Reaction of quinolines fluorinated at the benzene ring with nitrogen-centered nucleophiles

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A primary functionalization of quinolines polyfluorinated at the benzene ring (5,7-difluoro-, 5,7,8-trifluoro-, 5,6,8-trifluoro-, 8-chloro-5,7-difluoro-, 5,6,7,8-tetrafluoro-, and 5,7,8-trifluoro-6-(trifluoromethyl)quinolines) by the reaction with nitrogen-centered nucleophiles (aqueous and liquid ammonia, hydrazine hydrate, piperidine) has been studied. If the molecule of fluorinated quinoline contains three or four halogen atoms, their combined orientation effect outweighs the influence of the heterocycle N atom. It was found that the orientation of substitution in the reactions of 5,6,8-trifluoro- and 5,7,8-trifluoro-6-(trifluoromethyl)quinolines with piperidine depends on temperature, because the enthalpy control of the ratio of the rates of competing reactions changes to the entropy control. Nineteen new quinoline derivatives containing F atoms and amino or modified amino groups in the benzene ring have been obtained.

Key words: fluorinated quinolines, ammonia, piperidine, hydrazine hydrate, aromatic nucleophilic substitution, fluorinated aminoquinolines.

To study fluorine-containing heterocyclic compounds is of special interest because many of them possess biological activity.[1,2] Quinolines fluorinated at the benzene ring are among such compounds.[3—8] Their derivatives, fluoroquinolones, are known as antimicrobial medicines with a wide range of action.[9—12] In addition, quinolines fluorinated at the benzene ring can be used as starting compounds for preparing biologically active derivatives by the reaction of nucleophilic substitution of the fluorine atom (see, for example, Ref. 13). In this connection, it is an actual problem to develop methods for the synthesis of new compounds from the series of quinolines fluorinated at the benzene ring.

It is obvious that general approach to the synthesis of potentially biologically active functionalized fluoroquinolines consists in nucleophilic substitution of F atoms in polyfluorinated compounds of this series. There are described just a few reactions of nucleophilic substitution in perfluorinated quinoline and its homologs, in which F atoms at positions 2 and (predominantly) 4 of the pyridine ring undergo the substitution.[14—16] Functionalization of quinoline at the benzene ring is also of considerable interest,[5—13] but, as it follows from the aforesaid, the substitution of F atoms in the benzene ring of the quinoline framework is conditioned by the absence of these atoms at the activated positions of the heterocyclic fragment. Examples of such transformations include the action of various element-centered nucleophiles (MeONa, Me_2PSiMe_3, and $Me_2AsSiMe_3$) on quinolines fluorinated at the benzene ring.[17—20] A study of the reactions of difluoroquinolines of this type with sodium methoxide in DMSO showed that electrophilic activity of the C atoms of the benzene fragment decreases in the order C(5) > C(7) > C(6), C(8) due to the activating effect of the heterocycle.[20] In the case of quinolines containing three or four F atoms in the benzene ring, the ratio of the rates of substitution is determined by a combined effect of the heterocycle and substituents in the benzene ring,[17—19] with position 7 becoming the most active due to the orientation effect of the F atoms.

An amino group is used as one of the promising functional groups in the development of pathways for deeper functionalization of polyfluorinated quinolines. By now, a basic approach to the synthesis of quinolines containing an amino group and F atoms in the benzene fragment consisted in the reduction of the corresponding nitro derivatives,[21—23] that to a certain extent limited the scope of compounds of the type under consideration available

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for the study. The formation of 7-amino-5,6,8-trifluoroquinoline upon the action of ammonia on 5,6,7,8-tetrafluoroquinoline[17,18] represents the only example of the substitution of a F atom for an amino group in quinolines polyfluorinated at the benzene ring.

The present work is devoted to the study of reactions of quinolines containing F atoms in the benzene fragment with aqueous and liquid ammonia, piperidine, and hydrazine hydrate in order to find out how direction of aminodefluorination depends on the number and arrangement of F atoms in the substrate, as well as on the nature of nucleophile.

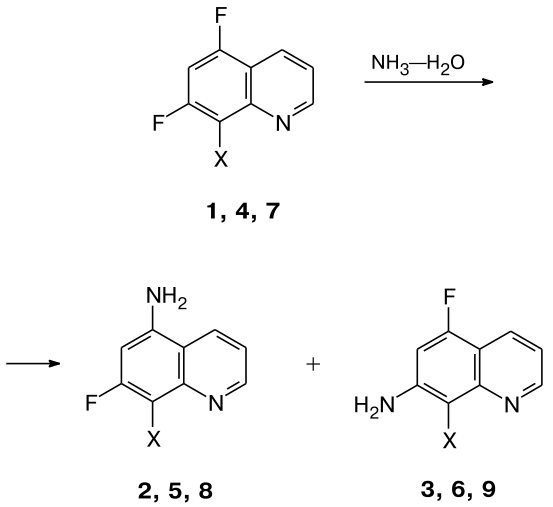
Results and Discussion

Conditions and results of the transformations studied are given in Table 1. The ratios of the reaction products were inferred from the NMR spectra of their mixtures. The compounds synthesized for the first time were isolated by TLC and completely characterized, their ^{1}H and ^{19}F NMR spectra are given in Table 2.

The reaction of 5,7-difluoroquinoline (**1**) with aqueous ammonia in a steel autoclave at 150 °C furnished 5-amino-7-fluoroquinoline (**2**) and 7-amino-5-fluoroquinoline (**3**) in the ratio 3.4 : 1.0 (Scheme 1; see Table 1, entry *1*).

The earlier undescribed amines **2** and **3** were isolated in the individual state and characterized. An assignment of signals in their ^{19}F NMR spectra is based on a comparison of the chemical shifts observed (δ_F) with the δ^{calc} value calculated starting from the δ_F value for the parent quinoline **1** (see Ref. 20) with allowance for the increment[24] responsible for the introduction of an amino group instead of F atom in *meta*-position. It turned out that of two electrophilic centers occupied by F atoms, position 5 is more active during ammonolysis of quinoline **1** with aqueous ammonia, which agrees with orientation of substitution of the F atom upon the action of sodium methoxide on the same substrate in DMSO.[20]

Scheme 1



X = H (**1**—**3**), F (**4**—**6**), Cl (**7**—**9**)

Table 1. The reaction of compounds **1**, **4**, **7**, **10**, **13**, and **20** with nucleophiles

Entry	Reagent (number of mmoles)		Conditions		Content of the reaction products in the mixture (mol.%)*	Yield (%)
	Polyfluoroquinoline	Nucleophile	*T*/°C	Time /h		
1	**1** (0.60)	Aqueous NH_3	150	9	22 (**1**); 68 (**2**); 20 (**3**)	32 (**2**); 9 (**3**)
2	**4** (0.56)	The same	150	3	11 (**4**); 12 (**5**); 77 (**6**)	64 (**6**)
3	**7** (0.56)	»»	150	3	18 (**8**); 77 (**9**)	9 (**8**); 52 (**9**)
4	**10** (0.56)	»»	150	8	8 (**10**); 43 (**11**); 46 (**12**)	35 (**11**); 13 (**12**)
5	**13** (1.00)	»»	130	3	3 (**13**); 16 (**14**); 79 (**15**)	55 (**15**)
6	**13** (1.00)	Liquid NH_3	80	3	4 (**13**); 18 (**14**); 71 (**15**)	—
7	**13** (1.00)	$C_5H_{10}NH$ (20.2)	106	2	15 (**16**); 76 (**17**)	3.8 (**16**); 40 (**17**)
8	**13** (1.00)	Hydrazine hydrate (2.5)	102	6	7 (**13**); 13 (**18**); 68 (**19**)	—
9	**20** (0.80)	Liquid NH_3	10—15	8	86 (**21**)	68 (**21**)
10	**20** (0.80)	Aqueous NH_3	60	12	5 (**21**); 84 (**22**)	55 (**22**)
11	**20** (0.80)	$C_5H_{10}NH$ (16.0)	50	24	49.6 (**23**); 12.5 (**24**); 20 (**25**)	33 (**23**); 3.5 (**24**); 11 (**25**)
12	**20** (0.40)	$C_5H_{10}NH$ (8.1)	106	2	20 (**20**); 5.3 (**23**); 10.6 (**24**); 59 (**25**)	32 (**25**)
13	**20** (0.20)	$C_5H_{10}NH$ (4.0)	17	120	10 (**20**); 59 (**23**); 11 (**24**); 9 (**25**)	—
14	**10** (0.28)	$C_5H_{10}NH$ (7.1)	17	333	12 (**10**); 17 (**27**); 69 (**28**)	—
15	**10** (0.55)	$C_5H_{10}NH$ (29.4)	106	12	10 (**27**); 89 (**28**)	67 (**28**)

*According to the ^{19}F NMR spectra; in cases when the overall content of compounds specified is less than 100%, unidentified components are present in the mixtures.

