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PYRIMIDO[4,5-*f*]QUINAZOLINES

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The corresponding 6-dimethylaminomethylen-5-oxo-5,6,7,8-tetrahydroquinazolines were obtained from reactions of 2-substituted and 2,7-disubstituted 5-oxo-5,6,7,8-tetrahydroquinazolines with the dimethylacetal of DMF. Sixteen 2,8-disubstituted 5,6-dihydropyrimido[4,5-f]quinazolines were obtained from the reaction of 2-phenyl- and 6-(dimethylamino)methylen-5-oxo-2-(4-pyridyl)-5,6,7,8-tetrahydroquinazolines with guanidine and eight amidines. The corresponding 6-hydroxymethylene derivative was obtained by hydrolysis of 6-(dimethylamino)methylen-5-oxo-1-phenyl-5,6,7,8-tetrahydroquinazoline.

Keywords: 6-(dimethylamino)methylen-5-oxo-5,6,7,8-tetrahydroquinazolines, 2,8-disubstituted 5,6-dihydro[4,5-*f*]quinazolines.

In a continuation of our study on the modification of the carbocyclic portion of α-oxocyclohexenoheterocycles – 4-oxo-4,5,6,7-tetrahydroindazoles [1-4] and 5-oxo-5,6,7,8-tetrahydroquinazolines [5, 6] – we have investigated the reaction of 5-oxo-5,6,7,8-tetrahydroquinazolines **1** with the dimethylacetal of DMF (**2**). The are reports in the literature that α-oxocyclohexeno heterocycles form β-dimethylaminomethylene-α-hydroxy derivatives [7-10]. For example , as in the case of oxidation of 4-oxo-4,5,6,7-tetrahydroindazoles, differences were observed in the reactions of 5-oxo-5,6,7,8-tetrahydroquinazolines with the acetal **2**, depending on the nature of the substituents. For example both the 7-unsubstituted and 7-phenyl-substituted quinazolines **1** gave the 6-dimethylaminoaminomethylene-5-oxo-5,6,7,8-tetrahydroquinazolines **3** in 49-89% yield on refluxing with an excess of acetal **2**, whereas the reaction of 7,7-dimethyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline gave only traces of products on heating with acetal **2** under the same conditions. The same thing was observed with 4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole.

Hydrolysis of compound **3a** on refluxing in ethanol in the presence of KOH with subsequent oxidation gave 6-hydroxymethylen-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline (**4a**) [12]. In the ^{1}H NMR spectrum of this compound a lowfield signal for an OH proton at 14.21 ppm was observed, which indicates the formation of a hydroxymethylene substituted six-membered H-chelate ring, stabilised by an intramolecular hydrogen bond of the O–H···O= type.

We have established that (dimethylamino)methylene group in compound **3** is readily transaminated by nitrogen nucleophiles – amines , hydrazines, and amidines. In the present work we report on the interaction of β-aminovinyl ketones **3a** and **3b** with amidines **5** which, on refluxing in pyridine or DMF in the presence of K_2CO_3, gave 2,8-substituted 5,6-dihydropyrimido[4,5-*f*]quinazolines **6-21**.

The structures of the β-aminovinyl ketones **3** and pyrimido[4,5-*f*]quinazolines **6-21** were confirmed by IR and ^{1}H NMR spectroscopy. The signal of the methylene protons at 3.05-3.21 ppm is characteristic of the (dimethylamino)methylene groups of compounds **3**. The carbonyl groups of these compounds absorb in the 1657-1650 cm^{-1} region. The ^{1}H NMR spectra of all of the pyrimido[4,5-*f*]quinazolines contain, apart from the

