approach to the synthesis of 4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolines. The interest to these substances is due to the existence in this series of efficient nonsteroid antiimplant agents [6, 7]. The proper preparation methods of the scanty representatives of this heterocyclic system are multistage and involve fusion of the pyrazole ring to dihydroquinoline skeleton [6, 7]. The synthetic strategy we developed was based on the formation of the 4,5-dihydroquinoline ring by intramolecular amination of the *ortho*-chloro-substituted

phenyl ring in the *N*-[3-(2-chlorophenyl)-4-pyrazolyl]methylamine and its *N*-alkylated analogs. To this end we performed a synthesis of previously unknown 1-phenyl-4-formyl-3-(2-chlorophenyl)pyrazole (**I**) that via 4-hydroxymethyl-1-phenyl-3-(2-chlorophenyl)pyrazole (**II**) and 1-phenyl-4-chloromethyl-3-(2-chlorophenyl)pyrazole (**III**) was converted into *N*-[3-(2-chlorophenyl)-pyrazol-4-yl]methylamine (**IV**). The condensation of aldehyde **I** with alkylamines **Va–Ve** provided azo-methines **VIa–VIe** which on reduction gave *N*-alkyl-*N*-pyrazolylmethylamines **VIIa–VIIe**.

It was established that heating hydrochlorides of *N*-pyrazolylmethylamine (**IV**) and *N*-alkyl-*N*-pyrazolylmethylamines **VIIb–VIIId** in boiling DMF in the presence of potassium carbonate for 5 h led to the formation of the target 2-phenyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolines **VIIIa–VIIIf** that were isolated as free bases (compounds **VIIIc–VIIIe**) or as hydrochlorides (compounds **VIIIa**, **VIIIb**, and **VIIIf**) (in 58–69% yields). It was also found that the reaction was sensitive to the amine basicity and therefore *N*-(phenyl, 4-tolyl)-*N*-(4-pyrazolyl)methylamines under similar conditions did not undergo such cyclocondensation.

The structure of intermediate compounds **I–VII** was confirmed by IR and NMR spectroscopy. The individual state and cyclic structure of the target compounds were

* For Communication XVII see [1].



V-VII, Alk = Bu (**a**), C₆H₁₁ (**b**), HOCH₂CH₂ (**c**), HOCH₂CH₂CH₂ (**d**), CH₂Ph (**e**); **VIII**, R = H (**a**), Bu (**b**), C₆H₁₁ (**c**), HOCH₂CH₂ (**d**), HOCH₂CH₂CH₂ (**e**), CH₂Ph (**f**).

proved by GC-MS method and ¹H NMR spectra. In the ¹H NMR spectra of bases **VIIIc-VIIIe** the singlets of the methylene protons of the dihydroquinoline ring appeared at 3.53–3.57 ppm, whereas in the spectra of hydrochlorides **VIIIa**, **VIIIb**, and **VIIIf** they are shifted downfield approximately by 0.3–0.4 ppm. The singlets of H⁵ protons of the pyrazole ring in the spectra of bases **VIIIc-VIIIe** are observed in the range 8.41–8.45 ppm, those of hydrochlorides **VIIIa**, **VIIIb**, and **VIIIf** are also shifted downfield by about 0.5–0.6 ppm.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from samples pelletized with KBr. ¹H NMR spectra were registered on a spectrometer Varian-Gemini (300MHz) from solutions in (CD₃)₂SO, internal reference TMS. GC-MS measurements were carried out on an instrument Agilent 1100 /DAD/ MSD VL 61965a.

1-Phenyl-4-formyl-3-(2-chlorophenyl)pyrazole (I) was obtained as described in [8]. Yield 73%, mp 150–151°C (ethanol). IR spectrum, ν, cm⁻¹: 1700 (C=O). ¹H NMR spectrum, δ, ppm: 7.38–7.60 m (7H_{arom}), 7.97 d (2H_{arom}), 9.30 s (1H, H⁵_{pyr}), 9.78 s (1H, CH=O). Found, %: C 67.80; H 3.83; N 9.97. C₁₆H₁₁ClN₂O. Calculated, %: C 67.97; H 3.92; N 9.91.

