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KINETICS OF THE CYCLOADDITION OF MALEIC ANHYDRIDE TO ARYLAMINOMETHYLENE DERIVATIVES OF 3-METHYL-1-PHENYLPYRAZOLE-5-THIONE

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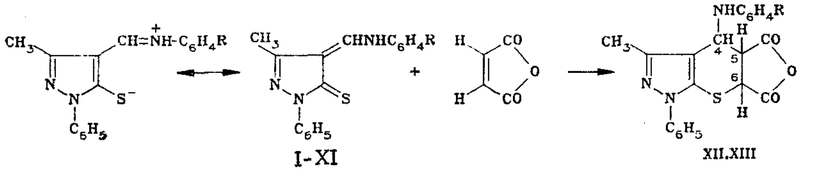
A series of arylaminomethylene derivatives of 3-methyl-1-phenylpyrazole-5-one have been synthesized, which take part in a cycloaddition reaction with maleic anhydride. The kinetics of cycloaddition and the influence of the nature of substituents in the phenyl ring of the aminomethylene fragment, of the temperature, and of the solvent on the course of the reaction have been studied.

The synthesis of 3-methyl-4-methylamino-5,6-dihydro-4H-thiopyrano[2,3-d]pyrazole-5,6-dicarboxylic acids by the cycloaddition of maleic anhydride (MA) to 3-methyl-4-methylaminomethylene-1-phenylpyrazole-5-thione has been described previously [1]. In order to elucidate the mechanism of this reaction, a series of 3-methyl-1-phenyl-4-R-phenylaminomethylenepyrazole-5-thiones (I-XI) differing by the nature of the substituent in the phenyl ring has been obtained by the reaction of 4-formyl-5-mercapto-3-methyl-1-phenylpyrazole with the corresponding aromatic amines (Table 1).

When solutions of the aminoethylene derivative (compounds (I-XI)) were mixed with MA, decoloration took place with the formation of a precipitate of the corresponding adduct:



Of the adducts, the products of the addition of MA to the thiones (VI) and (XI) — (XII) and (XIII) — were isolated in the form of yellow crystalline substances. The IR spectrum of compounds (XII) and (XIII) lacked the absorption band at 1650 cm^{-1} characteristic for the initial substances, and exhibited bands in the 1745-1730 and 3450-3470 cm^{-1} regions (CO and NH, respectively). In the PMR spectra in DMSO-d_6, the signals of isolated protons (4.6, 4.2, and 3.4 ppm) were assigned to the protons in positions 4, 6, and 5 of the thiopyran ring, respectively. The signal of the proton of the NH group fell into the region of aromatic protons, as could be judged from the appearance in the spectrum in the presence of trifluoroacetic acid of a greatly broadened signal at 8.2 ppm (as the result of a downfield shift). The electronic absorption spectra in toluene of the products of MA to compounds (I)-(XI) each had an absorption maximum at 320-330 nm and did not absorb in the 440-460 nm region.

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TABLE 1. Physicochemical and Spectral Properties of Arylaminoethylene Derivatives of 3-Methyl-1-phenylpyrazole-5-thione (I-XI).

Compound	R	T_{mp},* °C	UV spectrum, λ_{max}, nm	PMR spectrum, ppm		pK_a (10° C)	Found, %				Empirical formula	Calculated, %			
				CH	NH		C	H	N	S		C	H	N	S
I	p-$N(CH_3)_2$	187	460 (4,3), 385 (4,3)	8,10	15,00	13,16	68,1	6,0	16,6	9,5	$C_{19}H_{20}N_4S$	67,8	6,0	16,7	9,5
II	p-OCH_3	153	435 (4,2), 360 (4,5)	7,99	15,10	12,47	66,8	5,4	13,1	9,8	$C_{18}H_{17}N_3OS$	66,9	5,3	13,0	9,9
III	p-CH_3	183	435 (3,9), 355 (4,3)	8,05	14,90	12,60	70,5	5,6	13,5	10,4	$C_{18}H_{17}N_3S$	70,3	5,5	13,7	10,4
IV	m-$N(CH_3)_2$	119	435 (4,1), 348 (4,4)	8,22	15,00	12,72	67,8	5,9	16,8	9,6	$C_{19}H_{20}N_4S$	67,9	6,0	16,7	9,5
V	m-CH_3	105	435 (3,9), 353 (4,3)	8,13	15,00	12,45	70,5	5,7	13,8	10,2	$C_{18}H_{17}N_3S$	70,3	5,5	13,7	10,4
VI	H	155	440 (3,9), 355 (4,3)	8,09	15,10	12,09	69,8	5,4	14,3	10,9	$C_{17}H_{15}N_3S$	69,6	5,1	14,3	10,9
VII	m-OCH_3	133	435 (4,0), 355 (4,4)	8,19	14,90	12,10	66,7	5,3	12,9	9,9	$C_{18}H_{17}N_3OS$	66,9	5,3	13,0	9,9
VIII	m-$COOC_2H_5$	160	445 (3,9), 362 (4,4)	8,14	15,00	11,34	65,6	5,2	11,4	8,8	$C_{20}H_{19}N_3O_2S$	65,8	5,2	11,5	8,8
IX	p-$COOC_2H_5$	157	440 (3,7), 353 (4,2)	8,25	15,00	11,31	65,5	5,2	11,4	8,8	$C_{20}H_{19}N_3O_2S$	65,8	5,2	11,5	8,8
X	m-NO_2	190	445 (3,8), 355 (4,4)	8,80	15,10	10,59	60,2	4,2	16,6	9,4	$C_{17}H_{14}N_4O_2S$	60,4	4,1	16,6	9,5
XI	p-NO_2	208	460 (4,0), 375 (4,5)	8,30	15,00	10,36	59,8	4,2	16,4	9,7	$C_{17}H_{14}N_4O_2S$	60,4	4,1	16,6	9,5