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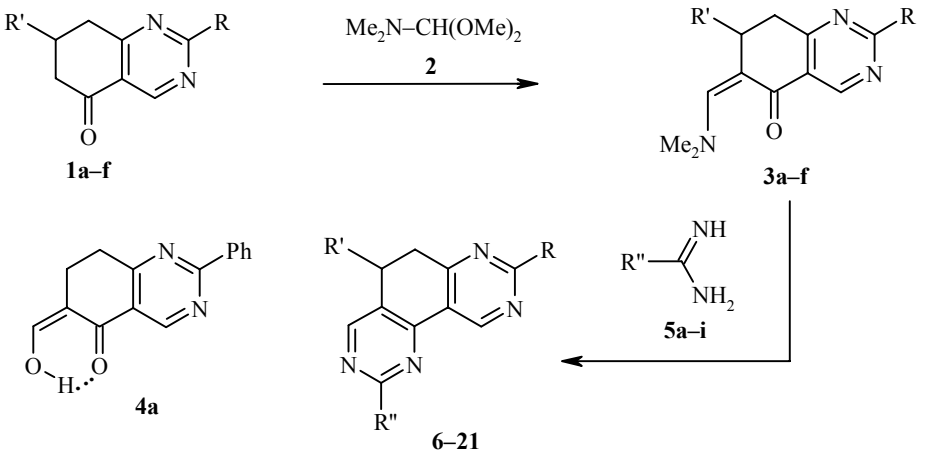
TABLE 1. IR and ^{1}H NMR Spectra of the Compounds Synthesised

