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2-SUBSTITUTED 5-OXO-5,6,7,8-TETRAHYDROQUINAZOLINES

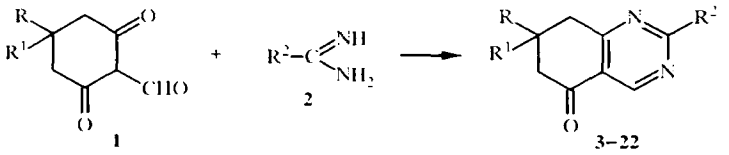
N. N. Tonkikh, A. Ya. Strakov, and M. V. Petrova

Twenty novel 2-substituted 5-oxo-5,6,7,8-tetrahydroquinazolines in reactions of 2-formyl-1,3-cyclohexanedione and its 5,5-dimethyl- and 5-phenyl derivatives with 4-chloro- and 4-carbonylaminobenzamidines, 3- and 4-carbamidinopyridines, 2-carbamidinopyrazine, 2-carbamidino-5-trifluoromethylpyridine, 1-carbamidinopyrrolidine, 4-carbamidinomorpholine, and 1-carbamidino-3,5-dimethylpyrazole have been obtained.

Keywords: 2-(3,5-dimethyl-1-pyrazolyl)-, 2-(4-morpholyl)-, 2-(2-pyrazinyl)-, 2-(3-pyridyl)-, 2-(4-pyridyl)-5-oxo-5,6,7,8-tetrahydroquinazolines.

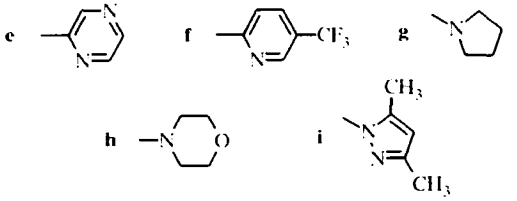
In an extension of work done in [1,2], we have obtained 2-substituted 5-oxo-5,6,7,8-tetrahydroquinazolines **3-22** in reactions of 2-formyl-1,3-cyclohexanediones (**1**) with amidines **2**, mainly in the heterocyclic series.

We utilized the synthesis method used in [1,2]: boiling 2-formyl-1,3-cyclohexanedione and the amidine salt in methanol in the presence of piperidine, to obtain quinazolines **3-22**. In reactions with 4-carbonylaminobenzamidine, considerably higher yields of quinazolines **5-7** are achieved for a 2-formyl derivative – amidine mole ratio of 2:1.



1 **2** **3–22**

1 a R = R^1 = H; **b** R = R^1 = CH$_3$; **c** R = C$_6$H$_5$, R^1 = H;
2 a R^2 = C$_6$H$_4$Cl-4; **b** C$_6$H$_4$CONH$_2$-4; **c** C$_5$H$_4$N-4; **d** C$_5$H$_4$N-3;



3 b = R,R^1, **a** = R^2; **4 c** = R,R^1, **a** = R^2; **5 a** = R,R^1, **b** = R^2; **6 b** = R,R^1, **b** = R^2; **7 c** = R,R^1, **b** = R^2; **8 a** = R,R^1, **c** = R^2; **9 a** = R,R^1, **d** = R^2; **10 b** = R,R^1, **e** = R^2; **11 c** = R,R^1, **e** = R^2; **12 b** = R,R^1, **f** = R^2; **13 c** = R,R^1, **f** = R^2; **14 a** = R,R^1, **g** = R^2; **15 b** = R,R^1, **g** = R^2; **16 c** = R,R^1, **g** = R^2; **17 a** = R,R^1, **h** = R^2; **18 b** = R,R^1, **h** = R^2; **19 c** = R,R^1, **h** = R^2; **20 a** = R,R^1, **i** = R^2; **21 b** = R,R^1, **i**= R^2; **22 c** = R,R^1, **i** = R^2

Riga Technical University, Riga LV-1658, Latvia; e-mail: marina@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 212-26, February, 2000. Original article submitted February 11, 1999.

