PYRROLO[2,1-b]BENZOTHIAZOLE DERIVATIVES

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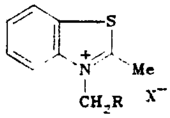
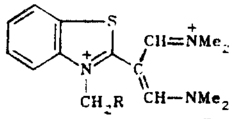
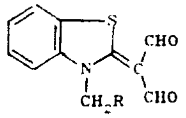
A new method for obtaining pyrrolobenzothiazole derivatives, which can be used for the specific synthesis of polymethine dyes with predesignated properties, was developed.

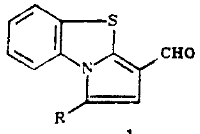
Cyanine dyes with a benzothiazole ring have important practical value for the sensitization of silver halide light-sensitive photographic materials [1] and are of theoretical interest for elucidation of the interrelationship between the chemical structure and the chromaticity of organic compounds [2]. In this connection a search for methods for the synthesis of new derivatives of condensed benzothiazoles with a nodal nitrogen atom that are suitable for obtaining polymethine dyes is necessary.

With this end in mind we studied the reaction of 2-methylbenzothiazolium quaternary salts Ia-e with the Vilsmeier reagent.


I a-e, II f,g

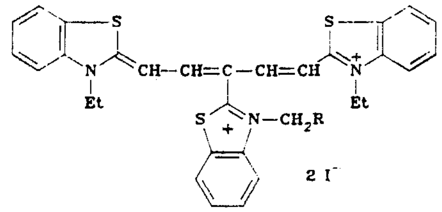

III f,g


IV e-g


VI a-d

I X=Br, II X=ClO$_4$; I, VI a R=CN, b R=COOMe, c R=COPh, d R=COC$_6$H$_4$Br-*p*;
I, IV e R=Ph; I—IV f R=H, g R=Me

It is known that diquaternary salts III are formed in the aminoformylation of salts of heterocycles with a methyl group in the α position with respect to the nitrogen atom (the Vilsmeier—Haack reaction) such as IIf,g [3]. These compounds and their hydrolysis products IV can be used for the synthesis of three-ring dyes [4] of the neocyanine Vg type.


V e,g

3-Benzyl-2-methylbenzothiazolium bromide (Ie) reacts precisely in the indicated direction to give dialdehyde IVe. The structure of this formylation product is confirmed by data from the PMR spectrum, in which one observes singlets of protons of N-methylene and formyl groups with chemical shifts of 6.03 and 9.50 ppm, respectively, while the signal of the methyl group of starting salt Ie is absent (Table 1). The absorption maximum of thiadicarbocyanine Ve, synthesized by condensation of 2-methyl-3-ethylbenzothiazolium iodide with dialdehyde IVe, is virtually the same as the maximum of dye Vg (601 nm), which was previously obtained [5].

However, the reaction of salts Ia-d with the phosphorus oxychloride—DMF complex leads to products with a completely different structure. In fact, signals of protons of both the methyl and methylene groups of starting bromides I are absent in their PMR spectra (Table 2). In addition to signals of protons of substituent R and a benzothiazole ring at 7-8 ppm, one observes a singlet of yet another proton but at weaker field (≈9.9 ppm) — the signal of one aldehyde group. The presence of the latter is also confirmed by the IR spectra. The data obtained made it possible to assign structures VIa-d to the synthesized compounds.

This structure is confirmed in the PMR spectra of VIb-d by a shift of the signal of the proton in the 8 position of the benzothiazole ring to weak field (8.8-9.3 ppm) because of the deshielding effect of the electron pair of the close-lying oxygen atom of the carbonyl group of the substituent in the 1 position

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TABLE 1. Characteristics of 2-Methylbenzothiazolium Quaternary Salts Ia-e

