CONDENSED HETEROCYCLES WITH A THIAZOLE RING. 6.* NEW METHOD FOR THE PREPARATION OF IMIDAZO[1,2-c]THIAZOLIUM AND THIAZOLO[3,4-a]PYRIMIDINIUM SALTS

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New derivatives of condensed heterocyclic systems with a thiazole ring, viz., thiazolo[3,4-a]pyrimidinium and imidazo[1,2-c]thiazolium salts, were obtained by the reaction of α -cyanobenzyl benzenesulfonate with N-[(methylthio)thiocarbonyl]amino acids. The structures of the synthesized compounds were proved by means of the IR and PMR spectral data.

Valuable physiologically active preparations, such as immunostimulators of the levamisole type, have been found among derivatives of condensed heterocyclic systems with a nodal nitrogen atom that are constructed on the basis of thiazole and imidazole or pyrimidine rings [2]. Least study has been devoted to imidazo[1,2-c]thiazoles because of their inaccessibility. Only specific methods for obtaining some derivatives of this series have been described [3, 4].

In order to develop a general method for the preparation of new imidazo[1,2-c]thiazoles we studied the reaction of α -cyanobenzyl benzenesulfonate (I) with amino acid derivatives (IIa-c). Inasmuch as it is known [5, 6] that 4-aminothiazoles are formed by the action of sulfonate I on dithiocarbamates, one also might have expected the formation of thiazolium salts of the III type in the case under consideration. However, it was found that the reaction does not stop at this stage but is immediately followed by intramolecular acylation, which leads to imidazothiazoles (IVa-c, Table 1).



II, IV a R = H, b $R = CH_3$, c $R = C_6H_5$

The structures of the compounds obtained are confirmed by data from the IR and PMR spectra. The IR spectra of the condensation products do not contain bands of stretching vibrations of C=S, C=O, N-H, and O-H bonds of the starting N-[(methylthio)thiocarbonyl]- α -amino acids IIa-c (1500-1510, 1690-1710, and 3200-3330 cm⁻¹) or of the C=N bond of sulfonate I (2200 cm⁻¹) but do contain bands that are characteristic for the vibrations of the C=O bond of cyclic five-membered amides (1750-1760 cm⁻¹). Signals of protons of methylthio groups, of the 3-H protons of the imidazolone ring [4.53, 4.80 (q, J = 7 Hz), 5.70 ppm, respectively], and of protons of phenyl groups (7.00-7.04 ppm) are observed in the PMR spectra of IVa-c. The small shift of the signal of the methylthio group of IVc to the strong-field region (2.43 ppm) as compared with the analogous signal of imidazothiazoles IVa, b (2.57 ppm) can be explained by the shielding effect of the ring currents of the close-lying phenyl group in the 3 position.

The formation of condensed heterocycles also occurs in the reaction of benzenesulfonate I with the corresponding β -amino acid derivatives. For example, thiazolo[3,4-a]pyrimidine V $\overline{*}$ See [1] for communication 5.

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TABLE 1. Perchlorates IV and V and Dyes VI and VII

Com- pound	mp, deg C	Found, %		Empirical formula	Calculated, %		Yield, %
		Cl (N)	s		C1 (N)	s	
IVa IVb IVc V VI VI	$\begin{array}{r} 242-244\\ 238-240\\ 235-236\\ 200-202\\ 301-303\\ 319-321 \end{array}$	$ \begin{array}{r} 10,0 \\ 9,4 \\ 8,3 \\ 9,5 \\ 6,8' \\ (10,8) \end{array} $	18,0 17,0 14,6 17,1 12,4 24,3	$\begin{array}{c} C_{12}H_{11}ClN_2O_5S_2\\ C_{13}H_{13}ClN_2O_5S_2\\ C_{18}H_{15}ClN_2O_5S_2\\ C_{13}H_{13}ClN_2O_5S_2\\ C_{22}H_{20}ClN_3O_5S_2\\ C_{22}H_{20}ClN_3O_5S_3\\ C_{16}H_{15}N_2O_2S_3 \end{array}$	9,8 9,5 8,1 9,5 7,0 (10,8)	17,7 17,0 14,6 17,0 12,7 24,7	$ \begin{array}{r} 65\\ 80\\ 88\\ 45\\ 82\\ 60\\ \end{array} $

was obtained in the reaction with N-[(methylthio)thiocarbonyl]- β -alanine. The composition and structure of perchlorate V were proved by the results of **elemental analysis and data** from the IR and PMR spectra (see the Experimental section). The 55-cm⁻¹ decrease in the frequency of the stretching vibrations of the C=O bond in the V molecule (1695 cm⁻¹) as compared with imidazothiazole IVa is in agreement with the increase in the ring size from a five-membered system to a six-membered system, i.e., with the decrease in the strain in it.

The ease of formation of imidazole or pyrimidine rings can be explained by the close orientation of the carboxy group and the extremely nucleophilic amino group in intermediate III, which is also responsible for cyclization to give a condensed system.