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Amidines **2g-i**, which can also be considered as N,N-disubstituted guanidines, are characterized by lower reactivity. So quinazolines **14-22** are synthesized under more vigorous conditions, with fusion of the potassium salts of 2-formyl-1,3-cyclohexanediones and the corresponding amidine salts according to the method used in [3] for synthesis of 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinazoline.

The structure of the compounds obtained was confirmed by IR and ^{1}H NMR spectra. IR absorption of the carbonyl group $C_{(5)}$ of compounds **3-22** is observed in the range from 1700 to 1665 cm^{-1}. Proton signals also are observed in the ^{1}H NMR spectra which are completely consistent with structures **14-22**. The proton at $C_{(4)}$ common to all the compounds is characterized by a chemical shift of 8.78-9.48 ppm.

^{1}H NMR spectra of quinazolines not substituted at the 7 position are characterized by three multiplet signals from the methylene protons at 2.09-2.25 ppm, 2.52-2.73 ppm, and 2.82-3.16 ppm, while the 7-phenyl derivatives are characterized by five-proton multiplets in the 2.60-3.70 ppm region. Six-proton singlets from the two methyl groups of the $C_{(7)}$ atoms are observed at 1.03-1.16 ppm; signals from the $C_{(6)}$-methylene protons are observed at 2.38-2.65 ppm, while signals from the $C_{(8)}$-methylene protons are observed at 2.59-3.18 ppm. Signals from the protons of the substituent groups at $C_{(2)}$ also correspond to structures **14-22**.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical Formula	Found, % / Calculated, %				mp, °C	Crystallization solvent	Yield, %
		C	H	N	Cl			
3	$C_{16}H_{15}ClN_2O$	66.81 / 67.02	5.30 / 5.27	9.62 / 9.77	12.20 / 12.36	163-164	Methanol	52
4	$C_{20}H_{17}ClN_2O$	71.48 / 71.75	4.45 / 4.52	8.21 / 8.37	10.40 / 10.59	187-188	Toluene	36
5	$C_{14}H_{14}N_4O_2$	67.60 / 67.41	4.85 / 4.90	15.50 / 15.72		253-254	Toluene	63
6	$C_{19}H_{16}N_4O_2$	68.90 / 69.13	5.63 / 5.81	14.00 / 14.23		265-266	Toluene	57
7	$C_{25}H_{20}N_4O_2$	73.28 / 73.45	4.89 / 4.99	12.09 / 12.23		235-236	Toluene	65
8	$C_{13}H_{11}N_3O$	69.11 / 69.32	4.80 / 4.92	18.46 / 18.64		140-141	Ethanol	42
9	$C_{13}H_{11}N_3O$	69.08 / 69.32	4.71 / 4.92	18.51 / 18.64		95-96	Water	33
10	$C_{14}H_{13}N_3O$	65.91 / 66.13	5.40 / 5.55	21.90 / 22.03		146-147	Isopropanol	71
11	$C_{18}H_{13}N_3O$	71.30 / 71.51	4.61 / 4.67	18.42 / 18.53		80-82	Isopropanol	42
12	$C_{16}H_{12}F_3N_3O$	59.66 / 59.81	4.28 / 4.39	13.01 / 13.08		132-134	Ethanol	37
13	$C_{20}H_{14}F_3N_3O$	72.31 / 72.49	4.14 / 4.26	12.49 / 12.68		124-125	Ethanol	53
14	$C_{12}H_{13}N_3O$	66.09 / 66.34	6.81 / 6.96	19.11 / 19.34		74-75	Ethanol	26
15	$C_{13}H_{15}N_3O$	68.66 / 68.54	7.70 / 7.81	16.92 / 17.13		125-126	Ethanol	73
16	$C_{18}H_{15}N_3O$	73.47 / 73.70	6.50 / 6.53	14.13 / 14.32		106-108	Ethanol	46
17	$C_{12}H_{13}N_3O_2$	61.61 / 61.79	6.33 / 6.48	17.85 / 18.01		79-80	Ethanol	40
18	$C_{14}H_{15}N_3O_2$	64.11 / 64.35	7.09 / 7.33	16.01 / 16.08		104-105	Ethanol	83
19	$C_{18}H_{15}N_3O_2$	69.66 / 69.89	6.12 / 6.19	13.50 / 13.58		88-90	Ethanol	70
20	$C_{13}H_{13}N_3O$	64.51 / 64.45	5.80 / 5.82	22.92 / 23.12		105-106	Isopropanol	40
21	$C_{15}H_{15}N_3O$	66.49 / 66.65	6.63 / 6.71	20.50 / 20.72		118-120	Isopropanol	31
22	$C_{19}H_{15}N_3O$	71.71 / 71.68	5.60 / 5.69	17.50 / 17.59		150-151	Isopropanol	75

