LITERATURE CITED

1. O. A. Burova, I. D. Bystryakova, N. M. Smirnova, and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, No. 5, 662 (1990).
2. J. L. Shim, R. Niess, and A. D. Broom, *J. Org. Chem.*, **37**, 578 (1972).
3. H. A. Parish and R. D. Gilliom, Jr., *J. Med. Chem.*, **25**, 98 (1982).
4. E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch, and C. A. Nichol, *J. Med. Chem.*, **23**, 327 (1980).
5. S. Nishigaki, K. Senda, and F. Joneda, *Chem. Pharm. Bull.*, **19**, 1526 (1971).
6. N. D. Heindel and P. D. Kennewel, *Chem. Commun.*, No. 1, 38 (1969).
7. N. A. Ryabokon', N. A. Andreeva, M. P. Nemeryuk, A. F. Keremov, V. A. Chernov, and T. S. Safonova, *Khim.-farm. Zh.*, No. 4, 15 (1975).
8. E. B. Berkhin and Yu. I. Ivanov, *Methods for the Experimental Investigation of the Kidneys and Water-Salt Metabolism* [in Russian], Alt. Kn. Izdat., Barnaul (1972).

4-TRIFLUOROMETIIYLPYRIMIDINES

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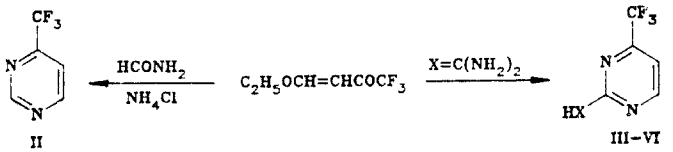
It is shown that β-alkoxyvinyl trifluoromethyl ketones are convenient reagents for the synthesis of 4-trifluoromethylpyrimidines that contain a hydrogen atom or hydroxy, mercapto, and amino groups in the 2 position. The NMR, IR, and UV spectra of the synthesized compounds were studied. The absorption bands in the IR spectra of some of the 4-trifluoromethylpyrimidines were assigned empirically.

4-Trifluoromethyl-substituted pyrimidines are of interest as potential physiologically active substances: among them are known antibacterial [1, 2] and antidiabetic compounds and herbicides [3]. Pyrimidines that contain a trifluoromethyl group in the 4 position and an alkyl group in the 6 position have traditionally been synthesized from the corresponding β-diketones [2, 3]. The multistep character of the synthesis of 5- and 6-unsubstituted 4-trifluoromethylpyrimidines is due to the difficulty in obtaining trifluoroacetylacetaldehyde, which has not yet been described in the literature. We recently proposed that the accessible β-alkoxyvinyl trifluoromethyl ketones be used for the synthesis of trifluoromethyl-containing heterocycles [4].

The aim of the present research was to synthesize 4-trifluoromethylpyrimidines by means of β-ethoxyvinyl trifluoromethyl ketone (I) and study the physicochemical properties of the heterocycles obtained.



III X=O; IV X=S; V X=NH; VI X=$NSO_2C_6H_4NHCOCH_3$-4

Pyrimidine II with a trifluoromethyl group in the 4 position was obtained in low yield by heating butenone I with ammonium chloride in formamide. Pyrimidine II is a volatile liquid with a characteristic odor. In its PMR spectrum (Table 1) the signal of the 5-H proton has the form of a doublet of doublets as a result of spin-spin coupling (SSC) with the other two protons of the pyrimidine ring, although the proton in the 2 position shows up in the form of a broad singlet (rather than a doublet) with a spin-spin coupling constant (SSCC) of 1.5 Hz.

The reaction of butenone I with gem-diamino compounds leads to 4-trifluoromethylpyrimidines containing diverse functional groups in the 2 position. Heating butenone I with urea at 120-130°C gives pyrimidine III, the yield of which increases from 35 to 75% when the reaction is carried out in the presence of hydrochloric acid for 2 days at 20°C. Compound III is a colorless crystalline substance that is only slightly soluble in water and low-polarity organic solvents.

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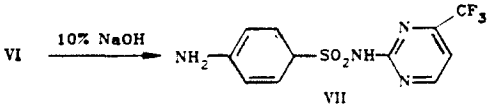
TABLE 1. ^1H and ^{19}F NMR Spectra of 4-Trifluoromethylpyrimidines II-X

Compound	Solvent	Chemical shifts, δ, ppm				SSCC, $J_{H_5H_6}$, Hz
		5-H, d	6-H	other protons	CF_3	
II	CD_2Cl_2	7,6 d*	8,95d	9,3 br.s (2,H)	70,3s	5,0
III	$(CD_3)_2CO$	6,8	8,4br.d	—	71,2br .s	6,1
IVa	CCl_4	6,6	8,2d	3,9 br.s (SH)	70,8s	4,8
IVa	CD_2Cl_2	7,3	8,6d	4,6 br.s (SH)	70,8s	5,1
IVb	CD_2Cl_2	7,4	8,8d	8,6 br.s (NH)	69,9br.s	5,1
IVb	CD_3CN	7,1	8,1br.d	12,5br.s (NH)	70,5br.s	6,1
V	$(CD_3)_2CO$	6,9	8,5d	6,5br.s (NH_2)	70,4br.s	4,8
VII	CD_3OD	7,25	8,65d	7,7 d, 6,5 d (C_6H_4)	70,0s	5,0
VIII	$CDCl_3$	7,2	8,7d	4,0 s (OCH_3)	70,7s	4,8
IX	CD_2Cl_2	6,5	7,9br.d	3,5 s (NCH_3)	70,6s	6,5
X	$CDCl_3$	7,2	8,7d	2,5 s (SCH_3)	70,9s	4,9

*Note that $J_{H_2H_5}$ = 1.5 Hz.

