CYCLAZINES AND THEIR ANALOGS
3.* THIAZOLOPYRIDO- AND THIAZOLO-PYRIMIDOPYRIMIDINES

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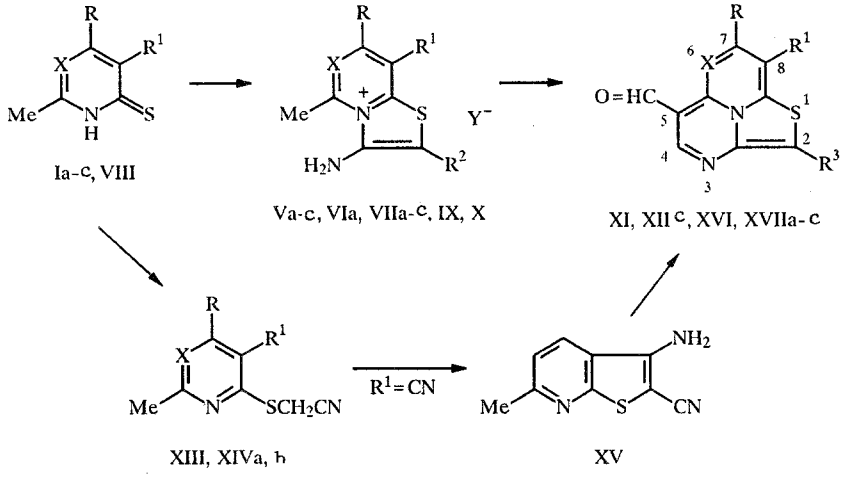
The formylation of 2-methyl-6-cyanomethylthiopyridines, 2-methyl-4-cyanomethylthiopyrimidines, or 3-amino-5-methylthiazolopyrimidinium salts gave cyclazine derivatives of new heterocyclic systems with an angular nitrogen atom, which were used for the preparation of polymethine dyes. The relationship of the color and structure of these compounds was studied.

In previous work [1, 2], we found that formyl derivatives of thiazolo[2′,3′,4′:1,9,8]pyrimido[3,4-*c*]pyrimidine have extremely unusual spectral characteristics and may be used for the preparation of highly-colored dyes. Thus, we undertook a study of the relationship of color and the structure of thiazolopyrido- and thiazolopyrimidopyrimidines.

Formylation of the corresponding 2-methyl-6-cyanomethylthiopyridines, 4-cyanomethylthio-2-methylpyrimidines, 3-amino-5-methylthiazolo[3,2-*a*]pyridinium salts, and 3-amino-5-methyl-7-phenylthiazolo[3,2-*c*]pyrimidinium salts was required for the synthesis of this type of new heterocycles by analogy to our previous procedure [1].

The required starting reagents for the thiazolopyridinium salts were obtained by the alkylation of the corresponding mercaptopyridines (Ia)-(Ic), α-cyanobenzylbenzenesulfonate (II), α-bromoacetonitrile (III), or α-bromopropionitrile (IV) upon heating.



a R = R¹ = H; b R = Ph, R¹ = H; c R = H, R¹ = CN; V R² = H; VI R² = Me; VII, VIII, XII R², R³ = Ph; XVI, XVII R³ = CH=O; VII, IX Y = PhSO₃; V, VI Y = Br; X Y = ClO₄; I—VII, XII, XIV, XVII X = CH; VIII—XI, XVI X = N, R = Ph, R¹ = H

*For Communication 2, see ref. [1].

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TABLE 1. PMR Spectral Data for V-XVII

