CYCLAZINES AND THEIR ANALOGS.
2*. DIFORMYL-SUBSTITUTED THIAZOLOPYRIMIDOPYRIMIDINES

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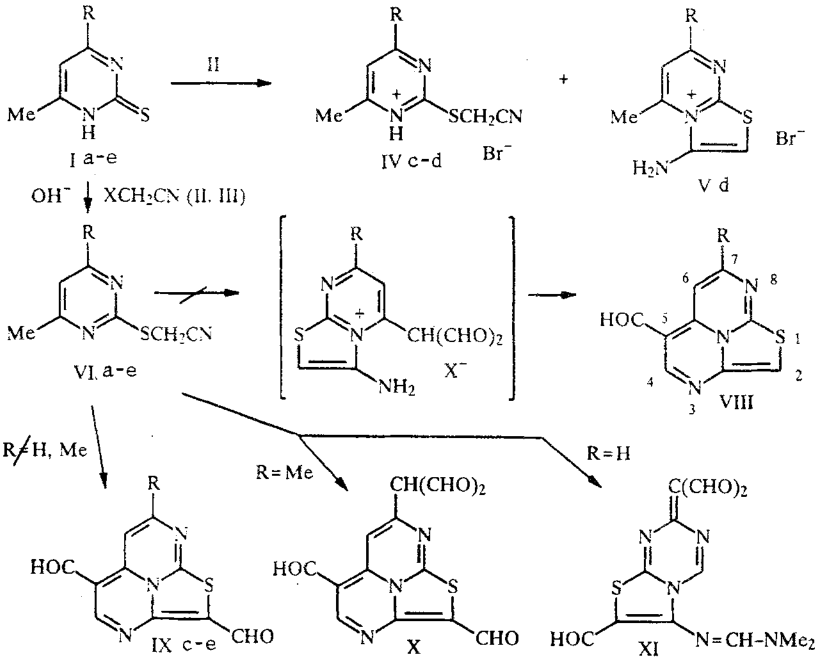
Substituted 2,5-diformylthiazolopyrimidopyrimidines are synthesized through reaction of 6-R-4-methyl-2-cyanomethylthiopyrimidines with the Vilsmeier reagent. They can be used to prepare cyanine dyes.

In continuation of the previous work [1], where the first representatives of the new heterocycle thiazolopyrimidopyrimidine were reported, we have investigated the reaction of 6-R-4-methylpyrimidine-2-thiones Ia-e with haloacetonitriles II and III.

In analogy with the reaction of 4-methyl-6-phenylpyrimidine-2-thione (I) with α-bromopropionitrile [1], formation of 3-aminothiazolo[3,2-*a*]pyrimidinium bromide Vd unsubstituted in the 2-position was expected. However, the isolated product was a mixture of two isomers, the hydrobromide IVd and the salt Vd. The reaction under these conditions of the trifluoromethylthione Ic produces only the hydrobromide IVc.

Scheme 1



I, IV—IX a R=H, b R=Me, c R=CF_3, d R=Ph; e R=C_6H_4OMe; II X=Br; III X=Cl

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[*] For Communication 1, see [1].

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TABLE 1. PMR Parameters for Cyanomethylthiopyrimidines VI

Compound	Solvent	Chemical shift, δ, ppm					
		$-SCH_2$	$4-CH_3$	5-H	o-H(2H)	Ar–H	R
VI b	$CDCl_3$	3,94	2,45	5,80	—	—	2,45
	CF_3COOD	4,36	2,86	7,53	—	—	2,86
VI d	DMSO-D_6	4,30	2,50	7,81	8,22	7,57(3H)	*
	CF_3COOD	4,44	2,90	8,33	8,38	7,76(3H)	*
VI e	$CDCl_3$	3,97	2,51	7,25	8,05, d (J=6 Hz)	7,00, d (2H)	3,87(OCH_3)
	CF_3COOD	4,40	2,81	7,88	8,40, d (J=7 Hz)	7,23, d (2H)	4,06(OCH_3)

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*The signal corresponds to a multiplet of aromatic protons.

Alkylation of thiones Ia-e in basic solution gives the pyrimidines VIa-e. The structure of these is confirmed by PMR spectra (Table 1).