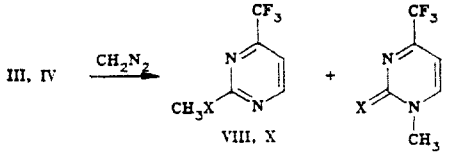
The reaction of butenone I with thiourea in the presence of hydrochloric acid proceeds smoothly to give 2-mercaptopyrimidine IV — a volatile red-orange crystalline substance with a weak odor. A solution of IV in CCl_4 is colorless. The color of the solutions becomes more intense as the polarities of the solvents increase in the order $CHCl_3$—CH_2Cl_2—CH_3CN; this is associated with thione—thiol tautomerism (see below).

2-Aminopyrimidines V and VI were obtained by condensation of butenone I with guanidine and its sulfo derivative, respectively. Pyrimidine V is formed in 45% yield when the reaction is carried out with guanidinium chloride in anhydrous ethanol in the presence of sodium ethoxide; the yield increases to 60% when butenone I is heated with guanidinium carbonate in benzene. Aminopyrimidine V was previously synthesized in low yield by a laborious three-step method and was used to obtain an antibacterial preparation — a trifluoromethyl-containing analog of sulfazine [1]. We obtained this sulfonamide (VII) in two steps in 34% overall yield.



VII

We alkylated pyrimidines III and IV with diazomethane to obtain compounds with a fixed isomeric structure in order to interpret the spectral characteristics of III and IV, which exist in a tautomeric equilibrium. Products of alkylation at both the oxygen atom and the nitrogen atom — VIII and IX, respectively — are formed in the reaction of a suspension of pyrimidine III with diazomethane in ether at 0°C. Using ^1H and ^{19}F NMR spectroscopy we established from the ratio of the integral intensities of the signals of the methyl and trifluoromethyl groups that the ratio of products VIII and IX in the reaction mixture is 9:1. No difficulty is encountered in separating the reaction products, since pyrimidine IX is insoluble in pentane, whereas VIII is soluble. Methoxypyrimidine VIII is a colorless liquid with a characteristic odor and crystallizes on cooling below 0°C. Pyrimidinone IX is a pale-yellow crystalline substance. The accurate determination of the regiospecificity of the alkylation of the nitrogen atoms of unsymmetrical pyrimidinones is a complex task. However, the lower accessibility of the nitrogen atom in the 3 position due to the steric hindrance of the two ortho substituents probably leads to the formation of a product of methylation at the nitrogen atom in the 1 position of the ring.



VIII, IX X=O; X X=S

VIII, X

IX

Methylation of mercaptopyrimidine IV under similar conditions leads to a single product — methylthiopyrimidine X, which is a yellow liquid with an unpleasant odor and crystallizes at 0°C.

The compositions and structures of the synthesized 4-trifluoromethylpyrimidines were confirmed by the results of elementary analysis and by ^1H and ^{19}F NMR spectral data. The PMR spectra of pyrimidines II-X contain doublets of 5-H and 6-H protons with spin-spin coupling constants (SSCC) of 4.8-6.5 Hz. Singlets of trifluoromethyl groups are present in the ^{19}F NMR spectra at 70-71 ppm at strong field relative to CCl_3F; the chemical shift of the