TABLE 2. IR Spectra and ^{1}H NMR Spectra of 2-Substituted 5-Oxo-5,6,7,8-tetrahydroquinazolines **3-22**

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm
3	1690, 1585, 1562, 1546	$CDCl_3$; 1.16 (6H, s, $2CH_3$); 2.58 (2H, s, CH_2); 3.05 (2H, s, CH_2); 7.49 (2H, m, ^3J = 9.0 Hz, Ar); 8.53 (2H, m, ^3J = 9.0 Hz, Ar); 9.21 (1H, s, =CH-)
4	1685, 1581, 1574, 1560	$CDCl_3$; 2.85-3.68 (5H, m, CH, $2CH_2$); 7.33 (5H, m, C_6H_5); 7.50 (2H, m, ^3J = 9.0 Hz, Ar); 8.49 (2H, m, ^3J = 9.0 Hz, Ar); 9.26 (1H, s, =CH-)
5	3364, 3164, 1667, 1620, 1593, 1576	DMSO: 2.16 (2H, m, ^3J = 7 Hz, CH_2); 2.72 (2H, t, ^3J = 7 Hz, CH_2); 3.14 (2H, t, ^3J = 7 Hz, CH_2); 7.49 (2H, br. s, NH_2); 8.10 (2H, m, ^3J = 8.0 Hz, Ar); 8.52 (2H, m, ^3J = 8.0 Hz, Ar); 9.14 (1H, s, =CH-)
6	1690, 1685, 1625, 1577, 1535; 3400, 3140	DMSO: 1.07 (6H, s, $2CH_3$); 2.62 (2H, s, CH_2); 3.09 (2H, s, CH_2); 7.42 (2H, br. s, NH_2); 8.03 (2H, m, ^3J = 8.0 Hz, Ar); 8.53 (2H, m, ^3J = 8.0 Hz, Ar); 9.16 (1H, s, =CH-)
7	1683, 1673, 1585, 1565; 3440,3140	DMSO: 2.60-3.70 (5H, m, CH, $2CH_2$); 7.43 (1H, br. s, NH); 7.45 (5H, m, C_6H_5); 8.06 (3H, m, ^3J = 8.0 Hz, Ar, NH); 8.53 (2H, m, ^3J = 8.0 Hz, Ar); 9.24 (1H, s, =CH-)
8	1683, 1616, 1580, 1563, 1554	$CDCl_3$; 2.22 (2H, m, ^3J = 7 Hz, CH_2); 2.73 (2H, t, ^3J = 7 Hz, CH_2); 3.15 (2H, t, ^3J = 7 Hz, CH_2); 8.32 (2H, m, Py); 8.80 (2H, m, Py); 9.30 (1H, s, =CH-)
9	1691, 1590, 1575, 1545	$CDCl_3$; 2.25 (2H, m, ^3J = 7 Hz, CH_2); 2.52 (2H, t, ^3J = 7 Hz, CH_2); 3.16 (2H, m, ^3J = 7 Hz, CH_2); 7.44 (1H, m, Py); 8.78 (2H, m, Py); 9.29 (1H, s, =CH-); 9.71 (1H, m, Py)
10	1689, 1571, 1555	$CDCl_3$; 1.15 (6H, s, $2CH_3$); 2.65 (2H, s, CH_2); 3.18 (2H, s, CH_2); 8.77 (1H, d, ^3J = 2.5 Hz, =CH-); 8.88 (1H, dd, ^4J = 1.5, ^3J = 2.5 Hz, =CH-); 9.35 (1H, s, =CH-); 9.83 (1H, d, ^4J = 1.5 Hz, =CH-)
11	1697, 1569, 1506	$CDCl_3$; 3.07 (2H, m, CH_2); 3.54 (3H, m, CH_2, CH); 7.38 (5H, m, C_6H_5); 8.77 (1H, d, ^3J = 2.5 Hz, =CH-); 8.87 (1H, dd, ^4J = 1.5, ^3J = 2.5 Hz, =CH-); 9.48 (1H, s, =CH-), 9.81 (1H, d, ^4J = 1.5 Hz, =CH-)