Table 2. The ^{19}F and ^{1}H[a] NMR spectra of fluorinated quinolines (R are substituents in the benzene ring) in acetone-d_6

Compound	δ^{exp} [δ^{calc}][b], J/Hz			
	RC(5)	RC(6)	RC(7)	RC(8)
2	5.58 (br.s, 2 H, NH_2)	6.63 or 6.94 (dd, $J_{H,F\text{-}o}$ = 11, $J_{H,H\text{-}m}$ = 2)	53.3 [51.4] (t, 1 F, 2 $J_{F,H\text{-}o}$ = 11)	6.63 or 6.94 (dd, 1 H, $J_{H,F\text{-}o}$ = 11, $J_{H,H\text{-}m}$ = 2)
3	38.8 [39.7] (d, 1 F, $J_{F,H\text{-}o}$ = 12)	6.84 (dd, 1 H, $J_{H,H\text{-}m}$ = 1.5, $J_{F,H\text{-}o}$ = 12)	5.51 (br.s, 2 H, NH_2)	6.96 (d, 1 H, $J_{H,H\text{-}m}$ = 1.5)
5	5.71 (br.s, 2 H, NH_2)	6.84 (dd, 1 H, $J_{H,F\text{-}o}$ = 13, $J_{H,F\text{-}m}$ = 6)	26.6 [25.1] (dd, 1 F, $J_{F,F\text{-}o}$ = 20, $J_{F,H\text{-}o}$ = 13)	−4.7 [−2.1] (dd, 1 F, $J_{F,F\text{-}o}$ = 20, $J_{F,H\text{-}m}$ = 6)
6	35.1 [34.8] (dd, 1 F, $J_{F,F\text{-}p}$ = 18, $J_{F,H\text{-}o}$ = 12)	7.05 (dd, 1 H, $J_{H,F\text{-}m}$ = 6, $J_{H,F\text{-}o}$ = 12)	5.50 (br.s, 2 H, NH_2)	5.7 [8.9] (dd, 1 F, $J_{F,F\text{-}p}$ = 18, $J_{F,H\text{-}m}$ = 6)
8	6.00 (br.s, 2 H, NH_2)	6.80 (d, 1 H, $J_{H,F\text{-}o}$ = 12)	53.5 [53.7] (d, 1 F, $J_{F,H\text{-}o}$ = 12)	
9	38.0 [39.4] (d, 1 F, $J_{F,H\text{-}o}$ = 11)	6.77 (d, 1 H, $J_{H,F\text{-}o}$ = 11)	4.62 (br.s, 2 H, NH_2)	
11	8.1 [12.5] (dd, 1 F, $J_{F,F\text{-}p}$ = 19, $J_{F,H\text{-}m}$ = 7)	5.30 (br.s, 2 H, NH_2)	7.2 (dd, 1 H, $J_{H,F\text{-}m}$ = 7, $J_{F,H\text{-}o}$ = 12)	33.7 [30.5] (dd, 1 F, $J_{F,F\text{-}p}$ = 19, $J_{F,H\text{-}o}$ = 12)
12	−4.3 [1.5] (dd, 1 F, $J_{F,F\text{-}o}$ = 20, $J_{F,H\text{-}m}$ = 7)	23.8 [22.2] (dd, 1 F, $J_{F,F\text{-}o}$ = 20, $J_{F,H\text{-}o}$ = 13)	6.78 (dd, 1 H, $J_{F,H\text{-}m}$ = 7, $J_{F,H\text{-}o}$ = 13)	5.85 (br.s, 2 H, NH_2)
15	7.7 [7.7] (dd, 1 F, $J_{F,F\text{-}p}$ = 15, $J_{F,F\text{-}o}$ = 18)	8.5 [7.6] (dd, 1 F, $J_{F,F\text{-}o}$ = 18, $J_{F,F\text{-}m}$ = 10)	5.65 (br.s, 2 H, NH_2)	10.4 [14] (dd, 1 F, $J_{F,F\text{-}p}$ = 15, $J_{F,F\text{-}m}$ = 10)
16	24.4 (dm, 1 F, $J_{F,F\text{-}p}$ =15)	3.29—3.34 (br.m, 4 H, NC_5H_{10}); 1.62—1.79 (br.m, 4 H, NC_5H_{10}); 1.68 (br.m, 2 H, NC_5H_{10})	20.7 (dd, 1 F, $J_{F,F\text{-}o}$ = 17, $J_{F,F\text{-}m}$ = 4)	7.6 (ddd, 1 F, $J_{F,F\text{-}o}$ = 17, $J_{F,F\text{-}p}$ = 15, $J_{F(8),H(4)}$ = 1.5)
17	8.7 (dd, 1 F, $J_{F,F\text{-}o}$ = 18, $J_{F,F\text{-}p}$ = 16)	17.4 (dd, 1 F, $J_{F,F\text{-}o}$ = 18, $J_{F,F\text{-}m}$ = 4)	3.28—3.33 (br.m, 4 H, NC_5H_{10}); 1.60—1.76 (br.m, 6 H, NC_5H_{10})	23.5 (d, 1 F, $J_{F,F\text{-}p}$ = 16)
18[c]	13.6 (ddd, 1 F, $J_{F,F}$ = 17.5, $J_{F,F\text{-}m}$ = 7.5, $J_{F,H}$ = 2) or 13.1 (br.d, 1 F, $J_{F,F}$ = 18.5)	6.47 (br.s, 1 H, N<u>H</u>NH_2)	13.6 (ddd, 1 F, $J_{F,F}$ = 17.5, $J_{F,F\text{-}m}$ = 7.5, $J_{F,H}$ = 2) or 13.1 (br.d, 1 F, $J_{F,F}$ = 18.5)	6.9 (br.t, 1 F, 2 $J_{F,F}$ = 17.0—18.5)
19[c]	7.7 (dd, 1 F, $J_{F,F\text{-}o}$ = 18.5, $J_{F,F\text{-}p}$ = 15.5)	10.3 (ddd, 1 F, $J_{F,F\text{-}o}$ = 18.5, $J_{F,F\text{-}m}$ = 8.5, $J_{F,H}$ = 2)	6.62 (br.s, 1 H, N<u>H</u>NH_2)	12.5 (br.dd, 1 F, $J_{F,F\text{-}p}$ = 15.5, $J_{F,F\text{-}m}$ = 8.5)
21	6.32 (br.s, 2 H, NH_2)	109.4 (d, 3 F, CF_3, $J_{F,CF_3\text{-}o}$ = 24)	21.9 [19.3] (m, 1 F, $J_{F,CF_3\text{-}o}$ = 24, $J_{F,F\text{-}o}$ = 18)	−4.1 [0.9] (d, 1 F, $J_{F,F\text{-}o}$ = 18)
22[d]	7.48 (br.s, 2 H, NH_2)		26.7 (d, 1 F, $J_{F,F\text{-}o}$ = 18)	−5.1 (d, 1 F, $J_{F,F\text{-}o}$ = 18)
23[e]	3.13—3.21 (br.m, 4 H, NC_5H_{10}); 1.68—1.79 (br.m, 6 H, NC_5H_{10})	106.2 (d, 3 F, CF_3, $J_{F,CF_3\text{-}o}$ = 28)	24.6 (m, 1 F, $J_{F,F\text{-}o}$ = 18, $J_{F,CF_3\text{-}o}$ = 28)	9.1 (d, 1 F, $J_{F,F\text{-}o}$ = 18)
24	40.2 (m, 1 F, $J_{F,CF_3\text{-}o}$ = 36, $J_{F,F\text{-}p}$ = 19)	108.7 (d, 3 F, CF_3, $J_{F,CF_3\text{-}o}$ = 36)	3.27, 3.08 (both m, 2 H each, NC_5H_{10}); 1.85, 1.44 (both m, 1 H each, NC_5H_{10}); 1.72 (m, 4 H, NC_5H_{10})	29.0 (br.d, 1 F, $J_{F,F\text{-}p}$ = 19)
25[e]	35.1 (q, 1 F, $J_{F,CF_3\text{-}o}$ = 28)	105.7 (dd, 3 F, CF_3, $J_{F,CF_3\text{-}o}$ = 28, 20)	37.5 (q, 1 F, $J_{F,CF_3\text{-}o}$ = 20)	3.36—3.42, 1.75—1.83 (both br.m, 4 H each, NC_5H_{10}); 1.64—1.72 (br.m, 2 H, NC_5H_{10})
26[e]	3.10—3.17, 3.34—3.40 (both br.m, 4 H each, 2 NC_5H_{10}); 1.61—1.81 (br.m, 12 H, 2 NC_5H_{10})	106.1 (d, 3 F, CF_3, $J_{F,CF_3\text{-}o}$ = 29.5)	39.5 (q, 1 F, $J_{F,CF_3\text{-}o}$ = 29.5)	3.10—3.17, 3.34—3.40 (both br.m, 4 H each, NC_5H_{10}); 1.61—1.81 (br.m, 12 H, 2 NC_5H_{10})
27	24.1 (dd, 1 F, $J_{F,F\text{-}p}$ = 20, $J_{F,H\text{-}m}$ = 8)	3.22—3.27, 1.72—1.81 (both br.m, 4 H each, NC_5H_{10}); 1.60—1.69 (br.m, 2 H, NC_5H_{10})	7.4 (dd, 1 H, $J_{H,F\text{-}o}$ = 13, $J_{H,F\text{-}m}$ = 8)	35.0 (dd, 1 F, $J_{F,F\text{-}p}$ = 20, $J_{F,H\text{-}o}$ = 13)
28	2.9 (dd, 1 F, $J_{F,F\text{-}o}$ = 20, $J_{F,H\text{-}m}$ = 8)	23.9 (dd, 1 F, $J_{F,F\text{-}o}$ = 20, $J_{F,H\text{-}o}$ = 13)	7.1 (dd, 1 H, $J_{H,F\text{-}o}$ = 13, $J_{H,F\text{-}m}$ = 8)	3.31—3.37, 1.77—1.85 (both br.m, 4 H each, NC_5H_{10}); 1.60—1.69 (br.m, 2 H, NC_5H_{10})

[a] In the ^{1}H NMR spectra of all the quinoline derivatives, the signals for the pyridine fragment are observed, δ: 8.6—9.2 (H(2)), 7.2—7.8 (H(3)), 8.2—8.8 (H(4)), $J_{H(3),H(4)}$ = 8.0—8.5 Hz, $J_{H(2),H(3)}$ = 4.0 Hz, $J_{H(2),H(4)}$ = 1.5 Hz (see Ref. 28). In addition, the spectra of compounds **5**, **6**, **11**, **12**, **15**, **16**—**19** and **21**—**28** exhibit the spin-spin coupling constants $J_{H(4),F(8)}$ = 1.5 Hz.

