Chemistry of Heterocyclic Compounds, Vol. 32, No. 7, 1996

REACTIONS OF POLYHALOGENOPYRIDINES.
12.* REACTIONS OF 4-PENTAFLUOROETHYLTHIO-2,3,5,6-TETRAFLUOROPYRIDINE WITH NUCLEOPHILIC AGENTS

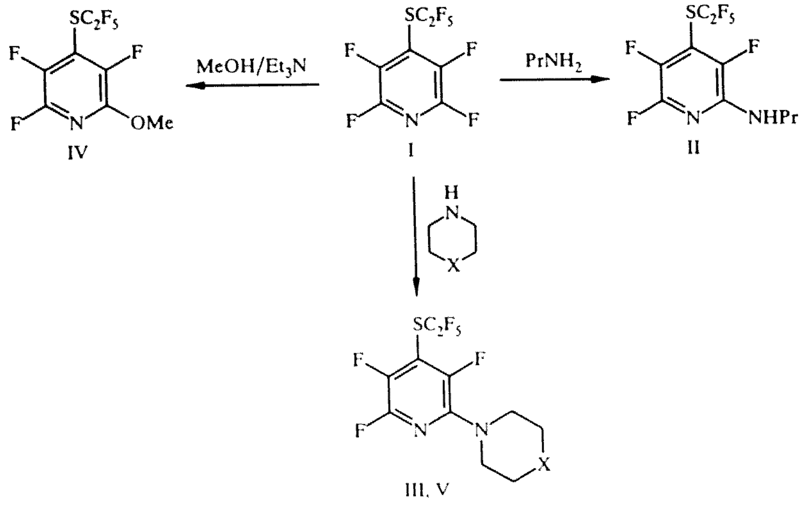
I. V. Efremov, A. M. Sipyagin, and I. A. Pomytkin

The reactions of 4-perfluoroethylthio-2,3,5,6-tetrafluoropyridine with various nucleophilic agents were investigated. It was shown that the pentafluoroethylthio group is inert toward N- and O-nucleophiles.

Earlier [2], we showed that the perfluoroalkylthio group in 4-perfluoroalkylthio-2,3,5,6-tetrachloropyridines is easily substituted by S- and O-containing nucleophilic agents and is considerably more stable toward N-nucleophiles. In the last case the reactions take place with retention of the CF_3S substituent. In spite of the fact that this method of modification makes it possible to obtain a series of new compounds with potential biological activity, containing "superlipophilic" substituents [2], it is restricted to the introduction of only nitrogen-containing fragments.

One of the possible approaches to extension of the range of reactions taking place with retention of the perfluoroalkyl group in the molecules of 4-perfluoroalkylthiopolyhalogenopyridines in the presence of N-, O-, and S-containing agents may be to replace the chlorine atoms in the pyridine ring by fluorine atoms, which are more active in nucleophilic substitution reactions [3].

In the present work we studied the reaction of 4-pentafluoroethylthio-2,3,5,6-tetrafluoropyridine (I), obtained by the method in [4], with a series of nucleophilic agents. It was shown that the pentafluoroalkylthio group in the molecule of compound (I) is more resistant to substitution than in the perchloropyridine analogs [2]. In the presence of both N- and O-nucleophiles substitution of the α-fluorine atoms of the pyridine ring takes place preferentially with retention of the SC_2F_5 group and the formation of compounds (II-IV).



III X = CH_2, V X = O

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*For Communication 11, see [1].

Chernogolovka Institute of Chemical Physics, Russian Academy of Sciences, Chernogolovka. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 932-935, July, 1996. Original article submitted June 22, 1996.

0009-3122/96/3207-0796$15.00

TABLE 1. Mass Spectra of the Compounds Obtained During the Reaction of Compound (I) with a Methanol Solution of Sodium Methanethiolate

Compound	Molecular formula	Main peaks
IV*	$C_8H_3F_5NOS$	313 (100) M^+, 284 (50) $[M-CH_2O]^+$, 192 (12) $[M-C_2F_5]^+$, 119 (22) $[C_4F_3N]^+$
V	$C_9H_6F_7NO_2S$	325 (81) M^+, 275 (100) $[M-CF_2]^+$, 256 (34) $[M-CF_3]^+$, 225 (14) $[M-2CF_2]^+$
VI	$C_6H_3F_4NS$	197 (100) M^+, 164 (15) $[M-SH]^+$, 151 (5) $[M-CH_2S]^+$, 138 (17) $[C_4H_4N]^+$
VII	$C_8H_9F_2NS_3$	253 (93) M^+, 220 (100) $[M-SH]^+$, 207 (13) $[M-CH_2S]^+$
VIII	$C_7H_7F_2NOS$	191 (6) M^+, 144 (5) $[M-SMe]^+$, 143 (100) $[M-SMe-H]^+$
IX	$C_8H_5F_2NO_2$	161 (15) M^+, 144 (5) $[M-OH]^+$, 143 (100) $[M-OH-H]^+$, 129 (7) $[M-OH-Me]^+$
X	$C_{13}H_3F_{11}N_2S_2$	460 (77) M^+, 429 (27) $[M-Me]^+$, 428 (35) $[M-S]^+$, 341 (100) $[M-C_2F_5]^+$, 326 (15) $[M-C_2F_3-Me]^+$, 308 (26) $[M-C_2F_5SH]^+$, 266 (13) $[M-MeO-C_5F_3NS]^+$