Compound	Empirical formula	mp,* °C	PMR spectrum,** δ, ppm (CF_3CO_2D)			IR spectrum, ν, cm^{-1}		Yield, %
			Ar—H	—CH_2, s	—CH_3, s	C=O	C=N	
I a	$C_{10}H_9BrN_2S$	210 ... 212	8,30 ... 7,91 (m, 4H)	6,05	3,44	—	1580***	20
I b	$C_{11}H_{12}BrNO_2S$	172 ... 174	8,53 ... 7,86 (m, 4H)	5,92	3,24 (CCH_3); 3,79 (OCH_3)	1700	1620	61
I c	$C_{16}H_{14}BrNOS$	228 ... 230	8,30 ... 7,60 (m, 9H)	6,51	3,22	1680	1590	48
I d	$C_{16}H_{13}Br_2NOS$	195 ... 197	8,30 ... 7,62 (m, 8H)	6,50	3,32	1690	1590	27
I e	$C_{15}H_{14}BrNS$	210 ... 211	8,54 (d, 1H); 8,23 (d, 1H); 7,82 ... 7,36 (m, 7H)	6,13	3,30	1700	1600	23

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*The compounds were crystallized: Ia-c from CH_3OH, Id from iso-PrOH, and Ie from C_2H_5OH.

**The PMR spectra of Ib,e were recorded in DMSO.

***There is a $\nu_{C\equiv N}$ band at 2260 cm^{-1}.

TABLE 2. Characteristics of 1-R-3-Formylpyrrolo[2,1-b]benzothiazoles VIa-d

Compound	Empirical formula	mp,* °C	PMR spectrum, δ, ppm						IR spectrum, ν C=O, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Yield, %
			solvent	CHO, s	8-H, d	2-H, s	ArH, m	R			
VIa	$C_{12}H_6N_2OS$	235 ... 237	DMSO	9,85	8,21	8,11	8,24 ... 7,55 (3H)	—	1660**	321 (4,27)	52
VIb	$C_{13}H_{11}NO_4S$	201 ... 203	$CDCl_3$	9,90	9,25	7,77	7,80 ... 7,40 (3H)	3,96 (OCH_3)	1650, 1700	323 (4,28)	61
VIc	$C_{18}H_{11}NO_2S$	174 ... 176	$CDCl_3$	9,88	8,93	—***	8,00 ... 7,20 (8H)	—***	1610, 1650	339 (4,27)	53
VId	$C_{18}H_{10}BrNO_2S$	192 ... 193	DMSO	9,89	8,83	—***	8,20 ... 7,60 (8H)	—***	1630, 1650	342 (4,25)	78

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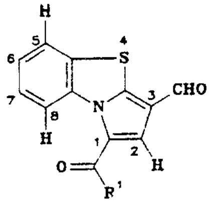
*The compounds were crystallized: VIa from ethanol, and VIb-d from acetonitrile.

**There is a $\nu_{C\equiv N}$ band at 2210 cm^{-1}.

***In the aromatic-proton region.

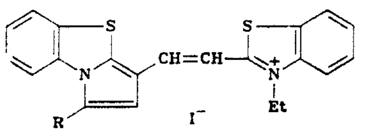


b $R^1=OCH_3$; c $R^1=C_6H_5$; d $R^1=C_6H_4Br$-*p*

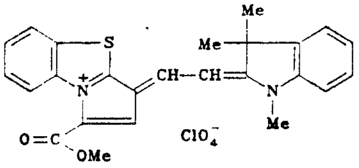
Precisely this conformation of VIb-d is evidently preferable because of steric factors. In the case of cyano-substituted aldehyde VIa the signal of this proton is naturally observed at appreciably stronger field (8.21 ppm).

The formation of a pyrrolobenzothiazole nucleus in this case is evidently due to the increased activity of the methylene group under the influence of the acceptor substituent bonded to it and occurs either during the formylation of salts Ia-d in the step involving the formation of dimethylamino-substituted dications of the III type or during isolation of dialdehydes IV from them.

