REACTION OF 1-ALKYLTHIO-3,3-DIARYLTHIOPHTHALYLIUM SALTS WITH CH ACIDS

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It was shown that the reaction of 1-alkylthio-3,3-diarylthiophthalylium salts with Meldrum's acid, methylphenylpyrazolone, N-ethylrhodanine, and ethyl cyanoacetate does not depend on the character of the substituents in the substrate and the nature of the methylene component and leads to the corresponding condensation products with thiophthalylidene structures.

In [1] it was shown that thiophthalylium salts that contain an alkylthio group attached to the $C_{(1)}$ atom react with O nucleophiles at the α-carbon atom of the heteroring; the stabilities of the products of nucleophilic addition depend on the nature of the reagent. Thus, hydrolysis of the salts proceeds irreversibly to give thiophthalides, whereas the corresponding alkoxy derivatives can be isolated in reactions with alkali metal alkoxides.

Within the framework of a further investigation of the electrophilic activity of 1-alkylthio-substituted thiophthalylium salts it seemed of interest to us to study the peculiarities of their reactions with other nucleophilic reagents, particularly with CH acids.

As substrates for this purpose we used 1-ethylthio-3,3-diarylthiophthalylium tetrafluoroborates I-III with variable substituents attached to the $C_{(3)}$ atom, as well as 1-methylthio-3,3-diphenylthiophthalylium tetrachloroferrate (IV). As reagents we selected CH acids with the following structures: 2,2-dimethyl-4,6-dioxo-1,3-dioxane (Meldrum's acid), 3-methyl-1-phenylpyrazol-5-one, 3-ethylthiazolidine-2-thion-4-one (N-ethylrhodanine), and ethyl cyanoacetate, some of which, as is well known, are the principal structural fragments of many medicinal agents with a broad spectrum of activity.

The reactions were carried out in solutions in methylene chloride in the presence of triethylamine by brief heating; in all cases we isolated, in high yields, yellow or orange crystalline products V-XI, which contain a thiophthalylidene grouping.

As in the case of O nucleophiles [1], the reaction also probably proceeds through a step involving the addition of the CH acids to the conjugated carbonium-thionium ion. The resulting unstable products of nucleophilic addition are stabilized by splitting out of a mercaptan to give derivatives V-XI.

The IR spectra of V-VII in the region characteristic for the vibrations of double bonds contain two absorption bands: less intense bands with maxima at 1732-1734 cm^{-1} and more intense bands with pronounced asymmetry of the bands with maxima at 1697-1700 cm^{-1}, which are due to, respectively, the asymmetrical and symmetrical stretching vibrations of the carbonyl groups. One asymmetrical band (1670-1683 cm^{-1}) is present in this region in the spectra of VIII-XI. Such low values of the frequencies of the carbonyl groups are explained by conjugation of the C=O group with the carbon–carbon double bond, which leads to delocalization of the π electrons of the carbonyl group and a decrease in the double-bond character of the C=O bond. The effect of an unshared electron pair of the nitrogen pair attached directly to the carbonyl group (VIII-X) is responsible for an additional shift of the C=O band to the low-frequency side. The asymmetry of these bands is explained by superimposition on them of the stretching vibrations of the $C_{(1)}$=C bond, which was established in a study of the H complexes of V-XI with p-nitrophenol. When a proton donor is added, the absorption bands at 1670-1700 cm^{-1} undergo changes: the changes involve substantial broadening to the point of splitting, which, in the case of VIII and IX, reaches 27 cm^{-1}.

