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SYNTHESIS OF SOME NEW DERIVATIVES OF DITHIENE- AND OXATHIENECARBOXYLIC ACIDS

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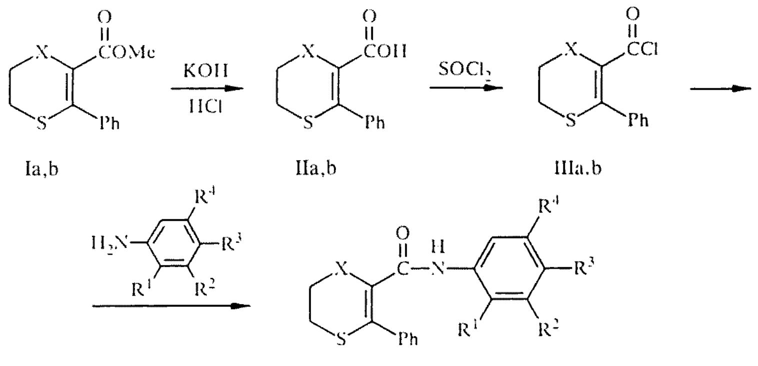
Substituted anilides of 1,4-dithiene- and oxathienecarboxylic acids were synthesized. It was shown that the reaction of 3-phenyl-1,4-dithi-2-ene-2-carboxyl chloride with 2-aminopyridines, depending on the base used and the reaction conditions, leads to the formation of N-[3'-phenyl-2'-(1',4'-dithi-2'-en)ylcarbonyl]-2-aminopyridine and/or N,N'-bis[3-phenyl-2-(1,4-dithi-2-en)-ylcarbonyl]pyridonimine. The data of IR, UV, and PME spectroscopy were used to confirm the structure of the synthesized compounds.

The discovery of fungicidal activity among derivatives of 1,4-oxathiene, in particular, 5,6-dihydro-2-methyl-1,4-oxathiene-3-carboxyanilide (Vitavax) and its sulfone (Plantavax) [1] has stimulated interest in the chemistry of 1,4-oxathiene and dithiene.

We showed earlier that in the reaction of the methyl ester of 3-phenyl-3-chloro-2-oxopropionic acid [2] with dithioglycol and mercaptoethanol in the presence of a base, products of substitution of chlorine are formed, and in the presence of catalytic amounts of p-toluenesulfonic acid they are dehydrated, being converted to 2-carbmethoxy-3-phenyl-1,4-dithiene (Ia) and oxathiene (Ib) [3].

In this work we report the results of an investigation of the reactions of the chlorides of dithiene- and oxathienecarboxylic acids (IIIa,b) with various anilines and 2-aminopyridines, which lead to new derivatives of dithiene- and oxathienecarboxylic acids. The dithiene- and oxathienecarboxylic acid chlorides (IIIa,b) were produced from the corresponding acids (IIa,b), which in turn are formed in the alkaline hydrolysis of their methyl esters (Ia,b).



Ia,b IIa,b IIIa,b

IVa,b

I - III a X = S, b X = O;
IV a X = S, $R^1 = R^2 = R^3 = R^4 = H$; b X = S, $R^1 = R^3 = Me$, $R^2 = R^4 = H$; c X = S, $R^1 = R^4 = Me$, $R^2 = R^3 = H$; d X = S, $R^1 = Cl$, $R^2 = R^3 = R^4 = H$; e X = O, $R^1 = R^2 = R^3 = R^4 = H$; f X = O, $R^1 = R^3 = Me$, $R^2 = R^4 = H$

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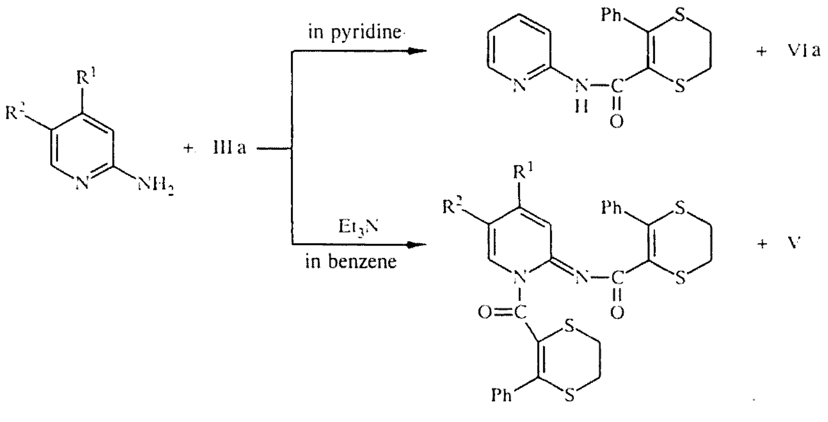
TABLE 1. Characteristics of Compounds IVa–f

