

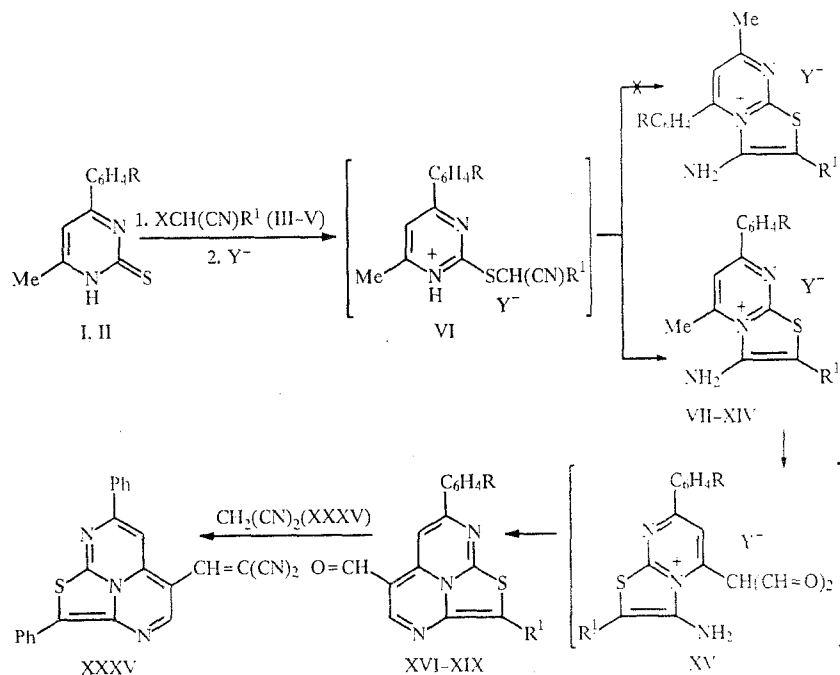
## CYCLAZINES AND THEIR ANALOGS.

### 1. THIAZOLOPYRIMIDOPYRIMIDINES

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*Derivatives of a new heterocyclic system, formyl-substituted thiazolopyrimidopyrimidines, are synthesized through reaction of 3-amino-5-methyl-thiazolo[3,2-a]pyrimidinium salts, prepared by alkylation of 2-mercaptopyrimidines with substituted acetonitriles, and the Vilsmeier reagent. These can be used to synthesize polymethine dyes.*

Polymethine dyes possess narrow strong absorption bands, the position of which is determined by the cyanine structure [1]. They provide important information about the electronic structure of the terminal heterocyclic residues. Recently, more and more attention has been focused on unusual heterocycles such as cyclazines and related compounds with bridgehead N atoms. The interest arises owing to theoretical problems of heteroaromaticity and the possibility of practical applications [2-4]. However, polymethine dyes based on cyclazine heterocycles were until now unknown. Therefore, it seemed interesting to develop synthesis methods for derivatives of cyclazine analogs suitable for preparing new classes of dyes. Thus, we studied the reaction of 2-mercaptopyrimidines I and II with an  $\alpha$ -cyanobenzylbenzenesulfonate (III), an  $\alpha$ -bromopropionitrile (IV), and an  $\alpha$ -bromocynoacetic ester (V).



I, VII—XII, XVI—XVIII R=H; II, XIII, XIV, XIX R=OMe; III, XI—XIV, XVIII, XIX R<sup>1</sup>=Ph;  
IV, VII, IX, XVI R<sup>1</sup>=Me; V, VIII, X, XVII R<sup>1</sup>=COOEt; III, X=PhSO<sub>3</sub>; IV, V X=Br;  
VII, VIII Y=Br; IX—XI, XIII Y=ClO<sub>4</sub>; XII, XIV Y=PhSO<sub>3</sub>

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TABLE 1. Characteristics of VII-XIX