The corresponding polymethine dyes are formed in the condensation of the formyl-substituted pyrrolobenzothiazoles obtained with quaternary salts of nitrogen heterocycles that contain an active methyl group. Thus unsymmetrical thia- and indocyanines VIIa-d and VIIIb (see Table 3) were synthesized with 2-methyl-3-ethylbenzothiazolium iodide or 1,2,3,3-tetramethyl-3H-indolium perchlorate.



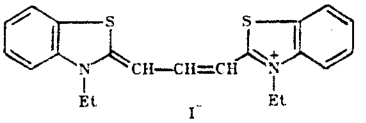
VII a-d



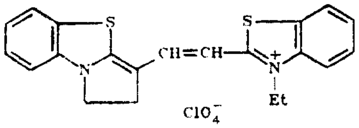
VIII b

In contrast to ordinary thiacarbocyanines [6], the presence of two rather intense bands is characteristic for the electronic absorption spectra of solutions of these dyes; this indicates the existence of two electron transitions in the cations of these compounds. A π–π^* electron transition in the conjugation chain evidently corresponds to the longer-wave and more intense band, while the short-wave transition is localized in the pyrrolobenzothiazole nucleus. The position of this band is similar to the analogous characteristics of starting aldehydes VI; however, the effect of substituents on the shift of the absorption maximum is different. Thus in the case of phenacyl-substituted dyes VIIc,d the short-wave band is shifted bathochromically as compared with the maxima of aldehydes VIc,d (16-19 nm), while the hypsochromic shift is 3-13 nm for cyanines VIIa,b and VIIIb. The position of the maximum of the long-wave band depends to a lesser extent on the nature of the substituent. Thus, with the exception of cyano-substituted VIIa, all of the thiacyanines VIIb-d absorb in the same region of the spectrum. It is important that when the benzothiazole nucleus is replaced by an indolenine nucleus, which has a smaller effective length [7], one does not observe a hypsochromic shift, as one should have expected, but rather a bathochromic shift of the maximum of the long-wave band. This is evidently due to the fact that the pyrrolobenzothiazole residue in the dyes has a small degree of electron-donor character. In this connection, since the indolenine terminal heteroresidue also has a small degree of electron-donor character, the deviation of the absorption maximum decreases significantly in indocyanine VIII because of the high degree of electronic symmetry of the dye [2], and this leads to the observed effect.

On the whole, from a comparison of the spectral characteristics of dyes VII and thiacarbocyanine IX (560 nm, ε $15.07 \cdot 10^4$) [2, pp. 27, 29] it is apparent that partial cyclization of the chromophore with the aid of the vinyl group between the nitrogen atom and the α position of the polymethine chain, in contrast to the corresponding fixation by the dimethylene bridge (carbocyanine X, λ_{max} 561 nm, ε $17.51 \cdot 10^4$ [8]) leads to a substantial heightening of the color.



IX



X

Thus we have developed a new method for obtaining pyrrolobenzothiazole derivatives that can be used for the specific synthesis of polymethine dyes with predesignated properties.

TABLE 3. Characteristics of Dyes VIIa-d and VIIIb with a Pyrrolo[2,1-b]benzothiazole Nucleus

Compound	Empirical formula	mp,* °C	UV spectrum, λ_{max}, nm (log ε)	Yield, %
VIIa	$C_{22}H_{16}IN_3S_2$	247...248	317 (4,23), 457 (4,45)	62
VIIb	$C_{23}H_{19}IN_2O_2S_2$	257...260	321 (4,31), 472 (4,66)	74
VIIc	$C_{28}H_{21}IN_2OS_2$	245...248	345 (4,15), 474 (4,68)	62
VIId	$C_{28}H_{20}BrIN_2OS_2$	237...239	357 (4,17), 471 (4,61)	53
VIIIe	$C_{25}H_{23}ClN_2O_6S$	270...272	320 (4,18), 485 (4,64)	68

*The compounds were crystallized: VIIa,c and VIIIb from CH_3CN, and VIIb,d from CH_3NO_2.

