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PYRAZOLO[5,4-*h*]QUINAZOLINES

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The reaction of 1-phenyl- and 4-chloro-5-formyl-3-methyl-1-(2-pyridyl)-6,7-dihydroindazoles with carbamidinopyrrolidine, 4-carbamidinomorpholine, creatine, 2-carbamidinopyrazine, and 2-carbamidino-5-trifluoromethylpyridine gives the corresponding 3,8-substituted 1-methyl-4,5-dihydropyrazolo-[5,4-h]quinazolines and with 2-aminobenzimidazole gives 3-phenyl- and 3-(2-pyridyl)-1-methyl-4,5-dihydrobenzo[h]indazolo[4,5-e]imidazolo[1,2-a]pyrimidines.

Keywords: 3,8-substituted 1-methyl-4,5-dihydropyrazolo[5,4-*h*]quinazolines, 1-(2-pyridyl)- and 1-phenyl-4-chloro-5-formyl-3-methyl-6,7-dihydroindazoles.

We continue work [1-4] describing the synthetic uses of 1-phenyl- (**1**) and 1-(2-pyridyl)- (**2**) 4-chloro-5-formyl-3-methyl-6,7-dihydroindazoles in their reaction with a series of amidines and their cyclic analogs (2-aminobenzimidazole and 5-aminotetrazole). In addition to C-carbamidines 2-carbamidino-5-trifluoromethylpyridine and 2-carbamidinopyrazine, N-carbamidines carbamidinopyrrolidine, 4-carbamidinomorpholine, and creatine were also used. In all cases, the single reaction products were the 3,8-substituted 1-methyl-4,5-dihydropyrazolo[5,4-*h*]quinazolines (**3-9**).

Reaction of chlorovinylaldehydes **1** and **2** with salts of carbamidinopyrrolidine and morpholine was carried out with prolonged (10-15 h) refluxing in absolute ethanol in the presence of two equivalents of KOH or, in the case of creatine hydrate, two hour refluxing in the presence of an equimolar amount of KOH. The reaction with 2-carbamidino-5-trifluoromethylpyridine and 2-carbamidinopyrazine salts also needed prolonged heating. In the first example it was best to use an equimolar amount of alcoholate and in the second KOH.

The reaction with the free bases of cyclic amidine analogs (5-aminotetrazole and 2-aminobenzimidazole) was also carried out in the presence of an equimolar amount of alcoholate. Moreover, for the reaction of phenylindazole **1** with 5-aminotetrazole, the single reaction product is tetrazolo[1,5-*a*]pyrazolo[5,4-*h*]quinazoline **10** and with 2-aminobenzimidazole benzimidazolo[1,2-*a*]pyrazolo[5,4-*h*]quinazoline **11**. Treatment of 1-(2-pyridyl)indazole **2** with 2-aminobenzimidazole leads to formation of both compound **12** and 5-aminomethyleneindazole **13**. In contrast, the reaction of enol ether **14** (prepared from the chloro derivative **2** and sodium ethylate) with 2-aminobenzimidazole gave only compound **12**.

IR and ^{1}H NMR spectroscopic data are fully in agreement with the proposed structures. Hence the ^{1}H NMR spectra confirm the presence in compound **13** of a trans orientated aminomethylene group, identified by the doublet signals at 7.67 ppm (J = 13 Hz) for CH and at 11.34 ppm for NH (J = 13 Hz), together with the signal for the NH proton of the imidazole fragment at 11.56 ppm. In the IR spectrum, the NH bond frequency is seen in the range 3200-3050 cm^{-1}. In the spectra of compounds **3-12** no NH bonds were observed but for compound **9** the presence of the carboxylic hydroxyl function was established by ν_{COOH} at 2650-2450 cm^{-1} and δ_{COOH} at 10.5 ppm.