[b] Calculated starting from the δ value for the parent compound[20,25] with allowance for the increment responsible for the introduction of an amino group instead of a fluorine atom.[24]

[c] Solution in 1,4-dioxane; the signals of the protons of the hydrazo group in the spectra of quinolines **18** and **19** overlap with the signals of unreacted hydrazine hydrate.

[d] In DMSO-d_6.

[e] In $CDCl_3$.

The ammonolysis of 5,7,8-trifluoroquinoline (**4**) under the same conditions gives rise to 5-amino-7,8-difluoroquinoline (**5**) and 7-amino-5,8-difluoroquinoline (**6**) in the ratio ~1.0 : 6.5 (Scheme 1; see Table 1, entry *2*). The latter product was isolated and characterized. Chemical shifts δ_F in the ^{19}F NMR spectra of amines **5** and **6** are in good agreement with the calculated, as it was described for quinolines **2** and **3**, values of δ^{calc}. It should be noted that all the signals are characterized by doublet splittings with the spin-spin coupling constants J = 15—20 Hz related, as it was shown earlier,[19,25] to the interaction of the F atoms in *ortho*- and *para*-positions to each other in the benzene fragment of the quinoline molecule. Thereby, the structure of 8-amino-5,7-difluoroquinoline is excluded. Compound **5** was also obtained alternatively (see below).

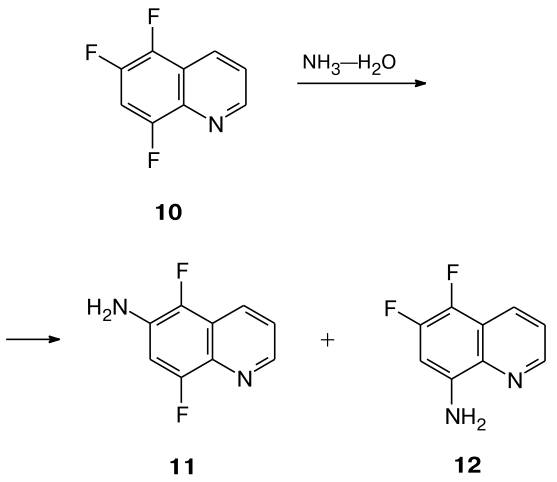
The ammonolysis of 8-chloro-5,7-difluoroquinoline (**7**) afforded 5-amino-8-chloro-7-fluoroquinoline (**8**) and 7-amino-8-chloro-5-fluoroquinoline (**9**) in the ratio ~1 : 4 (Scheme 1; see Table 1, entry *3*). The products **8** and **9** were isolated and characterized. The δ_F value for the F(7) atom in the ^{19}F NMR spectrum of amine **8** is close to the δ_F value for the analogous atom in amine **2**, whereas δ_F for F(5) atom in the spectrum of amine **9**, to the corresponding characteristic of compound **3**. In both cases, the experimental chemical shifts agree with the calculated values (see Table 2).

A predominant substitution of the F(7) atom by the amino group in compounds **4** and **7** agrees with the orientation realizing in the reaction of quinoline **4** with element-centered nucleophiles,[19] in contrast to a predominant aminodefluorination of quinoline **1** at position 5. This testifies that a combined effect of three halogen atoms outweighs the influence of the heterocycle N atom. This is also indicated by the change in the ratio of aminodefluorination products at positions 5 and 7 from 1.0 : 6.5 to 1 : 4 going from trifluoroquinoline **4** to difluorochloroquinoline **7**, which agrees with the ratio of the orientation effects of F and Cl atoms in the reactions of nucleophilic substitution in polyfluorinated benzenes.[26]

The reaction of 5,6,8-trifluoroquinoline (**10**) with aqueous ammonia under conditions specified above results in 6-amino-5,8-difluoroquinoline (**11**) and 8-amino-5,6-difluoroquinoline (**12**) in the ratio ~1 : 1 (Scheme 2; see Table 1, entry *4*).

Chemical shifts δ_F in the ^{19}F NMR spectra of both compounds agree with the calculated values (see Table 2). The presence of splittings with J = 20 Hz in all the signals and the absence of signals in the region 24—27 ppm exclude the structure of 5-amino-6,8-difluoroquinoline. The ^1H NMR spectra of all the mentioned above quinolines containing F(8) atom exhibit indicative doublet splitting of the signal due to the F(8)—H(4) coupling with $J_{H(4),F(8)}$ = 1.5 Hz, which has been found earlier for the interaction of H and F atoms at positions 4 and 8, respectively, in the naphthalene[27] and quinoline[25] molecules. In the ^1H NMR spectra of quinolines containing no F(8) atom, only doublet splittings of the H(4) signal are observed, which is characteristic of the spin-spin interaction of the pyridine ring protons.[24]

Scheme 2

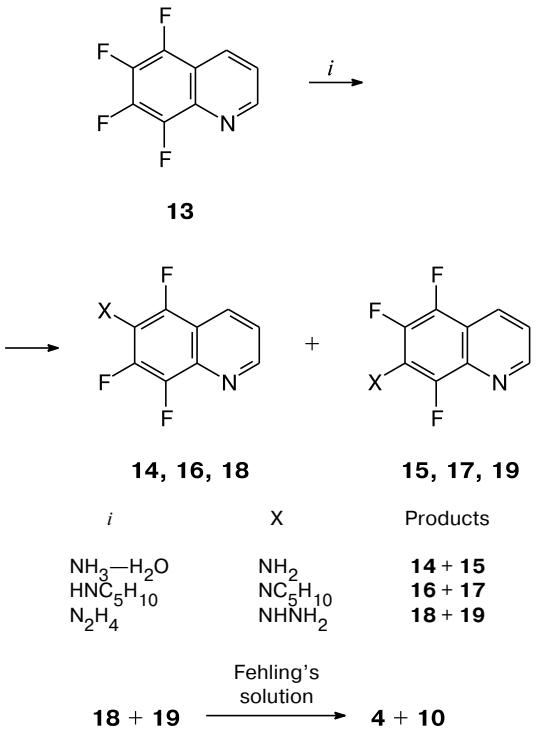


The result of ammonolysis of compound **10** indicates that, despite the presence of F(5) atom, the substitution takes place only at positions 6 and 8, which are not activated by the N atom of the heterocycle. In the case when amine **11** is formed, such a direction of substitution agrees with that observed for the methoxydefluorination of 1,2,4-trifluorobenzene[26] and is an additional evidence that a combined orientation effect of F atoms outweighs the influence of the heterocycle. The formation of compound **12**, possibly, is due to the inductive effect of the heterocycle N atom.

The reaction of 5,6,7,8-tetrafluoroquinoline (**13**) with aqueous ammonia at 130 °C produces 6-amino-5,7,8-trifluoroquinoline (**14**) and 7-amino-5,6,8-trifluoroquinoline (**15**) in the ratio 1 : 5. The latter was isolated in the individual state in 55% yield (Scheme 3; see Table 1, entry *5*).

Quinoline **15** has been described earlier as the only product (21% yield) in the reaction of tetrafluoroquinoline **13** with aqueous ammonia.[17,18] In this case, the authors did not analyze composition of the mixture of products by NMR spectroscopy, which apparently did not allow them to find out the presence of the minor product **14** in it. Quinoline **14** was obtained from 5,7,8-trifluoroquinoline-6-carboxamide.[25] The ^{19}F NMR spectrum of amine **15** exhibits the doublets of doublets at δ_F 7.7, 8.7, and 10.4. This excludes the structures of 5-amino-6,7,8-trifluoro- and 8-amino-5,6,7-trifluoroquinolines, since the signal for the F(8) atom in the first case or for the F(5) atom in the second should be expected in the region δ_F 2.0—3.0 due to the electron-donating effect of the amino group in

Scheme 3



para-position.[24] A direction of aminodefluorination of quinoline **13** is similar to that in the reactions of this substrate with sodium methoxide[17–19] and the reagents Me_2EMMe_3 (E = P, M = Si, Sn; E = As, M = Si).[19]

The reaction of quinoline **13** with liquid ammonia at 80 °C in an autoclave leads to amines **14** and **15** in the ratio ~1 : 4 (see Table 1, entry *6*). Therefore, the same orientation of the substitution is realizing as in the case of aqueous ammonia.

