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STUDIES IN QUINAZOLINE CHEMISTRY. 3*. SYNTHESIS OF 2-(2-PYRIDON-3-YL)- AND 2-[THIENO[2,3-*b*]PYRIDIN-2(3)-YL]-3,4-DIHYDROQUINAZOLINES

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We have studied the reaction of o-aminophenyldiphenylcarbinol with substituted cyanothienopyridine, cyanopyridines, cyanopyridones, and cyanopyridinethiones. We have shown that in the case of pyridine derivatives, the reaction occurs with formation of 3,4-dihydroquinazolines, which exist in solution in two tautomeric forms. We have determined the general characteristics of initial fragmentation of the indicated products under electron impact.

Keywords: 3,4-dihydroquinazolines, cyanopyridines, cyanopyridinethiones, cyanopyridones, tautomeric forms, fragmentation.

Continuing our work on synthesis of 3,4-dihydroquinazolines [2], in this report we describe the reaction of *o*-aminophenyldiphenylcarbinol (**1**) with 3-amino-2-cyano-4-methoxymethylene-6-methylthieno[2,3-*b*]-pyridine (**2a**), substituted 3-cyanopyridines **2b-c**, 3-cyano-2(1H)-pyridones **2d-f**, and 3-cyano-2(1H)-pyridinethiones **2g-h**.

The reaction of nitriles **1a-h** with carbinol **1** was carried out according to the procedure previously developed in [2], in the presence of equimolar amounts of $HClO_4$. We established that the direction of the reaction and the product yields are mainly determined by the structure of the nitrile (see Scheme 1).

Thus in the case of cyanothienopyridine **2a**, cyanopyridines **2b,c**, and N-unsubstituted cyano-2-pyridones **2d-e**, the corresponding dihydroquinazolinium perchlorates **3a-e** are formed; and from N-ethyl-3-cyano-6-methyl-4-methoxymethyl-2-pyridone (**2f**) and 3-cyano-2-pyridinethiones **2g-h**, instead of products of type **3**, the 9-phenylacridinium perchlorate (**4**) is formed according to a competing reaction [3].

We have established that in the conversions under consideration, the solvent plays an important role. In nitromethane, we obtain salts **3** in good yields (Table 1). In chloroform, the yields of the latter decrease as a result of a secondary reaction to form the acridinium salt **4**. In DMSO, no products of type **3** or **4** are formed. Thus we determined the optimal conditions for synthesis of salts **3**: boiling nitromethane as the solvent, equimolar ratios of carbinol **1**, nitrile **2**, and $HClO_4$. Under these conditions, the perchlorates **3a-e** were obtained in 50%-85% yields (see Table 1). When treated with an aqueous solution of base, salts **3** are converted to the corresponding free bases **5a-e**.

* For Communication 2, see [1].

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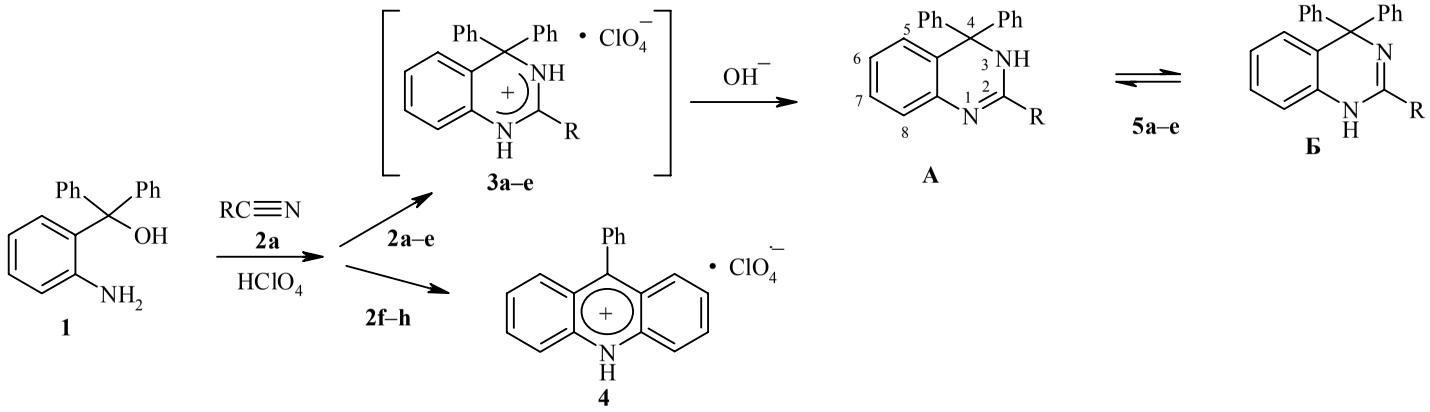
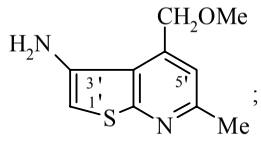
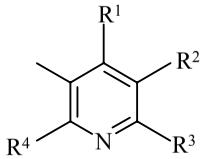
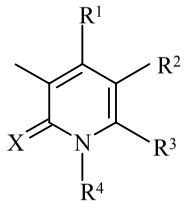
Scheme 1