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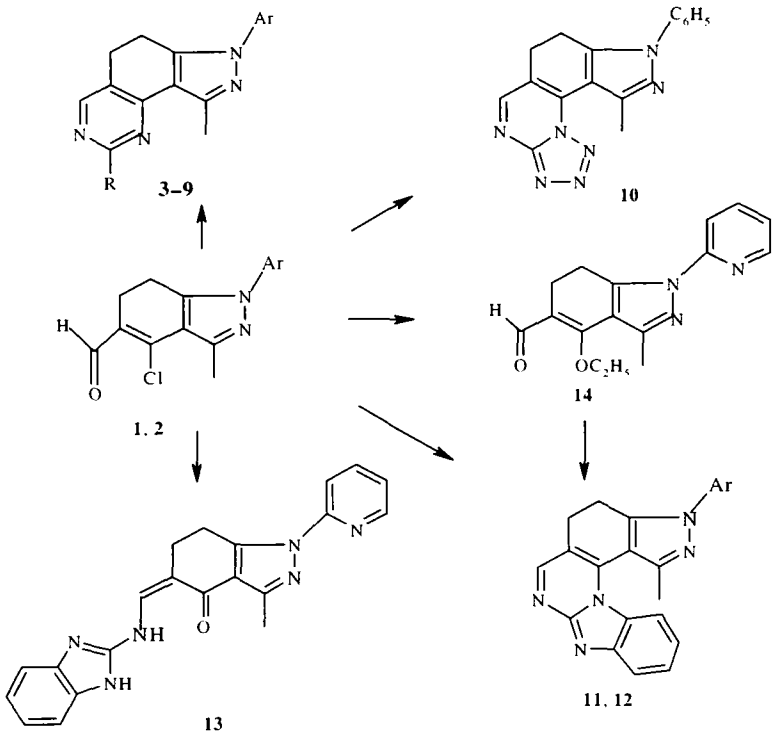

1, 11 Ar = C_6H_5; **2, 12** Ar = C_5H_4N-2; **3** Ar = C_6H_5, R = $N(CH_2)_4$;
4 Ar = C_5H_4N-2, R = $(CH_2)_4$; **5** Ar = C_6H_5, R = $N(CH_2CH_2)_2O$;
6 Ar = C_5H_4N-2, R = $N(CH_2CH_2)_2O$; **7** Ar = C_6H_5, R = 4-$CF_3C_5H_3N$-2;
8 Ar = C_5H_4N-2, R = 2-pyrazinyl; **9** Ar = C_5H_4N-2, R = $N(CH_3)CH_2COOH$

EXPERIMENTAL

IR spectra were taken on a Specord 75-IR spectrometer for suspensions of the compounds in vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}); frequencies for the C–H stretching vibrations in the region 3050-2800 cm^{-1} are not reported. ^1H NMR spectra were taken in $CDCl_3$ and DMSO-d_6 on a Bruker WH-90/DS (90 MHz) spectrometer with TMS as internal standard. Amidine salts used were supplied by Acros and the Maybridge Chemical Company.

3-Phenyl-8-pyrrolidyl- (3), 3-(2-Pyridyl)-8-pyrrolidyl- (4), 8-(4-Morpholyl)-3-phenyl- (5), and 8-(4-Morpholyl)-3-(2-pyridyl)- (6) 1-Methyl-4,5-dihydropyrazolo[5,4-*h*]quinazolines. Chlorovinylaldehyde **1** or **2** (2 mmol), hydrobromides of carbamidine of pyrrolidine or 4-carbamidine of morpholine (2 mmol), and KOH (4 mmol) in absolute ethanol (10-15 ml) were refluxed for 12 h. After cooling, the product was diluted with water to 100 ml and left for one day at 20°C. The precipitated compounds **3-6** were filtered off and recrystallized.

3. Yield 68%; mp 139-140°C (ethanol–water, 2:1). IR spectrum: 1596, 1553, 1500 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 1.98 (4H, m, $(CH_2)_2$); 2.67 (3H, s, CH_3); 2.87 (4H, m, 4-H, 5-H); 3.63 (4H, m, CH_2–N–CH_2); 7.45 (5H, m, C_6H_5); 8.07 ppm (1H, s, 6-H). Found, %: C 72.25; H 6.30; N 21.21. $C_{20}H_{21}N_5$. Calculated, %: C 72.48; H 6.38; N 21.13.