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum ($CDCl_3$)*, δ, ppm (*J*, Hz)
1	2	3
3a	1651 (C=O), 1595, 1575, 1560, 1525 (C=S, C=N)	3.05 (4H, m, CH_2CH_2); 3.16 (6H, s, $N(CH_3)_2$); 7.49 (5H, m, C_6H_5); 7.73 (1H, s, =CH–); 9.24 (1H, s, H(C_4))
3b	1657 (C=O), 1600, 1557, 1535 (C=S, C=N)	3.05 (4H, m, CH_2CH_2); 3.19 (6H, s, $N(CH_3)_2$); 7.82 (1H, s, =CH–); 8.36 (2H, m, C_5H_4N); 8.76 (2H, m, C_5H_4N); 9.32 (1H, s, H(C_4))
3c	1652 (C=O), 1587, 1565, 1545 (C=S, C=N)	3.03 (4H, m, CH_2CH_2); 3.21 (6H, s, $N(CH_3)_2$); 7.45 (1H, dd, ^3J = 8, ^3J = 6, C_5H_4N); 7.78 (1H, s, =CH–); 8.76 (2H, m, C_5H_4N); 9.29 (1H, s, H(C_4)); 9.67 (1H, br. s, C_5H_4N)
3d	1650 (C=O), 1590, 1565, 1550-1525 (C=S, C=N)	2.73-3.92 (4H, m, CH_2CH_2); 3.09 (6H, s, $N(CH_3)_2$); 3.60-3.85 (8H, m, $N(CH_2CH_2)_2O$); 7.45 (1H, s, =CH–); 8.67 (1H, s, H(C_4))
3e	1650 (C=O), 1600, 1585, 1537, 1500 (C=S, C=N)	3.09 (6H, s, $N(CH_3)_2$); 3.21-3.78 (2H, m, CH_2); 4.81 (1H, dd, ^3J = 3, ^3J = 6, $C_{(7)}H$); 7.14 (5H, m, C_6H_5); 8.01 (1H, s, =CH–); 8.25 (2H, m, C_5H_4N); 8.68 (2H, m, C_5H_4N); 9.32 (1H, s, H(C_4))
3f	1685(C=O), 1650, 1585, 1570, 1540 (C=S, C=N)	3.05 (6H, s, $N(CH_3)_2$); 3.34 (1H, dd, ^2J = 16.5, ^3J = 2, CH_2); 3.59 (1H, dd, ^2J = 16.5, ^3J = 6.5, CH_2); 4.78 (1H, dd, ^3J = 6.5, ^3J = 2, $C_{(7)}H$); 7.20 (5H, m, C_6H_5); 7.41 (2H, m, ^3J = 8, C_6H_4); 7.98 (1H, s, =CH–); 8.36 (2H, m, ^3J = 8, C_6H_4); 9.31 (1H, s, H(C_4))
4a	1655, 1635(C=O), 1590, 1575, 1565, 1540 (C=S, C=N)	2.74 (2H, t, ^3J = 6.5, CH_2); 3.08 (2H, t, ^3J = 6.5, CH_2); 7.52 (3H, m, C_6H_5); 8.27 (1H, s, =CH–); 8.54 (2H, m, C_6H_5); 9.19 (1H, s, $C_{(4)}H$); 14.21 (1H, br. s, OH)
6	1640, 1600, 1575, 1555 (C=S, C=N); 3450, 3300, 3170 (NH)	2.89-3.29 (4H, m, CH_2CH_2); 6.63 (2H, s, NH_2); 7.56 (5H, m, C_6H_5); 8.32 (1H, s, H(C_4)); 9.33 (1H, s, H(C_{10}))
7	1595, 1575, 1560, 1525 (C=S, C=N)	3.18 (4H, m, CH_2CH_2); 7.52 (6H, m, C_6H_5); 8.56 (4H, m, C_6H_5); 8.69 (1H, s, H(C_4)); 9.77 (1H, s, H(C_{10}))
8	1595, 1580, 1570, 1555, 1525 (C=S, C=N)	3.21 (4H, m, CH_2CH_2); 7.52 (5H, centre of m, C_6H_5, C_6H_4); 8.52 (4H, centre of m, C_6H_5, C_6H_4); 8.63 (1H, s, H(C_4)); 9.72 (1H, s, H(C_{10}))
9	1625 (C=O), 1600, 1575, 1562, 1550 (C=N, C=C); 3380, 3200 (NH)	3.20 (4H, m, CH_2CH_2); 7.50 (1H, br. s, NH); 7.53 (3H, m, C_6H_5); 8.05 (2H, m, ^3J = 8, C_6H_4); 8.09 (1H, br. s, NH); 8.43 (2H, m, C_6H_5); 8.61 (2H, m, ^3J = 8, C_6H_4); 8.85 (1H, s, H(C_4)); 9.69 (1H, s, H(C_{10}))
10	1595, 1580, 1563, 1550 (C=N, C=C)	3.21 (4H, m, CH_2CH_2); 7.52 (3H, m, C_6H_5); 8.38 (2H, m, C_5H_4N); 8.58 (2H, m, C_6H_5); 8.78 (3H, centre of m, C_5H_4N, H(C_4)); 9.78 (1H, s, H(C_{10}))
11	1590, 1580, 1565, 1525 (C=N, C=C)	3.25 (4H, m, CH_2CH_2); 7.49 (4H, centre of m, C_5H_4N, C_6H_5); 8.58 (2H, m, C_6H_5); 8.78 (3H, centre of m, C_5H_4N, H(C_4)); 9.78 (1H, s, H(C_{10})); 9.81 (1H, m, C_5H_4N)
12	1610, 1595, 1580, 1575, 1560, 1530 (C=N, C=C)	3.25 (4H, m, CH_2CH_2); 7.58 (3H, m, C_6H_5); 8.18 (1H, dd, ^3J = 8, ^4J = 2, C_5H_3N); 8.58 (2H, m, C_6H_5); 8.74 (1H, d, ^3J = 8, C_5H_3N); 8.88 (1H, s, H(C_4)); 9.18 (1H, d, ^4J = 2, C_5H_3N); 9.76 (1H, s, H(C_{10}))
13	1600, 1580, 1565, 1545, 1530 (C=N, C=C)	3.23 (4H, m, CH_2CH_2); 7.52 (3H, m, C_6H_5); 8.56 (2H, m, C_6H_5); 8.80 (2H, m, $C_4H_3N_2$); 8.89 (1H, s, H(C_4)); 9.73 (1H, s, H(C_{10})); 9.87 (1H, d, ^4J = 1.7, $C_4H_3N_2$)
14	1620, 1600, 1582, 1575, 1530 (C=N, C=C)	2.36 (3H, s, CH_3); 2.83 (3H, s, CH_3); 3.25 (4H, m, CH_2CH_2); 6.14 (1H, s, =CH–); 7.56 (3H, m, C_6H_5); 8.58 (2H, m, C_6H_5); 8.76 (1H, s, H(C_4)); 9.58 (1H, s, H(C_{10}))
15	1640 (NH_2-δ), 1600, 1575, 1550, 1525 (C=N, C=C); 3480, 3290, 3160 (NH)	2.98–3.21 (4H, m, CH_2CH_2); 6.72 (2H, br. s, NH_2); 8.30 (1H, s, H(C_4)); 8.34 (2H, m, C_5H_4N); 8.83 (2H, s, C_5H_4N); 9.41 (1H, s, H(C_{10}))

