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REACTIONS OF POLYHALOGENOPYRIDINES. 13.* REACTION OF ISOMERIC TETRAFLUORO-CYANOPYRIDINES AND PENTAFLUOROPYRIDINE WITH SODIUM N,N-DIMETHYLDITHIOCARBAMATE

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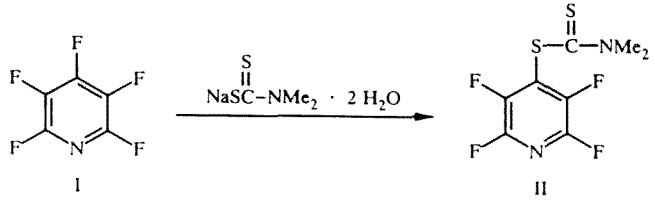
The reactions of isomeric tetrafluoropyridines and pentafluoropyridine with sodium N,N-dimethyldithiocarbamate were studied. Substantial differences were found between the nature of their chemical transformations and those of the chlorine analogs. It was shown that tetrafluorocyanopyridines do not undergo heterocyclization with sodium N,N-dimethyldithiocarbamate to form derivatives of 1,3-dithiolo[4,5-c]pyridine. Instead, extrusion of the CS_2 molecule from the N,N-dimethyldithiocarbamate substituent at position 2 of the pyridine ring occurs.

Earlier [2] we showed that the direction of the reactions of isomeric tetrachloro-2-, tetrachloro-3-, and tetrachloro-4-cyanopyridines and also of pentachloropyridine with sodium N,N-dimethyldithiocarbamate is determined by the structure of the initial polychloropyridine; either the chlorine atoms of the pyridine ring are substituted by dithiocarbamate fragments (pentachloropyridine, tetrachloro-3-cyanopyridine), or subsequent intramolecular processes, leading to derivatives of 1,3-dithiolo[4,5-*c*]pyridine (tetrachloro-2-cyanopyridine) or bis-1,3-dithiolo[4,5-*b*:4′,3′-*e*]pyridine (tetrachloro-4-cyanopyridine) occur. Thus, cyclization takes place by substitution of only the chlorine atoms activated by the cyano group by the negatively charged sulfur atoms of the thioamide fragment [2].

Another approach to activation of the halogen atoms in aromatic compounds (facilitating nucleophilic substitution and, consequently, heterocyclization) may be to substitute the chlorine atoms in the pyridine ring by fluorine atoms [3]. For this purpose in the present work we studied the reaction of pentafluoropyridine and isomeric tetrafluoro-2-, tetrafluoro-3-, and tetrafluoro-4-cyanopyridines with sodium N,N-dimethyldithiocarbamate in order to develop methods for the annelation of 1,3-dithioles to the pyridine ring.

The reactions of polyfluoropyridines with sodium N,N-dimethyldithiocarbamate were conducted in acetone under various temperature regimes. It was found that pentafluoropyridine was substituted by the N,N-dimethyldithiocarbamate fragment at position 4 at room temperature with the formation of compound (II). The latter did not undergo further intramolecular transformations when heated at 50-100°C in various organic solvents.



I II

*For communication 12, see [1].

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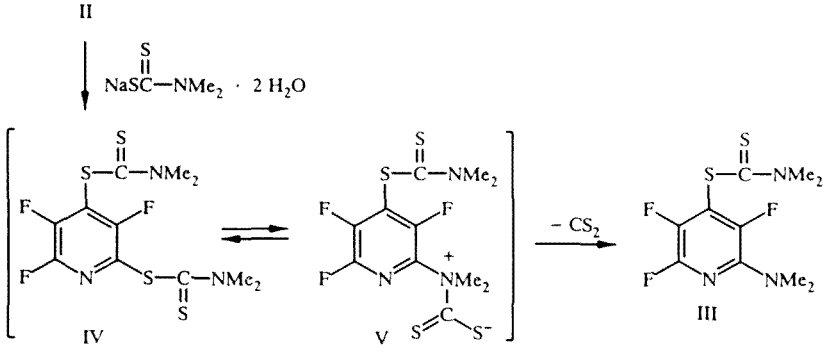
The conclusion about the position of the dithiocarbamate substituent was reached on the basis of analysis of the NMR spectra. Thus, the ^{19}F NMR spectra contain two multiplets in the regions of -12 ppm and -55 ppm, characteristic of the 2-F, 6-F and 3-F, 5-F fluorine atoms respectively [4], confirming the symmetrical structure of compound (II). The presence of the dimethyldithiocarbamate group is confirmed by the presence in the ^{13}C NMR spectrum of signals for the carbon atoms of the two methyl groups at 42.6 and 45.8 ppm and also a signal for the C=S group at 187.6 ppm. In addition, in the ^{1}H NMR spectrum the protons of the methyl groups appear as two singlets at 3.55 and 3.57 ppm [2].