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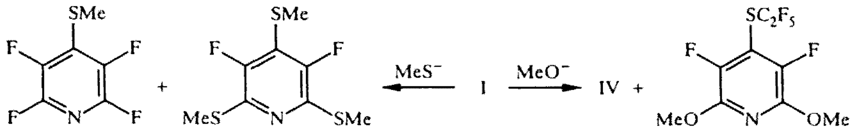
*Mass spectrum coincided fully with the spectrum of compound (IV), obtained in a mixture of methanol and triethylamine.

The position of the substituent in the pyridine ring was determined on the basis of the ^{19}F NMR data from the disappearance of one of the signals for the α-fluorine atoms in the region of −10 ppm [4] and the appearance of two signals for the $F_{(3)}$ and $F_{(5)}$ atoms at −43 to −56 and −65 to −75 ppm. A considerable amount of information on the mutual positions of the fluorine atoms in the polyfluoropyridines can be obtained by examining the spin—spin coupling constants of the fluorine atoms [5].

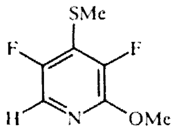
The ^{19}F NMR spectra of compounds (II)-(V) also contain two signals at −6 and −12 ppm, characteristic of the SC_2F_5 group [4]. In the mass spectra there are strong molecular ions, and the presence of the pentafluoroethyl group in the molecule is demonstrated by the presence of peaks for the $[M - C_2F_5]^+$ ions.

In a methanol solution of sodium methanethiolate, compound (I) undergoes more complex transformations. Analysis of the reaction mixture by chromato-mass spectrometry shows the presence of at least seven compounds (Table 1). The formation of four of them can be explained by the occurrence of nucleophilic processes due to the simultaneous presence of the methoxide and methanethiolate anions in the reaction mixture. During the reaction of compound (I) with the methoxide anion, the α-fluorine atoms of the pyridine ring are substituted by methoxy groups with the formation of the monomethoxy (IV) and dimethoxy (V) derivatives with retention of the SC_2F_5 fragment; with the methanethiolate ion the SC_2F_5 group is substituted first, giving 4-methylthiotetrafluoropyridine (VI), and the α-fluorine atoms of the pyridine ring are then substituted, leading to the symmetrical trimethylthiodifluoropyridine (VII).

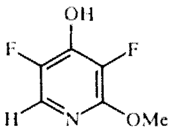


VI VII V

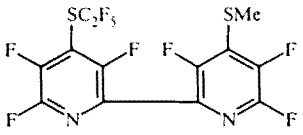
The formation of the other three compounds with the probable structures (VIII-X) may be due to the occurrence of complex substitution and oxidation—reduction processes in the reaction mixture.



VIII



IX



X

EXPERIMENTAL

The IR spectra of the compounds were recorded on an M-80 instrument in thin films or in Vaseline oil. The NMR spectra were recorded in deuterochloroform solutions on a Bruker AC-200 instrument at 200 MHz (^{1}H) and 188 MHz (^{19}F) with TMS as internal standard and trifluoroacetic acid as external standard (^{19}F). The mass-spectral measurements were made on a Finnigan 1420 chromato-mass spectrometer (ionization energy 50-70 eV). The molecular masses were measured on a VG Autospec high-resolution mass spectrometer.

2-Methoxy-4-pentafluoroethylthio-3,5,6-trifluoropyridine (IV) ($C_8H_3F_8NOS$). A 0.2-g sample (0.66 mmole) of compound (I) was kept at room temperature for four days in 3 ml of absolute methanol, to which 0.3 g of triethylamine had been added. We added 20 ml of water to the reaction mixture and extracted the mixture twice with 10 ml of benzene. The extracts were combined, washed with water (10 ml), and dried with anhydrous sodium sulfate. After removing a large part of the solvent we chromatographed the residue on a column of silica gel with benzene as eluant. We obtained 0.1 g (48%) of compound (IV) as a colorless oil. IR spectrum, cm^{-1}: 2960 (C—H), 1218, 1024 (C—O, C—F). PMR spectrum (δ, ppm): 4.06 (s). ^{19}F NMR spectrum, ppm: −6.00 (3F, s), −12.70 (2F, s), −13.80 ($F_{(6)}$, dd), −53.20 ($F_{(3)}$, dd), −65.00 ($F_{(5)}$, dd), J_{35} = 6.0, J_{36} = 30.5, J_{56} = 21.5 Hz. Mass spectrum, m/z (I_{rel}, %): 313 (100) M^+, 284 (43) $[M - CH_2O]^+$, 194 (11) $[M - C_2F_5]^+$, 119 (22) $[C_4NF_3]^+$. Found: M^+ 312.9800. $C_8H_3F_8NOS$. Calculated: M^+ 312.9808.