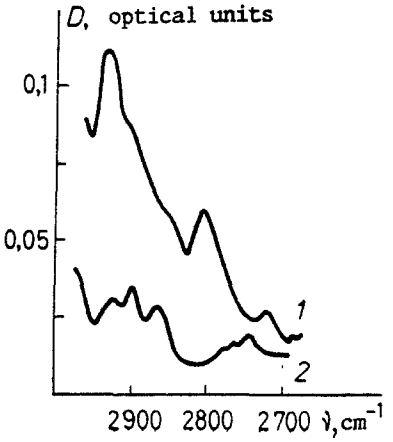


Fig. 1

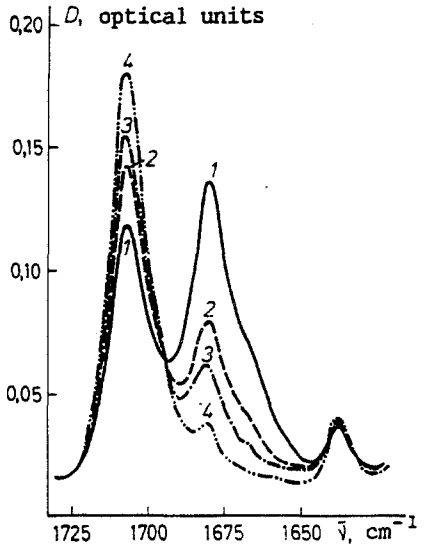


Fig. 2

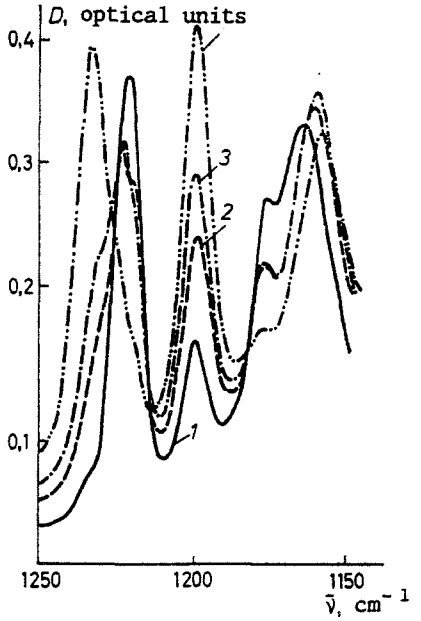


Fig. 3

Fig. 1. IR spectrum of IV in a KBr pellet (1) and in solution (c = 10^{-2} M, d = 10 mm) in CCl_4 (2).

Fig. 2. IR spectrum of pyrimidine III (in CH_2Cl_2): 1) c = $1.4 \cdot 10^{-3}$ M, d = 1 mm; 2) c = $0.47 \cdot 10^{-3}$ M, d = 3 mm; 3) c = $0.28 \cdot 10^{-3}$ M, d = 5 mm; 4) c = $0.07 \cdot 10^{-3}$ M, d = 20 mm.

Fig. 3. IR spectra of pyrimidine IV at 1150-1250 cm^{-1} (in CCl_4 and CH_3CN and mixtures of them): 1) 100% CCl_4; 2) 10% CH_3CN; 3) 20% CH_3CN; 4) 100% CH_3CN (concentration 0.1 M, layer thickness 0.126 mm).

trifluoromethyl groups is virtually independent of the nature of the substituent in the 2 position. The amino group of pyrimidine V shows up in the PMR spectrum as a broad singlet at 6.5 ppm, while the proton bonded to the nitrogen atom in 2-oxopyrimidine III is not recorded over the 0-20 ppm range in either deuteroacetone or d_6-DMSO, probably because of rapid deuterium exchange. The presence in the PMR spectra of pyrimidine IV of two pairs of doublets of 5-H and 6-H protons, the ratio of the integral intensities of which depends on the polarity of the solvent, attests to the existence of thione—thiol tautomerism. Only the thiol form is present in solution in CCl_4, only the thione form is present in solution in CD_3CN, while both tautomers of pyrimidine IV, with 80-90% of the thiol form in the mixture, are present in solution in CD_2Cl_2.

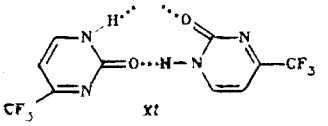
We studied the effect of the trifluoromethyl group in the 4 position of the ring on the electron structures of pyrimidines III and IV by IR and UV spectroscopy [5, 8-12]. On the basis of the results obtained we made an

empirical assignment of some of the frequencies of the IR spectra of pyrimidines III, IV, and VIII-X, as well as the bands of the in-plane and out-of-plane electron transitions of the pyrimidine ring in these compounds (Tables 2 and 3).

Two absorption bands of C–H vibrations of the pyrimidine ring, which correspond to $\nu_{C_5\text{-}H}$ and $\nu_{C_6\text{-}H}$ vibrations [6, 11], appear in the IR spectra of III, IV, and VII-X at 3050-3100 cm^{-1}. The assignment of the band of the stretching vibrations of the N–H bond of the pyrimidine ring is open to discussion [5, 6, 12]. On passing from the crystalline state to a solution in an inert solvent (Fig. 1) the $\nu_{NH\cdots S}$ band at 2936 cm^{-1} virtually vanishes, since IV exists primarily in the thiol form in inert nonpolar solvents. This band is also absent in the spectrum of pyrimidine X. As in the case of 2-pyrimidinone, which in the solid phase is completely self-associated and has a $\nu_{NH\cdots O}$ band at 2820 cm^{-1} [13, 14], we assigned the band at 2874 cm^{-1} in the spectrum of III to the $\nu_{N\text{-}H}^{ass}$ band of an intermolecular hydrogen bond. In solutions of III in weakly polar solvents association via a hydrogen-bond mechanism is observed (Fig. 2) up to concentrations of $c = 10^{-3}$ M, at which we could not record a $\nu_{N\text{-}H}^{mon}$ band because of the high absorption of the solvent (cuvettes with $d \geq 10$ mm were used).