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*Compounds (I) and (IX) were crystallized from toluene, (II), (II), (VIII), (X), and (XI) from benzene, and (IV)-(VII) from ethanol.

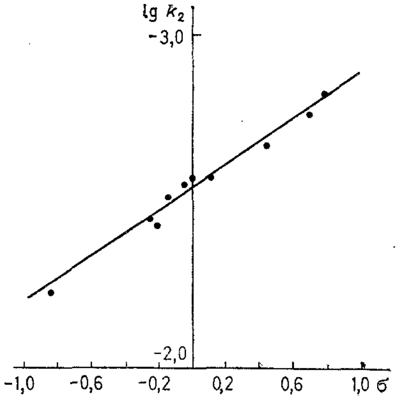

Fig. 1. Correlation of the rate constants of the cycloaddition of MA to arylaminomethylene derivatives of pyrazolethione with Hammett's σ-constants of the substituents.

TABLE 2. Second-Order Rate Constants and Thermodynamic Parameters of the Activation of 3-Methyl-1-phenyl-4-R-phenylaminomethylene pyrazole-5-thiones with MA in Toluene.

Compounds	R	$k_2 \cdot 10^3$, liter/(mole·sec)				$-\Delta S^{\neq}$, J/(mole·K)				$\Delta H^{\neq}$, kJ/mole
		303 K	313 K	323 K	333 K	303 K	313 K	323 K	333 K	
I	p-$N(CH_3)_2$	3,80	6,49	13,00	22,00	128,5	129,9	129,5	130,1	49,22
II	p-OCH_3	2,00	3,74	6,80	10,90	145,0	145,2	145,3	146,1	45,86
III	p-CH_3	1,55	3,03	6,15	8,28	149,5	149,3	148,4	150,6	45,12
IV	m-$N(CH_3)_2$	1,74	3,96	7,27	12,20	140,9	139,6	139,8	140,4	47,45
V	m-CH_3	1,44	2,88	5,50	8,85	139,7	139,6	139,5	140,6	48,28
VI	H	1,12	2,81	4,49	7,10	153,7	151,3	152,4	153,2	44,68
VII	m-OCH_3	1,30	2,80	4,97	8,87	133,3	132,8	133,5	133,9	50,49
VIII	m-$COOC_2H_5$	1,34	2,50	5,48	8,24	137,1	137,7	136,5	138,2	49,26
IX	p-$COOC_2H_5$	1,20	2,30	5,00	7,70	134,6	135,1	134,1	135,7	50,29
X	m-NO_2	0,92	1,80	3,59	5,82	139,9	140,1	139,7	140,8	49,36
XI	p-NO_2	0,81	1,56	3,22	4,76	146,7	146,8	146,1	147,7	47,62

The course of the reaction can be affected by the electronic and steric properties of the substituent in position 1 of the initial aminomethylene derivatives, and, to investigate this, the phenol group was replaced by a methyl group and the resulting 1,3-dimethyl-4-phenylaminomethylenepyrazole-5-thione (XIV) [2] was subjected to the cycloaddition reaction under similar conditions. The adduct (XV) was isolated, and its PMR spectrum showed the signals of isolated protons at 5.4, 4.4, and 3.4 ppm, assigned to the protons in positions 4, 6, and 5 of the thiopyran ring, respectively. The IR spectrum of compound (XV) showed absorption bands at 1712 and 3010 cm^{-1} (CO and NH, respectively). The electronic absorption spectrum in ethanol showed a shoulder at 240 nm.