4-Hydroxymethyl-1-phenyl-3-(2-chlorophenyl)-pyrazole (II) was obtained by procedure [9]. Yield 87%,

mp 81–83°C (ethanol). IR spectrum, ν, cm⁻¹: 3435 (OH). ¹H NMR spectrum, δ, ppm: 4.62 d (2H, CH₂), 4.97 t (1H, OH), 7.29–7.59 m (7H_{arom}), 7.86 d (2H_{arom}), 8.51 c (1H, H⁵_{pyr}). Found, %: C 67.30; H 4.51; N 9.66. C₁₆H₁₃ClN₂O. Calculated, %: C 67.49; H 4.60; N 9.84.

1-Phenyl-4-chloromethyl-3-(2-chlorophenyl)-pyrazole (III) was obtained by procedure [9]. Yield 83%, mp 75–76°C (ethanol). ¹H NMR spectrum, δ, ppm: 4.88 s (2H, CH₂), 7.32–7.64 m (7H_{arom}), 7.82 d (2H_{arom}), 8.75 s (1H, H⁵_{pyr}). Found, %: C 63.24; H 4.18; N 9.11. C₁₆H₁₃Cl₂N₂. Calculated, %: C 63.38; H 3.99; N 9.24.

[3-(2-Chlorophenyl)-1-phenylpyrazolyl]methylamine hydrochloride (IV) was obtained by procedure [4]. Yield 67%, t.decomp. 220–230°C. ¹H NMR spectrum, δ, ppm: 3.82 s (2H, CH₂), 7.34–7.58 m (7H_{arom}), 7.76 d (2H_{arom}), 8.58 br.s (3H, NH₃⁺), 8.91 s (1H, H⁵_{pyr}). Found, %: C 59.74; H 4.75; N 12.91. C₁₆H₁₅Cl₂N₃. Calculated, %: C 60.01; H 4.72; N 13.12.

N-Alkyl-N-[[3-(2-chlorophenyl)-1-phenyl-4-pyrazolyl]methylene]amines VIa-VIe. To a mixture of 5.64 g (20 mmol) of aldehyde **I** and 20 mmol of amine **Va-Ve** in 40 ml of toluene was added 5 drips of glacial acetic acid, and the mixture was boiled with a Dean-Stark trap for 1 h. The reaction mixture was cooled, the formed precipitate was filtered off and crystallized from a mixture benzene–hexane, 5:1.

N-Butyl-N-[[1-phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methylene]amine (VIa). Yield 87%, mp 69–

70°C. IR spectrum, ν , cm^{-1} : 1665 (C=N). ^1H NMR spectrum, δ , ppm: 0.89 t (3H, CH_3), 1.32 q (2H, CH_2), 1.50–1.56 m (2H, CH_2), 3.21 t (2H, CH_2), 7.36–7.53 m (7H_{arom}), 7.92 d (2H_{arom}), 7.97 s (1H, CH=N), 8.87 s (1H, H⁵_{Pyr}). Found, %: C 70.92; H 6.08; N 12.28. $\text{C}_{20}\text{H}_{20}\text{ClN}_3$. Calculated, %: C 71.10; H 5.97; N 12.44.

***N*-Hexyl-*N*-{[1-phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methylene}amine (VIb).** Yield 90%, mp 72–74°C. IR spectrum, ν , cm^{-1} : 1660 (C=N). ^1H NMR spectrum, δ , ppm: 0.87 t (3H, CH_3), 1.17–1.27 m (6H, 3 CH_2), 1.53–1.58 m (2H, CH_2), 3.45 t (2H, CH_2), 7.32–7.55 m (7H_{arom}), 7.94 d (2H_{arom}), 7.97 s (1H, CH=N), 8.86 s (1H, H⁵_{Pyr}). Found, %: C 72.12; H 6.48; N 11.29. $\text{C}_{22}\text{H}_{24}\text{ClN}_3$. Calculated, %: C 72.22; H 6.61; N 11.48.