TABLE 1 (continued)

1	2	3
16	1595, 1585, 1575, 1565, 1552, 1525 (C=N, C=C)	3.25 (4H, m, CH_2CH_2); 7.52 (3H, m, C_6H_5); 8.34 (2H, m, C_5H_4N); 8.54 (2H, m, C_6H_5) 8.69 (1H, s, H(C_4)); 8.81 (2H, m, C_5H_4N); 9.78 (1H, s, H(C_{10}))
17	1590, 1575, 1560, 1525 (C=N, C=C)	3.18 (4H, m, CH_2CH_2); 7.47 (2H, m, C_6H_4); 8.34-8.52 (4H, m, C_6H_4, C_5H_4N); 8.67 (1H, s, H(C_4)); 8.82 (2H, m, C_5H_4N); 9.71 (1H, s, H(C_{10}))
18	1600, 1577, 1565, 1550, 1525, 1500 (C=N, C=C)	3.27 (4H, m, CH_2CH_2); 8.41 (4H, m, C_5H_4N); 8.80 (1H, s, H(C_4)); 8.89 (4H, m, C_5H_4N); 9.72 (1H, s, H(C_{10}))
19	1600, 1585, 1575, 1560, 1530 (C=N, C=C)	3.29 (4H, m, CH_2CH_2); 7.61 (1H, dd, ^3J = 8, ^3J = 5, C_5H_4N); 8.38 (2H, m, ^3J = 8, C_5H_4N); 8.85 (1H, s, H(C_4)); 8.86-9.61 (4H, m, C_5H_4N); 9.72 (1H, d, ^4J = 1, C_5H_4N); 9.87 (1H, s, H(C_{10}))
20	1605, 1595, 1575, 1560, 1525 (C=N, C=C)	3.29 (4H, m, CH_2CH_2); 8.18 (1H, dd, ^3J = 8, ^4J = 1, C_5H_3N); 8.41 (2H, m, ^3J = 8, C_5H_4N); 8.78-8.92 (4H, m, H(C_4), C_5H_4N, C_5H_3N); 9.16 (1H, d, ^4J = 1.7, C_5H_3N); 9.86 (1H, s, H(C_{10}))
21	1670, 1610, 1595, 1575, 1552, 1537 (C=N, C=C)	3.29 (4H, m, CH_2CH_2); 8.18–8.83 (6H, m, C_5H_4N, $C_4H_3N_2$); 8.89 (1H, s, H(C_4)); 9.76 (1H, s, H(C_{10})); 9.86 (1H, d, ^4J = 1.5, $C_4H_3N_2$)

* The ^{1}H NMR spectra of compounds **6**, **15**, and **19** were recorded in DMSO-d_6.