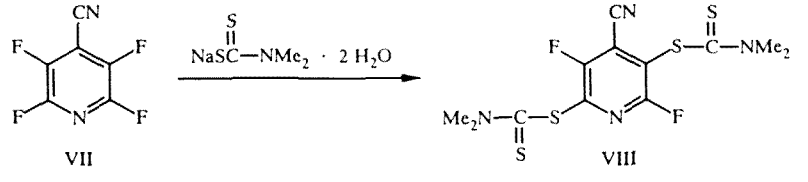
When compound (II) is boiled in acetone in the presence of an excess of sodium N,N-dimethyldithiocarbamate, it is partly transformed into the 2-dimethylamino derivative (III).



According to data in [5], the formation of compound (III) may be due either to the reaction of trace quantities of water with the intermediate 2,4-bis-N,N-dimethyldithiocarbamate derivative (IV) or to intramolecular attack by the nitrogen atom of the N,N-dimethyldithiocarbamate group in the intermediate zwitterion (V). It should be noted that previously processes leading to the transformation of N,N-dimethyldithiocarbamates into dimethylamino derivatives were also only observed for substituents at position 2 of the pyridine ring [2].

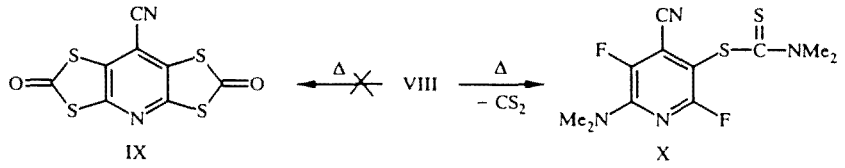
In the ^{13}C NMR spectrum of compound (III) only one signal for the carbon atom of the N,N-dimethyldithiocarbamate substituent at 189.8 ppm and four signals for the two different dimethylamino groups are observed. The group attached to the pyridine ring is characterized by the presence of a pair of signals both at 39.6 and 39.8 ppm in the ^{13}C spectrum and at 3.07 and 3.08 ppm in the ^{1}H spectrum. The signals of the methyl groups of the N,N-dimethyldithiocarbamate substituent are shifted downfield [42.3 and 45.7 ppm (^{13}C) and 3.55 ppm (^{1}H)]. The ^{19}F NMR spectrum of compound (III) is characterized by the signals of the three fluorine atoms at -13.7, -48.1, and -71.4 ppm, belonging to the 6-F, 3-F, and 5-F atoms respectively. The signals of the 3-F and 5-F atoms appear as doublets with characteristic spin—spin coupling constants J_{36} and J_{56} of 26 Hz.

The presence of the cyano group in the molecule of the polyfluoropyridines greatly increases the reactivity of the fluorine atoms in the pyridine ring. This results in the formation of complex mixtures during their reaction with sodium N,N-dimethyldithiocarbamate even at $-30°C$. Attempts to separate these mixtures into the individual components by various methods did not give the desired results. Only in the case of tetrafluoro-4-cyanopyridine (VII) was it possible to produce and isolate with an 81% yield an individual compound, which was the bis-N,N-dimethyldithiocarbamate derivative (VIII) disubstituted at positions 2 and 5 of the pyridine ring, as established by means of the ^{19}F NMR spectrum. It contained two doublets for the fluorine atoms at 14.5 (2-F) and -30.00 (5-F) ppm with spin—spin coupling constants of 26.4 Hz, characteristic of the spin—spin coupling of fluorine atoms situated at positions 2 and 5 of the pyridine ring [4]. The presence of the four methyl groups of the N,N-dimethyldithiocarbamate fragments in the molecule was established by the presence of three singlets in the region of 3.53-3.57 ppm in the ^{1}H NMR spectra. The signal at 3.53 ppm results from the superimposition of the resonance peaks of the protons of the two CH_3 groups.