Compound	Empirical Formula	mp °C in 2-propanol	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (DMFA-D_7)	Yield, %
IVa	$C_{17}H_{15}NOS_2$	156...158	3310 (N—H), 1650 (C=O), 1600 (C=O)	3,45 (4H, s, CH_2CH_2), 6,70...7,36 (10H, m, $2C_6H_5$), 9,48 (1H, br. s,, NH)	66
IVb	$C_{19}H_{19}NOS_2$	123...124,5	3285 (N—H), 1660 (C=O), 1590 (C=C)	1.83 (3H, s, CH_3), 2,20 (3H, s, CH_3), 3,50 (4H, s, CH_2CH_2), 6,63...7,90 (8H, m, C_6H_5 and C_6H_3), 8,86 (1H, br. s, NH)	58
IVc	$C_{19}H_{19}NOS_2$	168...169	3285(N—H), 1645 (C=O), 1585 (C=C)	1,76 (3H, s, CH_3), 2,16 (3H, s, CH_3), 3,50 (4H, s, CH_2CH_2), 6,66...7,40 (8H, m, C_6H_5 and C_6H_3), 8,86 (1H, br. s, NH)	48
IVd	$C_{17}H_{14}ClNOS_2$	87...88	3305 (N—H), 1655 (C=O), 1590 (C=C)	3.50 (4H, s, CH_2CH_2), 6.86...7,76 (9H, m, C_6H_5 and C_6H_4), 8,90 (1H, br. s, NH)	82
IVe	$C_{17}H_{15}NO_2S$	122...123,5	3330 (N—H), 1660 (C=O), 1600 (C=C)	3.23 (2H, t, CH_2S), 4.33 (2H, t, CH_2O), 6.66...7,66 (5H, m, C_6H_5N), 7.16 (5H, s, C_6H_5), 9,53 (1H, br. s, NH)	50
IVf	$C_{19}H_{19}NO_2S$	185...187	3325 (N—H), 1680 (C=O), 1600 (C=C)	1,93 (3H, s, CH_3), 2,22 (3H, s, CH_3), 3.20 (2H, t, CH_2S), 4,26 (2H, t, CH_2O), 6,60...7,16 (3H, m, C_6H_3), 7,10 (5H, s, C_6H_5), 8,83 (1H, br. s, NH)	79

In the IR spectra of anilides of dithiene- and oxathienecarboxylic acids (IVa–f) there are absorption bands of the groups $\nu_{N\text{-}H}$ and $\nu_{C=O}$ within the intervals 3285-3330 and 1645-1660 cm^{-1}, respectively. The presence of broadened singlet signals of the NH group in the region of 8.83-9.53 ppm in the PMR spectra of compounds IVa-f (see Table 1) also confirms the formation of the anilides IVa-f.

Substituted anilines in reactions with dithiene and oxathienecarboxylic acid chlorides IIIa,b, regardless of the reagent ratio and the solvent used, give only monosubstituted anilides IVa-f. The results of the reaction of IIIa with 2-aminopyridines proved unexpected. Thus, depending on the reaction conditions, the interaction of 2-aminopyridine with the acid chloride IIIa leads to the formation of the monosubstituted anilide (V) with an admixture of the disubstituted anilide (VIa) or to the formation of the disubstituted anilide (VIa) with traces of the monosubstituted anilide (V).