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TABLE 1. Chemical Shifts (δ, ppm) of the Protons of V-XI*

Comp.	Alkyl group protons	7-H, d	6-H,t	5-H,t	4-H,d	Other aromatic protons
V	1,83, s [$C(CH_3)_2$]	8,59	7,43	7,51	7,21	7,29, s
VI	1,83, s [$C(CH_3)_2$]	8,60	7,45	7,54	7,16	7,19—7,28, m
VII	1,82, s [$C(CH_3)_2$]; 2,32, s (2 p-CH_3)	8,55	7,40	7,49	7,21	7,08—7,16, m
VIII	2,66, s (C—CH_3) (2,66,s)	8,22 (8,03)	7,57 (7,39)	7,59 (7,15)	7,29 (7,33)	7,26—7,31, m
IX	2,34, s (2 p-CH_3); 2,56, s (C—CH_3) (2,32, s ; 2,64, s)	8,18 (8,03)	7,57 (7,39)	7,57 (7,16)	7,28 (—)†	7,08—7,22, m
X	1,29, t; 4,21, q (N—C_2H_5)	7,78	7,48	7,53	7,29	7,29, s
XI	1,38, t; 4,35, q (O—C_2H_5)	8,95	7,54	7,54	7,27	7,26,s ; 7,28,s

*The chemical shifts of the protons of the B forms are presented in parentheses.

†The signal of the 4-H proton of the B form is overlapped by the multiplet of the aromatic protons.

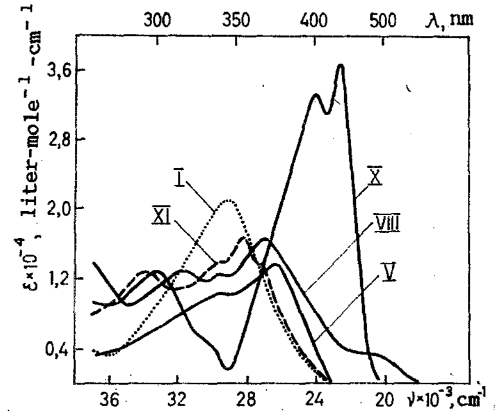
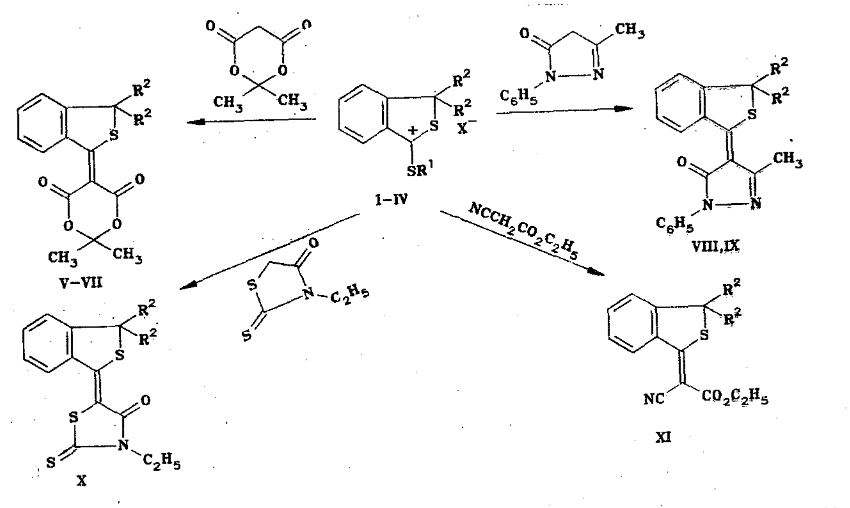


Fig. 1. Electronic absorption spectra of I, V, VIII, X, and XI.



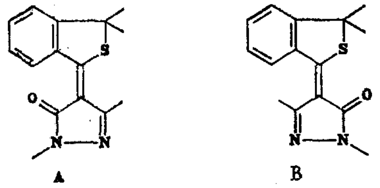
I—III $R^1=C_2H_5$, $X=BF_4$; IV $R^1=CH_3$, $X=FeCl_4$; I, IV, V, VIII, X, XI $R^2=C_6H_5$; II, VI $R^2=4\text{-}ClC_6H_4$; III, VII, IX $R^2=4\text{-}CH_3C_6H_4$

