SYNTHESIS, PROPERTIES, AND X-RAY DIFFRACTION STUDY OF 4-TRIFLUOROMETHYL-6-PHENYL-2-CHLORO-3-CYANOPYRIDINE

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4-Trifluoromethyl-6-phenyl-2-chloro-3-cyanopyridine was synthesized, and its molecular-crystal structure was established. The chlorine atom was replaced by amino, mercapto, thiocyanato, and azido groups. The possibility of the direct amination of 4-trifluoromethyl-6-phenyl-3-cyano-2-pyridone by the action of hexamethylphosphoric triamide (HMPT) was demonstrated.

The lability of the halogen atom in 2-chloro-3-cyanopyridines [1-3] makes it possible to obtain various 2-substituted derivatives of nicotinic acid.

Continuing our investigation of fluorine-containing 2-pyridones [4], we have synthesized 4-trifluoromethyl-6-phenyl-2-chloro-3-cyanopyridine (II), which Portnoy was unable to obtain by the action of $POCl_3$ or a mixture with PCl_5 on pyridone I. Compound II was formed in 78% yield by heating pyridone with $POCl_3$ only in the presence of DMF, as in the method in [6].

We conducted an x-ray diffraction study to determine the molecular-crystal structure of II. Two crystallographically nonequivalent molecules, which differ with respect to their conformations, are situated in the independent part of the unit cell of the crystal: the dihedral angle between the planar six-membered rings in one molecule (A) is 23.0°, as compared with 5.1° in the other (B). The corresponding geometrical characteristics of the A and B molecules coincide, within the limits of the experimental error, and their average values are therefore presented in Fig. 1, in which the designations of the atoms in the II molecule are also given. The values of the dihedral angles between the median planes of the six-membered rings do not interfere with conjugation in the molecule, as indicated by the length of the $C_{(6)}-C_{(7)}$ bond, which is 1.472 Å. The length of the $C_{(2)}-Cl$ bond, which is 1.719 Å, constitutes evidence for the existence of conjugation between the pyridine ring and the unshared electron pair of the chlorine atom. The average value of the lengths of the C—F bonds (which is 1.299 Å) is lower than the standard value; this is a consequence of the significant thermal vibrations of the fluorine atoms [7].

The result of the presence of electron-acceptor sucstituents in the pyridine ring is that the $C_{(2)}$ atom is an active center of nucleophilic substitution. The reactions of II with amines proceed smoothly in ethanol, dioxane, or DMF with the formation of 2-aminopyridines IIIa-i (Table 1). Uracil and related compounds on heating with phosphoric acid amides give aminopyridine derivatives [8]; we therefore investigated the reaction of pyridone I with hexamethylphosphoric triamide (HMPT) and obtained 2-(N,N-dimethylamino)pyridine IIIe in 50% yield. This reaction opens up the possibility for the synthesis of 2-aminopyridines by the direct amination of 2-pyridones.

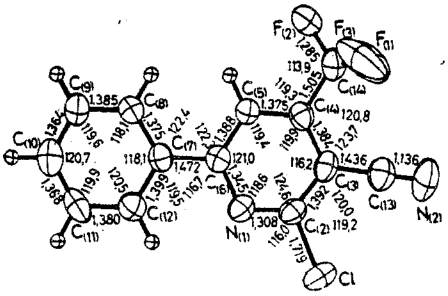

Fig. 1. Molecular structure of 4-trifluoromethyl-6-phenyl-2-chloro-3-cyanopyridine (II): $F_{(1)}-C_{(14)} = 1.307$; $F_{(3)}-C_{(14)} = 1.304$; $F_{(1)}-C_{(14)}-F_{(2)} = 106.2$; $F_{(1)}-C_{(14)}-F_{(3)} = 104.7$; $F_{(1)}-C_{(14)}-C_{(4)} = 112.3$; $F_{(2)}-C_{(14)}-F_{(3)} = 107.0$; $F_{(3)}-C_{(14)}-C_{(4)} = 112.0$; $C_{(3)}-C_{(13)}-N_{(2)} = 178.9$.

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TABLE 1. 2-Aminopyridines IIIa-j