EXPERIMENTAL

The PMR spectra were obtained with a Bruker WP-100 SY spectrometer (100 MHz) with tetramethylsilane (TMS) as the internal standard. The electronic spectra of solutions in methanol were recorded with a Specord M-40 spectrophotometer. The IR spectra of KBr pellets were obtained with a UR-10 spectrometer.

The characteristics of the synthesized compounds are presented in Tables 1-3. The results of elementary analysis for C, H, N, S, and Hal were in agreement with the calculated values.

2-Methylbenzothiazolium Quaternary Salts Ia-e. A mixture of 3.7 g (25 mmole) of 2-methylbenzothiazole, 30 mmole of the corresponding alkylating agent (α-bromo ketone, bromoacetic acid nitrile or ester), and 2 ml of dimethylacetamide was heated for 4 h in an oil bath at 100-110°C, after which it was diluted with acetone. The precipitate was removed by filtration and washed with acetone and ether. The products were colorless crystals. The constants of salts Ic,d were in agreement with those presented in [9].

3-Benzyl-2-(diformylmethylene)benzothiazoline (IVe, $C_{17}H_{13}N_2$). The Vilsmeier reagent was prepared from 4 ml (50 mmole) of DMF and 4 ml (40 mmole) of phosphorus oxychloride, a suspension of 2 g (6 mmole) of bromide Ie in 20 ml of DMF was added to it dropwise with stirring at 0°C, and the mixture was heated for 4 h at 75-80°C. It was then cooled and poured into 50 ml of water, and the aqueous mixture was neutralized to pH 9 with 10% alkali solution. The resulting precipitate was removed by filtration and washed with water to give colorless crystals with mp 168-170°C (from ethanol). IR spectrum, $\nu_{C=O}$: 1690 cm^{-1}. PMR spectrum ($CDCl_3$): 9.50 (2H, s, CHO), 6.95-7.82 (9H, m, Ar—H), 6.03 ppm (2H, s, CH_2). The yield was 1.5 g (81%).

3-Ethyl-2-{3-(3-benzylbenzothiazolio-2-yl)-5-[3-ethyl-2(3H)-benzothiazolylidene]-1,3-pentadienyl}benzothiazolium Diiodide (Ve, $C_{37}H_{33}I_2N_3S_3$). A mixture of 0.35 g (1 mmole) of iodide IIg and 0.15 g (0.5 mmole) of dialdehyde IVe was heated for 10 min at 100°C in 3 ml of acetic anhydride, after which it was cooled, and the dye was removed by filtration and washed with ether to give dark crystals with a bronze luster, mp 150°C (from acetonitrile), and λ_{max} 605 nm (log ε 5.12). The yield was 0.21 g (48%).

1-R-Formylpyrrolo[2,1-b]benzothiazoles VIa-d. The Vilsmeier reagent was prepared from 4 ml (50 mmole) of DMF and 4 ml (40 mmole) of $POCl_3$, a suspension of 10 mmole of the corresponding salt Ia-d in 10 ml of DMF was added dropwise to it with cooling and stirring, and the mixture was maintained for 30 min at 20-25°C. It was then heated for 3 h at 75-80°C, after which the viscous orange mass was poured over ice. The resulting solution was neutralized to pH 8 with sodium carbonate, and the precipitate was removed by filtration and washed with water.

1-R-3-{2-[3-Ethyl-2(3H)-benzothiazolylidene]ethylidene}-3II-pyrrolo[2,1-b]benzothiazolium Iodides VIIa-d. A 1-mmole sample of 3-ethyl-2-methylbenzothiazolium iodide and 1 mmole of anhydrous sodium acetate were added to a solution of 1 mmole of benzothiazole VIa-d in 5 ml of acetic anhydride, and the mixture was refluxed for 15 min. It was then cooled and diluted with ether, and the precipitate was removed by filtration and washed with water, alcohol, and ether.

