DERIVATIVES OF 2H-PYRAZOLO[4,5-b]-1,4-THIAZINE

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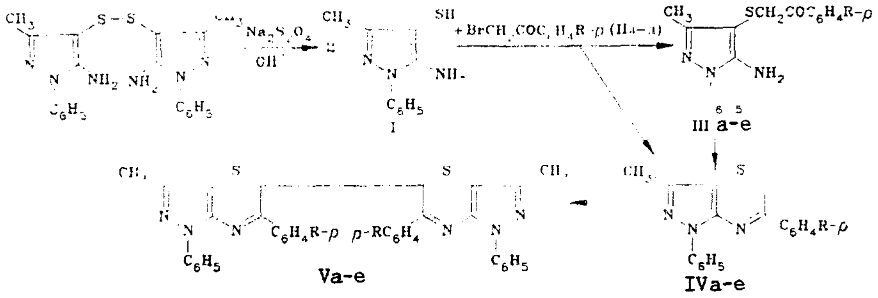
Derivatives of 2H-pyrazolo[4,5-b]-1,4-thiazine, which tend to undergo dimerization at the 2-methylene group were synthesized by reaction of 5-amino-3-methyl-4-thio-1-phenylpyrazole with ω-bromoacetophenones.

In continuation of the study of 1,4-thiazines [1], the present work was directed to the investigation of the reaction of 5-amino-3-methyl-4-thiophenylpyrazole (I) the ω-bromo-4-R-acetophenones (II). The intended process is realized directly by the reduction of the initial disulfide without isolation of compound I from the reaction mixture [2]:



a R=H, b R=C_6H_5, c R=Cl, d R=Br, e R=NO_2

Under these conditions, the main reaction products were derivatives of pyrazolo[4,5-b]-1,4-thiazine IVa-e, accompanied by the formation of compounds III and V was observed, the yield of the latter increasing substantially with increase in time of boiling of the reaction mixture. Compounds V are also formed on boiling alcoholic solutions of compounds IV or by their fusion. Individual substitution products (compounds IIIa, d) could be isolated in sufficient quantities for the investigation.

Compounds IIIa,d are in the form of white crystals. In their IR spectra the $\nu_{C=O}$ (1670 ...1675 cm^{-1}) and ν_{NH} (3361...3474 cm^{-1}) bands are observed, while in the PMR spectra (in pyridine) proton singlets of the CH_3 and CH_2 groups (δ 2.45 and 3.70 ppm) are seen. When alcoholic solutions of compounds IIIa,d are boiled with the addition of acetic acid, they are converted into compounds IVa,d, which confirms the scheme of their formation.

TABLE 1. Characteristics of Compounds III–V

Compound	Empirical formula	mp, °C	λ_{max} (ε·10^{-3})	Yield, %
IIIa	$C_{18}H_{17}N_3OS$	124	254 (19,8)	40
IIId	$C_{18}H_{16}ClN_3OS$	108...109	256 (20,1)	42
IVa	$C_{18}H_{15}N_3S$	103...104	344 (8.6)	28
IVb	$C_{24}H_{20}N_3S$	110	353 (10,3)	23
IVc	$C_{18}H_{14}ClN_3S$	145...146	350 (10,5)	25
IVd	$C_{18}H_{14}BrN_3S$	156	353 (11.5)	25
IVe	$C_{18}H_{14}N_4O_2S$	179...180	382 (9.8)	30
Va	$C_{36}H_{28}N_6S_2$	276	352 (6,0)	49
Vb	$C_{48}H_{38}N_6S_2$	320	361 (7,1)	58
Vc	$C_{36}H_{26}Cl_2N_6S_2$	280	353 (6,3)	49
Vd	$C_{36}H_{26}Br_2N_6S_2$	300	352 (7,2)	35
Ve	$C_{36}H_{26}N_8O_4S_2$	294	384 (6.2)	45

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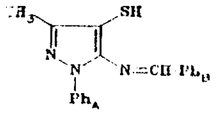
TABLE 2. Data of Calculation of a Planar Model of a Molecule of Compound



Electronic transition	Band in the UV spectrum	Calc.		Experiment		Localization of transition, %					Change in electron density				
		E, eV	f	E, eV	f	S	Pyr	C=N	Ph_A	Ph_B	S	Pyr	C=N	Ph_A	Ph_B
0—1	1	3,37	0,39	3,43	0,57	18,2	35,6	29,5	2,8	13,9	−0,35	−0,28	0,43	0,02	0,18
0—2	2	3,91	0,68	3,92	0,13	1,0	41,1	22,8	21,6	13,5	−0,003	−0,23	0,28	−0,14	0,09
0—3	—	4,52	0,09	—	—	0,5	3,2	11,1	0,6	84,6	−0,006	−0,005	0,095	0,003	0,087
0—4	—	4,53	0,08	—	—	0,6	11,3	0,8	86,6	0,7	−0,01	−0,13	0,006	0,074	0,004
0—5	3	4,67	0,26	5,11	0,87	10,5	44,9	11,7	22,5	10,7	−0,21	−0,22	0,127	0,23	0,073

TABLE 3. Mass Spectra of Compounds IVe and Va

Compound	m/z (intensity, %)*
IVd	350 (M^+, 83), 349 (100), 320 (18), 304 (14), 303 (48), 149 (9), 118 (18), 103 (11), 91 (9), 78 (25), 77 (62)
Va	606 (2), 305 (100), 304 (100), 222 (28), 221 (27), 118 (32), 103 (44), 102 (19), 91 (22), 89 (19), 77 (99)

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*The ion with the largest mass, and ten most intense ion peaks are given.

