REACTION OF MERCAPTOPYRIMIDINE DERIVATIVES WITH PERFLUORO OLEFINS

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The reaction of methyl and hydroxy derivatives of 2- and 4-mercaptopyrimidines with perfluoropropylene and perfluoro-1-hexene was investigated. The corresponding perfluoroalkenylthio-substituted pyrimidines are described.

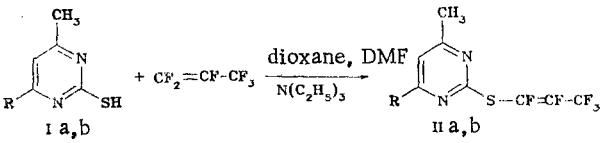
We have previously described a number of di- and trifluoromethylthio derivatives of pyrimidine and have studied some of their reactions [1-3]. The synthesis of these fluoroalkylthiopyrimidines was accomplished by difluoromethylation of mercaptopyrimidines with difluorocarbene, which was generated from difluorochloromethane (khladon-22) by the action of alkali, and also by ion-radical perfluoroalkylation.

The aim of the present research was to investigate the reaction of mercaptopyrimidines with fluoro olefins. It is known that the latter react with S-nucleophiles to give, depending on the conditions, products of addition to the electrophilic double bond of the fluoro olefin or products of substitution of the fluorine atom in the terminal difluoromethylene group [4].

As subjects of this investigation we used 2-mercapto-4,6-dimethyl- (Ia) [5], 2-mercapto-6-hydroxy-4-methyl- (Ib) [6], and 4-mercapto-6-methylpyrimidine (III) [7], which were subjected to reaction with perfluoropropylene (PRP) and perfluoro-1-hexene (PFH).

The reaction of mercaptopyrimidines Ia, b with PFP was carried out in an autoclave in dioxane–DMF (the latter was used as a solvent for the mercaptopyrimidine derivatives that were only slightly soluble in dioxane) in the presence of triethylamine as the base at 100°C. Products of vinyl substitution of the fluorine atom in the PFP molecule, viz., 2-perfluoropropenylthio-4,6-dimethyl- (IIa) and 2-perfluoropropenylthio-6-hydroxy-4-methylpyrimidine (IIb), respectively, were isolated from the reaction mixture.

The fluoroalkenylation of mercaptohydroxypyrimidine Ib takes place at the sulfur atom; this is confirmed by data from the IR spectra – the absence of a band of vibration of the SH group and the presence of a broad band of stretching vibrations of a hydroxy group tied up in an intermolecular hydrogen bond at 3400 cm^{-1}.



I a,b II a,b

I, II a R=CH_3; b R=OH

When fluoroalkenylation is carried out with excess triethylamine, it leads to significant resinification. It is interesting to note that under the same conditions the yield of the fluoroderivative (IIa) of dimethylpyrimidine is almost two times higher than the yield of hydroxy-substituted IIb. Taking into account the fact that the molar ratio of the reagents, viz., starting dimethylmercaptopyrimidine Ia and triethylamine, is 4:1, this can be explained by assuming that the more basic dimethylpyrimidine Ia is evidently capable of tying up the hydrogen fluoride that is liberated during fluoroalkenylation. In fact, the reaction of mercaptopyrimidine Ia with PFP also takes place in the absence of triethylamine to give the corresponding S-fluoroalkenylation product IIa but in lower yield.

Fluoroalkenylthiopyrimidines IIa and IIb are colorless liquids that can be distilled in vacuo without decomposition. Their compositions and structures were confirmed by the results of elementary analysis and NMR and mass spectroscopy.

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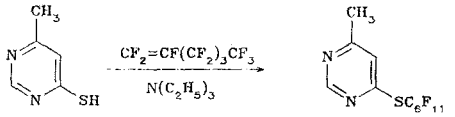
It follows from the ratios of the integral intensities of the corresponding signals in the ^{19}F NMR spectra of IIa, b that these products are mixtures of cis and trans isomers in a ratio of ∿1:2. This is also confirmed by data from gas chromatography.

