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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 K_2CO_3 undergo an intramolecular cyclocondensation yielding 4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolines.

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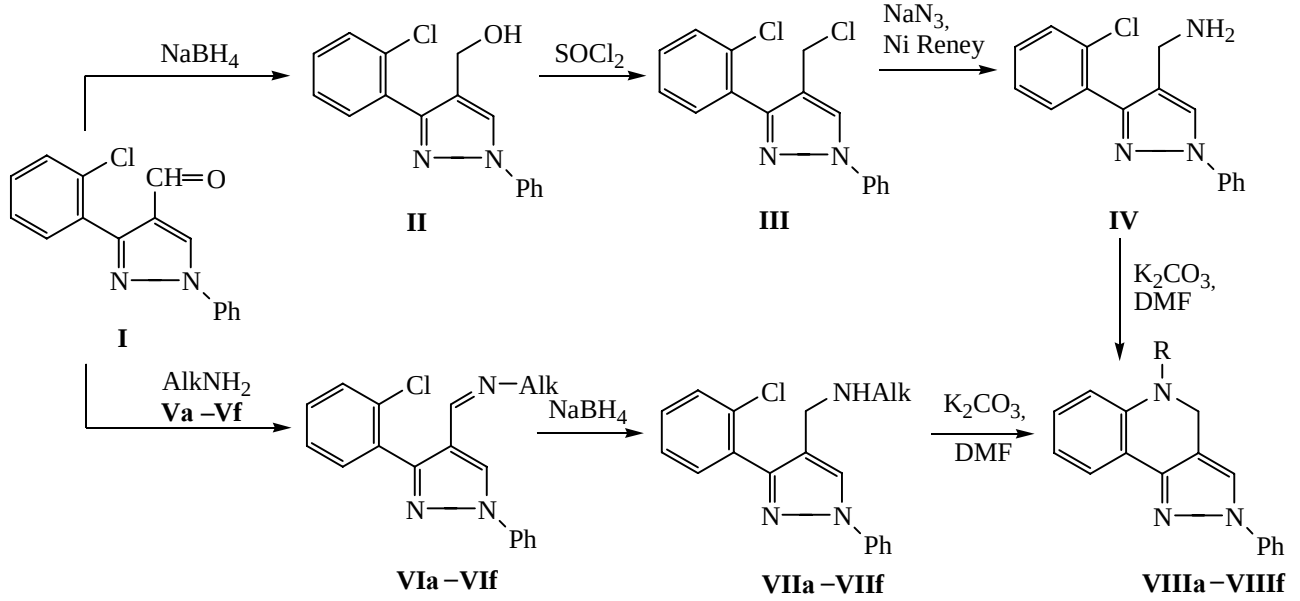
We formerly discovered in a series of 4-functionally substituted 3-arylpyrazoles intramolecular electrophilic cyclizations involving the aromatic substituent, carboxy [2] and isocyanate [3] groups. The possibility of formation of pyrazole-containing fused heterocyclic systems through a reaction of a 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*-pyrazolyl-methylamines **VIIb–VIId** 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**), C_6H_{11} (**b**), $HOCH_2CH_2$ (**c**), $HOCH_2CH_2CH_2$ (**d**), CH_2Ph (**e**); **VIII**, R = H (**a**), Bu (**b**), C_6H_{11} (**c**), $HOCH_2CH_2$ (**d**), $HOCH_2CH_2CH_2$ (**e**), CH_2Ph (**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 H^5 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 $(CD_3)_2SO$, 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, H^5_{Pyr}), 9.78 s (1H, CH=O). Found, %: C 67.80; H 3.83; N 9.97. $C_{16}H_{11}ClN_2O$. 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, CH_2), 4.97 t (1H, OH), 7.29–7.59 m ($7H_{arom}$), 7.86 d ($2H_{arom}$), 8.51 c (1H, H^5_{Pyr}). Found, %: C 67.30; H 4.51; N 9.66. $C_{16}H_{13}ClN_2O$. Calculated, %: C 67.49; H 4.60; N 9.84.

1-Phenyl-4-chloromethyl-3-(2-chlorophenyl)-pyrazole (II) was obtained by procedure [9]. Yield 83%, mp 75–76°C (ethanol). ^1H NMR spectrum, δ, ppm: 4.88 s (2H, CH_2), 7.32–7.64 m ($7H_{arom}$), 7.82 d ($2H_{arom}$), 8.75 s (1H, H^5_{Pyr}). Found, %: C 63.24; H 4.18; N 9.11. $C_{16}H_{13}Cl_2N_2$. Calculated, %: C 63.38; H 3.99; N 9.24.