From the aforesaid, it can be concluded that the variations in the medium and temperature have little effect on the orientation of aminodefluorination of quinoline **13**. To find out how the type of nitrogen-centered nucleophile affects the direction of this reaction, we studied reactions of quinoline **13** with piperidine and hydrazine hydrate.

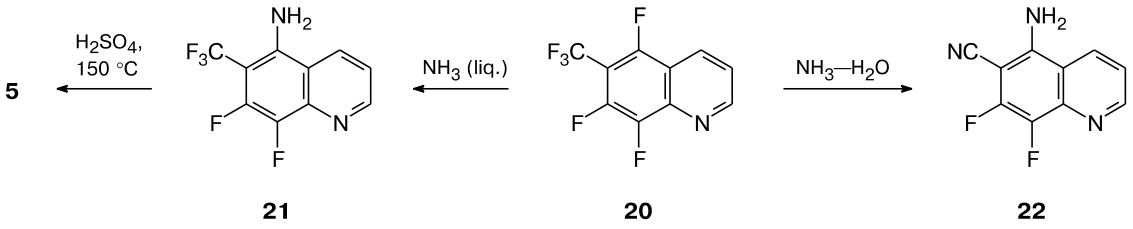
The reaction of quinoline **13** with boiling piperidine for the first time produces 5,7,8-trifluoro-6-piperidinoquinoline (**16**) and 5,6,8-trifluoro-7-piperidinoquinoline (**17**) in the ratio ~1 : 5 (Scheme 3; see Table 1, entry *7*). The ^{19}F NMR spectrum of quinoline **16** (see Table 2) exhibits the signal at δ_F 7.6 consisting of doublet splittings with $J_{F,F}$ = 15.0 and 17 Hz, based on which it was assigned to the F(8) atom. Similarly, the signal at δ_F 8.7 in the ^{19}F NMR spectrum of quinoline **17**, having doublet splittings with $J_{F,F}$ = 16 and 18 Hz, was assigned to the F(5) atom. In addition, the spectra of both compounds exhibit two downfield signals, which were impossible to assign unambiguously, but, reasoning from their positions, they belong to the two remained fluorine atoms, *viz.*, F(5) and F(7) in quinoline **16** and F(6) and F(8) in quinoline **17**. A broadening of these signals observed, apparently, is due to the interaction of the F atoms specified with the protons of the *ortho*-located piperidine fragment. In the ^{19}F NMR spectrum of quinoline **16**, for the signal at δ_F 7.6 in addition to the splittings indicated, the doublet splitting with J = 1.5 Hz is also observed, which can be assigned only to the interaction with the H(4) proton (see above). This confirms the assignment given for the structures.

In the reaction of quinoline **13** with hydrazine hydrate in boiling dioxane, 5,7,8-trifluoro-6-hydrazinoquinoline (**18**) and 5,6,8-trifluoro-7-hydrazinoquinoline (**19**) are formed in the ratio ~1 : 5 (Scheme 3; see Table 1, entry *8*). The assignment of the signals in the ^{19}F NMR spectra of compounds **18** and **19** (see Table 2) was made similarly to that described above for amines **16** and **17**. We failed in isolation of the products **18** and **19** in the individual state, however, their structures are confirmed by the fact that the action of the Fehling's solution on their mixture leads to the corresponding trifluoroquinolines **4** and **10** in the ratio ~1 : 6, whereas the treatment with benzaldehyde, to 7-(2-benzylidenehydrazino)-5,6,8-trifluoroquinoline as the major product.

The research results on the reactions of quinoline **13** with ammonia, piperidine, and hydrazine indicate that a modification of the nitrogen-centered nucleophile by the introduction of an alkyl substituent or an amino group exhibiting electron-donating α-effect does not significantly affect the direction of substitution of the F atom in the benzene ring of the quinoline molecule. A predominant substitution of the F(7) atom in all the cases agrees with orientation of the substitution in the reactions of this substrate with other nucleophilic reagents[17–19] and results from the combined orientation effects of the heterocycle N atom and the F atoms. For the latter, such an effect is similar to that observed in analogous reactions of polyfluorinated benzenes and naphthalenes.[28,29] However, a predominance of substitution of the F(7) atom, activated by the combined orientation effect of the fluorine atoms, over substitution of the F(5) atom, activated by the heterocycle, testifies that the influence of the first structural factor specified is predominant.

The reaction of 5,7,8-trifluoro-6-(trifluoromethyl)-quinoline (**20**) with liquid ammonia at 10—15 °C gives rise to the only product, *viz.*, 5-amino-7,8-difluoro-6-(trifluoromethyl)quinoline (**21**) (Scheme 4; see Table 1, entry *9*). Its structure was established based on the X-ray diffraction data. Heating of aminoquinoline **21** with sulfuric acid leads, obviously, resulting from the hydrolysis of the trifluoromethyl group and subsequent decarboxylation, to amine **5** in 60% yield, which was obtained as the minor product during ammonolysis of quinoline **4** (see

Scheme 4



Scheme 1). The major product of the reaction of quinoline **20** with aqueous ammonia at 60 °C is 5-amino-7,8-difluoroquinoline-6-carbonitrile (**22**) (Scheme 4; see Table 1, entry *10*) formed apparently from amine **21** by ammonolysis of the trifluoromethyl group. Analogous transformations are reported in the literature (see, for example, Ref. 30). The close values of δ_F in the ^{19}F NMR spectra of compounds **21** (except the signal for the CF_3 group) and **22**, as well as the presence of characteristic absorption bands at 2223 cm^{-1} (C≡N) and 3389 and 3357 cm^{-1} (N—H) in the IR spectrum of the latter confirm the structure assigned to product **22**.

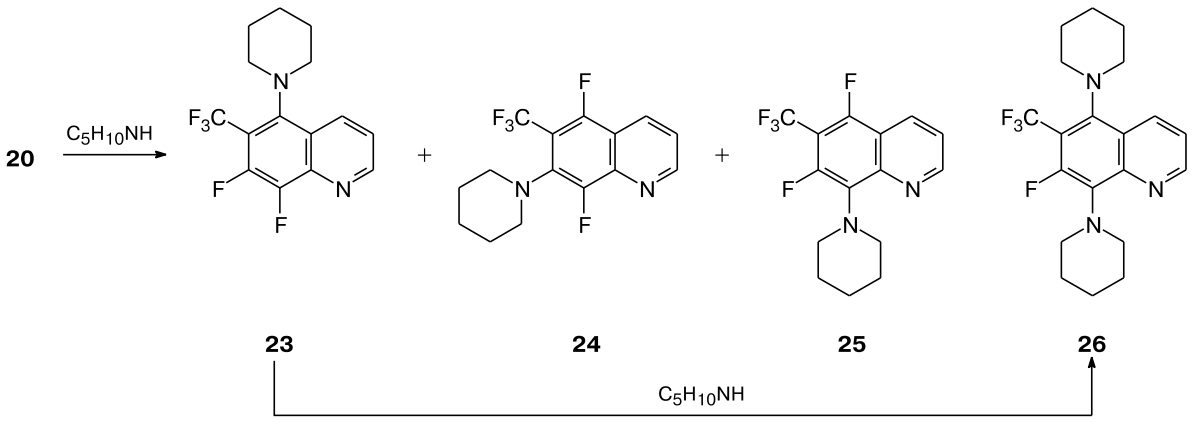
A plausible reason that position 5 is the most active during ammonolysis of quinoline **20** (as well as during ammonolysis of quinoline **1**) is a predominance of a combined influence of the heterocycle and trifluoromethyl group as a substituent possessing strong electron-withdrawing effect over the collective effect of the F atoms present in the same ring. It cannot be excluded that position 5 is activated by the trifluoromethyl group to a greater extent than position 7 due to the fact that in the molecule of the starting compound **20** (CCDC 663072 in the Cambridge Structural Database System, see Ref. 31), the C(5)—C(6) bond (an average distance (d_{av}) is 1.359 Å) is shorter than the C(6)—C(7) bond (d_{av} = 1.405 Å).

The reaction of 5,7,8-trifluoro-6-(trifluoromethyl)-quinoline (**20**) with piperidine at 50 °C furnishes 7,8-difluoro-5-piperidino-6-(trifluoromethyl)quinoline (**23**), 5,8-difluoro-7-piperidino-6-(trifluoromethyl)quinoline (**24**) and 5,7-difluoro-8-piperidino-6-(trifluoromethyl)-quinoline (**25**) in the ratio 4.0 : 1.0 : 1.6 (Scheme 5; see Table 1, entry *11*). All the products were isolated and characterized as individual compounds.