Compounds IVa-e are 3-aryl-7-methyl-5-phenyl-2H-pyrazolo-[4,5-b]thiazines, as follows from the data of the elemental analysis and spectral characteristics (Table 1). Thus, in the IR spectra the $\nu_{C=O}$ and ν_{NH_2} bands are absent, while the $\nu_{C=N}$ band (1610...1625 cm^{-1}) is one of the most intense. The electronic spectra are typical of annelated 1,4-thiazine systems [1]: the long-wave band is characterized by low intensity, while its λ_{max} values are sensitive to the electron acceptor effect of the substituents R (in particular, the electron acceptor effect of the NO_2 group, Table 1). The quantum-chemical calculation of a planar model of compound IVa that has been carried out showed the localization of the long-wave transition over the entire chromophore chain of the S–Pyr–N=C–C_6H_4R molecule. The transition is accompanied by a substantial redistribution of the electron density (0.35e) from the pyrazole ring to the azomethine bond and the phenyl ring (Table 2).

In the PMR spectra of compounds IV proton singlets of the CH_3 and CH_2 groups (δ 2.20... 2.22 and 3.68...3.70 ppm, respectively) and a multiplet of the aromatic protons (δ 7.30... 7.98 ppm) are observed. In the mass spectrum of compound IVe, an intense peak of the molecular ion is seen (Table 3).

The transformation of compounds IVa-e into compounds Va-e little influences their IR spectra, and the changes involve mainly the regions of the "fingerprints". Also the general form of the electronic absorption spectra does not change greatly, and only an insignificant (2...3 nm) bathochromic shift of the long-wave absorption band takes place.

In the PMR shift of this series of compounds, the methylene group singlet disappears, but a singlet appears in the 4.94...502 ppm region, which was assigned to the methine proton (the intensity ratio of this signal to that of CH_3 group singlet is equal to 1:3). In the mass spectrum of compound Va (Table 3) ions with m/z 305 and 304, i.e., the ions of the monomeric fragment, are the intense. However, these are accompanied by low intensity ion peaks with large masses (606, 368, 349, 331; intensity not more than 2%), which indicates the instability of the molecular ion and the absence of its peak in the mass spectrum.

All these data lead us to conclude that the molecules of IV are dimerized into molecules of V. The process does not affect the p, π-systems of the molecules of IV, since the changes in the spectral characteristics would otherwise be much more pronounced. It can be realized only through the oxidative dimerization at the 2-methylene group. A similar process has been previously described for the benzo-1,4-thiazine derivatives [3].

The above data allow us to understand why the formation of compounds V is not observed in the fusion of compounds IV in the absence of atmospheric oxygen. We should note that in [2] it is possible that the authors isolated compound Va (as indicated by the mp 282...284°C), to which they erroneously ascribed the structure of 3,5-diphenyl-7-methylpyrazolo[4,5-b]-1,4-thiazine.

The spectral investigations (IR, PMR spectra) indicate that the pyrazolo[4,5-b]-1,4-thiazine derivatives that we synthesized (compounds IV and V) exist preferentially in the form of a 2H-tautomer.

EXPERIMENTAL

The IR spectra were measured on a Specord IR-75 spectrophotometer in KBr tablets, and the electronic absorption spectra on a Specord UV-Vis spectrophotometer in ethanol at a concentration of $1...5 \cdot 10^{-5}$ mole/liter. The PMR spectra were run on a Tesla BS-487 spectrometer (80 MHz) in deuteropyridine-D_6, the concentration of the sample was 10...20%, and TMS was used as internal standard. The mass spectra were obtained on a Varian MAT-311A apparatus with direct introduction of the sample to the ionic source, at evaporation temperatures of 100...150°C and the energy of the ionizing electrons of 70 eV*. The calculation of the electronic characteristics of the excited states of compound Va was varried out by the MO LCAO SCF quadrupole coupling methods in the CNDO variant with a standard set of parameters. The data of the elemental analysis for N match the calculated values.

7-Methyl-3,5-diphenylpyrazolo[4,5-b]-2H-1,4-thiazine (IV)a). A mixture consisting of 2.0 g (5 mmoles) of bis(1-phenyl-3-methyl-5-aminopyrazol-4-yl) disulfide, 30 ml of methanol and 50 ml of water is heated to boiling. A 0.3 g portion of sodium hydroxide and 0.3 g of $Na_2S_2O_4$ are added. The reaction mixture is boiled for 2 h, then 1.0 g (5 mmole) of ω-bromoacetophenone, dissolved in 30 ml of methanol is added, and heating is continued for another 4 h. After cooling, the crystals obtained are filtered off and crystallized from methanol. Yield, 0.43 g of compound IVa. Compounds IVb-e are obtained in a similar way.

5-Amino-4-(ω-phenacetylthio)-3-methyl-1-phenylpyrazole (IIIa). The preparation is carried out in a similar way, but the overall duration of boiling of the reaction mixture was 2 h...2 h 30 min. White crystals of IIIa precipitated from a hot solution. Yield 0.64 g of compound IIIa.

Bis(7-amino-3,5-dimethylpyrazolo[4,5-b]-2H-1,4-thiazin-2-yl) (Va). The preparation was carried out in a similar way, but the time of boiling of the reaction mixture was 7 h. Yield 0.75 g of compound Va. Compound Va is obtained in quantitative yield on fusion of compound IVa in air (control by TLC and spectral characteristics).

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