The assignment of the vibrations of the C=S group in heterocyclic systems raises certain difficulties, since it is generally mixed with ring deformation vibrations [5, 6, 12]. According to Bellamy [15], in the spectra of aryl thioketones the $\nu_{C=S}$ band lies at 1205-1225 cm^{-1}. Calculations made for thiopyrimidines [6, 12] showed that the band at 1210 cm^{-1} is a composite of $\nu_{C=S}$ and the $\delta_{C\text{-}H}$ in-plane deformation vibrations. Proceeding from these considerations, the band of medium intensity at 1200-1202 cm^{-1} in the spectrum of pyrimidine IV was assigned to the $\nu_{C=S} + \delta_{C\text{-}H}$ composite.

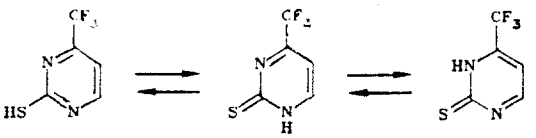
An intense band at 1654 cm^{-1} (in a KBr pellet) is observed in the spectrum of III. Two bands at 1710 and 1676 cm^{-1} are observed in the spectra of dilute solutions in weakly polar solvents (Fig. 2). A decrease in the concentration of pyrimidine III leads to redistribution of the intensities of the indicated bands; in our opinion, this is explained by the existence in solution of self-associates of XI that decompose upon dilution.



XI

The bands at 1654 (KBr) and 1676 cm^{-1} ($CDCl_3$) were assigned to a hydrogen-bond associated carbonyl group, while the band at 1710 cm^{-1} was assigned to a monomeric $\nu_{C_2=O}$ band. As in the case of 2-methoxypyrimidine [9], this band is absent in the spectrum of VIII, while in the spectrum of pyrimidine IX one observes an intense band at 1690 cm^{-1} that is not shifted on passing from the crystalline phase to solution in weakly polar solvents; this is explained by the absence of a hydrogen bond at the carbonyl group.

A band at 1200 cm^{-1}, which we assigned to a $\nu_{C=S}$ band, is observed in the spectra of IV (see Fig. 3). Its intensity is minimal in CCl_4; this is explained by the realization of primarily thiol form IVa under these conditions.



IVa IVb

The concentration of thione form IVb and the intensity of the band at 1200 cm^{-1} increase with an increase in the polarity. The effect of the polarity of the solvent on the ratio of tautomers is determined by the differences in the energies of solvation of the π system of the heteroring [16]. Pyrimidine-2-thione exists in the thione form in the solid phase and in polar solvents [6]. The effect of the electron-acceptor trifluoromethyl group in the 4 position on the π system of the ring probably increases the conjugation of the unshared pair of electrons of the sulfur atom with the aromatic system, since the $\nu_{S\text{-}C}$ band in the spectrum of IV lies $\approx$340 cm^{-1} higher than in the spectrum of 4,6-dimethyl-2-mercaptopyrimidine, and, consequently, the S–H bond is strengthened. The change in the electron structure of the heterocyclic ring on passing from thiol form IVa to thione form IVb leads to an appreciable decrease in the intensity of the band at 1180 cm^{-1}, which we assigned to ring deformation vibrations (see Table 2 and Fig. 3). A shift of the band at 1221 cm^{-1} to the high-frequency region is observed simultaneously. According to [6, 12], this band is a $\delta_{C\text{-}H} + \delta_{N\text{-}H} + \nu_{C=S}$ composite band, and its shift on passing to a more polar solvent is evidently explained by a shift of $\delta_{N\text{-}H}$ as a result of the formation of a hydrogen bond with proton-acceptor molecules such as acetonitrile; $\delta_{C\text{-}H}$ and $\nu_{C=S}$ show up in the form of low-frequency shoulders on a new band at 1235 cm^{-1}. The presence of a free

TABLE 2. IR Spectra of 4-Trifluoromethylpyrimidines III, IV, VIII, and X and Their Unfluorinated Analogs