In addition to the indicated characteristic groupings in the IR spectra one observes absorption bands corresponding to the stretching vibrations of the C—O bond with maxima at 1287-1291 cm^{-1} and deformation vibrations of the C—H bond in geminal CH_3 groups in the form of doublets at 1375-1377 cm^{-1} and 1388-1390 cm^{-1} (V-VII), stretching vibrations of a C—N bond at 1322-1327 cm^{-1} (VIII-X), stretching vibrations of a C≡N bond at 1594-1595 cm^{-1} (VIII, IX), and stretching vibrations of a C=S bond at 1242 cm^{-1} (X). In the IR spectrum of ester XI the C—O stretching vibrations show up in the form of two bands in the regions typical for α-unsaturated esters [2]; a more intense and broad band at 1264 cm^{-1} [C(C=O)—O] and a less intense band at 1133 cm^{-1} (O—C—C), whereas the cyano group is characterized by a narrow absorption band with a maximum at 2214 cm^{-1}. The low value of this frequency and its high intensity confirm the presence of an unsaturated conjugated Ph—$C_{(1)}$=C grouping in the α position relative to the C≡N group [3].

The character of the absorption of V-XI in the visible region of the spectra depends substantially on the structure of the methylene component (Fig. 1) and to a small extent on the nature of the R^2 substituents: only p-tolyl groups, as compared with unsubstituted phenyl groups, give rise to a small (3-5 nm) bathochromic shift of the long-wave absorption maximum. Virtually no change is observed in the extinction coefficients when the R^2 substituents are varied in monotypic derivatives.

A comparative analysis of the PMR spectra shows that good correspondence between the chemical shifts of the monotypic protons is observed for all of the investigated compounds (Table 1). This made it possible to assign the singlet signals of the methyl protons to definite positions of the CH_3 groups in the molecules. There also were no difficulties in assigning the signals of the ethyl groups (X and XI), which show up in the form of characteristic triplet and quartet signals. The aromatic protons of the phenyl rings attached to the $C_{(3)}$ and nitrogen atoms are represented in the spectra by either intense singlet signals (V, X, and XI) or by complex multiplets at 7.08-7.31 ppm (VI-IX). The utilization of the homonuclear double-resonance method made it possible to isolate the spin systems of the aromatic protons of the thiophthalane ring (4-H—7-H) in the spectra of V-XI; it was observed that the chemical shift of the signal of only one of the protons depends substantially on the nature of the substituent in the 1 position. This made it possible to assign the indicated signal to the 7-H proton.

It should be noted that in the spectra of VIII and IX there are two sets of signals of all of the protons*, which can be ascribed to the two stereoisomeric A and B forms:


A

B

The assignment of the signals to the A and B forms was made on the basis of an analysis of the position of the signal of the 7-H proton, which, as a consequence of the effect of the carbonyl group in the A form, is found at weaker field. In a comparison of the integral intensities of the signals of each of the forms it was found that the percentages of the A forms for VIII and IX are, respectively, 38% and 33%.

Judging from the PMR spectra, X, for which stereoisomers of the A and B type are theoretically also possible, exists exclusively in one form. Since the doublet signal of the 7-H proton is shifted significantly to strong field (7.78 ppm) as compared with the analogous signal for the A forms (V-IX), it may be assumed that X has a configuration of the B type.

EXPERIMENTAL

The IR spectra of solutions of the compounds in CCl_4 were recorded with a Specord 75-IR spectrometer (layer thickness 0.97 mm). The UV spectra of solutions in dichloroethane were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were obtained under pulse conditions with a Varian SC spectrometer (300 MHz) equipped with a 620/L computer (the temperature of the samples was 33°C). The chemical shifts were measured relative to a tetramethylsilane (TMS) standard. Tetrafluoroborate I was obtained by the method in [1].

1-Ethylthio-3,3-bis(p-chlorophenyl)thiophthalylium Tetrafluoroborate (II). A 0.4-g (2.1 mmole) sample of triethyloxonium tetrafluoroborate was added to a solution of 0.8 g

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*In the spectrum of VIII the signals of the protons of the CH_3 groups of the two forms coincide.