12	1685, 1601, 1544	$CDCl_3$; 1.14 (6H, s, $2CH_3$); 2.62 (2H, s, CH_2); 3.13 (2H, s, CH_2); 8.14 (1H, dd, ^4J = 2.5, ^3J = 9.0 Hz, Py); 8.83 (1H, d, ^3J = 9.0 Hz, Py); 9.14 (1H, d, ^4J = 2.5 Hz, Py); 9.37 (1H, s, =CH-)
13	1684, 1605, 1585, 1570, 1550	$CDCl_3$; 3.04-3.54 (5H, m, CH, $2CH_2$); 7.22 (5H, m, C_6H_5); 8.14 (1H, dd, ^4J = 2.0, ^3J = 9.0 Hz, Py); 8.72 (1H, d, ^3J = 9.0 Hz, Py); 8.96 (1H, d, ^4J = 2.0 Hz, Py); 9.42 (1H, s, =CH-)
14	1665, 1590, 1535, 1525	$CDCl_3$; 2.01 (4H, m, $(CH_2)_2$); 2.09 (2H, m, ^3J = 7 Hz, CH_2); 2.58 (2H, t, ^3J = 7 Hz, CH_2); 2.86 (2H, t, ^3J = 7 Hz, CH_2); 3.66 (4H, m, CH_2-N-CH_2); 8.92 (1H, s, =CH-)
15	1675, 1590, 1550, 1530	$CDCl_3$; 1.07 (6H, s, $2CH_3$); 1.98 (4H, m, $2CH_2$); 2.43 (2H, s, CH_2); 2.72 (2H, s, CH_2); 3.66 (4H, m, $2CH_2$); 8.85 (1H, s, =CH-)
16	1671, 1580, 1548, 1514	$CDCl_3$; 1.98 (4H, m, $(CH_2)_2$); 2.85-3.40 (5H, m, CH, $2CH_2$); 3.65 (4H, m, $2CH_2$); 7.29 (5H, m, C_6H_5); 8.89 (1H, s, =CH-)
17	1664, 1590, 1545, 1530	$CDCl_3$; 2.09 (2H, m, ^3J = 7 Hz, CH_2); 2.58 (2H, t, ^3J = 7 Hz, CH_2); 2.82 (2H, t, ^3J = 7 Hz, CH_2); 3.75-3.96 (8H, m, $N(CH_2CH_2)_2O$); 8.87 (1H, s, =CH-)
18	1667, 1600, 1590, 1540, 1525	$CDCl_3$; 1.08 (6H, s, $2CH_3$); 2.40 (2H, s, CH_2); 2.69 (2H, s, CH_2); 3.76-3.91 (8H, m, $N(CH_2CH_2)_2O$); 8.78 (1H, s, =CH-)
19	1673, 1593, 1535, 1525	$CDCl_3$; 2.78-3.41 (5H, m, CH, $2CH_2$); 3.74-3.98 (8H, m, $N(CH_2CH_2)_2O$); 7.34 (5H, m, C_6H_5); 8.89 (1H, s, =CH-)
20	1693, 1589, 1550	$CDCl_3$; 2.21 (2H, m, ^3J = 7 Hz, CH_2); 2.35 (3H, s, CH_3); 2.68 (2H, t, ^3J = 7 Hz, CH_2); 2.73 (3H, s, CH_3); 3.14 (2H, t, ^3J = 7 Hz, CH_2); 6.08 (1H, s, =CH-); 9.21 (1H, s, =CH-)
21	1697, 1660, 1575	$CDCl_3$; 1.16 (6H, s, $2CH_3$); 2.38 (3H, s, CH_3); 2.59 (2H, m, CH_2); 2.74 (3H, s, CH_3); 3.07 (2H, s, CH_2); 6.12 (1H, s, =CH-); 9.23 (1H, s, =CH-)
22	1700, 1590, 1578, 1555	$CDCl_3$; 2.31 (3H, s, CH_3); 2.67 (3H, s, CH_3); 2.98-3.43 (5H, m, CH, $2CH_2$); 6.05 (1H, s, =CH-); 7.23 (5H, centr m, C_6H_5); 9.21 (1H, s, =CH-)