Compound	Solvent	Absorption bands,** cm^{-1}																					
		Pyrimidine ring ν_{C-H}	ν^{ass}_{N-H}	(ν_{S-H}) $\nu^{mon}_{C=O}$	$\nu^{ass}_{C=O}$	ν ring	ν ring + δ_{N-H}	δ_{C-H} + ν_{C-N}	δ_{C-H} + ν_{C-F}	δ_{C-H}	$\nu_{C=S}$ + δ_{C-H}	δ_{C-H} + δ ring + $\nu_{(C-F)}$	γ_{N-H} + $\gamma_{(C-H)}$	ring breathing	γ_{N-H}	ring breathing	γ_{C-H}	δ ring + $\nu_{C=S}$	$\nu_{S-C_{Alk}}$	γ_{C-H}	δ ring	$\gamma_{C=S}$, δ ring	$\delta_{C=S}$
PT		3080, 3050 2950	3150			1608, 1565, 1490	1475	1420	1335	1225	1210 1188	1182	1050 ub	1040 ub	980 852	965 738	795 ub	750 ub	— —	735 ub	620 —	485	405 462
DPT		3070	3140	(2250)		1625, 1490	1440																
IV	KBr	3080, 3048	2936			1608, 1572	1478	1424	1330	1256	1202	1186, 1154	1088	1075	976	—	808	760	—	732	—	478	ub
	CCl_4	3090, 3052		(2592)		1565		1434	1348, 1335	1221	1200	1176, 1165	—	—	—	—	1t	1t	1t	732	—	1t	—
MTP		3108, 3058 3029				1568, 1548		1432	1382	1254	1208	1186	1068	1088	—	982	803	—	719	774	630	476	
X	KBr	3080, 3050				1570	1466	1430	1356, 1336	1228	1208	1180, 1152		1088	—	980	—	—	718	784		472	
	CCl_4	3088, 3052				1568	1460	1428	1356, 1336	1228	1210	1180, 1164		1086	—	980	—	—	720	1t		1t	—
P		3110, 3070, 3019	2820		1648	1618, 1540, 1471	1434		1350, 1230	1198	1106	1160	ub	1053	952	—	802	866	—	782	585	518	—
III	KBr	3096, 3034	2874		1654	1632, 1555, 1482	1450		1324, 1261	1201	1114	1167	ub	1086	948	998	820	ub	—	765	578	534	—
	$CDCl_3$	3092, 3032	2876	1710	1676	1632, 1544, 1476	1456		1324, 1t	1204	1105	1165	ub	1080	1t	1t	1t	1t	—	1t	1t	1t	1t
IX	KBr	3108, 3048		1690		1632, 1588, 1550, 1476	1440		1318, 1260	1196	→	1175, 1150	ub	1060	956	—	812	ub	—	776	—	—	—
	CH_2Cl_2			1690		1632, 1t, 1544, 1480	1430		1316, 1t	1194	→	1180, 1156	ub	1060	952	—	820	1t	—	1t	1t	1t	—
MP						1627, 1580, 1564, 1470	1483		1340, 1225	1187	1083	1176	ub	1054	—	986	833	—	—	790	—	—	—
VIII	CH_3CN	3100, 3032				1616, 1590, 1578, 1452	1476		1344, 1228	1196	1096	1188, 1162	ub	1050	—	988	840	1t	—	1t	1t	1t	—
	CCl_4	3104, 3024				1616, 1590, 1582	1478		1344, 1228	1196	1100	1156	ub	1048	—	988	846	1t	—	1t	1t	1t	—

*Symbols: PT) pyrimidine-2-thione [6], DPT) 4,6-dimethylpyrimidine-2-thione [5], MTP) 2-methylthiopyrimidine [7], P) 2-pyrimidinone [8], MP) 2-methoxypyrimidine [9, 10].

**Note that lt is the low-transmission region of the solvent, and ub is an unidentified band.

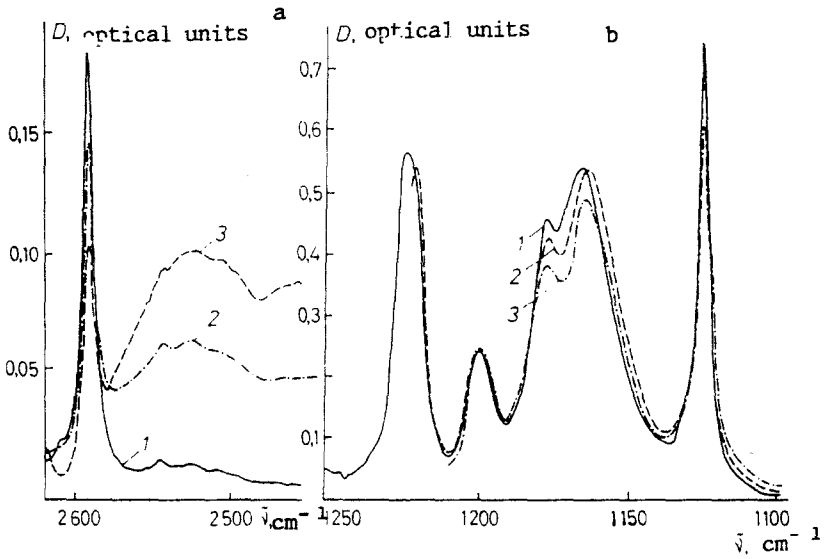


Fig. 4. IR spectrum of a mixture of pyrimidine IV (c = 10^{-2} M) with deuteroacetone in CCl_4: 1) c = 0 M; 2) c = 0.5 M; 3) c = 1 M; a) layer thickness 2.9 mm; b) layer thickness 0.126 mm.