2-([1-Phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methylene)amino)ethanol (VIc). Yield 91%, mp 145–147°C. IR spectrum, ν , cm^{-1} : 1660 (C=N), 3490 (OH). ^1H NMR spectrum, δ , ppm: 3.61–3.70 m (4H, CH_2), 4.49 t (1H, OH), 7.33–7.54 m (7H_{arom}), 7.95 d (2H_{arom}), 7.98 s (1H, CH=N), 8.90 s (1H, H⁵_{Pyr}). Found, %: C 66.10; H 4.87; N 12.72. $\text{C}_{18}\text{H}_{16}\text{ClN}_3\text{O}$. Calculated, %: C 66.36; H 4.95; N 12.90.

3-([1-Phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methylene)amino)propan-1-ol (VIId). Yield 94%, mp 142–144°C. IR spectrum, ν , cm^{-1} : 1660 (C=N), 3485 (OH). ^1H NMR spectrum, δ , ppm: 2.51–2.56 m (2H, CH_2), 3.38–3.42 m (2H, CH_2), 3.56 t (2H, CH_2), 4.29 m (1H, OH), 7.27–7.53 m (7H_{arom}), 7.83 d (2H_{arom}), 8.00 s (1H, CH=N), 8.43 s (1H, H⁵_{Pyr}). Found, %: C 66.90; H 5.23; N 12.50. $\text{C}_{19}\text{H}_{18}\text{ClN}_3\text{O}$. Calculated, %: C 67.16; H 5.34; N 12.37.

***N*-Benzyl-*N*-{[1-phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methylene}amine (VIe).** Yield 97%, mp 81–83°C. IR spectrum, ν , cm^{-1} : 1665 (C=N). ^1H NMR spectrum, δ , ppm: 4.66 s (2H, CH_2), 7.26–7.55 m (12H_{arom}), 7.95 d (2H_{arom}), 8.16 s (1H, CH=N), 8.95 s (1H, H⁵_{Pyr}). Found, %: C 73.97; H 4.91; N 11.13. $\text{C}_{23}\text{H}_{18}\text{ClN}_3$. Calculated, %: C 74.29; H 4.88; N 11.30.

***N*-Alkyl-*N*-{[1-phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methyl}amines VIIa–VIIe.** To a dispersion of 10 mmol of azomethine VIa–VIe in 20 ml of ethanol was added a dispersion of 1 g (26 mmol) of sodium tetrahydroborate in 20 ml of ethanol, the mixture was brought to boiling, then kept for 3 h at room temperature, and diluted with 200 ml of water. After 1 h the reaction mixture was extracted with chloroform (2×40 ml), and the combined extracts were evaporated in a vacuum. The oily residue of compounds VIIb–VIId crystallized within 2–3 days. The oily residue of compounds VIIa

and VIIe was dissolved in 25 ml of benzene, saturated with hydrogen chloride, the formed precipitate was filtered off, washed with hexane, and dried.

***N*-Butyl-*N*-{[1-phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methyl}amine hydrochloride (VIIa).** Yield 81%, mp 145–147°C. ^1H NMR spectrum, δ , ppm: 0.84 t (3H, CH_3), 1.22–1.26 m (2H, CH_2), 1.52–1.54 m (2H, CH_2), 2.73–2.77 m (2H, CH_2), 3.93 s (2H, CH_2), 7.37–7.61 m (7H_{arom}), 7.79 d (2H_{arom}), 9.05 s (1H, H⁵_{Pyr}), 9.52–9.56 m (2H, NH₂⁺). Found, %: C 63.63; H 5.97; N 11.02. $\text{C}_{20}\text{H}_{23}\text{Cl}_2\text{N}_3$. Calculated, %: C 63.83; H 6.16; N 11.17.