The cyanomethylthiopyrimidines VI readily react with the Vilsmeier reagent. This produces solid molecular deep blue or green compounds. Formation of the cyclazine ring is confirmed by comparing the IR spectra of the starting nitriles VI, which contain stretches of C=N and C≡N bonds (1520-1580 and 2240-2260 cm^{-1}), with those of the resulting compounds, which contain only bands characteristic of C=N and C=O vibrations at 1500-1560, 1610-1630, and 1640-1660 cm^{-1}. The slightly reduced frequencies of the aldehyde stretches are characteristic for absorption of carbonyl derivatives of nonbenzenoid aromatic hydrocarbons [2]. It was supposed that treatment of VIa-e with a mixture of DMF and phosphoryl chloride would simultaneously fuse the thiazole ring to the pyrimidine ring due to the influence of the electrophiles and formylate the methyl group [3] to form thiazolo-[2′,3′,4′:1,9,8]pyrimido[3,4-*c*]pyrimidines VIII.

However, according to the elemental analyses and PMR data, the composition and structure of the resulting compounds did not correspond to the proposed structure VIII. The PMR spectra of the formylation products of VIc-e (Table 2) lack signals for methyl and methylene protons of the starting materials. Like in spectra of 2-substituted 5-formylthiazolopyrimidopyrimidines [1], signals are observed for protons in the 4- and 6-positions of the ring with chemical shifts 7.7-8.7 ppm, which depend on the solvent used, and for a formyl proton at 9.4-9.6 ppm. A signal of yet another proton is observed near 9.9 ppm. Judging from the large chemical shift of this signal, it does not correspond to an aromatic proton in the 2-position of the ring (VIII) but most likely to the proton of still another formyl group bound to the C atom in this position. This enables the synthesized compounds to be assigned as 2,5-diformyl-substituted thiazolopyrmidopyrimidines IXc-e. This is confirmed by experiments involving the homonuclear Overhauser effect. Thus, irradiation at the frequency of the proton at the weakest field for the trifluoromethyl derivative IXc, which has the simplest PMR spectrum, has no perceptible effect. Conversely, the signal of the proton in the 4-position is markedly decreased for the proton of the formyl group on C_5 (predominant conformation). The dialdehydes IXc-e can form as a result both of formylation at the C atom of the cyanomethyl group with subsequent cyclization of the thiazole moiety and of formylation at the nucleophilic center (2-position) and the methyl group of the initial intermediate, a 3-aminothiazolopyrimidinium salt of type V.

Signals of methylene and both methyl groups are absent in the PMR spectrum of formylated 4,6-dimethyl-2-cyanomethylthiopyrimidine VIb. However, a two-proton singlet at weak field occurs besides the signals of the two formyl protons. Obviously, aldehyde X is formed (one of the possible tautomers is shown).

The structure XI can be assigned to the formylation product of monomethylpyrimidine VIa on the basis of the PMR spectrum. Obviously, XI forms owing to the direction of the thiazole cyclization, which favors the sterically least hindered N atom of the pyrimidine ring. In this respect, the synthesis of thiazolo[3,2-*a*]pyrimidine 3-oxides is similar to cyclocondensation of substituted 2-pyrimidinylthioacetic acids [4].

The electronic spectra of the thiazolopyrimidopyrimidines are similar to those of previously prepared compounds of this series [1] (Table 3). The longest-wavelength weak band λ_1 also has distinct vibrational structure ($\Delta\nu$ = 1200-1400 cm^{-1}).

TABLE 2. PMR Parameters of Aldehydes IX and X

Compound	Solvent	Chemical shift, δ, ppm						
		2-CH=O	5-CH=O	4-H	6-H	o-H(2H)	Ar—H	R
IXc	$CDCl_3$	9,88	9,42	7,77	7,68	—	—	—
	CF_3COOD	9,87	9,57	8,37	8,17	—	—	—
IXd	$CDCl_3$	9,93	9,45	8,11	7,78	8,02	7,56 (3H)	*
	CF_3COOD	9,87	9,63	8,77	8,12	8,31	7,69 (3H)	*
IXe	CF_3COOD	9,90	9,63	8,70	8,15	8,40 д	7,20, d (2H)	4,08 (OCH_3)
						(J=8 Hz)		
X	CF_3COOD	9,86	9,61	9,37	8,12	—	—	9,15 (2H) (CHO)

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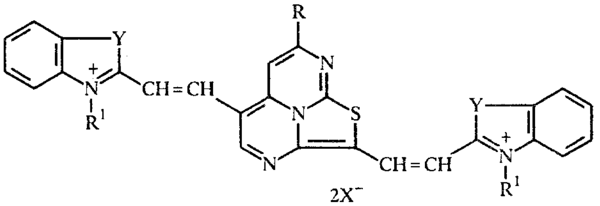
*The signal corresponds to a multiplet of aromatic protons.