VIa-c

VI a $R^1 = R^2 = H$; b $R^1 = Me$, $R^2 = H$; c $R^1 = H$, $R^2 = NO_2$

TABLE 2. Characteristics of Compounds V, VIa–c, VII

Compound	Empirical formula	mp, °C (solvent of recryst.)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (SSCC, J, Hz) in DMSO-D_7	Yield, %
V	$C_{16}H_{14}N_2OS_2$	165...166 (CH_3OH)	3310 (NH), 1685 (C=O), 1605 (C=O)	3,44...3,54 (4H, m, SCH_2CH_2S), 7,07 (1H, t, $H_{(5)}$, J_{54} = 7,2, J_{53} = 1,2, J_{56} = 6,5), 7,28...7,48 (5H, m, C_6H_5), 7,73 (1H, t, $H_{(4)}$, J_{45} = 7,2, J_{43} = 8,1, J_{46} = 1,1), 7,87 (1H, d, $H_{(3)}$, J_{34} = 8,1), 8,24 (1H, d, $H_{(6)}$, J_{65} = 6,5, J_{64} = 1,1), 10,29 (1H, s, NH)	55
VIa	$C_{27}H_{22}N_2O_2S_4$	223...224 DMSO	1690(C=O), 1595(C=O)	2.50...2.56 and 2.96...3,11 (8H. 2m, $2SCH_2CH_2S$), 6,57 (1H, d, $H_{(3)}$, J_{34} = 7,5), 7,05 (11H, br. s, $2C_6H_5$ and $H_{(4)}$), 7,52 (1H, t, $H_{(5)}$, J_{54} = J_{56} = 7,5), 8,12 (1H, d, $H_{(6)}$, J_{65} = 5.0)	71
VIb	$C_{28}H_{24}N_2O_2S_4$	217...218 CH_3OH	1685 (C=O), 1605 (C=C)	2.37 (3H, s, CH_3), 2,95...3,12 and 3.29...3,44 (8H, 2m, $2SCH_2CH_2S$), 6,55 (1H, s, $H_{(3)}$), 7,24 (1H, d, $H_{(5)}$, J_{56} = 5,1, 7,73 (10H, br. s, $2C_6H_5$), 8,31 (1H, d, $H_{(6)}$, J_{65} = =5,1)	58
VI c	$C_{27}H_{21}N_3O_4S_4$	236...239 DMSO	1685 (C=O), 1600 (C=O), 1570, 1540, 1290, 1350 (NO_2)	2,54...2,60 and 3,35...3,45 (8H, 2m, $2SCH_2CH_2S$), 7,15 (1H, d, $H_{(3)}$, J_{34} = 9), 7,40 (10H, br. s, $2C_6H_5$), 8,66 (1H, d, $H_{(4)}$, J_{43} = 9, J_{46} = 2,7), 9,26 (1H, d, $H_{(6)}$, J_{64} = 2,7)	32
VII	$C_{27}H_{23}N_3O_2S_4$	262...262,5 DMSO	3360 (NH), 1675 (C=O), 1590 (C=O)	3,38...3,48 (8H, m, $2SCH_2CH_2S$), 7,32...7,68 (13H, m, $2C_6H_5$, $H_{(3)}$, $H_{(4)}$ and $H_{(5)}$), 9,99 (2H, br.s, 2NH)	86

The presence of a broadened signal in the region of 10.3 ppm from the NH group in the PMR spectrum of the compound obtained in the reaction of the acid chloride IIIa with 2-aminopyridine in dry pyridine in an argon atmosphere is evidence of the formation of the monosubstituted anilide V. The presence of an absorption band of the stretching vibrations of the NH group at 3170 cm^{-1} in the IR spectrum additionally confirms this. We also isolated slight amounts of the compound VIa from the reaction mixture.

When the reaction was conducted in the presence of Et_3N in benzene, we isolated only one compound from the reaction mixture, in the EU mass spectrum of which the peak of the molecular ion [M^+] 537 was detected, which corresponds to the disubstituted derivative of 2-aminopyridine VIa. Compound V is formed with a negligible yield. Under these conditions the 4-methyl- and 5-nitro-2-aminopyridines behaved analogously, giving dianilides.

The best yields of dianilides VIa-c are achieved when the acid chlorides, 2-aminopyridine, and ET_3N are used in a 2.0:1.0:2.1 ratio.

It is known that 2-aminopyridines [4, 5], as well as other nitrogen-containing heterocycles [6-8], possessing an amine group in the α-position relative to the nitrogen atom of the ring, depending on the reaction conditions, can be converted to acyl derivatives of the α-aminohetaryl (V) or N-acyl-α-hetarylidonimine (VI).