[3-(2-Chlorophenyl)-1-phenylpyrazolyl]methyl-amine hydrochloride (IV) was obtained by procedure [4]. Yield 67%, t.decomp. 220–230°C. ^1H NMR spectrum, δ, ppm: 3.82 s (2H, CH_2), 7.34–7.58 m ($7H_{arom}$), 7.76 d ($2H_{arom}$), 8.58 br.s (3H, NH_3^+), 8.91 s (1H, H^5_{Pyr}). Found, %: C 59.74; H 4.75; N 12.91. $C_{16}H_{15}Cl_2N_3$. 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). ^{1}H 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, H$^5_{Pyr}$). Found, %: C 70.92; H 6.08; N 12.28. $C_{20}H_{20}ClN_3$. 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). ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3), 1.17–1.27 m (6H, 3CH_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, H$^5_{Pyr}$). Found, %: C 72.12; H 6.48; N 11.29. $C_{22}H_{24}ClN_3$. 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). ^{1}H 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, H$^5_{Pyr}$). Found, %: C 66.10; H 4.87; N 12.72. $C_{18}H_{16}ClN_3O$. Calculated, %: C 66.36; H 4.95; N 12.90.

3-({[1-Phenyl3-(2-chlorophenyl)-4-pyrazolyl]-methylene}amino)propan-1-ol (VId). Yield 94%, mp 142–144°C. IR spectrum, ν, cm^{-1}: 1660 (C=N), 3485 (OH). ^{1}H 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, H$^5_{Pyr}$). Found, %: C 66.90; H 5.23; N 12.50. $C_{19}H_{18}ClN_3O$. 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). ^{1}H 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, H$^5_{Pyr}$). Found, %: C 73.97; H 4.91; N 11.13. $C_{23}H_{18}ClN_3$. 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. ^{1}H 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, H$^5_{Pyr}$), 9.52–9.56 m (2H, NH_2^+). Found, %: C 63.63; H 5.97; N 11.02. $C_{20}H_{23}Cl_2N_3$. 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. ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3), 1.12–1.38 m (8H, 4CH_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, H$^5_{Pyr}$). 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. $C_{22}H_{26}ClN_3$. 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. ^{1}H 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, H$^5_{Pyr}$). Proton NH is involved into exchange with protons of water present in the solvent. Found, %: C 65.72; H 5.45; N 12.63. $C_{18}H_{18}ClN_3O$. 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. ^{1}H 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, H$^5_{Pyr}$). 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. $C_{19}H_{20}ClN_3O$. 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. ^{1}H 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, H$^5_{Pyr}$), 9.97 br.s (2H, NH_2^+). Found, %: C 67.11; H 5.21; N 10.01. $C_{23}H_{21}Cl_2N_3$. 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-2*H*-pyrazolo-[4,3-*c*]quinoline hydrochloride (VIIIa). Yield 58%, mp 150–152°C. ^{1}H 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^5_{Pyr}). Found, %: C 67.55; H 4.80; N 14.73. [*M* + 1]$^+$ 284. $C_{16}H_{14}ClN_3$. Calculated, %: C 67.72; H 4.97; N 14.81. *M* 283.76.

5-Butyl-2-phenyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]-quinoline hydrochloride (VIIIb). Yield 61%, mp 134–136°C. ^{1}H NMR spectrum, δ, ppm: 0.81 t (3H, CH_3), 1.25 q (2H, CH_2), 1.50–1.54m (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 C (1H, H^5_{Pyr}), 9.53 br.s (1H, NH^+). Found, %: C 70.44; H 6.43; N 12.30. [*M* + 1]$^+$ 340. $C_{20}H_{22}ClN_3$. Calculated, %: C 70.68; H 6.52; N 12.36. *M* 339.87.

5-Hexyl-2-phenyl-4,5-dihydro-2*H*-pyrazolo-[4,3-*c*]-quinoline (VIIIc). Yield 64%, mp 50–51°C. ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3), 1.14–1.36m (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^5_{Pyr}). Found, %: C 79.55; H 7.48; N 12.41. [*M* + 1]$^+$ 332. $C_{22}H_{25}N_3$. Calculated, %: C 79.72; H 7.60; N 12.68. *M* 331.46.

2-(2-Phenyl-2,4-dihydro-5*H*-pyrazolo[4,3-*c*]-quinolin-5-yl)ethanol (VIIId). Yield 69%, mp 67–68°C. ^{1}H 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^5_{Pyr}). Found, %: C 74.03; H 5.71; N 14.50. [*M* + 1]$^+$ 292. $C_{18}H_{17}N_3O$. Calculated, %: C 74.21; H 5.88; N 14.42. *M* 291.36.

3-(2-Phenyl-2,4-dihydro-5*H*-pyrazolo[4,3-*c*]-quinolin-5-yl)propan-1-ol (VIIIe). Yield 67%, mp 106–107°C. ^{1}H 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^5_{Pyr}). 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. $C_{19}H_{19}N_3O$. Calculated, %: C 74.73; H 6.27; N 13.76. *M* 305.38.

5-Benzyl-2-phenyl-4,5-dihydro-2*H*-pyrazolo-[4,3-*c*]quinoline hydrochloride (VIIIf). Yield 59%, mp 191–193°C. ^{1}H 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^5_{Pyr}), 9.91 br.s (1H, NH^+). Found, %: C 73.67; H 5.24; N 11.03 [*M* + 1]$^+$ 374. $C_{23}H_{20}ClN_3$. Calculated, %: C 73.89; H 5.39; N 11.24. *M* 373.87.

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