EXPERIMENTAL

The IR spectra were taken on Specord 75-IR instruments for suspensions in vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}; the frequencies of the stretching vibrations of the C–H bonds in the 3050-2800 cm^{-1} region are not given). The 1H NMR spectra were recorded on a Bruker WH 90/DS spectrometer in $CDCl_3$ and DMSO-d_6 solutions; internal standard TMS.

2-(4-Chlorophenyl)-7,7-dimethyl- (3), 2-(4-Chlorophenyl)-7-phenyl- (4), 2-(4-Carbonylaminophenyl)- (5), 2-(4-Carbonylaminophenyl)-7,7-dimethyl- (6), 2-(4-Carbonylaminophenyl)-7-phenyl- (7), 2-(4-Pyridyl)- (8), 2-(3-Pyridyl)- (9), 2-(2-Pyrazinyl)-7,7-dimethyl- (10), 2-(2-Pyrazinyl)-7-phenyl- (11), 2-(5-Trifluoromethyl)-2-pyridyl-5,7-dimethyl- (12), and 2-(5-Trifluoromethyl-2-pyridyl)-7-phenyl- (13) 5-Oxo-5,6,7,8-tetrahydroquinazolines. 2-Formyl-1,3-cyclohexanedione **1** (5 mmol), salt of the corresponding amidine **2** (5 mmol), and piperidine (0.5 ml) in methanol (50 ml) were boiled for 5 h. Methanol 30-35 ml was distilled off, the mixture was cooled, and the precipitate was filtered off and recrystallized.

In synthesis of quinazolines **5-7**, we took only 2.5 mmol of the amidine salt, boiled for 30 min, and the quinazoline precipitate formed was filtered off from the hot reaction mixture.

The characteristics of the synthesized compounds, the IR and ^1H NMR spectra of **3-22** are given in Tables 1 and 2.

2-Pyrrolidyl- (14-16) and 2-(4-Morpholyl)- (17-19) 5-Oxo-5,6,7,8-tetrahydroquinazolines. Potassium salt of the corresponding 2-formyl-1,3-cyclohexanedione (5 mmol) and amidine hydrochloride (5 mmol) were fused at 160-170°C. To obtain compounds **15, 16, 18,** and **19**, the entire reaction mass was subjected to crystallization, and in the case of compounds **14** and **17** they were treated with $CHCl_3$ (50 ml) and then filtered, the chloroform was driven off to dryness, and the residue was recrystallized from ethanol.

2-(3,5-Dimethylpyrazolyl)-5-oxo-5,6,7,8-tetrahydoquinazolines (20-22). Potassium salt of the corresponding 2-formyl-1,3-cyclanedione (2.5 mmol) and nitrate of 1-carbamidino-3,5-dimethylpyrazole (2.5 mmol) were stirred in methanol (30 ml) at 20°C. KNO_3 precipitate was filtered off, methanol was distilled off, and the residue was held for 1.5 h at 100°C and recrystallized.

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