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4,5-DIHYDROPYRAZOLO-[3,4-*f*]QUINAZOLINES

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By reaction of 6-dimethylamino-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline with hydrazine, phenylhydrazine, 4-bromo-, 4-chlorophenylhydrazines, and also reaction of 6-dimethylaminomethylene-5-oxo-2-(4-pyridyl)-5,6,7,8-tetrahydroquinazoline with hydrazine, 4-methoxy- and 2-carboxyphenylhydrazines, we have obtained the corresponding 7-phenyl(4-pyridyl)-substituted 1H(2H)- or 1-aryl-4,5-dihydropyrazolo[3,4-f]quinazolines. Methylation of 7-phenyl-4,5-dihydro-1(2H)-pyrazolo[3,4-f]-quinazoline by methyl iodide led to its 2-methyl derivative.

Keywords: 2-methyl-7-phenyl-4,5-dihydropyrazolo[3,4-*f*]quinazolines, 2-phenyl- and 6-dimethylaminomethylene-2-(4-pyridyl)-5-oxo-5,6,7,8-tetrahydroquinazolines, 1-aryl-7-phenyl(4-pyridyl)-4,5-dihydropyrazolo[3,4-*f*]quinazolines, 7-phenyl(4-pyridyl)-1(2H)-4,5-dihydropyrazolo[3,4-*f*]quinazolines, methylation.

In the course of research on using 6-dimethylaminomethylene-5-oxo-2-phenyl- (**1a**) and 2-(4-pyridyl)-5,6,7,8-tetrahydroquinazoline (**1b**) in syntheses, we have studied the reaction of these compounds with arylhydrazines and hydrazine hydrate.

We know that reaction of cyclic α-dimethylaminomethylene ketones (obtained in reactions of the corresponding ketones with DMF dimethylacetal [1] or bis(dimethylamino)*tert*-butoxymethane (Bredereck's reagent) [2, 3]) with hydrazine hydrate leads to the corresponding 4,5-dihydro-2H-pyrazolo[3,4-*a*]acridines [1] and 1,4,5,6-tetrahydropyrazolo[3,4-*d*]pyrido[3,2-*b*]azepines [2].

We carried out reactions of β-dimethylaminovinyl ketones **1a,b** with salts of phenylhydrazine (**2a**) and substituted phenylhydrazines **2b-e** by refluxing the indicated reagents in pyridine. In this case, we obtained the corresponding pyrazolo[3,4-*f*]quinazolines **3a-e**; we should note that reaction of quinazoline **1a** with 4-nitrophenylhydrazine led to the hydrazine derivative **4**. Formation of products **3a-e** was confirmed by the ^{1}H NMR spectra, in which there are no signals from protons of the NH group (see Experimental).

Refluxing aminovinyl ketones **1a,b** with hydrazine hydrate leads to pyrazolo[3,4-*f*]quinazolines **5(6)a,b**. A signal from the proton of the NH group is observed in the ^{1}H NMR spectra at 12.48 ppm in the case of product **5(6)a** and at 13.08 ppm for product **5(6)b**. We obtained the N-methyl derivative **7** by treatment of pyrazoloquinazoline **5(6)a** with methyl iodide.

Assignment of compounds **3a-e** to the 1-substituted series and assignment of the methylation product **7** to the 2-substituted series were established by ^{1}H and NOE NMR spectroscopy.

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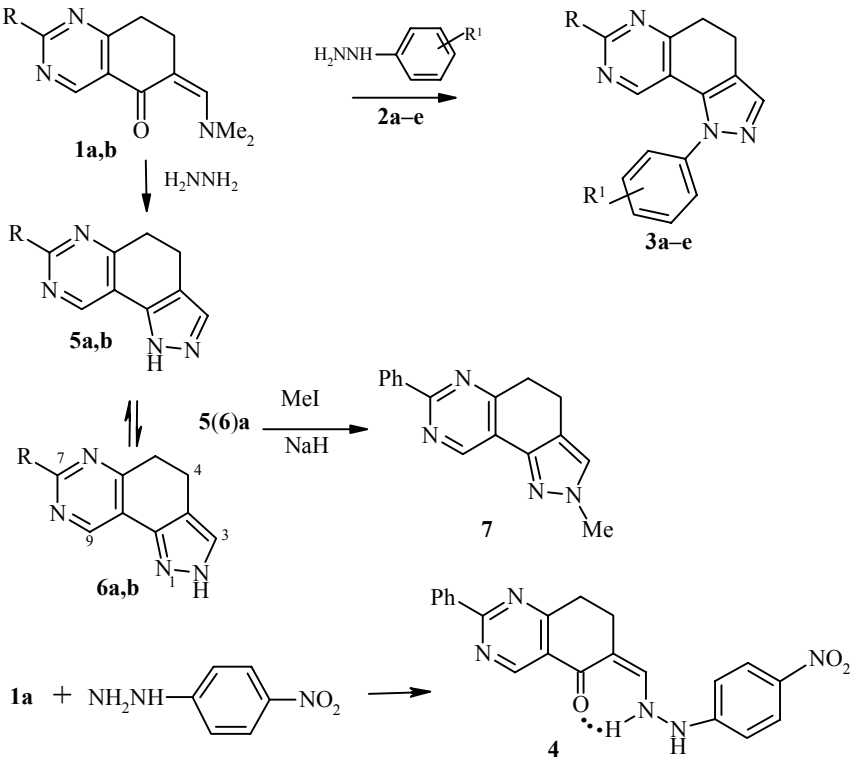