We supposed that by analogy with its chlorine analog [2] compound (VIII) would be transformed on heating into a derivative of bis-1,3-dithiolo[4,5-*b*:4′,5′-*e*]pyridine (IX). However, the experiments led to a different result. Not even traces

of compound (IX) were detected after compound (VIII) had been boiled in acetone or benzene for 15 min. Instead the main component of the reaction mixture was the product from thermal extrusion of a molecule of CS_2 from the N,N-dimethyldithiocarbamate substituent, i.e., compound (X). It was also the main component (31%) of the reaction mixture produced by boiling compound (VII) with a twofold excess of sodium N,N-dimethyldithiocarbamate in acetone. Here the yield of the dimethyldithiocarbamate derivative was reduced to 15% (compared with the low-temperature synthesis).



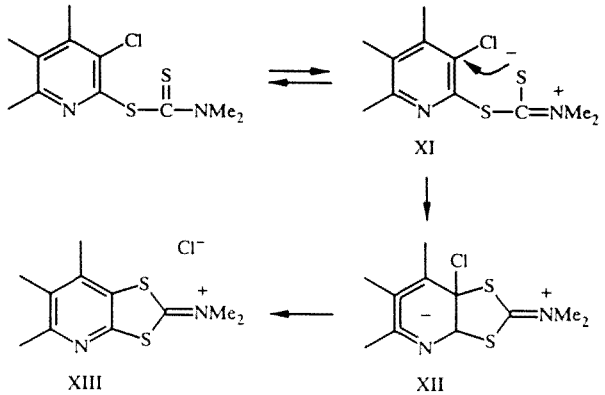
IX X

The ^1H and ^{13}C NMR spectra of compound (X) show an upfield shift of the signals for the methyl groups belonging to the substituent NMe_2 attached to the pyridine ring, whereas the other two signals, belonging to the N,N-dimethyldithiocarbamoyl fragment, do not change their position and appear at 3.52 and 3.54 ppm (^1H) and 4.21 and 4.61 ppm (^{13}C), which agrees with the data presented above for compound (III). The doublets of the fluorine atoms in the ^{19}F NMR spectrum at −12.5 (6-F) and −54.1 (3-F) ppm with a spin—spin coupling constant J_{36} of 27.4 Hz and also the signals of the carbon atoms $C_{(3)}$ and $C_{(6)}$, attached to the fluorine atoms, at 146.2 ppm with spin—spin coupling constant $J_{(3)}3\text{-F} = 254.9$ Hz and at 158.2 ppm with $J_{C(6)}6\text{-F} = 234.0$ Hz and $J_{C(6)}3\text{-F} = 10$ Hz favor a 2,5-disubstituted ring [6].

Comparison of the chemical shifts of the fluorine atoms in the ^{19}F NMR spectra of compounds (II, III, VIII, X) with those in the spectra of the previously described mono- and bisdimethylamino-substituted fluoropyridines [4] made it possible to show that substitution of the N,N-dimethyldithiocarbamate group by a dimethylamino group led to a shift of −20 ppm for the α- and γ-fluorine atoms and −5 ppm for the β-fluorine atoms. It was established from these increments that the dimethylamino group in compound (VIII) is at position 2 of the pyridine ring.

Thus, in the course of the experiments substantial differences were found both in the nature of the reaction between the tetrachloro- and tetrafluoropyridines and sodium N,N-dimethyldithiocarbamate and in the subsequent transformations of their N,N-dithiocarbamate derivatives. First, it was shown that the tetrafluorocyanopyridines are much more active in these reactions; second, subsequent heterocyclization does not occur in spite of the high reactivity of the activated fluorine atoms at positions 3 and 6 of the pyridine ring. Instead the N,N-dimethyldithiocarbamate substituent at the α position to the pyridine nitrogen atom loses a CS_2 group.

The obtained result cannot be explained in terms of the previously proposed ionic mechanism for the formation of 1,3-dithiolopyridine [2], involving intramolecular attack by the negatively charged sulfur atom of the N,N-dimethyldithiocarbamate group in the mesomeric form (XI) followed by the elimination of a Cl^- anion from the σ complex (XII) with the formation of the iminium intermediate (XIII).