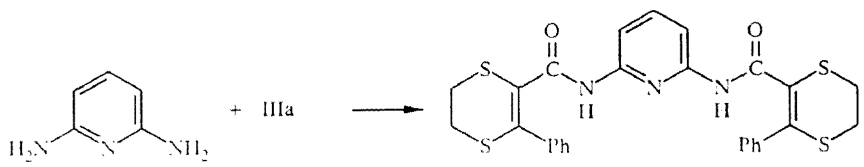
In the IR spectra of compounds VIa-c there are no absorption bands of N–H bonds, which confirms the occurrence of the reaction with the acid chloride IIIa utilizing both hydrogen atoms of the amino group. At the same time, the stretching vibrations of the C=O group for crystalline compounds appear in the form of absorption bands with a long-wave shoulder, whereas for solutions in $CHCl_3$ they appear as two merging bands (for compound VIa in liquid petrolatum an absorption band with maximum 1684 and shoulder 1655, and in $CHCl_3$ solution the doublets 1715 and 1700 cm^{-1}).

Thus, the bands of the stretching vibrations of the C=O group of the two carbonyl groups virtually coincide, although it was noted in [9] that for acetyl derivatives of aminopyridine and pyrydonimine $\nu_{C=O}$ differ by 50 cm^{-1}, appearing in the region of 1700 and 1640 cm^{-1}, respectively. Such a lowering of $\nu_{C=O}$ in pyridonimines is explained by conjugation in the chain $-C=N-C=O$. At the same time, there are other data [10] according to which $\nu_{C=O}$ in acetyl derivatives of pyridonimine appears in the region of 1675 cm^{-1}. The data presented do not permit an unambiguous determination of the structure of compounds VIa-c. The noncoincidence of the signals of the 1,4-dithi-2-enylcarbonyl fragments in the PMR spectra of disubstituted derivatives of 2-aminopyridines is evidence that the dithienylcarbonyl substituents are found on different kinds of nitrogen atoms in compounds VIa-c (Table 2). According to the literature data [9-11], transition from the amino- to the imino-structure is accompanied by a substantial bathochromic shift of the absorption maximum by ~ 50 nm (~300 → 350 nm).

The UV spectra of the investigated compounds (Table 3) show that the 3-phenyl-2-(1,4-dithi-2-en)ylcarbonyl fragment (Ia and IVa) is characterized by a long-wave maximum at 325 nm (log ε = 4.3), whereas the aminopyridine group is characterized by a maximum at 280 nm (log ε = 3.9). For compounds IVa−c a long-wave maximum is detected at 353 nm (log ε = 4.02) in the absence of signs of the aminopyridine absorption band noted above.

All this rather definitely indicates that compounds VIa−c are in the pyridonimine form.

The fact that aminopyridines exist chiefly in the amine form, and not in the imine form [12], is well confirmed on the example of the reaction of the acid chloride IIIa with 2,6-diaminopyridine. A change in the reagent ratio, as well as the reaction conditions, does not influence the structure of compound VII. In the EU mass spectrum, the peak of the molecular ion $[M^+]$ 549 which corresponds to the disubstituted derivative of 2,6-diaminopyridine, is detected. On the basis of UV and IR spectral investigations, the structure N,N′-bis[3′-phenyl-2′-(1′,4′-dithi-2′-en)-ylcarbonyl]-2,6-diaminopyridine (VII) was assigned to the reaction product.



VII

In the IR spectrum of compound VII the absorption peak ν_{NH} (3348 cm^{-1} in liquid petrolatum and 3400 cm^{-1} for a solution in $CHCl_3$), characteristic of the aminopyridine structure, is detected. An additional confirmation of the formation of an aminopyridine structure of compound VII is the presence of an absorption maximum in the UV spectrum in the region of 324 nm, just as in the spectrum of compound V.

EXPERIMENTAL

The PMR spectra of compounds IIa,b and IVa-f were recorded on a Varian T-60 spectrometer with working frequency 60 MHz, and those of compounds V and VIa-c on a Bruker WV-250 spectrometer with working frequency 250.13 MHz. The IR spectra were taken on a UR-20 instrument (in liquid petrolatum). The UV spectra were taken in acetonitrile on a Specord M-40 spectrophotometer (Carl Zeiss, Jena). The mass spectra of compounds (VIa-c) were recorded on an MX-1310 instrument with energy of ionizing electrons 70 eV; the sample was incorporated into the ion source with an SVP-5 at a temperature of the ion source 50°C, current of the collector I_c = 30 μA.

The characteristics of the compounds obtained are presented in Tables 1, 2, and 3.

The data of elementary analysis for C, H, N, and S correspond to the calculated values.