Salts IV and V react in the usual way with the nucleophilic reagents that are used for the synthesis of polymethine dyes. Thus, for example, monomethylidynecyanine VI and nullomethylidynemerocyanine VII, respectively, are formed in the reaction of perchlorate V with 2-methyl-3-ethylbenzothiazolium toluenesulfonate or 3-ethylrhodanine. The absorption maxima of the synthesized dyes are close to the analogous characteristics of the corresponding dyes from 4-amino-3-ethyl-5-phenylthiazolium salts (452 nm) [6].

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CF_3COOH were obtained with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were obtained with a UR-10 spectrometer. The electronic spectra of solutions in DMF were recorded with an SF-10 spectrophotometer.

 $\frac{3-R-5-Methylthio-2-oxo-7-phenyl-2, 3-dihydro-1H-imidazo[1,2-c]thiazolium Perchlorates}{(IVa-c, Table 1). A mixture of equimolar amounts of sulfonate I and the corresponding N-[(methylthio)thiocarbonyl]-<math>\alpha$ -amino acid (IIa-c) was heated at 50-70°C for 1 h, after which the melt was triturated with acetone, and the thiazolium salt was removed by filtration and converted to the perchlorate in alcohol solution. The product was crystallized from alcohol.

 $\frac{6-\text{Methylthio-2-oxo-8-phenyl-1,2,3,4-tetrahydrothiazolo[3,4-a]pyrimidinium Perchlorate}{\text{This compound was similarly obtained from sulfonate I and N-[(methylthio)thiocarbonyl]$ β-alanine. PMR spectrum: 2.57 (3H, s, SCH₃), 2.83 (2H, t, J = 6 Hz, 3,3-H₂), 4.20 (2H, t, 4,4-H₂), and 7.02 ppm (5H, s, 8-C₆H₅).

 $\frac{2-0 \times o-8-\text{phenyl-6-[(3-ethylbenzothiazolin-2-ylidene)methyl]-1,2,3,4-tetrahydrothiazolo[3, 4-a]pyrimidinium Perchlorate (VI). A mixture of 0.37 g (1 mmole) of perchlorate V, 0.35 g (1 mmole) of 2-methyl-3-ethylbenzothiazolium toluenesulfonate, and 5 ml of absolute alcohol was heated to the boiling point, and 0.1 g (1 mmole) of triethylamine was added. The precipitated dye was removed by filtration and crystallized from alcohol-DMF (3:1) to give 0.33 g of a product with <math display="inline">\lambda_{\max}$ 450 nm (log ε 4.57).

2-Oxo-6-(4-OxO-2-thioxo-3-ethylthiazolidin-5-ylidene)-8-phenyl-1,2,3,4-tetrahydro-6Hthiazolo[3,4-a]pyrimidine (VII). A mixture of 0.37 g (1 mmole) of perchlorate V and 0.16 g (1 mmole) of 3-ethylrhodanine was dissolved by heating in 7 ml of absolute alcohol, and 0.1g (1 mmole) of triethylamine was added. The precipitated dye was removed by filtration and crystallized from alcohol with DMF (4:1) to give 0.23 g of a product with λ 455 nm (log ϵ 4.59).

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CONDENSED HETEROCYCLES WITH A THIAZOLE RING. 7.* THIAZOLO[3,4-a]THIAZOLO[5,4-e]PYRIMIDINES

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The condensation of 4-amino-2-methylthio-5-phenylthiazolium benzenesulfonate with 2-oxo-5-formyl-4-chloro-4-thiazoline gave a salt of a previously unknown three-ring heterosystem, which was used for the synthesis of thia- and 4-quinomonomethylidyne-cyanine dyes. The absorption spectra of these dyes are similar to the spectra of the analogous dyes obtained from thiazolo[3,4-a]pyrimidine.

It has been previously shown that, in contrast to their analogs, which are ordinarily used in the chemistry of polymethine dyes (benzothiazole, benzimidazole, quinoline, and other dyes), several absorption bands are observed in the visible part of the absorption spectra of solutions of polymethine dyes obtained from thiazolo[3,4-a]pyrimidine derivatives [2]. This phenomenon is due to the specific characteristics of the thiazolopyrimidine ring. It therefore seemed of interest to continue the synthesis and study of dyes based on heterocyclic compounds of this type. In order to obtain derivatives of a new heterocyclic system that contains a thiazolo[3,4-a]pyrimidine fragment we studied the reaction of benzenesulfonate I with 2-oxo-5-formy1-4-chlorothiazoline (II).



III a $X = C_6H_5SO_3$; b $X = ClO_4$

Considering the data in [3] on the formation of a condensed system in the reaction of chloro aldehyde II with 2-aminopyridine, one might have hoped that in our case also cyclization would lead to compounds of the III type. In fact, according to the results of elemental analysis (Table 1), the reaction gives salts III, the structure of which was proved by data from the IR and PMR spectra. Thus only bands of stretching vibrations of C=N and C=O bonds (1645 and 1740 cm⁻¹) are observed in the IR spectrum of perchlorate IIIb, and absorption bands of the N-H bonds of starting salt I and of the C=O and C-H bonds of the aldehyde group of II (1690, 1720, and 2710 cm⁻¹ [4]) do not appear. A singlet of protons of the methyl-thio group, a multiplet of protons of two phenyl groups, and a singlet of a proton in the 4

*See [1] for communication 6.

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