1, **3 a** R = Ph, **b**, **e** R = 4-pyridyl, **c** R = 3-pyridyl, **d** R = morpholino, **f** R = C_6H_4Cl-4; **a-d** R' = H, **e**, **f** R' = Ph; **6-14** R = Ph, **15-21** R = 4-pyridyl; **6-17**, **19-21** R' = H, **18** R' = Ph; **5a**, **6** R" = NH_2, **5b**, **7**, **15** R" = Ph, **5c**, **8**, **17** R" = C_6H_4Cl-4, **5d**, **9** R" = $C_6H_4CONH_2$-4, **5e**, **10**, **16**, **18** R" = 4-pyridyl, **5f**, **11**, **19** R" = 3-pyridyl, **5g**, **12**, **20** R" = 5-CF_3-2-pyridyl, **5h**, **13**, **21** R" = 2-pyrazinyl, **5i**, **14** R" = 3,5-dimethyl-1-pyrazolyl

signals of the protons of the substituent groups at positions 2 and 8, characteristic resonances for the protons of the $C_{(5)}H_2$–$C_{(6)}H_2$ fragment at 2.98-3.29 ppm and singlets for the protons at $C_{(4)}$ and $C_{(10)}$ in the regions of 8.30-8.82 and 9.30-9.87 ppm respectively.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 of mulls in nujol (1800-1500 cm^{-1}) or hexachlorobutadiene (3600-2000 cm^{-1}). C–H stretching vibrations in the 3050-2800 cm^{-1} region were not recorded. ^{1}H NMR spectra were recorded with a Bruker WH-90/DS (90 MHz) with TMS as internal standard.

TABLE 2. Characteristics of the Compounds Synthesised

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Crystalization solvent	Yield, %
		C	H	N	Cl			
3a	$C_{17}H_{17}N_3O$	72.90 / 73.9	5.97 / 6.13	14.91 / 15.04		184-185	Ethanol	79
3b	$C_{16}H_{16}N_4O$	68.67 / 68.55	5.70 / 5.75	19.83 / 19.99		208-210	Ethanol	87
3c	$C_{16}H_{16}N_4O$	68.50 / 68.55	5.63 / 5.75	19.90 / 19.99		131-132	Ethanol	89
3d	$C_{15}H_{20}N_4O_2$	62.38 / 62.48	6.90 / 6.99	19.56 / 19.43		169-170	Isopropanol	66
3e	$C_{22}H_{20}N_4O$	73.88 / 74.14	5.55 / 5.65	15.55 / 15.72		220-221	Ethanol	70
3f	$C_{22}H_{20}ClN_3O$	69.70 / 69.93	5.28 / 5.34	11.30 / 11.12	9.20 / 9.38	198-199	Ethanol	49
4a	$C_{15}H_{12}N_2O_2$	71.65 / 71.42	4.66 / 4.79	10.90 / 11.11		108-110	Isopropanol	43
6	$C_{16}H_{13}N_5$	69.66 / 69.80	4.70 / 4.76	25.30 / 25.44		219-220	Pyridine	61
7	$C_{22}H_{16}N_4$	78.30 / 78.55	4.88 / 4.79	16.49 / 16.65		162-163	Pyridine	65
8	$C_{22}H_{15}ClN_4$	71.10 / 71.26	3.95 / 4.08	15.10 / 15.11	9.70 / 9.56	200-201	Pyridine	51
9	$C_{23}H_{17}N_5O$	72.71 / 72.81	4.40 / 4.52	18.40 / 18.46		300-301	DMF	55
10	$C_{21}H_{15}N_5$	74.83 / 74.76	4.50 / 4.48	20.60 / 20.76		228-230	Pyridine	88
11	$C_{21}H_{15}N_5$	74.52 / 74.76	4.50 / 4.48	20.61 / 20.76		199-200	Pyridine	88
12	$C_{22}H_{14}F_3N_5$	65.01 / 65.18	3.50 / 3.48	17.37 / 17.28		233-234	DMF	66
13	$C_{20}H_{14}N_6$	70.77 / 70.99	4.14 / 4.17	24.69 / 24.84		194-195	DMF	62
14	$C_{21}H_{18}N_6$	71.01 / 71.17	5.09 / 5.12	23.80 / 23.71		241-242	DMF	56
15	$C_{15}H_{12}N_6$	65.10 / 65.21	4.31 / 4.38	30.60 / 30.42		299-300	Pyridine	76
16	$C_{21}H_{15}N_5$	74.58 / 74.76	4.42 / 4.48	20.66 / 20.76		209-210	DMF	59
17	$C_{21}H_{14}ClN_5$	67.70 / 67.84	3.82 / 3.79	18.92 / 18.84	9.60 / 9.53	192-193	Pyridine	59
18	$C_{20}H_{14}N_6$	70.08 / 70.99	4.11 / 4.17	24.98 / 24.84		244-245	DMF	56
19	$C_{20}H_{14}N_6$	70.90 / 70.99	4.02 / 4.17	24.80 / 24.84		214-215	DMF	56
20	$C_{21}H_{13}F_3N_6$	62.17 / 62.07	3.20 / 3.22	20.45 / 20.68		268-269	DMF	59
21	$C_{19}H_{13}N_7$	67.11 / 67.25	3.92 / 3.86	28.67 / 28.89		233-234	DMF	82

