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CYCLAZINES AND THEIR ANALOGS.
4.* SYNTHESIS OF TRIAZOLOPYRIDO[1,2-*c*]PYRIMIDINES

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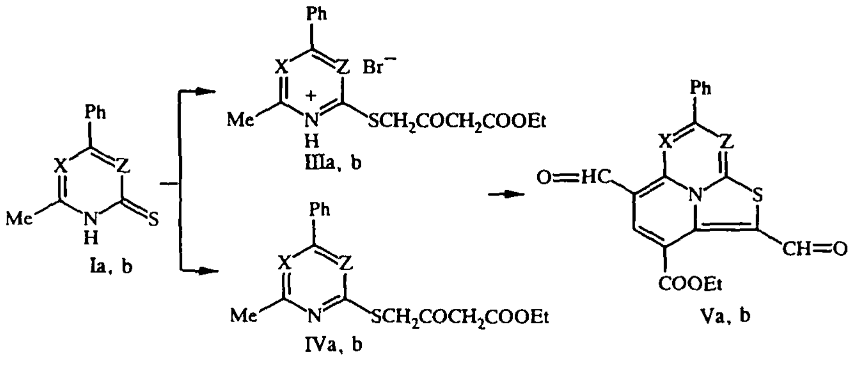
Alkylation of isomeric 2-mercapto-6- and 4-mercapto-2-methylpyrimidines by ethyl γ-bromoacetoacetate yields the corresponding S-substituted pyrimidines. Formylation of these intermediates by the Vilsmeier reagent gives diformyl derivatives of a new cyclazine series, namely, thiazolopyridopyrimidines. These cyclazine dialdehydes react with nucleophilic reagents used for the synthesis of polymethine dyes to give highly colored biscyanines. The interrelationship between the color and structure of these heterocyclic products and derived dyes was analyzed.

The reaction of 2- and 4-mercaptopyrimidines with ethyl γ-bromoacetoacetate was studied in an attempt to synthesize new condensed cyclazine heterocycles.

The corresponding thiazolo[3,2-*a*]pyrimidines are usually formed in the reaction of 2-mercaptopyrimidines with α-haloketones [2]. However, we found that closure of the thiazole ring does not occur in the alkylation of mercaptopyrimidines Ia and Ib by ethyl γ-bromoacetoacetate (II) in neutral media but rather the hydrobromide salts of the corresponding substituted alkylthiopyrimidines IIIa and IIIb are formed. In alkaline media, this reaction leads to pyrimidines IVa and IVb.



I–V a X = CH, Z = N; b X = N, Z = CH

The composition and structure of the compounds synthesized were indicated by elemental analysis and PMR spectroscopy. Thus, for example, the PMR spectrum of IVa (Table 1) shows signals for the ethoxy group and two methylene groups of the γ-substituted ethyl acetoacetate residue and also signals for the protons of the methyl group, phenyl substituent, and pyrimidine ring.

Our study showed that treatment of IIIa, IIIb, IVa, and IVb by DMF-$POCl_3$ leads to formylation at the methylene and methyl groups with concurrent construction of thiazole and pyridine rings fused to the pyrimidine residue to give dialdehydes of a new cyclazine series, namely, thiazolo[2′,3′,4′:1,9,8]pyrido[1,2-*c*]pyrimidine (Va) and thiazolo[2′,3′,4′:4,5,6]pyrido-[1,2-*a*]pyrimidine (Vb).

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*For Communication 3, see [1].

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TABLE 1. PMR Spectra of IV and V

Compound	Solvent	Chemical shift, δ, ppm (rel. intensity)			
		CH_3	CH_2	Ar—H	CH=O
IVa	DMSO	1,15 t, 2,48 s	3,82 s*, 4,08 q, 4,28 s	7,4...7,6 and(3H); 8,1...8,2 and (2H); 7,77 s (1H)	
IVb	CF_3COOD	1,41 t, 3,07 s	4,11 s, 4,43 q, 4,54 s	7,7...7,9 m(6H)	
Va	$CDCl_3$	1,38 t	4,35 q	7,5 m (3H); 7,82 s (1H); 8,0 m (2H); 8,41 s (1H)	9,42 s, 10,42 s
Vb	$CDCl_3$	1,39 t	4,30 q	7,6...7,9 m(5H); 8,25 s (1H); 9,81 s (1H)	10,26 s, 10,48 s

*This signal disappears upon the addition of D_2O due to deuteroexchange.