1, 5 (6) a R = Ph, **b** R = 4-C_5H_4N; **2 a** R^1 = H, **b** R^1 = 4-Br, **c** R^1 = 4-Cl, **d** R^1 = 4-OMe, **e** R^1 = 2-COOH; **3a–c** R = Ph, **d,e** R = 4-C_5H_4N, **a** R^1 = H, **b** R^1 = 4-Br, **c** R^1 = 4-Cl, **d** R^1 = 4-OMe, **e** R^1 = 2-COOH

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer for suspensions in vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}); the frequencies of the stretching vibrations for the C–H bonds in the 3050-2806 cm^{-1} region are not given.

The ^1H NMR spectra were recorded on a Varian-Mercury BB spectrometer (200 MHz) and a Bruker WH-90/DS in $CDCl_3$ and DMSO-d_6 solutions, internal standard HMDS.

1-Phenyl-(3a)-, 1-(4-Bromophenyl)- (3b), and 1-(4-Chlorophenyl)-7-phenyl-4,5-dihydropyrazolo-[3,4-*f*]quinazolines (3c) 1-(4-Methoxyphenyl)- (3d), and 1-(2-Carboxyphenyl)-7-(4-pyridyl)-4,5-dihydropyrazolo[3,4-*f*]quinazolines (3e). (General Procedure). A mixture of quinazoline **1** (2 mmol) and of the hydrochloride of the corresponding arylhydrazine **2a-e** (2 mmol) was refluxed for 5 h in pyridine (20 ml). Pyridine was distilled off to dryness on a rotary evaporator, the residue was recrystallized twice from 2-propanol with activated carbon added.

3a. Yield 83%; mp 199-200°C. IR spectrum, ν, cm^{-1}: 1596, 1560, 1522, 1512. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.75-3.20 (4H, m, $2CH_2$); 7.50 (3H, m, H_{Ph}); 7.56 (5H, m, H_{Ph}); 7.68 (1H, s, 3-H); 7.92 (1H, s, 9-H); 8.31 (2H, m, H_{Ph}). Found, %: C 77.58; H 4.90; N 17.17. $C_{21}H_{16}N_4$. Calculated, %: C 77.75; H 4.97; N 17.27.

3b. Yield 73%; mp 213-214°C. IR spectrum, ν, cm^{-1}: 1594, 1580, 1565, 1520, 1510. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.81-3.22 (4H, m, $2CH_2$); 7.53 (5H, m, $3H_{Ph}$, $2H_{Ar}$); 7.82 (3H, m, ^3J = 9, $2H_{Ar}$, 3-H); 8.12 (1H, s, 9-H); 8.36 (2H, m, H_{Ph}). Found, %: C 62.41; H 3.70; Br 19.60; N 14.00. $C_{21}H_{15}BrN_4$. Calculated, %: C 62.54; H 3.75; Br 19.81; N 13.89.

3c. Yield 58%; mp 195-197°C. IR spectrum, ν, cm^{-1}: 1594, 1580, 1562, 1525, 1510. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.85-3.22 (4H, m, $2CH_2$); 7.47-7.85 (7H, m, $3H_{Ph}$, $4H_{Ar}$); 7.61 (1H, s, 3-H); 8.11 (1H, s, 9-H); 8.41 (2H, m, H_{Ph}). Found, %: C 70.11; H 4.25; Cl 10.10; N 15.53. $C_{21}H_{15}ClN_4$. Calculated, %: C 70.29; H 4.21; Cl 9.88; N 15.61.

3d. Yield 85%; mp 212-213°C. IR spectrum, ν, cm^{-1}: 1596, 1533, 1505; 3070. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.94 (2H, t, ^3J = 7, CH_2); 3.21 (2H, t, ^3J = 7, CH_2); 3.87 (3H, s, OCH_3); 7.13 (2H, m, ^3J = 8, H_{Ar}); 7.47 (2H, m, ^3J = 8, H_{Ar}); 7.68 (1H, s, 3-H); 7.98 (1H, s, 9-H); 8.18 (2H, m, ^3J = 6, H_{Het}); 8.73 (2H, m, ^3J = 6, H_{Het}). Found, %: C 70.73; H 4.70; N 19.60. $C_{21}H_{17}N_5O$. Calculated, %: C 70.97; H 4.82; N 19.71.