TABLE 2. Characteristics of V-XI

Comp.	mp,* °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	S(Cl)		C	H	S(Cl)	
V	199—200	72,6	4,9	7,2	$C_{26}H_{20}O_4S$	72,9	4,7	7,5	80, 75†
VI	125—128 (dec.)	62,8	4,0	6,2 (13,9)	$C_{26}H_{18}Cl_2O_4S$	62,8	3,7	6,4 (14,2)	71
VII	228—230	73,6	5,6	6,8	$C_{28}H_{24}O_4S$	73,6	5,3	7,0	87
VIII	198—199	78,3	4,9	6,8	$C_{30}H_{22}N_2OS$	78,6	4,8	7,0	88, 80†
IX	148—150	78,8	5,6	6,5	$C_{32}H_{26}N_2OS$	79,0	5,4	6,6	74
X	242—244	67,2	4,5	21,7	$C_{25}H_{19}NOS_3$	67,4	4,3	21,6	89
XI	154—156	75,3	4,9	7,8	$C_{25}H_{19}NO_2S$	75,5	4,8	8,1	78

*The compounds were recrystallized: VI, VII, IX, and XI from ethanol, V from ethanol—methanol, and VIII and X from ethanol—dichloroethane.

†The yields in the reaction with tetrachloroferrate IV.

(2.1 mmole) of 3,3-bis(p-chlorophenyl)dithiophthalide [4] in 7 ml of anhydrous methylene chloride, after which the reaction mixture was heated for 3 min, cooled, and diluted with 10 ml of ether. The precipitate that formed upon standing was removed by filtration and washed with ether to give 0.77 g (74%) of salt II with mp 205-208°C (from dichloroethane—ether). Found: C 52.3; H 3.5; S 12.6%. $C_{22}H_{17}BCl_2F_4S_2$. Calculated: C 52.5; H 3.4; S 12.7%. UV spectrum, λ_{max} (log ε): 346 nm (4.37).

Tetrafluoroborate III. This salt, with mp 181-184°C (from dichloroethane—ether), was similarly obtained in 94% yield from 3,3-bis(p-tolyl)dithiophthalide [4]. Found: C 62.2; H 5.4; F 16.2; S 13.5%. $C_{24}H_{23}BF_4S_2$. Calculated: C 62.2; H 5.0; F 16.4; S 13.9%. UV spectrum, λ_{max} (log ε): 344 nm (4.28).

1-Methylthio-3,3-diphenylthiophthalylium Tetrachloroferrate (IV). A solution of 5 g (15.7 mmole) of 3,3-diphenyldithiophthalide [5] in 10 ml of dimethyl sulfate was heated until the color of the mixture changed from red to green, after which 10 ml of a solution of ferric chloride, prepared by dissolving anhydrous $FeCl_3$ in a mixture of concentrated hydrochloric and glacial acetic acids (1:3), and the resulting mixture was refluxed for 5 min. The next day, the yellow crystalline precipitate was removed by filtration and washed with ether to give 6 g (72%) of salt IV with mp 179-181°C (from CH_3COOH). Found: C 47.9; H 3.5; Cl 27.0; S 12.5%. $C_{21}H_{17}Cl_4FeS_2$. Calculated: C 47.5; H 3.2; Cl 26.7; S 12.1%.

1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-3,3-diphenylthiophthalane (V). A 0.12-g (1.18 mmole) sample of triethylamine in 2 ml of CH_2Cl_2 was added to a solution of 0.25 g (0.58 mmole) of tetrafluoroborate I and 0.17 g (1.18 mmole) of isopropylidenemalonate in 5 ml of anhydrous methylene chloride. After brief heating, the reaction mixture was maintained at room temperature for 24 h. The solvent was then removed, and the residue was purified by double crystallization.

Compounds VI-XI (Table 2). These compounds were similarly obtained. The reactions of tetrachloroferrate IV with isopropylidenemalonate and methylphenylpyrazolone were also carried out.

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