Com- pound	T <sub>mp</sub> , °C	Empirical formula	Yield, %	Com- pound	T <sub>mp</sub> , °C	Empirical formula	Yield, %
VII	171...172	C <sub>14</sub> H <sub>14</sub> BrN <sub>3</sub> S	70	XIII	231...232	C <sub>20</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>5</sub> S	70
VIII	151...152	C <sub>16</sub> H <sub>16</sub> BrN <sub>3</sub> O <sub>2</sub> S	65	XIV	155...156	C <sub>26</sub> H <sub>23</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	68
IX	199...200	C <sub>14</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>4</sub> S	68	XVI	262...263	C <sub>16</sub> H <sub>11</sub> N <sub>3</sub> OS	47
X	199...200	C <sub>16</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>6</sub> S	70	XVII	218...219	C <sub>18</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S	71
XI	224...225	C <sub>19</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>4</sub> S	60	XVIII	231...232	C <sub>21</sub> H <sub>13</sub> N <sub>3</sub> OS	57
XII	169...170	C <sub>25</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> S <sub>2</sub>	58	XIX	251...252	C <sub>22</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	60

TABLE 2. PMR Spectra of 3-Aminothiazolopyrimidinium Salts VII, IX-XI, XIII

Com- pound	Solvent	Chemical shift, $\delta$ , ppm						
		N-H	5-CH <sub>3</sub>	6-H	o-H (2H)	Ar-H	R	R <sup>1</sup>
VII	DMSO-D <sub>6</sub>	5,75	3.32	8,51	8,38	7,70 (3H)	—*	2,52
IX	CF <sub>3</sub> COOD	—	3,45	7,98	8,31	7,65 (3H)	—*	2,63
X	CF <sub>3</sub> COOD	—	3,44	8,05	8,35	7,73 (3H)	—*	1,54 t; 4,60 q
XI	DMSO-D <sub>6</sub>	5,96	3,30	8,49	8,37	7,67 (8H)	—*	—*
XI	CF <sub>3</sub> COOD	—	3,47	8,02	8,34	7,64 (8H)	—*	—*
XIII	DMSO-D <sub>6</sub>	5,93	3,33	8,42	8,40 d**	7,65 (5H); 7,20 (2H) d**	3,91	—*
XIII	CF <sub>3</sub> COOD	—	3,42	7,95	8,38 d**	7,74 (5H); 7,22 (2H) d**	4,06	—*

\*The signal corresponds to an aromatic multiplet.

\*\* $J = 8$  Hz.

Heating the reagents readily produces 3-aminothiazolo[3,2-*a*]pyrimidinium salts VII-XIV (Table 1). Their IR spectra lack nitrile absorptions at 2200-2250  $\text{cm}^{-1}$  but do contain C=N and N-H absorptions at 1580-1620  $\text{cm}^{-1}$ . The formation of these salts is confirmed by their PMR spectra (Table 2), which contain signals of aromatic, methyl, and amino protons (the last easily exchanged with deuterium). However, signals of aliphatic protons of substituted nitriles III-V are absent.

It was expected that the thiazole moiety could cyclize to form isomeric products. However, the isolated compounds were pure according to the PMR spectra. A comparison of the chemical shift of the methyl protons in the pyrimidine ring (3.3-3.5 ppm) with the corresponding data [5, 6] for their structural analogs, 5,7-dimethyl-2-phenyl- and 5-methyl-2,7-diphenylthiazolo[3,2-*a*]pyrimidinium-3-oxides (3.30 and 3.50 ppm, respectively, in  $\text{CDCl}_3$ ), confirms this.

Obviously, the direction of the cyclization of the initially formed nitriles VI is determined by steric factors such as the radii of the substituents on the pyrimidine moiety (methyl and phenyl groups).

The 5-methyl group is formylated and a new cyclazine heterocycle is formed on heating the 3-aminothiazolo[3,2-*a*]pyrimidinium salts in a mixture of DMF and phosphoryl chloride. The composition and structure of the synthesized compounds were confirmed by elemental analysis and IR and PMR spectra. The IR spectra exhibit absorptions in the range 1600-1680  $\text{cm}^{-1}$ , characteristic of C=N and C=O stretches. However, N-H absorptions of the starting amino-substituted thiazolopyrimidinium salts are absent. Signals of the  $\text{NH}_2$  and the 5-methyl protons are also absent in the PMR (Table 3). However, singlets of two protons in the range 7.7-8.7 and 9.0-9.6 ppm are observed at weak field. The signal at the weakest field can be assigned to the proton of a formyl group conjugated to an electron donor, the bridgehead N atom. The position of the new singlet in the range of aromatic protons significantly depends on the solvent used to measure the PMR spectra. For example, the signal of this proton in  $\text{CF}_3\text{CO}_2\text{D}$ , analogously to the  $\alpha$ -pyrimidine proton, shifts to weak field (by  $\sim 0.7$  ppm) compared with that in  $\text{CDCl}_3$ . This enables it to be assigned to the azomethine moiety ( $-\text{OCH}-\text{N}-$ ) of the cyclazine. All these data agree with the structure of XVI-XIX.