The following signals were observed in the ^{19}F NMR spectrum of fluoropyrimidine IIa (the assignment of the signals was made on the basis of the data in [8]): F^1 41.1, F^2 71.0, CF_3, −10.6 ppm, $J_{(F^1,F^2)}$ = 146 Hz (trans isomer), F^1 21.6, F^2 55.4, CF_3, −12.7 ppm, $J_{(F^1,F^2)}$ = 20 Hz (cis isomer). Signals of the 5-H proton of the pyrimidine ring (singlet at 6.9 ppm) and of the protons of two methyl groups (singlet at 2.5 ppm) with an intensity ratio of 1:6 are noted in the PMR spectrum of this compound.

4-Mercapto-6-methyl- (III) and 2-mercapto-4,6-dimethylpyrimidine (Ia) were subjected to reaction with PFH.

1-(6-Methyl-4-pyrimidinylthio)perfluorohexene (IV) was obtained in the form of a liquid mixture of isomers as a result of the reaction of methylmercaptopyrimidine III with an equivalent amount of PFH and triethylamine in a mixture of solvents that ensured dissolving of the mercaptopyrimidine at 60°C for 20 h.



III IV

The compositions and structures of the reaction products can be judged from the results of elementary analysis and the NMR and mass spectra. Three singlets, viz., a 2-H singlet at 6.30, a 5-H singlet at 4.56, and a CH_3 singlet at 2.76 ppm, with an integral intensity ratio of 1:1:3, respectively, are observed in the PMR spectrum.

The ^{19}F NMR spectrum contains several groups of signals at 1.6-61.2 ppm. Pairs of doublets with spin—spin coupling constants (SSCC) that can be assigned to cis and trans isomers of pyrimidinylthioperfluorohexene IV are observed. The character of the signals indicates that isomers that contain both terminal (—S—CF=CF—) and internal double bonds in the perfluorohexenyl group are also present in this mixture.

The literature contains data that provide evidence for the possibility of migration of the terminal double bond of a fluoro olefin under the influence of an attacking nucleophile [9].

A liquid mixture of isomeric 1-(4,6-dimethyl-2-pyrimidinylthio)perfluorohexenes (V), which, as in the preceding case, according to data from the ^{19}F NMR spectra, is a mixture of cis and trans isomers that contain terminal and internal double bonds,* was obtained under similar conditions from dimethylmercaptopyrimidine Ia and PFH.

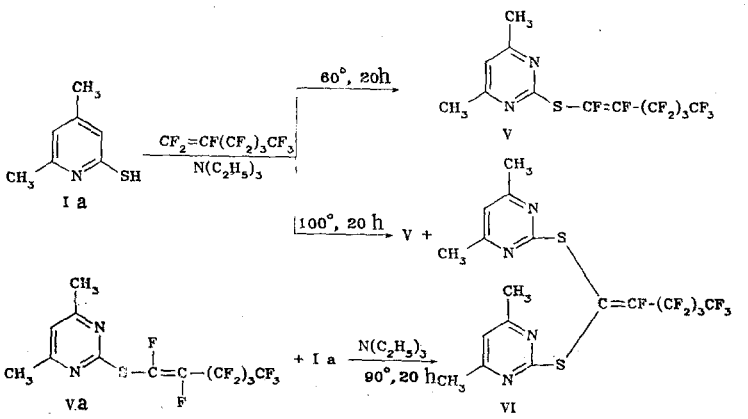
By means of preparative gas chromatography of this mixture we were able to isolate a fraction rich in the trans isomer of terminal pyrimidinylthioperfluorohexene Va. A multiplet at 2.24 ppm (fluorine atoms of a perfluorobutyl fragment) and a doublet centered at 55.5 ppm with SSCC ≈ 140 Hz are present in its ^{19}F NMR spectrum.