Hydrolysis of the Methyl Ester of 3-Phenyl-1,4-dithi-2-ene-2-carboxylic Acid. A mixture of 50.4 g (0.2 mole) of the ether (Ia), 39.2 g (0.7 mole) KOH, 50 ml of water, and 100 ml of ethanol was boiled for 4 h, and the solvent was distilled off under vacuum. The residue was dissolved in water, and with cooling with ice, concentrated HCl was added dropwise to pH 1. The crystals that precipitated were filtered off, washed with water, and dried in air. Yield 35.7 g (75%) of the acid IIa, mp 164-165°C (propanol-2).

3-Phenyl-1,4-oxathi-2-ene-2-carboxylic Acid (IIb). Produced analogously to IIa from 47.2 g (0.2 mole) of the corresponding ester Ib with a yield of 31.9 g (72%), mp 188-189°C (methanol).

3-Phenyl-1,4-dithi-2-ene-2-carboxylic Acid Chloride (IIIa). A mixture of 23.8 g (0.1 mole) of the acid (II) and 17.8 g (0.15 mole) $SOCl_2$ in 100 ml of benzene was mixed for 2 h at 50°C. The solvent and excess $SOCl_2$ were distilled off under vacuum. Yield 25 g (100%) of the crude acid chloride (IIIa), dense liquid. IR spectrum: $\nu_{C=O}$ 1780, $\nu_{C=C}$ 1600 cm^{-1}.

TABLE 3. Parameters of the UV Spectra of 2-Aminopyridine and Compounds Ia, IVa, V, VIa, VIb, VIc, and VII (acetonitrile)

Compound	λ_{max}, nm	lg ε	Compound	λ_{max}, nm	lg ε
2-Aminopyridine	293	3,93	VIa	221	4,30
				353	4,02
Ia	238	4,67	VIб	229	4,49
	325	4,33		345	4,04
IVa	235	4,09	VI c	203	5,13
	324	3,78		255 (NO_2)	4,52
				357	4,27
V	279	3,90	VII	224	5,14
	326	3,80		305	4,46
				324	Shoulder

3-Phenyl-1,4-oxathi-2-ene-2-carboxylic acid chloride (IIIb) was produced from 4.4 g (0.02 mole) of the corresponding acid (IIb) with a yield of 4.7 g (100%), dense liquid. IR spectrum: $\nu_{C=O}$ 1775, $\nu_{C=C}$ 1600 cm^{-1}. The acid chlorides were used further without additional purification.

Anilide of 3-Phenyl-1,4-dithi-2-ene-2-carboxylic Acid (IVa). A solution of 2.5 g (0.01 mole) of the acid chloride (IIIa) in 10 ml of benzene was added dropwise with mixing at 20°C to a mixture of 0.03 g (0.01 mole) of aniline and 1.01 g (0.01 mole) Et_3N in benzene. The mixture was left for 8 h at 20°C. It was filtered off, and the filtrate was evaporated under vacuum. The residue obtained was recrystallized from the corresponding solvent.

The anilides IVb-f were produced analogously (see Table 1).

N-[3′-Phenyl-2′-(1′,4′-dithi-2′-en)ylcarbonyl]-2-aminopyridine (V). To a solution of 0.2 g (0.01 mole) 2-aminopyridine in 25 ml of pyridine we added 2.5 g (0.01 mole) of the acid chloride (IIIa) with mixing in an atmosphere of argon at 0-5°C. Mixing was continued at 20°C. The pyridine was distilled off, water was added to the residue, and it was extracted with chloroform (3 × 50) and dried with $MgSO_4$. After removal of the solvent, the residue was recrystallized from methanol. The compound V was obtained with a yield of 67% (2.1 g). The methanol-insoluble residue was recrystallized from DMSO. Compound VIa was obtained with a yield of 3% (0.1 g).

N,N′-Bis[3-phenyl-2-(1,4-dithi-2-en)ylcarbonyl]pyridonimine (VIa). To a solution of 0.9 g (0.01 mole) 2-aminopyridine and 2.2 g (0.21 mole) Et_3N in 50 ml of benzene, we added 5.1 g (0.2 mole) of the acid chloride IIIa with mixing in an atmosphere of argon at 5-10°C; the mixture was mixed for 1.5 h at 20°C, then left overnight. The solvent was distilled off, and the residue was washed with water and dried in air, then recrystallized from DMSO. Compound VIa was obtained with a yield of 61% (3.2 g). When DMSO was replaced by MeOH, trace amounts (0.08, 1.5%) of compound V, mp 165-166°C, were obtained. A mixed sample with compound V produced in the previous experiment gave no deflection of the melting point.

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