TABLE 2. Absorption Spectra of Products

Compound	λ_{max}, nm (log ε) in CH_3CN	Compound	λ_{max}, nm (log ε) in CH_3CN
Va	603 (3,84); 456 (4,45); 327 (4,48)	VIIa	743 (4,78)
Vb	613 (3,00); 474 (4,42); 317 (4,40)	VIIb	722 (4,82)

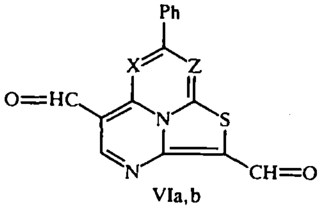
TABLE 3. Physical Indices of Products

Compound	Chemical formula	Found, % / Calculated, %		mp, °C	Yield, %
		N	S		
IIIa	$C_{17}H_{19}BrN_2O_3S$	$\frac{6{,}12}{6{,}10}$	$\frac{7{,}75}{7{,}78}$	298...299	71
IIIb	$C_{17}H_{19}BrN_2O_3S$	$\frac{6{,}00}{6{,}10}$	$\frac{7{,}69}{7{,}78}$	274...275	58
IVa	$C_{17}H_{18}N_2O_3S$	$\frac{8{,}49}{8{,}48}$	$\frac{9{,}79}{9{,}70}$	218...220	60
IVb	$C_{17}H_{18}N_2O_3S$	$\frac{8{,}48}{8{,}48}$	$\frac{9{,}72}{9{,}70}$	196...197	52
Va	$C_{20}H_{14}N_2O_4S$	$\frac{8{,}47}{8{,}46}$	$\frac{7{,}27}{7{,}41}$	241...242	41
Vb	$C_{20}H_{14}N_2O_4S$	$\frac{8{,}36}{8{,}46}$	$\frac{7{,}26}{7{,}41}$	239...240	48
VIIa	$C_{40}H_{34}ClN_4O_{10}S_3$	$\frac{6{,}60}{6{,}51}$	$\frac{10{,}64}{10{,}70}$	278...280	62
VIIb	$C_{40}H_{34}ClN_4O_{10}S_3$	$\frac{6{,}50}{6{,}51}$	$\frac{10{,}56}{10{,}70}$	254...255	54

The structures of these aldehydes were also indicated by chemical analysis, IR and PMR spectroscopy, and chemical transformations. Indeed, the PMR spectra of diformylcyclazines V (Table 1) lack signals for the protons of the pyrimidine methyl group and methylene groups of the ethyl acetoacetate residue of starting pyridines III but have downfield singlets for the protons of the two aldehyde groups and upfield signals for the cyclazine ring protons.

The electronic absorption spectra of Va and Vb (Table 2), similar to the case of previously described similar dialdehydes VIa and VIb [1], have strong bands in the vicinity of 450 nm and a broad, much weaker band in the visible region with pronounced vibrational structure, which is similar in shape to the absorption curves of typical polymethine dyes [4, 5].

We note that the maxima of the bands at longest wavelength of these new cyclazines are shifted toward longer wavelengths by 40-50 nm relative to their analogs [1, 3].

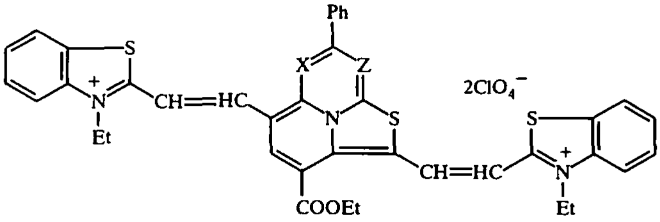


VIa,b

a X = CH, Z = N; b X = N, Z = CH

Aldehydes Va and Vb may be used to obtain polymethine dyes. For example, the reaction of these compounds with 2-methyl-3-ethylbenzothiazolium perchlorate gives biscyanines VIIa and VIIb.