2, **3**, **5** **a** R =  ;

b–c R =  ;

d–e R =  ;

b $R^1 = R^3 = Me$, $R^2 = R^4 = Cl$; **c** $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = Me$, $R^4 = OEt$; **d** X = O, $R^1 = R^3 = Me$, $R^2 = R^4 = H$;

e X = O, $R^1 = CH_2OMe$, $R^2 = R^4 = H$, $R^3 = Me$;

2, 5 f X = O, $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = Me$, $R^4 = Et$; **g** X = S, $R^1 = CH_2OMe$, $R^2 = R^4 = H$, $R^3 = Me$;

h X = S, $R^1 = CH_2OMe$, $R^2 = Cl$, $R^3 = Me$, $R^4 = H$; **i** $R = CH_2Ph$

TABLE 1. Characteristics of Substituted 3,4-Dihydroquinolinium Perchlorates **3a-e**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	IR spectrum, ν, cm^{-1}		Yield, %
		C	H	Cl	N		HN⁺NH	ClO_4^-	
3a	$C_{30}H_{27}ClN_4O_5S$	61.12 / 60.96	4.25 / 4.57	6.22 / 6.01	9.75 / 9.48	225-227	3220, 1630, 3320 (NH_2)	1130, 1090, 1050	75
3b	$C_{27}H_{22}Cl_3N_3O_4$	58.52 / 58.01	4.05 / 3.94	18.85 / 19.07	7.31 / 7.52	>160 (dec.)	3200, 1655	1170, 1120, 1040	50
3c	$C_{30}H_{30}ClN_3O_6$	63.55 / 63.89	5.54 / 5.32	6.15 / 6.30	7.32 / 7.45	230-232	3190, 1635	1150, 1110, 1050	65
3d	$C_{27}H_{27}ClN_3O_5$	64.31 / 64.09	4.53 / 4.75	7.30 / 7.02	8.15 / 8.31	>210 (dec.)	3180, 3290, 1620, 1635 (C=O)	1160, 1100, 1050	70
3e	$C_{28}H_{26}ClN_3O_6$	62.52 / 62.74	4.70 / 4.85	6.51 / 6.63	7.45 / 7.84	170-72 (dec.)	3200, 1640, 1615 (C=O)	1130, 1100, 1065	85

In the ^{1}H NMR spectra of compounds **5a-d**, there are signals from the proton of the NH group of the heterocycle as two broadened singlets, with total intensity corresponding to the intensity of a signal from a single proton. The signals from protons of the 4'-CH_2O group (compounds **5a,c,e**) and the 6'-CH_3 group (compounds **5b,c**) in this case have the shape of two singlets with intensity equal to 2H and 3H intensities respectively. These data suggest the existence of the indicated compounds in solution in two tautomeric forms: 3,4-dihydroquinazoline (form **A**) and 1,4-dihydroquinazoline (form **B**).

In the IR spectra of dihydroquinazolinium perchlorates **3a-e** and dihydroquinazolines **5a-e**, there are vibrational bands for all the characteristic groups (see Tables 1 and 3), which also confirms the structure of these products.