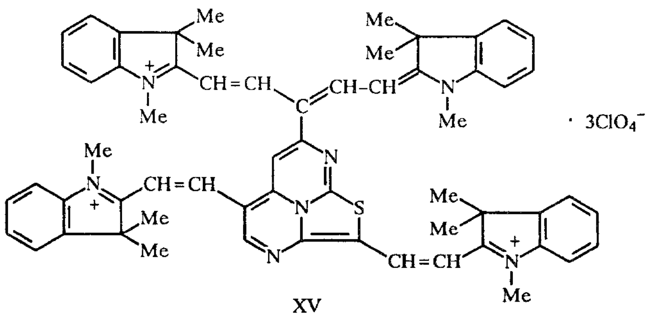
Its position depends on the solvent. The position and intensity of the third shortest-wavelength band is determined by the nature of the substituent in the 7-position. For IXc, which contains the electron-accepting trifluoromethyl group, it is practically absent. For 7-phenyl IXd, which contains an additional isolated π-electron system, it is observed near 320 nm. Introduction of an electron-donating p-methoxyphenyl group in the 7-position (IXe) induces a 30-40 nm bathochromic shift of the maximum. On going from 7-phenyl-5-formylthiazolopyrimidopyrimidine to 7-phenyl-2,5-diformyl-substituted IXd, addition of the second formyl group in the 2-position causes a significant hypsochromic shift of λ_1 ($\sim$50 nm) and a bathochromic shift of λ_2 ($\sim$40 nm). The band λ_2 has a shape close to that of typical polymethine dyes and is observed in the visible region. Such a high sensitivity of the band maxima to the nature of the substituent in the 2-position is extremely interesting. It is indicative of involvement of C_2 in the first two electronic transitions.

Scheme 2



XIIc, XIIId, XIVe

XII—XIV c $R=CF_3$, d R=Ph, e $R=C_6H_4OMe$; XII, XIV $X=ClO_4$; XIII $X=MeC_6H_4SO_3$;
XII $Y=CMe_2$, R^1=Me; XIII, XIV Y=S, R^1=Et



XV

TABLE 3. Electronic Absorption Spectra of Aldehydes IX and Dyes XII-XV

Compound	Solvent	λ_{max}, nm (log ε)		
		λ_1	λ_2	λ_3
IXc	CH_3CN	580 (2,76)	420 (4,85)	402 (4,68)
IXd	CH_3CN	553 (2,48)	430 (4,63)	320 (4,51)
	CH_3COOH	540	424	330
	C_2H_5OH	549	429	328
	DMF	552	433	328
	$CHCl_3$	556	422	332
IXe	CH_3CN	540 (2,76)	430 (4,83)	360 (4,79)
	$CHCl_3$	544	433	376
XIIc	CH_3CN	710 (4,76)	440 (4,20)	
XIIId	CH_3CN	710 (4,95)	440 (4,34)	
XIVe	CH_3CN	718 (4,95)	450 (4,45)	
XV	CH_3CN	740 (4,79)	630 (5,33)	

All synthesized aldehydes readily react with the nucleophiles usually used to prepare cyanines. Thus, the dicationic dyes XII-XIV are synthesized from dialdehydes IXc-e and the quaternary 2-methyl-3-ethylbenzothiazolium and 1,2,3,3-tetramethyl-3H-indolium salts. More complicated polymethines of type XV are formed from the tetraaldehyde X.

One feature of the new dyes is their deep color. Thus, a comparison of the long-wavelength absorption maxima of XII-XIV with the corresponding data for their structural analogs from 2,7-diphenyl-5-formylthiazolopyrimidopyrimidine shows that replacing the 2-phenyl by benzazoliovinyl produces a ~ 100 nm bathochromic shift of the maximum. Apparently, such an effect may be due to the interaction of the conjugated chromaphores [5] in their molecules.

Thus, a simple preparation method is developed for a new type of thiazolopyrimidopyrimidine derivatives, which can be used to synthesize deeply colored polymethine dyes.

EXPERIMENTAL

PMR spectra were obtained on a WP-100SY radiospectrometer (TMS internal standard). IR spectra were taken on a UR-20 spectrophotometer in KBr pellets. UV spectra were recorded on an SF-8 spectrophotometer. Data for the properties of the synthesized compounds are presented in Table 4. Elemental analyses for Cl, N, and S agreed with those calculated.

2-Cyanomethylthiopyrimidines VIa-e. A mixture of the appropriate thione Ia-e (10 mmole), NaOH (25 ml of 4% solution, 25 mmole), and haloacetonitrile II or III (10 mmole) was stirred at room temperature for 1 h. The precipitated product was filtered off (VIb, -d, -e) or extracted by ether (VIa, -c).