The structure of the major product, amine **23**, was inferred from the X-ray diffraction data. In the ^{19}F NMR spectrum of compound **23**, the multiplet at δ_F 24.6, assigned to the F(7) atom, contains quartet (1 : 3 : 3 : 1) splitting with $J_{F,F}$ = 28 Hz, which is due to the interaction with the F atoms of the CF_3 group, the signal of which at δ_F 106.2 has the corresponding doublet splitting (see Table 2). Similarly, the signal at δ_F 40.2 in the ^{19}F NMR spectrum of compound **24** is assigned to the F(5) atom and the interaction with the CF_3 group results in the quartet splitting with the spin-spin coupling constant $J_{F,F}$ = 36 Hz, which is significantly higher than the value of $J_{F,F}$ for quinoline **23**, obviously, due to the closer spatial proximity of the F(5) atom to the CF_3 group as compared to the F(7) atom. In the ^{19}F NMR spectrum of compound **25**, the signal for the CF_3 group at δ_F 105.7 contains the doublet splittings with $J_{F,F}$ = 28 and 20 Hz, which are observed for the signals assigned to the F(5) and F(7) atoms, respectively (*cf.* with the data for compound **20** in Ref. 25).

Quinoline **20** in boiling piperidine is converted to a mixture of the same quinolines **23**—**25,** but in another ratio, 1 : 2 : 11 (see Table 1, entry *12*). Therefore, under these conditions, a product of substitution of the F(8)

Scheme 5

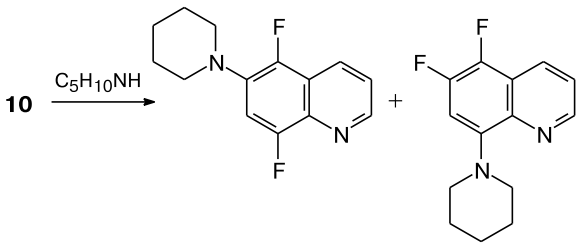


atom predominates. And vice versa, if the reaction is carried out at reduced temperature (17 °C), the content of the product of substitution of the F(5) atom increases: quinolines **23**—**25** are formed in the ratio 5.7 : 1.0 : 1.0 (see Table 1, entry *13*). A possibility of interconversion of isomers **23**—**25** is excluded by the fact that the keeping of quinoline **20** with piperidine at 17 °C with subsequent reflux resulted in compounds **23**—**25** in qualitatively similar ratio 3 : 1 : 1. Some decrease in the content of quinoline **23** in the mixture of isomeric products of monosubstitution, most likely, is due to its partial transformation to 7-fluoro-5,8-dipiperidino-6-(trifluoromethyl)quinoline (**26**) (the content in the mixture is 38% according to the ^{19}F NMR spectra). To confirm this, the latter was obtained by the reaction of quinoline **23** with piperidine in 83% yield (see Scheme 5).

From the data considered above, it follows that there exists a temperature dependence of orientation of piperidinodefluorination of quinoline **20** with isokinetic temperature in the range of 50—100 °C and at low temperatures (17—50 °C), *i.e.*, in the region of the enthalpy control, substitution of the F atom at position 5 predominates, whereas at high temperatures (>100 °C), *i.e.*, in the region of the entropy control, at position 8.

Such a temperature dependence of orientation of substitution of F atom by the piperidine residue was also found for quinoline **10**. For instance, the reaction of the latter with piperidine at 17 °C leads to 5,8-difluoro-6-piperidinoquinoline (**27**) and 5,6-difluoro-8-piperidinoquinoline (**28**) in the ratio 1 : 4 (Scheme 6; see Table 1, entry *14*), whereas in boiling piperidine, the products specified are formed in the ratio 1 : 9 (see Table 1, entry *15*). A predominant isomer **28** was isolated and characterized as an individual compound.

Scheme 6

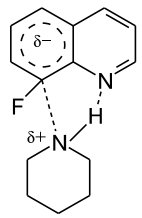


27 **28**

In the ^{19}F NMR spectra of compounds **27** and **28**, the signals for all the F atoms have the doublet splittings with $J_{F,F}$ = 15—20 Hz, which should not be observed in the case of 6,8-difluoro-5-piperidinoquinoline. In the ^{1}H NMR spectrum of quinoline **27**, a characteristic doublet splitting of the signal for the proton H(4) with $J_{H(4),F(8)}$ = 1.5 Hz is observed (see above), whereas such a splitting is absent in the ^{1}H NMR spectrum of quinoline **28**.

Therefore, in contrast to the ammonolysis of compound **10** proceeding with the formation of the substitution products of the F atoms at positions 6 and 8 in virtually equal amounts, the reaction of the same substrate with piperidine leads predominantly to the product of substitution at position 8, *i.e.*, quinoline **28**, the fraction of which on temperature elevation increases similarly to the observed for quinoline **20**. In contrast to the latter, in the case of quinoline **28** the isokinetic temperature apparently is in the region of low temperatures.

The temperature dependence of orientation of piperidinodefluorination found can presumably be interpreted as follows. A predominant substitution of the F(5) atom in the reaction of quinoline **20** with piperidine at 17—50 °C is determined by the electronic effect of the N atom of the pyridine ring, which in this case is amplified by the effect of the CF_3 group. The entropy-controlled predominant substitution of the F(8) atom in the reaction of compounds **10** and **20** with piperidine at elevated temperature, possibly, is due to the specific interaction of the piperidine fragment with the N atom of the heterocycle in the transition state, *i.e.*, the formation of the intramolecular hydrogen bond (the structure **29**). In contrast to this, an additional molecule of piperidine is involved into the formation of the hydrogen bond in the transition state for the substitution of the F(5) atom (the structure **30**), as a result, the entropy of solvation for this transition state is more negative than in the first case. Similar interpretation has also been suggested for the dependence of the ratio of rates for *ortho*- and *para*-alkoxydefluorination of fluoronitrobenzenes versus the structure of the alcohol alkyl group.[32]



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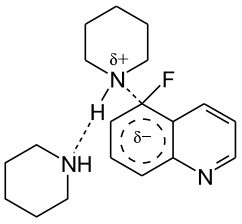

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Similar interactions, apparently, take also place in the transition states of aminodefluorination of compounds **1** and **20**. However, it can be suggested that in this case the differences in the entropy of solvation of transition states of competing reactions are less than during piperidinodefluorination. This is due to the fact that the fragment of the structure of transition state corresponding to the ammonia molecule incoming in the substrate has a possibility to form three hydrogen bonds and, therefore, a relative decrease in the number of molecules involving

into the solvation as a result of formation of intramolecular hydrogen bond in the transition state for the substitution at position 8 as compared to position 5 is not that high.

To sum up, note that in the reactions of quinolines fluorinated at the benzene ring under study with nitrogen-centered nucleophiles (aqueous and liquid NH_3, N_2H_4—H_2O, and $C_5H_{10}NH$), a direction of aminodefluorination is determined by the ratio of the influence of the heterocycle and orientation effect of the F atoms and

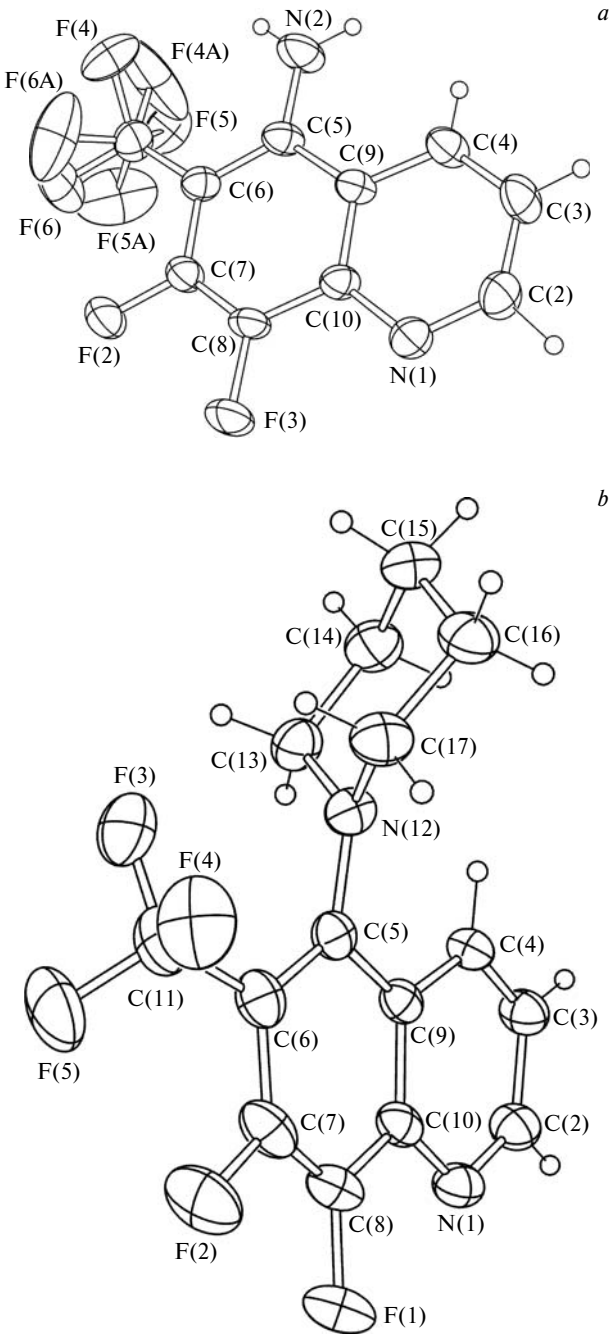

Fig. 1. Spatial structure of compounds **21** (*a*) and **23** (*b*) according to the X-ray diffraction data.