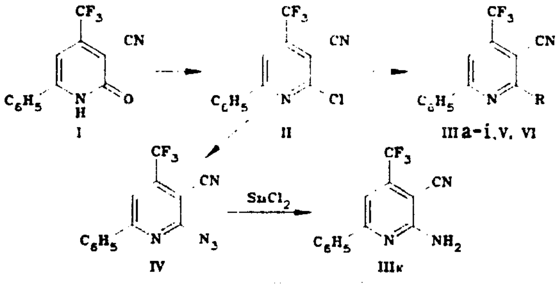
Compound	Reaction conditions		T_{mp}, °C	Found, %			Empirical formula	Calc., %			Yield, %
	solvent	time, h		C	H	N		C	H	N	
IIIa	Ethanol	1	155—157	62,0	3,9	14,7	$C_{15}H_{12}F_3N_3$	61,9	4,2	14,4	72
IIIb	Dioxane	3	122—123,5	64,2	5,0	13,1	$C_{17}H_{16}F_3N_3$	64,0	5,1	13,2	80
IIIc	Dioxane	4	175,5—178	67,8	3,8	12,0	$C_{20}H_{14}F_3N_3$	68,0	4,0	11,9	76
IIId	Ethanol	1	134—136	58,8	4,0	13,5	$C_{12}H_{12}F_3N_3O$	58,6	3,9	13,7	84
IIIe	Ethanol	1	95—96	62,4	3,8	14,6	$C_{15}H_{12}F_3N_3$	61,9	4,2	14,4	74
IIIf	Ethanol	1	103—104,5	64,1	4,8	14,0	$C_{17}H_{16}F_3N_3$	64,0	5,1	13,2	90
IIIg	Dioxane	:	135,5—137	65,5	4,9	12,1	$C_{18}H_{16}F_3N_3$	65,3	4,9	12,7	91
IIIh	Dioxane	1	157—159	61,6	4,5	12,3	$C_{17}H_{14}F_3N_3O$	61,3	4,2	12,6	89
IIIi	DMF	0,25	118								90
IIIi	Dioxane	4,5	118	66,5	3,1	12,0	$C_{19}H_{12}F_3N_3$	67,3	3,6	12,4	60
IIIj			158—160	59,5	2,8	16,2	$C_{13}H_8F_3N_3$	59,3	3,0	16,0	76

Sodium azide reacts with 2-chloropyridine II to give 2-azidopyridine IV. 2-Aminopyridine IIIj was obtained by its reduction with stannous chloride.

In the IR spectra of amines IIIa-j we observed ν_{CN} bands at 2208-2234 cm^{-1}; we also observed ν_{NH} bands at 3230-3470 cm^{-1} in the IR spectra of IIIa-d, i, j. The PMR spectra also confirm the structures of the compounds obtained (Table 2).

The action of sodium sulfide on II in solution in DMF leads to the previously described mercaptopyridine V [13].

2-Thiocyanatopyridine VI is formed only when 2-chloropyridine II is heated with potassium thiocyanate in DMF.



IIIa) R = $NHCH_2CH_3$; b) R = $NH(CH_2)_3CH_3$; c) R = $NHCH_2C_6H_5$;
d) R = $NHCH_2CH_2OH$; e) R = $N(CH_3)_2$; f) R = $N(C_2H_5)_2$; g) R =
piperidino; h) R = morpholino; i) R = NHC_6H_5; j) R = NH_2;
V) R = SH; VI) R = SCN

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with an IKS-14A spectrometer. The PMR spectra were obtained with a Tesla BS-487C spectrometer (80 MHz) with tetramethylsilane (TMS) or hexamethyldisiloxane (HMDS) as the internal standard. The individuality of the compounds was monitored by means of TLC on Silufol UV-254 plates in acetone—hexane (1:1) or chloroform—ethanol (10:1) with development in UV light.

Single crystals of II with the composition $C_{13}H_6ClF_3N_2$, which were grown from DMF, were monoclinic and had the following parameters: a = 14.303(4), b = 7.326(1), c = 23.753(5) Å, β = 101.95(2)°, V = 2434.9(9) Å^3, d_{calc} = 1.54 g·cm^{-3}, Z = 8, space group $P2_1/c$. The intensities of 3301 independent reflections were measured with a Syntex $P2_1$ automatic diffractometer (Cu Kα emission, graphite monochromator, θ/2θ scanning, θ ≤ 75°). The structure was decoded by the direct method and was refined by the method of least squares within the total-matrix anisotropic approximation. The coordinates of the atoms are presented in Table 3. For the nonhydrogen atoms the standard deviations of the bond lengths range from 0.007 to 0.015 Å, and the standard deviations of the bond angles range from 0.5° to 0.9°. The final R value was 0.064.

4-Trifluoromethyl-6-phenyl-2-chloro-3-cyanopyridine (II). A 14.5-ml (0.19 mole) sample of DMF was added in the course of 1 h at 130°C (oil bath) to a solution of 20 g (0.076 mole)