The kinetics of the cycloaddition of MA to compounds (I)-(XI) and (XIV) were studied spectrophotometrically in toluene at four temperatures in the range of 303-333 K. The concentration was varied within the range of 10^{-4}-10^{-3} M. i.e., in the region where the Bouguer—Lambert—Beer law is obeyed. The measurements showed that the reaction had the first order with respect to each reactant. The bulk of the investigation was performed with the use of a 50-fold excess of MA, i.e., under the conditions of a pseudo-first-order reaction. The results obtained were used to calculate the rate constants of the second-order reaction (Table 2).

It can be seen from the figures in Table 2 that the rate of the reaction rises with an intensification of the electron-donating and falls with a rise in the electron-accepting properties of a substituent in the phenyl ring. However, the change in the rate constant of the cycloaddition reaction on passing from a p-nitro to a p-dimethylamino groups is small (only 5-fold) Figure 1 shows the dependence of the rate of the reactions of the compounds studied on Hammett's σ-constant. The correlation coefficient is 9.97, $\rho = -0.345$, $S = 0.122$. (When Hammett's σ°constants were used, the correlation coefficient was 0.95.) The negative value of ρ shows the occurrence of the reaction in the diene—donor, dienophile—acceptor manner. The low absolute value of ρ makes a mechanism with a zwitterionic intermediate unlikely. The reaction most probably takes place as a concerted process [3]. Judging from the values obtained (Table 3), the replacement of a phenyl group (VI) by a methyl group (XIV) has no sub-

TABLE 3. Second-Order Rate Constants and Thermodynamic Parameters of Activation of the Cycloaddition of MA to Compounds (VI) and (XIV) in Various Solvents.

Compound	Solvent	$k_2 \cdot 10^3$, liter/(mole·sec)				$-\Delta S^{\neq}$, J/(mole·K)				$\Delta H^{\neq}$, kJ/mole
		303 K	313 K	323 K	333 K	303 K	313 K	323 K	333 K	
VI	Toluene	1,12	2,81	4,49	7,10	153,7	151,3	152,4	153,2	44,68
VI	Acetonitrile	5,16	8,71	12,50	21,95	156,1	155,2	158,0	157,5	40,12
VI	Dioxane	4,91	8,98	16,80	30,30	132,4	132,9	132,9	133,0	50,05
VI	Chloroform	4,20	6,40	10,55	2,13*	163,2	164,3	164,5	163,9*	38,57
VI	Dimethylacetamine	6,31	11,55	19,49	32,34	150,3	150,2	150,5	150,6	41,35
XIV	Dimethylacetamide	6,33	12,36	19,08	32,39	153,8	153,0	153,9	153,5	40,29

*At 293 K.

stantial influence on the activities of these compounds. For all the compounds studied a linear dependence of log k_2 on 1/T was observed. The correlation coefficient is 0.99.

The thermodynamic activation parameters are characterized by large negative values of the activation entropy and relatively small values of the activation enthalpy (Tables 2 and 3). For all the compounds differing by the substituent in the phenyl residue of the aminomethylene group a linear dependence of ΔH on $\Delta S^{\neq}$ is observed, which shows the monotypical nature of the reaction mechanism. High negative values of $\Delta S^{\neq}$ (from −30 to −40 e.u.) are characteristic for a concerted mechanism, although they do not contradict a two-stage biological mechanism either, provided that the closure of the ring is rate-determining [4].

We also studied the influence of the solvent on the rates of the cycloaddition of compounds (I-XI) and (XIV) to MA. As can be seen from Table 3, the influence of the solvent is shown to a very slight degree. A tendency is observed to an increase in the rate of the reaction with a rise in the basicity of the solvent, which is apparently connected with the fact that the initial compounds (I-XI) and (XIV) are weak acids and the anions formed from them in basic solvents are more reactive than the neutral molecules. These facts are in harmony with those given in the literature [5] explaining the effect of the solvent as the result of its donor—acceptor interactions. The rise in the rate of cycloaddition in chloroform (in comparison with its basicity) is apparently connected, as in [6], with its capacity for giving hydrogen bonds with carbonyl-containing compounds.

Thus, the study of kinetics has permitted the formation of derivatives of 3-methyl-1-phenyl-4R-phenylamino-5,6-dihydro-4H-thiopyrano[2,3-d]pyrazole-5,6-dicarboxylic anhydride as the result of addition by a concerted (or radical) mechanism.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument (in chloroform), UV spectra on a SF-8 spectrophotometer (in toluene), and PMR spectra on a Varian-60 instrument (in DMSO) with TMS as internal standard.