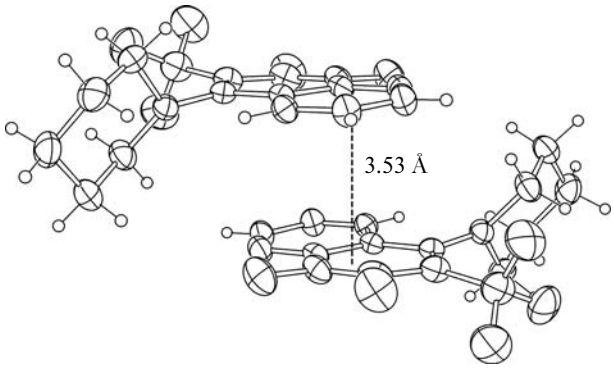

Fig. 2. π-Stacking interaction in the crystals of compound **21**.

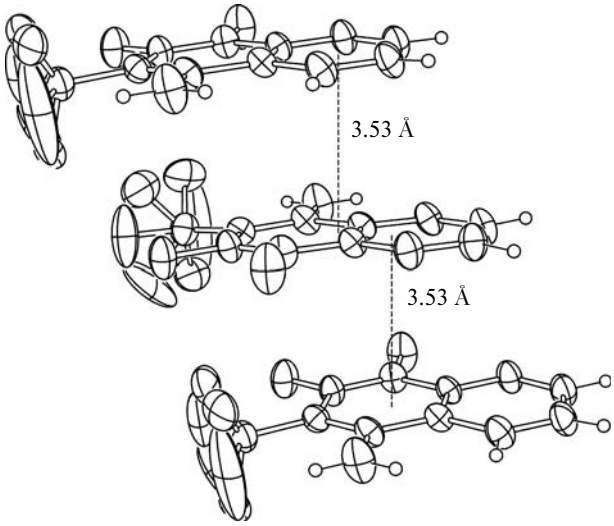

Fig. 3. π-Stacking interaction in the crystals of compound **23**.

when these two effects oppose each other, the latter has a predominance. In the reactions of 5,6,8-trifluoroquinoline and 5,7,8-trifluoro-6-(trifluoromethyl)quinoline with piperidine, it was found that the orientation of aminodefluorination depends on temperature, which is obviously due to the change of the enthalpy control at low temperature to the entropy control upon its elevation.

The spatial structures of compounds **21** and **23** are given in Fig. 1 (the X-ray diffraction data). Analysis of molecular geometry and intermolecular interactions was performed using the PLATON program[33,34] (Table 3). The quinoline framework of these molecules is virtually plane, the mean-square deviation of atoms from the plane is 0.015 and 0.030 Å for compounds **21** and **23**, respectively. The piperidine ring in the molecule of **23** has the "chair" conformation. The values of similar bond distances and bond angles in the molecules of **21** and **23** coincide within 3σ and are close to the average statistical values.[35] Geometry of the heterocycle is analogous to that for nonfluorinated quinoline.[36] In the fluorinated ring of quinolines **21** and **23**, the bonds C(7)—C(8) (1.346(5) and 1.341(3) Å, respectively) and C(8)—C(10) (1.404(5)

Table 3. Crystallographic data and parameters of X-ray diffraction experiments for compounds **21** and **23**

Parameter	**21**	**23**
Molecular formula	$C_{10}H_5F_5N_2$	$C_{15}H_{13}F_5N_2$
T/K	296	296
Molecular weight	248.16	316.27
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	$P2_1/c$
Region of scanning, θ/deg	2.10—25.50	2.50—26.00
Parameters of unit cell		
a/Å	12.922(3)	10.9797(6)
b/Å	7.684(2)	12.3682(8)
c/Å	19.020(4)	10.3751(7)
β/deg		96.561(6)
V/Å^3	1888.6(8)	1399.7(2)
Z	8	4
d_{calc}/g cm^{-3}	1.746	1.501
μ/mm^{-1}	0.176	0.136
Crystal size/mm	1.00×0.12×0.04	0.40×0.30×0.10
Number of reflections		
measured	1764	2918
independent	1743	2758
Allowance for absorption	Empirical	Empirical
Transmission	0.90—0.95	0.93—0.96
Number of reflections with $I > 2\sigma(I)$	775	1640
Number of refining parameters	203	199
R_1 for $F > 4\sigma(F)$	0.0548	0.0474
wR_2 for all reflections	0.1992	0.1366
GOOF	0.99	1.02

and 1.402(3) Å, respectively) are somewhat shortened as compared to those in nonfluorinated quinoline: for two independent quinoline molecules, the average bond distances for C(7)—C(8) and C(8)—C(10) are 1.363 and 1.415 Å, respectively. However, these values are close to the distances of analogous bonds in 1,2,3,4-tetrafluoronaphthalene: C(7)—C(8) is 1.349(3)Å, C(8)—C(10) is 1.404(3) Å (see Ref. 37). This means that a substitution of the H atom for the F atom leads to a shortening of the bond distances. Vice versa, due to the presence of substituents at positions 5 and 6, the bonds C(5)—C(9) and C(5)—C(6) are elongated, respectively, to 1.443(5) and 1.391(5) Å in compound **21** and to 1.438(3) and 1.388(3) Å in compound **23** as compared to nonfluorinated quinoline (for two independent quinoline molecules, the average bond distances for C(5)—C(9) and C(5)—C(6) are 1.413 and 1.360 Å, respectively[36]).

A crystal supramolecular architecture of compound **21** is determined by a π-stacking interaction of the arene—polyfluoroarene type, due to which the staircase-like stacks are formed (Fig. 2). The distance between the planes of neighboring molecules is 3.533 Å, whereas the intercentroid distance is 3.657(2) Å. The stacks are bound to each other by weak hydrogen bonds N—H...N (N(1)...H(2B) is 2.28(5) Å, the distance N(2)...N(1) is 3.091(5) Å, the angle N(2)—H(2B)...N(1) is 154(5)°).

The molecules of compound **23** in crystal are packed as the sandwich-like herring-bone patterns (Fig. 3).[38] Despite the presence of two bulky substituents, the herring-bone motive consists of pairs formed due to the π-stacking arene—polyfluoroarene interaction of the "head-to-tail" type. The interplanar distance in the pairs is 3.53 Å, the intercentroid, 3.596(1) Å. A structurizing interaction for the herring-bone pattern, most likely, is the contact N(1)...H(3A) shortened to 2.65 Å (the sum of the Van der Waals radii is 2.74 Å).[39]

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker AC-200, Bruker AV-300, and Bruker AM-400 spectrometers in acetone-d_6, $CDCl_3$, and DMSO-d_6 for solutions of the individual compounds and in CH_2Cl_2, for the reaction mixtures using C_6F_6 as the internal standard.

Mass spectra (EI, 70 eV) were recorded on a Finnigan MAT-8200 and DFS high resolution mass spectrometers. Identification of components by GC-MS was performed on a Hewlett—Packard G1081A instrument consisting of an HP 5890

Series II gas chromatograph and an HP 5971 mass-selective detector (EI, 70 eV). Temperature conditions for the column: 2 min at 50 °C, further, 10 deg min^{-1}, and 5 min at 280 °C. The source of ions temperature was 173 °C. A 30×0.25×0.25 mm column was filled with HP5 sorbent (5% of polydiphenyl, 95% of polydimethylsiloxane), He was the carrier gas (1 mL min^{-1}). The data were collected at 1.2 scan s^{-1} in the region of masses 30—650 a.m.u.

IR spectrum was recorded on a Bruker Vector-22 spectrometer in KBr pellets.

X-ray diffraction experiments were performed on a Bruker P4 diffractometer (Mo-Kα irradiation, graphite monochromator, 2θ/θ-scanning). Samples of crystals of compounds **21** and **23** were obtained by crystallization from CH_2Cl_2, their crystallographic data and parameters of X-ray experiments are given in Table 3. The structures were decoded by the direct method using the SHELXS-97 program, refining of structural parameters was performed using the SHELXL-97 program (see Ref. 40). Parameters for the structure **21** were refined using the least squares method in the full-matrix anisotropic-isotropic (for the H atoms) approximation. The trifluoromethyl group in the molecule of **21** is disordered over two positions with the ratio of weights 0.77 : 0.23 (2). The refining of parameters for the structure **23** was performed by the least squares method in the full-matrix anisotropic approximation for the nonhydrogen atoms. Parameters of the H atoms were calculated in every cycle of refining using the coordinates of the corresponding carbon atoms (the riding model).

Commercial aqueous NH_3 was saturated with gaseous ammonia to the concentration of 32% (d = 0.883 g cm^{-3}). Commercial $N_2H_4 \cdot H_2O$ (98%) was used.

Quinolines **1**, **4**, **10**, **13**, and **20** were obtained according to the procedures described earlier,[25] the chlorine-containing quinoline **7** was also synthesized according to the described procedure.[41]

Individual compounds were isolated by TLC on plates with binded layer of a sorbent (LSL_{254} silica gel, 5.0/0.4 mm with 13 wt.% of gypsum), visualization of dried plates were made under the UV light. Separated fractions were washed off the sorbent with acetone.