TABLE 2. Spectral Characteristics of 2-Aminopyridines IIIa-j

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum	
		solvent	δ, ppm
IIIa	1538, 1574, 2213, 2884—2930, 3371	CCl_4+CDCl_3	1,33 (3H, t, CH_3); 3.65 (2H, m, CH_2); 5,65 (1H, NH); 7,2 (1H, s, 5-H); 7,43—7,95 (5H, m, C_6H_5)
IIIb	1551, 1580, 1590, 2220, 2863—2940	$CDCl_3$	0,95 (3H, t, CH_3); 1,35—1,8 (4H, m, CH_2); 3,63 (2H, q, CH_2); 5,63 (1H, NH); 7,23 (1H, s, 5-H); 7,43—8,03 (5H, m, C_6H_5)
IIIc	1539, 1576, 1589, 2218, 2927, 3361	$CDCl_3$ + d_6-DMSO	3,35 (2H, s, CH_2); 4,76 (1H, NH); 7,18—7,98 (11H, m, C_6H_5, 5-H)
IIId	1539, 1570, 1583, 2218, 2878—2958	CCl_4+CDCl_3	3,75 (4H, s, CH_2); 4,55 (1H, s, OH); 6,75 (1H, NH); 7,23 (1H, s, 5-H); 7,45—8,0 (5H, m, C_6H_5)
IIIe	1524, 1568, 1582, 2213, 2841—2993	CCl_4	3,31 (6H, s, CH_3); 7,28 (1H, s, 5-H); 7,38—7,93 (5H, m, C_6H_5)
IIIf	1560, 1593, 2215, 2876—2989	$CDCl_3$	1,33 (6H, t, CH_3); 3,75 (4H, q, CH_2); 7,35 (1H, s, 5-H); 7,38—7,95 (5H, m, C_6H_5)
IIIg	1561, 1579, 2220, 2854, 2936	d_6-DMSO	1,68 (6H, s, CH_2); 3,73 [4H, m, $N(CH_2)_2$]; 7,73 (1H, s, 5-H); 7,55—8,18 (5H, m, C_6H_5)
IIIh	1559, 1581, 2221, 2830—2989	d_6-DMSO	3,75 (8H, s, CH_2); 7,55—8,18 (5H, m, C_6H_5); 7,80 (1H, s, 5-H)
IIIi	1533, 1567, 1586, 2213, 3400		
IIIj	1543, 1560, 1588, 1636, 2229, 3232, 3348, 3473	CCl_4 + d_6-DMSO	7,05 (2H, s, NH_2); 7,30 (1H, s, 5-H); 7,45—8,03 (5H, m, C_6H_5)

TABLE 3. Coordinates of the Atoms in the A and B Molecules of II (·10^4; ·10^3 for the H atoms)

Atom	Molecule A			Molecule B		
	x	y	z	x	y	z
$N_{(1)}$	4287(4)	2934(8)	2640(2)	482(4)	7343(8)	4937(2)
$C_{(2)}$	3844(4)	2875(9)	3068(3)	291(5)	6797(9)	4401(3)
$C_{(3)}$	4283(5)	2592(9)	3643(3)	−624(5)	6565(9)	4071(3)
$C_{(4)}$	5268(5)	2355(10)	3757(3)	−1368(5)	6912(9)	4344(3)
$C_{(5)}$	5741(6)	2398(11)	3310(3)	−1190(5)	7494(10)	4907(3)
$C_{(6)}$	5239(5)	2709(9)	2755(3)	−247(5)	7693(9)	5200(3)
$C_{(7)}$	5704(5)	2774(9)	2255(3)	−4(5)	8285(9)	5803(3)
$C_{(8)}$	6660(5)	3169(12)	2314(3)	−676(6)	8528(12)	6134(3)
$C_{(9)}$	7083(6)	3174(14)	1833(4)	−432(6)	9056(13)	6699(3)
$C_{(10)}$	6539(7)	2826(13)	1305(4)	511(7)	9323(12)	6951(4)
$C_{(11)}$	5587(7)	2407(13)	1236(4)	1202(6)	9103(12)	6639(3)
$C_{(12)}$	5164(6)	2394(12)	1708(3)	955(6)	8581(11)	6068(3)
$C_{(13)}$	3715(5)	2529(12)	4074(3)	−756(5)	5967(11)	3484(3)
$N_{(2)}$	3249(5)	2500(12)	4407(3)	−870(5)	5491(10)	3019(3)
$C_{(14)}$	5815(6)	2058(16)	4366(3)	−2385(6)	6677(18)	4036(3)
$F_{(1)}$	5494(4)	640(8)	4605(2)	−2553(4)	5076(11)	3798(3)
$F_{(2)}$	6722(4)	1788(9)	4394(2)	−3004(3)	6879(11)	4345(2)
$F_{(3)}$	5737(4)	3465(9)	4696(2)	−2620(4)	7781(11)	3604(3)
Cl	2624(1)	3162(3)	2895(1)	1264(1)	6377(3)	4102(8)
$H_{(5)}$	646(5)	218(10)	340(3)	−169(5)	766(9)	509(3)
$H_{(8)}$	706(5)	354(9)	269(3)	−136(6)	821(10)	597(3)
$H_{(9)}$	778(7)	350(12)	191(4)	−92(5)	913(9)	693(3)
$H_{(10)}$	681(6)	272(11)	95(3)	64(6)	983(12)	730(4)
$H_{(11)}$	514(6)	212(11)	85(3)	191(4)	932(8)	681(2)
$H_{(12)}$	447(6)	233(12)	170(4)	149(6)	845(11)	586(3)