4. Yield 60%; mp 161-162°C (ethanol). IR spectrum: 1588, 1552, 1500 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 1.96 (4H, m, $(CH_2)_2$); 2.68 (3H, s, 1-CH_3); 2.85 (2H, t, ^3J = 7 Hz, 4-H); 3.54 (2H, t, ^3J = 7 Hz, CH_2); 3.61 (4H, m, CH_2–N–CH_2); 7.20 (1H, m, 3-C_5H_4N); 7.81-7.88 (2H, m, C_5H_4N); 8.02 (1H, s, 6-H); 8.42 ppm (1H, dd, ^3J = 5, ^4J = 1.5 Hz, C_5H_4N). Found, %: C 68.39; H 5.91; N 25.20. $C_{19}H_{20}N_6$. Calculated, %: C 68.65; H 6.07; N 25.28.

5. Yield 58%; mp 179-180°C (ethanol). IR spectrum: 1597, 1557, 1505 cm^{-1}. ^1H NMR spectrum: ($CDCl_3$): 2.65 (3H, s, 1-CH_3); 2.87 (4H, m, 4-H, 5-H); 3.78 (8H, center m, $N(CH_2CH_2)_2O$); 7.41 (5H, m, 3-C_6H_5); 8.07 ppm (1H, s, 6-H). Found, %: C 68.91; H 5.97; N 20.12. $C_{20}H_{21}N_5O$. Calculated, %: C 69.14; H 6.09; N 20.16.

6. Yield 73%; mp 154-155°C (from isopropanol). IR spectrum: 1593, 1561, 1500 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 2.65 (3H, s, 1-CH_3); 2.87 (2H, t, ^3J = 7 Hz, 4-H); 3.52 (2H, t, ^3J = 7 Hz, 5-H); 3.78 (8H, center m, $N(CH_2CH_2)_2O$); 7.16 (1H, m, 3-C_5H_4N); 7.65-7.96 (2H, m, 3-C_5H_4N); 8.05 (1H, s, 6-H); 8.38 ppm (1H, m, 3-C_5H_4N). Found, %: C 65.31; H 5.80; N 23.92. $C_{19}H_{20}N_6O$. Calculated, %: C 65.50; H 5.79; N 24.12.

1-Methyl-3-phenyl-8-(5-trifluoromethylpyrid-2-yl)-4,5-dihydropyrazolo[5,4-*h*]quinazoline (7). Indazole **1** (0.54 g, 2 mmol), 2-carbamidino-5-trifluoromethylpyridine hydrochloride (0.50 g, 2 mmol) and an equimolar amount of sodium methylate were refluxed in methanol (15 ml) for 10 h. The product was cooled, diluted with water (30 ml), and left for one day at 0°C. The precipitated **7** was filtered off and recrystallized from a mixture of ethanol and water (1: 1) to give **7** (0.40 g, 50%); mp 209-210°C. IR spectrum: 1583, 1549, 1509 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 2.78 (3H, s, 1-CH_3); 3.05 (4H, m, 4-H, 5-H); 7.43 (5H, m, 3-C_6H_5); 8.05 (1H, dd, ^3J = 8, ^4J = 2 Hz, 8-C_5H_4N); 8.65 (1H, d, ^3J = 8 Hz, 8-C_5H_4N); 8.58 (1H, s, 6-H); 9.01 ppm (1H, d, ^4J = 2 Hz, 8-Py). Found, %: C 64.66; H 4.05; N 17.15. $C_{22}H_{16}F_3N_5$. Calculated, %: C 64.86; H 3.96; N 17.19.

1-Methyl-8-(2-pyrazinyl)-3-(2-pyridyl)-4,5-dihydropyrazolo[5,4-*h*]quinazoline (8). Indazole **2** (0.54 g, 2 mmol), 2-carbamidinopyrazine hydrochloride (0.30 g, 2 mmol), and KOH (0.25 g) were refluxed in absolute ethanol (15 ml) for 20 h. Ethanol (10 ml) was distilled off on a rotary evaporator, the residue diluted with water (30 ml), and then allowed to stand for one day in the fridge. The precipitated, oily product was recrystallized from isopropanol to give **8** (0.20 g, 29%); mp 215-217°C. IR spectrum: 1599, 1541, 1511; 3060 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 2.78 (3H, s, 3-CH_3); 3.12 (2H, t, ^3J = 8 Hz, 4-H); 3.65 (2H, t, ^3J = 7 Hz, 5-H); 7.21 (1H, m, 3-C_5H_4N); 7.87 (2H, center m, 3-C_5H_4N); 8.38 (1H, d, ^3J = 6 Hz, 3-C_5H_4N); 8.61 (1H, s, 6-H); 8.67 (2H, center m, 8-$C_4H_3N_2$); 9.74 ppm (1H, d, ^4J = 1.5 Hz, 3-$C_4H_3N_2$). Found, %: C 66.63; H 4.40; N 28.49. $C_{19}H_{15}N_7$. Calculated, %: C 66.85; H 4.43; N 28.72.