TABLE 2. 2-Substituted 4,4-Diphenyl-3,4-dihydroquinolines **5a-e**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
5a	$C_{30}H_{26}N_4OS$	73.95 / 73.44	5.02 / 5.34	11.12 / 11.42	171-173 (heptan)	0.25	70
5b	$C_{27}H_{21}Cl_2N_3$*[2]	71.17 / 70.75	4.33 / 4.62	9.46 / 9.13	>250 (heptan)	0.20	75
5c	$C_{30}H_{25}N_3O_2$	77.32 / 77.73	6.64 / 6.31	8.85 / 9.06	159-160 (alcohol)	0.33	65
5d	$C_{27}H_{23}N_3O$	80.14 / 79.98	5.38 / 5.72	10.55 / 10.36	>260 (acetone)	0.05	73
5e	$C_{18}H_{25}N_3O_2$	77.59 / 77.22	5.08 / 5.79	9.31 / 9.75	240-242 (alcohol)	0.08	80

* Solvent system: ether–benzene (compounds **5a-c**) and benzene–acetone 1:1 (compounds **5d,e**).

*[2] Found, %: Cl 15.82. Calculated, %: Cl 15.47.

TABLE 3. Spectral Characteristics of Compounds **5a-e**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum (DMSO), δ, ppm (*J*, Hz)
5a	3300-3450 (NH, NH_2); 1590 (C=N)	2.60 (3H, s, CH_3); 3.41 (3H, s, OCH_3); 4.80 and 4.85 (2H, two s, OCH_2); 6.55 (1H, dd, $^3J_{8.7}$ = 7.7, $^4J_{8.6}$ = 1.6, H-8); 6.96 (1H, s, H-5'); 7.50 (15H, m, H_{arom} + NH_2); 8.20 and 9.33 (1H, two s, NH)
5b	3340 (NH); 1640 (C=N)	1.92 and 1.96 (3H, two s, CH_3); 2.51 and 2.57 (3H, two s, CH_3); 6.60 (1H, dd, $^3J_{8.7}$ = 7.7, $^4J_{8.6}$ = 1.5, H-8); 7.15 (13H, m, H_{arom}); 9.00 and 10.05 (1H, two s, NH)
		[1.87 and 2.00 (3H, two s, CH_3); 2.55 (3H, s, CH_3); 6.80 (4H, m, H_{arom}); 7.18 and 7.22 (10H, two s, $2C_6H_5$); 5.35 and 7.92 (1H, two s, NH)]*
5c	3340 (NH); 1585 (C=N)	1.25 (3H, t, *J* = 7.1, CH_3); 2.41 and 2.44 (3H, two s, CH_3); 3.05 and 3.08 (3H, two s, OCH_3); 4.00 and 4.09 (2H, two s, OCH_2); 4.32 (2H, q, ^3J = 7.1, OCH_2); 6.62 (1H, dd, $^3J_{8.7}$ = 7.8, $^4J_{8.6}$ = 1.7, H-8); 7.10 (14H, m, H_{arom}); 8.60 and 9.55 (1H, two s, NH)
5d	3230-3280 (NH); 1600 (C=O); 1580 (C=N)	1.85 (3H, s, CH_3); 2.20 (3H, s, CH_3); 5.90 (1H, s, H-5'); 6.95 (14H, m, H_{arom}); 9.40 and 9.65 (1H, two s, NH); 11.66 (1H, br. s, N'H)
5e	3150, 3200 (NH); 1635 (C=O); 1620 (C=N)	2.22 (3H, s, CH_3); 3.01 (3H, s, OCH_3); 3.95 and 4.45 (2H, two s, OCH_2); 6.15 (1H, s, H-5'); 7.00 (14H, m, H_{arom}); 9.85 (1H, br. s, NH); 11.82 (1H, br. s, N'H)

* ^{1}H NMR spectrum taken in $CDCl_3$.

Analysis of the mass spectra (Tables 4 and 5) for compounds **5a-e** and the previously obtained 2-(R-nitrophenyl)-, 2-benzyl-, 2-methyl-, and 4,4-diphenyl-2-vinyl-3,4-dihydroquinazolines (**5f-i** respectively) [2] shows the presence in all the spectra of peaks from singly-charged molecular ions (M^+), with relative intensities that vary from 92% for dihydroquinazoline **5a** to 0.5% for 2-benzyl-4,4-diphenyl-3,4-dihydroquinazoline **5g** (Table 4). A characteristic feature of fragmentation of the molecular ions for 3,4-dihydroquinazolines **5a-i** is detachment of a phenyl radical from the $C_{(4)}$ atom to form the cation F_1, which has the maximum intensity in the spectra of compounds **5a,b,e,h,i**. For the cations F_1 formed from the molecular ions of **5g-i** having aliphatic substituents at $C_{(2)}$, extrusion of a benzene molecule is typical, leading to the cation F_2 (Scheme 2). In neither case do we observe fragmentation of the molecular ion with breakdown of the dihydroquinazoline ring, which is an essential distinction between the primary mass degradation of dihydroquinazolines and their hetero analogs, 4-H-3,1-benzoxazine derivatives [4, 5].