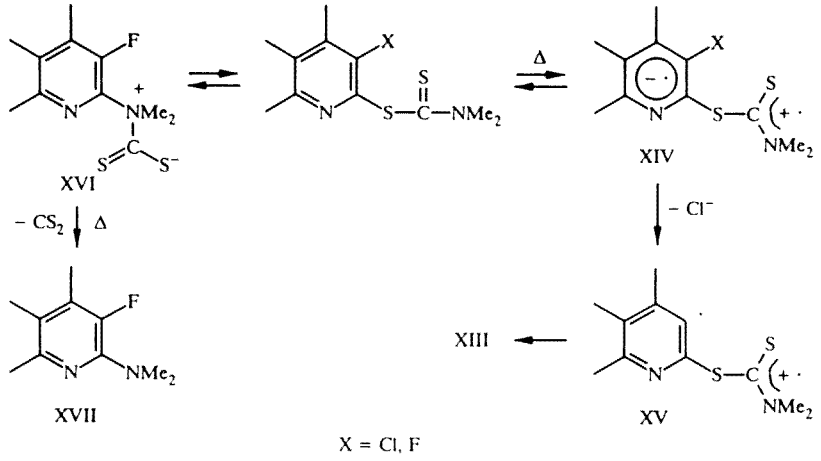


XI

XIII XII

The substantial differences in the direction of the chemical transformations of the N,N-dimethyldithiocarbamates of chloro- and fluoropyridines can probably be explained in the light of the radical-ion nature of the processes that occur. The mechanism of the heterocyclization of the chlorine derivatives includes initial intramolecular thermal migration of an electron from the donating dithiocarbamate substituent to the accepting halogenopyridine ring with the formation of the intermediate (XIV); this is followed by the loss of a chloride ion by the radical-ion of the halogenopyridine fragment [the intermediate (XV)] and, finally, intramolecular recombination of the radicals of the pyridine ring and the dithiocarbamate substituent with the

formation of the iminium intermediate (XIII). It is known that the radical-anions of fluoropyridines have higher stability than other halogenopyridines [7] and do not usually eliminate fluoride ions. Therefore, intramolecular cyclization is unlikely in the case of fluoropyridines, and the main direction of the transformations is loss of the CS_2 molecule from the intermediate zwitterion (XVI) and the formation of the dimethylamino derivative (XVII).



It should be noted that accepting substituents at position 4 of the pyridine ring must stabilize the radical (XV), thereby facilitating the elimination of the chloride ion.

EXPERIMENTAL

The NMR spectra were recorded in solutions in deuterochloroform on a Bruker AC-200 instrument at 200 (^{1}H), 188 (^{19}F), and 50 (^{13}C) MHz with TMS as internal standard and trifluoroacetic acid as external standard. The mass-spectral measurements were made on a Finnigan 4021 instrument (direct injection, ionization energy 70 eV).

Reaction of Pentafluoropyridine with Sodium N,N-Dimethyldithiocarbamate. To a solution of 1.69 g (0.01 mole) of pentafluoropyridine in 50 ml of acetone while stirring at room temperature we added 2.70 g (0.015 mole) of sodium N,N-dimethyldithiocarbamate in 50 ml of acetone. The mixture was then boiled and stirred for 3 h. The solvent was removed under vacuum, and the residue was washed with water and extracted with chloroform. The organic layer was dried with sodium sulfate. The chloroform was distilled, and the residue was chromatographed on a column of silica gel with a 1:1 mixture of benzene and hexane as eluant. We isolated 2.0 g of compound (II) and 0.6 g of compound (III).

2,3,5,6-Tetrafluoro-4-pyridyl N,N-Dimethyldithiocarbamate (II) ($C_8H_6F_4N_2S_2$). The yield was 74%; mp 147-148°C (from hexane), white crystals. M^+ 270. Found, %: C 35.8, H 2.0, N 10.1. Calculated, %: C 35.6, H 2.2, N 10.4. ^{1}H NMR spectrum, ppm: 3.55 (s), 3.57 [c, S(C=S)N$\underline{Me_2}$]. ^{19}F NMR spectrum, ppm: −55.29 (m, 3-F, 5-F), −11.92 (m, 2-F, 6-F). ^{13}C NMR spectrum, ppm: 42.6 (s), 45.8 [s, S(C=S)N$\underline{Me_2}$], 140.8 (m), 145.7 (m, Py), 187.6 (s, C=S).