1-Methyl-8-methylcarboxymethylamino-3-(2-pyridyl)-4,5-dihydropyrazolo[5,4-*h*]quinazoline (9). Indazole **2** (0.54 g, 2 mmol), creatine hydrate (0.30 g, 2 mmol), and KOH (0.20 g, 4 mmol) were refluxed in absolute ethanol (20 ml) for 2 h. The reaction mixture was diluted with water (80 ml), neutralized with HCl to pH 7, and left for 3 days in the fridge. The solid, brownish product was recrystallized from isopropanol to give **9** (0.19 g, 28%); mp 217-219°C. IR spectrum: 1605, 1592, 1552, 1516, 2650-2450 cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 2.56 (3H, s,1-CH_3); 2.85 (2H, m, 4-H); 3.18 (3H, s, N–CH_3); 3.37 (2H, m, 5-H); 4.32 (2H, s, N–CH_2); 7.38 (1H, m, 3-C_5H_4N); 7.89 (2H, center m, 3-C_5H_4N); 8.15 (1H, s, 6-H); 8.45 (1H, m, 3-C_5H_4N); 10.5 ppm (1H, br. s, OH). Found, %: C 61.44; H 5.11; N 24.11. $C_{18}H_{18}N_6O_2$. Calculated, %: C 61.70; H 5.18; N 23.99.

1-Methyl-3-phenyl-4,5-dihydrotetrazolo[1,5-*a*]pyrazolo[5,4-*h*]quinazoline (10). Indazole **1** (0.54 g, 2 mmol) and 5-aminotetrazole (0.32 g, 2 mmol) were refluxed in absolute ethanol (40 ml) containing sodium ethylate (2 mmol) for 12 h. After cooling, the product was diluted with water (120 ml) and left for one day in the fridge. The precipitate was filtered and recrystallized from ethanol to give **10** (0.30 g, 49%); mp 180-183°C. IR spectrum: 1625, 1591, 1571, 1525, 1509 cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 2.65 (3H, s, 1-CH_3); 3.16 (4H, m, 4-H, 5-H); 7.58 (5H, m, 3-C_6H_5); 9.42 ppm (1H, s, 6-H). Found, %: C 63.12; H 4.24; N 32.30. $C_{16}H_{13}N_7$. Calculated, %: C 63.35; H 4.32; N 32.33.

1-Methyl-3-phenyl-4,5-dihydrobenzimidazo[1,2-*a*]pyrazolo[5,4-*h*]quinazoline (11). Indazole **1** (0.54 g, 2 mmol), and 2-aminobenzimidazole (0.26 g, 2 mmol) were refluxed in absolute ethanol (25 ml) containing sodium ethylate (2 mmol) for 12 h. A bright yellow solid began to precipitate from the deep yellow solution after 3 h. For completion of the reaction, water (10 ml) was added and the product allowed to stand for 12 h in a fridge. The precipitate was filtered off and recrystallized from ethanol to give **11** (0.30 g, 43%); mp 321-322°C. IR spectrum: 1598, 1582, 1538, 1500, 3070 cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 2.25 (3H, s, 1-CH_3); 3.02 (4H, m, 4-H, 5-H); 7.32-7.96 (9H, m, 3-C_6H_5, 9-12 H); 8.67 ppm (1H, s, 6-H). Found, %: C 74.97; H 4.80; N 19.76. $C_{22}H_{17}N_5$. Calculated, %: C 75.19; H 4.88; N 19.93.