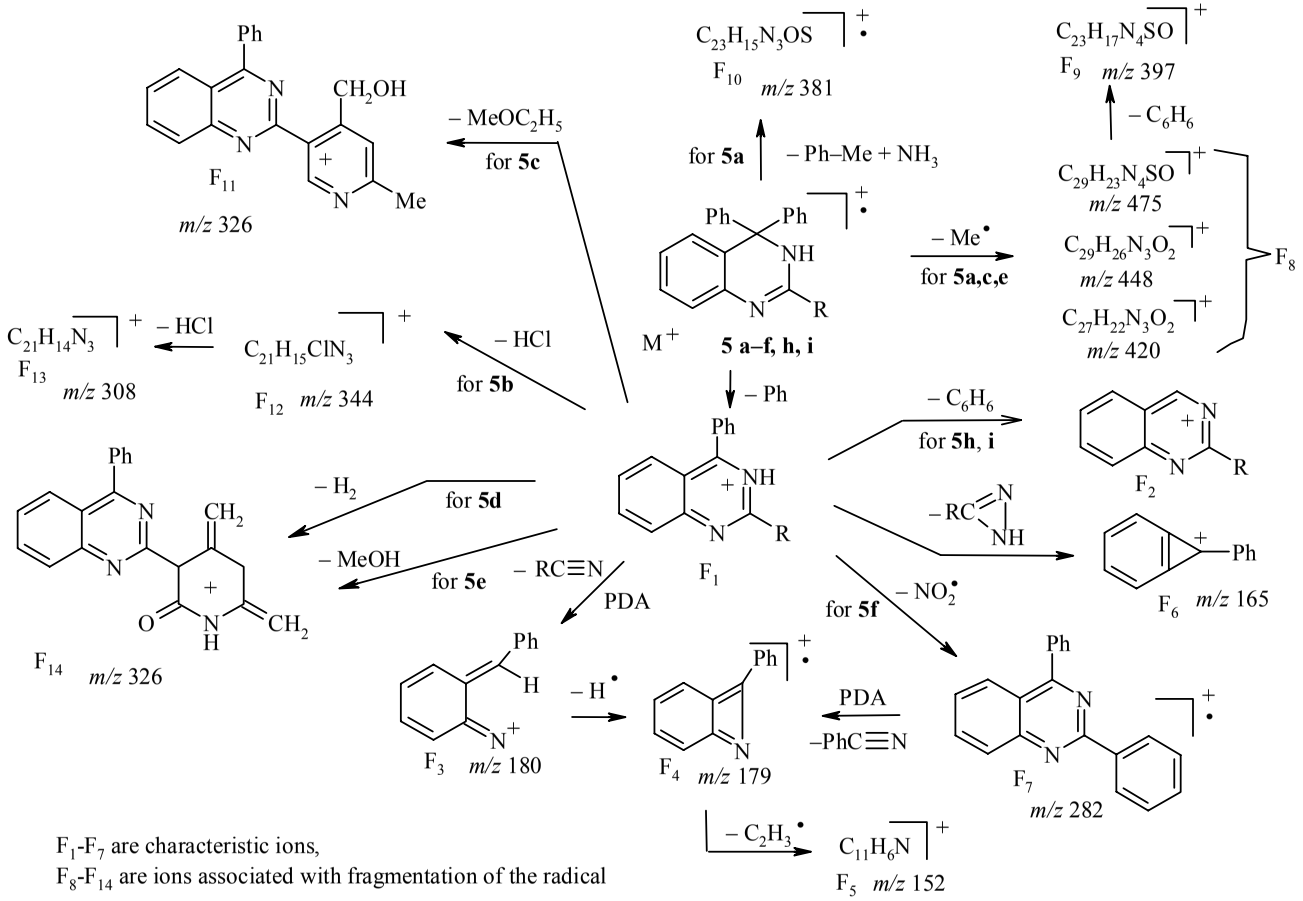
Fragmentation of the cations F_1 with breakdown of the heterocycle for all the studied compounds occurs in two directions: a) with loss of a nitrile molecule RC≡N (retrodiene decomposition [6, 7]); b) with detachment of an RCN_2H molecule [8] to form respectively cations F_3 and F_6. Such fragmentation is distinguished from the previously described decomposition of the molecular ion of quinazoline and its homologs due to sequential ejection of two nitrile molecules from the molecular ion [ref. 7, pp. 79-80].