3e. Yield 52%; mp 271-272°C. IR spectrum, ν, cm^{-1}: 1720, 1612, 1592, 1514; 2500-2350. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.91-3.27 (4H, m, $2CH_2$); 7.58-8.08 (6H, m, $4H_{Ar}$, 3-H, 9-H); 8.24 (2H, m, ^3J = 6.3, H_{Het}); 8.77 (2H, m, ^3J = 6.3, H_{Het}); 12.86 (1H, br. s, COOH). Found, %: C 68.06; H 4.05; N 18.77. $C_{21}H_{15}N_5O_2$. Calculated, %: C 68.28; H 4.09; N 18.96.

6-[(4-(2-Nitrophenyl)hydrazinomethylene]-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline (4). Product **4** was obtained by the procedure described above, by refluxing a mixture of compound **1a** and nitrophenylhydrazine for 6 h. Yield 88%; mp 285-286°C. IR spectrum, ν, cm^{-1}: 1635, 1600, 1565, 1510; 3300, 3100. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 3.20-3.50 (4H, m, $2CH_2$); 7.11 (2H, m, ^3J = 9, H_{Ar}); 7.48 (3H, m, HPh); 8.13 (1H, s, =CH–); 8.27 (2H, m, ^3J = 9, H_{Ar}); 8.50 (2H, m, H_{Ph}, NH); 9.87 (1H, s, 9-H); 11.54 (1H, br. s, NH). Found, %: C 65.22; H 4.33; N 17.90. $C_{21}H_{17}N_5O_3$. Calculated, %: C 65.11; H 4.42; N 18.08.

7-Phenyl- (5(6)a) and 7-(4-Pyridyl)-1H(2H)-4,5-dihydropyrazolo[3,4-*f*]quinazolines (5(6)b). Compound **1a,b** (2 mmol) and hydrazine hydrate (3 ml) were boiled in a flask under reflux. Methanol (8 ml) was added to the reaction mixture after cooling; the precipitate of the product **5(6)a,b** was filtered out and recrystallized from pyridine.

5(6)a. Yield 95%; mp 260-261°C. IR spectrum, ν, cm^{-1}: 1592, 1578, 1534; 3120-3100, 3060. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.90-3.05 (4H, m, $2CH_2$); 7.55 (3H, m, H_{Ph}); 7.69 (1H, s, 3-H); 8.24 (2H, m, H_{Ph}); 8.49 (1H, m, 9-H); 12.48 (1H, br. s, NH). Found, %: C 72.40; H 4.77; N 22.51. $C_{15}H_{12}N_4$. Calculated, %: C 72.56; H 4.87; N 22.57.

5(6)b. Yield 92%; mp 288-289°C. IR spectrum, ν, cm^{-1}: 1592, 1562, 1532; 3180. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.94-3.16 (4H, m, $2CH_2$); 7.27 (2H, m, ^3J = 6.3, H_{Het}); 7.66 (1H, s, 3-H); 8.86 (2H, m, ^3J = 6.3, H_{Het}); 9.05 (1H, s, 9-H); 13.08 (1H, br. s, NH). Found, %: C 67.33; H 4.52; N 27.92. $C_{14}H_{11}N_5$. Calculated, %: C 67.45; H 4.45; N 28.10.

2-Methyl-7-phenyl-4,5-dihydropyrazolo[3,4-*f*]quinazoline (7). A suspension of NaH in mineral oil (4 mmol) was added in small portions to a solution of pyrazoloquinazoline **5(6)a** (2 mmol) in DMF (20 ml); the reaction mixture was stirred for 15 min, methyl iodide (4 mmol) was added, and the reaction mixture was stirred for another 30 min. The reaction mixture was carefully poured into water in small portions, the precipitate was filtered out and purified, chromatographed on a column (silica gel Aeros, 35-77 μm, pore diameter 6 nm, eluent chloroform–ethyl acetate, 6:1), eluting the fraction with R_f 0.21. Yield 38%; mp 120-121°C. IR spectrum, ν, cm^{-1}: 1596, 1575, 1560, 1530, 1520. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.89 (2H, t, ^3J = 7, CH_2); 3.14 (2H, t, ^3J = 7, CH_2); 3.91 (3H, s, CH_3); 7.14 (1H, s, 3-H); 7.45 (3H, m, H_{Ph}); 8.44 (2H, m, H_{Ph}); 9.07 (1H, s, 9-H). Found, %: C 73.11; H 5.20; N 21.12. $C_{16}H_{14}N_4$. Calculated, %: C 73.26; H 5.38; N 21.36.

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