TABLE 3. UV Spectra of III, IV, and VIII-X

Compound	Solvent	Absorption maximum, λ, nm			
		$I_{n-\pi^*}$	$II_{\pi-\pi^*}$	$I_{\pi-\pi^*}$	$II_{n-\pi^*}$
III	C_6H_{14}	—	265	—	—
	CH_2Cl_2	314	270	—	—
	H_2O	314	270	—	—
	CH_3OH	322	—	—	—
VIII	CH_2Cl_2	—	274	—	—
IX	CH_2Cl_2	324	—	—	—
IV	C_6H_{14}	—	290	242	200
	CH_3OH	397	291	—	220
	H_2O	366	292	—	216
X	C_6H_{14}	—	302	258	215
	CH_3OH	—	299	256	215
	H_2O	—	299	255	209
DT*	$CHCl_3$	361	290	—	—
	CH_3OH	350	287	220	208**
	H_2O	335	278	219	209**

*Note that DT is 4,6-dimethyl-2-thiopyrimidine [5].
**An n—σ* transition.

TABLE 4. Thermodynamic Parameters of the Formation of Complexes of IV with Various Proton Acceptors

Acceptor	ν, cm^{-1}		Δν, cm^{-1}	$-\Delta H$, kJ/mole
	monomeric	complex		
CH_3CN	2592	2548	44	4,6
$(CD_3)_2CO$	2592	2528	64	6,7

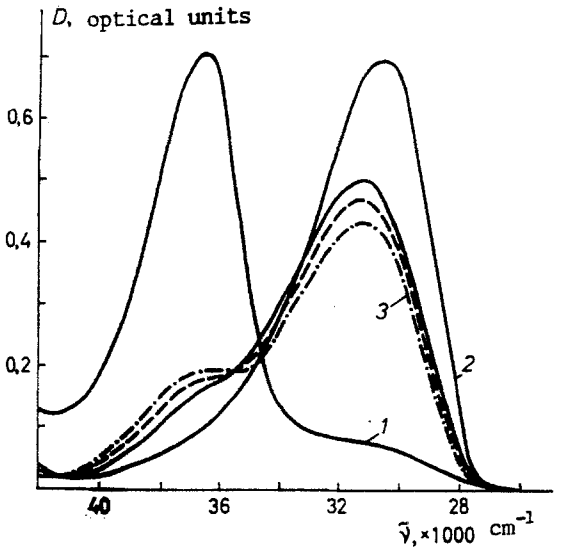


Fig. 5. UV spectra of pyrimidines VIII (1) and IX (2) in CH_2Cl_2 (c = $1.4 \cdot 10^{-4}$ M) and pyrimidinone III (3) in CH_3CCl_3 (c = 10^{-4} M).

TABLE 5. Characteristics of 4-Trifluoromethylpyrimidines II-X

Compound	Empirical formula	mp, °C	Crystallization solvent	Yield, %
II	$C_5H_3F_3N_2$	—*		23
III	$C_5H_3F_3N_2O$	222	Acetonitrile	35 (A), 75 (B)
IV	$C_5H_3F_3N_2S$	167...168	CCl_4	65
V	$C_5H_4F_3N_3$	175 (175 [1])	Toluene	45 (A), 60 (B)
IV	$C_{13}H_{11}F_3N_4O_3S$	250...260	Ethanol	67
VII	$C_{11}H_9F_3N_4O_3S$	250...252 (245 [1])	Methanol	52
VIII	$C_6H_5F_3NO$	—**		61
IX	$C_6H_5F_3NO$	169...170	CH_2Cl_2: ether (1:1)	8
X	$C_6H_5F_3N$	≃0***		73

*bp 118-119°C (760 mm); n_D^{20} 1.4200.
**bp 67-68°C (17 mm); n_D^{20} 1.4323.
***n_D^{20} 1.4898.

SH group in thiol form IVa makes it possible to assume the possibility of the formation of hydrogen bonds with proton acceptors. A hydrogen bond at the thiol group is formed when deuteroacetone is added to a solution of pyrimidine IV in CCl_4 (see Fig. 4): the intensity of the $\nu_{C=S}$ band at 1200 cm^{-1} remains virtually unchanged. A similar pattern is observed when acetonitrile is added to a solution of IV in CCl_4; however, an appreciable band of a hydrogen bond is observed when c_{CH_3CN} = 4 M (20% by volume), as compared with a similar observation for deuteroacetone when c = 1 M (5% by volume). An approximate evaluation of the enthalpy of the hydrogen bond was calculated from the Badger—Bauer expression (see Table 4). The $-\Delta H$ values found show that the strength of the hydrogen bond and, consequently, stabilization of thiol form IVa depend not only on the polarity but also on the proton-acceptor strength of the solvent. Thione form IVb is also capable of forming hydrogen bonds at the NH group with solvent molecules, as indicated by the shift of the band at ν 1221 cm^{-1} (see above). Direct evidence for the existence of tautomerism could not be obtained in the spectra of pyrimidine III. Two very intense structured bands, which we assigned to, respectively, complex ν_{C-F} bands of stretching vibrations and ring ν_{C-H} deformation vibrations, are present at 1230-1360 and 1150-1180 cm^{-1} in the spectra of all of the investigated 4-trifluoromethylpyrimidines [5-7, 10].