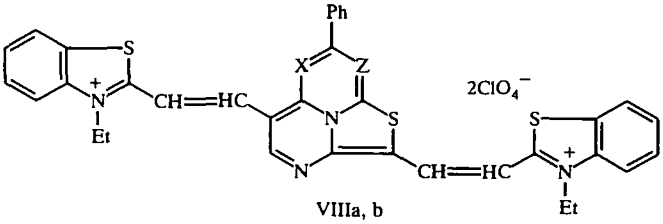
Analysis of the relationship of the color and structure of dyes VIIa and VIIb (Table 2) with the analogous indices of corresponding products derived from isomeric thiazolopyrimidopyrimidines VIIIa and VIIIb [1, 3] showed that the effect of the relative position of the methine group and the more electron-withdrawing nitrogen atom is opposite to that for dyes derived from thiazolopyrido- (VII) and thiazolopyrimidine dialdehydes (VIII). Thus, for example, thiacyanine VIIa has deeper color (21 nm) than its isomer VIIb. On the other hand, the analogous change in structure in cyanines VIII leads to the opposite effect, namely, the absorption band maximum for VIIIa is 10 nm higher than for its isomer VIIIb [1, 3]. New heterocyclic dyes VIIa and VIIb, similar to starting dialdehydes Va and Vb, have deeper color than their structural analogs VIIIa, VIIIb, VIa, and VIb. This effect is probably related to alteration of the effective length of the cyclazine system in the dyes.



VIIa, b

a X = CH, Z = N; bX = N, Z = CH

The absorption maxima of the dyes derived from cyclazine analogs are found at longer wavelengths in comparison with derivatives of ordinary nitrogen heterocycles. For example, the absorption maximum of the symmetrical benzothiazole carbocyanine dye is at 558 nm [5].



VIIIa, b

Thus, this chemical behavior may be used for the synthesis of new polymethine dyes with given characteristics.

EXPERIMENTAL

The absorption spectra for acetonitrile solutions were carried out on an SF-8 spectrophotometer. The PMR spectra were carried out on a Bruker WP-100SY spectrometer at 100 MHz with TMS as the internal standard. The purity of the products was monitored by thin-layer chromatography on Silufol UV-254 plates using 9:1 chloroform–methanol as the eluent. Data for these compounds are given in Table 3.

4-Methyl-6-phenyl-2- and 2-Methyl-6-phenyl-4-(3-ethoxycarbonyl-2-oxopropylthio)pyridinium Hydrobromide Salts (IIIa and IIIb). A mixture of 2 mmoles corresponding pyridine Ia-Ic and 2 mmoles ethyl γ-bromoacetoacetate II was fused at 100°C for 2 h. The precipitate was triturated with acetone. The product was filtered off and washed with acetone.

4-Methyl-6-phenyl-2- and 2-Methyl-6-phenyl-4-(3-ethoxycarbonyl-2-oxopropylthio)pyridines (IVa and IVb). A mixture of 2 mmole corresponding pyridine Ia-Ic, 10 ml 2% aq. NaOH, and 3 mmoles ethyl γ-bromoacetoacetate was stirred for 1 h at room temperature. The precipitated product was filtered off, washed with water, and crystallized from aqueous ethanol.

2,5-Diformyl-7-phenyl-3-ethoxycarbonylthiazolo[2',3',4':1,9,8]pyrido[1,2-*c*]pyrimidine (Va). A sample of 1 mmole hydrobromide IIIa or pyrimidine IVa was added to a mixture of 1.5 ml $POCl_3$ and 1.5 ml dimethylformamide prepared at 0°C and heated for 5 h at 80°C. The reaction mixture was poured onto ~ 100 g ice. The precipitated product was filtered off, dissolved in 200 ml chloroform, and subjected to chromatography on a column packed with ~ 10 g alumina using chloroform as the eluent. The highly colored fraction with $R_f \sim 0.7$ was collected.

2,5-Diformyl-7-phenyl-3-ethoxycarbonylthiazolo[2',3',4':4,5,6]pyrido[1,2-*a*]pyrimidine (Vb) was obtained by analogy to the previous procedure from hydrobromide IIIb or pyrimidine IVb.

2,5-Bis[2-(3-ethylbenzothiazolio-2-yl)vinyl]-7-phenylthiazolo[2',3',4':1,9,8]pyrido[1,2-*c*]pyrimidinium Diperchlorate (VIIa). A mixture of 1 mmole dialdehyde Va, 2 mmoles 2-methyl-3-ethylbenzothiazolium perchlorate, and 4 ml acetic anhydride was heated at reflux for 5 min. 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]pyrido[1,2-*a*]pyrimidinium diperchlorate (VIIb) was obtained by analogy to the previous procedure from 1 mmole corresponding dialdehyde Vb and 2 mmoles benzothiazolium salt.

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