When the temperature is raised to 100°C, primarily a crystalline product of the reaction of PFH with 2 moles of mercaptopyrimidine Ia, viz., 1,1-bis(4,6-dimethyl-2-pyrimidinylthio)perfluorohexene (VI), is formed along with a mixture of isomeric monosubstituted V as a result of the reaction of mercaptopyrimidine Ia with PFH.

Its structure was confirmed by independent synthesis from monosubstituted Va and mercaptopyrimidine Ia in the presence of triethylamine. Signals that are characteristic for a —CF=CF— fragment are absent in the ^{19}F NMR spectrum of VI. The formation of a bis derivative is evidently explained by the fact that the electrophilicity of pyrimidinylthioperfluorohexene Va in this reaction is higher than that of PFH.

Bis product VI was obtained in high yield under milder conditions by the action of PFH on the lithium derivative of mercaptopyrimidine Ia.

*The existence of double bonds in IV and V was confirmed qualitatively by ozonation (with an ozonator of the ADS-3 type) in solution in CCl_4.



In contrast to the corresponding di- and trifluoromethylthio derivatives of pyrimidine [2, 3], fluoroalkenylthiopyrimidines IIa and V are not oxidized to sulfoxides by the action of m-chloroperbenzoic acid.

EXPERIMENTAL

The individuality of the compounds obtained was established by thin-layer chromatography (TLC) on activity II Al_2O_3 in a benzene–methanol system (10:1) with irradiation with UV light and also by means of gas chromatography with a Tsvet-4 chromatography with a flame-ionization detector and a column packed with 11% PMFS [l = 3 m, D = 3 mm, thermostat temperature 150°C, and carrier-gas (nitrogen) flow rate 20 ml/min]. Preparative gas-liquid chromatography (GLC) was carried out with a PAKhV-3 chromatograph with a catharometer as the detector and a column packed with 10% PMFS on Chromosorb (l = 1 m, D = 3 mm, thermostat temperature 150°C, and helium flow rate 1 liter/min). The PMR spectra were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the external standard. The ^{19}F NMR spectra were recorded with a Tesla 487B spectrometer (80 MHz) with trifluoroacetic acid as the external standard. The IR spectra of KBr pellets of the compounds were recorded with a Specord IR-71 spectrometer. The UV spectra of $\approx 10^{-4}$ mole/liter solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer.

The mass spectra were recorded with an MS-30 spectrometer with a DS-50 computer system at an ionizing voltage of 70 eV and a source temperature of 200°C. Molecular-ion peaks with m/z values corresponding to the molecular masses of the synthesized fluoroalkenyl derivatives of pyrimidine were observed in the spectra. The results of elementary analysis and the physical constants of the synthesized compounds are presented in Table 1.

2-(Perfluoropropenyl)thio-Substituted Pyrimidines (IIa,b). A 250-ml stainless steel autoclave was charged with 0.05 mole of the corresponding pyrimidine, 0.012 mole of anhydrous triethylamine, 25 ml of dioxane, and 15 ml of dimethylformamide (DMF). The autoclave was cooled to −70°C and evacuated, 0.06 mole of PFP was introduced, and the mixture was heated with shaking at 100°C for 7 h. It was then cooled, and the brown mass was poured into water. The product was extracted with ether, and the extract was washed with water and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was distilled in vacuo.

Pyrimidinylthioperfluorohexenes (IV, V). A 5-mmole sample of perfluoro-1-hexene [10] and 1 ml of triethylamine were added to a solution of 7.5 mmole of the corresponding pyrimidine in a mixture of 8 ml of anhydrous DMF, 2 ml of anhydrous DMSO, and 2 ml of dry THF, and the mixture was heated with vigorous stirring on an oil bath at 60-65°C for 20 h. It was then cooled and poured into a tenfold volume of water, and the product was extracted with ether (three 20-ml portions). The extract was washed successively with water, 10% HCl, 10% NaOH solution (three 10-ml portions for removal of the excess mercaptopyrimidine), and water and dried with $MgSO_4$. The ether was removed by distillation, and the mixture of cis and trans isomers was distilled in vacuo. Individual trans isomer Va was isolated from the mixture of isomers of V by preparative gas chromatography.