The tautomeric equilibrium for III and IV and the effect of the polarity of the solvent on it were also studied by UV spectroscopy. The absorption maximum of the C=S group of 2-mercaptopyrimidines [5] and 2-mercaptopurines

[16] lies at ≥330 nm. This maximum (Table 3) is absent in the absorption spectra of IV in hexane; this is confirmed by the IR and PMR spectral data, which indicate the primary formation of thiol form IVa in nonpolar solvents. An absorption maximum at 370-400 nm, which was assigned to an $I_{n-\pi^*}$ transition, is characteristic for pyrimidine IV in polar solvents. This maximum is absent in the spectrum of X. Three absorption bands at 287, 251, and 220 nm, which correspond to $II_{n-\pi^*}$, $I_{\pi-\pi^*}$, and $II_{\pi-\pi^*}$ transitions, are presented in [14] for 2-methylthiopyrimidine. A comparison of these data with the spectral data for X shows that the introduction of a trifluoromethyl group into the 4 position leads to a bathochromic shift of the $II_{n-\pi^*}$ and $I_{\pi-\pi^*}$ transitions. This constitutes evidence for an increase in the aromatic character of the heterocyclic ring and an increase in the p—π conjugation of the unshared electron pair of the sulfur atom with the π electrons of the ring.

The addition of proton acceptors (deuteroacetone, triethylamine) to a solution of thiopyrimidine IV in hexane does not lead to the appearance of a band at 400 nm in the spectrum. A small bathochromic shift (3-5 nm) of the principal absorption bands, which is evidently due to the formation of hydrogen bonds at the SH group, is observed.

An investigation of the spectra of pyrimidine III and its derivatives VIII and IX made it possible to detect an equilibrium of tautomeric forms for hydroxypyrimidine III and an effect of the polarity of the solvent on it. A shoulder at ≈270 nm, which coincides with the maximum at 274 nm in the spectrum of VIII, is observed in the spectrum of a solution in CH_2Cl_2 (see Fig. 5) on the principal band at 314 nm, which corresponds to the keto form of pyrimidine III. An increase in the temperature shifts the equilibrium to favor the hydroxy form of pyrimidine III; an isobestic point, which also indicates the existence of an equilibrium between two tautomeric forms, is observed. In hexane pyrimidine III evidently exists exclusively in the hydroxy form, to which only one maximum at 265 nm corresponds.

EXPERIMENTAL

The ^1H and ^{19}F NMR spectra were recorded with a Bruker WP-200 spectrometer (200 and 188.28 MHz) with hexamethyldisiloxane (HMDS) and CCl_3F, respectively, as the internal standards. The IR spectra were recorded with a Specord M-80 spectrometer. The UV spectra were obtained with a Specord M-40 spectrophotometer.

The yields and properties of pyrimidines II-X are presented in Table 5. The results of elementary analysis were in agreement with the calculated values.

β-Ethoxyvinyl trifluoromethyl ketone (I) was obtained by the method in [17] from ethyl vinyl ether and trifluoroacetic anhydride in the presence of pyridine.

4-Trifluoromethylpyrimidine (II). A 3.6-g (21.43 mmole) sample of butenone I was added in the course of 1 h at 170-180°C to a mixture of 0.6 g of NH_4Cl and 0.5 ml of formamide, and the mixture was heated for 2 h at ≈160°C. It was then poured into 50 ml of 5% aqueous NaOH, and the alkaline mixture was extracted with methylene chloride (three 20-ml portions). The organic phase was dried with $MgSO_4$ and filtered, and the solvent was removed by distillation with a fractionating column. The residue (≈1 ml) was fractionated at atmospheric pressure to give 0.73 g of pyrimidine II.

4-Trifluoromethyl-2-oxopyrimidine (III). A. A mixture of 1 g (6.1 mmole) of butenone I and 0.37 g (6.17 mmole) of urea was maintained for 1.5 h at 150°C, after which it was treated with hot acetonitrile (≈20 ml) and cooled, and the precipitated crystals were removed by filtration to give 0.35 g of pyrimidine III.

B. A 2-ml sample of concentrated HCl was added to a mixture of 0.6 g (10 mmole) of urea and 1.6 g (9.7 mmole) of butenone I in 6 ml of ethanol, and the mixture was maintained for 2 days at ≈22°C. It was then evaporated in vacuo, and the residue was crystallized to give 1.18 g of pyrimidinone III.

4-Trifluoromethyl-2-mercaptopyrimidine (IV). A 1-ml sample of concentrated HCl was added to a mixture of 3.6 g (21.4 mmole) of butenone I and 1.6 g (21 mmole) of thiourea in 10 ml of ethanol, and the mixture was maintained for 2 days at 20°C. The ethanol was then evaporated in vacuo, and the residue was extracted with ether (three 50-ml portions). The extract was dried with $MgSO_4$ and filtered, the filtrate was evaporated, and the residue was crystallized to give 2.5 g of pyrimidine IV.

4-Trifluoromethyl-2-aminopyrimidine (V). A. A solution of 0.7 g (7.29 mmole) of guanidinium chloride in 10 ml of anhydrous ethanol was added to a solution of sodium ethoxide obtained from 0.165 g (7.2 mmole) of Na in 5 ml of anhydrous ethanol. After 10 min, 1.2 g (7.1 mmole) of butenone I was added, and the mixture was maintained for 3 h at 25°C and for 2 h at 60°C. The solvent was evaporated to dryness, and the residue was crystallized from toluene to give 0.55 g of pyrimidine V.