Compound	Solvent	Chemical shift, δ, ppm			
		CH_3	CH_2	Ar—H	CH=O
Va	DMSO	3,20		8,52 d (1H); 8,00 t (1H); 7,60 d (1H); 1,17 s (1H)	
Vc	CF_3COOD	3,56		8,42 d (1H); 7,73 d (1H); 7,55 s (1H)	
VIa		2,50; 3,27		8,52 d (1H); 8,00 t (1H); 7,66 d (1H)	
VIIa		3,29		8,58 d (1H); 8,09 t (1H); 7,5...7,8 (9H); 7,28 m (2H)	
XII[c]	CF_3COOD			8,22 d (1H); 7,95 d (1H); 7,6 m (6H)	9,21
XIVa	$CDCl_3$	2,54	4,04	7,47 t (1H); 7,04 d (1H); 6,90 d (1H)	
XIV[b]	DMSO	2,56	4,33	7,8 (2H); 7,0...7,4 (5H)	
XV	CF_3COOD	3,08		7,90 d (2H); 8,95 d (2H)	
XVIIa	$CDCl_3$			7,86 d (1H); 7,51 s (1H); 7,31 t (1H); 6,76 d (1H)	9,80; 9,25
XVIIa	CF_3COOD			8,41 d (1H); 7,99 t (1H); 7,81 s (1H); 7,73 d (1H)	9,79; 9,46
XVIIb	CF_3COOD			8,77 d (1H); 7,6...8,0 (7H)	9,79; 9,53
XVIIc	CF_3COOD			8,51 (2H); 7,97 (1H)	9,87; 9,52

A typical PMR spectrum of thiazolopyridine Va in DMSO-d_6 (Table 1) shows a methyl group singlet as well as signals for thiazole and pyridine ring protons at 3.20, 7.17, 8.52 d, 8.00 t, and 8.52 ppm. Furthermore, these spectra show a broad signal for the amino group protons, which disappears upon the addition of heavy water due to deuterium exchange.

On the other hand, the thiazolopyrimidinium salts may be obtained only upon alkylation of 4-mercaptopyrimidine (VIII) by benzenesulfonate (II).

We found that aldehydic derivatives of the new heterocyclic cyclazine systems (analogously to the reaction of the corresponding thiazolo[3,2-*a*]pyrimidinium salt derivatives of 2-mercaptopyrimidine [1]) are found upon the formulation of Va-Vc, VIa, VIIa-VIIc, IX, and X by the DMF—$POCl_3$ complex only in the case of the thiazolo[3,2-*c*]pyrimidinium salts and the use of 8-cyano-substituted 3-aminothiazolopyridinium salts. This result is apparently related to the strong activation of the methyl group protons in such derivatives by electron-withdrawing substituents such as the nitrile group or nitrogen atom.

The structures of the aldehyde products also were indicated by elemental analysis, IR and PMR spectroscopy, and chemical transformations. Thus, for example, the PMR spectrum of diformylcyclazine XVIIc (in CF_3COOD) lacks signals for methyl group protons and the thiazole group fragment of starting thiazolopyridine Vc but shows singlets for the protons of two aldehyde groups at lower field (9.87 and 9.52 ppm) and cyclazine ring proton signals at higher field.

The corresponding 2-cyanomethylthiopyridines, XIVa and XIVb, and 4-cyanomethylthiopyrimidine, XIII were obtained by the usual method upon alkylation of mercaptopyridines Ia and Ib and mercaptopyrimidine VIII by α-chloro- or α-bromoacetonitriles in an alkaline medium. However, in the case of cyanopyridine Ic, the reaction does not stop at this step, but rather intramolecular cyclization of pyridine XIVc to give thienopyridine XV occurs immediately by analogy to the results of Shvedov [3] and Elgemeic [4].

The composition and structure of the products were supported by elemental analysis, IR and PMR spectroscopy, and their chemical transformations. Thus, for example, the PMR spectrum of pyrimidine XIII (in $CDCl_3$) shows singlets for the methyl and methylene group protons and signals for the phenyl protons and proton of the pyrimidine ring at 2.75 (3H), 3.90 (2H), 7.4-7.6 (4H), and 8.0-8.1 ppm (2H).

Cyanomethylthioazine products XIII, XIVa, and XIVb, in contrast to the corresponding thiazolopyrimidinium salts, are readily formylated by Vilsmeier reagent to give dialdehydes XVI, XVIIa, and XVIIb.

Thus, for example, the PMR spectrum of diformylcyclazine XVI (in CF_3COOD) lacks signals for the methyl and methylene group protons of starting pyrimidine XIII but display singlets for the protons of the two aldehyde groups at lower field (10.17 and 9.83 ppm) and signals for the protons of the phenyl substituent and two protons of the cyclazine ring at 7.71 (3H), 8.19 (2H), and 8.00 (1H), and 8.25 ppm (1H), respectively.