Amidines were obtained from Arcos and Maybridge.

2-Phenyl- (3a), 2-(4-Pyridyl)- (3b), 2-(3-Pyridyl)- (3c), 2-(4-Morpholino)- (3d), 7-Phenyl-2-(4-pyridyl)- (3e), and 2-(4-Chlorophenyl)-7-phenyl- (3f) 6-Dimethylaminomethylen-5-oxo-5,6,7,8-tetrahydroquinazolines. A solution of quinazoline **1** (5 mmol) in acetal **2** (5 ml) was refluxed for 40 min and then cooled. The precipitate was filtered off, washed on the filter with diethyl ether, and recrystallized.

6-Hydroxymethylen-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline (4a). A mixture of compound **3a** (0.84 g, 3 mmol) and powdered KOH (0.90 g) in ethanol (10 ml) was refluxed for 30 min. After 1 day, the green precipitate was filtered off, dissolved in water (20 ml), and carefully acidified with 1:1 dilute hydrochloric acid to pH 5-6. The precipitate was filtered off and recrystallized.

2-Amino-8-phenyl- (6), 2,8-Diphenyl- (7), 2-(4-Chlorophenyl)-8-phenyl- (8), 2-(4-Carbamoyl-phenyl)-8-phenyl- (9), 8-Phenyl-2-(4-pyridyl)- (10), 8-Phenyl-2-(3-pyridyl)- (11), 8-Phenyl-2-(5-trifluoromethyl-2-pyridyl)- (12), 2-Amino-8-(4-pyridyl)- (15), 2-Phenyl-8-(4-pyridyl)- (16), 2-(4-Chlorophenyl)-8-(4-pyridyl)- (17), 2,8-Di(4-pyridyl)- (18), 2-(3-Pyridyl)-8-(4-pyridyl)- (19), and 8-(4-Pyridyl)-2-(5-trifluoromethyl-2-pyridyl)- (20) 5,6-Dihydropyrimido[4,5-*f*]quinazolines. A mixture of compound **3** (2 mmol) with an equimolar amount of the salt (**5a** - carbonate, **5b-h** - hydrochlorides, **5i** - nitrate) of the corresponding amidine **5** in pyridine (10 ml) was refluxed for 5 h. The precipitate which separated on cooling was filtered off, washed on the filter with ethanol, and recrystallized.

8-Phenyl-2-(2-pyrazinyl)- (13), 2-(3,5-Dimethyl-1-pyrazolyl)-8-phenyl- (14), and 2-(2-Pyrazinyl)-8-(4-pyridyl)- (21) 5,6-Dihydropyrimido[4,5-*f*]quinazolines. A mixture of compound **3** (2 mmol) and equimolar amounts of the amidine salt **5** and K_2CO_3 in DMF (10 ml) was refluxed for 5 h. The precipitate, which separated on cooling, was filtered off, washed on the filter with ethanol, and recrystallized.

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