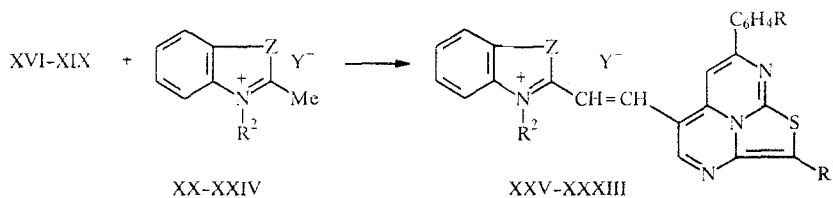
TABLE 3. PMR and Electronic Spectra of Aldehydes XVI-XIX

Compound	PMR spectrum, $\delta$ , ppm										Electronic spectrum		
	solvent	-CH=O	4-H	6-H	o-H (2H)	Ar-H	R	R <sup>1</sup>	solvent	$\lambda^1$	$\lambda^2$	$\lambda^3$	
XVI	CF <sub>3</sub> COOD	9,30	8,49	—*	8,12	7,68 (4H)	—*	2,36	CH <sub>3</sub> CN	596 (2,40)	360**	321 (4,51)	
	DMSO-D <sub>6</sub>	9,12	7,73	—*	7,92	7,55 (4H)	—*	2,09	CHCl <sub>3</sub>	596	357	328	
	CDCl <sub>3</sub>	9,05	7,82	7,24	7,90	7,45 (3H)	—*	2,05					
XVII	CF <sub>3</sub> COOD	9,56	8,72	8,05	8,29	7,68 (3H)	—*	1,51 t; 4,49 q	CH <sub>3</sub> CN	558 (2,30)	413 (4,08)	320 (4,46)	
	CDCl <sub>3</sub>	9,36	8,00	7,80	7,90	7,50 (3H)	—*	1,30 t; 4,36 q	CHCl <sub>3</sub>	558	415	328	
							—*	—*	CH <sub>3</sub> CN	609 (2,48)	387 (4,42)	335 (4,44)	
XVIII	CF <sub>3</sub> COOD	9,34	8,57	7,71	8,24	7,59 (8H)	—*	—*	CHCl <sub>3</sub>	609	390	341	
	DMSO-D <sub>6</sub>	9,22	—*	—*	—*	7,3...8,0 (12H)	—*	—*	CH <sub>3</sub> COOH	585	388	338	
									C <sub>2</sub> H <sub>5</sub> OH	582	388	339	
XIX	CF <sub>3</sub> COOD	9,33	8,51	7,74	8,28 d (J=8 Hz)	7,58 (5H); 7,20 (2H) d	4,06	—*	PMF	613	392	340	
	DMSO-D <sub>6</sub>	9,22	—*	—*	—*	7,0...8,0 (11H)	3,86	—*	CH <sub>3</sub> CN	591 (2,30)	410**	358 (4,64)	
	CDCl <sub>3</sub>	9,15	7,88	7,42	7,95 d (J=8 Hz)	7,36 (3H); 6,94 (2H) d	3,86	—*	CHCl <sub>3</sub>	591	410**	369	

\*The signal corresponds to a multiplet of aromatic protons.

\*\*Inflection.