1,1-Bis(4,6-dimethyl-2-pyrimidinylthio)perfluorohexene (VI). A) A reaction mixture prepared as indicated above was sealed in a rotating glass ampul with a stirrer and heated on

TABLE 1. Perfluoroalkenylthio-Substituted Pyrimidines

Compound	bp, °C (mm)	Found, %					Empirical formula	Calc., %					n_D^{20}	R_f	Yield, %
		C	H	F	N	S		C	H	F	N	S			
IIa	83—84 (5)	40,0	2,5	35,0	9,8	11,8	$C_9H_7F_5N_2S$	40,0	2,6	35,2	10,4	11,9	1,4520	0,67	50
IIb	72—74 (0,4)	35,1	1,7	35,1	10,0	11,5	$C_8H_5F_5N_2OS$	35,3	1,8	35,0	10,3	11,8	1,4381	0,75	22
IV	62—64 (0,2)	32,5	1,3	51,0	6,6	7,8	$C_{11}H_5F_{11}N_2S$	32,5	1,3	51,5	6,9	7,9	1,4144	0,61	48
V	69—71 (0,4)	34,4	1,6	49,7	6,5	7,4	$C_{12}H_7F_{11}N_2S$	34,3	1,7	49,7	6,7	7,6	1,4178	0,64	64
Va	72—73 (0,4)	34,2	1,6	49,7	6,6	7,5	$C_{12}H_7F_{11}N_2S$	34,3	1,7	49,7	6,7	7,6	1,4185	—	—
VI	117—118*	40,1	2,6	34,5	10,2	12,0	$C_{18}H_{14}F_{10}N_4S_2$	40,0	2,6	35,2	10,4	11,9	—	—	33, 58, 68

*This is the melting point.

an oil bath at 100°C for 20 h, after which it was worked up as indicated above. The finely crystalline precipitate of bis derivative IV that formed from the ether extract upon standing was separated by filtration. A mixture of isomers of monosubstituted V was isolated by vacuum distillation of the residue obtained after evaporation of the ether mother liquor.

B) A 0.88-g sample of thoroughly dried mercaptopyrimidine Ia was added to a solution of lithium methoxide (from 0.047 g of lithium and 50 ml of anhydrous methanol), and the mixture was refluxed for 30 min. The methanol was then removed by distillation to dryness in a stream of nitrogen, and the residue was dried in vacuo (0.01 mm) at 60°C for 2 h. The yield of lithium pyrimidinylmercaptoate was 0.89 g (92%). It was dissolved in a mixture of anhydrous DMF, DMSO, and THF in the ratio indicated above, 2 g (6 mmole) of distilled perfluoro-1-hexene was added, and the mixture was stirred at 60°C for 4 h. The cooled solution was poured into a tenfold volume of water, and the aqueous mixture was extracted with ether. The extract was washed with 10% NaOH and water and dried with $MgSO_4$. Acidification of the alkaline washings gave the starting mercaptopyrimidine. The ether was removed by distillation, and the residue, which began to crystallize, was dissolved in benzene. The benzene solution was refluxed with activated charcoal, and the benzene was evaporated.

C) A 0.3-g sample of mercapto derivative Ia and two drops of triethylamine were added to a solution of 0.4 g of fluoroalkenylthiopyrimidine Va in a mixture of anhydrous DMF, DMSO, and THF, and the mixture was stirred at 90°C for 20 h. It was then poured into water, and the product was extracted with ether. The ether extracts were washed with 10% HCl, 10% NaOH, and water and dried.

No melting-point depression was observed for mixtures of samples of VI obtained by methods A-C.

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