7-R-2,5-Diformylthiazolo[2′,3′,4′:1,9,8]pyrimido-[3,4-*c*]pyrimidines (IXc-e). The appropriate 6-R-4-methyl-2-cyanomethylthiopyrimidine VIc-e (1 mmole) was added to a mixture of phosphoryl chloride (1.5 ml) and DMF (1.5 ml) prepared at 0-5 °C. The mixture was heated for 1 h at 80 °C, cooled, and poured on ice. The precipitated product was filtered off, dried, dissolved in $CHCl_3$, and chromatographed on alumina.

7-(1,1-Diformyl)methyl-2,5-diformylthiazolo[2′,3′,4′:1,9,8]pyrimido[3,4-*c*]pyrimidine (X). The compound VIb was formylated analogously to the preceding one. The mixture was poured on ice. The solution was made basic, filtered, and acidified with HCl until the pH was 5. The product was filtered off.

4,7-Dihydro-3-(dimethylaminomethylene)amino-7-diformylmethylene-2-formylthiazolo[3,2-*a*]pyrimidine (XI). The compound 4-methyl-2-cyanomethylthiopyrimidine was formylated analogously to the preceding one. The mixture was decomposed with water. The solution was made basic until the pH was 8. The precipitate was filtered off and crystallized from alcohol. PMR spectrum (CF_3CO_2D): 9.94 (1H, s), 9.45 (1H, d, J = 8 Hz), 9.21 (2H, s), 9.15 (1H, d), 8.47 (1H, s), 3.47 ppm (6H, s).

Diperchlorate of 2,5-Di[2-(1,3,3-trimethyl-3H-indol-2-yl)vinyl]-7-trifluoromethylthiazolo[2′,3′,4′:1,9,8]pyrimido[3,4-c]pyrimidine (XII). A mixture of dialdehyde IXc (0.3 g, 1 mmole), 1,2,3,3-tetramethyl-3H-

TABLE 4. Properties of Synthesized Compounds

Compound	T_{mp}, °C	Empirical formula	Yield, %
VIa	—	$C_7H_7N_3S$	65
VIb	97...98	$C_8H_9N_3S$	67
VIc	—	$C_8H_6F_3N_3S$	60
VId	141...142	$C_{13}H_{11}N_3S$	83
VIe	137...138	$C_{14}H_{13}N_3OS$	73
IXc	213...214	$C_{11}H_4F_3N_3O_2S$	93
IXd	263...264	$C_{16}H_9N_3O_2S$	75
IXe	277...278	$C_{17}H_{11}N_3O_3S$	51
X	258...259	$C_{13}H_7N_3O_4S$	67
XI	198...200	$C_{13}H_{12}N_4O_3S$	40
XIIc	271...273	$C_{35}H_{32}C_2F_3N_5O_8S$	44
XIIId	250...252	$C_{50}H_{43}N_5O_6S_5$	61
XIVe	291...292	$C_{37}H_{31}C_2N_5O_9S_3$	58
XV	298...300	$C_{61}H_{62}C_3N_7O_{12}S$	60

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*Compound VIb was crystallized from water; VId, -e, and XI, from alcohol; XIIc and XV, from alcohol—CH_3CN; XIIId and XIVe, from acetic anhydride.

indolium perchlorate (0.55 g, 2 mmole), and acetic anhydride (5 ml) was boiled for 2 min and cooled. The precipitated dye was filtered off and crystallized from alcohol—CH_3CN.

Di(*p*-toluenesulfonate) of 2,5-Di[2-(3-ethylbenzothiazol-2-yl)vinyl]-7-phenylthiazolo[2′,3′,4′:1,9,8]pyrimido[3,4-*c*]pyrimidine (XIII). A mixture of IXd (0.31 g, 1 mmole), 2-methyl-3-ethylbenzothiazolium *p*-toluenesulfonate (0.7 g, 2 mmole), and acetic anhydride (5 ml) was boiled for 5 min and cooled. The precipitated dye was filtered off and crystallized from acetic anhydride.

Thiacyanine XIVe. This was prepared analogously to the preceding from IXe and 2-methyl-3-ethylbenzothiazolium perchlorate.

Indocyanine XV. A mixture of X (0.15 g, 0.5 mmole), 1,2,3,3-tetramethyl-3H-indolium perchlorate (0.55 g, 2 mmole), and acetic anhydride (3 ml) was boiled for 3 min and cooled. The dye was filtered off and crystallized from alcohol—CH_3CN.

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