***N*-Hexyl-*N*-{[1-phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methyl}amine (VIIb).** Yield 79%, mp 49–51°C. ^1H NMR spectrum, δ , ppm: 0.86 t (3H, CH_3), 1.12–1.38 m (8H, 4 CH_2), 2.45 t (2H, CH_2), 3.55 s (2H, CH_2), 7.26–7.57 m (7H_{arom}), 7.82 d (2H_{arom}), 8.42 C (1H, H⁵_{Pyr}). Proton NH was not observed due to the exchange with protons of water present in the solvent. Found, %: C 72.09; H 6.98; N 11.26. $\text{C}_{22}\text{H}_{26}\text{ClN}_3$. Calculated, %: C 71.82; H 7.12; N 11.42.

2-([1-Phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methyl)amino)ethanol (VIIc). Yield 86%, mp 69–71°C. ^1H NMR spectrum, δ , ppm: 2.60 t (2H, CH_2), 3.42–3.46 m (2H, CH_2), 3.60 C (2H, CH_2), 4.20–4.25 m (1H, OH), 7.30–7.49 m (7H_{arom}), 7.85 d (2H_{arom}), 8.40 s (1H, H⁵_{Pyr}). Proton NH is involved into exchange with protons of water present in the solvent. Found, %: C 65.72; H 5.45; N 12.63. $\text{C}_{18}\text{H}_{18}\text{ClN}_3\text{O}$. Calculated, %: C 65.95; H 5.53; N 12.82.

3-([1-Phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methyl)amino)propan-1-ol (VIId). Yield 89%, mp 108–110°C. ^1H NMR spectrum, δ , ppm: 1.52 t (2H, CH_2), 2.56 t (2H, CH_2), 3.43 t (2H, CH_2), 3.54 s (2H, CH_2), 7.26–7.54 m (7H_{arom}), 7.82 d (2H_{arom}), 8.41 s (1H, H⁵_{Pyr}). Protons OH and NH were not observed due to the exchange with protons of water present in the solvent. Found, %: C 66.61; H 5.77; N 12.14. $\text{C}_{19}\text{H}_{20}\text{ClN}_3\text{O}$. Calculated, %: C 66.76; H 5.90; N 12.29.

***N*-Benzyl-*N*-{[1-phenyl-3-(2-chlorophenyl)-4-pyrazolyl]methyl}amine hydrochloride (VIIe).** Yield 84%, mp 195–196°C. ^1H NMR spectrum, δ , ppm: 3.93 s (2H, CH_2), 4.06 s (2H, CH_2), 7.33–7.53 m (12H_{arom}), 7.78 d (2H_{arom}), 9.05 s (1H, H⁵_{Pyr}), 9.97 br.s (2H, NH₂⁺). Found, %: C 67.11; H 5.21; N 10.01. $\text{C}_{23}\text{H}_{21}\text{Cl}_2\text{N}_3$. Calculated, %: C 67.32; H 5.16; N 10.24.

2-Phenyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolines VIIa–VIIf. A mixture of 5 mmol of amine IV, VIIa–VIIf and 3.38 g (25 mmol) of potassium carbonate in

25 ml of DMF was boiled for 5 h, then cooled and poured into 100 ml of water. The solid residue (compounds **VIIIc–VIIIe**) was filtered off, washed with water, dried, and crystallized from ethanol. Oily substances (compounds **VIIIa**, **VIIIb**, and **VIIIf**) were extracted into chloroform (2×20 ml), the extract was dried with anhydrous MgSO_4 , the solution was evaporated, the residue was dissolved in 30 ml of benzene and saturated with gaseous hydrogen chloride. The formed precipitate of compounds **VIIIa**, **VIIIb**, and **VIIIf** hydrochloride was filtered off, washed with hexane, and dried.

2-Phenyl-4,5-dihydro-2H-pyrazolo-[4,3-c]quinoline hydrochloride (VIIIa). Yield 58%, mp 150–152°C. ^1H NMR spectrum, δ , ppm: 3.85 s (2H, CH_2), 7.39–7.64 m (7H_{arom}), 7.78 d (2H_{arom}), 8.58–8.61 m (2H, NH_2^+), 8.93 s (1H, H_{Pyr}^5). Found, %: C 67.55; H 4.80; N 14.73. $[M + 1]^+$ 284. $\text{C}_{16}\text{H}_{14}\text{ClN}_3$. Calculated, %: C 67.72; H 4.97; N 14.81. M 283.76.