Then the cation F_3 eliminates a hydrogen atom and then a $C_2H_3\cdot$ radical with breakdown of the aromatic ring [ref. 6, p. 140], which leads to the ions F_4 and F_5 (see Scheme 2).

Fragmentation of the cation F_1 of compound **5f** has a somewhat different scheme compared with what is described above. The absence of an ion peak with *m*/*z* 180 (F3) in the mass spectrum leads to the hypothesis that it is not the F_1 cation but rather the F_7 ion that undergoes retrodiene decomposition (see Scheme 2) to form the odd-electron species F_4. The latter, by eliminating a $C_2H_3\cdot$ radical [ref. 6, p. 140], is converted to cation F_5. The appearance of an F_7 ion peak is quite logically seen as the result of decomposition of the F_1 cation by cleavage of an $NO_2\cdot$ radical with simultaneous migration of a hydrogen [ref. 6, pp. 134, 145].

The structure of the obtained dihydroquinazolines **5a-e** and their salts **3a-e** is confirmed by the spectral data and elemental analysis results (Tables 1-5).

Scheme 2



F_1-F_7 are characteristic ions,
F_8-F_{14} are ions associated with fragmentation of the radical

TABLE 4. Mass Spectra of Substituted 3,4-Dihydroquinoline Azolines **5a-i**

Compound	*m/z* (I_{real}, %)
5a	490 (92); 475 (72); 413 (100); 397 (5); 381 (92); 258 (30); 229 (20); 199 (23); 190 (29); 180 (32); 179 (6); 165 (19); 152 (13); 77 (44)
5b*	457 (19); 380 (100); 344 (25); 308 (14); 254 (13); 210 (8); 180 (8); 179 (4); 165 (12); 152 (9); 77 (28)
5c	463 (39); 448 (100); 386 (8); 326 (11); 258 (9); 202 (9); 180 (18); 179 (5); 172 (20); 165 (10); 152 (4); 77 (12)
5d	405 (8); 328 (100); 326 (6); 310 (3); 254 (3); 203 (5); 180 (3); 179 (2); 165 (3); 164 (5); 152 (4); 104 (4); 77 (19)
5e	435 (52); 420 (100); 358 (25); 326 (36); 258 (45); 256 (15); 255 (13); 254 (13); 180 (44); 179 (2); 171 (25); 165 (22); 152 (8); 77 (34)
5f	405 (8); 328 (100); 282 (30); 281 (3); 203 (3); 179 (6); 178 (4); 165 (3); 152 (5); 117 (10); 77 (12)
5g	374 (0.5); 297 (6); 226 (11.5); 225 (65); 219 (4); 180 (2); 179 (1); 167 (4); 165 (1); 152 (0.5); 104 (5); 92 (52); 91 (100); 77 (6); 65 (25)
5h	298 (19); 254 (6); 222 (14); 221 (100); 180 (6); 179 (3); 165 (4); 152 (9); 143 (25); 102 (6); 77 (30)
5i	310 (17); 254 (4); 234 (7); 233 (100); 205 (3); 180 (3); 179 (2); 165 (3); 155 (19); 152 (5); 77 (16)

* The values of *m/z* for the ions were calculated based on the light isotope of the halogen (^{35}Cl).

On Scheme 2, we also show the F_8-F_{14} ions associated with fragmentation of the substituent R on $C_{(2)}$ of the molecular ion (M^+) and the F_1 cations of compounds **5a-e**.

Analysis of the mass spectral decomposition of 2-benzyl-4,4-diphenyl-3,4-dihydroquinazoline (**5g**, Scheme 3) shows that along with the fragmentation of M^+ described above that includes cleavage of the phenyl radical and formation of the F_1 cation and then F_2-F_6 (see Scheme 2), we observe competing decompositions in