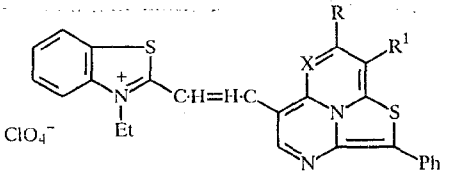
The electronic absorption spectra of XI, XII, XVI, and XVII, as in the case of the isomeric aldehydes discussed in our previous work [1, 2], show a broad, much less intense band in the visible region with pronounced vibrational structure in addition to strong bands at 400-450 nm. The absorption curve for dialdehydes XVI and XVII is similar in shape to the spectra of typical polymethine dyes (narrow band with pronounced maximum and inflection in its short-wavelength tail) [5].

TABLE 2. Indices of Thiazolopyrimidopyrimidine Products

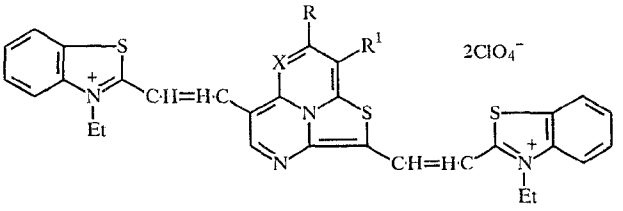
Compound	Chemical formula	Mp, °C	λ_{max}, nm (lg ε)	Yield, %
IX	$C_{25}H_{21}N_3O_3S_2$	213...214		53
X	$C_{19}H_{16}ClN_3O_4S$	262...264		58
XIII	$C_{13}H_{11}N_3S$	123...124		83
XI	$C_{21}H_{13}N_3OS$	242...243	430 (4,32); 602 (2,31)	57
XVI	$C_{18}H_9N_3O_2S$	274...275	449 (4,63); 571 (2,30)	55
XVIII	$C_{31}H_{23}ClN_4O_4S_2$	263...264	454 (4,19); 576 (4,69)	65
XIX	$C_{36}H_{29}Cl_2N_4O_8S_3$	271...272	438 (4,25); 720 (4,92)	51

We note that the maxima of the bands at longest wavelength for these new cyclazine products are shifted by ~ 10-20 nm toward longer wavelengths but have lower molecular extinction coefficients in comparison with their analogs [1]. On the other hand, the maxima of the second bands have similar intensity and are also shifted bathochromically. These results indicate a significant effect of the position of the nitrogen atom in formyl-substituted thiazoloazinopyrimidine derivatives.

Aldehydes XI, XVI, XII, and XVII react readily with nucleophilic reagents to give polymethine dyes. For example, these aldehydes react with 2-methyl-3-ethylbenzothiazolium perchlorate to give thiacyanines XVIII and XX and biscyanines XIX and XXI, respectively.



XVIII, XX



XIX, XXIa-c

a R = R^1 = H; b R = Ph, R^1 = H; c R = H, R^1 = CN; XVIII, XIX R = Ph, R^1 = H, X = N; XX R = H, R^1 = CN, X = CH; XXI X = CH

Analysis of the relationship of the color and structure of dye products XVIII and XIX (Table 2) with the analogous characteristics of the corresponding isomeric compounds showed that the effect of altering the site of substitution of the methine group by an electron-withdrawing nitrogen atom is opposite for dyes derived from mono- and dialdehydes. Thus, for example, thiacyanine XVIII has a maximum at higher wavelength (24 nm), while biscyanine XIX has a maximum at lower wavelength (10 nm) in comparison with the isomeric polymethines [1, 2]. This effect may be related to the difference in the effective length of the cyclazine system in the dyes. In such a case, absorption at higher wavelength should be observed for the mono derivatives, while absorption at lower wavelength should be observed for the bis dyes due to an increase in the interaction of the chromophores [5] as a result of approximation of the absorption maxima of the corresponding "mother" dyes. It is interesting that the absorption maxima of the dyes derived from the cyclazine analogs obtained are observed at longer wavelengths in comparison with derivatives of ordinary nitrogen heterocycles. For example, the absorption maximum of the symmetrical carbocyanine dye derived from benzothiazole is at 558 nm [6]. We should note that an additional bathochromic shift is found upon going from the mono- to biscyanines. Thus, the bathochromic shift upon this structural alteration for dyes XX and XXIc is 100 nm, which indicates a significant role of the cyclazine system in the interaction of the chromophores in such molecules.