The synthesized formyl-substituted thiazolopyrimidopyrimidines are solid dark-blue crystalline compounds. Their electronic absorption spectra contain strong UV bands and a broad much weaker band with distinct vibrational structure ( $\Delta\nu = 1200-1400 \text{ cm}^{-1}$ ) ( $\lambda_1$ ) near 600 nm (see Table 3). Apparently, this can be assigned to either a  $\pi-\pi^*$ -transition or a charge-transfer band. It is noteworthy that a similar situation is observed in the electronic spectra of azulene derivatives [7]. The position and shape of the solution absorptions of XVI-XIX substantially depend on the nature of the substituent. For example, replacing the 2-methyl by phenyl produces a small bathochromic shift in all three bands and a noticeable increase of the intensity of the second band. However, an analogous replacement of the ethoxycarbonyl group produces a further bathochromic shift of the second band and an increase of its relative intensity whereas the long-wavelength (first) band undergoes a hypsochromic shift. Conversely, changing from the aldehyde XVIII to its methoxy-substituted analog XIV produces a large bathochromic shift of the third band and a hypsochromic shift of the first. These data suggest that  $\lambda^3$  in the spectra of XVI-XIX is mainly due to an electronic transition localized on the atoms of the 7-phenyl group. The second band is most likely due to a redistribution of electron density on the thiazole moiety.



XX, XXV, XXVIII Y=MeC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>; XXI, XXIII, XXVII, XXX, XXXI Y=Cl<sub>4</sub>; XXII, XXIV, XXIX, XXXII, XXXIII Y=I; XXV-XXVII, XXIX-XXXII R=H; XXIII, XXXIII R=OMe; XX, XXI, XXV-XXVIII Z=S; XXII, XXIII, XXIX-XXXI Z=CMe<sub>2</sub>; XXIV, XXXII, XXXIII Z=CH=CH; XXV, XXIX R<sup>1</sup>=Me; XXVI, XXX R=COOEt; XXVII, XXVIII, XXXI-XXXIII R<sup>1</sup>=Ph; XX, XXI, XXIV-XXVIII R<sup>2</sup>=Et; XXII, XXIII, XXIX-XXXI R<sup>2</sup>=Me

The synthesized thiazolopyrimidopyrimidine derivatives readily react with the quaternary 2-methyl-substituted nitrogenous heterocycles (XX-XXIV) that are usually used to synthesize polymethine dyes.

Aldehydes also readily react with the nucleophiles used to synthesize merocyanine dyes. For example, XXXIV and malonic acid dinitrile form the dicyanomethylene derivative XXXV. Two bands of similar intensity  $\lambda_{\text{max}}$ , nm (log  $\epsilon$ ): 410 (4.50) and 498 (4.64) are observed in the visible spectrum of XXXV.

The synthesized dyes XXV-XXXIII (Table 4) are rather deeply colored. Their long-wavelength solution absorption maxima occur in the same part of the spectrum as for cyanines based on ordinary heterocycles with a long polymethine chain. The position of the long-wavelength band is largely determined by the substituents in the thiazolopyrimidopyrimidine moiety and to a lesser extent by the nature of the second terminal heterocycle. The long-wavelength bands of the dyes shift under the influence of the substituents in the same direction as the second band in the spectra of the starting aldehydes XVI-XIX for analogous structural changes. In fact, replacing the 2-methyl by phenyl or ethoxycarbonyl in the series XXV-XXVII is accompanied by a bathochromic shift of the absorption maximum by 20 and 70 nm, respectively. Thus, the sensitivity of the dye to the nature of the second terminal heterocycle increases. In fact, whereas the methyl-substituted indo- (XXIX) and thiacyanines (XXV) absorb at the same wavelength (580 nm), their ethoxycarbonyl analogs XXX and XXVI have maxima differing by 30 nm. This indicates that most of the atoms of the cyclazine are involved in the first  $\pi-\pi^*$ -transition responsible for the dye color. This transition is most probably similar in nature to a transition in the starting heterocycle.

Thus, a preparation method is developed for derivatives of a new heterocyclic system with a bridgehead N atom that can be used to synthesize polymethine dyes.

## EXPERIMENTAL

PMR spectra were obtained on a WP-100 SY (100 MHz) radiospectrometer with TMS internal standard. IR spectra were measured on a UR-10 spectrophotometer in KBr pellets. Electronic spectra were taken from SF-20 and M-40 spectrophotometers.