1-Methoxycarbonyl-3-{2-[1,3,3-trimethyl-2,3-dihydroindol-2-ylidene]ethylidene}-3H-pyrrolo[2,1-b]benzothiazolium Perchlorate (VIIIb). This compound was obtained from benzothiazole VIb and 1,2,3,3-tetramethylindolinine perchlorate in the same way as dyes VIIa-d.

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SYNTHESIS AND TRANSFORMATIONS OF 2-AMINO-1,3,4-THIADIAZINES

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Depending on the reaction conditions, 2-amino-1,3,4-thiadiazine and 2-hydrazinothiazole derivatives were obtained by cyclization of thiosemicarbazide with ethyl bromopyruvate in concentrated hydrochloric acid. The rearrangements of 5-carbonyl-substituted 2-amino-1,3,4-thiadiazines to thiazole derivatives in an acidic medium were studied.

One of the promising directions in the search for preparations that have biological activity is the synthesis of labile heterocyclic compounds. 2-Amino-1,3,4-thiadiazine derivatives, among which substances that have antibacterial, antiviral, fungicidal, herbicidal, and other types of activity have been observed [1-3], can be classified as compounds of this sort. It is known that 5- and (or) 6-alkyl-substituted 2-amino-1,3,4-thiadiazines react like labile cyclic thiosemicarbazones, undergoing intramolecular rearrangements under the influence of a proton [4]. In this connection the aim of the present research was to synthesize and study the reactivities (primarily the stabilities in an acidic medium) of 2-amino-1,3,4-thiadiazines with a carbonyl group in the 5 position.

We have observed that the structure of the products of cyclization of thiosemicarbazide (I) with ethyl bromopyruvate (II) in concentrated hydrochloric acid depends on the reaction temperature and time. Cyclization at 0°C led to 2-amino-5-ethoxycarbonyl-1,3,4-thiadiazine (III) hydrochloride, while brief heating to the boiling point led to 2-amino-5-carboxy-1,3,4-thiadiazine (IV) hydrochloride. The expected 2-imino-3-aminothiazolines V [4] were not observed.

Prolonged heating of I and II in concentrated HCl gave 2-hydrazino-4-carboxythiazole (VI), which was also isolated from the reaction mixture after prolonged heating of IV in hydrochloric acid. These facts attest to intramolecular rearrangement of 2-amino-5-carboxy-1,3,4-thiadiazine (IV), which includes cleavage of the $N_{(4)}$—$C_{(5)}$ bond of the thiadiazine and subsequent cyclization. This sort of recyclization is not characteristic for 2-amino-1,3,4-thiadiazines with alkyl substituents in the 5 or 6 position of the ring, which under similar conditions are converted to 2-imino-3-aminothiazolines V without opening of the thiadiazine ring [5] (see scheme below).

The structures of the reaction products were confirmed by spectral data and alternative synthesis. In the PMR spectra of thiadiazines III and IV resonance of the protons of the SCH_2 group was observed at 4.0-4.2 ppm, while a singlet of a proton in the 5 position of the thiazole ring at 7.9 ppm was present in the spectrum of thiazole VI.

In the ^{13}C NMR spectrum of IV the triplet at 20.54 ppm with an order I spin-spin coupling constant (SSCC) was assigned to an sp^3-hybridized carbon atom in the 6 position of the thiadiazine ring. A signal at weak field (165.18 ppm, $J_{^{13}C-^1H}$ = 5.19 Hz) is due to resonance of the carbon atom of a carbonyl group. The assignment of the signals of the $C_{(2)}$ (141.67 ppm) and $C_{(5)}$ (162.67 ppm) atoms was accomplished on the basis of a comparison of the SSCC — 5.19 (order III SSCC) and 2.14 Hz (order II SSCC), respectively.

The structure of 2-hydrazinothiazole VI was confirmed by its esterification in absolute ethanol in the presence of thionyl chloride to 2-hydrazino-4-ethoxycarbonylthiazole (VII) and by oxidation with mercuric oxide, as in [6], to 4-carboxythiazole (VIII). The physicochemical characteristics of VII and VIII were in agreement with those presented in [7-9].

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