Analysis of the relationship of color and the structure of the thiazolopyrididopyrimidine dye products XX and XXI (Table 3) with the analogous azaanalogs XVIII and XIX showed that replacement of the electron-withdrawing nitrogen atom

TABLE 3. Indices of the Thiazolopyrimidopyrimidine Derivatives Synthesized

Compound	Chemical formula	Mp, °C	λ_{max}, nm (lg ε)	Yield, %
Va	$C_8H_9BrN_2S$	168...169		68
Vb	$C_{14}H_{13}BrN_2S$	175...176		74
Vc	$C_9H_8BrN_3S$	143...144		83
VIa	$C_9H_{11}BrN_2S$	206...207		64
VIIa	$C_{20}H_{18}N_2O_3S_2$	227...228		71
VIIb	$C_{26}H_{22}N_2O_3S_2$	233...234		74
VIIc	$C_{21}H_{17}N_3O_3S_2$	236...237		60
XIIc	$C_{17}H_9N_3OS$	278...279	403 (4,41); 611 (3,51)	75
XVIIa	$C_{11}H_6N_2O_2S$	232...234	450 (4,67); 567 (2,58)	58
XVIIb	$C_{17}H_{10}N_2O_2S$	277...278	453 (4,60); 567 (2,78)	77
XVIIc	$C_{12}H_5N_3O_2S$	272...273	446 (4,32); 591 (3,38)	66
XIVa	$C_8H_8N_2S$	161...162		70
XIVb	$C_{14}H_{12}N_2S$	144...145		80
XV	$C_9H_7N_3S$	173...174		71
XX	$C_{26}H_{19}ClN_4O_4S_2$	268...269	632 (4,79)	64
XXIa	$C_{31}H_{26}Cl_2N_4O_8S_3$	293...294	435 (4,20); 773 (5,08)	73
XXIб	$C_{37}H_{30}Cl_2N_4O_8S_3$	273...274	443 (4,43); 776 (5,12)	80
XXIв	$C_{32}H_{25}ClN_5O_8S_3$	286...287	441 (4,27); 725 (4,91)	68

of the methine group leads to a strong shift in the absorption spectrum toward the infrared region. For example, this shift for dye XXIb (λ_{max} 776) in comparison with the corresponding isomeric thiazolopyridopyrimidine derived from 2-mercaptopyrimidine is 66 nm. Analogously, the introduction of an electron-withdrawing nitrile group at C^8 also leads to a shift in the absorption maximum of the corresponding thiacyanine by 48 nm. This effect may be related to a decrease in the effective length of the cyclazine system in the dyes upon increasing the electron-withdrawing capacity of the group located at C^8. In this case, a slight bathochromic shift should be observed for the mono derivatives, while a somewhat greater bathochromic shift due to a further "band separation" as a consequence of chromophore interaction should be seen for the bis dyes [6].

Thus, these findings may be used for the planned synthesis of new polymethine dyes with predictable properties.

EXPERIMENTAL

The absorption spectra were taken on an SF-8 spectrometer in acetonitrile, while the PMR spectra were taken on a WP-100 SY spectrometer with TMS as the internal standard. The purity of the compounds was monitored by thin-layer chromatography on Silufol UV-254 plates using 9:1 chloroform-methanol as the eluent.

The elemental analysis data for these products for N, S, and Cl corresponded to the calculated values.

3-Amino-5-methyl-7-R-8-R^1-2-R^2-thiazolo[3,3-*a*]pyrimidinium salts (V) and (VII). A mixture of 2 mmoles of the corresponding pyridine Ia-Ic and 2 mmoles sulfonate II or bromonitrile III or IV was heated for 2 h at 100°C. The precipitate was triturated with acetone, filtered off, and washed with acetone. The salts were used without purification.

3-Amino-5-methyl-2,7-diphenylthiazolo[3,2-*c*]pyrimidinium salts (IX) and (X). A mixture of 0.4 g (2 mmoles) pyrimidine VIII and, 0.54 g (2 mmoles) sulfonate II was heated for 2 h at 100°C. The precipitate was triturated with acetone. The benzenesulfonate was filtered off and washed with acetone. In order to obtain the perchlorate, an equimolar amount of ethanolic sodium perchlorate was added to a solution of salt IX in ethanol. The precipitate formed was filtered off, washed with ethanol, and crystallized from ethanol.