3-Methyl-1-phenyl-4R-phenylaminomethylene Derivatives of Pyrazole-5-thione. A mixture of 30 mmoles of 5-chloro-4-formyl-3-methyl-1-phenylpyrazole in 150 ml of ethanol and 150 mmoles of 50% KHS was boiled for 3 h [7].

The cooled reaction mixture was poured into 300 ml of H_2O, the mixture was filtered, and the filtrate was cooled to 5°C and was acidified with dilute HCl to pH 7. Then it was treated with 90 mmole of the appropriate amine in the form of the base or in the form of a salt with a mineral acid, the mixture was heated to 40°C and was kept there for 2 h, and the precipitate that had deposited was filtered off, washed with water, and dried. The yields were 80-95%, see Table 1.

1,3-Dimethyl-4-phenylaminomethylenepyrazole-5-thione (XIV) was obtained as described in [2].

3-Methyl-1-phenyl-4-phenylaminodihydrothiopyrano[2,3-d]pyrazole-5,6-dicarboxylic anhydride (XII). After the addition of 0.18 g (0.6 mmole) of 3-methyl-1-phenyl-4-phenylaminomethylenepyrazole-5-thione in 15 ml of absolute toluene to a solution of 0.06 g (0.6 mmole) of freshly sublimed maleic anhydride in 12 ml of absolute toluene the reaction mixture was boiled for 30 min. The excess of toluene was distilled off, and then petroleum ether was added to the reaction mixture. The precipitate that deposited was filtered off and dried. Yield 0.19 g (81%). mp 220-221°C (from ethanol). IR spectrum, cm^{-1}: 1715 (CO). UV spectrum, λ_{max}, nm (log ε): 325 (3.8). PMR spectrum, ppm: 4.6 (1 H, 4-CH), 4.2 (1 H, 6-CH), 3.4 (1 H, 5-CH). Found: C 65.4; H 4.6; N 10.4; S 8.0%. $C_{22}H_{18}N_3O_3S$. Calculated: C 65.3; H 4.5; N 10.4; S 7.9%.

3-Methyl-1-phenyl-4-(p-nitrophenylamino)-dihydrothiopyrano[2,3-d]pyrazole-5,6-dicarboxylic anhydride (XIII) was obtained in a similar manner to compound (II). Yield 80%. mp 135-136°C (from ethanol). IR spectrum, cm^{-1}: 1730 (CO). UV spectrum, λ_{max}, nm (log ε): 330 (3.9). PMR spectrum, ppm: 4.6 (1 H, 4-CH), 4.2 (1 H, 6-CH), 3.4 (1 H, 5-CH). Found: C 58.7; H 4.1; N 20.2; S 6.7%. $C_{22}H_{17}N_4O_5S$. Calculated: C 58.7; H 3.8; N 10.2; S 6.8%.

1,3-Dimethyl-4-phenylaminodihydrothiopyrano[2,3-d]pyrazole-5,6-dicarboxylic anhydride (XV) was obtained in a similar manner to compound (XII). Yield 91%. mp 256-257°C (from ethyl acetate). IR spectrum, cm^{-1}: 1712 (CO). UV spectrum (in ethanol), nm: 240 (sh). PMR spectrum, ppm: 5.4 (1 H, 4-CH), 4.4 (1 H, 6-CH), 3.4 (1 H, 5-CH). Found: C 58.3; H 4.4; N 12.5%. $C_{16}H_{15}N_3O_3S$. Calculated: C 58.3; H 4.6; N 12.7%.

Acid—Base Properties of the Initial Compounds. Ionization constants were determined on a ÉP-74 universal pH meter by the potentiometric method in 75% aqueous dioxane at 10°C. The ionization constants were calculated in [8].

Kinetics of the Cycloaddition of MA. The rate constants of the cycloaddition reaction were determined spectrophotometrically from the change in the absorption of the reaction solutions in a SF-4A spectrophotometer fitted with thermostable cells. The study was performed in the region of the long-wave maximum (440-460 nm) of the initial arylaminomethylene derivatives, where the adducts do not adsorb. The solvents used were purified by standard methods [9]. The working concentrations of the solutions of the arylaminomethylene derivatives were 10^{-5}-10^{-4} M. The MA was purified by sublimation before each series of experiments. The reaction was performed with a 70-fold excess of MA. The moment of mixing was taken as the start of the reaction. The optical densities were measured after predetermined intervals of time. The first-order rate constants were calculated (as the means of three experiments) from the optical density figures, and from then the second-order rate constants and thermodynamic activation parameters were calculated by well-known formulas [4].

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