of pyridone I in 75 ml of freshly distilled $POCl_3$, after which the mixture was heated for 8 h. It was then cooled and poured over 250 g of ice. The precipitate was washed on the filter with water to give 16.7 g (78%) of a product with mp 93-94°C (from ethanol). IR spectrum: 3086, 2234, 1590, 1552 cm^{-1}. PMR spectrum (d_6-DMSO): 8.56 (1H, s, 5-H), 7.60-8.29 (5H, m, C_6H_5). Found: 55.9; H 2.2; Cl 12.6; N 9.8%. $C_{13}H_6ClF_3N_2$. Calculated: C 56.4; H 2.2; Cl 12.6; N 10.1%.

2-Amino-4-trifluoromethyl-6-phenyl-3-cyanopyridines IIIa-i (Tables 1 and 2). A solution of 0.43 g (1.5 mmole) of chloropyridine II and 3.2 mmole of the corresponding amine in

3 ml of solvent was refluxed for 15 min to 4.5 h (Table 1), after which it was poured into 25 ml of water. The precipitate was recrystallized (IIIb, g, h from aqueous dioxane, and the remaining compounds from aqueous ethanol) and air dried. The synthesis of IIIb, c was carried out at 20°C.

2-(N,N-Dimethylamino)-4-trifluoromethyl-6-phenyl-3-cyanopyridine (IIIe). A 0.8-g (3 mmole) sample of pyridone I was heated in 2 ml of hexamethylphosphoric triamide at 190°C for 1 h, after which the mixture was cooled and diluted with 20 ml of water. The aqueous mixture was made alkaline to pH ~ 8-9 with 1 M NaOH solution, and the precipitate was recrystallized from aqueous ethanol to give 0.5 g (50%) of a product that did not depress the melting point of amine IIIe obtained from chloropyridine II and dimethylamine.

2-Azido-4-trifluoromethyl-6-phenyl-3-cyanopyridine (IV). A suspension of 0.86 g (3 mmole) of chloropyridine II and 0.40 g (6 mmole) of sodium azide in 5 ml of acetone was refluxed for 3 h, after which it was poured into 25 ml of water, and the precipitate was recrystallized from aqueous ethanol to give 0.79 g (90%) of a product with mp 116-117°C. IR spectrum: 2230, 2162, 2129, 1592, 1549 cm^{-1}. Found: C 54.6; H 2.2; N 24.6%. $C_{13}H_6F_3N_5$. Calculated: C 54.0; H 2.1; N 24.2%.

2-Amino-4-trifluoromethyl-6-phenyl-3-cyanopyridine (IIIj). A mixture of 0.92 g (3.18 mmole) of azide IV, 30 ml of ethanol, 15 ml of hydrochloric acid, and 1.5 g of $SnCl_2 \cdot 2H_2O$ in 10 ml of water was refluxed for 3 h, after which it was poured into 50 ml of water. The precipitate was recrystallized from aqueous ethanol (Tables 1 and 2).

2-Thiocyanato-4-trifluoromethyl-6-phenyl-3-cyanopyridine (V). A mixture of 0.71 g (2.5 mmole) of chloropyridine II and 0.73 g (7.5 mmole) of potassium thiocyanate in 10 ml of DMF was heated at 120-125°C for 3 h, after which it was diluted with 20 ml of water. The precipitate was recrystallized from nitromethane to give 0.48 g (62%) of a product with mp 189-191°C. IR spectrum: 2236, 2221, 1590, and 1545 cm^{-1}. Found: C 55.6; H 2.2; N 13.5; S 10.9%. $C_{14}H_6F_3N_3S$. Calculated: C 55.1; H 2.0; N 13.8; S 10.5%.

4-Trifluoromethyl-6-phenyl-3-cyano-2(1H)-pyridinethione (VI). A mixture of 0.85 g (3 mmole) of chloropyridine II and 2.17 (9 mmole) of $Na_2S \cdot 9H_2O$ in 10 ml of DMF was stirred at 20°C for 10 h, after which it was diluted with 20 ml of water, and the aqueous solution was acidified to pH ~ 4 with hydrochloric acid. The precipitate was recrystallized from aqueous ethanol to give 0.53 g (63%) of a product with mp 178-180°C (mp 179-182°C [9]). IR spectrum: 2800-3200, 2220, 1600 cm^{-1}. Found: C 55.4; H 2.3; N 10.3; S 11.5%. Calculated: C 55.7; H 2.5; N 10.0; S 11.4%.

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