TABLE 4. Characteristics of Thiazolopyrimidopyrimidine Dyes

Compound	Empirical formula	T <sub>mp</sub> , °C	λ <sub>max</sub> (CH <sub>3</sub> CN), nm (log ε)	Yield, %
XXV	C <sub>33</sub> H <sub>28</sub> N <sub>4</sub> O <sub>3</sub> S <sub>3</sub>	278...279	370 (3,85), 580 (4,67)	64
XXVI	C <sub>28</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	252...253	650 (4,40)	82
XXVII	C <sub>31</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>4</sub> S <sub>2</sub>	198...200	380 (4,23), 600 (4,75)	75
XXVIII	C <sub>39</sub> H <sub>28</sub> N <sub>4</sub> O <sub>4</sub> S <sub>3</sub>	279...280	390 (4,62), 619 (4,84)	57
XXIX	C <sub>28</sub> H <sub>25</sub> IN <sub>4</sub> S	283...284	580 (4,60)	63
XXX	C <sub>30</sub> H <sub>27</sub> ClN <sub>4</sub> O <sub>6</sub> S	218...220	620 (4,64)	55
XXXI	C <sub>33</sub> H <sub>27</sub> ClN <sub>4</sub> O <sub>4</sub> S	202...203	612 (4,75)	81
XXXII	C <sub>33</sub> H <sub>25</sub> IN <sub>4</sub> S	292...293	390 (4,60), 630 (4,81)	69
XXXIII	C <sub>34</sub> H <sub>27</sub> IN <sub>4</sub> OS	272...273	390 (4,60), 630 (4,80)	68
XXXV	C <sub>24</sub> H <sub>13</sub> N <sub>5</sub> S	189...190	498 (4,64)	90

\*Dyes XXV and XXIX-XXXI were crystallized from alcohol; XXVII, from 4:1 CH<sub>3</sub>CN—DMF; XXVI and XXXII, from 3:1 alcohol—CH<sub>3</sub>CN; XXVIII, from acetic anhydride; XXXIII, from 2:1 acetic anhydride—acetic acid.

**3-Amino-2-R<sup>1</sup>-5-methyl-7-phenylthiazolo[3,2-a]pyrimidinium Salts (VII-XII).** A mixture of 2-mercapto-4-methyl-2-phenylpyrimidine (I) (1 g, 5 mmole) and the corresponding nitrile III-V (5.2 mmole) was heated for 2 h at 90-100 °C. The melt was triturated with acetone. The precipitate was filtered off and washed with ether. It was converted to the perchlorate using an alcohol solution of sodium perchlorate and crystallized from alcohol. For the phenylsulfonates XII and XIV, λ<sub>max</sub>, nm (log ε) in CH<sub>3</sub>CN: 300 (4.32), 391 (4.09) and 342 (4.25), 401 (4.37).

**3-Amino-5-methyl-7-(4-methoxyphenyl)-2-phenylthiazolo[3,2-a]pyrimidinium Salts (XIII, XIV).** A mixture of II (0.46 g, 2 mmole) and cyanobenzylbenzenesulfonate (0.55 g, 2 mmole) was heated for 1 h at 90 °C. The melt was triturated with acetone. The product was filtered off. The perchlorate was prepared analogously to the preceding one.

**2-R<sup>1</sup>-7-Aryl-5-formylthiazolo[2',3',4':1,9,8]pyrimido[3,4-c]pyrimidines (XVI-XIX).** Phosphoryl chloride (1 ml) was cooled to 0 °C and slowly treated with DMF (1 ml). The corresponding salt of VII-XIV (1 mmole) was added to the resulting mixture. The mixture was heated for 1-2 h at 100-110 °C. The resulting solution was poured onto ice (100 g). The precipitate was filtered off, dried in air, dissolved in CHCl<sub>3</sub>, and chromatographed on alumina.

**Dimethylcyanines XXV-XXXIII.** These were prepared by heating equimolar amounts of XVI-XIX and the corresponding quaternary 2-methylbenzazolium salts XX-XXIV in acetic anhydride. The dye was filtered off and washed with alcohol.

**2,7-Diphenyl-5-(2,2-dicyanoethenyl)thiazolo[2',3',4':1,9,8]pyrimido[3,4-c]pyrimidine (XXXV).** A mixture of XVIII (0.36 g, 1 mmole), malononitrile (0.07 g, 1 mmole), and acetic anhydride (5 ml) was heated to boiling. After cooling, the product was filtered off and washed with acetic anhydride and then alcohol.

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