5-Butyl-2-phenyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline hydrochloride (VIIIb). Yield 61%, mp 134–136°C. ^1H NMR spectrum, δ , ppm: 0.81 t (3H, CH_3), 1.25 q (2H, CH_2), 1.50–1.54 m (2H, CH_2), 2.77 t (2H, CH_2), 3.94 s (2H, CH_2), 7.34–7.62 m (7H_{arom}), 7.76 d (2H_{arom}), 9.05 s (1H, H_{Pyr}^5), 9.53 br.s (1H, NH^+). Found, %: C 70.44; H 6.43; N 12.30. $[M + 1]^+$ 340. $\text{C}_{20}\text{H}_{22}\text{ClN}_3$. Calculated, %: C 70.68; H 6.52; N 12.36. M 339.87.

5-Hexyl-2-phenyl-4,5-dihydro-2H-pyrazolo-[4,3-c]quinoline (VIIIc). Yield 64%, mp 50–51°C. ^1H NMR spectrum, δ , ppm: 0.86 t (3H, CH_3), 1.14–1.36 m (8H, 4CH_2), 2.47 t (2H, CH_2), 3.57 s (2H, CH_2), 7.27–7.55 m (7H_{arom}), 7.82 d (2H_{arom}), 8.43 s (1H, H_{Pyr}^5). Found, %: C 79.55; H 7.48; N 12.41. $[M + 1]^+$ 332. $\text{C}_{22}\text{H}_{25}\text{N}_3$. Calculated, %: C 79.72; H 7.60; N 12.68. M 331.46.

2-(2-Phenyl-2,4-dihydro-5H-pyrazolo[4,3-c]quinolin-5-yl)ethanol (VIId). Yield 69%, mp 67–68°C. ^1H NMR spectrum, δ , ppm: 2.58 t (2H, CH_2), 3.43 t (2H, CH_2), 3.58 s (2H, CH_2), 4.30–4.34 m (1H, OH), 7.29–7.55 m (7H_{arom}), 7.84 d (2H_{arom}), 8.45 s (1H, H_{Pyr}^5). Found,

%: C 74.03; H 5.71; N 14.50. $[M + 1]^+$ 292. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}$. Calculated, %: C 74.21; H 5.88; N 14.42. M 291.36.

3-(2-Phenyl-2,4-dihydro-5H-pyrazolo[4,3-c]quinolin-5-yl)propan-1-ol (VIIIe). Yield 67%, mp 106–107°C. ^1H NMR spectrum, δ , ppm: 1.52 t (2H, CH_2), 2.56 t (2H, CH_2), 3.43 t (2H, CH_2), 3.53 s (2H, CH_2), 7.27–7.55 m (7H_{arom}), 7.82 d (2H_{arom}), 8.41 s (1H, H_{Pyr}^5). Proton OH was not observed due to the exchange with protons of water present in the solvent. Found, %: C 74.48; H 6.13; N 13.89. $[M + 1]^+$ 306. $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$. Calculated, %: C 74.73; H 6.27; N 13.76. M 305.38.

5-Benzyl-2-phenyl-4,5-dihydro-2H-pyrazolo-[4,3-c]quinoline hydrochloride (VIIIf). Yield 59%, mp 191–193°C. ^1H NMR spectrum, δ , ppm: 3.97 s (2H, CH_2), 4.11 s (2H, CH_2), 7.36–7.62 m (12H_{arom}), 7.81 d (2H_{arom}), 9.09 s (1H, H_{Pyr}^5), 9.91 br.s (1H, NH^+). Found, %: C 73.67; H 5.24; N 11.03. $[M + 1]^+$ 374. $\text{C}_{23}\text{H}_{20}\text{ClN}_3$. Calculated, %: C 73.89; H 5.39; N 11.24. M 373.87.

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