1-Methyl-3-(2-pyridyl)-4,5-dihydrobenzimidazo[1,2-*a*]pyrazolo[5,4-*h*]quinazoline (12). Enol ether **14** (0.56 g, 2 mmol) and 2-aminobenzimidazole (0.26 g, 2 mmol) were refluxed in absolute ethanol (25 ml) containing sodium ethylate (2 mmol) for 5 h. After cooling, a yellow precipitate was filtered off and recrystallized from

ethanol to give **11** (0.31 g, 44%); mp 285-287°C. IR spectrum: 1637, 1510, 1593, 1571, 1529, 1500 cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 2.67 (3H, s, 1-CH_3); 3.09-3.56 (4H, m, 4-H, 5-H); 7.41-8.51 (8H, m, 9-12 H); 9.21 ppm (1H, s, 6-H). Found, %: C 71.51; H 4.63, N 23.70. $C_{21}H_{16}N_6$. Calculated, %: C 71.57; H 4.58; N 23.85.

Reaction of Chlorovinylaldehyde 2 with 2-Aminobenzimidazole. Compound **2** (2.16 g, 8 mmol) and 2-aminobenzimidazole (1.04 g, 8 mmol) were refluxed in absolute ethanol (100 ml) containing sodium ethylate (16 mmol) for 4 h. Two thirds of the volume of ethanol was removed on a rotary evaporator and water (15 ml) was added to the residue. The precipitate was filtered and recrystallized from ethanol to give **12** (0.55 g, 19%); mp 285-287°C; this melting point was not depressed by a sample from the preceding experiment.

The filtrate after separation of **12** was neutralized with conc. HCl to pH 7 and the precipitated indazole derivative **13** was recrystallized from ethanol to give 3-methyl-5-(2-benzimidazolylaminomethylene)-4-oxo-1-(2-pyridyl)-6,7-dihydroindazole **13** (0.60 g, 20%); mp 147-149°C. IR spectrum: 1650, 1625, 1580, 1560, 1535, 3200-3050 cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 2.49 (3H, s, 1-CH_3); 2.82 (2H, m, 7-H); 3.39 (2H, m, 6-H); 6.96-7.32 (4H, m, C_6H_4); 7.34 (1H, m, 1-C_5H_4N); 7.67 (1H, d, ^3J = 13 Hz, α-CH_2); 7.70-8.15 (2H, m, 1-C_5H_4N); 8.45 (1H, dd, ^3J = 2.5 Hz, ^4J = 1.5 Hz, 1-C_5H_4N); 11.34 (1H, d, J = 13 Hz, NH); 11.56 ppm (1H, br. s, NH). Found, %: C 67.88; H 4.75; N 22.50. $C_{21}H_{18}N_6O$. Calculated, %: C 68.09; H 4.90; N 22.69.

4-Ethoxy-5-formyl-3-methyl-1-(2-pyridyl)-6,7-dihydroindazole (14). A solution of sodium ethylate (4 mmol) in absolute ethanol (10 ml) at 60-70°C was added to a solution of indazole **2** (1.08 g, 4 mmol) in absolute ethanol (15 ml) which had been heated to the same temperature. The reaction mixture was refluxed for 5 min, cooled, the precipitated sodium chloride filtered off, two thirds of the volume of ethanol removed on a rotary evaporator, a mixture of benzene and hexane (1: 2, 15 ml) added, and the product was allowed to stand for one day in a fridge. The precipitate was filtered off and recrystallized from petroleum ether to give **14** (0.60 g, 53%); mp 93-94°C. IR spectrum 1678, 1616, 1594, 1582, 1554, 1500 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 1.33 (3H, t, ^3J = 7 Hz, 3-CH_3); 2.60 (3H, s, 3-CH_3); 2.84 (2H, t, ^3J = 7 Hz, 7-H); 3.47 (2H, t, ^3J = 7 Hz, 6-H); 4.11 (2H, q, ^3J = 7 Hz, O–CH_2); 7.22 (1H, m, 1-C_5H_4N); 7.44 (1H, t, ^3J = 1 Hz or less, CHO); 7.80 (1H, d, ^3J = 8, ^4J = 1.5 Hz, 1-C_5H_4N); 7.85 (1H, m, 1-C_5H_4N); 8.4 ppm (1H, dd, ^3J = 6, ^4J = 1.5 Hz, 1-C_5H_4N). Found, %: C 67.89; H 17.20; N 15.00. $C_{16}H_{17}N_3O_2$. Calculated, %: C 67.82; H 6.05; N 14.83.

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