Reaction of Compound (I) with Nitrogen-Containing Nucleophiles. To a solution of 1.32 mmole of the nucleophile in 5 ml of absolute methanol at room temperature with stirring we added a solution of 0.2 g (0.66 mmole) of compound (I) in 2 ml of methanol. The homogeneous mixture was left at room temperature until the reaction was complete, which took from 2 to 24 h (monitored by TLC by the disappearance of the spots of the initial compounds). The reaction mixture was added to 20 ml of water and extracted twice with 10 ml of benzene. The extracts were combined, washed with water (10 ml), and dried with anhydrous sodium sulfate. A large part of the solvent was evaporated, and the reaction products were isolated from the residue by column chromatography on silica gel with benzene as eluant.

4-Pentafluoroethylthio-2-propylamino-3,5,6-trifluoropyridine (II) ($C_{10}H_8F_8N_2S$). The yield was 0.145 g (65%), and the product was a colorless oil. IR spectrum, cm^{-1}: 3460 (N—H), 2972, 2940, 2880 (C—H), 1220, 1112 (C—F). PMR spectrum (δ, ppm): 0.99 (3H, t), 1.66 (2H, m), 3.39 (2H, dd), 4.75 (1H, bs). ^{19}F NMR spectrum, ppm: −5.95 (3F, s), −12.81 (2F, s), −13.82 ($F_{(6)}$, dd), −57.49 ($F_{(3)}$, dd), −74.57 ($F_{(5)}$, dd), J_{35} = 6.3, J_{36} = 30.4, J_{56} = 25.8 Hz. Mass spectrum, m/z (I_{rel}, %): 340 (22), M^+, 311 (100) $[M-C_2H_5]^+$, 192 (74), $[M-C_2H_5—C_2F_5]^+$. Found: M^+ 340.0288. $C_{10}H_8F_8N_2S$. Calculated: M^+ 340.0280.

4-Pentafluoroethylthio-2-piperidino-3,5,6-trifluoropyridine (III) ($C_{12}H_{10}F_8N_2S$). The yield was 0.21 g (83%), and the product was a colorless oil. IR spectrum, cm^{-1}: 2944, 2860 (C—H), 1228, 1108 (C—F). PMR spectrum (δ, ppm): 1.66 (6H, bs), 3.43 (4H, bs). ^{19}F NMR spectrum, ppm: −5.95 (3F, s), −11.73 ($F_{(6)}$, dd), −12.88 (2F, s), −43.64 ($F_{(3)}$, dd), −68.24 ($F_{(5)}$, dd), J_{35} = 5.8, J_{36} = 29.3, J_{56} = 25.0 Hz. Mass spectrum, m/z (I_{rel}, %): 366 (79) M^+, 365 (34) $[M-H]^+$, 247 (100) $[M-C_2F_5]^+$, 119 (20) $[C_4NF_3]^+$. Found: M^+ 366.0432. $C_{12}H_{10}F_8N_2S$. Calculated: M^+ 366.0437.

2-Morpholino-4-pentafluoroethylthio-3,5,6-trifluoropyridine (V) ($C_{11}H_8F_8N_2OS$). The yield was 0.17 g (70%), and the product was a colorless oil. IR spectrum, cm^{-1}: 2946, 2868 (C—H), 1228, 1110 (C—F). PMR spectrum (δ, ppm): 3.5 (6H, m), 3.8 (4H, m). ^{19}F NMR spectrum, ppm: −82.54 (3F, s), −87,83 ($F_{(6)}$, dd), −89.34 (2F, s), −120.96 ($F_{(3)}$, dd), −142.63 ($F_{(5)}$, dd), J_{35} = 5.4, J_{36} = 30.5, J_{56} = 24.5 Hz. Mass spectrum, m/z (I_{rel}, %): 368 (53) M^+, 337 (20) $[M - CH_3O]^+$, 310 (36) $[M-CH_3O—C_2H_4]^+$, 283 (100) $[M-CH_3O—C_2H_4—HCN]^+$, 249 (11) $[M-C_2F_5]^+$, 119 (24) $[C_4NF_3]^+$. Found: M^+ 368.0232. $C_{11}H_8F_8N_2OS$. Calculated: M^+ 368.0230.

Reaction of Compound (I) with Sodium Methanethiolate. To a solution of 0.465 g (0.66 mmole) of sodium methanethiolate in 5 ml of absolute methanol at room temperature with stirring we added a solution of 0.2 g (0.66 mmole) of compound (I) in 2 ml of methanol. After 2 h the homogeneous mixture was poured into 20 ml of water and extracted twice with 10 ml of benzene. The extracts were combined, washed with water (10 ml), and dried with anhydrous sodium sulfate. After evaporation of the solvent the residue was a mobile yellow oil.

Chromato-mass spectrometric analysis showed the presence of a large number of components in the mixture. The most important were compounds (VI)-(VIII).

The work was carried out with financial support from the International J. Soros Research Fund (grant RE 1300).

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