2-Dimethylamino-3,5,6-trifluoro-4-pyridyl N,N-Dimethyldithiocarbamate (III) ($C_{10}H_{12}F_3N_3S_2$). The yield was 20%; mp 112-113°C (from hexane), beige crystals. M^+ 295. Found, %:C 40.9, H 4.0, N 14.4. Calculated, %: C 40.7, H 4.1, N 14.2. ^{1}H NMR spectrum, ppm: 3.07, (3H, s), 3.08 (3H, s, NMe_2), 3.55 [6H, s, S(C=S)N$\underline{Me_2}$]. ^{19}F NMR spectrum, ppm: −71.36 (d, J_{56} = 25.5 Hz, 5-F), −48.05 (d, J_{36} = 25.5 Hz, 3-F), −13.70 (m, 6-F). ^{13}C NMR spectrum, ppm: 39.6 (s), 39.8 (s, NMe_2), 42.3 (s), 45.7 (s, S(C=S)N$\underline{Me_2}$), 132.6-146.8 (m, Py), 189.8 (s, C=S).

Reaction of Tetrafluoro-4-cyanopyridine with Sodium N,N-Dimethyldithiocarbamate Dihydrate. A. To a solution of 0.176 g (0.001 mole) of tetrafluoro-4-cyanopyridine in 10 ml of acetone, cooled to −30°C, we added dropwise with stirring a solution of 0.358 g (0.002 mole) of sodium N,N-dimethyldithiocarbamate dihydrate, while keeping the temperature no higher than −20°C. The mixture was kept at this temperature for a further 30 min and was then brought to room temperature. The solvent was removed under vacuum, and the residue was washed with water and extracted with chloroform. The organic layer was dried with sodium sulfate. The chloroform was distilled, and the residue was chromatographed on aluminum oxide with benzene as eluant. We obtained 0.31 g of compound (VIII).

B. To a solution of 0.176 g (0.001 mole) of tetrafluoro-4-cyanopyridine in 10 ml of acetone we added with stirring a solution of 0.358 g (0.002 mole) of sodium N,N-dimethyldithiocarbamate dihydrate. The mixture was boiled for 30 min and acquired a dark-red color. The product was then treated as in method A. After chromatography we isolated 0.095 g of compound (X) and 0.055 g of compound (VIII).

3,6-Difluoro-4-cyanopyridyl 2,5-Bis-N,N-dimethyldithiocarbamate (VIII) ($C_{12}H_{12}F_2N_4S_4$). The yield was 81% (method A); 15% (method B); mp 175-176°C (from hexane), yellow crystals. M^+ 378. Found, %: C 38.3, H 3.1, N 14.6. Calculated, %: C 38.1, H 3.2, N 14.8. ^1H NMR spectrum, ppm: 3.53 (6H, s, NMe_2), 3.54 (3H, S, Me), 3.57 (3H, s Me). ^{19}F NMR spectrum, ppm: −30.0 (d, J_{36} = 26.4 Hz, 3-F), −14.52 (d, J_{63} = 26.4 Hz, 6-F).

2-Dimethylamino-3,6-difluoro-4-cyano-5-pyridyl N,N-Dimethyldithiocarbamate (X) ($C_{11}H_{12}F_2N_4S_2$). The yield was 31% (method B); mp 206-207°C (from hexane), light-yellow crystals. M^+ 302. Found, %: C 43.9, H 4.2, N 18.4. Calculated, %: C 43.7, H 4.0, N 18.5. ^1H NMR spectrum, ppm: 3.26 (s), 3.27 (s, $N\underline{Me}_2$), 3.52 (s), 3.54 (6H, s, $S(C{=}S)N\underline{Me}_2$). ^{19}F NMR spectrum, ppm: −51.14 (d, J_{36} = 27.4 Hz, 3-F), −12.46 (d, J_{63} = 27.4 Hz, 6-F). ^{13}C NMR spectrum, ppm: 39.8 (s), 40.0 (s, $N\underline{Me}_2$), 42.1 (s), 46.1 (s, $S(C{=}S)N\underline{Me}_2$), 158.2 (d, $|J_{C(6)F(6)}|$ = 234.0 Hz, $C_{(6)}$), 193.7 (s, C=S).

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