2-Phenyl-5-formylthiazolo[2′,3′,4′:4,5,6]pyrimido[1,2-*c*]pyrimidine (XI). A sample of 1 mmole thiazolopyrimidinium salt IX or X was added to a mixture of 1.5 ml $POCl_3$ and 1.5 ml DMF prepared at 0°C and heated for 2 h at 100°C. The reaction mixture was poured into about 100 g ice. The precipitate formed was filtered off, dissolved in 200 ml chloroform, and subjected to chromatography on about 10 g alumina using chloroform as the eluent. The highly colored fraction was collected ($R_f \sim 0.7$).

2-Methyl-4-cyanomethylthio-6-phenylpyrimidine (XIII). A mixture of 0.2 g (1 mmole) pyrimidine VIII, 4 ml 5% aqueous sodium hydroxide, and 0.1 g (1 mmole) chloroacetonitrile was stirred for 2 h. The mixture was diluted with 100 ml water and XIII was filtered off and crystallized from aqueous ethanol. The yield of XIII was 0.2 g.

2-Methyl-6-cyanomethylthio-4-R-pyridine (XIVa) and (XIVb). A mixture of 1 mmole pyridine I, 4 ml 5% aqueous sodium hydroxide, and 1 mmole of chloro- or bromoacetonitrile was stirred for 2 h. The mixture was diluted with water. The precipitate was filtered off and crystallized from aqueous ethanol.

3-Amino-6-methyl-2-cyanothieno[2,3-*b*]pyridine (XV) was obtained by analogy to the previous procedure and crystallized from ethanol.

2,5-Diformylthiazolo[2′,3′,4′:4,5,6]pyrimido[1,2-*c*]pyrimidine (XVI) was obtained by analogy to the previous procedure from pyrimidine XIII.

5-Formyl-8-cyano-2-R^3-thiazolo[4′,3′,2′:1,9,8]pyrido[1,2-*c*]pyrimidines (XIIc) and (XVIIc). A sample of 1 mmole thiazolopyridinium salt Vc or VIIc was added to a mixture of 1.5 ml $POCl_3$ and 1.5 ml DMF prepared at 0°C and heated for 2 h at 100°C. The reaction mixture was poured onto ice. The precipitate formed was filtered off and subjected to chromatography on alumina using chloroform as the eluent.

2,5-Diformyl-7-R-thiazolo[4′,3′,2′:1,9,8]pyrido[1,2-*c*]pyrimidines (XVIIa) and (XVIIb) were obtained analogously to the previous procedure from pyridines XIVa and XIVb.

5-[2-(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-2,7-diphenyl-5H-thiazolo[2′,3′,4′:4,5,6]pyri-mido[1,2-*c*]pyrimidinium perchlorate (XVIII). A mixture of 0.33 g (1 mmole) aldehyde XI, 0.28 g (1 mmole) 2-methyl-3-ethylbenzothiazolium perchlorate and 4 ml acetic anhydride was heated to reflux. The precipitated dye was filtered off and crystallized from acetonitrile.

2,5-Bis[2-(3-ethylbenzothiazolio-2-yl)vinyl]-7-phenylthiazolo[2′,3′,4′:4,5,6]pyrimido[1,2-*c*]pyrimidinium diperchlorate (XIX) was obtained by analogy to the previous procedure from 1 mmole dialdehyde XVI and 2 mmoles benzothiazolium salt.

5-[2-(3-ethyl-2(3H)-benzothiazolylidene)ethylidene]-2-phenyl-8-cyano-5H-thiazolo[4′,3′,2′:1,9,8)pyrido[1,2-*c*]pyrimidinium perchlorate (XX). A mixture of 0.30 g (1 mmole) aldehyde XIIc, 0.28 g (1 mmole) 2-methyl-3-ethylbenzothiazolium perchlorate, and 4 ml acetic anhydride was heated to reflux. The precipitated dye was filtered off and crystallized from acetonitrile.

2,5-Bis[2-(3-ethylbenzothiazolio-2-yl)vinyl]-7R-thiazolo[4′,3′,2′:1,9,8]pyrido[1,2-*c*]pyrimidinium diperchlorate (XXIa) and (XXIb) was obtained analogously to the previous procedure from the corresponding dialdehydes XVII (1 mmole) and 2 mmole benzothiazolium salt.

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