Reactions of quinolines with aqueous NH_3 (general procedure). A mixture of quinoline and aqueous NH_3 (40 mL) was kept in a 80-mL steel rotary autoclave. The products were extracted from the cooled reaction mixture with CH_2Cl_2 (4×25 mL). The extract was dried with $MgSO_4$, the solvent was evaporated on a rotary evaporator, a solid residue was analyzed by GC-MS and ^{19}F NMR spectroscopy.

Reactions of quinolines 13 and 20 with liquid NH_3 (general procedure). A mixture of quinoline and liquid NH_3 (30 mL) was kept at required temperature in a 80-mL steel rotary autoclave. After completion of the reaction, NH_3 was evaporated, a solid residue was dissolved in CH_2Cl_2 (30 mL). The extract was dried with $MgSO_4$, the solvent was evaporated, a solid residue was analyzed by ^{19}F and ^1H NMR spectroscopy.

Reaction of quinolines with piperidine (general procedure). A mixture of quinoline and piperidine was stirred at required temperature. The reaction conditions and experimental results are given in Table 1.

5-Amino-7-fluoroquinoline (2) and 7-amino-5-fluoroquinoline (3). From a mixture of products of the reaction of compound **1** with aqueous NH_3 (0.1 g) (see Table 1, entry *1*), products **2** and **3** were isolated using TLC (eluent, Et_2O).

Quinoline **2** (R_f 0.35), the yield was 0.032 g (32%), m.p. 137—138 °C. HRMS, found: m/z 162.0594 $[M]^+$. $C_9H_7FN_2$. Calculated: M = 162.0593. MS, m/z (I_{rel} (%)): 162 $[M]^+$ (100), 161 (99), 142 (4), 136 (4), 135 (32), 134 (16), 115 (9), 108 (14), 107 (18), 81 (9), 57 (5), 28 (12). Quinoline **3** (R_f 0.12), the yield was 0.009 g (9%), m.p. 158.0—159.5 °C. HRMS, found: m/z 162.0592 $[M]^+$. $C_9H_7FN_2$. Calculated: M = 162.0593. MS, m/z (I_{rel} (%)): 162 $[M]^+$ (100), 161 (5), 136 (7), 135 (76), 134 (21), 108 (19), 107 (20), 81 (12), 68 (5), 57 (6), 28 (15).

7-Amino-5,8-difluoroquinoline (6). From a mixture of products of the reaction of compound **4** with aqueous NH_3 (0.1 g) (see Table 1, entry *2*), quinoline **6** was isolated using TLC (eluent, hexane—Et_2O, 1 : 5) (R_f 0.32), the yield was 0.064 g (64%), m.p. 136—138 °C. HRMS, found: m/z 180.0498 $[M]^+$. $C_9H_6F_2N_2$. Calculated: M = 180.0499. MS, m/z (I_{rel} (%)): 180 $[M]^+$ (100), 154 (5), 153 (45), 152 (17), 133 (9), 132 (6), 126 (8), 125 (9), 74.9 (4), 28 (13).

5-Amino-8-chloro-7-fluoroquinoline (8) and 7-amino-8-chloro-5-fluoroquinoline (9). From a mixture of products of the reaction of compound **7** with aqueous NH_3 (0.1 g) (see Table 1, entry *3*), quinoline **9** was isolated using TLC (eluent, hexane—Et_2O, 1 : 5) (R_f 0.46), the yield was 0.052 g (52%), m.p. 164—166 °C. HRMS, found: m/z 196.01951 $[M]^+$. $C_9H_6ClFN_2$. Calculated M = 196.02035. MS, m/z (I_{rel} (%)): 198 $[M + 2]^+$ (36), 197 $[M + 1]^+$ (13), 196 $[M]^+$ (100), 171 (10), 170 (6), 169 (33), 168 (10), 161 (13), 160 (17), 141 (6), 135 (5), 134 (39), 133 (15), 132 (11), 107 (12), 106 (6), 98 (8), 81 (4). A fraction with R_f 0.24 (0.016 g) was also collected, which contained 85% of quinoline **8**. The latter was isolated by repeated (5 times) TLC (eluent, hexane—Et_2O, 1 : 3) as a fraction with R_f 0.45, the yield was 0.009 g (9%), m.p. 213—215 °C. HRMS, found: m/z 196.0201 $[M]^+$. $C_9H_6ClFN_2$. Calculated: M = 196.02035. MS, m/z (I_{rel} (%)): 198 $[M + 2]^+$ (33), 197 $[M + 1]^+$ (14), 196 $[M]^+$ (100), 169 (11), 160 (7), 141 (6), 134 (12), 133 (4), 132 (5), 107 (6).

6-Amino-5,8-difluoroquinoline (11) and 8-amino-5,6-difluoroquinoline (12). From a mixture of products of the reaction of compound **10** with aqueous NH_3 (0.1 g) (see Table 1, entry *4*), two fractions were isolated by TLC (eluent, hexane—Et_2O, 1:5).

The fraction with R_f 0.67 (0.03 g) contained 87% of quinoline **12**, from which it was isolated by double crystallization from benzene, the yield was 0.013 g (13%), m.p. 83—84 °C. HRMS, found: m/z 180.0503 $[M]^+$. $C_9H_6F_2N_2$. Calculated: M = 180.0499. MS, m/z (I_{rel} (%)): 180 $[M]^+$ (100), 179 (8), 154 (5), 153 (35), 152 (14), 133 (4), 126 (13), 125 (10), 90 (5), 75 (5), 28 (12).

The fraction with R_f 0.39 contained quinoline **11**, the yield was 0.035 g (35%), m.p. 175—176 °C. HRMS, found: m/z 180.0501 $[M]^+$. $C_9H_6F_2N_2$. Calculated: M = 180.0499. MS, m/z (I_{rel} (%)): 180 $[M]^+$ (100), 179 (4), 153 (13), 152 (13), 133 (15), 132 (6), 126 (4), 125 (6), 90 (7), 28 (13).

7-Amino-5,6,8-trifluoroquinoline (15). From a mixture of products of the reaction of compound **13** with aqueous NH_3 (0.17 g) (see Table 1, entry *5*), a fraction with R_f 0.4—0.5 was isolated using TLC (eluent, Et_2O), which contained quinoline **15**, the yield was 0.11 g (55%), m.p. 187—189 °C (the data in Ref. 17: m.p. 186—187 °C).

5,7,8-Trifluoro-6-piperidinoquinoline (16) and 5,6,8-trifluoro-7-piperidinoquinoline (17). After completion of the reaction of quinoline **13** with piperidine (see Table 1, entry *7*), the

reaction mixture was poured into H_2O (20 mL), a precipitate was filtered off, washed with H_2O (5×5 mL), dissolved in CH_2Cl_2, and dried with $MgSO_4$. The solvent was evaporated, two fractions were isolated from the solid residue (0.2 g) by repeated (3 times) TLC (eluent, hexane—Et_2O, 3 : 1).

Quinoline **16** was obtained from the fraction with R_f 0.46—0.62 (0.018 g) by sublimation at ~60—70 °C (10 Torr), the yield was 0.01 g (3.8%), m.p. 80.0—81.5 °C. Found (%): C, 63.33; H, 4.71; F, 21.41; N, 10.52. $C_9H_7FN_2$. Calculated (%): C, 63.15; H, 4.92; F, 21.41; N, 10.52.

Quinoline **17** was obtained from the fraction with R_f 0.37—0.46 (0.149 g) by sublimation at ~75—80 °C (10 Torr), the yield was 0.1 g (39.7%), m.p. 75—77 °C. HRMS, found: *m/z* 266.1032 $[M]^+$. $C_9H_7FN_2$. Calculated: M = 266.1031. MS, *m/z* (I_{rel} (%)): 266 $[M]^+$ (91), 265 (100), 237 (5), 225 (18), 211 (11), 210 (36), 209 (44), 196 (9), 183 (6), 182 (19), 162 (12), 57.1 (6), 55.2 (10), 42 (5), 41 (9), 29 (6), 28 (16).

Reaction of quinolines 18 and 19 with Fehling's solution. A mixture of quinoline **13** (0.20 g, 1 mmol), hydrazine hydrate (0.13 g, 2.5 mmol), and 1,4-dioxane (6 mL) was refluxed for 6 h. Then, the solution was decanted and the precipitate was washed with dioxane (3×1 mL). The solvent was evaporated from the combined solution on a rotary evaporator. A solution of $CuSO_4 \cdot 5H_2O$ (1.44 g) in H_2O (12 mL) and a solution of NaOH (1.33 g) and K,Na tartrate (4.52 g) in H_2O (12 mL) were added to the solid residue containing quinolines **18** and **19**. The mixture was refluxed for 40 min and steam distilled. The products were extracted with CH_2Cl_2 (4×15 mL) from the condensate, dried with $MgSO_4$, the solvent was evaporated on a rotary evaporator to obtain a solid residue (0.12 g) containing quinolines **13** (6%), **10** (72 %), and **4** (13%) according to the ^{19}F and ^1H NMR spectra.