B. A mixture of 2.4 g (14.3 mmole) of butenone I and 1.4 g (7.8 mmole) of guanidinium carbonate in 30 ml of benzene was heated for 6 h at 120°C with a Dean—Stark adapter. The hot benzene solution was decanted, the solvent was evaporated in vacuo, and the residue was crystallized to give 1.41 g of V.

4-Trifluoromethyl-2-N-(4-N′-acetylaminophenylsulfo)aminopyrimidine (VI). A mixture of 4.1 g (16 mmole) of the arylsulfonylguanidine, 2.68 g (16 mmole) of butenone I, and 1 g of sodium acetate in 20 ml of acetic acid was

maintained for 12 h at 100-110°C, after which the solvent was evaporated in vacuo, and the residue was treated with water (two 20-ml portions), removed by filtration, and dried to give 3.86 g of VI.

4-Trifluoromethyl-2-N-(4-aminophenylsulfo)aminopyrimidine (VII). A mixture of 9.7 mmole of pyrimidine with 2 ml of 10% aqueous NaOH was maintained for 6 h at 100°C, after which 1 g of activated charcoal was added, and the mixture was filtered. The pH of the filtrate was brought up to 4.0 with acetic acid, and the mixture was cooled to 10°C. The resulting precipitate was removed by filtration, dried, and crystallized to give 1.6 g of pyrimidine VII.

Methylation of Pyrimidine III with Diazomethane. A 50% excess of a solution of diazomethane in ether was added at 0°C to a suspension of 2 g (12.2 mmole) of pyrimidine III in 10 ml of ether, and the mixture was maintained for 2 h at 22°C. The ether was then evaporated in vacuo, and the residue was treated with pentane (three 10-ml portions). The precipitate was removed by filtration and crystallized to give 0.18 g of pyrimidine IX. The pentane solution was evaporated, and the residue was fractionated in vacuo (with a water aspirator) to give 1.33 g of pyrimidine VIII.

4-Trifluoromethyl-2-methylthiopyrimidine (X). A 50% excess of a solution of diazomethane in ether was added at 0°C to a solution of 0.7 g (3.9 mmole) of pyrimidine IV in 3 ml of ether. After 10 h, the mixture was evaporated, and the residue was chromatographed with a column (1.5 by 20 cm) packed with silica gel (L 100/160) (elution with pentane, R_f 0.4) to give 0.55 g of pyrimidine X.

LITERATURE CITED

1. R. Dohmori, S. Nagasaki, Y. Oshima, and T. Naito, *Yakugaku Zasshi*, **87**, 419 (1967); *Chem. Abstr.*, 90760 (1967).
2. D. Rendzo, T. Yoshiaki, and N. Takeo, Japanese Patent Application No. 12425; *Ref. Zh. Khim.*, 17N386 (1968).
3. A. Kreutzberger, *J. Fluorine Chem.*, **29**, 385 (1985).
4. I. I. Gerus, M. G. Gorbunova, S. I. Vdovenko, Yu. L. Yagupol'skii, and V. P. Kukhar', *Zh. Org. Khim.*, **26**, 1877 (1990).
5. S. P. Gupta, S. Sharma, and R. K. Goll, *Spectrochim. Acta*, **42A**, 1171 (1986).
6. D. N. Sathyanarayana and S. V. Kasmir Raja, *Spectrochim. Acta*, **41A**, 809 (1985).
7. G. Mille, M. Guiliano, J. Rister, J. Chouteau, and J. Metzger, *Spectrochim. Acta*, **36A**, 713 (1980).
8. E. Picquenard and A. Lautie, *Spectrochim. Acta*, **38A**, 641 (1982).
9. A. J. Lafaix, *Spectrochim. Acta*, **26A**, 1243 (1970).
10. O. P. Shkurko and I. K. Korobeinicheva, *Zh. Prikl. Spektrosk.*, **23**, 860 (1975).
11. E. Allenstein, P. Kiembe, E. Schlipf, and W. Podszun, *Spectrochim. Acta*, **34A**, 423 (1978).
12. A. Lautie, J. Hervien, and J. Belloc, *Spectrochim. Acta*, **93A**, 367 (1983).
13. S. Furberg and J. Solbakk, *Acta Chem. Scand.*, **24**, 3230 (1970).
14. J. Kister, D. B. Rouband, L. Bouscasse, and J. Metzer, *Spectrosc. Lett.*, **13**, 1 (1980).
15. L. Bellamy, *Infrared Spectra of Complex Molecules*, Methuen, London (1958).
16. S. F. Mason, *J. Chem. Soc.*, 2071 (1954).
17. M. Hojo, R. Masuda, Y. Koruyo, H. Shioda, and S. Matsuo, *Chem. Lett.*, No. 5, 499 (1976).