Scheme 3

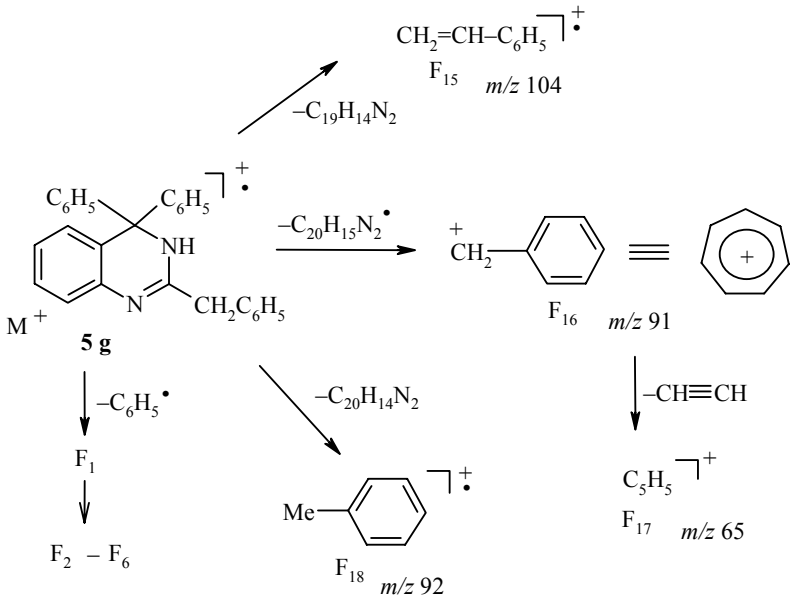


TABLE 5. Intensity of Characteristic Ion Peaks in Mass Spectra of Compounds **5a-i** (Σ_{50}, %)

Compound	W_m	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_{16}	F_{18}
5a	6.2	6.7	—	2.2	0.4	0.9	1.3	—	—	—
5b	5.7	30.2	—	2.4	1.2	2.7	3.6	—	—	—
5c	15.2	3.1	—	7.0	2.0	1.6	3.9	—	—	—
5d	2.5	31.9	—	1.0	0.7	1.3	1.0	—	—	—
5e	7.9	3.8	—	6.6	0.2	1.3	1.0	—	—	—
5f	3.5	44.2	—	—	2.7	2.2	1.3	13.3	—	—
5g	0.1	1.6	1.1	0.5	0.3	0.1	0.3	—	26.3	13.7
5h	4.9	25.5	6.4	1.4	0.6	2.3	1.0	—	—	—
5i	5.7	33.4	6.4	0.6	0.4	1.8	0.7	—	—	—

several directions. This is probably connected with the anomalously low stability (in the considered series) of the molecular ion of compound **5a** (its intensity is only 0.1%, Table 4). Possibly in the presence of a benzyl substituent, the major direction of fragmentation of M^+ becomes formation of a stable benzyl (tropyl) cation F_{16} [ref. 6, p. 104; ref. 8, p. 30], with *m*/*z* 91, having the maximum intensity in the spectrum. From this it follows that compound **5g**, at least in the gas phase, has the structure of 3,4-dihydroquinazoline with an endocyclic C=N bond [2]. A characteristic feature of the mass degradation of compound **5g** is the presence of an intense peak with *m*/*z* 92 (F_{18}) in its mass spectrum that corresponds to the toluene radical cation. The ion F_{15} may also be a decomposition fragment of M^+.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 at room temperature in nujol. The ^{1}H NMR spectra were taken on a Tesla BS (68 MHz) and a Bruker DRX 500 (500 MHz). The mass spectra were obtained on a Varian CH-6 with direct injection of the material into the ionization chamber at a temperature of 50-180°C and electron ionization energy 70 eV.

2-(4-Methoxymethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4,4-diphenyl-3,4-dihydroquinazolinium Perchlorate (3e). A solution (suspension) of carbinol **1** (0.34 g, 1.25 mmol) in nitromethane (3 ml) was added dropwise over a 30-40 min period to a boiling mixture of nitrile **2g** (0.22 g, 1.25 mmol) and (0.13 ml, 1.25 mmol) of 70% $HClO_4$ in nitromethane (3 ml). After the reaction mass was cooled down (ice bath), 0.57 g of perchlorate **3e** was extracted with ether and filtered out.

Salts 3a-d were obtained in a similar manner.

2-(4-Methoxymethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4,4-diphenyl-3,4-dihydroquinazoline (5e). Salt **3e** (1 g, 1.8 mmol) was mixed with excess (10 ml) 25% aqueous ammonia and boiled for 10 min. The precipitate was filtered out, washed with water, dried in air, and recrystallized from alcohol. Yield 0.62 g (80%).

Bases 5a-d were obtained in a similar manner.

The synthesis of compounds **5f-i** is described in [2].

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