7-(2-Benzylidenehydrazino)-5,6,8-trifluoroquinoline. A mixture of quinoline **13** (0.20 g, 1 mmol), hydrazine hydrate (0.13 g, 2.5 mmol), and 1,4-dioxane (6 mL) was refluxed for 6 h. Then, the solution was decanted and the precipitate was washed with dioxane (3×1 mL). The solvent was evaporated from the combined solution on a rotary evaporator. Ethanol (2 mL), H_2O (2 mL), and benzaldehyde (0.19 g, 1.8 mmol) were added to the solid residue. The reaction mixture was stirred for 15 min at ~40 °C (water bath) and 1 h at ~60 °C (water bath) and poured into H_2O (40 mL). A precipitate was filtered off, washed with H_2O (3×3 mL), and dried *in vacuo* over KOH. 7-(2-Benzylidene-hydrazino)-5,6,8-trifluoroquinoline was obtained by crystallization from MeOH, the yield was 0.12 g (41%), m.p. 212—214 °C. Found (%): C, 63.67; H, 3.29; F, 18.68; N, 13.60. $C_{16}H_{10}F_3N_3$. Calculated (%): C, 63.79; H, 3.35; F, 18.92; N, 13.95. ^{19}F NMR (acetone-d_6), δ: 9.0 (dd, F(6), J = 15.5 Hz, 18 Hz); 13.9 (dm, F(6) or F(8), J = 18 Hz). ^1H NMR (acetone-d_6), δ: 10.10 (br.s, 1 H, NH); 7.35—7.48 (3 H); 7.54 (ddd, 1 H, H(3), J = 4 Hz, 8 Hz, 0.5 Hz); 7.72—7.76 (2 H); 8.30 (t, 1 H, HC=N, J = 2 Hz); 8.43 (dt, 1 H, H(4), J = 1.5 Hz, 1.5 Hz, 8.0 Hz); 8.92 (dd, 1 H, H(2), J = 1.5 Hz).

5-Amino-7,8-difluoro-6-(trifluoromethyl)quinoline (21). From a mixture obtained by the reaction of compound **20** with liquid NH_3 (0.2 g) (see Table 1, entry *9*), aminoquinoline **21** was isolated by sublimation at 120—130 °C (10 Torr), the yield was 0.13 g (68%), m.p. 183.0—184.5 °C. Found (%): C, 48.32; H, 2.09; F, 38.20; N, 11.10. $C_{10}H_5F_5N_2$. Calculated (%): C, 48.40; H, 2.03; F, 38.28; N, 11.29.

5-Amino-7,8-difluoroquinoline-6-carbonitrile (22). After the autoclave reaction was completed (see Table 1, entry *10*), a precipitate was filtered off, washed with H_2O (4×10 mL), dried *in vacuo* over KOH, and crystallized from acetic acid to obtain quinoline **22**, the yield was 0.09 g (55%), m.p. 270—272 °C. IR (KBr), ν/cm^{-1}: 2223 (C—N); 3389 (N—H); 3357 (N—H). HRMS, found: *m/z* 205.0451 $[M]^+$. $C_{10}H_5F_2N_3$. Calculated: M = 205.0446. MS, *m/z* (I_{rel} (%)): 206 [M + 1] (12), 205 $[M]^+$ (100), 204 (5), 178 (21), 177 (7), 158 (5), 151 (11), 150 (8).

5-Amino-7,8-difluoroquinoline (5). Aminoquinoline **21** (0.05 g, 0.2 mmol) and H_2SO_4 (1.3 mL) were stirred for 2 h at a bath temperature of 160 °C, the mixture was poured into H_2O followed by addition of aqueous NaOH (10 mL, ~18%) and extraction with CH_2Cl_2 (5×10 mL). The extract was dried with $MgSO_4$, the solvent was evaporated, and aminoquinoline **5** was isolated from the residue by vacuum sublimation at 90—100 °C (10 Torr), the yield was 0.023 g (63%), m.p. 181—182 °C. Found (%): C, 60.32; H, 3.76; F, 20.29; N, 15.17. $C_9H_6F_2N_2$. Calculated (%): C, 60.00; H, 3.36; F, 21.09; N, 15.55.

7,8-Difluoro-5-piperidino-6-(trifluoromethyl)quinoline (23), 5,8-difluoro-7-piperidino-6-(trifluoromethyl)quinoline (24), and 5,7-difluoro-8-piperidino-6-(trifluoromethyl)quinoline (25). After the reaction was completed (see Table 1, entry *11*), the mixture was kept for 3 days at ~4 °C. A precipitate was filtered off, washed with H_2O, dissolved in CH_2Cl_2, and dried with $MgSO_4$, the solvent was evaporated. Quinoline **23** in the fraction with R_f 0.38 was isolated from the solid residue by repeated (4 times) TLC (eluent, hexane—CH_2Cl_2, 1 : 1), the yield was 0.031 g. The filtrate was poured into H_2O (30 mL), a precipitate was filtered off, washed with H_2O, dissolved in CH_2Cl_2, and dried with $MgSO_4$, the solvent was evaporated. Several fractions, containing (according to the ^{19}F NMR spectra) quinolines **23** (40%), **24** (17%), **25** (27%), and apparently **26** (11%) were isolated from the solid residue using (twice) TLC (eluent, hexane—CH_2Cl_2, 1 : 1).

The fraction with R_f 0.6 contained quinoline **25**, the yield was 0.027 g (11%).

Quinoline **23** (0.052 g) was isolated from the fraction with R_f 0.26 (0.065 g) by sublimation at 70—80 °C (10 Torr), the overall yield was 33%, m.p. 127—128 °C. Found (%): C, 56.86; H, 4.24; F, 29.97; N, 8.90. $C_{15}H_{13}F_5N_2$. Calculated (%): C, 56.96; H, 4.14; F, 30.04; N, 8.86.

The fraction with R_f 0.38 (0.027 g) containing (according to the ^{19}F NMR spectra) compound **24** (88%) was subjected to repeated (12 times) TLC (eluent, hexane—CH_2Cl_2, 2 : 1) to obtain the fraction with R_f 0.3—0.43 (0.015 g). From the latter, quinoline **24** was isolated by sublimation at 60—65 °C (10 Torr), the yield was 0.009 g (3.5%), m.p. 64.0—65.5 °C. HRMS, found: *m/z* 315.0915 $[M - 1]^+$. $C_{15}H_{12}F_5N_2$. Calculated: M — 1 = 315.0993. MS, *m/z* (I_{rel} (%)): 317 $[M + 1]^+$ (7), 316 $[M]^+$ (51), 315 $[M - 1]^+$ (100), 297 (51), 275 (9), 261 (6), 260 (27), 259 (22), 246 (5), 241 (5), 239 (7), 232 (12).

5,7-Difluoro-8-piperidino-6-(trifluoromethyl)quinoline (25). In another experiment (see Table 1, entry *12*), the reaction mixture was poured into H_2O (30 mL), a precipitate was filtered off, washed with H_2O (3×5 mL), dissolved in CH_2Cl_2, and dried with $MgSO_4$, the solvent was evaporated. The residue containing (according to the ^{19}F NMR spectra) quinoline **25** (58%) was subjected to repeated (3 times) TLC (eluent, hexane—Et_2O,

2 : 1) to obtain the fraction with R_f 0.59—0.68 (0.10 g). Quinoline **25** was isolated from the latter by sublimation at 60—65 °C (10 Torr), the yield was 0.08 g (32%), m.p. 56—57 °C. Found (%): C, 56.91; H, 4.15; F, 29.85; N, 8.73. $C_{15}H_{13}F_5N_2$. Calculated (%): C, 56.96; H, 4.14; F, 30.04; N, 8.86.

7-Fluoro-5,8-dipiperidino-6-(trifluoromethyl)quinoline (26). A mixture of quinoline **23** (0.05 g, 0.2 mmol) and piperidine (2.5 g, 29.4 mmol) was refluxed for 12 h. Then, the mixture cooled to room temperature was poured into H_2O (30 mL), a precipitate was filtered off, washed with H_2O (3×5 mL), dissolved in CH_2Cl_2, and dried with $MgSO_4$, the solvent was evaporated. Quinoline **26** was isolated from the residue by sublimation at 100—110 °C (10 Torr), the yield was 0.05 g (83%), m.p. 118—120 °C. Found (%): C, 63.53; H, 5.87; F, 20.06; N, 11.01. $C_{20}H_{23}F_4N_3$. Calculated (%): C, 62.98; H, 6.08; F, 19.92; N, 11.02.

5,6-Difluoro-8-piperidinoquinoline (28). The mixture obtained in the reaction of quinoline **10** with piperidine (see Table 1, entry *14*), was poured into water (30 mL), a precipitate was filtered off, washed with H_2O (3×5 mL), dissolved in CH_2Cl_2, and dried with $MgSO_4$, the solvent was evaporated. The residue obtained was subjected to TLC (eluent, hexane—CH_2Cl_2, 1 : 1) to obtain the fraction with R_f 0.22—0.66 (0.11 g). Quinoline **28** was isolated from the latter by sublimation at 60—70 °C (10 Torr), the yield was 0.09 g (67 %), m.p. 83—84 °C. Found (%): C, 68.82; H, 5.74; F, 15.32; N, 11.24. $C_{14}H_{14}F_2N_2$. Calculated (%): C, 67.73; H, 5.68; F, 15.30; N, 11.28.

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